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Safety and Efficacy of Bioidentical Hormone Therapy in Menopause: A Literature Review

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Abstract

Vasomotor symptoms (VMS) experienced during menopause can negatively impact a woman's quality of life, productivity, sleep, and mood. Systemic hormone therapy (HT) is the most effective treatment for moderate to severe VMS, however safety concerns raised by the 2002 Women's Health Initiative (WHI) trial have led to a decrease in overall HT use and a growing demand for custom-compounded bioidentical HT. Misconceptions regarding the superior safety and efficacy of custom-compounded hormones and lack of clinician expertise in menopause management contribute to ongoing uncertainty and low uptake of United States (U.S.) Food and Drug Administration (FDA) approved bioidentical HT products. This literature review evaluates current evidence regarding the safety and efficacy of bioidentical HT to provide clinical guidance for patient education and prescribing practices. Twenty-eight articles published from 2015-2020 were included in the final review, consisting of systematic reviews, meta-analyses, randomized control trials (RCTs), cohort studies, case control studies, and literature reviews. Current evidence suggests that FDA approved bioidentical hormones are more effective than placebo and equally effective compared to synthetic hormones when used to treat menopausal VMS. Safety of bioidentical HT was evaluated based on its associated risk of breast cancer, endometrial cancer, venous thromboembolism (VTE), stroke, and cardiovascular disease (CVD). Findings suggest that safety profiles depend on the duration of therapy, route, regimen, and individual factors but bioidentical HT is generally safe for women without contraindications if low to medium doses are used for five years or less.

Keywords: menopause, vasomotor symptoms, hot flashes, night sweats, efficacy, bioidentical hormone therapy, estradiol, progesterone, safety, breast cancer, endometrial cancer, stroke, venous thromboembolism, cardiovascular disease

Safety and Efficacy of Bioidentical Hormone Therapy in Menopause: A Literature Review

Menopause is the cessation of menstruation due to the natural decline in ovarian function or surgical removal of the ovaries and can be clinically diagnosed 12 months following the final menstrual period (FMP) (Stuenkel et al., 2015). Menopausal VMS including hot flashes and night sweats "are associated with a sudden sensation of heat in the face, neck, and chest and persist for several minutes or less. Vasomotor symptoms may include flushing, chills, anxiety, sleep disruption, and palpitations" (Kauntiz & Manson, 2015, p. 2). The pathophysiology of VMS is not completely understood; however, it likely involves altered thermoregulation and release of neuroendocrine, cytokine, and stress hormones due to fluctuating sex hormone levels (Kaunitz & Manson, 2015).

The average age of natural menopause in the U.S. is 51 and menopausal transition, or perimenopause, may begin as early as age 40 (Kaunitz & Manson, 2015). VMS increase throughout perimenopause and peak approximately 1 year after the FMP (Kaunitz & Manson, 2015). Up to 80% of women experience VMS during the menopausal transition (Gold et al., 2006; Woods & Mitchell, 2005) and at least 50% report moderate to severe symptoms that interfere with quality of life (Freeman et al., 2014). A U.S. observational study showed that "frequent VMS lasted more than 7 years during the menopausal transition for more than half of the women and persisted for 4.5 years after the FMP" (Avis et al., 2015, p. 531). Frequent and severe VMS also occur following oophorectomy due to the sudden shift in estrogen and progesterone levels (Kaunitz & Manson, 2015).

VMS can negatively impact a woman's occupational, physical, emotional, and sexual quality of life and often prompt women in the U.S. to seek medical treatment (Nicholson et al., 2001; Utian, 2005; Williams et al., 2007). "Untreated menopausal symptoms are also associated

with higher health care costs and loss of work productivity" (Manson & Kaunitz, 2016, p. 803). Mild VMS can often be managed with lifestyle modifications such as weight reduction, smoking cessation, wearing layered clothing, and maintaining a cool environment (Goodman et al., 2011). Pharmaceutical treatment options for moderate to severe VMS include systemic HT, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), gabapentin, pregabalin, or clonidine patches (Goodman et al., 2011; North American Menopause Society, 2012; Stuenkel et al., 2015). For those without contraindications, estrogen therapy (ET) "with or without a progestogen is the most effective treatment of menopause-related vasomotor symptoms and their potential consequences, such as diminished sleep quality, irritability, difficulty concentrating, and subsequently reduced quality of life (QOL)" (North American Menopause Society, 2012, p. 3).

The dose, route, and regimen of HT can be individualized based on patient preferences, risk factors, hysterectomy status, symptomology, and goals of treatment. While systemic estrogen only therapy can be prescribed for women who have undergone hysterectomy, a progestogen must be added to provide endometrial protection for those with an intact uterus (Goodman et al., 2011; North American Menopause Society, 2012; Stuenkel et al., 2015). Estrogen is available in oral, transdermal (TD), or vaginal formulations and concurrent progestogens may be given orally or vaginally in a combined continuous (CC), sequential continuous (SC), or alternate day regimen. With CC estrogen progestogen therapy (EPT), both hormones are taken daily and with SC EPT the progestogen is given for 12-14 days each month (Yang et al., 2017). The lowest effective dose of HT should be given to control VMS and minimize adverse effects such breast tenderness, vaginal bleeding, bloating, and headaches. Current guidelines suggest that HT is safe for women "within 10 years of menopause who are at

low risk of cardiovascular disease and breast cancer" (Ward & Deneris, 2018, p. 169). Extended use may be warranted in some situations after informed, shared decision making, and discontinuation of HT should not be based on age alone (Santoro et al., 2019; Ward & Deneris, 2018).

The use of systemic HT dramatically decreased among U.S. women after the initial findings of the Women's Health Initiative (WHI) were published in 2002 (Manson & Kaunitz, 2016). Although the WHI was designed to evaluate the risks and benefits of long-term synthetic hormone therapy for postmenopausal women (average age 63 at therapy initiation), it is now being used to guide treatment decisions for women in their 40s and 50s who have distressing VMS (Manson & Kaunitz, 2016). While there are several FDA approved bioidentical HT options and sufficient research to support their use, they remain underutilized in the U.S. (Manson & Kaunitz, 2016). This is in part due to the misconception that compounded hormones are safer and more 'natural' than pharmaceutical bioidentical HT. The purpose of this literature review is to synthesize the current evidence regarding the following clinical question: In perimenopausal and postmenopausal women, what is the safety and efficacy of bioidentical hormone therapy in treating vasomotor symptoms?

Background

Initial findings from the WHI trial (Rossouw et al., 2002) reported that the combination of conjugated equine estrogen (CEE) with medroxyprogesterone (MPA) (both synthetic hormones) increased the risk of coronary heart disease (CHD), stroke, breast cancer, and VTE in postmenopausal women. This resulted in a 32% reduction in HT prescriptions and a greater than 60% reduction in CEE/MPA prescriptions in the U.S. despite further analysis suggesting that the WHI findings may not apply to peri- and newly menopausal women (Majumdar et al., 2004).

Since that time many women have opted for custom-compounded bioidentical HT "on the assumption that it would be safer than other forms of HT" (Gaudard et al., 2016, p. 3).

Bioidentical hormones from compounding pharmacies are often referred to as 'natural hormones' and have been marketed as having "fewer risks and side effects, and greater efficacy than commercially available HT preparations" (Stanczyk et al., 2021, p. 38). One million to 2.5 million U.S. women ages 40 and older currently use compounded HT, accounting for 28% to 68% of HT prescriptions (Pinkerton & Santoro, 2015). Most women who use compounded bioidentical HT report that it was recommended by their physician and are not aware that these products lack FDA-approval (Pinkerton & Santoro, 2015). Professional organizations including the American College of Obstetricians and Gynecologists, American Society for Reproductive Medicine, North American Menopause Society, Endocrine Society, American Association of Clinical Endocrinologists, and American College of Endocrinology recommend against the use of compounded HT "due to concerns regarding reliability of dosage, purity, lack of evidence regarding superior effectiveness over FDA-approved hormonal formulations and lack of FDA oversight" (Santoro et al., 2019, p. 30). In 2020, the National Academies of Sciences, Engineering, and Medicine (NASEM) conducted an extensive study of compounded bioidentical HT and recommend prescribers restrict its use to two circumstances: "patients with allergies to specific components of FDA-approved hormone therapy, or patients who require a dosage form not currently available as an FDA-approved drug product" (p. 195).

"The term 'bioidentical hormone' generally refers to sex steroid hormones, usually an estrogen, an androgen or progesterone, that has the same chemical and molecular structure [and physiological effect] as the endogenous hormone produced in the body" (Stanczyk et al., 2021, p. 38). Bioidentical hormones are often derived from natural plant substances; however, all

bioidentical hormones, whether they are custom-compounded or pharmaceutical formulations, require some degree of chemical synthesis in the lab (Stanczyk et al., 2021). S*ynthetic hormone* is a term used to describe formulations that differ in chemical structure and physiologic effect compared to endogenous hormones (Stanczyk et al., 2021). It is implied that all synthetic hormones are 'manufactured' in the lab, which is not the case. Conjugated equine estrogen (CEE) is derived from female horse urine and does not require any chemical synthesis, however it is considered a synthetic estrogen because it does not share the same chemical and physiologic properties as human estrogen (Stanczyk et al., 2021).

The following terms will be used in this literature review to differentiate between bioidentical and synthetic formulations. *Progestogen* encompasses both synthetic progestin (P) and bioidentical progesterone (P4). *Bioidentical estrogen* encompasses estrone (E1), estradiol (E2), estriol (E3), and estetrol (E4). E2 and E3 are widely used in Europe and Asia but only E2 products are FDA approved for use in the U.S. (Moskowitz, 2006). Custom compounded HT formulations may include any combination of P4, E1, E2, or E3 (Stanczyk et al., 2021).

FDA approved 17-beta estradiol is available in the U.S. in oral, transdermal, and vaginal formulations; under generic and brand names such as Estrace, Alora patch, and Vagifem (Santoro et al., 2019). Products combining oral or transdermal 17-beta estradiol with a synthetic progestin are also available (i.e. Activella, Climara Pro) (Santoro et al., 2019). Not all estradiol products are bioidentical which can create confusion for patients and clinicians; for example estradiol acetate is considered bioidentical whereas ethinyl estradiol is synthetic. Bioidentical P4 is available in an oral micronized formulation prepared in peanut oil (Prometrium), vaginal preparation (Prochieve 4%), or in a combined oral capsule with 17-beta estradiol (Bijuva)

(Santoro et al., 2019). MPA, norethindrone acetate (NETA), and levonorgestrel (LNG), are synthetic progestins that are completely man-made (Stanczyk et al., 2021).

Numerous FDA approved formulations of 17-beta estradiol and progesterone are available for U.S. women seeking bioidentical HT for the treatment of menopausal VMS. Clinicians caring for menopausal women often report having received inadequate training and many do not realize that FDA approved bioidentical hormones are available (Kling et al., 2019; Files et al., 2016; Manson & Kaunitz, 2016). This leads to reluctance in prescribing HT and ineffective counseling of women who might benefit from bioidentical therapies.

Method

Data abstraction process

A literature search was completed from 10/24/20 to 1/17/21 using CINAHL, Academic Search Premier, PubMed, and Cochrane Database of Systematic Reviews. Table 1 in the attached appendix includes details on search restrictions, dates included, and general subjects covered by each database.

Study Selection

Search terms comprised of “bioidentical hormone replacement therapy”, “bioidentical hormones", “menopause”, “perimenopause”, “vasomotor symptoms”, “estradiol”, “CEE”, “conjugated equine estradiol”, “progesterone”, “REPLENISH trial”, “safety”, “risk”, and “cancer”. Search limits included publications from 2015-2020, full text availability, English language, and peer reviewed academic journals. Articles were initially reviewed and eliminated if the title and abstract did not address the clinical question. Duplications were also eliminated. A

bibliographic review identified five additional articles that were ultimately included. See Table 2 in the appendix for search term combinations and the number of unique hits from each database.

Search Strategies

Table 3 in the appendix includes all articles that were reviewed for inclusion or exclusion criteria. Articles were included if they (1) included perimenopausal and/or postmenopausal women, (2) evaluated the efficacy of oral or TD bioidentical hormones in treating VMS, (3) evaluated the safety of bioidentical hormones regarding VTE, stroke, cardiovascular, breast cancer, or endometrial cancer risk, (4) compared bioidentical HT to non-users, placebo, and/or synthetic HT, or (5) compared various formulations, doses, regimens, or routes of bioidentical HT. Articles were excluded if they (1) evaluated the safety or efficacy of low-dose vaginal estrogen, (2) measured menopausal outcomes of genitourinary symptoms, sleep quality, or mood, (3) were expert reviews or commentary on original studies, (4) were available in abstract only, (5) or did not differentiate between bioidentical and synthetic hormones when evaluating the efficacy or risk of HT.

Literature Review Process

Twenty-eight articles met inclusion criteria and consisted of systematic reviews, meta-analyses, RCTs, case control studies, cohort studies, and literature reviews. The systematic reviews and meta-analyses included large, well-designed RCTs, observational, and population-based case control and cohort studies. Retrospective observational studies often relied on insurance claims to determine HT use, type of HT, co-morbid conditions, and participant demographics. This introduced a potential for error in International Classification of Diseases, Tenth Revision (ICD-10) coding, and did not provide specific dosing, duration, regimen, or

adherence data. Safety studies were more likely to be observational in nature compared to efficacy studies due to the longer duration required to evaluate for risk and the associated cost of long-term controlled studies.

Methodological Assessment

The twenty-eight articles included in the literature review were categorized into three groups: bioidentical HT efficacy, safety, or both. The safety articles were further categorized into five groups: breast cancer, endometrial cancer, VTE, stroke, or cardiovascular disease. Synthesizing the data was challenging due to heterogeneity of the studies and numerous factors impacting safety outcomes. The search terms and databases most likely to yield results were utilized for this literature review, however it is possible that some relevant literature was missed. By limiting search dates to the past five years, older studies with valuable findings may have been excluded, but the systematic reviews and meta-analyses included in this review encompass individual studies dating back over 20 years. This literature review therefore represents the current state of evidence regarding the safety and efficacy of bioidentical HT for the treatment of menopausal VMS.

Literature Review

Efficacy of Oral Estradiol

Gaudard et al. (2016) conducted a systematic review and meta-analysis of 23 RCTs comparing the efficacy of 17-beta estradiol to CEE or placebo and found low to moderate quality evidence suggesting that bioidentical estradiol is more effective than placebo in treating moderate to severe VMS. Efficacy was dose dependent but higher doses also resulted in more adverse effects such headache, vaginal bleeding, breast tenderness, and skin reactions. There was

no evidence to suggest a difference in efficacy between estradiol and CEE. The authors were unable to make specific treatment recommendations due to individual study limitations including risk of bias due to poor reporting of methods, imprecision, and lack of analyzable data.

The REPLENISH trial (Lobo et al., 2018) investigated the efficacy of TX-001HR, a combined oral E2/P4 capsule, given daily at various doses to treat moderate to severe VMS. Frequency and severity of VMS significantly decreased from baseline with the 1mg/100mg and 0.5mg/100mg doses compared to placebo at week 4 and week 12. Additional analyses of the REPLENISH trial demonstrated a clinically meaningful reduction in hot flashes (Constantine et al., 2019) and more VMS-free days (Kaunitz et al., 2020) in the treatment groups versus placebo.

Coelingh Bennink et al. (2016) conducted a small, partly randomized open-label, multiple-rising-dose study (*N*=49) comparing the efficacy of 2mg oral estradiol valerate (E2V) and 2mg and 10mg oral E4 in treating postmenopausal VMS. Oral E4 is a weak estrogen steroid hormone produced by the fetal liver and is only present at detectable levels during human pregnancy (Coelingh Bennink et al., 2016). Neither of these products are FDA approved for menopausal HT however oral E2V is widely used in Europe. Participants with an intact uterus were randomized to receive 2mg of unopposed E2V or 2mg of unopposed E4 on days 1-28. During the dose escalation phase of the study, women who experienced 35 or more hot flashes per week at baseline were then given 10mg of E4 on days 29-56. Hot flashes and sweating were recorded in a daily diary by all participants on days 1-56. The authors concluded that all treatment groups were equally effective at decreasing VMS (see Table 4).

Efficacy of Transdermal Estradiol

Transdermal estradiol can be administered as a gel, patch, or spray to treat moderate to severe VMS in menopause. Derzko et al. (2016) performed a systematic review and network meta-analysis to indirectly compare the efficacy of several estradiol gels and doses. The authors concluded that Divigel 0.25 mg, Divigel 0.5 mg, and Estrogel 0.75 mg showed similar efficacy and were all statistically superior to Estrogel 1.5 mg (see Table 4). Divigel 1.0 mg provided the best efficacy profile but was also associated with a higher risk of adverse effects including postmenopausal bleeding, headache, breast pain, infection, nausea, rash, and vaginitis. The discontinuation rate with Divigel 1.0 mg was only 5% which suggests that the benefits of improved efficacy may outweigh the risk of adverse effects for some women.

A systematic review and network meta-analysis by Kovács et al. (2016) indirectly compared the efficacy of estradiol metered dose transdermal spray (MDTS) and estradiol patches given at doses ranging from 14-50mcg. Both formulations resulted in similar reductions in hot flash frequency over a 12-week period with a dose dependent response. All but the 14mcg estradiol patch resulted in statistically significant improvements in VMS when compared to placebo. These findings suggest that estradiol MDTS and estradiol patches produce comparable reductions in VMS when given at similar doses.

Efficacy of Low-Dose Estradiol

The Kronos Early Estrogen Prevention Study (KEEPS) (Harman et al., 2005) was a multicenter RCT that compared the effects of low-dose oral CEE (0.45mg), TD estradiol (50mcg), and a placebo on cardiovascular outcomes in recently menopausal women (average 22 months post FMP). A secondary analysis of the KEEPS trial by Santoro et al. (2017) showed that both treatment arms experienced a significant and similar reduction in moderate to severe VMS when compared to the placebo group. Subgroup analyses also showed that symptom relief was

not significantly modified by body mass index (BMI), race, or ethnicity (Santoro et al., 2017). The authors concluded that "recently menopausal women had similar and substantial reductions in hot flashes and night sweats with lower than conventional doses of oral or TD estrogen. These reductions were sustained over 4 years" (Santoro et al., 2017, p. 3).

Malik et al. (2016) conducted a randomized single blind, four arm, parallel assignment study (*N*=200) comparing the efficacy of low-dose oral E2V, oral CEE, and a placebo in reducing postmenopausal VMS. Self-reported severity and frequency of hot flashes were used to calculate a hot flash score (average hot flash severity x daily frequency). Follow up at 24 weeks revealed a significant reduction in mean hot flash score for both E2V and CEE (91.9% and 89.2% reduction respectively). The authors concluded that low doses of oral E2V and CEE were equally effective in treating VMS over 24 weeks.

A systematic review of nine double blind placebo-controlled trials (*N*=3069) by Corbelli et al. (2015) found that low-dose TD estradiol (less than 50mcg) was more effective than placebo at reducing the frequency of moderate to severe hot flashes. A dose dependent response was observed with estradiol doses ranging from 0.003mg-0.045mg (see Table 4).

Efficacy of Progesterone Only Therapy

Progesterone only therapy can be used to treat VMS in women who have contraindications or a personal preference to avoid estrogen. Systematic reviews by Dolitsky et al. (2021) and Prior (2018) included a limited number of smaller RCTs that showed mixed therapeutic efficacy of standalone progesterone. One RCT (*N*=133) concluded that 300mg of daily oral micronized P4 significantly decreased VMS scores in the treatment group compared to

placebo (Hitchcock & Prior, 2012). There is insufficient evidence to support the use of low-dose TD P4 for menopausal VMS (Prior, 2018).

Safety of Bioidentical HT: Breast Cancer

The E3N-Epic study by Fournier et al. (2005) was a prospective study (*N*=98,997) conducted in France that followed menopausal women over an eight-year period and calculated the hazard ratio (HR), or likelihood of developing breast cancer after receiving HT. A hazard ratio of 1.0 indicates that the HT intervention had no impact on the outcome (breast cancer) whereas HR greater than 1.0 represents an increased risk and HR less than 1.0 represents a decreased risk (Melnyk & Fineout-Overholt, 2015). Fournier et al. (2005) concluded that breast cancer risk was lowest for those receiving bioidentical EPT (HR 0.9; 95% CI 0.7, 1.2) and bioidentical ET (HR 1.1; 95% CI 0.8, 1.6), and higher for those receiving bioidentical estrogen with synthetic progestin (HR 1.4; 95% CI 1.2, 1.7). These findings suggest than regimens containing a synthetic progestin pose a greater risk of breast cancer than bioidentical formulations.

A retrospective study by Zeng et al. (2018) compared breast cancer incidence among 12,404 women who received various types of HT after age 50 and 27,642 non-HT users. The authors concluded that ET with CEE or estradiol both resulted in a significant reduction in breast cancer risk (see Table 4). CEE plus MPA also significantly reduced breast cancer risk which conflicts with previous WHI findings (Rossouw et al., 2002). A non-significant increase in breast cancer risk occurred with estradiol plus progesterone (see Table 4). In a direct comparison of the two combination therapies, the authors concluded that CEE plus MPA is superior to estradiol plus progesterone from a breast cancer safety standpoint.

A systematic review and meta-analysis by Yang et al. (2017) evaluated breast cancer risk associated with unopposed estradiol and estradiol plus progestogen including subgroup analysis based on progestogen type, duration of exposure, and regimen. All 14 studies used E2V or 17-beta estradiol with a synthetic progestin or micronized P4, however doses and routes of administration were not specified. Breast cancer risk was increased in the EPT group, but subgroup analysis showed that the risk varied based on progestogen type. A statistically significant increase in breast cancer risk was noted with EPT containing synthetic progestins (MPA, NETA, and LNG) but there was no increased risk with EPT containing oral micronized P4 or dydrogesterone (see Table 4). Estradiol-only therapy showed no increased risk of breast cancer (see Table 4). Bioidentical estradiol combined with a progestogen increased breast cancer risk when used for longer than five years; however, the authors were unable to perform subgroup analysis based on progestogen type due to small sample sizes. Bioidentical estradiol given with CC or SC progestogen increased breast cancer risk with more significant risk associated with a CC regimen.

Stute et al. (2018) conducted a systematic review evaluating breast cancer incidence associated with EPT containing micronized P4. Estrogen (synthetic or bioidentical) paired with oral or vaginal P4 did not increase breast cancer risk if used for five years or less. However, limited evidence suggests that breast cancer risk increases after five years. Only two studies (Espié et al., 2007; Fournier et al., 2005) measured breast cancer incidence after five years of HT use; both were prospective cohort studies and lacked detailed reporting of compliance, dosage, and route of P4.

A systematic review of three observational studies (*N*=86,881) compared breast cancer risk based on progestogen type (Asi et al., 2016). Meta-analysis conducted on two of the cohort

studies showed that EPT with P4 may be associated with lower breast cancer risk compared to EPT with synthetic progestin (RR 0.67; 95% CI 0.55-0.81) however the included studies had a moderate risk of bias (Asi et al., 2016). A population-based case control study showed no increased risk of breast cancer associated with estrogen plus progesterone, (*OR* 0.80; 95% CI 0.44–1.43) and a non-significant increase with estrogen plus progestin, (*OR* 1.57; 95% CI 0.99-2.49) (Cordina-Duverger et al., 2013). Findings suggest that P4 may be safer than progestins, however study limitations include the risk of bias and confidence intervals crossing the null hypothesis (1).

Safety of Bioidentical HT: Endometrial Cancer

Mirkin et al. (2020) conducted a secondary analysis of the REPLENISH trial (Lobo et al., 2018) and concluded that all doses of the combined E2/P4 capsule provided adequate endometrial protection for up to one year. Coelingh Bennink et al. (2016) measured endometrial thickness over an eight-week period of daily unopposed E4 use. The 10mg dose resulted in endometrial hyperplasia but the 2mg dose did not. Findings suggest that higher doses of E4 require endometrial protection with a progestogen whereas the 2mg dose may not.

Systematic reviews by Sjögren et al. (2016) and Tempfer et al. (2020) evaluated endometrial cancer risk based on type of progestogen and regimen used. Both reviews included two large European cohort studies (Allen et al., 2010; Fournier et al., 2014) and concluded that micronized P4 increases endometrial cancer risk (see Table 4). Subgroup analysis of the E3N study (Fournier et al., 2014) found that short term use (five years or less) of P4 may be safe; however, endometrial cancer risk increased after five years of use. A large systematic review by Stute et al. (2016) included 40 studies utilizing EPT with various forms, regimens, and doses of P4 and concluded:

> (1) oral micronized progesterone provides endometrial protection if applied sequentially for 12–14 days/month at 200 mg/day for up to 5 years; (2) vaginal micronized progesterone may provide endometrial protection if applied sequentially for 10 days/month at 4% (45 mg/day) or every other day at 100 mg/day for up to 3–5 years (off-label use); (3) transdermal micronized progesterone does not provide endometrial protection. (p. 327)

Safety of Bioidentical HT: Cardiovascular Disease, VTE, and Stroke

Simon et al. (2016) were the first to provide a direct comparison of oral estrogen and TD estradiol. In this large matched cohort study (*N*=5102) conducted over a 10-year period, women receiving TD estradiol were found to have a significantly lower incidence of CVD events compared with those receiving oral ET (see Table 4). Subgroup analysis revealed statistically significant reductions of VTE overall, DVT, and heart failure; and non-statistically significant reductions of pulmonary embolism, myocardial infarction, stroke, transient ischemic attack, and angina in the TD estradiol group compared to the oral ET group. Unfortunately, the type of oral estrogen was not specified in this study, so it is unclear if patients received synthetic or bioidentical formulations.

A nested case control study in France (Canonico et al., 2016) identified 3,144 women who were hospitalized for their first episode of ischemic stroke (IS) and 12,158 matched controls. Insurance claims data were obtained to identify current users of oral or TD 17-beta estradiol (with or without a progestogen) and odds ratios were adjusted based on medications and diagnostic codes for diabetes, hypertension, and dyslipidemia. Compared to nonusers, oral E2 was found to increase IS risk in a dose dependent manner whereas no increased risk occurred with TD E2 (see Table 4). The authors also investigated IS risk based on progestogen type and

found that TD E2 plus P4 did not increase IS risk whereas TD E2 plus synthetic norpregnane derivatives did (see Table 4).

A meta-analysis of seven well-designed population-based observation studies evaluated VTE risk based on progestogen type and found that "in transdermal estrogen users, there was no change in VTE risk in women using micronized progesterone (RR 0.93, 95% CI 0.65–1.33), whereas norpregnane derivatives were associated with increased VTE risk (RR 2.42, 95% CI 1.84–3.18)" (Scarabin, 2018, p. 341).

Lobo et al. (2019) completed a secondary analysis of the REPLENISH trial (Lobo et al., 2018) and found that continuous oral E2/P4 had no significant effect on cardioembolic markers including lipids, coagulation factors, or blood glucose. The non-significant effect on triglyceride levels seen with the E2/P4 capsule were similar to findings by Harman et al. (2005) using TD E2 and cyclic P4. Although the study by Lobo et al. (2019) lacked statistical power to determine cardiovascular outcomes such as stroke, VTE, and coronary heart disease, the incidence of cardiovascular events in those receiving the E2/P4 capsule was comparable to expected rates in the general population.

A single center RCT by Hodis et al. (2016) explored the relationship between timing of HT initiation and progression of subclinical atherosclerosis, measured by carotid-artery intima-media thickness (CIMT). Healthy post-menopausal women (*N*=643) were randomized to receive oral 17-beta estradiol (with SC vaginal progesterone if their uterus was intact) or a placebo. For women in early menopause (less than 6 years since FMP), the rate of CIMT progression was significantly lower in the estradiol group than in the placebo group. Women in late menopause (10 years or more since FMP) did not demonstrate any difference in CIMT progression as compared to the control group (see Table 4). Estradiol had no significant impact on clinical

atherosclerosis in either group; however, cardiac computed tomography was not performed at baseline and not all participants followed up after study completion.

Limited evidence suggests that P4 does not diminish the cardiovascular benefits of estrogen and is likely safer than progestins; however, existing RCTs have not measured coronary heart disease directly (Eden, 2017). Asi et al. (2016) attempted to conduct a systematic review and meta-analysis of studies comparing cardiovascular events with EPT containing P4 versus progestin. The authors were unable to find any studies that met inclusion criteria and suggested that further research be conducted in this area. When given at 300mg daily for 12 weeks to treat VMS, oral P4 caused no change in weight, waist circumference, blood pressure, fasting glucose, lipids, C-reactive protein, or D-dimer compared to placebo (Prior, 2018).

Quality Indicators

This literature review included systematic reviews, meta-analyses, RCTs, and prospective and retrospective observational studies with varied sample sizes, risk of bias, reporting detail, and heterogeneity which made it difficult to interpret findings and formulate specific recommendations for clinical practice. Most of the efficacy studies were RCTs whereas safety studies were more often observational in nature. The observational studies allowed for longer duration of follow up and larger sample sizes but were limited by the lack of control groups. Multiple studies also provided limited details regarding HT doses, routes, and formulations. Many studies were well-designed with adequate sample sizes to power statistical significance, yet the confidence interval occasionally crossed 1 (e.g. 95% CI 0.9-1.1) which implies no difference between arms of the study (Melnyk & Fineout-Overholt, 2015). Many studies reported a low risk of bias or explained methods used to exclude studies with higher bias.

Variables such as hormone formulation, dose, regimen, route, application method, participant age, timing of HT initiation, severity of symptoms, and health status impact the outcomes of interest and complicate the evaluation and synthesis of research findings. This review included studies conducted in the U.S. and Europe, therefore some of the HT formulations are not FDA approved or available in the U.S. Dropout rates were reported in some studies and although significant at times, re-analysis often confirmed that results were not impacted by attrition. Studies reported severity and/or frequency of VMS using a validated tool or self-report method. Validated tools increase the accuracy of VMS reporting but also increase the burden on participants and may lead to higher attrition rates. VMS diaries were maintained before and during the treatment period which promoted accurate recall of symptoms. The REPLENISH trial was funded and supported by TherapeuticsMD, manufacturer of the now FDA approved Bijuva, however bias was minimized due to its double blinded, randomized design.

Gaps in Literature

Overall there was a lack of diversity in study subjects with most participants being white, non-Hispanic, healthy, and well educated. Additional research is needed to evaluate the safety and efficacy of bioidentical HT in a more ethnically and socially diverse population and in women with underlying health conditions. There is also a needed for well-designed RCTs comparing different doses, regimens, and routes of bioidentical hormones. It is difficult to determine long-term safety outcomes with RCTs due to their relatively shorter duration compared to observational studies, however observational studies lack controls and are more prone to bias. Research regarding the safety of low-dose TD estradiol is lacking particularly in the areas of cardiovascular disease and breast cancer risk. Additional research involving perimenopausal women is also needed as most studies included postmenopausal women only.

Discussion

Efficacy

Evidence suggests that various doses of TD and oral estradiol, including lower than standard TD doses, are more effective than placebo in reducing menopausal VMS (Gaudard et al., 2016; Kovács et al., 2016; Lobo et al., 2018; Santoro et al., 2017) and equally effective compared to synthetic estrogen/CEE (Corbelli et al., 2015; Malik et al., 2016; Santoro et al., 2017). The efficacy of low-dose TD E2 (50mcg/day) was consistent across ethnic and racial groups and was not impacted by BMI (Santoro et al., 2017). TD and oral estradiol reduce VMS in a dose dependent manner however higher doses often result in unwanted adverse effects, which may lead to discontinuation (Corbelli et al., 2015; Derzko et al., 2016; Gaudard et al., 2016). When given in equivalent doses, estradiol TD patches and MDTS were equally effective although MDTS may produce fewer localized skin reactions resulting in better tolerability and adherence (Kovács et al., 2016).

The E2/P4 combined daily capsule studied in the REPLENISH trial resulted in statistically significant (Lobo et al., 2018) and clinically meaningful (Constantine et al., 2019) reductions in the frequency and severity of VMS and more symptom free days (Kaunitz et al., 2020) compared to a placebo. The 1mg/100mg dose has since been approved by the FDA, under the brand name Bijuva, as the first combined bioidentical EPT for the treatment of menopausal VMS. Once daily dosing with a single combined capsule may improve patient adherence and control of symptoms. Unlike oral micronized progesterone, Bijuva does not contain peanut oil and can be safely used by those with a peanut allergy.

E4 may be a safe and effective bioidentical HT option for treating menopausal VMS (Coelingh Bennink et al., 2016) but is not currently approved for use in the U.S. or Europe. Additional E4 research is needed with larger sample sizes and longer duration of treatment. Evidence is lacking to support widespread use of progesterone-only therapy to treat VMS; however, it may be an option for women who are unable or unwilling to use systemic estrogen. Barriers to using progesterone-only treatment include lack of provider awareness and patient discontinuation due to headache and vaginal bleeding (Dolitsky et al., 2021; Prior, 2018).

Breast Cancer

Research suggests that EPT containing P4 does not increase breast cancer risk and is safer than EPT with synthetic progestins (Asi et al., 2016; Fournier et al., 2005; Yang et al., 2017; Zeng et al., 2018). Estradiol plus P4 resulted in a non-significant increase (Zeng et al., 2018) or no change in breast cancer risk (Fournier et al., 2005), and estradiol plus synthetic progestin increased breast cancer risk (Yang et al., 2017). ET (estradiol or CEE) was found to decrease or have no significant effect on breast cancer risk (Fournier et al., 2005; Zeng et al., 2018). EPT with synthetic or bioidentical estrogen plus oral or vaginal P4 did not increase breast cancer risk if used for five years or less; limited evidence suggests that this risk may increase after five years (Stute et al., 2018). No conclusions can be drawn regarding breast cancer risk associated with SC and CC regimens containing P4 due to inadequate sample sizes (Stute et al., 2018). Most studies evaluating breast cancer risk did not specify HT doses, routes, or regimens however current evidence suggests that ET (synthetic or bioidentical) and EPT with oral or vaginal P4 do not increase the risk of breast cancer if used for five years or less.

Endometrial Cancer

Women with an intact uterus should receive EPT due to the increased risk of endometrial cancer associated with unopposed estrogen (Goodman et al., 2011). Oral P4 provides adequate endometrial protection when given continuously at 100mg (Eden, 2017; Lobo et al., 2018) or sequentially at 200mg (Eden, 2017; Stute et al., 2016). Vaginal P4 can be administered every other day at 100mg or sequentially at 4% (45 mg/day) for 10 days per month (Eden, 2017; Stute et al., 2016). Transdermal P4 does not provide adequate endometrial protection (Stute et al., 2016). Short term use (five years or less) of oral P4 for endometrial protection did not statistically increase the incidence of endometrial cancer (Sjögren et al., 2016; Tempfer et al., 2020). Continuous oral P4 may provide greater endometrial protection than cyclic use however neither regimen resulted in elevated endometrial cancer risk after five years (Tempfer et al., 2020). Since there is no clinical benefit to giving oral P4 sequentially, continuous use is recommended to minimize endometrial cancer risk (Zeng et al., 2018).

Cardiovascular, VTE, and Stroke

Oral E2 was found to increase VTE and IS risk in a dose dependent manner however no increased risk occurred with TD E2 or TD E2 plus P4 (Canonico et al., 2016; Scarabin et al., 2018; Simon et al., 2016). These findings suggest that "TD estrogens alone or combined with micronized progesterone may be the best option to improve the risk benefit ratio of HT use and may represent the safest option with respect to both VTE and stroke risk" (Canonico et al, 2016, p. 1740).

Research on bioidentical HT and CVD is lacking. None of the included studies measured CVD directly and instead used surrogate markers such as lipids, vascular function, weight, waist circumference, blood pressure, and fasting glucose. While these markers represent CVD risk factors, they do not always predict future development of CVD. Findings from the REPLENISH

trial showed no significant effect on cardioembolic markers with all doses of the E2/P4 capsule (Lobo et al., 2019). Standalone P4 used to treat VMS may also have a neutral effect on surrogate markers for CVD (Prior, 2018). One RCT (Hodis et al., 2016) found that estradiol may slow the progression of subclinical atherosclerosis if initiated within six years of menopause, however the authors acknowledged that CIMT is not the only predictor of CVD.

Implications for Future Practice

Recommendations for Clinical Practice

Clinicians have a responsibility to their patients "to ensure that their decision making is based on evidence-based health information and is supported by techniques of shared decision making" (NASEM, 2020, p. 196). Based on current evidence, clinicians can confidently recommend FDA approved bioidentical hormones to women who are seeking an alternative to conventional synthetic hormones, have no contraindications to HT, and experience moderate to severe VMS despite lifestyle modifications. If bioidentical HT is prescribed, clinicians should initiate oral or TD estradiol at a low-dose (0.003mg-0.05mg) and titrate to optimally balance symptom control with adverse effects. The timing of HT discontinuation should be individualized and never based on age alone, although discontinuation within five years may pose a lower risk of breast and endometrial cancer depending on the regimen. CC, SC, or alternate day vaginal P4 provides adequate endometrial protection in women with an intact uterus. There are a variety of FDA approved formulations available to meet the needs of most women. Custom-compounded hormones should generally be avoided except for rare cases where a woman does not tolerate FDA approved therapies due to allergies or the recommended dose is not commercially available (NASEM, 2020).

Recommendations for Research

Additional well-designed RCTs and observational studies evaluating various routes, doses, and regimens of FDA approved bioidentical hormones are needed to determine which are safest and most effective in treating VMS. These studies should include a broad and diverse demographic sample (ethnicity, race, health status, education, etc.), longer duration of follow-up, adequate sample sizes, and direct comparison of different bioidentical hormones. Current gaps in the literature include direct comparisons of TD E2 preparations, RCTs evaluating the efficacy of oral P4 in treating VMS, and safety studies evaluating the impact of bioidentical HT on CVD. Additional research involving perimenopausal women is also needed as most studies included postmenopausal women only. Well-designed RCTs are needed to better understand the potential health benefits and risks, scope, and financial costs associated with commonly prescribed compounded bioidentical HT preparations.

Recommendations for Education

Physicians and advance practice providers often receive inadequate training in menopause management which leads to uncertainty and confusion regarding the efficacy and safety of HT, ineffective counseling of women seeking care, and overall reluctance to prescribe HT for those who may benefit (Manson & Kaunitz, 2016). Primary care and OB-GYN residency programs and advanced practice provider programs should include menopause management as a core competency and provide clinical opportunities to further develop knowledge and skills. Advanced practice provider fellowship programs are one option for newly graduated family nurse practitioners and physician assistants to gain women's health experience. Ongoing continuing education should be offered to primary care and women's health providers to ensure that evidence-based recommendations are being implemented in practice.

Recommendations for Policy

Collaboration between the FDA, state medical and pharmacy boards, and other stakeholders is needed to increase state and federal regulatory oversight of custom compounded bioidentical HT to ensure that adequate quality standards are maintained and documented (NASEM, 2020). Oversight should also include processes to improve data collection and surveillance of adverse events associated with compounded products. Compounding pharmacies are not currently required to include comprehensive product labels or standardized package inserts which:

> provide opportunities for ambiguous instructions for use, incomplete listing of active and inactive ingredients, or an omission of potential contraindications, all of which creates the potential for patients and prescribers to be inadequately informed about possible safety concerns related to the use of these medications. (NASEM, 2020, p. 6)

Additional labeling and packaging requirements including black box warnings, non-FDA approved status, indications and guidance for use, dosage, ingredients, expiration date, contraindications, side effects, and instructions on how to report adverse events would enhance patient awareness and safe use of compounded HT (NASEM, 2020).

Conclusion

FDA approved bioidentical hormones provide a safe and effective treatment option for peri- and postmenopausal women with moderate to severe VMS who are seeking a bioidentical option and have no contraindications to HT. Bioidentical HT is available in a variety of formulations, doses, routes, and regimens, is more effective than placebo, and equally effective compared to synthetic hormones. Research included in this literature review suggests that

estradiol and progesterone are generally safe to use from a breast cancer, endometrial cancer, VTE, and stroke perspective although safety depends on the route, dose, regimen, duration of treatment, and individual risk factors. Estradiol with or without P4 poses no additional risk of breast cancer if used for five years or less. TD estradiol with or without P4 is safer than oral estrogen or EPT with progestin when considering VTE risk. Oral E2 was found to increase ischemic stroke risk in a dose dependent manner however no increased risk occurred with TD E2 or TD E2 plus P4. Additional research is needed to evaluate CVD risk although research with surrogate markers are reassuring. "Midwives and nurse practitioners are ideally suited to provide evidence-based care for menopause-related symptoms as professionals committed to assessing each woman based on her overall risks and personal preferences" (Ward & Deneris, 2018, p. 168). This includes counseling women on the risks and benefits of FDA approved bioidentical HT, recommending its use when clinically appropriate, and offering an individualized treatment plan to effectively reduce VMS and improve the quality of life for women during the menopause transition and beyond.

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Appendix

Table 1

Database Search Description

Database (or Search Engine)	Restrictions Added to Search	Dates Included in Database	General Subjects Covered by Database
1. Cochrane Database of Systematic Reviews	Full Text	2015-2020	Systematic reviews and meta-analyses; Full text articles, as well as protocols focusing on the effects of healthcare.
2. CINAHL Plus with Full Text	Full Text; Academic Journals; English Language	2015-2020	Robust collection of full text for nursing & allied health journals, providing full text for more than 770 journals indexed in *CINAHL*.
3. PubMed	Full Text; English Language	2015-2020	Provides citations, abstracts, and selected full text to articles about "medicine, nursing, dentistry, veterinary medicine, the health care system, and the preclinical sciences."
4. Academic Search Premier	Full Text, Peer Reviewed; English Language	2015-2020	Provides citations and abstracts to articles, as well as full text of articles from over 4,600 publications, covering almost every academic subject.

Table 2

Data Abstraction Process

Date of Search	Key Words	Results in CDSR	Results in CINAHL Plus	Results in PubMed	Results in ASP
10/24/20	“bioidentical hormone replacement therapy”	**1** (1)	**9**	**34**	**6**
10/24/20	“bioidentical hormone replacement therapy” AND “menopause”	**1**	**6**	**28**	**5**
10/24/20	"bioidentical hormones" AND "menopause"	**1**	**6**	**39**	**9**
10/24/20	"bioidentical hormones" AND "vasomotor symptoms"	**1**	**1**	**8**	**1**

Date of Search	Key Words	Results in CDSR	Results in CINAHL Plus	Results in PubMed	Results in ASP
10/24/20	"bioidentical hormone replacement therapy" AND "vasomotor symptoms"	**1**	**1**	**3**	**1**
10/25/20	“bioidentical hormone replacement therapy” AND “perimenopause”	0	0	**2**	0
10/25/20	"bioidentical hormones" AND "perimenopause"	0	0	**3**	**1**
11/22/20	“estradiol” AND “CEE” AND “vasomotor symptoms”	**1**	**1**	**6** (3)	**1**
11/22/20	“estradiol” AND “conjugated equine estradiol”	**1**	**4**	**73** (3)	**8**
11/22/20	“conjugated equine estrogen” AND “estradiol” AND “vasomotor symptoms”	**1**	**4** (1)	**7**	**1**
11/22/20	“REPLENISH trial”	0	**3**	**13** (3)	
11/22/20	“progesterone” AND “vasomotor symptoms”		**5** (1)	**51**	
1/16/21	“Bioidentical hormone replacement therapy” AND “safety” AND “menopause”	**1**	**3**	**18** (1)	**2**
1/16/21	“Bioidentical hormone replacement therapy” AND “risk” AND “menopause”	**3**	**4**	**2** (1)	**1**
1/16/21	“Bioidentical hormone replacement therapy” AND “cancer” AND “menopause”	0	**4**	**1**	**1**
1/16/21	“Estradiol” AND “safety” AND “menopause”	**2**	**11**	**65** (3)	**13**
1/16/21	“Estradiol” AND “risk” AND “menopause”	**3**	**27**	**62** (3)	**35**
1/16/21	“Estradiol” AND “cancer” AND “menopause”	0	**16**	89	**15**
1/16/21	“Progesterone” AND “safety” AND “menopause”	0	**3**	**38** (1)	**9**
1/16/21	“Progesterone” AND “risk” AND “menopause”	**2**	**23**	**60** (1)	**26**
1/16/21	“Progesterone” AND “cancer” AND “menopause”	**1**	**17** (1)	79	**23**
1/17/21	Bibliography search **10**(5)				

***BOLD** = articles reviewed for match with systematic review inclusion criteria (parentheses indicate those articles meeting inclusion criteria)

Table 3

Characteristics of Literature Included and Excluded

Reference	Included or Excluded	Rationale
Asi, N., Mohammed, K., Haydour, Q., Gionfriddo, M. R., Vargas, O. L., Prokop, L. J., Faubion, S. S., & Murad, M. H. (2016). Progesterone vs. synthetic progestins and the risk of breast cancer: A systematic review and meta-analysis. *Systematic Reviews, 5*(1), 1-8. https://doi.org/10.1186/s13643-016-0294-5	Included	Systematic review and meta-analysis comparing progesterone versus synthetic progestins, in combination with estrogens, and their associated risk of breast cancer and cardiovascular events.
Archer, D. F., Bernick, B. A., & Mirkin, S. (2019). A combined, bioidentical, oral, 17β-estradiol and progesterone capsule for the treatment of moderate to severe vasomotor symptoms due to menopause. *Expert Review of Clinical Pharmacology*, *12*(8), 729-739. https://doi.org/10.1080/17512433.2019.1637731	Excluded	Expert review of REPLENISH study; not original research
Bitner, D., Brightman, R., Graham, S., Bernick, B., & Mirkin, S. (2019). E2/P4 capsules effectively treat vasomotor symptoms irrespective of age and BMI. *Menopause, 26*(12), 1460.	Excluded	Abstract only
Canonico, M. (2015). Hormone therapy and risk of venous thromboembolism among postmenopausal women. *Maturitas, 82*, 303–306. https://doi.org/10.1016/j.maturitas.2015.06.040	Excluded	Compares VTE risk associated with estrogen route (transdermal vs. oral) but does not differentiate between bioidentical vs. synthetic. Progesterone articles are included in another systematic review.
Canonico, M., Carcaillon, L., Plu-Bureau, G., Oger, E., Singh-Manoux, A., Tubert-Bitter, P., Elbaz, A., Scarabin, P. (2016). Postmenopausal hormone therapy and risk of stroke: Impact of the route of estrogen administration and type of progestogen. *Stroke, 47,* 1734–1741. https://doi.org/10.1161/STROKEAHA.116.013052	Included	Evaluated ischemic stroke risk in postmenopausal women based on route of estrogen administration (oral vs. transdermal), dose of estradiol and type of progestogen
Chang, W. C., Wang, J. H., & Ding, D. C. (2019). Hormone therapy in postmenopausal women associated with risk of stroke and venous thromboembolism: A population-based cohort study in Taiwan. *Menopause*, *26*(2), 197-202. https://doi.org/doi:10.1097/GME.0000000000001182	Excluded	Did not differentiate between bioidentical and synthetic hormone therapy
Coelingh Bennink, H., Verhoeven, C., Zimmerman, Y., Visser, M., Foidart, J. M., & Gemzell-Danielsson, K. (2016). Clinical effects of the fetal estrogen estetrol in a multiple-rising-dose study in postmenopausal women. *Maturitas, 91*, 93–100. https://doi.org/10.1016/j.maturitas.2016.06.017	Included	Study evaluating the safety and efficacy of estetrol (E4), a natural fetal estrogen, in treating postmenopausal vasomotor symptoms
Constantine, G. D., Revicki, D. A., Kagan, R., Simon, J. A., Graham, S., Bernick, B., & Mirkin, S. (2019). Evaluation of clinical meaningfulness of estrogen plus progesterone oral capsule (TX-001HR) on moderate to severe vasomotor symptoms. *Menopause*, *26*(5), 513-519. https://doi.org/10.1097/GME.0000000000001261	Included	Evaluated clinical meaningfulness of vasomotor symptom reduction in REPLENISH trial

Reference	Included or Excluded	Rationale
Corbelli, J., Shaikh, N., Wessel, C., & Hess, R. (2015). Low-dose transdermal estradiol for vasomotor symptoms: A systematic review. *Menopause, 22*(1), 114–121. https://doi.org/10.1097/gme.0000000000000258	Included	Systematic review of randomized control trials evaluating the effectiveness of low-dose transdermal estrogen vs. placebo in postmenopausal women with moderate to severe hot flashes.
Crandall, C. J., Diamant, A., & Santoro, N. (2020). Safety of vaginal estrogens: A systematic review. *Menopause*, *27*(3), 339-360. https://doi.org/doi: 10.1097/GME.0000000000001468	Excluded	Evaluated safety of vaginal estrogens for treatment of genitourinary symptoms of menopause (excluded studies with high-dose estradiol ring used for vasomotor symptom).
Derzko, C., Sergerie, M., Siliman, G., Alberton, M., & Thorlund, K. (2016). Comparative efficacy and safety of estradiol transdermal preparations for the treatment of vasomotor symptoms in postmenopausal women: An indirect comparison meta-analysis. *Menopause, 23*(3), 294–303. https://doi.org/10.1097/GME.0000000000000552	Included	Indirect comparison meta-analysis comparing efficacy of different estradiol transdermal preparations for the treatment of vasomotor symptoms in postmenopausal women
Dolitsky, S. N., Cordeiro Mitchell, C. N., Sheehan Stadler, S., & Segars, J. H. (2020). Efficacy of progestin-only treatment for the management of menopausal symptoms: A systematic review. *Menopause, 28*(2), 1-8. https://doi.org/10.1097/GME.0000000000001676	Included	Systematic review of randomized control trials to evaluate the efficacy of standalone progesterone in treating vasomotor symptoms associated with menopause.
Eden, J. (2017). The endometrial and breast safety of menopausal hormone therapy containing micronised progesterone: A short review. *Australian & New Zealand Journal of Obstetrics & Gynaecology, 57*(1), 12–15. https://doi.org/10.1111/ajo.12583	Included	Review of literature regarding effects of micronized progesterone on endometrial and breast cancer safety
Gaudard A., Silva de Souza, S., Puga, M., Marjoribanks, J., da Silva, E., & Torloni, M. R. (2016). Bioidentical hormones for women with vasomotor symptoms. *Cochrane Database of Systematic Reviews, 8*(CD010407), 1-103. https://doi.org/10.1002/14651858.CD010407.pub2	Included	Systematic review of randomized control trials evaluating efficacy of various bioidentical and synthetic estrogen-based hormone therapies in treating vasomotor symptoms
Hodis, H. N., Mack, W. J., Henderson, V. W., Shoupe, D., Budoff, M. J., Hwang-Levine, J., Li, Y., Feng, M., Dustin, L., Kono, N., Stanczyk, F. Z., Selzer, R. H., & Azen, S. P. (2016). Vascular effects of early versus late postmenopausal treatment with estradiol. *New England Journal of Medicine, 374*(13), 1221-1231. https://doi.org/10.1056/NEJMoa1505241	Included	Evaluated the impact of oral estradiol, with or without progesterone, on cardiovascular markers
Kaunitz, A. M., Bitner, D., Constantine, G. D., Bernick, B., Graham, S., & Mirkin, S. (2020). 17β-estradiol/progesterone in a single, oral, softgel capsule (TX-001HR) significantly increased the number of vasomotor symptom-free	Included	Examined vasomotor symptom-free days with oral 17b-estradiol/progesterone (E2/P4; TX-001HR) versus placebo in the REPLENISH trial.

Reference	Included or Excluded	Rationale
days in the REPLENISH trial. *Menopause, 27*(12), 1-6. https://doi.org/10.1097/GME.0000000000001615		
Kovács, G., Zelei, T., & Vokó, Z. (2016). Comparison of efficacy and local tolerability of estradiol metered-dose transdermal spray to estradiol patch in a network meta-analysis. *Climacteric, 19*(5), 488–495. https://doi.org/10.1080/13697137.2016.1221919	Included	Network meta-analysis comparing efficacy of estradiol metered-dose transdermal spray to estradiol patch
Lieberman, A.& Curtis, L. (2017). In defense of progesterone: A review of the literature. *Alternative Therapies in Health and Medicine, 23*(6), 24-32.	Excluded	Review of existing literature on progesterone efficacy and safety but did not focus solely on HT for vasomotor symptoms, duplicate studies
Lobo R. A., Archer, D. F., Kagan, R., Kaunitz, A. M., Constantine, G. D., Pickar, J. H., Graham, S., Bernick, B., & Mirkin, S. A. (2018). 17β-estradiol-progesterone oral capsule for vasomotor symptoms in postmenopausal women: A randomized controlled trial. *Obstetrics & Gynecology, 132*(1), 161-170. https://doi.org/10.1097/AOG.0000000000002645	Included	Original REPLENISH trial that evaluated the efficacy of a single-capsule 17b-estradiol–progesterone (TX-001HR) for treating menopausal moderate-to-severe vasomotor symptoms.
Lobo, R. A., Kaunitz, A. M., Santoro, N., Bernick, B., Graham, S., & Mirkin, S. (2019). Metabolic and cardiovascular effects of TX-001HR in menopausal women with vasomotor symptoms. *Climacteric, 22*(6), 610-616. https://doi.org/10.1080/13697137.2019.1640197	Included	Evaluated the effects of TX-001HR (17β-estradiol [E2] and progesterone [P4] in a single oral capsule) on cardiometabolic markers and outcomes.
Malik, S., Pannu, D., Prateek, S., Sinha, R., & Gaikwad, H. (2016). Comparison of the symptomatic response in Indian menopausal women with different estrogen preparations for the treatment of menopausal symptoms: A randomized controlled trial. *Archives of Gynecology and Obstetrics*, *293*(6), 1325-1333. https://doi.org/10.1007/s00404-016-4034-9	Included	Evaluated the severity and frequency of hot flashes in four comparison groups: estradiol valerate (E2V), conjugated equine estrogen (CEE), isoflavones and placebo
Mikkola, T. S., Tuomikoski, P., Lyytinen, H., et al. (2016). Vaginal estradiol use and the risk for cardiovascular mortality. *Human Reproduction, 31*, 804–809. https://doi.org/10.1093/humrep/dew014	Excluded	Evaluated vaginal estradiol prescribed for vulvovaginitis and associated CV risk
Mirkin, S., Goldstein, S. R., Archer, D. F., Pickar, J. H., Graham, S., & Bernick, B. (2020). Endometrial safety and bleeding profile of a 17β-estradiol/progesterone oral softgel capsule (TX-001HR). *Menopause, 27*(4), 410-417. https://doi.org/10.1097/GME.0000000000001480	Included	Evaluated the effect of a single-capsule 17β-estradiol/progesterone (E2/P4), TX-001HR, on endometrial safety
Mirkin, S., Graham, S., Revicki, D. A., Bender, R. H., Bernick, B., & Constantine, G. D. (2019). Relationship between vasomotor symptom improvements and quality of life and sleep outcomes in menopausal women treated with oral, combined 17β-estradiol/progesterone. *Menopause*, *26*(6), 637-642. https://doi.org/10.1097/GME.0000000000001294	Excluded	Evaluated the impact of TX-001HR (17b-estradiol–progesterone) on quality of life and sleep.

Reference	Included or Excluded	Rationale
Prior, J. C. (2015). Progesterone or progestin as menopausal ovarian hormone therapy: Recent physiology-based clinical evidence. *Current Opinion in Endocrinology, Diabetes and Obesity, 22*(6), 495-501. https://doi.org/10.1097/MED.0000000000000205	Excluded	Focused on physiology of progestogens and E3N study (already included in literature review).
Prior, J. C. (2018). Progesterone for treatment of symptomatic menopausal women. *Climacteric*, *21*(4), 358–365. https://doi.org/10.1080/13697137.2018.1472567	Included	Review of evidence obtained from randomized control trials, population and observational data regarding safety and effectiveness of oral micronized progesterone in treating vasomotor symptoms
Santoro, N., Allshouse, A., Neal-Perry, G., Pal, L., Lobo, R. A., Naftolin, F., Black, D. M., Brinton, E. A., Budoff, M. J., Cedars, M. I., Dowling, N. M., Dunn, M., Gleason, C. E., Hodis, H. N., Isaac, B., Magnani, M., Manson, J. E., Miller, V. M., Taylor, H. S., Wharton, W., Wolff, E., Zepeda, V., Harman, S. M. (2017). Longitudinal changes in menopausal symptoms comparing women randomized to low-dose oral conjugated estrogens or transdermal estradiol plus micronized progesterone versus placebo: The Kronos Early Estrogen Prevention Study (KEEPS). *Menopause*, *24*(3), 238-246. https://doi.org/10.1097/GME.0000000000000756.	Included	Randomized control trial comparing efficacy of low dose CEE vs. transdermal estradiol plus micronized progesterone or placebo in treating menopausal vasomotor symptoms
Scarabin P. Y. (2018). Progestogens and venous thromboembolism in menopausal women: An updated oral versus transdermal estrogen meta-analysis. *Climacteric, 21*(4), 341–345. https://doi.org/10.1080/13697137.2018.1446931	Included	Updated meta-analysis evaluating risk of venous thromboembolism based on route of estrogen administration, hormone regimen, and progestogen type
Simon, J. A., Laliberté, F., Duh, M. S., Pilon, D., Kahler, K. H., Nyirady, J., Davis, P. J., & Lefebvre, P. (2016). Venous thromboembolism and cardiovascular disease complications in menopausal women using transdermal versus oral estrogen therapy. *Menopause, 23*, 600–610. https://doi.org/10.1097/GME.0000000000000590	Included	Evaluated risk of venous thromboembolism and cardiovascular disease complications for menopausal women using transdermal estradiol vs. oral estrogen
Sjögren, L. L., Mørch, L. S., & Løkkegaard, E. (2016). Hormone replacement therapy and the risk of endometrial cancer: A systematic review. *Maturitas, 91*, 25–35. https://doi.org/10.1016/j.maturitas.2016.05.013	Included	Compared endometrial cancer risk based on progestogen type
Stute, P., Wildt, L., & Neulen, J. (2018). The impact of micronized progesterone on breast cancer risk: A systematic review. *Climacteric, 21*(2), 111–122. https://doi.org/10.1080/13697137.2017.1421925	Included	Systematic review of studies evaluating breast cancer risk associated with estrogen plus micronized progesterone

Reference	Included or Excluded	Rationale
Stute, P., Neulen, J., & Wildt, L. (2016). The impact of micronized progesterone on the endometrium: A systematic review. *Climacteric*, *19*(4), 316-328. https://doi.org/10.1080/13697137.2016.1187123	Included	Systematic review to determine if estrogen plus oral, transdermal, or vaginal progesterone provides adequate endometrial protection
Tempfer, C. B., Hilal, Z., Kern, P., Juhasz-Boess, I., & Rezniczek, G. A. (2020). Menopausal hormone therapy and risk of endometrial cancer: A systematic review. *Cancers, 12*(8), 2195. https://doi.org/10.3390/cancers12082195	Included	Systematic review of cohort studies evaluating endometrial cancer risk associated with estrogen plus progesterone
Yang, Z., Hu, Y., Zhang, J., Xu, L., Zeng, R., & Kang, D. (2017). Estradiol therapy and breast cancer risk in perimenopausal and postmenopausal women: A systematic review and meta-analysis. *Gynecological Endocrinology,* (2), 87–92. https://doi.org/10.1080/09513590.2016.1248932	Included	Systematic review and meta-analysis of studies evaluating breast cancer risk related to estradiol only and estradiol plus progesterone
Zeng, Z., Jiang, X., Li, X., Wells, A., Luo, Y., & Neapolitan, R. (2018). Conjugated equine estrogen and medroxyprogesterone acetate are associated with decreased risk of breast cancer relative to bioidentical hormone therapy and controls. *PloS One, 13*(5), 1-12. https://doi.org/10.1371/journal.pone.0197064	Included	Retrospective study comparing breast cancer risk related to bioidentical hormone therapy vs. synthetic hormone therapy

Table 4

Literature Review Table of All Studies Included

Citation	Study Purpose	Pop (N)/ Sample Size (n) /Setting(s)	Design/ Level of Evidence	Variables/ Instruments	Intervention	Findings	Implications
Asi, N., Mohammed, K., Haydour, Q., Gionfriddo, M. R., Vargas, O. L., Prokop, L. J., Faubion, S. S., & Murad, M. H. (2016). Progesterone vs. synthetic progestins and the risk of breast cancer: A	Synthesize existing evidence regarding BC and CV risk with use of	*N*=86,881 PM ♀ age 45–59 and within 10 years of menopause	SR & MA Level 1	IV=Combined HT DV=incidence of BC or CV events	E+ P vs. E+ MP4 E TD or oral, mostly E2 but not	MA of CS: E+MP4 ↓BC risk compared to E+P; RR 0.67, (95 % CI 0.55–0.81) PBCCS: no ↑risk of BC with E+MP4; OR 0.80 (CI 95% 0.44–1.43). Non-	Observational studies suggest that E +MP4 may be associated with lower BC risk compared to E+P. Individualized HT regimens are recommended but cannot

Citation	Study Purpose	Pop (N)/ Sample Size (n) /Setting(s)	Design/ Level of Evidence	Variables/ Instruments	Intervention	Findings	Implications
systematic review and meta-analysis. *Systematic Reviews, 5*(1), 1-8. https://doi.org/10.1186/s13643-016-0294-5	E+MP4 vs. E+P		Includes 2 CS, 1 PBCCS		specified in PBCCS Follow up ≥6 months (mean 5 years)	significant ↑risk of BC with E+P; OR 1.57 (95% CI 0.99–2.49) Subgroup analysis: route of E did not impact BC risk No studies investigated risk of CV events	make firm clinical recommendations due to lower quality evidence and relatively small number of studies. Further research is needed to evaluate CV risk of EPT w/ MP4 and P.
Canonico, M., Carcaillon, L., Plu-Bureau, G., Oger, E., Singh-Manoux, A., Tubert-Bitter, P., Elbaz, A., Scarabin, P. (2016). Postmenopausal hormone therapy and risk of stroke: Impact of the route of estrogen administration and type of progestogen. Stroke, 47, 1734–1741. https://doi.org/10.1161/STROKEAHA.116.013052	Determine impact of oral vs. TD E2 and different progestogens on IS risk in PM ♀	*n*= 3144 PM ♀ with acute IS matched to 12,158 controls Mean age 57 France	Nested CCS Level 4	IV= E2 use prescription filled in past 3 months; oral or TD E2; E2 dose; type of progestogen DV=first hospitalization for IS Claims data from French national health insurance system	N/A	Compared with nonusers, adjusted ORs of IS: **↑risk** Oral E2: 1.58 (95% CI, 1.01–2.49) dose dependent **No ↑risk** TD E2 0.83 (95% CI, 0.56–1.24) **No ↑ risk** Progesterone 0.78 (95% CI, 0.49–1.26); Pregnanes 1.00 (95% CI, 0.60–1.67); Nortestosterone 1.26 (95% CI, 0.62–2.58) **↑risk** Norpregnanes 2.25 (95% CI, 1.05–4.81).	TD estrogens alone or combined with MP4 may be the best option to improve the benefit/risk ratio of HT use and may represent the safest option with respect to IS risk. RCTs are needed to confirm these results
Coelingh Bennink, H., Verhoeven, C., Zimmerman, Y., Visser, M., Foidart, J. M., & Gemzell-Danielsson, K. (2016). Clinical effects of the fetal estrogen estetrol in a multiple-rising-dose study in	Evaluate the safety and efficacy of estetrol (E4) in treating PM VMS	*N*=49 PM ♀ age <70, ≥6 months since LMP, BMI 18-30	PROL MRDS Level 3	DV=Episodes per day of hot flashes and sweating; self-recorded in diary on day 1-56 (all doses)	randomized with intact uterus: unopposed E4 2mg or E2V 2mg x 28 days	**VMS at day 28 follow up:** All groups: ↓ mean number of hot flashes/sweating Hot flashes (episodes/day): E2V 2mg: 11.5 → 6.5; E4	2mg and 10 mg E4 dose and 2mg E2V equally effective in reducing number of hot flashes and sweating Endometrial proliferation occurred with E4 10 mg but not 2mg indicating that

Citation	Study Purpose	Pop (N)/ Sample Size (n) /Setting(s)	Design/ Level of Evidence	Variables/ Instruments	Intervention	Findings	Implications
postmenopausal women. *Maturitas*, *91*, 93–100. https://doi.org/10.1016/j.maturitas.2016.06.017		Netherlands		DV=Endometrial thickness: ultrasound at baseline, day 14, 28, and 56. endometrial biopsy at baseline and day 28 if thickness ↑ ≥50%	non-randomized dose-escalation day 29-56 unopposed E4 10mg if intact uterus & ≥35 hot flashes per week	2mg: 9 → 5.6; E4 10mg: 8.4 → 5 Sweating (episodes/day): E2V 2mg: 3.5 → 2.3; E4 2mg: 4.4 → 2.4; E4 10mg: 2.6 → 1.4 **VMS at day 56 follow up:** Hot flashes (episodes/day): E2V 2mg 1.8; E4 2mg 1.8; E4 10mg 1.8 Sweating (episodes/day): E2V 2mg 0; E4 2mg 1.6; E4 10mg 0.9 **Endometrial thickness:** E4 2mg: stable E2V 2mg & E4 10mg: ↑	endometrial protection with progestogen is necessary for 10mg dose but may not be needed for 2mg dose. Further research of E4 in treating menopausal VMS is needed with a minimum treatment time of 12 weeks to further evaluate safety and efficacy. Small phase I and II studies cannot be generalized to practice without further research.
Constantine, G. D., Revicki, D. A., Kagan, R., Simon, J. A., Graham, S., Bernick, B., & Mirkin, S. (2019). Evaluation of clinical meaningfulness of estrogen plus progesterone oral capsule (TX-001HR) on moderate to severe vasomotor symptoms. *Menopause, 26*(5), 513-519. https://doi.org/10.1097/GME.0000000000001261	Determine the clinical meaningfulness of TX-001HR in reducing moderate to severe VMS	*n*=726 PM ♀ See Lobo et al. (2018)	RCT Level 2	DV= CID and minimal CID in VMS severity at weeks 4 and 12 Clinical Global Impression scale and Menopause-Specific Quality of Life (MENQOL) questionnaire	once-daily, oral E2/P4 (mg/mg) of 1/100, 0.5/100, 0.5/50, 0.25/50, or placebo	Significantly more women had a clinically meaningful improvement in the number of hot flashes in all treatment groups versus placebo	TX-001HR provided clinically meaningful improvements in menopausal VMS.

Citation	Study Purpose	Pop (N)/ Sample Size (n) /Setting(s)	Design/ Level of Evidence	Variables/ Instruments	Intervention	Findings	Implications
Corbelli, J., Shaikh, N., Wessel, C., & Hess, R. (2015). Low-dose transdermal estradiol for vasomotor symptoms: A systematic review. *Menopause, 22*(1), 114–121. https://doi.org/10.1097/gme.0000000000000258	Evaluate effectiveness of low dose TD estrogen in PM ♀ with moderate to severe hot flashes	*N*=3069 PM ♀ women ≥7 hot flashes per day and/or ≥50 hot flashes per week	SR Level 1 9 DBPC RCTs	DV=mean daily number of hot flashes	Low dose TD E (less than 0.05 mg 17β-estradiol) Mode of TD delivery varied (patch, gel, spray) Followed for 12-13 weeks	All doses of TD E more effective than placebo Mean daily # of hot flashes: Estrogen dose 0.0375-0.045mg: ↓9.36 Estrogen dose 0.020-0.029mg: ↓7.91 Estrogen dose 0.003-0.0125 mg: ↓7.07 Placebo groups: ↓5.07.	Strong evidence to suggest that low-dose TD E is more effective than placebo in reducing the frequency of moderate to severe hot flashes. Dose dependent relationship observed
Derzko, C., Sergerie, M., Siliman, G., Alberton, M., & Thorlund, K. (2016). Comparative efficacy and safety of estradiol transdermal preparations for the treatment of vasomotor symptoms in postmenopausal women: An indirect comparison meta-analysis. *Menopause, 23*(3), 294–303. https://doi.org/10.1097/GME.0000000000000552	Compare efficacy of different TD E2 preparations for the treatment of VMS in PM ♀	*N*=1517 Mean age 50.5-55.0 Mean BMI 25.8 to 27.9 North America and Europe	SR and network MA Level 1 5 RCTs	DV: frequency and severity of hot flashes	Divigel 0.25mg and 0.5mg, Estrogel 0.75mg and 1.5mg	Divigel 0.25 mg, Divigel 0.5 mg, and Estrogel 0.75 showed similar efficacy and all were statistically superior to Estrogel 1.5 mg. Best efficacy profile Divigel 1.0mg (mean difference 3.91 hot flushes/week vs placebo)	Best efficacy profile resulted from Divigel 1.0mg, but also associated with higher risk of AEs compared to other formulations. Despite AEs, only 5% of participants discontinued treatment with Divigel 1.0 mg. Further research is needed with head to head comparison of transdermal estradiol preparations.
Dolitsky, S. N., Cordeiro Mitchell, C. N., Sheehan Stadler, S., & Segars, J. H. (2020). Efficacy of progestin-only treatment for the management of menopausal	Assess if progestogen only treatment is effective for treating VMS	*N*=601	SR Level 1	DV=severity and frequency of hot flashes; VMS score	TD MP4 5-60 mg Oral MPA 10-20mg	Mixed efficacy results Largest study using transdermal progesterone: no improvement (*n* = 230).	Monotherapy with progestogens can be used to treat VMS in women with contraindications to estrogens.

Citation	Study Purpose	Pop (N)/ Sample Size (n) /Setting(s)	Design/ Level of Evidence	Variables/ Instruments	Intervention	Findings	Implications
symptoms: A systematic review. *Menopause, 28*(2), 1-8. https://doi.org/10.1097/GME.0000000000001676	associated with menopause.			Greene Climacteric Scale, Menopause Specific Quality of Life Questionnaire, weekly diary	Duration: 21 days to 12 months (median 12 weeks)	Side effects (headaches, vaginal bleeding, etc.) significant in 5 of 7 studies; treatment discontinuation 6%-21%	Current research with mixed results and additional RCTs with larger sample sizes are needed to determine efficacy, safety, and tolerability of progesterone only for VMS.
Eden, J. (2017). The endometrial and breast safety of menopausal hormone therapy containing micronised progesterone: A short review. *Australian & New Zealand Journal of Obstetrics & Gynaecology, 57*(1), 12–15. https://doi.org/10.1111/ajo.12583	Review of literature evaluating endometrial, breast, and CV safety of estrogen+MP4	N/A	Narrative review	IV=MP4; various forms and doses DV=endometrial hyperplasia & EC Transvaginal ultrasound Endometrial biopsy CV markers: lipids, metabolic syndrome, and vascular function	N/A	MP4 (oral CC or SC and alternate day vaginal) is effective in preventing endometrial hyperplasia/EC CV risk: MP4 likely safer than P CEE and oral E2 ↑ risk of VTE/stroke but TD E2 (gel or patch) does not. MPA significantly ↑risk of VTE. MP4 "could be safe" regarding VTE BC: HT regimens with MP4 have significantly ↓BC risk compared to P	Oral MP4 200mg cyclic or 100mg daily and vaginal MP4 100mg every other day adequately protects the endometrium when given with low to medium dosage estrogen to manage menopause symptoms. Transdermal E2 + oral or vaginal MP4 is most likely a safe and effective option for women with moderate to severe VMS seeking bioidentical HT. Need large RCTs comparing vaginal vs. oral MP4 Need RCTs evaluating MP4 with heart disease as measured outcome.
Gaudard A., Silva de Souza, S., Puga, M., Marjoribanks, J., da Silva, E., & Torloni, M. R.	Determine the effectiveness of bioidentical	*N*=5779 20/23 studies	SR & MA	IV=ET DV=Frequency and intensity of	Unopposed 17 beta-estradiol;	low to moderate quality evidence that E2 in various	E2 is likely more effective than placebo in treating moderate to severe VMS. No

Citation	Study Purpose	Pop (N)/ Sample Size (n) /Setting(s)	Design/ Level of Evidence	Variables/ Instruments	Intervention	Findings	Implications
(2016). Bioidentical hormones for women with vasomotor symptoms. *Cochrane Database of Systematic Reviews, 8*(CD010407), 1-103. https://doi.org/10.1002/14651858.CD010407.pub2	estrogen compared to placebo or synthetic estrogen for relief of menopausal VMS	included only ♀with moderate to severe hot flashes.	Level 1 23 RCTs	hot flushes and night sweats Symptom intensity measured on a 0-100 visual analogue scale	various doses and forms (patch, gel, oral, intranasal, emulsion) vs. CEE or placebo	forms and doses is more effective than placebo no evidence showing difference in effectiveness between bioidentical HT and CEE Not all studies reported analyzable data; no MA	clear difference in efficacy between E2 and CEE. Dose dependent response. Cannot make specific treatment recommendations due to study limitations: risk of bias/poor reporting of methods, imprecision, and lack of analyzable data.
Hodis, H. N., Mack, W. J., Henderson, V. W., Shoupe, D., Budoff, M. J., Hwang-Levine, J., Li, Y., Feng, M., Dustin, L., Kono, N., Stanczyk, F. Z., Selzer, R. H., & Azen, S. P. (2016). Vascular effects of early versus late postmenopausal treatment with estradiol. *New England Journal of Medicine, 374*(13), 1221-1231. https://doi.org/10.1056/NEJMoa1505241	Determine if CV effects of PM HT (E2) vary with timing of initiation	*N*=643 healthy PM ♀ with or without uterus Single center U.S.	RCT Level 2	IV=Early menopause <6 years or late ≥10 years DV=Rate of change in CIMT; at baseline then every 6 months with high resolution B-mode ultrasound Coronary atherosclerosis: cardiac CT upon completion of therapy (no baseline obtained, not all received)	oral 17b estradiol +/- sequential vaginal P4 gel vs. placebo	Mean CIMT (mm/year) at median of 5 years: Early menopause group: E2 w/ or w/o P4: ↑0.0044 Placebo ↑0.0078 Late menopause group: E2 w/ or w/o P4 ↑0.0100 Placebo 0.0088 Cardiac CT (all groups; mean 6 years follow up): coronary artery calcium, total stenosis, and plaque did not differ significantly	Oral E2 associated with less progression of subclinical atherosclerosis (measured by CIMT) than placebo if initiated within 6 years of menopause. CIMT progression was not impacted in late menopause group. There may be a CV benefit to starting estradiol within 6 years of menopause. E2 had no significant impact on atherosclerosis regardless of timing of initiation, however no baseline cardiac CT was obtained and there was a smaller sample size receiving post-completion CT.
Kaunitz, A. M., Bitner, D., Constantine, G. D., Bernick, B., Graham, S., & Mirkin, S. (2020). 17β-estradiol/progesterone in a	Determine the number of VMS-free days with E2/P4 versus placebo	*n*=726	RCT Level 2	DV=change in moderate to severe VMS, moderate to	once-daily, oral E2/P4	In all treatment groups:	Women treated with E2/P4 had a greater response to treatment with more VMS-free days than placebo.

Citation	Study Purpose	Pop (N)/ Sample Size (n) /Setting(s)	Design/ Level of Evidence	Variables/ Instruments	Intervention	Findings	Implications
single, oral, softgel capsule (TX-001HR) significantly increased the number of vasomotor symptom-free days in the REPLENISH trial. *Menopause, 27*(12), 1-6. https://doi.org/10.1097/GME.0000000000001615	in REPLENISH trial.	See Lobo et al. (2018)		severe VMS-free days at 12 weeks VMS diary	See Lobo et al. 2018	Significant ↑ in 50% and 75% responders at weeks 4 & 12 Significant ↑ in VMS-free days at week 12 43-56% of ♀ without severe hot flushes at week 12 versus 26% for placebo	
Kovács, G., Zelei, T., & Vokó, Z. (2016). Comparison of efficacy and local tolerability of estradiol metered-dose transdermal spray to estradiol patch in a network meta-analysis. *Climacteric, 19*(5), 488–495. https://doi.org/10.1080/13697137.2016.1221919	Compare efficacy of E2 MDTS vs. E2 patch in treating VMS	*N*=? (unable to access appendix)	SR and network MA for indirect comparison Level 1 8 RCTs	DV= relative change (%) in number of hot flashes between baseline and week 12	E2 MDTS, E2 patch, or placebo Dose range 14-50mcg	All treatment groups except 14mcg/day patch had a significant ↓ in number of hot flashes compared to placebo No significant difference in efficacy between E2 MDTS and E2 patch; dose dependent response	When applied in similar doses, E2 MDTS and E2 patches have similar efficacy in treating menopausal VMS.
Lobo R. A., Archer, D. F., Kagan, R., Kaunitz, A. M., Constantine, G. D., Pickar, J. H., Graham, S., Bernick, B., & Mirkin, S. A. (2018). 17β-estradiol-progesterone oral capsule for vasomotor symptoms in postmenopausal women: A randomized controlled trial. *Obstetrics & Gynecology, 132*(1), 161-170. https://doi.org/10.1097/AOG.0000000000002645	Evaluate the efficacy of a single-capsule 17b-estradiol–progesterone (TX-001HR) for treating menopausal moderate-to-severe VMS	*n*=726 PM ♀ w/ intact uterus mean age 55; mean BMI 27; White 67% AA 31%	RCT Level 2	DV=change in frequency and severity of moderate to severe VMS at weeks 4 and 12	once-daily, oral E2/P4 (mg/mg) of 1/100, 0.5/100, 0.5/50, 0.25/50, or placebo for up to 52 weeks	Frequency and severity of VMS significantly ↓ from baseline with E2/P4 1mg/100mg and 0.5mg/100mg compared with placebo at week 4 and week 12	TX-001HR is the first continuous combined oral E2/P4 capsule to treat moderate-to-severe PM VMS and provides an effective and convenient option for women seeking bioidentical HT.

Citation	Study Purpose	Pop (N)/ Sample Size (n) /Setting(s)	Design/ Level of Evidence	Variables/ Instruments	Intervention	Findings	Implications
Lobo, R. A., Kaunitz, A. M., Santoro, N., Bernick, B., Graham, S., & Mirkin, S. (2019). Metabolic and cardiovascular effects of TX-001HR in menopausal women with vasomotor symptoms. *Climacteric, 22*(6), 610-616. https://doi.org/10.1080/13697137.2019.1640197doi:10.1080/13697137.2019.1640197	Evaluate the effects of single capsule E2/P4 (TX-001HR) on cardiometabolic markers and outcomes when used to treat VMS	*N*=1835	RCT Level 2	DV=Lipid, coagulation factors, and blood glucose drawn at baseline, 6, 9, and 12 months CV events	See Lobo et al. 2018	No clinically significant effects on lipids, coagulation factors, or blood glucose between treatment groups and comparing treatment groups with placebo. CV adverse events (1 DVT, 3 CVD)	Neutral effects on TGs Lacked statistical power to determine CV outcomes (stroke, VTE, CHD). Incidence of CV events in treatment group similar to expected rates in general population.
Malik, S., Pannu, D., Prateek, S., Sinha, R., & Gaikwad, H. (2016). Comparison of the symptomatic response in Indian menopausal women with different estrogen preparations for the treatment of menopausal symptoms: A randomized controlled trial. *Archives of Gynecology and Obstetrics*, *293*(6), 1325-1333. https://doi.org/10.1007/s00404-016-4034-9	Determine VMS response comparing bioidentical estradiol, synthetic estrogen, isoflavones, and placebo	*N*=200 PM ♀ with surgical, natural, or premature menopause up to age 70 BMI <36 New Delhi, India	RCT single blind, 4 arm, parallel assignment Level 2	DV= Severity and frequency of hot flashes Hot flash score (average hot flash severity x daily frequency) calculated at baseline, 4, 12, 24, and 28 weeks.	oral E2V 0.5-1mg, oral CEE 0.3-0.625 mg, phyto-estrogens 60mg or placebo x 24 weeks CC MP4 200mg given if uterus intact	E2V and CEE ↓severity and frequency of hot flashes. Mean hot flash score at 24-week follow up: E2V: ↓91.9% CEE: ↓89.2% Isoflavones: ↓60.42% Placebo: ↓47.9%	Low doses of both CEE and E2V were equally effective for management of VMS when administered over 24 weeks.
Mirkin, S., Goldstein, S. R., Archer, D. F., Pickar, J. H., Graham, S., & Bernick, B. (2020). Endometrial safety and bleeding profile of a 17β-estradiol/progesterone oral softgel capsule (TX-001HR). *Menopause, 27*(4),	Evaluate endometrial safety of single capsule E2/P4 (TX-001HR) when used to treat VMS	*n*=1255	RCT Level 2	DV=endometrial hyperplasia endometrial biopsy at baseline and 52 weeks	See Lobo et al. 2018	Incidence of endometrial hyperplasia ≤0.36% regardless of dose after one year of use	All doses of TX-001HR provide adequate endometrial protection up to one year.

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410-417. https://doi.org/10.1097/GME.0000000000001480							
Prior, J. C. (2018). Progesterone for treatment of symptomatic menopausal women. *Climacteric*, *21*(4), 358–365. https://doi.org/10.1080/13697137.2018.1472567	Evaluate the efficacy and safety of MP4 only therapy for the treatment of menopausal VMS	*N*=varies PM ♀	SR Level 1	DV=frequency and intensity of hot flashes; VMS score calculated from daily log DV=CV makers	TD MP4, oral MP4, w/ or w/o ET	RCT (*N*=133): statistically significant ↓VMS score at 12 weeks (55% decrease w/ oral MP4 vs. 29% w/ placebo); no serious AEs RCT (*N*=24) no change in weight, BP, lipids, waist circumference, fasting glucose, CRP, or D-dimer at 12 weeks compared to placebo	Oral MP4 is likely safe and effective in treating menopausal VMS either alone or in combination with estrogen. Insufficient evidence to support transdermal P4 in treating VMS
Santoro, N., Allshouse, A., Neal-Perry, G., Pal, L., Lobo, R. A., Naftolin, F., Black, D. M., Brinton, E. A., Budoff, M. J., Cedars, M. I., Dowling, N. M., Dunn, M., Gleason, C. E., Hodis, H. N., Isaac, B., Magnani, M., Manson, J. E., Miller, V. M., Taylor, H. S., Wharton, W., Wolff, E., Zepeda, V., Harman, S. M. (2017). Longitudinal changes in menopausal symptoms comparing women randomized to low-dose oral conjugated estrogens or transdermal estradiol plus micronized progesterone versus placebo: The Kronos Early Estrogen Prevention	Compare the efficacy of low dose oral CEE vs. TD E2 plus MP$ or placebo in treating VMS in early MP ♀	*N*=727 ♀ age 42–58, ≥6 months but <36 months from last menses 9 sites across the U.S.	RCT Level 2	DV= reduction in moderate-severe hot flashes and night sweats Hot flashes and night sweats self-reported at baseline and at 6, 12, 24, 36, and 48 months.	oral CEE 0.45 mg or TD E2 50mcg both given w/ oral MP4 200mg x 12 days per month or placebo	Moderate to severe hot flashes and night sweats: Baseline: 44% and 35% respectively **At 6-month follow up:** Significant ↓ in all treatment groups. Hot flashes: placebo 28.3%; TD E2 7.4%; oral CEE 4.2% Night sweats: placebo 19%; TD E2 5.3%; oral CEE 4.7% No significant differences between CEE and TD E2	Lower than conventional doses of oral CEE and TD E2 provide significant relief of menopausal VMS up to 48 months. Both options are equally effective therefore TD E2 is a viable option for women seeking bioidentical HT for the treatment of VMS.

Citation	Study Purpose	Pop (N)/ Sample Size (n) /Setting(s)	Design/ Level of Evidence	Variables/ Instruments	Intervention	Findings	Implications
Study (KEEPS). *Menopause*, *24*(3), 238-246. https://doi.org/10.1097/GME.0000000000000756						Symptom relief was not significantly modified by BMI or race/ethnicity.	
Scarabin P. Y. (2018). Progestogens and venous thromboembolism in menopausal women: An updated oral versus transdermal estrogen meta-analysis. *Climacteric, 21*(4), 341–345. https://doi.org/10.1080/13697137.2018.1446931	Evaluate VTE risk based on route of estrogen administration, hormone regimen, and progestogen type	*N*=26,471 PM ♀ with VTE	MA Level 1 4 CCS, 3 CS	DV=First episode idiopathic VTE (DVT or PE), VTE recurrence, or secondary VTE Measured with objective imaging	studies comparing oral vs. TD estrogen +/- progestin or P4 vs. non-user	TD E+MP4: no change (RR 0.93, 95% CI 0.65–1.33) TD E+P: ↑VTE risk (RR 2.42, 95% CI 1.84–3.18)	Transdermal estrogen+MP4 is a safer option for menopausal women at risk for VTE. May improve risk/benefit ratio of HT for all PM women. Increased VTE risk associated with progestogens is not a class effect.
Simon, J. A., Laliberté, F., Duh, M. S., Pilon, D., Kahler, K. H., Nyirady, J., Davis, P. J., & Lefebvre, P. (2016). Venous thromboembolism and cardiovascular disease complications in menopausal women using transdermal versus oral estrogen therapy. *Menopause, 23*, 600–610. https://doi.org/10.1097/GME.0000000000000590	Evaluate risk of VTE and CVD complications for menopausal ♀ using TD estradiol vs. oral ET	*N*=5102 ♀ ≥ 50 U.S.	Uncontrolled CS Level 4	CVD events measured by ICD-9 codes on health insurance claims	TD E2 vs. oral estrogen (type not specified) Doses not available	TD E2 vs oral ET CVD complications: (adjusted IRR 0.81; 95% CI, 0.67-0.99). VTE (adjusted IRR 0.42; 95% CI, 0.19-0.96)	Findings suggest that unopposed TD E2 is safer from a CVD risk standpoint when compared to unopposed oral estrogens, but no conclusions can be drawn regarding the safety profiles of bioidentical vs. synthetic oral ET.
Sjögren, L. L., Mørch, L. S., & Løkkegaard, E. (2016). Hormone replacement therapy and the risk of endometrial cancer: A systematic review. *Maturitas, 91*, 25–35. https://doi.org/10.1016/j.maturitas.2016.05.013	Evaluate endometrial safety of PM HT use based on regimen and type of progestogen	*N*=902 PM ♀ w/ EC control= 180,202 Europe	SR Level 1 2 CS	IV= estrogen plus CC or SC MP4 DV= incidence & prevalence of EC	N/A	Study #1: HR 2.42; 95% CI 1.53–3.83 for ever use of MP4 vs. never use (SC/CC not specified) Study #2: HR 1.80; 95% CI 1.38–2.34 for ever use of CC with MP4	Increased risk of EC among MP4 users. EC risk higher if MP4 used for ≥5 years

Citation	Study Purpose	Pop (N)/ Sample Size (n) /Setting(s)	Design/ Level of Evidence	Variables/ Instruments	Intervention	Findings	Implications
						HR 1.39; 95% CI 0.99–1.97 for ≤5 years of CC with MP4 HR 2.66; 95% CI 1.87–3.77 for >5 years of CC with MP4	
Stute, P., Wildt, L., & Neulen, J. (2018). The impact of micronized progesterone on breast cancer risk: A systematic review. *Climacteric, 21*(2), 111–122. https://doi.org/10.1080/13697137.2017.1421925	Determine the impact of estrogen + MP4 on BC risk	*N*=varies Peri- and PM ♀ (mostly in their 50s) U.S. and Europe	SR Level 1	DV=BC measured by core needle biopsy or lumpectomy Medical records, self-administered questionnaire, in-person interviews, or scheduled visits at 2 month or 12-month intervals Mean duration of HT 2.8 years to ≥10 years	E+MP4; variety of regimens, routes (mostly oral) and doses not always specified Compared synthetic, bioidentical, placebo, and/or non-users	No ↑BC risk w/ E+ oral or vaginal MP4 use for ≤5 years Limited evidence suggests slight but significant ↑BC risk w/ E+MP4 >5 years Adherence high in two studies but not reported in others	Practice recommendations: (1) E+MP4 (oral or vaginal) does not increase breast cancer risk if used for ≤5 years. Limited evidence suggests that BC risk increases after 5 years E+ oral MP.
Stute, P., Neulen, J., & Wildt, L. (2016). The impact of micronized progesterone on the endometrium: A systematic review. *Climacteric*, *19*(4), 316-328. https://doi.org/10.1080/13697137.2016.1187123	Determine if EPT with MP4 provides adequate endometrial protection	*N*=varies Peri- and PM ♀	SR Level 1 (40 studies)	IV=EPT w/ MP4 (oral, TD, or vaginal) for minimum of 3 months DV=Endometrial hyperplasia & EC	N/A	Oral MP4: adequate endometrial protection if sequential 200mg/day for 12-14 day/month for up to 5 years Vaginal MP4: may provide endometrial protection if sequential for ≥10 days/ month at 4% (45 mg/day) or every other day at 100	Detailed expert panel recommendations to guide clinical practice

Citation	Study Purpose	Pop (N)/ Sample Size (n) /Setting(s)	Design/ Level of Evidence	Variables/ Instruments	Intervention	Findings	Implications
						mg/day for up to 3–5 years (off-label use) TD MP4 does not provide endometrial protection	
Tempfer, C. B., Hilal, Z., Kern, P., Juhasz-Boess, I., & Rezniczek, G. A. (2020). Menopausal hormone therapy and risk of endometrial cancer: A systematic review. *Cancers, 12*(8), 1-18. https://doi.org/10.3390/cancers12082195	Evaluate EC risk in ♀ related to type and regimen of progestogen	*n*=902 PM ♀ w/ EC, control= 180,202 Europe	SR (2 CS) Level 1	IV= estrogen plus CC or SC MP4 DV= incidence & prevalence of EC	N/A	Study #1: HR 2.42; 95% CI 1.53–3.83 for ever use of MP4 vs. never use (SC/CC not specified) Study #2: HR 1.80; 95% CI 1.38–2.34 for ever use of CC with MP4 HR 1.39; 95% CI 0.99–1.97 for ≤5 years of CC with MP4 HR 2.66; 95% CI 1.87–3.77 for >5 years of CC with MP4	Increased risk of EC among MP4 users. Short term use (≤5 years) of MP4 recommended
Yang, Z., Hu, Y., Zhang, J., Xu, L., Zeng, R., & Kang, D. (2017). Estradiol therapy and breast cancer risk in perimenopausal and postmenopausal women: A systematic review and meta-analysis. *Gynecological Endocrinology,* (2), 87–92. https://doi.org/10.1080/09513590.2016.1248932	Evaluate impact of estradiol with and without progestogen on BC risk	*N*=14,475 peri- and PM ♀ Mostly Europe	SR & MA Level 1 14 studies	IV=Estradiol therapy +/- progestogen, duration of exposure, type of regimen (CC/SC) DV=BC incidence	TD or oral E2V or 17-beta estradiol + MP4 or P	*OR* (95% CI): **E2V/E2 only** All studies 1.11 (0.98-1.27) RCT only 0.90 (0.40-2.02) **EPT w/ progestogen:** MP4 1.00 (0.83-1.20) MPA 1.19 (1.07-1.33) NETA 1.44 (1.26-1.65)	No increased risk of BC with EV and 17-beta estradiol. Statistically significant ↑in BC risk with EPT including synthetic P (MPA, NETA, LNG). No ↑BC risk with EPT containing MP4. ↑BC risk with EPT <5 years (MA included bioidentical estradiol but combined all progestogens). Use of EPT >5

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						LNG 1.47 (1.17-1.85) EPT <5yrs 1.39 (1.09-1.78) EPT >5yrs 2.25 (1.82-2.80) EPT SC 1.76 (1.28-2.42) EPT CC 2.90 (1.82-4.61)	years increases BC risk even further. Statistically significant ↑ BC risk with SC and CC EPT, however higher risk with CC.
Zeng, Z., Jiang, X., Li, X., Wells, A., Luo, Y., & Neapolitan, R. (2018). Conjugated equine estrogen and medroxyprogesterone acetate are associated with decreased risk of breast cancer relative to bioidentical hormone therapy and controls. *PloS One, 13*(5), 1-12. https://doi.org/10.1371/journal.pone.0197064	Determine BC risk associated with different synthetic and bioidentical HT protocols	*n*=12,404 ♀ initiated HT after age 50 control= 27,642 ♀ w/ no HT use after age 50 U.S.	Retrospective Level 4	DV=BC diagnosis ICD-9 codes from Northwestern Medicine Medical Data Warehouse Mean follow up time 15.4 years (HT use) and 17.8 years (controls)	ET +/- P or MP4 (oral) Drug doses not known	BC risk (95% CI): CEE (HR 0.31) Oral E2 (HR 0.65) CEE+MPA (HR 0.43) E2+MP4 (HR 1.05)	CEE and CEE+MPA had the lowest risk of BC. Oral E2 was associated with ↓BC risk but inferior to CEE. CEE+MPA findings differed from WHI Need additional studies to substantiate results

AA, African American; BC, breast cancer; BP, blood pressure; CC, continuous combined; CCS, case control study; CEE, conjugated equine estrogens; CI, confidence interval; CID, clinically important differences; CIMT, carotid artery intima-media thickness; CMA, chlormadinone acetate; CRP, C reactive protein; CS, cohort study; CV, cardiovascular; D, dydrogesterone; DBPC, double blind placebo-controlled; DV, dependent variable; E, estrogen; E2, estradiol; E2V, estradiol valerate; EPT, estrogen-progesterone therapy; ET, estrogen therapy; EV, estradiol valerate; HR, hazard ratio; HT, hormone therapy; ICD-9, International Classification of Diseases, Ninth Revision; IRR, Incidence Rate Ratio; IS, ischemic stroke; IV, independent variable; LNG, levonorgestrel; MA, meta-analysis; MP4, micronized progesterone; MPA, medroxyprogesterone acetate; MDTS, meter-dose transdermal spray; NETA, norethisterone acetate; *OR*, odds ratio; P, synthetic progestin; PBCCS, population based case control study; PM, post-menopause; PROLMRDS, partly randomized open-label, multiple-rising-dose study; RCT, randomized control trial; RR, relative risk; SC, sequential combined; SR, systematic review; TG, triglycerides