Fact or Fiction? The Role of Regulated Body-Identical Hormone Therapy for Menopausal Women
Laura Donnelly & Lynda G. Balneaves

ABSTRACT: Many menopausal women use hormone therapy, including regulated body-identical hormone therapy (rBHT), to relieve vasomotor symptoms and prevent cardiovascular disease. Despite growing interest in rBHT, there is uncertainty regarding potential benefits and risks. With this narrative review, we aimed to synthesize the literature regarding the efficacy of these therapies for managing vasomotor symptoms and preventing cardiovascular disease. Thirteen articles were identified, with authors of several studies showing rBHT and combination therapy (rBHT with synthetic hormone therapy) to be efficacious in managing vasomotor symptoms when compared to placebo. Conflicting evidence exists regarding the efficacy of rBHT in the prevention of cardiovascular disease, with some studies demonstrating improved cardiovascular biomarkers, particularly among women who are at the beginning of the menopausal journey and experiencing symptoms. In summary, rBHT may have a role in the care of women trying to manage vasomotor symptoms and in protecting against cardiovascular disease among menopausal women; however, larger, more rigorously designed randomized controlled trials are required.

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Menopause is a natural biological process that signifies the permanent cessation of menstrual cycles due to the decline of ovarian function, typically occurring between the ages of 40 and 50 years (Locke & Longcope, 1986). This period, known as the menopausal transition, is marked by a decrease in the production of estrogen and progesterone, hormones that play a crucial role in maintaining reproductive health. The absence of these hormones can lead to various symptoms, including vasomotor symptoms (VMSs) such as hot flashes and night sweats, which can negatively impact quality of life (QOL), sleep, and overall health (Hulley et al., 1998; Rossouw et al., 2002). Additionally, loss of estrogen also places many menopausal women at increased risk for cardiovascular disease (CVD), as it negatively affects cardiovascular health (Anderson & Limacher, 2004; Hulley et al., 1998; Rossouw et al., 2002). These findings led many clinicians to encourage women to use sHT not only for the management of VMSs but also to protect their hearts throughout menopause. However, the lack of randomized controlled trials (RCTs) confirming the protective effect of sHT in relation to CVD was greatly criticized (Anderson & Limacher, 2004). As a consequence, the Heart and Estrogen/Progestin Replacement Study (HERS) and the Women’s Health Initiative trials were carried out (Anderson & Limacher, 2004; Hulley et al., 1998; Rossouw et al., 2002). These studies, which compared CEE plus synthetic medroxyprogesterone acetate to placebo, showed an absence of primary or secondary CVD prevention and, conversely, found an increased risk of CVD and thromboembolic events (Rossouw et al., 2002).

Because of these concerning results, many menopausal women drastically reduced their use of sHT, with more than 60% reporting cessation (Hersh et al., 2004). Searching for a safer alternative to manage what can be extremely disruptive menopausal symptoms, some women began using so-called bioidentical HT. Primarily derived from plant products (e.g., yams and soybeans), these types of HT are purported to have the same molecular structure as the hormones found in a person’s body (Iftikhar et al., 2011; Newson & Rymer, 2019). In North America, unregulated and regulated forms of bioidentical HT are sold (North American Menopause Society, 2017; Society of Obstetricians and Gynaecologists of Canada [SOGC], 2011).

Unregulated forms of HT, also known as compounded bioidentical HT, are produced by a compounding pharmacy that uses a person’s saliva or a blood test to formulate a customized prescription that matches their personal levels of progesterone; estrogen (including estriol [E3], estradiol [E2], and estrone [E1]); and, sometimes, testosterone (North American Menopause Society, 2017; Pinkerton, 2014). Compounded hormone therapies are not currently approved by the U.S. Food and Drug Administration (Pinkerton, 2020), and the SOGC (2011) does not support their use because of the lack of regulation by Health Canada. Part of the hesitancy surrounding compounded HT has been the concern that these products lack proof of standardization and purity, have not been rigorously evaluated, and may be unsafe for women (Hill et al., 2016; Newson & Rymer, 2019; North American Menopause Society, 2017; Pinkerton, 2020; Pinkerton et al., 2019).

In contrast, regulated bioidentical HT products, such as 17-beta estradiol (E2) or micronized progesterone (P4), are standardized, have been subject to clinical research, and are controlled and monitored by the U.S. Food and Drug Administration and Health Canada (Pinkerton, 2020; SOGC, 2011).

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**CLINICAL IMPLICATIONS**

- There is growing interest in bioidentical hormone therapy among menopausal women.
- Regulated body-identical hormone therapy may be helpful for some menopausal women in managing the frequency and severity of vasomotor symptoms.
- Conflicting evidence exists regarding the role of regulated body-identical hormone therapy in protecting menopausal women’s cardiovascular health.
- More rigorously designed clinical trials are required to better inform women’s decisions related to the use of regulated body-identical hormone therapy.

Women experience numerous physiologic and mental health challenges during menopause that can negatively affect quality of life (QOL). Clinicians and women, however, have been hesitant to use hormone therapy (HT) to mitigate menopausal symptoms since the 1990s, when an alarming association between synthetic forms of HT and cardiovascular thromboembolic risk was identified (Anderson & Limacher, 2004; Hulley et al., 1998; Rossouw et al., 2002). Faced with limited options, many women began to consider what has been commonly referred to as “bioidentical” HT that is intended to mimic a woman’s endogenous hormones and has been touted as a natural alternative to synthetic HT (sHT; Fishman et al., 2015; Iftikhar et al., 2011). Women and clinicians, however, often lack adequate understanding of the efficacy and safety of bioidentical HT compared to sHT (Sood et al., 2013).

After the age of 40 years, many women begin to experience the first signs of menopause because of a reduction in endogenous estrogen and progesterone and an overall imbalance in reproductive hormones. These signs include mood swings, irregular periods, sleep issues, atrophic vaginitis, and vasomotor symptoms (VMSs; i.e., hot flashes and night sweats). Once menstruation has stopped for a full year, a woman is considered menopausal. VMSs can occur in up to 80% of menopausal women (Tuomikoski et al., 2011) and in those in the perimenopausal period (Avis et al., 2015), compelling many to look for treatment options, including HT. Until the early 2000s, the most common HT was sHT, primarily in the form of conjugated equine estrogens (CEE) produced by a compounding pharmacy that uses a person’s saliva or a blood test to formulate a customized prescription that matches their personal levels of progesterone; estrogen (including estriol [E3], estradiol [E2], and estrone [E1]); and, sometimes, testosterone (North American Menopause Society, 2017; Pinkerton, 2014). Compounded hormone therapies are not currently approved by the U.S. Food and Drug Administration (Pinkerton, 2020), and the SOGC (2011) does not support their use because of the lack of regulation by Health Canada. Part of the hesitancy surrounding compounded HT has been the concern that these products lack proof of standardization and purity, have not been rigorously evaluated, and may be unsafe for women (Hill et al., 2016; Newson & Rymer, 2019; North American Menopause Society, 2017; Pinkerton, 2020; Pinkerton et al., 2019).

In contrast, regulated bioidentical HT products, such as 17-beta estradiol (E2) or micronized progesterone (P4), are standardized, have been subject to clinical research, and are controlled and monitored by the U.S. Food and Drug Administration and Health Canada (Pinkerton, 2020; SOGC, 2011).
Although the efficacy and safety of HT is debated in the literature and in clinical communities, women continue to turn toward bioidentical HT in the hopes of managing life-altering menopausal symptoms.

More recently, the term regulated body-identical hormone therapy (rBHT) has been used to distinguish regulated from unregulated forms of bioidentical HT (British Menopause Society, 2019; Newson & Rymer, 2019). For the purposes of this review, this new terminology—rBHT—will be used, especially given concerns raised that the term bioidentical has been used as a marketing tool (British Menopause Society, 2019; Hill et al., 2016; National Academies of Sciences, Engineering, and Medicine, 2020).

Although the efficacy and safety of HT is debated in the literature and in clinical communities, women continue to turn toward bioidentical HT in the hopes of managing life-altering menopausal symptoms. Since the Women’s Health Initiative trial, researchers have conducted numerous RCTs to examine the risks associated with various forms of HT, with most of the trials focused on either sHT or rBHT. To date, only small, observational studies have been conducted on unregulated compounded HT, making it challenging to conduct a reliable and valid synthesis of this research. As such, given the urgent need by clinicians and women for greater clarity regarding the potential role of rBHT in managing VMSs and preventing CVD, the focus and purpose of this review is to summarize the current evidence regarding rBHT.

**Methods**

A narrative review was conducted. This type of review provides a synthesis of recently published literature, identifies existing gaps, and encourages critical reflection and future research (Grant & Booth, 2009). This methodology also aims to detect potential bias and critically appraise the quality of evidence. The databases searched included PubMed, CINAHL, Cochrane Systematic Reviews, and Scopus. Inclusion criteria were human studies; published in English between January 2009 and June 2019; and focused on evaluating the efficacy of rBHT among perimenopausal, menopausal, or postmenopausal women. Articles that focused on surgically induced menopause or unregulated compounded bioidentical HT were excluded. The types of studies eligible for inclusion were limited to systematic reviews, meta-analyses, and RCTs.

The primary author (L.D.) assessed the titles and abstracts for relevance and included only articles that met the inclusion criteria. The second author (L.G.B.) audited the list of articles to confirm relevance and eligibility (see Figure 1). Data extracted from eligible studies were then entered into a matrix to summarize the data (see Supplementary Table S1). The Joanna Briggs Institute critical appraisal tool for RCTs (Tufanaru et al., 2020) was used to assess the methodologic quality of the studies. This tool comprises 13 items that assess possible sources of bias. The studies were reviewed and scored by the two authors, and any disagreement was resolved through discussion. Only RCTs of moderate to high quality (scoring ≥7/13) on the critical appraisal tool were included. All studies scored sufficiently and were included in the final review (see Supplementary Table S2).

**Results**

Thirteen articles met the inclusion criteria: two systematic reviews (Casanova et al., 2015; Gaudard et al., 2016) and 11 RCTs (Archer et al., 2014; Constantine et al., 2018; Harman et al., 2014; Hitchcock & Prior, 2012; Hodis et al., 2016; Lin et al., 2011; Panazzolo et al., 2016; Santoro et al., 2017; Stevenson et al., 2010; Tuomikoski et al., 2010; Villa et al., 2011).

Authors of six RCTs (Archer et al., 2014;Constantine et al., 2018; Hitchcock & Prior, 2012; Lin et al., 2011; Santoro et al., 2017; Stevenson et al., 2010) examined the role of rBHT in managing VMSs (alone or in comparison or combination with sHT). Half of these studies were conducted in the United States (Archer et al., 2014; Constantine et al., 2018; Santoro et al., 2017), and the others took place in Canada (Hitchcock & Prior, 2012) and China (Lin et al., 2011), with one multisite study occurring in France, Poland, Romania, and Russia (Stevenson et al., 2010). Sample sizes of these RCTs ranged from 133 to 735 participants. One systematic review (Gaudard et al., 2016) examined the effect of rBHT on VMSs; this review included a total of 23 trials and encompassed 5,779 participants.

Five RCTs (Harman et al., 2014; Hodis et al., 2016; Panazzolo et al., 2016; Tuomikoski et al., 2010; Villa et al., 2011) focused on CVD protection, two of which were conducted in the United States (Harman et al., 2014; Hodis et al., 2016), with the remainder in Brazil (Panazzolo et al., 2016), Finland (Tuomikoski et al., 2010), and Italy (Villa et al., 2011). The samples in these RCTs ranged from 40 to 727 participants. One systematic review and meta-analysis (Casanova et al., 2015) focused on rBHT and CVD, which included 28 RCTs and a total of 3,360 participants.

The types of rBHT examined across the 11 RCTs were primarily those using E2, P4, or a combination formula called TX-001HR that integrates E2 and P4. Only one study assessed the effects of transdermal estradiol hemihydrate gel, another type of rBHT (Tuomikoski et al., 2010). No RCTs directly compared rBHT to sHT; instead, each type of HT was compared directly to placebo. As such, we will summarize the articles using the following comparisons: rBHT only versus placebo, rBHT or sHT versus placebo, and combination treatment (rBHT and sHT) versus placebo. The majority of combination treatment examined in the RCTs used E2 as the rBHT and drospirenone (DRSP) as the sHT. No studies were...
identified that examined rBHT use among perimenopausal women and met the inclusion criteria. See Table 1 for the specific types of HT discussed in the review.

TABLE 1 TYPES OF HORMONE THERAPY

<table>
<thead>
<tr>
<th>Name of Hormone</th>
<th>Type of HT</th>
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<tbody>
<tr>
<td>17-beta estradiol (E2)</td>
<td>rBHT</td>
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<tr>
<td>17-beta estradiol and micronized progesterone</td>
<td>rBHT</td>
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<tr>
<td>Transdermal estradiol hemihydrate gel</td>
<td>rBHT</td>
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<tr>
<td>Micronized progesterone</td>
<td>sHT</td>
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<tr>
<td>Drosiprenone</td>
<td>sHT</td>
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<tr>
<td>Oral conjugated equine estrogen</td>
<td>sHT</td>
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<tr>
<td>Oral estradiol valerate</td>
<td>sHT</td>
</tr>
<tr>
<td>Medroxyprogesterone acetate</td>
<td>sHT</td>
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Note. HT = hormone therapy; rBHT = regulated body-identical hormone therapy; sHT = synthetic hormone therapy. Sources: Society of Obstetricians and Gynaecologists of Canada (2011); U.S. Food and Drug Administration (2017).

rBHT and VMS Management

The following sections summarize the literature regarding the efficacy of rBHT on VMS management among menopausal or postmenopausal women.

rBHT Versus Placebo

Gaudard and colleagues (2016) conducted a systematic review that explored the efficacy and safety of rBHT in relieving moderate to severe VMSs. They identified a total of 23 RCTs ($n = 5,779$) of low to moderate quality that evaluated various dosages of rBHT (17-beta estradiol [E2]) that were administered through different routes (i.e., oral, patch, topical, and intranasal; Gaudard et al., 2016). Given the lower quality of the evidence, Gaudard et al. deduced that no definitive conclusions could be reached regarding the value of rBHT in managing VMSs. Some limitations in that systematic review were that the studies focused on a narrow range of rBHT types (i.e., strictly E2, with no other noncompounded or compounded formulas) and did not consider long-term adverse effects, such as cancer or cardiovascular events.

Hitchcock and Prior (2012) compared the efficacy of rBHT (oral micronized progesterone [P4]) to placebo in managing...
The science surrounding rBHT has not expanded quickly enough to meet the growing demand and interest

VMSs, randomly allocating 133 postmenopausal women to the two study arms. At the end of the 12-week trial, the frequency of VMSs was significantly reduced in both groups, but women receiving P4 reported less frequent VMSs compared to placebo (Hitchcock & Prior, 2012). However, this difference was not significant. In a similar well-designed, double-blinded RCT, Constantine et al. (2018) compared a variety of doses of combination E2 and P4 (TX-001HR) to placebo in managing VMSs among 726 menopausal women. VMS frequency was reported to be significantly less across all treatment groups compared to placebo after 4 and 12 weeks (Constantine et al., 2018). The authors concluded that this form of rBHT may be a beneficial alternative for women seeking natural HT (Constantine et al., 2018).

Combination Therapy Versus Placebo

Three RCTs tested a combination of sHT (DRSP) with rBHT (E2) in postmenopausal women (Archer et al., 2014; Lin et al., 2011; Stevenson et al., 2010). Archer et al. (conducted a short 12-week RCT comparing two different doses of combined DRSP and E2, oral E2, and placebo (n = 735). The postmenopausal participants receiving the combination treatment and rBHT alone reported significantly reduced VMS frequency and severity compared to placebo, with the most relief reported in the group receiving the highest dose of DRSP (0.5 mg) plus E2 (0.5 mg; Archer et al., 2014). Similarly, Stevenson et al. tested two different doses of DRSP and E2 against placebo to assess daily hot flash severity in a three-arm, 13-week trial (n = 313). At trial completion, the severity of hot flashes declined significantly in both combination groups compared to placebo, with no difference between treatment arms (Stevenson et al., 2010). Lin et al. evaluated the mean change in frequency of hot flashes over 16 weeks among 244 Chinese women receiving DRSP and E2 combination therapy or placebo. A significant mean reduction in hot flash frequency per week was found among women receiving the combination therapy compared to placebo (80.4% vs. 51.9%; p < .0001); however, no significant change in severity of hot flashes was found (Lin et al., 2011).

Santoro et al. (2017) conducted a 4-year, three-arm RCT that compared an rBHT arm (transdermal E2) and sHT arm (oral CEE; both combined with rBHT [P4]) to placebo (n = 727). Hot flash severity decreased significantly across both treatment arms compared to placebo, with the greatest relief reported among women receiving sHT plus rBHT (Santoro et al., 2017). Results were first observed at 6 months and sustained throughout the 4-year trial (Santoro et al., 2017).

rBHT and CVD Protection and Risk

This section summarizes six articles (Casanova et al., 2015; Harman et al., 2014; Hodis et al., 2016; Panazzolo et al., 2016; Tuomikoski et al., 2010; Villa et al., 2011) that assessed the possible protective role of rBHT in relation to CVD among menopausal or postmenopausal women. In these studies, CVD progression was measured by the development of atherosclerosis as evidenced by the following biomarkers: carotid artery mean thickness (CIMT), blood pressure (BP), lipid profile (total cholesterol [TC], low-density lipoprotein [LDL] cholesterol, triglycerides [TG], and high-density lipoprotein [HDL] cholesterol), blood viscosity, and inflammatory markers. These indicators can all contribute toward significant CVD and possible thromboembolic events, such as stroke, myocardial infarction, deep vein thrombosis (DVT), or pulmonary embolism (PE).

Several of the RCTs reviewed directly evaluated the incidence of thromboembolism; however, it was assessed as an adverse event instead of as a primary outcome indicator of CVD. In a 5-year trial (n = 596) by Hodis et al. (2016), only one individual taking rBHT (17-beta estradiol [E2]) experienced a myocardial infarction, and three women reported a DVT or pulmonary embolism. The number of women, however, who experienced a thromboembolism did not differ significantly between the rBHT and placebo groups (Hodis et al., 2016). Similarly, in an RCT of transdermal E2 by Harman et al. (2014), only two women experienced thromboembolism among 727 menopausal women. In an RCT conducted by Stevenson et al. (2010; n = 313), only one case of coronary artery disease was found among women receiving the DRSP/E2 combination. In addition, only one trial in the VMS literature (Constantine et al., 2018) identified a single participant out of 421 with a DVT.

Turning toward the biomarker studies, a systematic review and meta-analysis (n = 3,360) conducted by Casanova et al. (2015) compared the effect of rBHT (E2 with or without micronized progesterone [P4]) or combination therapy (DRSP and E2) to either placebo or alone. Various cardiovascular markers were evaluated, including lipid profile, BP, and the inflammatory marker C-reactive protein (CRP). CRP is a plasma...
protein that can be elevated during inflammation and can be associated with CVD (American Heart Association, 2015). With regard to the lipid profile markers, significantly lower TC and LDL were observed among women receiving rBHT compared to placebo ($p < .00001$). When rBHT was compared to sHT, women receiving rBHT had significantly lower TG levels than those on sHT ($p < .01$). However, women receiving sHT had significantly lower TC and LDL compared to rBHT ($p = .02$). The meta-analysis by Casanova et al. (2015) also found no significant difference in BP between rBHT and combination therapy among nonhypertensive menopausal women.

**Carotid Artery Mean Thickness**

**rBHT versus placebo.** In the RCT by Hodis et al. (2016), the rate of CIMT change in two groups of women was assessed: those who were postmenopausal for less than 6 years (early) and those who were more than 10 years postmenopause (late). Both groups received rBHT treatment (E2 plus P4 for women with a uterus) versus placebo (Hodis et al., 2016). After 5 years, the early group receiving E2, with or without P4, had the least CIMT progression and subclinical atherosclerosis compared to the late group receiving E2, with or without P4 ($p = .007$). Furthermore, among early postmenopausal women, CIMT progression was significantly lower in the E2 group compared to the placebo group ($p = .008$), whereas no difference between treatment and placebo was observed in late postmenopausal women (Hodis et al., 2016). These findings led Hodis et al. to suggest that rBHT should only be used by women within 6 years of becoming menopausal.

**rBHT/sHT versus placebo.** Harman et al. (2014) conducted a 4-year, three-arm RCT ($n = 727$) comparing sHT (oral CEE with placebo patch) and rBHT (transdermal E2 plus placebo tablets) to placebo; participants in both treatment arms were given oral P4 for 12 days per month (see Table 1). No significant difference in CIMT progression was found between the treatment and placebo arms throughout the study (Harman et al., 2014).

**Blood Pressure**

**rBHT versus placebo.** Panazzolo et al. (2016) compared rBHT (transdermal E2) versus placebo on multiple CVD markers in a small double-blinded RCT ($n = 44$). Women in the E2 group had a significant reduction in BP compared to those receiving placebo ($p < .01$; Panazzolo et al., 2016).

**rBHT/sHT versus placebo.** Tuomikoski et al. (2010) recognized BP as one of the most influential determinants of CVD risk in women. In a double-blinded, four-arm RCT ($n = 147$), their aim was to establish if HT was safe for postmenopausal women, specifically comparing those with or without hot flashes, using BP reduction as the primary outcome. The four treatment protocols included rBHT (transdermal estradiol hemihydrate gel), sHT only (oral estradiol valerate [OEV]), sHT (OEV combined with medroxyprogesterone acetate), or placebo. No statistically significant differences between rBHT and sHT were identified; however, a significant interaction was found between treatment arms and hot flash status. The greatest reduction of BP was observed in the rBHT and sHT OEV treatment arms for only symptomatic women (Tuomikoski et al., 2010). As a result, the authors suggested that transdermal estradiol hemihydrate gel and OEV were more appropriate for symptomatic women and should be avoided by those without hot flashes seeking CVD protection (Tuomikoski et al., 2010). In a similar study examining the effect of rBHT or sHT (plus P4) versus placebo on healthy menopausal women, Harman et al. (2014) also found no significant change in BP.

**Lipid Profile**

**rBHT versus placebo.** In a small RCT (rBHT [transdermal E2] vs. placebo) by Panazzolo et al. (2016), TC and HDL remained relatively the same between study arms. Although a slight increase in LDL and TG was observed in the rBHT group compared to placebo, this was nonsignificant (Panazzolo et al., 2016).

**rBHT/sHT or placebo.** In the RCT by Harman et al. (2014), TG was disadvantageously elevated in the sHT group compared to the rBHT (transdermal E2) or placebo (Harman et al., 2014) groups. With regard to LDL and HDL levels, however, sHT was found to be more effective in improving the lipid profile. It is important to note, however, that statistical significance was not calculated for secondary outcomes (Harman et al., 2014).

**Combination therapy (rBHT plus sHT) versus placebo.** Villa et al. (2011) reported on lipid values from a small 6-month RCT ($n = 40$) that compared a combination of rBHT (oral E2) plus sHT (DRSP) versus placebo. Although both groups experienced a reduction in TC and LDL, only the combination therapy reached significance ($p < .05$).

**Blood Viscosity**

**rBHT versus placebo.** In the Panazzolo et al. (2016) trial, blood viscosity was found to be significantly lower in the rBHT (transdermal E2) group than placebo ($p < .01$); however, no significant difference was found in plasma viscosity between groups. Panazzolo et al. concluded that rBHT may reduce the risk for clot formation.

**Inflammatory Markers**

**rBHT/sHT versus placebo.** The American Heart Association (2015) reports that despite inflammation not directly causing CVD, it is common for individuals with CVD to have elevated inflammatory markers, which may contribute to atherosclerosis. Harman et al. (2014) examined the effect of rBHT (transdermal E2) or sHT (plus P4) on two key inflammatory biomarkers, CRP and interleukin 6. Of the three treatment arms in the study, sHT showed the most elevated CRP compared to rBHT or placebo (although no significance was measured for this secondary outcome). Moreover, no
For women considering switching from one form of HT to another, a conversation about motivations and expectations is warranted, as is a discussion about other relevant factors, such as accessibility and cost of treatment.

significant differences in interleukin 6 levels were found among the treatment groups.

**rBHT and Adverse Effects**

Overall, few life-threatening adverse events were reported in the trials of rBHT, suggesting a relatively high safety profile (see Supplementary Table S3). However, the rates of vaginal bleeding ranged considerably, with up to 50% of women reporting some spotting, mainly short term. Other relatively mild side effects of rBHT that were reported included headache (0.8%) and breast tenderness (0.5%–11%). Cardiovascular adverse effects were also quite low, with up to 3% of women using rBHT experiencing hypertension, hypercholesterolemia, and elevated CRP. For additional details on the potential adverse effects of rBHT, see Supplementary Table S3.

**Discussion**

In this narrative review, we summarize the recent evidence regarding the efficacy and safety of rBHT in the management of VMSs and the prevention of CVD among women at various stages of menopause. The substantial heterogeneity of the types and dosages of rBHT evaluated in the identified trials, however, prevent firm conclusions from being drawn regarding the overall efficacy of rBHT among menopausal or postmenopausal women. In addition, the lack of rBHT trials with perimenopausal women limits the generalizability of the findings to women early in the menopausal journey. Although specific practice recommendations cannot be provided with certainty, there are some commonalities across the research that can inform clinicians’ discussions with women interested in rBHT.

Our review expands on the work of Gaudard et al. (2016) through the inclusion of more recently published studies examining a greater diversity of rBHT types. Unfortunately, few studies to date have directly compared rBHT to sHT; instead, most trials have examined either rBHT alone, or combined rBHT and sHT, versus placebo. As a result, it remains challenging for clinicians to address questions in an evidence-based manner regarding the superiority of rBHT to sHT in the management of VMSs. In addition, although the majority of examined trials were found to be of high quality, a few trials lacked key information, such as how blinding was achieved, whether an intent-to-treat analysis was conducted, or the reasons for trial dropouts (Santoro et al., 2017; Tuomikoski et al., 2010; Villa et al., 2011). Notwithstanding these limitations, the results of several studies showed that rBHT (specifically TX-001HR) and a combination formula (DRSP plus E2) are safe and efficacious in reducing VMS frequency and, in some cases, severity when compared to placebo (Archer et al., 2014; Constantine et al., 2018; Lin et al., 2011; Stevenson et al., 2010). This research, though, was conducted with mainly healthy White women from North America, which may limit the applicability of these findings to women from more diverse ethnic or racial backgrounds and those living with more complex chronic health conditions.

Conflicting evidence regarding the efficacy of rBHT in preventing CVD was also found in our review. Although the meta-analysis by Casanova et al. (2015) found that combined rBHT and sHT resulted in a significant reduction in TC, LDL, and TG, no significant change was found with regard to HDL, BP, or CRP. The additional five RCTs reviewed (Harman et al., 2014; Hodis et al., 2016; Panazzolo et al., 2016; Tuomikoski et al., 2010; Villa et al., 2011), which did not meet the criteria of Casanova et al. for inclusion or were published since 2015, showed limited benefit of rBHT on reducing atherosclerosis. The findings from these trials suggest that rBHT may potentially reduce BP, particularly among women exhibiting menopausal symptoms, and could have a positive effect on blood viscosity as well as TC and LDL. There is also preliminary evidence that rBHT may prevent the progression of CIMT, especially among women within 6 years of beginning menopause (Hodis et al., 2016).

It is important to note that all of the reviewed studies used biomarkers as primary indicators of CVD instead of actual cardiovascular events. The low incidence of cardiovascular events that was reported in the trials (as adverse effects), although encouraging, may reflect the relatively short follow-up period (≤6 months) in several studies and the prolonged time required for CVD to develop and cardiovascular events to occur. In addition, a couple of the rBHT and CVD trials were limited by small sample sizes (Panazzolo et al., 2016; Villa et al., 2011). As such, the study findings must be applied with caution to clinical practice related to rBHT use in the prevention of CVD.

**Implications for Practice**

Women experiencing disruptive VMSs are looking for treatment alternatives that do not compromise their heart health. Clinicians, including physicians, nurses, nurse practitioners, and midwives, play key roles in screening and managing VMSs, addressing women’s unique health histories, and supporting an informed decision-making process. With this narrative review, we aimed to update clinicians regarding the current evidence surrounding rBHT so that they can better support women in making informed choices.

Nurses, midwives, and other clinicians who provide care to women will need to clarify that the current evidence is limited.
to only regulated types of bioidentical HT. The safety and efficacy of unregulated bioidentical HT created by compounding pharmacies is uncertain. Additionally, recommendations related to rBHT are, at present, only supported by studies conducted with menopausal and postmenopausal women. Perimenopausal women may not experience the same outcomes and side effects. Overall, rBHT does appear to have a high safety profile with few serious adverse events reported within the first 6 years of treatment. The long-term implications of rBHT with regard to female reproductive cancers, or other serious complications, however, remains to be determined.

Given the uncertainty with regard to the benefits and risks of rBHT across the menopausal trajectory and in comparison to sHT, it is essential that nurses, midwives, and other clinicians closely monitor women’s responses to treatment with frequent follow-ups that focus on patient-reported outcomes and cardiovascular biomarkers. Regular cancer screening will also be an important part of rBHT management. For women considering switching from one form of HT to another, a conversation about motivations and expectations is warranted, as is a discussion about other relevant factors, such as accessibility and cost of treatment. Finally, it is important to note that the conclusions drawn from this review related to the safety and efficacy of rBHT cannot be uncritically applied to transgender people, who may be concerned about the management of VMSs and preventing CVD.

Implications for Research

To date, most of the research on HT has focused on sHT options. The science surrounding rBHT has not expanded quickly enough to meet the growing demand and interest. Large, rigorously designed, placebo-controlled clinical trials that consider regulated and unregulated types of bioidentical HT are required, as are studies that directly compare rBHT to sHT. Moreover, replication studies using the same dosages, types, and routes of rBHT are urgently needed to inform future practice recommendations. Developing longitudinal cohort studies would also provide further evidence regarding the association between rBHT and serious adverse events with delayed onset, such as heart attack, stroke, and cancer.

Conclusion

Menopause can be an exceptionally challenging time of life. Frequent and sometimes severe VMSs and the potential decline in cardiovascular health can threaten women’s QOL and overall health and well-being. HT has been marketed to women as a possible solution; however, the potential risks of sHT have led many women to consider bioidentical HT as an alternative. Presently, the research surrounding rBHT is still in its nascent phase and provides preliminary support for the efficacy and short-term safety of rBHT. Continued advancement of this field of study is urgently needed to ensure that women’s choices are informed by the highest quality of evidence to allow them to achieve the best QOL possible.

Supplementary Materials

Note: To access the supplementary material that accompanies this article, visit the online version of Nursing for Women’s Health at http://nwhjournal.org and at https://doi.org/10.1016/j.nwh.2022.01.012.

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