Best practices in care for menopausal patients: 16 years after the Women’s Health Initiative

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ABSTRACT

The Women’s Health Initiative (WHI) was a large, randomized clinical trial funded by the National Institutes of Health to determine whether menopause hormone therapy (MHT) prevented heart disease, breast and colorectal cancer, and osteoporotic fractures in postmenopausal women. Two WHI trials were stopped early, and the findings had a profound effect on the clinical practice guidelines related to postmenopausal health. This article provides an overview of the WHI MHT clinical trials and findings, discusses the early stoppage of the trials and subsequent implications, and details the current nomenclature and treatment options for women transitioning through menopause in light of the WHI. This study is based on a comprehensive literature review and an education activity developed by the American Association of Nurse Practitioners. To best serve patients and individualize therapy, clinicians must provide the best estimate of potential risks or benefits to the individual patient. It is important to balance evidence of symptom relief with long-term risks and benefits that fit the patient’s characteristics of family and personal health history. Armed with evidence to support various hormonal and non-hormonal options, well-informed clinicians can counsel women about MHT and potentially avoid negative impact on quality of life.

Keywords: Hormone therapy; menopause; Women’s Health Initiative.

Introduction

Women’s Health Initiative: context and background

This article provides an overview of the Women’s Health Initiative (WHI) menopause hormone therapy (MHT) clinical trials and findings, discusses the early stoppage of the trials and subsequent implications, and details the current nomenclature and treatment options for women transitioning through menopause in light of the WHI. The WHI was a large, randomized clinical trial funded by the National Institutes of Health to determine whether MHT prevented heart disease, breast and colorectal cancer, and osteoporotic fractures in postmenopausal women. The WHI was launched at a time when observational studies suggested a protective effect of estrogen on the heart and bones of postmenopausal women. The initiative’s purpose was to determine whether postmenopausal hormone therapy should be prescribed for cardio- and osteoporosis protection for all women.

Estrogens were first approved by the US Food and Drug Administration (FDA) in 1942 for treating menopause-related symptoms, particularly vasomotor symptoms. By 1975, estrogen formulations were one of the most commonly prescribed drugs in the United States, and in 1992, the American College of Physicians published guidelines, advising postmenopausal women with previous hysterectomy and women at risk for coronary heart disease (CHD) that hormone therapy would likely be beneficial (Ghazal & Pal, 2013). By 1995, an estimated 37% of women aged 50 years or older reported using an estrogen formulation, with or without a progesterone formulation, in part because it was considered cardioprotective (Grant et al., 2015). At the onset of the study, conjugated equine estrogen (CEE) + medroxyprogesterone acetate (MPA) or CEE alone was the most widely used form of MHT.

Women’s Health Initiative: overall timeline, research goals, and design

The study, which began in 1991 and was to end in 2005, included the MHT clinical trials, an observational study, and two extension studies from 2005 to 2010 and 2010 to 2015 (Women’s Health Initiative, 2017). Research goals of the WHI were to 1) determine the efficacy of MHT on nonfatal myocardial infarction and death; 2) determine the safety or risk of MHT for invasive breast cancer; and 3) determine secondary outcomes on osteoporosis,
stroke, pulmonary embolism, venous thromboembolism, colorectal cancer, endometrial cancer, and mortality. Eligibility criteria for the hormone therapy clinical trials were designed to ensure participant safety but to be as inclusive as possible. Inclusion criteria were age 50–79 years and postmenopausal, and a 20% minority enrollment rate was set for all study components to accurately represent the proportion of minorities in the United States (17% in 1990) (Hays et al., 2003). Exclusion criteria were no history of hypertriglyceridemia, endometrial cancer, abnormal mammography, or myocardial infarction within the past 6 months. Global exclusion criteria included medical conditions that would be predictive of survival of less than 3 years or any characteristics or conditions that may diminish study adherence, such as substance abuse, mental illness, or cognitive impairment (Prentice et al., 1998). Cardiovascular risk factors such as hypertension and deep vein thrombosis were not exclusion factors, because MHT was thought to be cardioprotective Figure 1.

Women’s Health Initiative: hormone therapy trials design

Women with previous hysterectomy (N = 10,739) were randomized to either CEE (commonly known as Premarin) or placebo. For this group, the intervention lasted 7.2 years. Post-intervention follow-up and cumulative follow-up were 6.6 and 13 years, respectively. Women with an intact uterus (N = 16,608) were randomized to either CEE + MPA (commonly known as Prempro) or placebo. The intervention phase lasted 5.6 years; post-intervention follow-up and cumulative follow-up were 8.2 and 13.2 years, respectively (Manson et al., 2013).

Early stoppage of the hormone therapy trials. The CEE + MPA trial was stopped early (in 2002) by the WHI Data Safety and Monitoring Board because the test statistic for invasive breast cancer exceeded the stopping boundary for this adverse effect. Increases (29%) in coronary events were also noted, and the global index statistic supported risks exceeding benefits. The CEE trial was stopped in 2004 by the National Institutes of Health on the basis that the length of the trial had been sufficiently long to conclude that risks exceeded benefits and CEE should not be used as a treatment choice for preventing chronic disease. Results also indicated an increased risk of stroke.

Compared with placebo, the CEE + MPA treatment resulted in an increased risk of heart attack, stroke, blood clots, and breast cancer. The treatment group demonstrated a reduced risk of colorectal cancer and fewer fractures. For women in the study over age 65 years, treatment with CEE + MPA demonstrated no protection against mild cognitive impairment or increased risk of dementia.

Compared with women in the placebo group, those in the CEE treatment group had no difference in risk for heart attack or colorectal cancer, but they did have increased risk of stroke and blood clots. They had uncertain effect for breast cancer and reduced risk of fracture. The global index finding indicated no overall significant change in risk in the CEE treatment group compared with that in the placebo group (Women’s Health Initiative Steering Committee, 2004).

Impact of early stoppage of Women’s Health Initiative. When the WHI investigators announced early stoppage of the CEE + MPA trial, there was an immediate and widespread impact on patients and health care providers. The warnings about increases in cardiovascular disease and breast cancer with MHT alarmed many and were extrapolated to all MHT regardless of formulation, dose, or timing of treatment (Brown, 2012). The results were publicized as pertaining to women of all ages, and the findings contradicted widely practiced medical beliefs that hormone therapy was cardio- and osteoprotective in postmenopausal women (Pedersen & Ottesen, 2003). The ensuing media frenzy resulted in a precipitous and sustained drop in prescriptions for all forms of MHT (Corbelli & Hess, 2012). Numerous clinicians advised women to stop their MHT, which had a profound

impact on health-related quality of life; within days to weeks, many who suddenly stopped their treatment began experiencing menopausal symptoms, particularly hot flashes, depression, mood changes, and sleep disruption. Within 18 months of study publication, half of the women in the United States using MHT stopped treatment, including hysterectomized women using estrogen formulations that did not include the study drugs (Sprague, Trentham-Dietz, & Cronin, 2012).

Initial findings by the WHI also had a far-reaching effect on clinical practice guidelines related to postmenopausal health. Menopause treatment guidelines from authorities such as the North American Menopause Society, the American College of Obstetricians and Gynecologists, the American Association of Clinical Endocrinologists, and the National Institute for Health and Care Excellence help standardize the treatment for menopausal symptoms. All these guidelines are resources for clinicians and all are informed by findings from the WHI.

A research study of the size and importance of the WHI also affects health policy decisions. Before the early stoppage of the trials, it was a standard belief that MHT was cardio- and osteoprotective in postmenopausal women. The evidence from the WHI contradicted previous thinking, so health policy subsequently reflected using MHT in the lowest dose for the shortest possible duration limited to no more than 5 years. The US Preventative Services Task Force published recommendations against the use of estrogen and progestin therapy for the primary prevention of chronic conditions in postmenopausal women (Ghazal & Pal, 2013).

**Subsequent analyses of the Women's Health Initiative data**

Since the initial publication of WHI findings, subsequent analyses of the primary outcome measurements of CHD and breast cancer have shed some additional light on risks and benefits of MHT. Of mention, the primary age group that presents with new onset of menopausal symptoms are women in the early menopause transition (MT) phase, typically in their late forties or early fifties. Most MHT clinical trial data, however, are from women older than 60 years, despite newer evidence that the risk–benefit profile may be more favorable for women aged 50–59 years compared with older women (Manson et al., 2013).

**Coronary heart disease.** Multiple secondary analyses have concluded that the risk of CHD depends on the timing of initiating hormone exposure and the age of a woman at the time of its initiation. These new findings determined that CHD was trending toward a reduction in younger women within 10 years of menopause and that increased risk was confined to older women or women initiating therapy furthest from menopause (LaCroix et al., 2011; MacLaren & Stevenson, 2012; Rossouw et al., 2007).

Coronary heart disease risks with CEE were lower across ages, but there was a higher risk of nonfatal MI in older women. Women in the CEE-alone treatment group did not demonstrate different risks significantly by year, and post-intervention results were neutral. Risk versus benefit during the treatment phase of a clinical trial may differ from post-intervention phase(s) because there may be changes in risk once the treatment exposure is over. Time since treatment may also make a difference. Notably, women in the CEE-alone treatment group aged 50–59 years had significantly lower CHD risk and a significant reduction in breast cancer over time.

Women in the CEE + MPA group, however, were 80% more likely to develop CHD at year one than women receiving placebo (hazard ratio [HR], 1.80; 95% confidence interval [CI], 1.08–2.99). Compared with the placebo group, risks were higher in this group at treatment, neutral during post-intervention, and slightly exceeded placebo for cumulative follow-up (Manson et al., 2013).

Although CEE + MPA was stopped in the WHI because increased cardiovascular risk occurred, it is not necessarily that estrogen-mediated protection is invalidated (Moolman, 2006). There is scientific evidence for the protective effect of estrogen against atherosclerosis, such as short-term vasodilating effects and long-term vascular protective and anti-atherosclerotic effects (Moolman, 2006). More recent research suggests that a longer reproductive lifespan is associated with a lower estimated risk of CHD in the next 10 years for postmenopausal women, suggesting that estrogen has a long-term protective effect against CHD (Kim, Sim, & Park, 2015).

**Breast cancer.** For women in the CEE treatment group, there was a trend toward breast cancer risk reduction, though not statistically significant during the intervention phase; yet, the risk reduction became statistically significant during cumulative follow-up (HR, 0.79; 95% CI, 0.65–0.97) (Manson et al., 2013). Women in the CEE + MPA treatment group were 24% more likely to develop breast cancer than those in the placebo group (HR, 1.24; 96% CI, 1.10–1.53). The risk of breast cancer remained significantly elevated for the CEE + MPA treatment group during post-intervention and cumulative follow-up compared with the placebo group (HR for cumulative follow-up, 1.28; 95% CI, 1.11–1.48).

**Menopause symptom management**

Symptoms associated with the MT (early MT to late postmenopause) are well identified and reported (e.g., Elavsky & McAuley, 2009; Luoto, 2009). The most commonly identified symptoms are vasomotor symptoms (hot flashes, night sweats), sleep disruption, vaginal symptoms (dryness, dyspareunia with intercourse), nervous symptoms (anxiety, depression), and memory problems. In deciding whether MHT is right for symptomatic women, informed decision making by patients...
and their providers should consider age, patient and family history of risk, and degree of bothersome menopause-related symptoms present.

The most recent North American Menopause Society position statement on MHT proposes an individualized, evidence-based approach to determine the appropriate type, dose, route, and duration based on the unique goals and health risks of the woman (Pinkerton, 2017). This is in stark contrast to past recommendations of lowest dose of MHT for the shortest amount of time.

Types and forms of menopausal hormone therapy

The three major classes of reproductive hormones are estrogens, progesterones, and androgens, with estrogens and progesterones among the most commonly prescribed hormones for treating symptoms of MT (Files, Ko, & Pruthi, 2011). These hormones are available in a broad array of FDA-approved and non-FDA-approved formulations. When researching estrogen, progesterone, and androgen therapies, a clear understanding of the formulation(s) types the author(s) is referring to is essential for the interpretation of data because different types of hormone preparations and routes of administration are associated with distinct metabolic effects. The essential message is that generalizations from research results cannot be made from one preparation or route of administration to another (Table 1).

Food and Drug Administration-approved bioidentical and non-bioidentical hormone preparations. The FDA-approved hormone compounds include those that fulfill the definitions of bioidentical and non-bioidentical formulations (Table 2). These products may be formulated singly or in combination with various forms of estrogens and progesterones (Files et al., 2011).

Bioidentical hormones have been defined in the literature as exogenous hormones biologically identical to those produced in the ovaries and elsewhere in the human body (Files et al., 2011; Pinkerton, 2015). Bioidentical hormone formulations, such as estradiol, progesterone, and testosterone, are generally derived from soy and yam plants; the plant product is chemically altered to become a therapeutic agent for humans (Pinkerton, 2015). Non-bioidentical hormone preparations include synthetic conjugated estrogen (CE) or synthetic CEE and synthetic progestins (Files et al., 2011).

Compounded bioidentical hormone preparations are non-FDA approved, yet are widely used and marketed as safer and more efficacious alternatives to conventional,

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<tr>
<th>Table 1. Estrogen and Progesterone Preparations</th>
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<td>Type of Preparation</td>
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<td>Endogenous</td>
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<tr>
<td>Synthetic/Animal and Plant Derived</td>
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<th>Table 2. Food and Drug Administration-Approved Bioidentical and Non-Bioidentical Therapies</th>
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<td>Type of Therapy</td>
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<td>Oral</td>
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<tr>
<td>Estradiol</td>
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<td>Micronized progesterone</td>
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<td>Synthetic conjugated estrogens</td>
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<td>Conjugated estrogens</td>
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<td>Progestins</td>
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synthetic hormone therapies. To date, there are no long-term, large studies to support these claims (Files et al., 2011; Pinkerton, 2015). Though not approved by the FDA, compounded bioidentical testosterone preparations are highly FDA regulated and compounding pharmacies now face rigorous standards and regulations in custom-compounding these agents.

**Types and uses of estrogen.** The endogenous estrogens found in humans include 17β-estradiol, estriol, estrone, and their conjugates. Estrogens are available in many formulations and routes of administration, which have similar efficacy for symptom relief, although their metabolic effects differ; differences also exist between synthetic and bioidentical formulations of estrogens, because the mechanism of action in the body differs greatly.

Evidence from systematic reviews and guidelines support estrogen as effective in treating moderate to severe vasomotor symptoms and symptomatic vaginal atrophy and in preventing postmenopausal osteoporosis in women transitioning through menopause; estrogen therapy remains the gold standard for relief of menopausal symptoms (North American Menopause Society, 2012; Shanafelt, Barton, Adjei, & Loprinzi, 2002). Some formulations of estrogen have been shown to improve lipid parameters, improve insulin resistance, and lower blood pressure, thus reducing the risk of CHD.

Oral estrogen preparations metabolize via the “first-pass” mechanism through the liver, thereby reducing the systemic bioavailability of the hormone to 2–10% (O’Connell, 1995). The major differences between oral and transdermal administration lie in the metabolic changes produced by the first-pass effect and are expressed most notably in the cardiovascular system (Stevenson, 2009). The first-pass metabolism of oral estrogens has favorable effects on lipid parameters, insulin resistance, and inflammatory markers, but less favorable effects on triglycerides and clotting factors (Stevenson, 2009) (Table 3).

Generally, transdermal 17-beta estradiol delivery has a more physiologic, systemic effect and a decreased risk of deep vein thrombosis, stroke, and myocardial infarction, secondary to the decreased clotting risks compared with oral administration (Stevenson, 2009). Transdermal administration has shown no effect on insulin resistance compared with oral preparations, and transdermal routes have been shown to be superior in reducing triglycerides (Stevenson, 2009). Both oral and transdermal routes have been shown to decrease circulating angiotensin-1 converting enzyme, thereby lowering systemic blood pressure (Stevenson, 2009). Compounded subcutaneous estradiol pellets are available in the United States, but like all forms of compounded hormone preparations, they have not been widely studied.

Preliminary studies comparing oral 17-beta estradiol with CEE showed a greater risk of venous thromboembolism and myocardial events in the CEE group, suggesting not only the route but also the type of estrogen administration may be important to consider (Smith et al., 2014). It is important to note that the addition of certain progestins (synthetics) may reverse the positive impact oral estrogens have on serum lipids because of increased hepatic lipase activity, and some progestin preparations may increase insulin resistance (Stevenson, 2009). Consideration of oral micronized progesterone (MP) in lieu of progestins such as MPA may prove beneficial in protecting the positive effects seen with oral routes of 17-beta estradiol.

Low-dose vaginal preparations of estrogen are beneficial for women to improve symptoms of genitourinary syndrome with few, if any, systemic effects (Portman & Gass, 2014). These preparations are useful in women who,

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**Table 3. Effects of Oral, Transdermal, and Vaginal Estrogens**

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<th>Oral Estrogens</th>
<th>Transdermal Estrogens</th>
<th>Vaginal Estrogens</th>
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<tr>
<td>More favorable effects on lipid profiles&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Associated with lower risk of VTE, stroke, and hypertriglyceridemia</td>
<td>Low-dose ring topical spray, gel, cream for atrophy</td>
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<tr>
<td>Higher risks of VTE and stroke&lt;sup&gt;b&lt;/sup&gt;</td>
<td>As effective as oral estrogens for preserving bone density</td>
<td>High doses for vasomotor symptoms</td>
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</tbody>
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<sup>a</sup>Chetkowski, R. J. et al. (1988). New England Journal of Medicine, 314, 1615. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

based on medical history, cannot or do not desire oral, transdermal, or other therapies that increase systemic estradiol levels. In a systematic review examining the efficacy of vaginal estrogen preparations, it was noted that compared with placebo, vaginal estrogens improved vaginal dryness, dyspareunia, urinary urgency, urinary frequency, stress urinary incontinence, and urgency urinary incontinence, and also decreased the rates of urinary tract infection (Rahn et al., 2014). Formulations most commonly prescribed include topical sprays, gels, and creams; higher doses of vaginal estrogen can also be used to treat vasomotor symptoms (O’Connell, 1995; Santen, 2015).

**Types and uses of progesterone.** Synthetic forms of progesterone, known as progestins (or progestogens), are often mistakenly referred to in the literature as progesterone; however, only bioidentical or MP preparations are correctly referred to as progesterone. Progesterone and progestins are different types of hormones with distinctly different mechanisms of actions, metabolic effects, and side effect profiles. For instance, progesterone is progestational, whereas progestin, most commonly prescribed as MPA, is teratogenic. Furthermore, researchers note that MPA may have accounted for the early deleterious outcomes seen in the CEE/MPA arm of the WHI (Anderson et al., 2004; Rossouw et al., 2002).

Studies have demonstrated the efficacy of oral MP in conferring endometrial protection and decreased vaginal bleeding with minimal impact on lipid profile and minimization of breast cancer risk compared with MPA and other synthetic formulations (Ghazal & Pal, 2013; Stevenson, 2009). Unopposed estrogen use in women with an intact uterus increases the risk for endometrial hyperplasia and endometrial cancer (Schmidt, 2012). Combination hormone therapy with estrogen plus progesterone is the standard of care for MHT in women with an intact uterus. Other forms of progesterone include non–FDA-approved bioidentical cream, sublingual rapid dissolve tablets, and injectable formulations.

**Types and uses of testosterone.** Androgen receptors are found on virtually every cell in the female human body, indicating the role they play in normal tissue homeostasis (Elrayah et al., 2014). Produced primarily in the ovaries and adrenals, the chief androgen, testosterone, declines rapidly in the perimenopausal years. Androgen therapy is not approved by the FDA for use in women and has been used off-label in the United States and globally in MHT for decades (Bolour & Braunstein, 2005). Therapy options include oral synthetic and bioidentical preparations, bioidentical subcutaneous pellet implants, intramuscular preparations, transdermal patches, creams, gels, and sprays, as well as sublingual drops and tablets (Bolour & Braunstein, 2005).

Androgen use in women has been shown to improve mood, lift anxiety and depression, improve deep sleep patterns, and enhance sexuality (Barrett-Conner et al., 2008; Ebinger, Sievers, Ivan, Schneider, & Stalla, 2009; Glaser, York, & Dimitrakakis, 2010; Studd & Panay, 2004). Androgen therapy has been shown to increase bone and muscle mass, improve cognitive function, and increase the overall sense of well-being (Spolenti et al., 2014). In a systematic review investigating testosterone and androgen levels in women were associated with poorer cardiovascular health (Davis & Wahlin-Jacobsen, 2015; Spolenti et al., 2014). Observational data suggest that low free and total testosterone and low sex hormone binding globulin levels are associated with a higher risk of cardiovascular events, carotid atherosclerosis, and all-cause mortality (Davis & Wahlin-Jacobsen, 2015). Studies of testosterone administered by a subcutaneous implant, transdermal patch, or spray have not revealed altered levels of lipids, C-reactive protein, or glycosylated hemoglobin or worsened insulin sensitivity (Wierman et al., 2014).

Large-scale studies of the action and effects of testosterone in women have not been conducted to provide concrete evidence of safety and efficacy (Davis & Wahlin-Jacobsen, 2015), especially related to the various formulations and modes of delivery available. Consensus on what constitutes normal serum levels of testosterone, and the best method for testing these levels, has not been attained (Davis & Wahlin-Jacobsen, 2015). We need large randomized controlled trials to substantiate or refute previous observational reports before FDA approval can be attained. Until then, off-label use is likely to continue, as women seek medical assistance with menopausal symptoms related to androgen deficiency such as decreased libido.

**Non-hormonal therapies**

**Food and Drug Administration–approved and non–Food and Drug Administration–approved preparations.** For some women, traditional MHT is not an option because of personal or family history of breast cancer, or CHD, or because of personal preference. The first line of defense for these symptomatic women is lifestyle modifications such as smoking cessation, reducing alcohol use, increasing physical activity, and attaining a healthy weight. These strategies are all associated with the reduction in vasomotor symptoms and increased overall health (Al-Safi & Santoro, 2014). Selective serotonin reuptake inhibitors (SSRIs) have shown a modest effect in relief of vasomotor symptoms, and currently, the only FDA-approved SSRI to treat vasomotor symptoms is low-dose paroxetine. Tissue-selective estrogen complex combines a selective estrogen receptor modulator with a CE to mitigate tissue-specific adverse effects of estrogen (Pinkerton, Kommm, & Mirkin, 2013).

**Conclusion**

A robust understanding of the WHI and the impact of the trials on treatment options, guidelines, and health policy...
is imperative for any health care provider managing their patients through the menopausal transition. A profound impact of the WHI results was the extrapolation of the data using CEE and CEE/MPA to all forms of MHT, leaving many health care providers and their patients confused about how to safely transition during this key time in a woman’s life. Hormone preparations using CEE and MPA have vastly differing effects on the body than 17-beta estradiol and MP; a critical concept for practitioners is to understand these differences and not assume a single class effect of all hormone treatment modalities.

Since the early stoppage of the WHI, menopause symptom treatment has focused on symptom relief with the lowest dose hormone regimen for the shortest possible time. Current research on MHT is focused on theories of timing, dose, and route of administration to further clarify the risks and benefits to hormone options. The role of testosterone in menopausal women’s quality of life, mood, and sexual health warrants research focus to firmly establish safety and efficacy and potentially move testosterone treatment to FDA approval rather than off-label use. Compounded bioidentical hormone therapy, though not evidence based, requires rigorous study because it is appealing to many symptomatic women. Armed with evidence to support various hormonal and non-hormonal options, women could more confidently seek advice and treatment from well-informed clinicians and potentially avoid a negative impact on quality of life.

**Clinical case study**

MS is a 50-year-old woman who presents with the following clinical picture.

- **Chief subjective complaints:** Extreme fatigue, “brain fog,” mood swings, depression and anxiety, night sweats, insomnia, vaginal dryness with painful intercourse, and low libido. All her symptoms affect her personal and professional relationships.
- **Gynecologic history:** Last menstrual period 9 months ago, before that menses had been sporadic for over a year. Mammogram and pap up to date and unremarkable. G3P3 uncomplicated vaginal births.
- **Medical history:** Unremarkable.
- **Family history:** Paternal grandmother with breast cancer diagnosis at age 70 years, unknown type, deceased; mother aged 72 years, alive, with heart disease and diabetes; father aged 78 years, alive, with mild dementia.
- **Social history:** Occasional wine drinker (2–3 glasses per week); sedentary lifestyle, though previously active.
- **Occupation:** Customer service for an IT company.
- **Medications:** Recent SSRI from gynecologist 2 months before subjective symptoms, with no relief.
- **Laboratory results:** Complete blood count and comprehensive metabolic panel unremarkable; Thyroid panel within normal limits or parameters; follicle stimulating hormone, 78 IU/L; estradiol level, 12 pg/ml; testosterone, 15 ng/dl; Vitamin D3, 22 ng/ml.

**Diagnosis:** Hormone insufficiency or perimenopause.

**Food and Drug Administration-approved treatment options:** 1) 17-beta estradiol (via various routes) with oral MP; 2) low-dose vaginal estrogen preparation with oral MP; 3) selective estrogen receptor modulator or CE combination with oral MP; and 4) lifestyle modifications—eliminate alcohol, sugars, and processed foods, and re-institute regular exercise.

**Discussion**

MS has an elevated follicle stimulating hormone and low estradiol levels, indicating a hormonally deficient state; however, she did not complain of hot flashes and she had a menstrual cycle within the past year. Furthermore, many of her other presenting symptoms are not commonly regarded as hormone related. Women in the MT, such as MS, do not routinely present with the common complaints of menopause, and often vague symptoms are overlooked as stress or diet and exercise related, leaving women with few treatment options and a feeling of despair that the rest of their lives will continue a downward spiral. It is extremely helpful for women to understand their vague symptoms are not uncommon, thus “normalizing” their symptoms and feelings.

The clinical picture of MS is fairly common, and it is vitally important that health care providers open the dialogue with their female patients regarding the encumbering impact of the MT. Improving overall sense of well-being and health-related quality of life is a Healthy People 2020 goal, and guiding women through the MT with an individualized, evidence-based approach can have far-reaching impact not only on the individual but also on the family unit and communities as a whole.

**Authors’ contributions:** Terri DeNeui, Judith Berg, and Alexandra Howson developed the content and edited and revised the manuscript.

**Competing interests:** The authors report no conflicts of interest.

**References**


