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REVIEW

A Review of Hormone and Non-Hormonal Therapy Options for the Treatment of Menopause

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Abstract: Understanding the role of both menopausal hormone therapy (MHT) along with non-hormonal options for the treatment of vasomotor symptoms, sleep disruption, and genitourinary symptoms after menopause is critical to the health of women during middle and later life. Recent updates to the evidence for the treatment of menopausal symptoms pertaining to both hormonal and non-hormonal therapies as well as updated guidance from specialty societies can help guide clinicians in their treatment of women going through natural menopause or with estrogen deficiencies due to primary ovarian insufficiency or induced menopause from surgery or medications. The objective of this narrative review is to provide clinicians with an overview of MHT for the use of menopausal symptoms in women, incorporating updated primary evidence for risk versus benefit profiles, recent specialty society recommendations, and alternative, non-hormonal options. In this review, we summarize literature on the use of MHT for menopause-related symptomatology including options for formulations and dosages of MHT, non-hormonal treatment options, and the risk–benefit profile of MHT including long-term health consequences (eg, cardiovascular disease, cognitive decline, venous thromboembolism, and fracture risk). Finally, we highlight areas in which future research is needed to advance care of women after menopause. In summary, both hormonal (MHT) and non-hormonal options exist to treat symptoms of menopause. There is strong evidence for safety and effectiveness of MHT for the treatment of vasomotor symptoms among women who are less than 60 years of age, less than 10 years since menopause, and without significant cardiometabolic comorbidities. For others, treatment with hormonal versus non-hormonal therapies can be considered based on individual risk profiles, as well as other factors such as drug formulation, therapeutic goals, and symptom severity.

Keywords: menopause, hormone therapy, cardiovascular disease, stroke

Introduction

Understanding the use of exogenous hormones for the treatment of menopausal symptoms (ie, menopausal hormone therapy (MHT))[1] is of critical importance to the health of women, especially given that women spend approximately 40% of their lives post-menopause.[2] Postmenopausal symptoms that can be treated with MHT include vasomotor symptoms (VMS) (eg, hot flashes, night sweats), sleep disturbances, sexual dysfunction, and genitourinary tract symptoms (eg, vulvovaginal atrophy, dyspareunia, urinary frequency).[2] In addition to the treatment of menopausal symptoms, MHT may improve bone health among women after menopause, especially those with osteopenia or elevated risk of fracture.[3]

Notably, the temporal patterns of utilization of MHT have changed. Specifically, between the late 1980s and early 2000s, the rate of MHT use decreased precipitously following the publication of results from the Women's Health Initiative (WHI) hormone clinical trials demonstrating an increased risk of coronary heart disease (CHD) and stroke among those randomized to MHT.[4,5] Consequently, the rates of MHT use decreased from approximately 22% in 1999 to 5% in 2010 among women 40 years or older in the United States,[6] while other studies cite rates as low was 3%.[6,7]

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Despite the rapid decline in utilization of MHT after the turn of the century, more recent recommendations[3,8] based on additional evidence have further clarified the subgroups of women in whom the benefits of MHT for VMS and bone health exceed the risks.

Objectives

Given the current evidence base on the likely benefit of MHT in specific subgroups of women, a recent increased focus on outcomes such as cognitive function, and the continued emergence of non-hormonal options for treating symptoms of menopause, the objective of this narrative review is to provide clinicians with an overview of MHT and alternative, non-hormonal options for the use of menopausal symptoms in women, incorporating updated primary evidence for risk versus benefit profiles and recent specialty society recommendations.

Methods

This is a narrative review, designed to summarize the relevant literature for use by physicians and providers with peri- and postmenopausal female patients. To achieve our objectives, and following a review of the physiology of menopause, we performed a review to summarize key literature on the use of MHT for menopause-related symptomatology in peri- and postmenopausal women, options for formulations and dosages of MHT, non-hormonal treatment options for symptoms of menopause, and the risk–benefit profile of MHT (including its various formulations and routes of delivery) with respect to long-term health consequences such as cardiovascular disease (CVD), cognitive decline, venous thromboembolism, and fracture risk. The content described in this review pertain to individuals categorized as female at birth based on biologic criteria; namely the presence of two X sex chromosomes and ovaries. More research is needed to help understand the risks and benefits of MHT for transgender and non-binary individuals.

The Physiology of Menopause

Natural menopause is defined as the cessation of ovarian function with 12 consecutive months of amenorrhea. Based on an international pooled analysis of cross-sectional and observational data of 234,811 women, the median age of natural menopause is 51 years.[9,10] When natural menopause occurs before 40 years of age (as seen in approximately 1.9% of women), it is considered premature. If it occurs between the ages 40 to 45 years, it is considered early, and greater than 55 years is considered late.[9] Importantly, the transition to menopause is variable, as it occurs over 1 to 3 years and involves complex changes in physiology.[11] Moreover, hormonal changes and symptoms during the menopause transition are not always linearly correlated, highlighting the need for individualized assessment and care.[12] In addition, premature and early menopause differ pathophysiologically from natural menopause occurring at a typical age.[11]

The perimenopausal stage is characterized by the onset of menstrual cycle irregularities or other menopause-related symptoms and extends to 12 months after the cessation of menstruation. This stage encompasses the most symptomatic years, and menopause symptoms often develop before significant changes in menstrual cycles or hormone levels. Typically, physiologic changes in the early perimenopausal stage are associated with a low antral follicle count, which drives changes in estradiol, an increase in follicle-stimulating hormone (FSH), and to a lesser extent, decreases in anti-mullerian hormone and inhibin B.[2,11] In this regard, FSH has been implicated in contributing to the adiposity and cardiometabolic changes in the postmenopausal period.[13] Prospective studies, such as the Study of Women Across the Nation (SWAN) study, have demonstrated different patterns of change in these hormones surrounding the menopause transition, based in part on body size and race/ethnicity.[14,15] For example, estradiol first slowly increases leading up to the perimenopausal stage then sharply decreases within one to two years of menopause in approximately 45% of women, while it slowly declines or remains relatively steady in other women.[14,16] Even the hallmark increase in FSH can be variable, as it may first trend upward in a step-wise manner as follicle counts decline, then sharply increase within one year of menopause.[10,17]

The variability in natural menopause is different from primary ovarian insufficiency (POI); a distinct condition in which there is a loss of ovarian function before age 40.[3] In POI, there is still a potential for intermittent ovulation and menstrual cycles, but with insufficient reserve. In contrast, premature and early menopause are defined by permanent stopping of menstruation.[3] Surgically-induced menopause, such as via surgical bilateral salpingo-oophorectomy, or

menopause induced by chemotherapy or radiation, causes prompt and dramatic changes in hormonal levels and symptoms unlike other menopause transitions.[18] Premature, early, and surgical menopause confer a higher risk for incident CVD and earlier mortality.[2,17,19] Guidelines from several medical societies endorse treatment with MHT for women with premature or induced menopause, unless contraindicated, with the recommendation to continue treatment until at least the median population-based age of menopause.[2,3,20]

Menopause as a Critical Life Course Event

Menopause is a critical event in the life course for women, both in terms of physiologic changes as well as the effects that such changes have on quality of life. Data from SWAN indicate that the median total length of VMS is 7.4 years, with a median length of symptoms after the final menstrual period of 4.5 years.[21] Symptoms across the menopausal transition in addition to VMS include depressed mood and changes in sexual function.[22] Data on sleep quality and duration conflict; though insomnia is associated with VMS,[23] other data suggest that sleep duration does not decrease significantly over the menopause transition.[24]

The body composition and cardiometabolic changes associated with the menopause transition are well established. The increase in low-density lipoprotein cholesterol, changes in distribution of adiposity (ie, increased central and visceral adiposity), higher risk for metabolic syndrome, and decline in endovascular function that occur during midlife are linked to adverse outcomes and are likely more related to the menopausal transition than to aging.[25–28] MHT, in contrast to non-hormonal treatments, partially counters some of these metabolic shifts. However, MHT does not fully restore the premenopausal hormonal milieu, given the complexities of reproductive and biologic aging, and has a complex pattern of benefits and risks that vary by MHT formulation, dose, and risk factor profile of the patient. In this respect, the literature supports specific timing for the initiation of MHT use, such that it should be started before age 60 or within 10 years of menopause, as initiation after this time may increase risk of CVD and have a less favorable benefit-to-risk ratio.[2,20]

Menopausal Hormone Therapy: Formulations

MHT is FDA-approved for four indications in menopausal women: VMS, prevention of bone loss, premature hypoestrogenism, and moderate to severe vulvovaginal symptoms.[3] There are several formulations, doses, and routes of delivery for MHT. As both effectiveness and risk-to-benefit profiles differ by formulation and delivery route, therapy should be individualized based on each patient's own characteristics and personal preferences. Government-regulated, bioidentical hormone formulations, rather than compounded formulations, are recommended due to safety concerns related to untested, unregulated formulations, or atypical routes of administration, such as via pellets or sublingual troches.[3]

Estrogens

Estrogen MHT is available in transdermal, oral, and vaginal formulations. Transdermal estrogen HT can be applied as a patch, gel, or spray. For women without a uterus, estrogen alone can be used. Available estrogen formulations include micronized 17β-estradiol, conjugated equine estrogens (CEE), conjugated estrogens (CE), and ethinyl estradiol. Micronized 17β-estradiol is the same chemical structure as estradiol produced by the ovaries, while the other formulations are synthetic estrogens. When prescribing MHT, it is recommended that the lowest effective dose be used.[3] See Supplemental Tables 1 and 2 for dosing regimens for estrogen MHT.[29]

Systemic Vaginal Estrogens

A vaginal ring is available as vaginal estradiol acetate (12.4 mg or 24.8 mg). The vaginal ring remains in place for 90 days, then is replaced. In women with a uterus, a progestogen must also be used to protect against endometrial cancer.[29]

Local Low-Dose Vaginal Estrogens

Vaginal estrogen at low doses can also be used to treat genitourinary symptoms. It is imperative to distinguish between systemic vaginal estrogen MHT and local, low dose vaginal estrogen therapy for genitourinary symptoms, as systemic vaginal estrogen MHT must be prescribed with a progestogen in women with a uterus to protect the endometrium. Local

low-dose vaginal estrogen therapy does not require a progestogen, as there is minimal systemic absorption, and, therefore, no significant effect on the endometrium. Vaginal estrogens that are used as local low-dose treatment for genitourinary symptoms can be applied as a cream, tablet, insert, or ring. Supplemental Table 3 provides information on formulations and dosing for vaginal estrogens.[29]

Progestogens

For women with a uterus taking systemic estrogen, a progestogen must be added to estrogen therapy to protect against endometrial cancer.[3] The available progestogen formulations include micronized progesterone, levonorgestrel, norethindrone acetate, and medroxyprogesterone acetate (MPA). Micronized progesterone is the same chemical structure as progesterone produced by the corpus luteum, while the other formulations are synthetic progestins.[3] Supplemental Table 4, provides information on formulations and dosing for related progestins.[29]

Estrogen–Progestogen Combinations

Combination estrogen-progestogen therapy comes in oral and transdermal formulations. Combination therapy can be taken continuously where the estrogen and progestogen are taken every day, or cyclically where the estrogen is taken every day while the progestogen is taken only for 12–14 days of the month.[29] Supplemental Tables 5 and 6 provide information on formulations and dosing for combination therapies.

Transdermal versus Oral Formulations

It is important to consider potential differences between oral and transdermal formulations of MHT. Though there is no data concerning a difference in the effectiveness of oral versus transdermal MHT for treating VMS,[3] some observational data suggest a lower risk of VTE for transdermal formulations[30,31] (See the Venous Thromboembolism section below). With respect to risk of myocardial infarction, stroke, and breast cancer, clinical trial data are lacking, but the lack of first pass effect in the liver for transdermal formulations is thought to reduce the potential for thrombotic events.[3] Future disaggregated data (oral versus transdermal) and direct comparisons in clinical trials are needed.

Perimenopausal Contraception

An important consideration for women in the perimenopause is contraception. As the menstrual cycles become irregular, the risk of pregnancy decreases but women can still conceive during perimenopause until after 12 months from their final menstrual period. Therefore, women not interested in conceiving and having sexual activities that could result in pregnancy should use a form of birth control. There are several treatments for perimenopausal symptoms that also provide contraception, including a combined oral contraceptive pill, the patch, vaginal ring, or a progestin intrauterine device combined with an oral, topical, or systemic vaginal estrogen. Progestin-only options for women for whom estrogen is contraindicated or not tolerated include an oral, implantable, or injectable progestin.[29]

Non-Hormonal Treatments for Vasomotor Symptoms (VMS)

For women who are unable to or choose not to use MHT to treat VMS, there are several alternative pharmacologic and non-pharmacologic therapy options, but the efficacy is generally lower than MHT. Non-pharmacologic therapies include mind-body techniques such as cognitive behavioral therapy, clinical hypnosis, and mindfulness-based stress reduction. Other techniques include weight loss, exercise, yoga, acupuncture, and paced respirations, but these are not well supported in the literature. Dressing in layers, wearing breathable fabrics, and using fans or cold packs may help women as well, but there is insufficient evidence regarding their efficacy. There is also limited data regarding the efficacy of stellate ganglion blocks in treatment of VMS.[29]

S-equol and other derivatives of soy foods are herbal therapies that have also been used to treat VMS, but evidence regarding their efficacy is mixed. Other herbal therapies include black cohosh, crinum, dioscorea, dong quai, evening primrose, flaxseed, ginseng, hops, maca, omega-3, pollen extract, pine bark, and puerperia, but these have not been shown to improve VMS.[29]

There are various non-hormonal pharmacologic treatments for VMS. These include selective serotonin reuptake inhibitors (SSRI), serotonin norepinephrine reuptake inhibitors (SNRI), gabapentinoids, clonidine, oxybutynin, and neurokinin B antagonists.[29] Paroxetine is an SSRI that is FDA-approved for treating moderate to severe postmenopausal VMS when dosed at 7.5 mg daily, lower than the dose used for psychiatric indications. Side-effects include nausea, dizziness, and fatigue, which are dose-dependent,[29,32] and there are potential medication interactions through CYP enzymes.[33]

Other SSRI and SNRIs with evidence for efficacy in treating VMS include venlafaxine (37.5–150 mg daily), desvenlafaxine (100–150 mg daily), citalopram (10–20 mg daily), and escitalopram (10–20 mg daily). Gabapentin (600–2,400 mg in divided doses) has also been shown to reduce vasomotor symptoms.[34] For gabapentin, side-effects include dizziness, confusion, fatigue, and mood changes. Starting at a lower dose (100 mg daily) may help mitigate such side-effects.[35] Clonidine has also been used to treat VMS, though it has significant adverse effects that limit its use, including hypotension, rebound hypertension when discontinued, headaches, lightheadedness, dizziness, dry mouth, constipation, and sedation.[29] Oxybutynin, an anticholinergic and antimuscarinic medication used to treat overactive bladder, has been shown to be effective in treating VMS at a dose of 2.5 to 5 mg per day extended release.[29] Common side-effects include dry mouth, constipation, and blurred vision.[36] Other data point to an association between anticholinergic medications (such as oxybutynin) and cognitive decline.[37,38]

New and Emerging Therapies

Neurokinin B antagonists are a new class of centrally acting medications for the treatment of VMS.[29] For example, Fezolinetant is an investigational, oral nonhormonal neurokinin-3 receptor antagonist that is currently under FDA review to treat moderate to severe VMS. It targets the kisspeptin, neurokinin B, and dynorphin (KNDy) neurons to help regulate the thermoregulatory centers in the hypothalamus to treat hot flashes and night sweats.[39] The most common side-effect is headache.[40] In the SKYLIGHT 1 Phase 3 RCT, the most efficacious doses for treating moderate to severe VMS were 30 mg or 45 mg daily.[40,41]

Osteoporosis Prevention and MHT

For the prevention of osteoporosis, systemic estrogen MHT is approved via oral or transdermal preparations and is recommended by some specialty societies,[3] but it is not approved as a treatment for osteoporosis. Unfortunately, improvement in bone mineral density and prevention of fracture do not persist after stopping MHT, and this factor should be considered when considering initiating MHT for bone health. Much of the evidence for MHT for prevention of fracture comes from the WHI, where MHT use was associated with a significant reduction in incident fracture risk (28% for any fracture, 31% for vertebral fractures, 24% for non-vertebral fracture),[42] as well as a 4.5% and 3.7% increase in bone mineral density of the lumbar spine and total hip, respectively.[43]

Osteoporosis Treatment

For women diagnosed with primary osteoporosis, the goal of treatment is to reduce the risk of fractures and improve bone mineral density. Bisphosphonates and the monoclonal antibody RANK ligand inhibitor, denosumab, are anti-remodeling agents that help reduce fragility fracture risk by inhibiting osteoclastic bone resorption. These medications can reduce risk of osteoporotic fractures by modestly improving bone mineral density, but they do not fix the microarchitectural disruption of the trabecular structure of the bone.[29]

Bisphosphonates formulations include alendronate, risedronate, ibandronate, and zolendronic acid. Bisphosphonates can be taken orally daily, weekly, or monthly, as well as intravenously every three months or annually. Common side-effects include gastrointestinal distress when taken orally, and flu-like symptoms when taken intravenously. There is a small risk of osteonecrosis of the jaw and atypical femur fractures. Bisphosphonate drug holidays should be considered after a patient has taken the medication for three to five years.[29]

Denosumab is administered as a subcutaneous injection every six months and has specific side-effects including rash and infection, and a small risk of osteonecrosis of the jaw, as well as atypical femur fractures with long-term treatment. When denosumab is stopped, there is a rapid decrease in bone mineral density and an increased risk for vertebral

fractures. For this reason, doses should not be skipped, and patients should be switched to another antiresorptive medicine after discontinuing denosumab.[29]

Selective estrogen receptor modulators (SERMs), such as raloxifene, can also be used for treatment of osteoporosis due to their estrogen agonist effects on bone. Side-effects include increased hot flashes, and there is increased risk of venous thromboembolism and stroke in women at high risk of CVD.[29]

Anabolic agents work by building bone and include the parathyroid hormone (PTH) receptor agonists teriparatide and abaloparatide and the monoclonal antibody romosozumab.[29,44] The PTH receptor agonists activate osteoblastic bone formation, thereby remodeling bone and improving trabecular bone mass. These are administered as daily subcutaneous injections and can be used for up to two years.[29] Side-effects include hypercalciuria, dizziness, and muscle pain. When discontinued, patients should be switched to an antiresorptive agent to maintain bone mineral density and prevent further bone loss. There is a dose-dependent low risk of osteosarcoma that was found in rats, but not in humans.

Romosozumab acts by binding sclerostin, thereby increasing bone formation and decreasing bone resorption. It is administered as a monthly subcutaneous injection. Side-effects include injection-site reactions, arthralgias, nasopharyngitis, and back pain. Romosozumab is associated with an increased risk in cardiovascular events and is not recommended in patients with myocardial infarction or stroke within the last year.[44] See Supplemental Tables 7 and 8 for formulations, dosing, and duration of osteoporosis treatments.[29,44]

For women at risk for or diagnosed with osteoporosis, recommended nonpharmacologic treatments include fall prevention, weight bearing exercise, and consuming a calcium-rich diet (800–1,200 mg per day). For women who do not consume sufficient calcium from the diet, calcium supplements can be taken as well. Women can also take Vitamin D supplements (600–1,200 IU/day) to help optimize bone health.[29]

Risk Factor Profiles of Menopausal Hormone Therapy (MHT)

It is critical to understand the risks and benefits of MHT with respect to outcomes such as cancers, CVD (CHD and stroke), cognitive impairment, venous thromboembolism, and osteoporosis. Understanding the risks and benefits of MHT along with how these influences vary according to age of initiation, time since menopause, and duration of use allow physicians and patients to make informed decisions regarding MHT use based on individualized patient characteristics.

Cancer Risk

Concerns regarding increased risk of breast cancer with MHT use have been prevalent since the WHI hormone trials found an increased incidence of breast cancer in the estrogen-progestin (CEE+ MPA) arm, while a decreased incidence of breast cancer was found in the estrogen-only (CEE) arm.[45] In a 20-year follow up of the WHI, women in the estrogen-progestin arm had an increased incidence of breast cancer compared to placebo, with no significant difference in breast cancer mortality. In the estrogen-only arm, there was a lower incidence of breast cancer and breast cancer mortality.[45] In large-scale observational studies, both estrogen-progestin and estrogen-only MHT were associated with increased breast cancer risk and breast cancer mortality, with higher risk among those on estrogen-progestin therapy.[46,47] The conflicting data surrounding breast cancer risk with estrogen-only therapy may be due to several factors including patient age at MHT initiation, time elapsed since menopause, and screening biases in observational studies. Additionally, the type of progestogen may impact risk of breast cancer, as studies have shown that synthetic progestins used in the WHI may be associated with increased risk of breast cancer compared to micronized progesterone.[48] Per the North American Menopause Society, the absolute risk of breast cancer with estrogen-progestin therapy is rare, while the risk of breast cancer is reduced with estrogen-only therapy.[3]

The relationship between MHT and other cancers (eg, endometrial and colorectal cancer) has also been investigated. For instance, the WHI showed a statistically significant reduction in endometrial cancer with continuous combined CEE plus MPA,[49] which is in contrast to older observational data demonstrating a positive association between MHT and endometrial cancer.[50] Current recommendations are that women with a uterus receiving systemic estrogen therapy should also receive concomitant progestin therapy.[3]

The risk of colorectal cancer appears to decrease with MHT use. For participants in the WHI hormone trials, women who used MHT had a 44% decreased risk of colorectal cancer compared to placebo over a 5-year follow-up period.[51]

These results were replicated in a cohort study published in 2009 by the Breast Cancer Detection Demonstration Project follow-up study.[52] After an average 15 year follow-up period, women who reported any MHT use over the 15 year period had a 10% lower risk of colorectal cancer compared to never users.[52] When analysis was restricted to persons with a known MHT dose and regimen, estrogen-progestin users and estrogen-only users had a 36% and 26% decreased risk relative to non-users, respectively.[52]

Coronary Heart Disease and Stroke Risk

The association of MHT with CVD is complex and has been informed by a range of both observational studies and randomized controlled trials (RCT). In the 1990s, the observational Nurses' Health study (NHS) found a significant protective association between MHT and CVD.[53] In a 1991 analysis of a cohort of women enrolled in the NHS, estrogen users had a relative risk of 0.56 of major coronary disease (defined as non-fatal myocardial infarction or death from a coronary cause) compared to non-users.[53] A similar protective relationship was found in a subsequent publication from the NHS, looking at the relationship between combined estrogen-progestin use and CVD risk.[54] In this follow-up study of NHS participants, women who used a combined estrogen-progestin therapy were found to have a 61% decreased risk of major coronary disease relative to non-MHT users.[54] Based on these and other results from observational studies, MHT was believed to be an appropriate preventive treatment for CVD and was widely prescribed to peri- and postmenopausal patients.[55]

In 2002, however, the results of the WHI study demonstrated somewhat opposing findings. After an average 5-year follow up period, this study showed that estrogen-progestin users had a 29% increased risk of CHD compared to non-users.[5] In the estrogen-only WHI RCT, the risk of CHD was similar between participants in the treatment and placebo groups.[56] Based on these results and the increased risk of breast cancer, however, the WHI trial was terminated early, and MHT use decreased significantly.[55] However, it is important to note that the younger women generally had more favorable results than the older women (see Timing Hypothesis section).

With respect to stroke, WHI participants randomized to MHT had a 31% increase in stroke risk compared to the placebo group after a 5.6 year follow-up period.[4] Similarly, in the estrogen-only arm, those in the treatment arm had a 37% increase in stroke risk compared to placebo.[57] In both the combined MHT and estrogen-only MHT arms of WHI, those in the treatment arms had a higher risk of ischemic strokes, but there was no evidence for association between MHT and hemorrhagic strokes.[4,57] The marked difference in the data surrounding the impact of MHT and CVD (CHD and stroke) risk before and after the WHI study led many to question the cause of the discrepancy, leading to the discovery of the timing hypothesis.[4,57,58] Discrepancies in risks between WHI and other studies also raised concerns around use of synthetic versus bioidentical hormone formulations. As such, further research is warranted on this topic.

The Timing Hypothesis

Despite the findings of increased risk of CHD and stroke among participants in the WHI hormone therapy trials, subsequent analyses support the timing hypothesis. That is, the risk of MHT differs according to age at initiation of MHT and time since menopause. There has been speculation that the risks of CHD and stroke demonstrated in WHI were partially due to age at enrollment (mean of approximately 63 years compared with median age of menopause of 51),[5] more than a decade on average since the onset of menopause, and duration of time since completion of menopause. Also, a relatively high dose of an oral formulation of estrogen (CEE 0.625 mg daily) used in WHI may also have contributed to the elevated risk of CHD and stroke.

In a 13-year follow-up of the WHI, when stratified by age and time since menopause, women in the estrogen-progestin group who had entered menopause greater than 10 years prior to the study had increased risks of CHD, while women who had entered menopause less than 10 years prior to initiating treatment had lower risks of CHD. This was also reflected in the estrogen-only arm, with a greater time since menopause conferring a greater risk of CHD with initiation of MHT. Additionally, in the estrogen-only arm, younger women had lower rates of myocardial infarction and all-cause mortality compared in placebo.[48] Similarly, in an 18-year follow up analysis of the WHI, women aged 50–59 years old at enrollment had a reduced risk of all-cause mortality and CVD mortality in both the estrogen-only and estrogen-progestin

arms.[59] For stroke, data were stratified by both age and years since menopause, but no clear trends were observed, possibly due to small event rates in subgroups.[4,57]

More recent data from RCTs, including the ELITE study[60] and the Kronos Longevity Research Institute (KEEPS),[61] investigated the effect of MHT started early after natural menopause (<6 years in ELITE and <3 years in KEEPS) on progression of atherosclerosis (by carotid intima-medial thickness).[61] In KEEPS, and after a 4 year follow-up period, MHT (both the oral and transdermal arms) was not associated with progression of atherosclerosis.[61] In the ELITE trial, women started on oral MHT had slower progression of subclinical atherosclerosis compared with placebo when started within 6 years of menopause but not when MHT was started more than 10 years since menopause.[60] These findings support the hypothesis and support current recommendations that the benefits of MHT for VMS likely outweigh risks for women if started less than 10 years after menopause. It is important to note that, while both KEEPS and ELITE add important information on MHT started early after menopause, as well as safety of transdermal formulations, both trials are limited by relatively short-term follow-up and the surrogate outcome of subclinical atherosclerosis rather than incident CVD events. Furthermore, and in terms of stroke risk, a 2015 Cochrane meta-analysis found no significant impact of MHT on stroke risk for women starting MHT less than 10 years from onset of menopause, while stroke risk increased in women greater than 10 years since menopause.[62]

Cognitive Impairment

While changes in cognition may occur with the menopausal transition, clinical trial data have not demonstrated that treatment with MHT prevents development of dementia or cognitive impairment. Data from the WHI study demonstrated no protective effect of MHT on cognition, and when data from estrogen-progestin was combined with those from the estrogen-only arm, the risk of probable dementia and mild cognitive impairment increased.[63,64] Additionally, the WHI findings indicate that estrogen-progestin therapy initiated after age 65 may increase risk of dementia.[64] However, among women earlier in menopause, neutral results for MHT and cognition were observed in the WHI, KEEPS, and ELITE trials and support the hypothesis that a timing hypothesis may also apply to the effects of MHT on cognition.[65–68] Similar to other outcomes, more data are needed to understand the effect of factors including MHT timing, age, formulation, and dose as well as whether effects differ based on measures of cognitive impairment.

Venous Thromboembolism

Observational data suggest that transdermal formulations of estrogen are not associated with an increased risk of VTE, which is contrary to the results of multiple RCTs that have demonstrated an association between oral MHT use and the risk of venous thromboembolism (VTE). Examples of the latter include the Heart and Estrogen/Progestin Replacement Study (HERS) and the WHI. In the HERS study of 2,763 postmenopausal women with no previous VTE, oral MHT users had a 2.9 times excess risk of VTE per 1,000 woman years.[69] Similarly, a WHI study published in 2004 showed that, in comparison with non-MHT users, there was a 2.06-times greater relative risk of VTE in CEE+ MPA users as well as a 1.33-times greater relative risk of VTE in CEE users.[70]

With regard to observational data, in the observational hospital-based Oxford Family Planning Association Study (OFPAS) of 281 women aged 45 to 64, current use of either oral or transdermal MHT was found to have 3.5-times increased odds of VTE.[71] Though the majority of MHT users in this study used oral MHT, there appears to be a trend (though non-significant) toward lower VTE risk in those on oral vs transdermal therapy.[71] Subsequently, in two publications from the French Estrogen and Thromboembolism Risk Study, a hospital based case control study, oral but not transdermal therapy was associated with increased VTE risk, suggesting an important difference between the two formulations.[30,31,70] Other observational studies have shown no association between transdermal MHT and VTE risk, supporting these findings.[72,73]

Currently, clinical trial data comparing oral vs transdermal MHT formulations and VTE risk are lacking[3] and are needed for confirmation of data from observational studies.

Limitations

As this study was not designed as a systematic review, there may be literature not included in our summary of evidence on the risks and benefits of MHT and non-hormonal therapies for menopausal symptoms. Future research could include a focused systematic review on key questions around risks and benefits of MHT and other therapies as new primary evidence emerges. Also, the broad scope of our review makes it challenging to detail side-effects of the different non-hormonal medication options in great depth. Given this, we believe the ultimate decision on choice of therapeutics needs to be made on a case by case basis using shared decision-making between the patient and provider. Another limitation is the lack of trial data directly comparing bioidentical (estradiol and micronized progesterone) formulations to synthetic or non-bioidentical hormones (eg, MPA and CEE) with respect to the risks of CVD, cancer, and other chronic diseases. Though some data demonstrate the potential for an increased risk of adverse effects associated with the formulations of hormones used in the WHI study compared to bioidentical ones,[3] the main RCT-based evidence for use of MHT comes from WHI. As such, more data are needed in diverse populations to elucidate the comparative benefits and risks of different formulations of MHT.

Summary and Conclusions

In summary, there is clear evidence for the effectiveness of MHT for the treatment of VMS of menopause, and benefits may exceed risks of CHD, stroke, and VTE, especially among women who are less than 10 years since menopause, less than 60 years old, and without significant cardiometabolic comorbidities or contraindications to MHT. In terms of breast cancer risk, estrogen-only MHT has been shown to be protective against breast cancer while estrogen-progestin MHT confers an uncommon, higher risk of incident breast cancer but not breast cancer mortality. Contraindications to MHT include history of breast cancer (or other estrogen responsive cancers), CHD, stroke, or venous thromboembolism. There is no established age at which a woman should discontinue MHT, and the decision for how to long to use MHT should be based on a woman's symptoms and continued benefit versus risk discussions with her physician.[3]

Among women older than 60 years old, beyond 10 years since completing menopause, and those with risk factors such as prior CVD events, VTE, and breast cancer, the risks of MHT are likely greater than the benefits, and alternative therapies should be considered for menopausal symptoms including non-hormonal medications. Neurokinin 3 receptor antagonists are one new therapeutic option[41] whose efficacy has been demonstrated in phase 3 trials. This medication is pending approval by the FDA. Future research in the areas of CVD, VTE, and cancer risk among transgender individuals taking exogenous hormones during midlife is imperative, as many transgender individuals require gender affirming hormone therapies for extended periods of time. More data are needed regarding the physiology of the menopausal transition, how to optimize formulation and dose of MHT (eg, use of transdermal formulations for fewer thrombotic and metabolic effects), and the identification of other novel therapies during this period while minimizing future health risks.

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