Drugs & Aging (2023) 40:675–683
https://doi.org/10.1007/s40266-023-01043-3

CURRENT OPINION

Menopausal Hormone Therapy in Older Women: Examining the Current Balance of Evidence

Paru S. David[2] · Talia Sobel[2] · Sabrina Sahni[4] · Jaya Mehta[3] · Juliana M. Kling[1,2]

Accepted: 6 June 2023 / Published online: 21 June 2023

Abstract

Menopause occurs in all women. During the menopause transition, 80% of women experience vasomotor symptoms that can last an average of 7–10 years or longer, sometimes into the seventh and eighth decades of life. Understanding how to manage vasomotor symptoms (VMS) in older menopausal women is important since these symptoms can negatively impact quality of life. This review provides a practical guide on how to approach VMS treatment either with menopausal hormone therapy or non-hormone options. When initiating, as well as continuing hormone therapy, the factors clinicians should consider as they weigh risks and benefits include assessing a woman's risks related to cardiovascular disease, breast cancer, and osteoporosis. Utilizing a shared decision-making approach in regard to menopausal symptom management should aim to support women and help them maintain health and quality of life.

Key Points

The benefits of menopausal hormone therapy typically outweigh the risk when initiated in symptomatic women without contraindications who are < 60 years old or within 10 years of their final menstrual period.

Women may experience bothersome vasomotor symptoms for many years, so it is not clinically appropriate to set an arbitrary age-based cutoff for use of hormone therapy; instead, the decision regarding duration of HT should be considered in the context of each woman's risk–benefit profile and her preferences.

As non-oral routes and lower-dose estrogen therapy are associated with lower risks, they are ideal for older women continuing on hormone therapy. For women who cannot or choose not to use hormone therapy, there are non-hormone treatment options for management of the vasomotor symptoms of menopause.

1 Introduction

Menopause, defined retrospectively as 12 months past the final menstrual period (FMP), occurs in women at an average age of 51 years of age in the USA [1]. Symptoms are common during the menopause transition, which can include hot flashes and night sweats, also known as vasomotor symptoms (VMS), sleep disturbance, cognitive complaints, and vaginal dryness [2–4]. Approximately 80% of women report VMS, and for some they are severe with negative impacts to their quality of life and health [5, 6]. VMS persist on average for 7 years but can last up to 10 years or longer for some women, which may differ on the basis of race/ethnicity [7, 8]. The median VMS duration for Black women in the USA is 10.1 years [7]. Up to 16% of women continue to have VMS beyond age 60, and many continue to have moderate to severe VMS [8, 9].Women with frequent VMS experience higher rates of depression, anxiety, and difficulty with sleep [10–12]. VMS have also been found to be associated with increased risk of cardiovascular disease, bone disease, and cognitive

✉ Paru S. David
David.paru@mayo.edu

1 Mayo Clinic Women's Health, Rochester, MN, USA

2 Division of Women's Health, Department of Internal Medicine, Mayo Clinic, Scottsdale, AZ, USA

3 Primary Care Institute, Allegheny General Hospital, Allegheny Health Network, Pittsburgh, PA, USA

4 Division of Hematology/Oncology, Department of Internal Medicine, Mayo Clinic, Jacksonville, FL, USA

complaints [13–15]. Despite this, many women do not seek or receive treatment for their VMS, and women with untreated VMS have higher healthcare utilization and costs, as well as decreased work productivity [16, 17].

Menopausal hormone therapy (HT) is the most effective treatment for VMS, and for symptomatic women who start HT early in menopause, duration of use should be individualized. Increasing risks, including stroke and cardiovascular disease, are seen with advanced age and duration of use [18], so women should use the appropriate dose for the time needed with these risks in mind. It is unknown if women who start HT early in menopause and continue use into their 60s and beyond incur the same risks as women who initiate HT after age 60. However, given that women may experience bothersome VMS for many years, it is not clinically appropriate to set an arbitrary age-based cutoff for use; instead, the decision regarding duration should be considered in the context of each woman's risk–benefit profile and her preferences. This review will provide detailed information about the recommendations for HT in relation to a woman's age, including timing of initiation, duration of use, and factors to consider when evaluating risk–benefit profiles for longer-term use of HT. Research in this area has almost exclusively been conducted in cisgender women, and that is the focus of this article, but menopause and symptoms of menopause may be experienced by individuals who do not identify as women. An algorithm is provided to help clinicians when initiating or continuing HT for symptomatic women (Fig. 1). Additionally, a discussion of non-hormonal treatments for VMS is included for those who cannot use HT or decide not to use HT.

2 Treatment Options for VMS Management

2.1 Menopausal Hormone Therapy (HT)

HT is the most effective treatment for vasomotor symptoms, reducing vasomotor symptoms by up to 85%. By improving VMS, other menopausal symptoms such as sleep disturbances, mood changes, and cognitive complaints may improve [19, 20]. HT includes estrogens and progestogens (the latter is for women with a uterus), and is available in various routes, formulations, and dosages. Bazedoxifene is a tissue-selective estrogen receptor modulator that is paired with oral conjugated equine estrogen to treat VMS as it blocks the effects of the estrogen at the lining of the uterus. Tibolone, currently available outside of the USA, including Europe and Canada, is a synthetic steroid that has metabolites with estrogenic, progestogenic, and androgenic properties and is often utilized in VMS treatment [21]. Possible side effects of estrogen include breast tenderness and fluid retention, whereas progestogens can cause mood disturbance and bloating. Women on HT may experience vaginal discharge or unexpected bleeding, which should be explored if heavy or continues beyond 6 months. Evaluation may include pelvic ultrasound and/or endometrial sampling [9, 22, 23].

The North American Menopause Society (NAMS) position statement supports initiation of HT in women less than 60 years old or within 10 years of the FMP who have indications for HT and do not have contraindications through an individualized, shared decision-making approach that includes selection of formulation, route, and dosage [1]. HT is indicated for the treatment of bothersome VMS and for the prevention of osteoporosis [1]. Risks associated with HT are best understood from the Women's Health Initiative (WHI) where conjugated equine estrogen (CEE) and medroxyprogesterone acetate (MPA) were used. These risks include venous thromboembolism, gallbladder disease, and endometrial hyperplasia and/or cancer in women with unopposed estrogen [18]. The attributable risk of breast cancer in postmenopausal women using combined estrogen and progestogens is less than one additional case per 1000 women annually, but this risk has not been found with the use of estrogen-only therapy in women without a uterus [18]. Contraindications to HT include history of estrogen-sensitive cancer, breast cancer, coronary heart disease (CHD), stroke, venous thromboembolism, liver disease, and unexplained vaginal bleeding [1].

Analyses of both the WHI study and the 18-year follow-up of the WHI have supported the concept of "the timing hypothesis," which postulates that the risks associated with HT are related to the timing of initiation, and the safest time to start HT is in women less than 60 years of age or within 10 years of the FMP. In these women, usually the benefits of HT outweigh the risks [24]. Two large meta-analyses demonstrated that HT is associated with a reduction in all-cause mortality by nearly 40% [95% confidence interval (CI) 5–61%] and reduced (CHD) risk by 32% (95% CI 4–52%) across 30 randomized controlled trials (RCTs) when initiated in women younger than age 60 [25, 26]. Alternatively, the effects of HT on CHD, stroke, and venous thromboembolism (VTE) were considered null or showed increased risk in various RCTs in women who were initiated older than 60 years of age or more than 10 years since menopause [26]–[28]. For women initiating HT after 60 years of age or more than 10 years since the FMP, the risks of CHD, stroke, VTE, and dementia outweigh the benefits [29].

2.2 Non-hormone Treatments

For menopausal women with bothersome VMS who are not candidates for HT due to medical comorbidities or personal preference, effective non-hormone options exist.

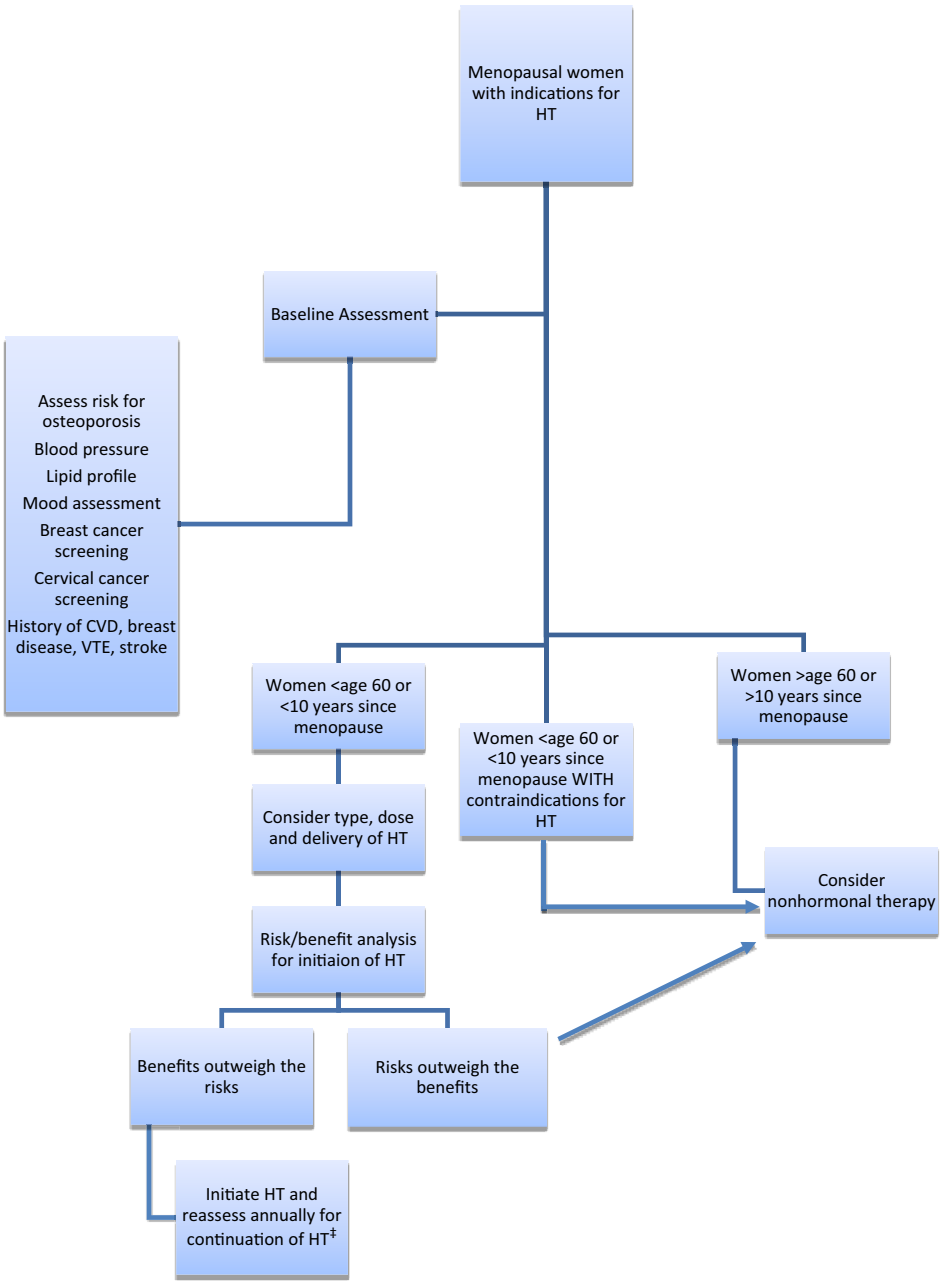

Fig. 1 Suggested algorithm for initiation of menopausal hormone therapy. *If diagnosed with a contraindicated condition such as breast cancer, stroke, or heart attack, recommend abruptly stopping the HT but provide follow-up regarding management of VMS. ‡Discuss risks and benefits and alternative therapy. If patient wishes to continue HT for another year, ensure they understand the risks and benefits. For continuation of HT, see Fig. 2. *HT* hormone therapy, *VMS* vasomotor symptoms, *CVD* cardiovascular disease, *VTE* venous thromboembolism

Pharmacological options include selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), gabapentin, and oxybutynin [30]. Of the SSRIs, low-dose paroxetine salt at 7.5 mg daily is the only SSRI that is US Food and Drug Administration (FDA) approved for treatment of bothersome VMS [31, 32].

Benefits of non-hormone options include treatment of VMS, but in some cases can also help with mood disturbance or sleep. For example, SSRIs or SNRIs can help with anxiety and depressive symptoms that women may experience alongside VMS. One of the side effects of gabapentin is somnolence, which is favorable in those women who experience sleep disturbance with nighttime VMS. In addition to the benefits, it is important to consider the side-effect profile of each. The somnolence and dizziness associated with gabapentin can increase risk of falls in adults over age 60 [33]. Clonidine, previously used for the treatment of VMS has side effects that include hypotension, sedation, dizziness, and, with abrupt cessation, rebound hypertension [30]. Due to these side effects, clonidine is no longer recommended for treatment of VMS in women. Finally, oxybutynin may cause urinary retention, dry mouth, or constipation [34, 35]. A recent systematic review of medications used for overactive bladder has shown an association between cognitive decline and oxybutynin use, even in patients without baseline

cognitive impairment [36]. Caution should be undertaken if using this medication in older patients.

New therapies for treating VMS are the neurokinin (NK) receptor antagonists. These medications act on NK receptors in the thermoregulatory center in the hypothalamus act by blocking the NK B, kisspeptin, and dynorphin neuron receptors to treat VMS. Fezolinetant, a NK receptor-3 antagonist, and elinzanetant, a dual NK receptor-3 and NK receptor-1 antagonist, have been found to be more effective than placebo [37–40]. In phase II trials, the NK receptor-3 receptor antagonist fezolinetant was found to reduce hot flash frequency by 50–90% compared with placebo, and also led to improvement in patient-reported quality of life [37]. Data from phase III trials of fezolinetant have reported efficacy at doses of 30 mg and 45 mg daily [38]. Side effects were typically mild, except for the rare but severe adverse events reported including elevated liver function tests, depressed mood, cholelithiasis, and detached retina [39]. The medication, fezolinetant 45 mg once daily, was FDA approved in May 2023 and is now the second FDA-approved non-hormone treatment available [41].

3 Baseline Assessment Prior to Initiation of VMS treatment

When evaluating a woman for treatment of VMS, assessing for absolute and relative contraindications can help guide if HT versus non-hormone treatments will be considered. Prior to initiation of HT, assessment of cardiovascular, breast cancer, and osteoporosis risk are recommended, which includes assuring she is up to date on her age-appropriate screenings.

Since cardiovascular disease (CVD) remains the leading cause of morbidity and mortality among postmenopausal women worldwide, the menopause transition serves as a critical opportunity to identify women who may be at an elevated risk for CVD. Traditional risk factors such as smoking, diabetes, and obesity pose a greater risk for CVD in women when compared with men [42]. Other considerations such as an obstetrical history of hypertensive disorders of pregnancy or gestational diabetes, polypharmacy, depression, and current physical condition have also been shown to be important determinants in cardiovascular risk [43, 44]. As a result, clinical risk assessment in women should not be limited to traditional risk assessment and may require a more holistic approach. Additionally, the use of coronary artery calcium score with CT is a validated diagnostic tool that can assess cardiovascular risk in women at intermediate risk and could be considered as part of a risk assessment if needed [45]. Optimization of blood pressure and cholesterol as well as counseling regarding a healthy body weight are considered staples when it comes to modifying cardiovascular risk. Another modifiable cardiovascular risk is diabetes. As rates of type 2 diabetes mellitus continue to rise worldwide, consideration of the effects of HT on blood glucose should be considered [46]. The WHI and two meta-analyses have shown that oral HT can reduce blood sugar and decrease hemoglobin A1C in women with type 2 diabetes or metabolic syndrome. Currently, it is unclear if transdermal estrogen therapy provides the same benefit to blood glucose and diabetes risk [18, 47, 48].

With regard to assessing breast cancer risk, in addition to breast cancer screening such as mammography, the use of a risk assessment model to determine lifetime breast cancer risk, such as the Tyrer–Cuzik, may be considered since it incorporates reproductive factors, history of breast biopsies, breast density, and family history. The use a model such as this may aid in clinical decision making as clinicians weigh risks and benefits of HT [49]. For women that are considered high risk, designated by a lifetime risk score above 20% or a genetic predisposition, enhanced breast cancer screening surveillance may be initiated. Additionally, women who have increased breast density on mammography have a two-fold increase in breast cancer risk compared with women with normal density. HT may increase breast density. Clinicians should discuss the role of supplemental breast cancer screening with women with dense tissue, regardless of their overall lifetime risk [50].

It has been estimated that approximately 30% of all breast cancers can be prevented with lifestyle factors alone [51]. As a result, appropriate counseling on healthy diet, increased physical activity, and limiting overall alcohol intake continue to be mainstays when counseling women on breast cancer risk. For high-risk women, a discussion about risk reducing medications such as tamoxifen or the aromatase inhibitors should take place. High-risk women may decide not to pursue combined estrogen and progestogen therapy due to increased risks or do so for a shorter period of time.

Lastly, an assessment of osteoporosis risk by inquiring about past medical, medication, and family history, as well as considering a bone densitometry along with a fracture risk assessment tool such as the Fracture Risk Assessment Tool, also known as FRAX, score when indicated can be useful when considering baseline assessment for hormone therapy. For women at a higher risk of osteoporosis due to family history or personal characteristics, such as prolonged history of steroid use, high-dose thyroxine, anticonvulsants, anticoagulants, history of bariatric surgery, early menopause, thin body habitus, or a history of eating disorders, initiation of HT may be more favorable due to the benefits of osteoporosis prevention [52].

4 Choice of HT

Considering the type, route, dose, timing or administration, and formulation of both estrogens and progestogens is necessary when making recommendations to patients. Factors to consider in addition to patient preference are their effects on CVD and breast health. Several large observational studies suggest that the type of estrogen or progestogen and the route in which it is administered may have different effects on overall CVD risk, as well as other outcomes such as VTE risk and other metabolic outcomes [53, 54]. The use of transdermal estrogen over oral estrogen may have more favorable effects on inflammatory markers, lipids, and clotting factors as demonstrated in observational studies, through avoidance of first-pass liver metabolism [54]. Initiating a lower-risk formulation at initiation can be beneficial when considering that some patients may continue these treatments well into their 60s. The concomitant use of progestogen with estrogen for women with an intact uterus have been studied compared with estrogen alone as it is related to CVD, stroke, and other health outcomes. In the WHI, the estrogen alone arm showed no increased risk in CVD; however, with the addition of a progestin, an increase in CVD was noted [55, 56]. As a result, the addition of a synthetic progestin has been thought to contribute to overall CVD risk. Data from the Nurse's Health Study also showed no increased risk for CVD or stroke in women on estrogen alone at 10 years follow-up if women were initiated on HT within 10 years of menopause [57]. For women who were initiated on HT, either combination or estrogen alone, after the age of 60 or > 10 years from the onset of menopause, results showed a null effect on coronary heart disease risk but an overall increased risk in stroke and VTE [18].

Progestogens including micronized progesterone and dydrogesterone (unavailable in the USA but available in Europe) have been found to be safer with regard to cardiovascular risk and may be preferred [58]. The Estrogen/Progesterone Intervention (PEPI) trial is the largest study to examine the impact of HT on both blood pressure and cholesterol. Nearly 900 women were included in the study and randomized to receive placebo, estrogen alone HT, or a combined regimen with estrogen and a progestin with four primary endpoints being high-density lipoprotein (HDL), systolic blood pressure, serum insulin, and fibrinogen. Results suggested favorable effects on HDL and fibrinogen levels with no significant impact on blood pressure or serum glucose [59]. A few additional small studies have looked at the use of HT in women with existing hypertension, and overall data suggest minimal effects on overall blood pressure [53, 60]. As women age, risks for developing CVD, VTE, and hypertension increase, so in addition to a transdermal formulation of estrogen, a reduction in dose to balance the risks and benefits is prudent [1].

Similar to cardiac risk, multiple personal risk factors may all contribute to HT impacts on the breast. The WHI remains the largest study at understanding HT and breast cancer risk. Long-term data from the WHI suggests that postmenopausal women on conjugated equine estrogen (CEE) alone had reductions in breast cancer risk compared with women on placebo after 7.2 years with 7 fewer cases per 10,000 person years [hazard ratio (HR) 0.78 95% CI 0.61–1.02] and remained low at 20 years follow-up [1, 18]. Conversely, women on combined HT with CEE and medroxyprogesterone acetate yielded an extra 9 cases per 10,000 person years of therapy and remained elevated for nearly 20 years at follow-up (HR 1.28 95% CI 1.13–1.45) [1, 61]. With regard to progestogens, it is believed that the use of synthetic progestins may in fact cause more stimulatory changes to the breast. This theory was further supported in a nested case–control study that found that, while an overall increase in breast cancer was noted among women on HT, it was largely mediated by the presence of synthetic progestins [odds ratio (OR) 1.28 95% CI 1.22–1.35] [62]. The use of micronized progesterone did not show similar elevations in cancer risk, and in a separate large systematic review, the use of micronized progesterone was not found to alter mammary tissue [62, 63].

5 Continuation of HT

The 2022 NAMS position statement of HT states that age alone is not a reason to discontinue HT in women above age 60 [1]. Annual benefit/risk assessment is needed, and if the benefits outweigh the risks, women may continue HT beyond age 60. If a woman continues to find benefit from HT with aspects to VMS, sleep, mood, and overall well-being, continuation of HT should be considered. Addressing changes in family history and current health along with risks for CVD, stroke, and breast cancer is recommended when reassessing the need for HT. The lowest dose of estrogen to control symptoms is recommended given in a non-oral route [1]. For women who remain healthy, ongoing use of HT can be considered in women over age 60 (Fig. 2).

6 Annual Assessment of Risks and Benefits

As women age, annual assessment of risks and benefits for continuation of HT become even more important. This includes a review of cardiovascular and VTE risk factors, an assessment of bone health, and breast cancer screening through a detailed history, physical, and appropriate testing. This should include assuring updated cervical and breast cancer screening, recommended screening laboratories such as glucose and lipid panels and measurement of bone density, if warranted.

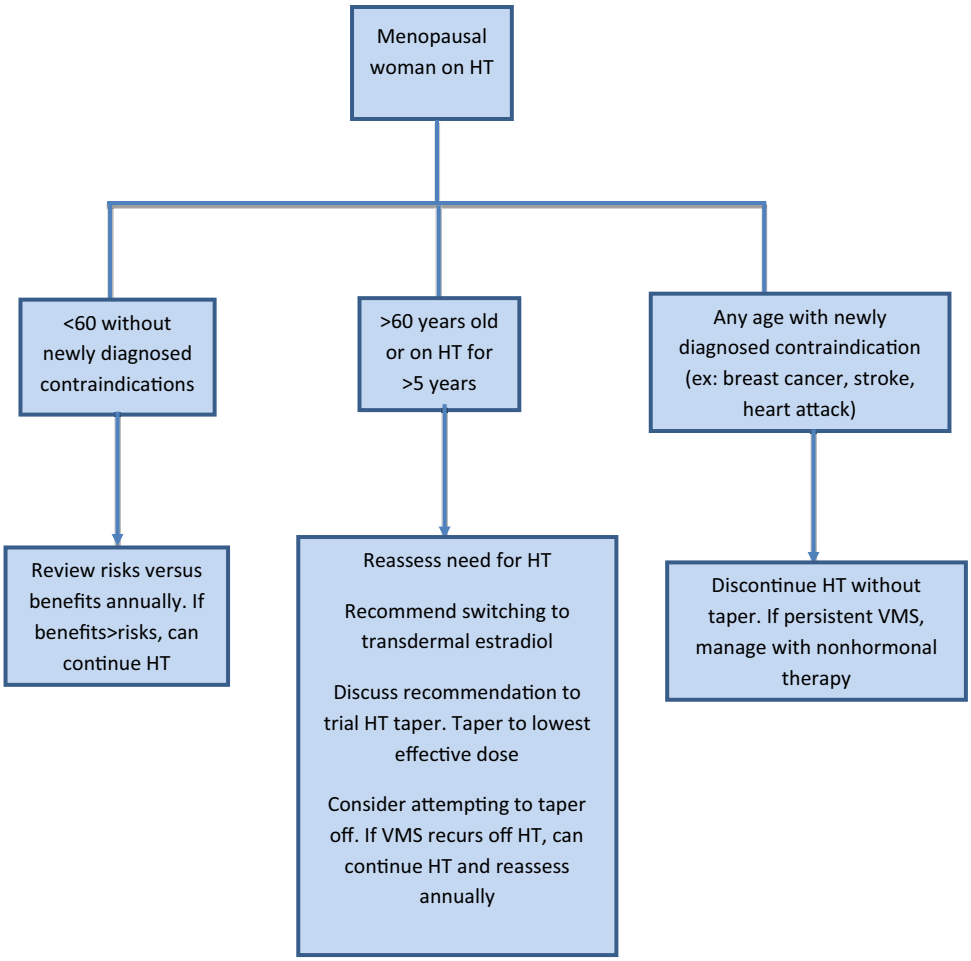

Fig. 2 Suggested algorithm for continuation of menopausal hormone therapy

7 Weaning off of HT

When it is determined that the risks of HT now outweigh the benefits, it is beneficial to develop a plan together to stop HT successfully. Although there are no studies that have found weaning superior to abruptly stopping HT, most patients prefer weaning gradually off HT when clinically indicated [64, 65]. A suggested approach is to do a trial of a lower-dosed patch for 1–3 months and assess for symptoms. For older women with persistent VMS who are interested in weaning off HT or for those out of the safe age range for HT initiation, there are a variety of alternative treatments to consider, including all the non-hormone options discussed above.

Some women will need to abruptly stop their HT due to newly diagnosed contraindicated conditions such as breast cancer or myocardial infarction. For these women, it may be worthwhile to proactively start a non-hormonal treatment to minimize symptoms.

8 Conclusion

Several studies have demonstrated that women over age 60 continue to have bothersome VMS that affect their quality of life [8, 9]. The benefits of HT outweigh the risks for most healthy symptomatic women who are younger than 60 years of age or within 10 years of menopause onset when initiating therapy, and the latest guidelines support that there is no upper age limit for the continuation of HT for persistent VMS [1]. HT counseling should include a thorough risk-versus-benefit discussion that includes detailed and personalized information on the risks of breast cancer, CVD, VTE, and hypertension with age and continued use of HT. Optimizing dose and formulation of HT is important as a woman ages. It may be appropriate to continue HT accompanied by yearly risk–benefit analysis and shared decision-making to assure optimal quality of life and symptom treatment for midlife and older women.

Declarations

Funding No funding was provided for the preparation of this manuscript.

Conflicts of Interest JMK: past consulting for proctor and gamble, triangle insights group, medical reviewer for Everyday health. PSD: consulting work for Med IQ. TS, SS, and JM have no conflicts of interest.

Availability of Data and Material Not applicable.

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Code Availability Not applicable.

Author Contributions All authors have made a substantial contribution to the concept of the article, participated in the acquisition of information, drafted the article or revised it critically for important intellectual content, approved the final version to be published, and have agreed to be accountable for all aspects of the manuscript.

References

1. Faubion SS, et al. The 2022 hormone therapy position statement of The North American Menopause Society'. Menopause. 2022;29(7):2022. https://doi.org/10.1097/GME.0000000000002028.
2. Greendale GA, Karlamangla AS, Maki PM. The menopause transition and cognition. JAMA J Am Med Assoc. 2020. https://doi.org/10.1001/jama.2020.1757.
3. Dennerstein L, Dudley EC, Hopper JL, Guthrie JR, Burger HG. A prospective population-based study of menopausal symptoms. Obstet Gynecol. 2000. https://doi.org/10.1097/00006250-200009000-00007.
4. Maki PM, Thurston RC. Menopause and brain health: hormonal changes are only part of the story. Front Neurol. 2020. https://doi.org/10.3389/fneur.2020.562275.
5. Freeman EW, Sherif K. Prevalence of hot flushes and night sweats around the world: A systematic review. Climacteric. 2007. https://doi.org/10.1080/13697130601181486.
6. Whiteley J, Wagner JS, Bushmakin A, Kopenhafer L, DiBonaventura M, Racketa J. Impact of the severity of vasomotor symptoms on health status, resource use, and productivity. Menopause. 2013. https://doi.org/10.1097/gme.0b013e31827d38a5.
7. Avis NE, Crawford SL, Greendale G, Bromberger JT, Everson-Rose SA, Gold EB, Hess R, Joffe H, Kravitz HM, Tepper PG, Thurston RC. Study of Women's Health Across the Nation. Duration of menopausal vasomotor symptoms over the menopause transition. JAMA Intern Med. 2015;175(4):531–9.
8. David PS, et al. Vasomotor symptoms in women over 60: results from the data registry on experiences of aging, menopause, and sexuality (DREAMS). Menopause. 2018. https://doi.org/10.1097/GME.0000000000001126.
9. Barnabei VM, et al. Menopausal symptoms in older women and the effects of treatment with hormone therapy. Obstet Gynecol. 2002. https://doi.org/10.1016/S0029-7844(02)02369-4.
10. Bromberger JT, et al. 'Does risk for anxiety increase during the menopausal transition? Study of Women's Health Across the Nation Menopause. 2013. https://doi.org/10.1097/gme.0b013e3182730599.
11. Bromberger JT, et al. Depressive symptoms during the menopausal transition: The Study of Women's Health Across the Nation (SWAN). J Affect Disord. 2007. https://doi.org/10.1016/j.jad.2007.01.034.
12. Kravitz HM, et al. Sleep disturbance during the menopausal transition in a multi-ethnic community sample of women. Sleep. 2008. https://doi.org/10.5665/sleep/31.7.979.
13. Thurston RC, Sutton-Tyrrell K, Everson-Rose SA, Hess R, Matthews KA. Hot flashes and subclinical cardiovascular disease. Circulation. 2008. https://doi.org/10.1161/circulationaha.108.776823.
14. Crandall CJ, et al. Associations of menopausal vasomotor symptoms with fracture incidence. J Clin Endocrinol Metab. 2015. https://doi.org/10.1210/jc.2014-3062.
15. Maki PM. Verbal memory and menopause. Maturitas. 2015. https://doi.org/10.1016/j.maturitas.2015.07.023.
16. Sarrel P, et al. Incremental direct and indirect costs of untreated vasomotor symptoms. Menopause. 2015. https://doi.org/10.1097/GME.0000000000000320.
17. Gartoulla P, Worsley R, Bell RJ, Davis SR. Moderate to severe vasomotor and sexual symptoms remain problematic for women aged 60 to 65 years. Menopause. 2015. https://doi.org/10.1097/GME.0000000000000383.
18. Manson JE et al. The Women's Health Initiative hormone therapy trials: update and overview of health outcomes during the intervention and post-stopping phases. JAMA. 2013;310(13):1353–68.
19. Santoro N, Roeca C, Peters BA, Neal-Perry G. The menopause transition: signs, symptoms, and management options. J Clin Endocrinol Metab. 2021. https://doi.org/10.1210/clinem/dgaa764.
20. Maki PM, et al. Guidelines for the evaluation and treatment of perimenopausal depression: Summary and recommendations. Menopause. 2018. https://doi.org/10.1097/GME.0000000000001174.
21. Mintziori G, et al. EMAS position statement: Non-hormonal management of menopausal vasomotor symptoms. Maturitas. 2015. https://doi.org/10.1016/j.maturitas.2015.04.009.
22. Cansino C. ACOG COMMITTEE OPINION number 734: the role of transvaginal ultrasonography in evaluating the endometrium of women with postmenopausal bleeding. Obstet Gynecol. 2018. https://doi.org/10.1097/AOG.0000000000002631.
23. Roberts H, Hickey M, Lethaby A. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia: A Cochrane review summary. Maturitas. 2014. https://doi.org/10.1016/j.maturitas.2013.10.002.
24. Thurston RC, et al. Menopausal vasomotor symptoms and risk of incident cardiovascular disease events in swan. J Am Heart Assoc. 2021. https://doi.org/10.1161/JAHA.120.017416.
25. Salpeter SR, Walsh JME, Greyber E, Ormiston TM, Salpeter EE. Mortality associated with hormone replacement therapy in younger and older women: a meta-analysis. J Gen Intern Med. 2004. https://doi.org/10.1111/j.1525-1497.2004.30281.x.
26. Salpeter SR, Walsh JME, Greyber E, Salpeter EE. 'Brief Report: Coronary heart disease events associated with hormone therapy in younger and older women—A meta-analysis. J Gen Intern Medicine. 2006. https://doi.org/10.1111/j.1525-1497.2006.00389.x. (Journal of General Internal Medicine, vol. 23, no. 10. 2008. doi: 10.1007/s11606-008-0762-2).
27. Hodis HN, Mack WJ. Menopausal hormone replacement therapy and reduction of all-cause mortality and cardiovascular disease: it is about time and timing. Cancer J. 2022. https://doi.org/10.1097/PPO.0000000000000591.

28. Stuenkel CA. Managing menopausal vasomotor symptoms in older women. Maturitas. 2021. https://doi.org/10.1016/j.maturitas.2020.08.005.
29. Manson JAE, Bassuk SS, Kaunitz AM, Pinkerton JAV. The Women's Health Initiative trials of menopausal hormone therapy: lessons learned. Menopause. 2020. https://doi.org/10.1097/GME.0000000000001553.
30. Shufelt, CL, et al. The 2023 nonhormone therapy position statement of The North American Menopause Society. Menopause. 2023;30(6):573–90. https://doi.org/10.1097/GME.0000000000002200.
31. Carroll DG, Lisenby KM, Carter TL. Critical appraisal of paroxetine for the treatment of vasomotor symptoms. Int J Women's Health. 2015. https://doi.org/10.2147/IJWH.S50804.
32. Riemma G, et al. Efficacy of low-dose paroxetine for the treatment of hot flushes in surgical and physiological postmenopausal women: systematic review and meta-analysis of randomized trials. Medicina (Lithuania). 2019. https://doi.org/10.3390/medicina55090554.
33. Schroeck JL, et al. Review of safety and efficacy of sleep medicines in older adults. Clin Therape. 2016. https://doi.org/10.1016/j.clinthera.2016.09.010.
34. Simon JA, et al. Extended-release oxybutynin therapy for vasomotor symptoms in women: a randomized clinical trial. Menopause. 2016. https://doi.org/10.1097/GME.0000000000000773.
35. Leon-Ferre RA, et al. Oxybutynin vs placebo for hot flashes in women with or without breast cancer: A randomized, double-blind clinical trial (ACCRU SC-1603). JNCI Cancer Spectrum. 2020. https://doi.org/10.1093/jncics/pkz088.
36. Duong V, Iwamoto A, Pennycuff J, Kudish B, Iglesia C. A systematic review of neurocognitive dysfunction with overactive bladder medications. Int Urogynecol J. 2021. https://doi.org/10.1007/s00192-021-04909-5.
37. Santoro N, et al. Effect of the neurokinin 3 receptor antagonist fezolinetant on patient-reported outcomes in postmenopausal women with vasomotor symptoms: Results of a randomized, placebo-controlled, double-blind, dose-ranging study (VESTA). Menopause. 2020. https://doi.org/10.1097/GME.0000000000001621.
38. Johnson KA, et al. Efficacy and safety of fezolinetant in moderate to severe vasomotor symptoms associated with menopause: a phase 3 RCT. J Clin Endocrinol Metab. 2023. https://doi.org/10.1210/clinem/dgad058.
39. Fraser GL, et al. A phase 2b, randomized, placebo-controlled, double-blind, dose-ranging study of the neurokinin 3 receptor antagonist fezolinetant for vasomotor symptoms associated with menopause. Menopause. 2020. https://doi.org/10.1097/GME.0000000000001510.
40. Trower M, Anderson RA, Ballantyne E, Joffe H, Kerr M, Pawsey S. Effects of NT-814, a dual neurokinin 1 and 3 receptor antagonist, on vasomotor symptoms in postmenopausal women: a placebo-controlled, randomized trial. Menopause. 2020. https://doi.org/10.1097/GME.0000000000001500.
41. 'FDA Approves Novel Drug to Treat Moderate to Severe Hot Flashes Caused by Menopause. https://www.fda.gov/news-events/press-announcements/fda-approves-novel-drug-treat-moderate-severe-hot-flashes-caused-menopause. Accessed 25 May 2023.
42. Goldsborough E, Osuji N, Blaha MJ. Assessment of cardiovascular disease risk: a 2022 update. Endocrinol Metab Clin N Am. 2022. https://doi.org/10.1016/j.ecl.2022.02.005.
43. Triantafyllou A, Douma S. 'Cardiovascular risk assessment in elderly individuals without overt CVD disease. Could traditional risk factors fit in all ages? J Clin Hypertens. 2019. https://doi.org/10.1111/jch.13616.
44. Rich-Edwards JW, Fraser A, Lawlor DA, Catov JM. Pregnancy characteristics and women's future cardiovascular health: An underused opportunity to improve women's health? Epidemiol Rev. 2014. https://doi.org/10.1093/epirev/mxt006.
45. Maas AHEM. Hormone therapy and cardiovascular disease: Benefits and harms. Best Pract Res Clin Endocrinol Metab. 2021. https://doi.org/10.1016/j.beem.2021.101576.
46. Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J. Epidemiology of Type 2 diabetes—Global burden of disease and forecasted trends. J Epidemiol Glob Health. 2020. https://doi.org/10.2991/JEGH.K.191028.001.
47. Salpeter SR, Walsh JME, Ormiston TM, Greyber E, Buckley NS, Salpeter EE. Meta-analysis: Effect of hormone-replacement therapy on components of the metabolic syndrome in postmenopausal women. Diabetes Obes Metab. 2006. https://doi.org/10.1111/j.1463-1326.2005.00545.x.
48. Xu Y, Lin J, Wang S, Xiong J, Zhu Q. Combined estrogen replacement therapy on metabolic control in postmenopausal women with diabetes mellitus. Kaohsiung J Med Sci. 2014. https://doi.org/10.1016/j.kjms.2014.03.002.
49. Brentnall AR, Cuzick J, Buist DSM, Bowles EJA. Long-Term accuracy of breast cancer risk assessment combining classic risk factors and breast density. JAMA Oncol. 2018. https://doi.org/10.1001/jamaoncol.2018.0174.
50. Bodewes FTH, van Asselt AA, Dorrius MD, Greuter MJW, de Bock GH. Mammographic breast density and the risk of breast cancer: A systematic review and meta-analysis. Breast. 2022. https://doi.org/10.1016/j.breast.2022.09.007.
51. Islami F, et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. CA Cancer J Clin. 2018. https://doi.org/10.3322/caac.21440.
52. LeBoff MS, et al. The clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int. 2022. https://doi.org/10.1007/s00198-021-05900-y.
53. Kapoor E, Kling JM, Lobo AS, Faubion SS. Menopausal hormone therapy in women with medical conditions. Best Pract Res Clin Endocrinol Metab. 2021. https://doi.org/10.1016/j.beem.2021.101578.
54. Shufelt CL, et al. Hormone therapy dose, formulation, route of delivery, and risk of cardiovascular events in women: Findings from the Women's Health Initiative Observational Study. Menopause. 2014. https://doi.org/10.1097/GME.0b013e31829a64f9.
55. Hsia J, et al. Conjugated equine estrogens and coronary heart disease: The women's health initiative. Arch Intern Med. 2006. https://doi.org/10.1001/archinte.166.3.357.
56. Manson JE, et al. Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med. 2003. https://doi.org/10.1056/nejmoa030808.
57. Stampfer MJ, et al. Postmenopausal estrogen therapy and cardiovascular disease: ten-year follow-up from the nurses' health study. Obstet Gynecol Surv. 1992. https://doi.org/10.1097/00006254-199202000-00027.
58. Shufelt CL, Manson JAE. Menopausal hormone therapy and cardiovascular disease: the role of formulation, dose, and route of delivery. J Clin Endocrinol Metab. 2021. https://doi.org/10.1210/clinem/dgab042.
59. Mebane Sims IL. Effects of estrogen or estrogen/ progestin regimens on heart disease risk factors in postmenopausal women: the Postmenopausal Estrogen/Progestin Interventions (PEPI)Trial. JAMA J Am Med Assoc. 1995;19:95. https://doi.org/10.1001/jama.273.3.199.
60. Felmeden DC, Lip GYH. Hormone replacement therapy and hypertension. Blood Press. 2000. https://doi.org/10.1080/08037050044861 4.

61. Chlebowski RT, et al. Association of menopausal hormone therapy with breast cancer incidence and mortality during long-term follow-up of the women's health initiative randomized clinical trials. JAMA J Am Med Assoc. 2020. https://doi.org/10.1001/jama.2020.9482.
62. Abenhaim HA, Suissa S, Azoulay L, Spence AR, Czuzoj-Shulman N, Tulandi T. Menopausal hormone therapy formulation and breast cancer risk. Obstet Gynecol. 2022. https://doi.org/10.1097/AOG.0000000000004723.
63. Stute P, Wildt L, Neulen J. The impact of micronized progesterone on breast cancer risk: a systematic review. Climacteric. 2018. https://doi.org/10.1080/13697137.2017.1421925.
64. Suffoletto JA, Hess R. Tapering versus cold turkey: Symptoms versus successful discontinuation of menopausal hormone therapy. Menopause. 2009. https://doi.org/10.1097/gme.0b013e3181a057db.
65. Haskell SG, Bean-Mayberry B, Gordon K. Discontinuing postmenopausal hormone therapy. Menopause. 2009. https://doi.org/10.1097/gme.0b013e31818fbff5.