Management of perimenopausal and menopausal symptoms

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Series explanation: State of the Art Reviews are commissioned on the basis of their relevance to academics and specialists in the US and internationally. For this reason they are written predominantly by US authors

Abstract

Most women worldwide experience menopausal symptoms during the menopause transition or postmenopause. Vasomotor symptoms are most pronounced during the first four to seven years but can persist for more than a decade, and genitourinary symptoms tend to be progressive. Although the hallmark symptoms are hot flashes, night sweats, disrupted sleep, and genitourinary discomfort, other common symptoms and conditions are mood fluctuations, cognitive changes, low sexual desire, bone loss, increase in abdominal fat, and adverse changes in metabolic health. These symptoms and signs can occur in any combination or sequence, and the link to menopause may even be elusive. Estrogen based hormonal therapies are the most effective treatments for many of the symptoms and, in the absence of contraindications to treatment, have a generally favorable benefit:risk ratio for women below age 60 and within 10 years of the onset of menopause. Non-hormonal treatment options are also available. Although a symptom driven treatment approach with individualized decision making can improve health and quality of life for midlife women, menopausal symptoms remain substantially undertreated by healthcare providers.

Introduction

Many women experience pronounced symptoms during and after the menopause transition. Studies show that 60-86% of women experience symptoms so bothersome that they seek medical care.[1-4] Afterwards, however, many feel misunderstood and disappointed that their concerns were not addressed. Effective, safe, well studied, and government approved medical treatments are available. However, many women never receive treatment owing to gaps in providers' knowledge and limited communication with their patients on this topic.[3-6] In a study of internal medicine, family medicine, and obstetrics and gynecology trainees, only 6.8% felt prepared to manage menopausal symptoms, and 20% did not receive any teaching on menopause during residency.[7]

As a result, women often pursue relief on their own with varying success, yielding a projected $22.7bn (£17.8bn; €20.8bn) commercial industry for over-the-counter menopausal supplements by 2028.[8] Undertreated menopausal symptoms have been associated with 1.5 million otherwise unnecessary outpatient visits annually, 26-33 million prescriptions for non-regulated treatments (costing more than $1bn annually), and negative effects on sleep, metabolism, mental health, personal relationships, and work productivity.[9]

The tide has been turning, however, as a result of rigorous investigation, advocacy, and education by medical societies and patient advocacy groups.[10-14] This review seeks to update clinicians on the latest guidelines for managing symptoms during the menopause transition and postmenopause. We review the epidemiology and physiology of menopause, followed by a discussion of menopausal hormone therapy's benefits, risks, and formulations. We cover hormonal and non-hormonal treatments for common symptoms and signs. Finally, we consider special populations and emerging treatments and compare guidelines from professional societies.

Gender terminology

This review is most relevant for people born with ovaries. To remain consistent with the research we reference, we will use the term "women"; however, we acknowledge that this term does not capture all those people who experience menopause. More research is needed to explore how diverse genders experience menopause, and we hope that the information contained herein will help any person experiencing this life transition.

Sources and selection criteria

We searched PubMed using the following terms: menopause, perimenopause, menopause transition, premature menopause, early menopause, primary ovarian insufficiency, surgical menopause, oophorectomy; vasomotor, hot flashes, hot flushes,

insomnia, sleep disorder, depression, mood changes, hypoactive sexual desire, low libido, sexual dysfunction, bone loss, osteopenia, osteoporosis, genitourinary syndrome of menopause, vulvovaginal atrophy, vaginal dryness, dyspareunia, weight gain, metabolic syndrome, perimenopausal bleeding; systemic treatment, topical treatment, hormone therapy, non-hormonal, complementary, behavioral, supplement, emerging treatments. We considered studies published between 1 January 2012 and 1 November 2022 to include the most up-to-date research. We included relevant publications outside this timeline when identified from references.

We predefined study selection priority according to the level of the evidence (systematic reviews, meta-analyses, consensus statements, randomized controlled trials (RCTs), and high quality population based observational studies), on the basis of the population of interest (adults experiencing symptoms of menopause or the menopause transition with clear description of intervention type, dose, and duration), the sample size (prioritizing larger studies), and the time of publication (prioritizing more recent studies).

Epidemiology and physiology of menopause

In 2021 an estimated 1.02 billion women were postmenopausal globally, with 1.65 billion anticipated by 2050.[15] The menopause transition consists of perimenopause and the first 12 months after the final menstrual period (FMP). Menses stop when the ovaries have insufficient follicles to respond to and sustain the hypothalamic-pituitary-gonadal axis. The onset of the transition is marked by changes in menses and/or development of hypoestrogenic symptoms such as hot flashes, mood changes, impaired concentration and memory, sleep disturbance, fatigue, reduced libido, joint pain, and increased central adiposity. The average age of menopause is 51 years.[16] Seven per cent of women enter menopause early between ages 40 and 45, and 1.9% enter before age 40, which is considered premature menopause.[17]

Trajectories of hormonal changes and symptoms vary. The symptoms of natural menopause can last from three years to more than 11 years.[18] Twenty per cent of women experience hot flashes into their late 50s, 10% into their late 60s, and 5% into their 70s.[19]

Racial and ethnic differences affect the menopause transition experience through both biological and cultural mechanisms. Cultures ascribe varied meaning to the transition, with some reflecting distress about loss of youth, whereas others consider this a natural part of aging so women are less likely to seek care.[20 21] In the Study of Women's Health Across the Nation (SWAN) cohort in the US, Black women experienced more severe and longer lasting symptoms than other women, a fact that warrants more attention and is also difficult to disentangle

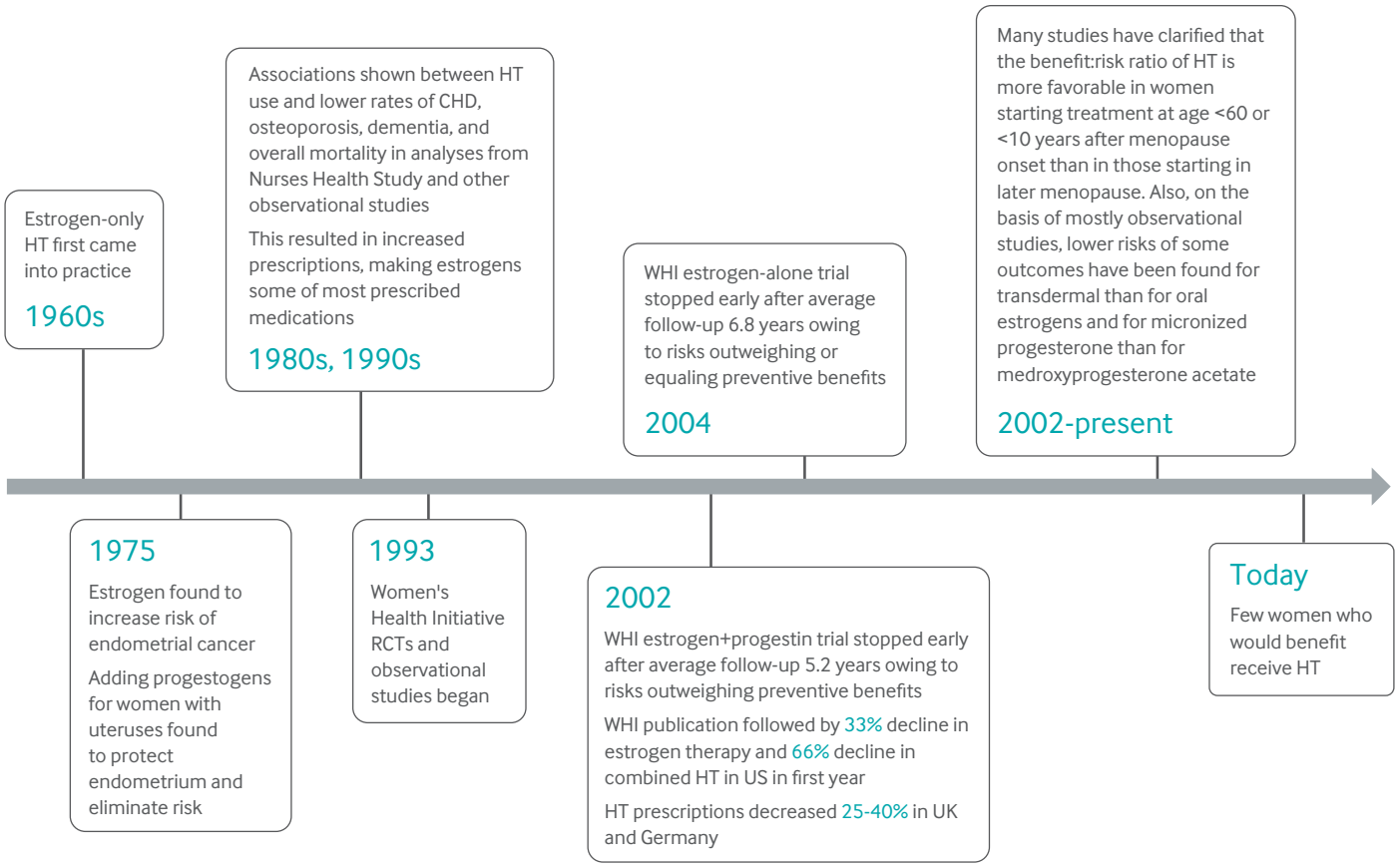

Fig 1 | Hormone therapy history timeline[24 25]; CHD=coronary heart disease; HT=hormone therapy; RCT=randomized controlled trial; WHI=women's health initiative

Box 1: Women's Health Initiative RCTs facts[26 27]

- NIH funded
- Largest RCTs of hormone therapy ever done
- Purpose:
  - To assess the efficacy of hormone therapy in preventing CHD and other chronic diseases
- Participants:
  - 27 347 postmenopausal women
  - No perimenopausal women
  - Women with and without menopausal symptoms
  - Randomized to CEE with MPA if had uterus; CEE alone if had hysterectomy
  - Ages 50-79 years; average age 63 years
- Results (versus placebo):
  - CEE+MPA:
    - Increased risks of stroke, pulmonary embolism, breast cancer
    - Decreased risks of fractures, colorectal cancer
  - CEE alone (women without a uterus):
    - Increased risk of stroke
    - Decreased risk of fracture (breast cancer risk also decreased during long term follow-up)
    - Neutral results for most other outcomes
  - Small absolute risk increases for each (~1 excess event/1000 person years)
    - Risks greater in older women
  - Neither regimen increased risk of all cause mortality
- Trials stopped early owing to risks exceeding preventive benefits

NIH=National Institutes of Health; CHD=coronary heart disease; CEE=conjugated equine estrogen; MPA=medroxyprogesterone acetate; RCT=randomized controlled trial.

from the effects of structural racism.[22 23] Clinicians can more effectively address menopausal symptoms and invite conversations by educating themselves about their patients' cultural contexts around menopause.

Decision making about treatment is influenced by many factors, including severity (or "bothersomeness") of symptoms, stage of menopause, need for perimenopausal contraception, presence of premature or early menopause, comorbidities, and the patient's personal preference about treatment.

Menopausal hormone therapy

The history of hormone therapy is detailed in figure 1 and box 1. Systemic menopausal hormone therapy is the most effective treatment for symptoms caused by low estrogen and hormone fluctuations.[10 13 28] Estrogen therapy alleviates vasomotor and many other menopausal symptoms. To mitigate the risk of endometrial hyperplasia and malignancy in women with a uterus, a progestogen must be added. This can be cycled or given continuously.

Indications for use

Hormone therapy is indicated to treat hot flashes and genitourinary syndrome of menopause (GSM) and to prevent osteoporosis when anticipated benefits outweigh individual risks (fig 2).[13 29 30] Premature and early menopause should be treated with hormone therapy until the average age of menopause. Contraindications and comorbidity considerations in clinical decision making are in box 2 and are discussed further below.

Cardiovascular risk and the timing hypothesis

The first Women's Health Initiative (WHI) publication showed concerning increased rates of venous thromboembolism and cerebrovascular disease, but age stratification revealed significant differences in cardiovascular disease outcomes. Participants aged 50-59 randomized to conjugated equine estrogen (CEE) alone had no increase in stroke and showed favorable trends for coronary heart disease (CHD), all cause mortality, and the global index (composite events), whereas those randomized to CEE plus medroxyprogesterone acetate had minimal differences by age group.[31] At 18 year follow-up, women aged 50-59 years in both treatment groups had no increase in all cause, cardiovascular, or cancer mortality.[32] This helps to explain why the WHI, which randomized women to hormone therapy on average more than a decade after menopause, reported such different findings from observational studies, which mainly comprised women starting hormone therapy early in menopause. Confounding by socioeconomic status, access to healthcare, and behavioral factors may have also contributed to the favorable findings seen in observational studies.

A Cochrane review including 19 good quality trials of hormone therapy use with more than 40 000 participants showed that risks of cardiovascular adverse events differed by age.[33] In a subgroup analysis with more than 9600 women from six RCTs who started hormone therapy within 10 years of menopause, use of hormone therapy was associated with reduced incidence of CHD (risk ratio 0.52, 95% confidence interval 0.29 to 0.96) and all cause mortality (0.70, 0.52 to 0.95), no change in stroke risk, but an increased risk of venous thromboembolism (1.74, 1.11 to 2.73) compared with placebo.[33] In absolute terms, for every 1000 women taking hormone therapy, eight fewer cases of CHD, six fewer deaths from any cause, four additional strokes, and five additional venous thromboembolisms occurred. These trials used oral estrogens and progestins, both of which may impose greater risk of venous thromboembolism and cerebrovascular disease than transdermal or intravaginal estrogens or micronized progesterone.

A potential explanation for the "timing hypothesis" is that women in early menopause have healthier blood vessels, which undergo vasodilation and experience overall anti-inflammatory effects in response to estrogen.[34 35] With age, the vasculature becomes more stenotic as a result of plaque accumulation, and the damaged endothelium has impaired vasodilation; on this substrate, estrogen has pro-inflammatory effects and can destabilize plaques.[36]

Breast cancer risks

Hormone therapy should be avoided in women who have had breast cancer, as its use has been associated with increased risk of recurrence.[37] Whether the recommendation differs according to type and extent of breast cancer requires further research. For those

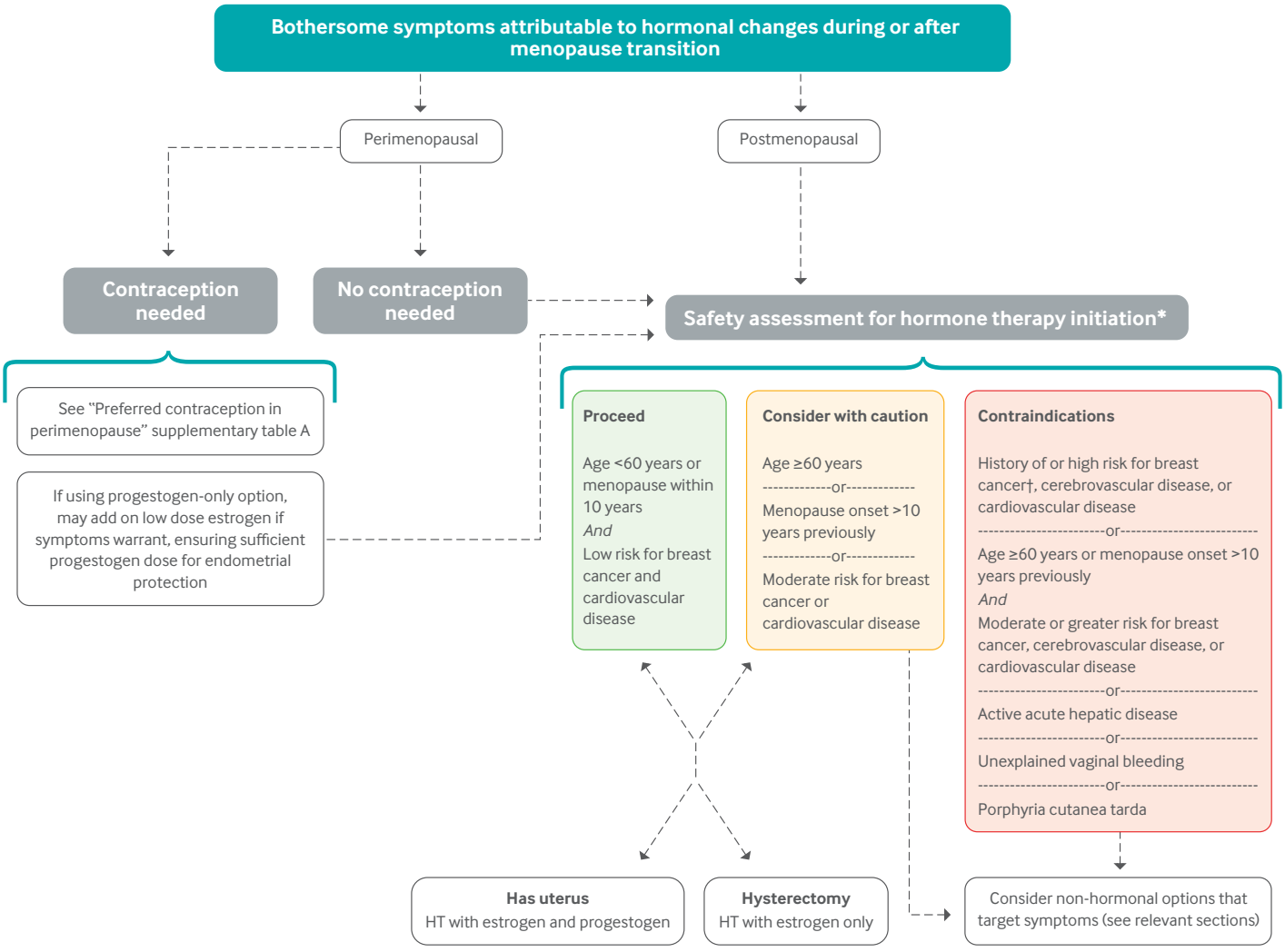

Fig 2 | Approach to initiating therapy for menopausal symptoms. HT=hormone therapy. *Clinicians may find the following risk assessment tools supportive, although neither is specifically designed and validated to assess risks as they relate to starting hormone therapy use. Breast cancer risk: Tyrer-Cuzick (https://ibis-risk-calculator.magview.com/). Cardiovascular risk: 2019 ACC/AHA guidelines on primary prevention of CVD using risk estimator plus and risk enhancers in guideline figure 3. †See hormone therapy "breast cancer risks" and special population "high risk for breast cancer" sections for further information

who have not had breast cancer, some formulations of hormone therapy may increase the absolute risk by a small amount, depending on formulation and duration.

Table 1 provides a comparison of findings on breast cancer from the 20 year follow-up of the WHI's RCTs and the Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC)'s meta-analysis of 58 prospective and retrospective observational studies of long term effects of hormone therapy on breast cancer. The different study designs do not lend themselves to perfectly analogous comparison.

The studies showed similar risks of breast cancer for combination estrogen-progestogen hormone therapy. The WHI's risk rate for incidence of breast cancer at 20 year follow-up was reported in cases per 10 000 person years with a mean duration of 5.6 years for combination therapy and 7.2 years for estrogen alone, whereas the CGHFBC's risks are reported as projected cases over a set 20 year period for women using hormone therapy for five years. To compare rates, the WHI findings are extrapolated to cases per 100 people over 20 years. The WHI's 1.8 additional cases are similar to the CGHFBC's range of 1.4-2.0 additional cases per 100 people for continuous versus cycled estrogen-progestogen users. Meanwhile, their findings for estrogen alone differed. In the WHI's RCTs, CEE users experienced 1.4 fewer cases whereas the CGHFBC estimated 0.5 additional cases per 100 people. The difference may lie in different estrogens studied, older age at start (on average 13.6 years older) for the WHI, or imperfect use within an RCT which would attenuate the effect seen. Furthermore, mammographic screening rates may be higher in hormone therapy users than non-users in observational studies.

Estimated risks from estrogen-progestogen therapy in both studies may be overstated, as the progestogens used today are thought to carry a

Box 2: Hormone therapy contraindications and comorbidities

Contraindications
- Breast cancer
- Endometrial cancer (advanced stage hormonal or non-hormonal)
- Untreated endometrial hyperplasia or cancer
- Unexplained vaginal bleeding
- Myocardial infarction, stroke, or transient ischemic attack
- Uncontrolled hypertension
- Peripheral artery disease
- Unprovoked venous thromboembolism
- Known clotting disorder
- Cirrhosis
- Active hepatitis
- Porphyria cutanea tarda

Comorbidities of concern
- Controlled hypertension
- Hyperlipidemia
- Diabetes
- Smoking
- Provoked venous thromboembolism
- Chronic inflammatory states
- HIV
- Gallbladder disease
- Ovarian or cervical cancer with suspected hormone responsiveness

lower risk. Few women in the CGHFBC meta-analysis and none in the WHI's RCTs used micronized progesterone or dydrogesterone. A large French cohort study showed that micronized progesterone and dydrogesterone used with estrogen were not associated with increased incidence of breast cancer for up to five years of use.[40] A large British nested case-control study of estrogen-progestins (no progesterone) showed that all progestins were associated with increased risk, although dydrogesterone had the lowest risk.[41] Although the levonorgestrel intrauterine system is thought to act locally, meta-analyses have found mixed evidence on its association with breast cancer.[42-44]

Treatment considerations by menopause phase

Premature and early menopause

Women with premature or early menopause due to primary ovarian insufficiency, bilateral oophorectomy, radiation/chemotherapy, or other causes should receive hormone therapy to support cardiovascular, genitourinary, bone, and cognitive health until the average age of menopause. Women with premature menopause who do not receive hormonal replacement have increased rates of dementia, parkinsonism, mood disorders, cardiovascular disease, osteoporosis, sexual dysfunction, and overall mortality.[45] Higher doses of estrogen are needed than would be used to treat symptoms in women closer to the average age of menopause, and both combined hormonal contraceptives (CHC) and hormone therapy should be considered. Multiple societies provide excellent guidelines for diagnosis and management.[13 14 46-48]

Perimenopause

During perimenopause, women can ovulate up until their FMP. Contraception is particularly important because pregnancy in perimenopause is associated with higher risk for maternal and fetal complications. The best contraceptive option should consider the woman's hormonal milieu, perimenopausal symptoms, comorbidities, drug treatments, and personal preferences (supplementary table A). Hormone therapy should not be used as contraception, as it rarely suppresses ovulation or alters cervical mucus substantially. For those who do not smoke and have no history of venous thromboembolism or stroke, low dose CHC pills are appropriate. CHCs contain ethinyl estradiol which is associated with higher rates of venous thromboembolism and stroke compared with the estradiol and CEEs used in hormone therapy.[49] Progestin-only options have fewer contraindications, and low dose estradiol can be added if vasomotor symptoms are prominent.

When to switch from contraceptive method to hormone therapy

When a woman who menstruates is no longer fertile is difficult to ascertain. However, the recommendations in table 2 may assist in determining when contraception is no longer needed.

Postmenopause

Decision making differs according to whether it is a new start or continuation of hormone therapy (see fig 2 and fig 3). When hormone therapy is newly prescribed, starting within 10 years of menopause and younger than age 60 is advisable. If hormone therapy is started during this critical window, women may continue to take it beyond 10 years, if indicated. Clinicians should aim to use the lowest effective dose and lower risk delivery via transdermal and intravaginal routes, when possible.

Hormone formulations

See table 3, table 4, and table 5 for approved hormone therapy formulations.

Alternative hormonal therapies

Women with a uterus who cannot use a progestogen for endometrial protection may prefer oral CEE-bazedoxifene, a single dose combination estrogen-estrogen receptor agonist-antagonist (ERAA).[57-59] CEE-bazedoxifene was not available from 2020 until June 2023 while the manufacturer improved packaging safety.[60] Insufficient data are available on its effect on risk of breast cancer.[13]

Tibolone is a synthetic steroid commonly used globally to treat vasomotor symptoms, but it is not approved in the US. A 2016 Cochrane review of RCTs found that tibolone reduced hot flashes better than placebo but not as well as estrogen therapy.[61] Tibolone improves bone mineral density and may improve sexual function. However, it carries an increased risk of recurrence of breast cancer and may increase risk of stroke in women over age 60.[61]

Table 1 | Comparison of WHI and CGHFBC findings on hormone therapy and breast cancer

Characteristic	WHI 20 year follow-up[38]		CGHFBC[39]
Study type	Randomized controlled trial		Nested case-control meta-analysis of 24 prospective and 34 retrospective observational studies
No of participants	CEE trial: 10 739; CEE+MPA trial: 16 608		Breast cancer cases: 128 435; controls: 366 965
Hormone exposure:			
Estrogen alone	CEE		CEE, estradiol
Estrogen+progestogen	CEE+MPA		CEE, estradiol; levonorgestrel, MPA, NETA; small No with dydrogesterone, micronized progesterone
Comparator groups	Women with hysterectomy: CEE *v* placebo; women with uterus: CEE+MPA *v* placebo		Current users *v* never users; past users *v* never users; subdivided by treatment type
Outcomes	Primary: heart disease; secondary: osteoporosis; primary adverse event: incident invasive breast cancer		Primary: incident invasive breast cancer
Mean duration of use, years:			
Estrogen alone	7.2		Analogous figures not available. Reported as mean years of use for all formulations of HT by age at start. Ranges from 10.7 years for those starting age 40-44 to 7.9 years for age 60-69
Estrogen+progestogen	5.6		
Relative risk of invasive breast cancer, HR (95% CI):			
Estrogen alone	All durations: 0.78 (0.65 to 0.93)		1-4 year use—current use: 1.17 (1.10 to 1.26); past use: 1.04 (0.98 to 1.11)
			5-9 year use—current use: 1.22 (1.17 to 1.28); past use: 1.09 (1.03 to 1.15)
Estrogen+progestogen	All durations: 1.28 (1.13 to 1.45)		1-4 year use—current use: 1.60 (1.52 to 1.69); past use: 1.10 (1.05–1.16)
			5-9 year use—current use: 1.97 (1.90 to 2.04); past use: 1.21 (1.16 to 1.26)
Relative risk of breast cancer mortality, HR (95% CI):			
Estrogen alone	0.60 (0.37 to 0.97)		Did not evaluate mortality
Estrogen+progestogen	1.35 (0.94 to 1.95)		
Absolute risk of invasive breast cancer:			
Measure	Reported: cases per 10 000 person years	Extrapolation: cases per 100 people over 20 years	Estimated cases per 100 people using HT for 5 years starting at age 50, over 20 year follow-up
Estrogen alone	−7	−1.4	0.5
Estrogen+progestogen	9	1.8	1.4 (cycled); 2 (continuous)
Absolute risk of breast cancer mortality:			
Estrogen alone	−2	−0.4	Did not evaluate mortality
Estrogen+progestogen	0	0	

CEE=conjugated equine estrogen; CGHFBC=Collaborative Group on Hormonal Factors in Breast Cancer; CI=confidence interval; HR=hazard ratio; HT=hormone therapy; MPA=medroxyprogesterone acetate; NETA=norethindrone acetate; WHI=Women's Health Initiative.

Routes of administration

Estrogen

Oral estrogens undergo first pass metabolism in the liver where they upregulate clotting proteins, increase sex hormone binding globulin (SHBG) and thyroid binding globulin, alter lipid handling, and may interact with other drugs metabolized by the CYP3A4 enzyme.[62 63] This effect is more pronounced with ethinyl estradiol than estradiol owing to differences in bioavailability and potency.[64]

Transdermal and intravaginal formulations avoid first pass metabolism. Two meta-analyses of mainly observational studies with a few RCTs showed that transdermal estradiol is not associated with an increased risk of venous thromboembolism, whereas oral estrogen (most studies are of CEE) may increase risk by 1.5-fold to fourfold, dose dependently.[65 66] According to a high quality nested case-control study including more than 15 000 women with strokes and nearly 60 000 matched controls, transdermal low dose estrogen was not associated with an increased risk of stroke, whereas high dose transdermal estrogen and any dose of oral estrogen were associated with minor increases in absolute risk in women aged 50-79.[67] Transdermal formulations are preferred in women with hyperlipidemia, diabetes, hypertension, or other risk factors for cardiovascular disease.[68] Observational studies have not found significant differences in risk of breast cancer between transdermal and oral estrogens, but no RCTs have compared them.[40 69]

Progestogens

With adequate progestogen use, the risk of endometrial neoplasia is not increased.[13] Oral progestogens undergo first pass metabolism, and some synthetic progestins including medroxyprogesterone acetate are associated with increased rates of stroke, CHD, and venous thromboembolism when combined with estrogen. Studies show low to no risk of these with oral micronized progesterone, low dose norethindrone acetate, and dydrogesterone.[26 70-72]

Cycled versus continuous progestogen

The choice between cycled and continuous progestogens is made by balancing the benefits and side effects for each patient. Continuous progestogen use minimizes hormone fluctuations but is associated with more irregular bleeding and spotting in the first six months of use. Cycled progestogens given for 12-14 consecutive days during anticipated or simulated luteal phases more often yield predictable withdrawal bleeds but may worsen side effects because of the higher dose needed and biphasic dosing.

Table 2 | Determining when to discontinue contraception[50]

Current method	Clinical evaluation	Laboratory evaluation	Contraception plan
Non-hormonal contraception	Amenorrhea for 12-24 months*	-	None needed
Combined hormonal contraception	Age ≥50	Stop CHC for 6 weeks; use non-hormonal contraception. Check FSH twice 4-8 weeks apart	If FSH >30 IU/L both times, contraception is no longer needed. If FSH <30 IU/L either time, resume CHC and repeat approach in 1 year
		Stop CHC at age 55	Spontaneous conception very rare
Depot medroxyprogesterone acetate		Check FSH on same day as and before DMPA dose twice	If FSH >30 IU/L on two occasions, can discontinue
Progestin implant, IUS, POP		Check FSH at any time while on progestin method.	If FSH >30 IU/L, continue method for 1 more year, then discontinue
Other		-	May stop all methods without laboratory evaluation. However, if menses resume, consider FSH testing and resumption of contraception

CHC=combined hormonal contraception; FSH=follicle stimulating hormone; IUS=intrauterine system; POP=progestin-only pills.
*North American Menopause Society: 12 months of amenorrhea at any age[13]; Faculty of Sexual and Reproductive Healthcare: 24 months of amenorrhea women 40-50 years old, 12 months for women 50 years and above[51]

Compounded formulations

Common compounded formulations include transdermal creams, gels, troches, and pellet implants. Variability in purity, dosing, and bioavailability can result in inappropriate dosing.[73] In a study by the US Food and Drug Administration (FDA) of 29 compounded hormone therapy samples ordered over the internet, 34% did not meet one or more FDA quality standards, compared with a 2% failure rate among FDA approved therapies.[74] A retrospective cohort study comparing compounded pellet therapy with FDA approved hormone therapy and including more than 500 women showed that pellet therapy had an odds ratio for side effects of 8.0 (95% confidence interval 4.5 to 14.2) and was associated with higher supraphysiologic estradiol and testosterone concentrations.[75]

Micronized progesterone can be found in compounded creams and gels; however, endometrial protection is inconsistent owing to varied production practices, content, and individual absorption, so these formulations are discouraged.[76] Societies recommend against using compounded hormones whenever FDA regulated forms are available.[13 77 78]

Treatment adjustment

Table 6 shows common symptoms seen at follow-up. If a patient develops venous thromboembolism or another condition precluding hormone therapy, hormone therapy should be stopped immediately. Risk of venous thromboembolism is highest in the first year of treatment.[79] In the event of gallstone disease, oral estrogen may be switched to a non-oral route as observational studies show a lower risk of gallstones with transdermal estrogens, although no RCT data are available to support this.[13]

Treatment goals and follow-up

Achieving a 70% reduction in symptoms with few to no side effects is a reasonable goal and expectation. When starting or modifying treatment, follow-up should be done within eight to 12 weeks. Treatment modification should be driven by the patient's preferred balance of symptom control with side effects and risks. Once patients are taking stable doses, at least annual clinical follow-up should be pursued. Tracking serum estradiol, estrone, or SHBG is not recommended as it has not been shown to correlate with symptoms.[13 80] For women on thyroid replacement and oral estrogens, thyroid stimulating hormone should be monitored and thyroid dosing adjusted as needed.

Discontinuation of hormone therapy

The American Geriatrics Society Beers Criteria recommends that clinicians consider deprescribing systemic hormone therapy in women over 65 years old. The American College of Obstetrics and Gynecology (ACOG) and North American Menopause Society (NAMS) have stated and reinforced that no particular age or years postmenopause exists at which patients must stop using hormone therapy if indications for it remain.[10 13 81 82] Refer to figure 2 for a stepwise process.

Treatment approach by symptom or sign

Vasomotor symptoms

Hot flashes are the most commonly recognized menopausal symptom. Low estrogen leads to upregulation of neurokinin B in the preoptic area, which acts on hypothalamic neurokinin 3 receptors, precipitating inappropriate hot and cold sensations.[83 84] Hot flashes can be particularly pronounced for women with abrupt entry into menopause or medical estrogen suppression. Vasomotor symptoms often begin in perimenopause, and moderate to severe symptoms last on average seven to 11 years.[18 85]

Hormonal options

Estrogen is the most effective treatment available for hot flashes.[13 86] In a meta-analysis of RCTs, both oral CEE and transdermal estradiol were 70-95% effective at reducing hot flashes.[87] Oral micronized progesterone, which is rarely used as monotherapy, may also provide some benefit. An RCT of 133 women with vasomotor symptoms aged 44-62 years showed a 55% reduction in symptoms after treatment with 300 mg of micronized progesterone nightly for 12 weeks, compared with a 29% reduction in the placebo group.[88] This is a high dose associated with greater side effects than estrogen.

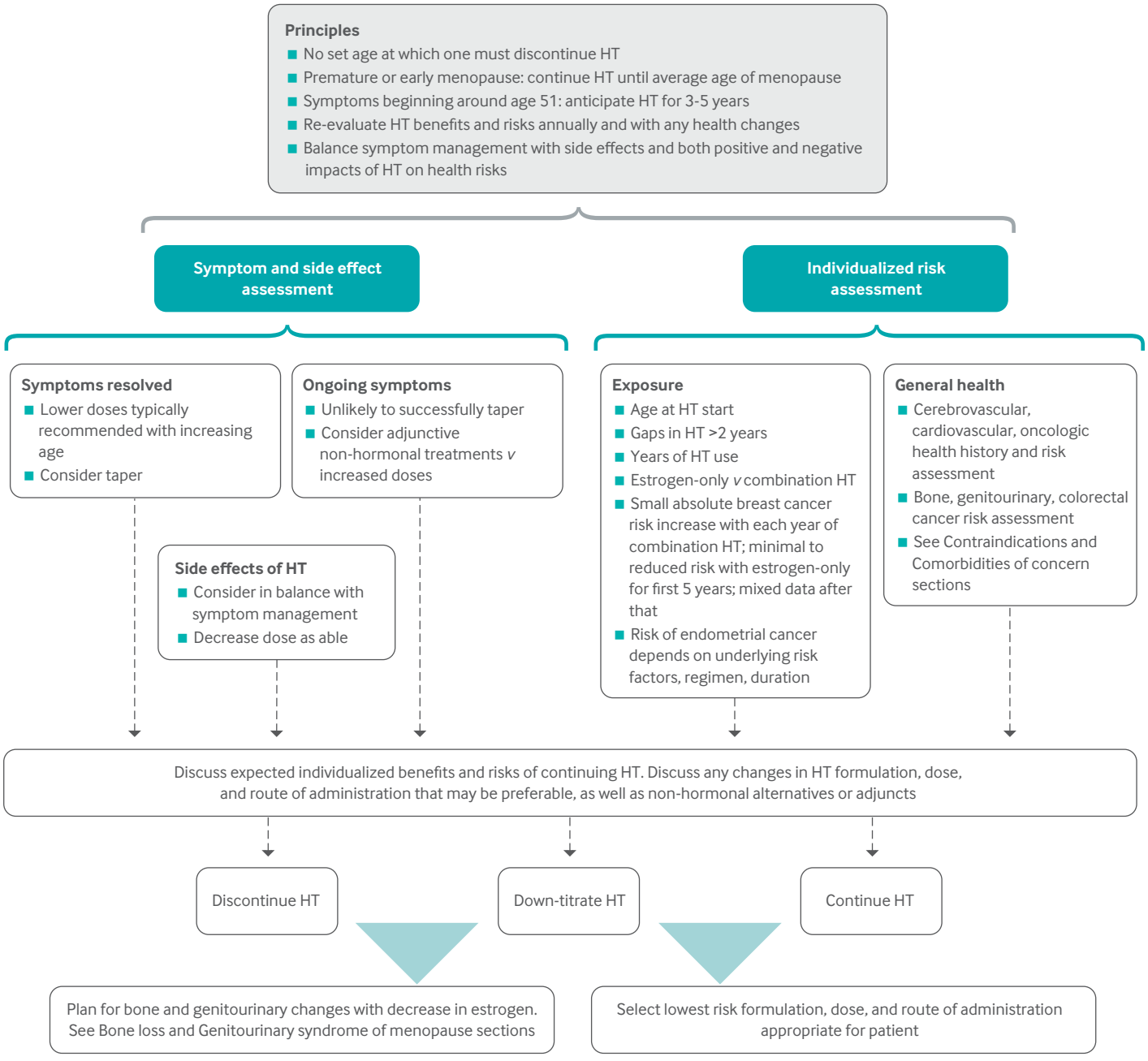

Fig 3 | Considerations for duration of systemic hormone therapy. HT=hormone therapy

Non-hormonal options

The UK National Institute for Health and Care Excellence's 2019 treatment guidelines for vasomotor symptoms recommend hormone therapy as first line treatment, with selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and clonidine as second line (table 7).[14] Other options include gabapentinoids and oxybutynin. The only FDA approved non-hormonal treatment for moderate to severe vasomotor symptoms until recently was the SSRI paroxetine. Because paroxetine inhibits the cytochrome P450 2D6, it is contraindicated in women using tamoxifen. See the emerging treatments section below for discussion of recently approved fezolinetant and investigational neurokinin modulators.

Complementary and alternative medicine

Approximately half of women in the menopause transition pursue complementary and alternative medicine treatments,[97-100] and many do not disclose this to their clinician. Phytoestrogens, including soy isoflavones, have long been used to variable effect, although a meta-analysis concluded that they do not reduce vasomotor symptoms more than placebo.[100] Population studies have found no improvement in vasomotor symptoms.[82 100] However, a difference may exist between women who can convert the isoflavone daidzein to equol and those who cannot, as equol is

Table 3 | Estrogens for systemic hormone therapy[52-54]

Name	Route	Typical dose range	Frequency	Equivalent dose
17-β estradiol	Oral	0.5-2 mg	Daily	1 mg
	Patch	0.014-0.1 mg	Once or twice weekly	0.05 mg
	Gel pouch	0.25-1.25 mg	Daily	1 mg
	Gel pump	1-4 pumps (0.52-0.75 mg per pump)	Daily	1-2 pumps
	Spra	1-3 sprays (1.53 mg per spray)	Daily	2-3 sprays
Conjugated equine estrogen	Oral	0.3-1.25 mg	Daily	0.625
Conjugated estrogen	Oral	0.3-1.25 mg	Daily	0.625 mg
Ethinyl estradiol	Oral	0.01-0.03 mg	Daily	0.01-0.015 mg
Esterified estrogen	Oral	0.3-2.5 mg	Daily	0.625 mg
Estradiol acetate	Vaginal ring	0.05 mg; 0.10 mg	90 days	0.05 mg
Estropipate	Oral	0.625-5 mg	Daily	0.625 mg

thought to be the biologically active metabolite.[82] The research on black cohosh is complex and conflicting. Variable findings may be due to heterogeneity in black cohosh compounds, which are not well regulated in most countries.[14] If confidence in the purity of the product is possible, black cohosh may be helpful and safe (supplementary table B).

Mood and cognitive changes

Compared with premenopause, women in perimenopause have three times the risk of a major depressive event regardless of previous history,[101] and women with a history of depression are more likely to have a recurrence.[102] This may be due to the fluctuations in estrogen and progesterone during the menopause transition and an increase in life stressors during this time.

Cognitive changes are common early in the menopause transition. These include challenges with learning and recalling new information and completing complex tasks, as well as shortened attention span.[103] Women may be concerned that these symptoms connote increased risk of dementia; however, the more likely causes are normal aging and impaired sleep, with no clear connection to future risk of dementia.

Treatment

For women who meet the diagnostic criteria for depression or anxiety, antidepressants are the first line of treatment.[102] When mood symptoms are correlated with hormonal fluctuations and symptoms of low estrogen in perimenopause, hormone therapy improves mood with or without antidepressant therapy.[102 103] This has not been shown in postmenopausal women. In a recent RCT, 172 euthymic perimenopausal and early postmenopausal women were given transdermal estradiol 0.1 mg

Table 4 | Progestogens for hormone therapy[52-54]

Name	Route	Dose range	Frequency	Side effects
Micronized progesterone	Oral	100-300 mg; 200-300 mg (300 mg rarely needed)	Daily; cycled	Somnolence, fatigue, bloating, abdominal pain, nausea, dizziness
Levonorgestrel	IUD	52 mg*†	5 years (approved in EU, off-label in US)	Pain with placement, pelvic pain, breast pain, irregular bleeding and spotting, acne, abdominal pain, nausea, dizziness, headache, fatigue
Drospirenone	Oral	4 mg*†	Daily	Acne, weight gain, nausea, headache, breast tenderness, low libido, hyperkalemia
Medroxyprogesterone acetate	Oral (depo unstudied)	2.5-5 mg; 5-10 mg	Daily; cycled	Bloating, weight gain, abdominal pain, dizziness, fatigue
Norethindrone‡	Oral	0.35-0.7 mg*†; 0.7 mg	Daily; cycled	Nausea, headache, breast tenderness
Norethindrone acetate	Oral	2.5 mg*† (lowest dose needed is 0.5 mg, but 2.5 mg is smallest dose available)	Daily; cycled	Edema, nausea, breast tenderness
Megestrol acetate	Oral	20-40 mg	Daily	Hypertension, rash, hot sweats, weight gain, diarrhea, nausea, insomnia, mood swings
Micronized progesterone	Capsule inserted vaginally†§	100-300 mg; 200-300 mg	Daily; cycled	As above for oral consumption, to a lesser degree
Progesterone	Vaginal gel†§	4-8% (45-90 mg); 8%	Daily; cycled	Same as oral micronized progesterone, to a lesser degree

*Provides contraception.
†Not approved by US Food and Drug Administration (FDA) for use in menopausal hormone therapy.
‡Little research is available to determine the lowest dose of norethrindrone that effectively protects the endometrium in the setting of menopausal estrogen use. A randomized controlled trial (RCT) randomized women taking 1 mg oral estradiol daily to no progestogen or norethrindrone 0.1, 0.25, or 0.5 mg daily. At 12 month follow-up, rare hyperplasia and no malignancy occurred in either 0.25 mg or 0.5 mg group, with the least breakthrough bleeding in those taking 0.5 mg.[55] The authors concluded that both 0.25 and 0.5 mg norethrindrone provides adequate protection. A British Menopause Society publication using the same data came to a more conservative recommendation of 0.5 mg norethrindrone.[54] In the US, only a 0.35 mg pill is available. The North American Menopause Society guidebook suggests that 0.35 mg, although not FDA approved, could be considered for endometrial protection with hormone therapy.[52] At higher estradiol doses or when cycling progestogens, 0.7 mg is recommended. If selecting norethrindrone, providers should inform patients of the limited data and consider FDA approved or more studied options first.
§Vaginal formulations may be preferred by some women; however, none are FDA approved or well studied. The ELITE trial paired oral estradiol 1 mg daily with progesterone vaginal gel 4% 10 days per month and showed increased rates of hyperplasia at median 4.8 year follow-up, concluding that this dose and regimen does not provide adequate endometrial protection.[56] Whether daily progesterone 4%, cycled progesterone 8%, or daily progesterone 8% would offer adequate protection is unknown. One small RCT that randomized women to estradiol 0.05 mg patch with continuous oral micronized progesterone 100 mg or 200 mg or vaginal progesterone 100 mg or 200 mg daily showed no significant differences in endometrial thickness at 12 month follow-up but provided no histologic outcomes. If using micronized progesterone capsules vaginally, equivalent dosing to oral dosing is suggested, even though vaginal absorption and effective dose to the uterus may be higher with this route of administration.[54]

Table 5 | Combined estrogen-progestogen options for hormone therapy[52-54]

Name	Route	Dose range	Frequency
17-β estradiol	Patch	0.05 mg+0.14 mg; 0.05 mg+0.25 mg	Twice weekly
NETA	Oral	0.5 mg+0.1 mg; 1.0 mg+0.5 mg	Daily
17-β estradiol+levonorgestrel	Patch	0.045 mg+0.015 mg	Weekly
CEE+MPA	Oral	0.625 mg+5 mg	CEE daily; CEE+MPA on days 15-28
		0.3 mg+1.5 mg; 0.45 mg+1.5 mg; 0.625 mg+2.5 mg; 0.625 mg+5 mg	Daily
17-β estradiol+norgestimate	Oral	1 mg+0.09 mg	Cyclic
17-β estradiol+micronized progesterone	Oral	0.5 mg+100 mg; 1 mg+100 mg	Daily
17-β estradiol+drospirenone	Oral	0.5 mg+0.25 mg; 1mg+0.5 mg; 1 mg+1 mg	Daily
BZA+CE	Oral	20 mg+0.45 mg; 20 mg+0.625 mg	Daily
Ethinyl estradiol+NETA	Oral	2.5 µg+0.5 mg; 5 µg+1 mg	Daily

BZA=bazedoxifene acetate; CE=conjugated estrogen; CEE=conjugated equine estrogen; MPA=medroxyprogesterone acetate; NETA=norethindrone acetate.

daily with intermittent oral micronized progesterone (200 mg daily for 12 days every two to three months) or placebo. At 12 months of intervention, only 17% of women in the hormone therapy group reported clinically significant depressive symptoms compared with 32% in the placebo group (P<0.05).[104]

In the SWAN study, women who started hormone therapy before their FMP had improvement in verbal memory and processing speed compared with women who started hormone therapy postmenopause.[105 106] Although the risk of dementia was increased in women who started hormone therapy at age 65 or later in the WHI trials, hormone therapy use was not associated with increased mortality from Alzheimer's disease or dementia at 18 year follow-up.[32 107]

Disordered sleep

New onset or worsening of sleep disorders is common in the menopause transition, with 40-60% of women experiencing major sleep difficulties.[108-110] Frequent awakenings are a hallmark of sleep disturbance in the menopause transition.[111] Sleep apnea, periodic limb movement, restless leg syndrome, and incidence of nocturia increase after menopause.

The preponderance of research suggests a bidirectional relation between hot flashes and sleep impairment.[112-115] In an RCT of 339 perimenopausal and postmenopausal women with two or more bothersome hot flashes daily, treatment with low dose oral estradiol or venlafaxine improved sleep quality and reduced insomnia symptoms compared with placebo.[116]

Hormonal treatments

According to a recent meta-analysis, hormone therapy improved self-reported sleep outcomes but not sleep parameters on polysomnography.[117] Both estradiol and CEE improved sleep quality, and the transdermal route was more beneficial than the oral route. Micronized progesterone reduced sleep disturbance more than medroxyprogesterone acetate did, although both helped.

For patients starting hormone therapy who have impaired sleep, bedtime micronized progesterone is the preferred progestogen owing to its sedating properties caused by binding to γ-aminobutyric acid A (GABA) receptors.[118] A systematic review and meta-analysis of RCTs found that micronized progesterone improves multiple sleep parameters, particularly sleep latency, although some users may feel groggy in the morning.[119]

Non-hormonal options

Sleep hygiene counseling is first line.[120] Cognitive behavioral therapy (CBT) for insomnia is the most efficacious treatment for insomnia in perimenopausal and postmenopausal women.[4 121 122] Data suggest that melatonin is useful for circadian rhythm disorders and reduces sleep onset latency, but it does not reduce awakenings.[123] First line drugs include GABA agonists such as zolpidem, certain benzodiazepines, and dual orexin receptor antagonists.

Decreased sexual desire

During the menopause transition, decline in sexual desire is common and multifactorial and can cause distress. Some women describe a change in their libido as a loss that affects their identity and relationships. In a survey of western European women, whereas 11% of those aged 20-29 experienced low sexual desire, 53% did so by ages 60-70, with 22% reporting associated distress.[124] A woman with at least six months of distressing low desire not primarily driven by extrinsic or directly treatable causes has hypoactive sexual desire disorder (HSDD).

Table 6 | Treatment adjustments in first six months of hormone therapy

Symptom	Cause and action
Breast tenderness	Most likely due to excess estrogen; decrease
	Consider progestogen selection and dosing as well
New onset or more frequent spotting or bleeding than previously; increased abdominal cramping	Most likely due to excess estrogen, although can occur with reduction in estrogen; modify
	Consider progestogen: may need higher dose or different formulation or route of administration
	More likely to occur in women with underlying adenomyosis, fibroids, polyps; consider treatment.
	If endometrial cancer risk factors present, and begins >3 months after hormone therapy start, consider investigation for abnormal uterine bleeding
Hot flashes persist	Insufficient estrogen most likely; if dose is high, consider alternative routes of administration and causes
	Inquire into how estrogen is used, any missed doses, patches falling off, etc
Skin irritation from patches	Contact or allergic dermatitis; switch to another brand with different adhesive or another route of administration without adhesives

Table 7 | Non-hormonal oral treatments for vasomotor symptoms

Name	Drug type	Dose range	Frequency	VMS reduction	Side effects
Paroxetine	SSRI	7.5 mg	Nightly	−33 to −43.5 per week (P<0.0001; P=0.009)[89]	Dizziness, nausea, fatigue, dry mouth, decreased libido, impaired orgasm, sweating
				Mean effect: −1.23 (95% CI −2.39 to −0.12) per day compared with placebo[90]	
Escitalopram		10-20 mg	Daily	Mean effect: −2.05 (95% CI −4.82 to 0.62) per day compared with placebo[90]	
Citalopram		10-30 mg	Daily	Mean effect: −0.54 (95% CI −2.00 to 0.83) per day compared with placebo[90]	
				No more than placebo[91]	
Fluoxetine		20-30 mg	Daily	Mean effect: −0.14 (95% CI −1.55 to 1.30) per day compared with placebo[90]	
				No more than placebo[91]	
Sertraline		50-100 mg	Daily	Mean effect: −0.83 (95% CI −3.44 to 1.64) per day compared with placebo[90]	
Venlafaxine	SNRI	37.5-75 mg	Daily	48% (95% CI 3.5% to 5.3%) per day[92]	As above, plus headache, palpitations, constipation; withdrawal with missed doses or weaning
Desvenlafaxine		100 mg	Daily		
Gabapentin	Gabapentinoid	100-300 mg	3 times daily	51% reduction per day with 300 mg 3 times daily (P<0.001)[93]	Drowsiness, unsteadiness, dizziness
Clonidine	α2 agonist	0.025- 0.1 mg	Daily	4 trials showed overall reduction compared with placebo; 5 trials found no difference from placebo[91]	Dry mouth, drowsiness, insomnia; rare: hypotension, rebound tachycardia, and hypertension
Oxybutynin	Antispasmodic anticholinergic	2.5-5 mg	Twice daily	Hot flash scores: 70-86% reduction (P=0.004; P<0.001); hot flash frequency: 60-77% reduction (P=0.002; P<0.001)[94]	Dry mouth, diarrhea, urinary tract infections, difficulty urinating, abdominal pain, dyspepsia; possible association with dementia (observational studies only)[95 96]

SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor.

Box 3 shows common causes of reduced sex drive. A thorough history is often sufficient to diagnose HSDD. If a contributing condition is clinically suspected, laboratory testing such as complete blood count, iron studies, thyroid function tests, testosterone, SHGB, prolactin, estradiol, and follicle stimulating hormone can be ordered, but these are not required to make the diagnosis of HSDD.[125]

Menopausal hormone therapy

Research in premenopausal and postmenopausal women suggests that estradiol can modulate central sexual desire.[127-129] However, in a Cochrane meta-analysis that included multiple routes of estrogen administration, estrogen was found to reduce sexual pain but not directly augment sexual desire.[130] In the KEEPS RCT, although both transdermal and oral estrogen improved vaginal dryness and dyspareunia, only transdermal estradiol improved libido and sexual satisfaction.[131] Oral estrogens may decrease sex drive by lowering free testosterone through upregulation of SHBG during first pass metabolism.[131-133]

Box 3: Common causes of reduced sex drive[125 126]

- Life and relationship stressors
- Decline in estrogen
- Decline in testosterone
- Reduced genital sensation
- Genital pain
- Impaired sleep
- Mood disorders
- Comorbidities
- Drug side effects: selective serotonin reuptake inhibitors, tricyclic antidepressants, antipsychotics, antiepileptics, narcotics, antihistamines, β blockers, antihypertensives, statins, gonadotropin releasing hormone agonists/antagonists, oral contraceptive pills, antiandrogens, tamoxifen, and chemotherapy agents

Non-hormonal options

Non-hormonal pharmacologic HSDD treatments are FDA approved only for use in premenopausal and perimenopausal women. Flibanserin, an oral mixed 5-HT1A agonist/5-HT2A antagonist, was shown in three RCTs of premenopausal women and one of naturally postmenopausal women with HSDD to promote one additional satisfying sexual event monthly.[134] An open label non-placebo controlled extension of the safety study included postmenopausal women (249 of 595 women) and showed comparable safety, with 59% experiencing adverse events, including dizziness, somnolence, insomnia, and nausea, with no serious adverse events.[135] Concurrent alcohol use may result in hypotension, so dose reduction and holding guidelines are recommended.

Bremelanotide, an on-demand self-injectable non-selective melanocortin receptor agonist, acts primarily on the MC4R receptors to modulate neurologic sexual response.[136] Phase 3 trials showed clinically small but statistically significant improvements in sexual desire with an increase in female sexual dysfunction-desire score of 0.30 out of 10 (P<0.001) and a reduction in distress from low desire of −0.33 on a 0-4 scale (P<0.001).[137] Bremelanotide has not been studied in postmenopausal women, so off-label use is not recommended. Common side effects include nausea, flushing, headache, skin hyperpigmentation, and injection site reactions.

Off-label bupropion can improve sex drive in women with or without depression, possibly via

Box 4: Diagnosing osteopenia and osteoporosis with DEXA[144]

Normal bone density:
- T score >−1.0

Osteopenia:
- T score −1.0 to −2.4

Osteoporosis:
- T score ≤−2.5
- Low trauma spine or hip fracture
- T score −1 to −2.5 and fragility fracture
- T score −1 to −2.5 and high FRAX or TBS adjusted FRAX based on country specified thresholds

DEXA=dual energy x ray absorptiometry; FRAX=fracture risk assessment tool; TBS=trabecular bone score

Make the diagnosis of osteopenia or osteoporosis on the basis of the lowest T score. Disease in one site indicates whole body disease

dopamine and norepinephrine modulation.[138] Studies have shown mixed effects on sexual function.[139 140] Short and long term safety are well documented. Monitoring for common side effects of anxiety, hypertension, and insomnia is important.

Behavioral treatments

Sex therapy provides education about sexual response, communication and negotiation, cultural concerns, and exercises for individuals and couples.[138] CBT, mindfulness, and sensate therapy are common modalities that are low risk and often helpful.[134] Providers should screen for physical, sexual, and emotional intimate partner violence and make appropriate referrals.

Bone loss

Women reach peak bone mass around age 30, followed by relative stability and then a 2% annual bone mass loss starting one to three years before menopause and lasting for five to 10 years. This results in a 10-15% average reduction in bone mineral density (BMD) across the menopause transition.[141] After this period, BMD declines by 0.4% annually.[142] In the US, more than half of all women 65 and older have osteopenia, and nearly one quarter have osteoporosis.[143] These progress with aging, and more than one third of women have osteoporosis by age 80.[143]

All postmenopausal women should be clinically assessed for osteoporosis and fracture risk using dual energy x ray absorptiometry (DEXA) scanning (box 4 and table 8). The FRAX calculator (https://frax.shef.ac.uk/FRAX/index.aspx) uses country specific criteria to quantify individual risk. The Association of Clinical Endocrinologists (AACE) and the US Preventive Services Task Force recommend BMD testing for premenopausal women with strong risk factors or significant fracture history, postmenopausal women at increased risk for bone loss and fracture, and all those 65 and older. Testing should be done at diagnosis for premature or early menopause.

Osteoporosis is preventable and treatable, but only a small fraction of women at risk receive treatment. Once the diagnosis of osteoporosis is made, it is a lifelong disease even if BMD improves.

Treatment

Antiresorptive agents inhibit bone turnover. These include estrogen, raloxifene, bisphosphonates (oral alendronate, risedronate, ibandronate, and intravenous zoledronic acid), and the RANK-ligand inhibitor denosumab. Anabolic agents stimulate bone formation. These are teriparatide, a parathyroid hormone analog, and abaloparatide, a parathyroid hormone related protein analog. The sole remodeling stimulator, romosozumab, increases bone formation and, to a lesser degree, decreases resorption. The FDA endorses estrogen for prevention, but not treatment, of osteoporosis as it is not as effective as other therapies for this degree of bone loss.[13]

Bisphosphonates or denosumab are first line for most women. For those at very high risk, anabolic therapy should be used first for rapid reduction of fracture risk and BMD improvement, followed by potent antiresorptive agents.[144-149] Adverse events of bisphosphonates and denosumab include osteonecrosis of the jaw and atypical femur fracture, both of which are rare.[150 151] Discontinuation of denosumab increases risk of vertebral fracture.[149]

Raloxifene is an ERAA used for prevention and treatment of osteoporosis in postmenopausal women.[152 153] It is not as effective as the therapies mentioned above.[154] Common side effects include hot flashes and vaginal dryness, and adverse events include stroke and venous thromboembolism.[154]

Genitourinary syndrome of menopause

GSM comprises the progressive effects of estrogen loss on the genitourinary system. The signs and symptoms include vaginal dryness, pruritis, insufficient vaginal lubrication, pain with sex, urinary urgency, dysuria, and urinary tract infections (UTIs).[12 155] As the hormonal environment changes, the vaginal pH increases and the microbiome shifts, increasing the risk of urinary and vaginal infections.[156] GSM affects 50-84% of postmenopausal women in the US,[155 156] but only 50% receive treatment, often owing to

Table 8 | Fracture risk assessment[144-149]

Factor	Low risk	Moderate risk	High risk	Very high risk
Previous fracture?	None	None	One more than 2 years earlier	Multiple within past 2 years
DEXA T score	>−1	−1 to −2.5	<−2.5 or −1 to −2.5 with high FRAX	<−3.0
FRAX probability of 10 year risk	<20% MOF; <3% hip fracture	<20% MOF; <3% hip fracture	>20% MOF; >3% hip fracture	>30% MOF; >3.5% hip fracture

Overall risk is determined by factor in highest risk category.
DEXA=dual energy x ray absorptiometry; FRAX=fracture risk assessment tool; MOF=major osteoporotic fracture.

Table 9 | Local vaginal hormonal therapies[52]

Name	Route	Dose range	Frequency
17-β estradiol	Cream	1-2 g	Daily or nightly for 2 weeks, then 2-3 time weekly
	Insert	4 or 10 µg	
	Ring	2 mg	90 days
Estradiol hemihydrate	Tablet	10 µg	Daily or nightly for 2 weeks, then 2-3 times weekly
Conjugated estrogen	Cream	0.5-2 g	Daily or nightly for 21 days, stop for 7 days and repeat
Prasterone (dehydroepiandrosterone)	Insert	6.5 mg	Daily or nightly

discomfort discussing the topic on the part of patient and provider.[12]

Local vaginal hormonal treatments

A systematic review of 53 studies found that vaginal estrogen products were the most effective treatment for GSM, with superiority over vaginal lubricants and moisturizers.[157] A Cochrane review found no difference in efficacy of the various vaginal estrogen forms.[158] Vaginal hormone therapies have been shown to reduce the risk of recurrent UTIs, whereas systemic estrogen has not.[159 160] Another effective option is dehydroepiandrosterone, which is converted to estradiol and testosterone within the vaginal mucosa (table 9).[12]

Local low dose vaginal estrogen and vaginal dehydroepiandrosterone therapy have a safer risk profile than systemic hormone therapy.[12] They are associated with low circulating estradiol concentrations and have not been shown to increase the risk of incident breast, endometrial, ovarian, or colorectal cancer or of cardiovascular disease, stroke, or venous thromboembolism.[12] They are thought to mainly act locally, although a systematic review found that vaginal estradiol absorption varies by formulation, dose, and placement within the vagina.[161] This is likely why breast tenderness and vaginal bleeding may rarely occur.[12]

For women at high risk of breast cancer, NAMS and ISSWSH recommend non-hormonal treatments first line. If these are ineffective, discussion of potential risks versus benefits between the patient and oncologist are warranted.[162]

A recent observational study contradicted previous research that showed no association between vaginal estrogen and recurrence of breast cancer.[163 164] This study of 8461 postmenopausal women with early stage estrogen receptor positive breast cancer taking aromatase inhibitors, tamoxifen, or no endocrine therapy found an association between vaginal estradiol and breast cancer recurrence in a secondary analysis of only those taking aromatase inhibitors (hazard ratio 1.39, 95% confidence interval 1.04 to 1.85), with no effect on breast cancer mortality.[165] Women taking systemic hormone therapy were not found to have an increased risk of breast cancer recurrence. Possible reasons for this contradiction include the dose of vaginal estrogen used (vaginal estrogen doses were higher during the time of data collection), unknown frequencies of human epidermal growth factor receptor 2 positivity among groups, and endocrine therapy used (the type and standards of endocrine therapy have since changed).

Despite considerable safety data, the black box warning for systemic estrogens is included on local vaginal therapies. Clinicians should educate their patients about differences in risk between local and systemic treatment. Unexplained vaginal bleeding contraindicates vaginal estrogen use, and caution is recommended in women with estrogen dependent cancers.[12] Women taking these drugs should promptly report any vaginal bleeding to their clinician.

Systemic hormone therapy

For women whose symptoms are limited to GSM, local vaginal therapies are preferred to systemic hormone therapy.[13] Women with moderate to severe GSM who also have concurrent vasomotor symptoms or osteopenia can consider hormone therapy with added local therapy as needed.[12] Once hormone therapy is stopped, GSM symptoms will likely recur.[12]

ERAAs

Ospemifene is a non-hormonal ERAA. It is the only oral treatment available in the US for GSM and has been shown to improve vaginal dryness, dyspareunia, and vaginal pH.[12] It acts as an estrogen agonist on vaginal and bone tissues, but its effect on the breast is neutral to antagonistic. Adverse effects include vasomotor symptoms and venous thromboembolism.

Non-hormonal therapies

Lubricants for sexual activity and moisturizers for regular use are first line for GSM.[12] Pelvic floor physical therapy and use of dilators benefit women with dyspareunia caused by pelvic floor dysfunction, urinary incontinence, and pelvic organ prolapse.[156]

Discontinuing therapy

Symptoms typically improve within one to three months of starting GSM therapy. Treatment should be continued for as long as a woman derives benefit. Discontinuation leads to the vaginal mucosa returning to a hypoestrogenic state.[12]

Weight gain and metabolic syndrome

During the menopause transition, visceral and overall body fat increase while lean body mass decreases. Basal metabolic rate also declines, resulting in an average weight gain of 1.5 lb (0.7 kg) annually.[13 166] Elevations in total cholesterol, low density lipoproteins, and non-high density lipoproteins have been seen in women after menopause,[52] along with an increased risk of metabolic syndrome.[167] Characteristic impaired sleep, stress, and mood changes can contribute to weight gain and obesity.[166]

Treatment

Oral and transdermal hormone therapy have not been shown to affect weight in menopausal women,[166] but they have been shown to decrease

Table 10 | Professional society guidelines on hormone therapy*[181]

Factor	North American Menopause Society 2022[13]	American College of Obstetrics and Gynecology 2014[10]	AACE and ACE 2011[182] and 2017[183]	Endocrine Society 2015[28]	US Preventive Services Task Force 2022[184]	British Menopause Society and Women's Health Concern 2020[185]	Korean Society of Menopause 2020[186]
Indication	Menopausal symptoms; bone loss prevention; premature hypoestrogenism; GSM	Menopausal symptoms	Menopausal symptoms; GSM	Menopausal symptoms	Menopausal symptoms	Menopausal symptoms; POI or early menopause; osteoporosis in menopausal women <60 years old	Menopausal symptoms; POI or early menopause; prevention and treatment of osteoporosis in menopausal women <60 years old or within 10 years of menopause
Risk considerations before initiation	Consideration of age and time from menopause onset recommended; initiate if patient <60 years of age or within 10 years after onset of menopause	None specifically recommended	Consideration of age, time from menopause, lipid profile, history of diabetes, smoking history, family history, and CVD risk	Assessment of risk of CVD and breast cancer recommended; avoid if risk is high	Not covered	Consider overall benefits including symptom control, improving quality of life, and bone and cardiovascular benefits alongside cardiovascular and oncologic risks. Starting before age 60 typically has favorable benefit:risk ratio	Pre-requisite history and physical examination including cardiovascular, endocrine, bone, breast, endometrial, hepatic, and lifestyle assessment. Laboratory evaluation of red cell parameters, liver and kidney function, fasting blood sugar, and lipids. Mammography, BMD testing, and pap smear
Recommendation on timing of therapy	Preferably before age 60 or within 10 years of menopause	Some data suggest better risk/benefit profile before age 60 or within 10 years of menopause	Some data suggest better risk/benefit profile before age 60 or within 10 years of menopause	Preferably before age 60 or within 10 years after menopause onset	Not covered	Preferably before age 60 and within 10 years of menopause. Data suggest possible benefit in prevention of CVD when initiated close to menopause	Preferable to start immediately once symptoms appear, before or after menopause. Should start before age 60 and within 10 years of menopause
Dosing consideration	Lowest effective dose of appropriate drug, with consideration of route and duration	Lowest effective dose for shortest time needed to relieve symptoms and minimize risks of therapy	Lowest effective dose for shortest time needed to manage symptoms	Shared decision making to determine formulation, dose, and route	Not covered	Dose and duration should be determined by symptom severity, treatment response, and consideration for dose and duration dependent risks such as breast cancer. Arbitrary limits should not be placed on dose or duration	Lowest effective dose
Duration of use	Extended for vasomotor symptoms, bone loss, or quality of life after attempt at stopping in healthy women with low CVD and breast cancer risk in whom benefits are greater than risks	Decision to continue should be based on individual risk/benefit analysis. Recommendation against routine discontinuation at age 65	Recommended for ≤5 years; longer term use controversial	Shortest total duration for treatment goals and risk assessment	Not covered	Dose and duration should be determined by symptom severity, treatment response, and consideration of dose and duration dependent risks such as breast cancer. Arbitrary limits should not be placed on dose or duration	No limit on duration if an effective minimum dose is used, women are aware of potential benefits and risks, and regular clinical follow-up occurs. Evaluate comorbidities; consider temporarily discontinuing or reducing dose and switching to transdermal over time
Recommendation for transdermal estrogen therapy	Observational data suggest lower risk of VTE and stroke than with oral estrogen, although randomized trial data are lacking. Transdermal is preferred for women with low libido given that oral estrogen increases sex hormone binding globulin and reduces bioavailability of testosterone	Transdermal may be associated with reduced VTE risk, although data are not strong enough to make recommendation	Preferred over oral therapy if elevated risk of VTE; may be associated with less risk of stroke and CAD	Preferred over oral therapy if elevated risk of VTE; may be preferred in metabolic syndrome, obesity, hypertriglyceridemia, diabetes, history of gallbladder disease, or hypertension	Not covered	Preferred over oral therapy if elevated risk of VTE or stroke and/or age >60	Preferred over oral therapy if elevated risk of VTE or stroke, obesity with metabolic syndrome, tobacco smoking, hypertension, and/or age >60

(*Continued*)

Table 10 | Continued

Factor	North American Menopause Society 2022[13]	American College of Obstetrics and Gynecology 2014[10]	AACE and ACE 2011[182] and 2017[183]	Endocrine Society 2015[28]	US Preventive Services Task Force 2022[184]	British Menopause Society and Women's Health Concern 2020[185]	Korean Society of Menopause 2020[186]
Recommendation for prevention of chronic disease	Not recommended for CHD prevention; supportive of bone loss prevention; Observational data suggest possible benefit in prevention of CVD when initiated close to menopause	Not recommended for CHD or osteoporosis prevention; however, data suggest possible benefit in prevention of CVD when initiated close to menopause	Not recommended for prevention of CHD or diabetes; however, data suggest reduced risk of CVD may occur when initiated close to menopause. Supportive of prevention of osteoporosis in select women	Not recommended for prevention of CHD, breast cancer, or dementia	Not recommended for primary prevention of chronic disease	Not recommended for primary or secondary CVD prevention; however, data suggest starting before age 60 or within 10 years of menopause is associated with reduction in atherosclerosis, CAD, and death from CVD and all cause mortality. Recommended for prevention of osteoporosis	Not recommended for primary or secondary prevention of CHD; however data suggest starting before age 60 or within 10 years of menopause in those without evidence of CVD is associated with reduced risk of CHD and all cause mortality. Recommended for osteoporosis prevention (and treatment)
Recommendation for vaginal therapy for genitourinary syndrome in women at risk for breast cancer	Involvement of oncologist recommended if history of breast cancer	Involvement of oncologist recommended if history of breast cancer	Not covered	Shared approach to decision making with oncologist	Not covered	Low dose vaginal estrogen not associated with increased risk breast cancer	Involvement of oncologist necessary if history of breast cancer, especially if using aromatase inhibitors

AACE=American Association of Clinical Endocrinologists; ACE=American College of Endocrinology; BMD=bone mineral density; CAD=coronary artery disease; CHD=coronary heart disease; CVD=cardiovascular disease; GSM=genitourinary syndrome of menopause; POI=primary ovarian insufficiency; VTE=venous thromboembolism.
*Women with premature menopause or primary ovarian insufficiency are encouraged to use hormone therapy at least until they reach the average age for the onset of menopause. The American Association of Clinical Endocrinologists, the American College of Endocrinology, the American College of Obstetricians and Gynecologists, the North American Menopause Society, the Endocrine Society, the British Menopause Society, and the Korean Society of Menopause advise against the use of compounded hormone therapy that has not been approved by the US Food and Drug Administration. These groups also generally advise against the use of hormone therapy in women with a history of breast cancer.

visceral fat and increase lean body mass.[168] Several reports have shown improved blood glucose, insulin resistance, and lipids in women using hormone therapy.[166 168] In the intervention phase of the WHI trials, women actively taking hormone therapy had reduced rates of type 2 diabetes, with a hazard ratio of 0.86 (95% confidence interval 0.76 to 0.98) in the CEE only arm and 0.81 (0.70 to 0.94) in the CEE plus medroxyprogesterone acetate arm. This difference attenuated at long term follow-up.[31] In a meta-analysis of 107 trials with 33 315 women, hormone therapy was found to increase lean body mass and high density lipoproteins, improve insulin resistance, and reduce type 2 diabetes, abdominal obesity, low density lipoprotein, average blood pressure, and lipoprotein(a); oral hormone therapy had pronounced benefits, whereas transdermal hormone therapy showed mild benefits. Oral hormone therapy, however, was associated with an increase in triglycerides, coagulation factors, and C reactive protein.[169]

Individualized dietary optimization, enhanced physical activity, stress reduction, and sleep may promote healthy weight and body composition. Both medical and surgical treatments can also treat obesity in midlife women.

Irregular and abnormal uterine bleeding

The investigation and management of irregular bleeding differ by menopausal status, underlying risk factors, and use of hormonal therapies. For women not taking hormone therapy, all postmenopausal bleeding is abnormal and requires diagnostic investigation. In perimenopause, longer or shorter menstruation, increased or mildly decreased intermenstrual length, and long periods of amenorrhea are all common and unconcerning.[170] Frequent, heavy, prolonged, and intermenstrual bleeding are abnormal and warrant diagnostic investigation.[171]

Irregular bleeding can be disruptive and lead to iron deficiency and anemia. Hormonal treatment for benign causes includes a progestogen course, CHC, progestin-only pills, and progestin intrauterine devices. Non-hormonal treatments include non-steroidal anti-inflammatories and tranexamic acid. For more definite bleeding control dilation and curettage, uterine artery embolization, endometrial ablation, and hysterectomy can be considered.[172]

For postmenopausal women on cyclic hormone therapy, bleeding is expected with progestogen withdrawal. Progestogen dosing can be adjusted. Unscheduled bleeding persisting beyond six months is abnormal. For postmenopausal women on continuous hormone therapy, bleeding persisting beyond six months or beginning after this timeframe is abnormal.[13 54]

Considerations for special populations

Women >10 years after final menstrual period with bothersome symptoms

Distinguishing between new onset and ongoing symptoms with delayed presentation is necessary.

Fig 4 | Guidelines for systemic testosterone use in women with hypoactive sexual desire disorder. Schematic adapted and modified from the International Society for the Study of Women's Sexual Health clinical practice guideline for the use of systemic testosterone for hypoactive sexual desire disorder in women[193]

New onset of hot flashes many years after menopause raises concern about non-menopausal causes, requiring investigation.[13]

Because of the age related increased risk of cardiovascular disease and venous thromboembolism, non-hormonal options should be explored first for women whose symptoms are attributable to hypoestrogenism. If these do not adequately treat symptoms, an individual risk assessment should be conducted. If the patient opts for hormone therapy, the lowest effective dose should be used for the shortest duration and non-oral routes are preferred. Close follow-up and routine consideration of tapering and discontinuation are important.

High risk of breast cancer

For women with vasomotor symptoms at increased risk of breast cancer, non-hormonal options are first line, but women with no history of breast cancer may cautiously consider hormone therapy. The Tyrer-Cuzick model (https://ibis-risk-calculator.magview.com/) may help in determining a woman's risk of incident breast cancer.

Few data are available on whether hormone therapy simply adds or might amplify breast cancer risk for women at high underlying risk. In a perspective piece responding to the CGHFBC meta-analysis, investigators stratified the participants in the Million Women Study into low, medium, and high risk groups on the basis of five year National Cancer Institute or IBIS breast cancer risk assessment. The risk attributable to combination hormone therapy was 12, 42, and 85 per 1000 people who developed breast cancer in each group, respectively; in estrogen-only users, it was 4.8, 9.9, and 19 per 1000.[173] This raises concern that hormone therapy may have a stronger effect on those at higher risk, although the methods involve inherent bias.

Women with BRCA 1 or 2 mutations are at higher risk of cancer, including breast and ovarian cancers. Some women undergo risk reducing bilateral salpingo-oophorectomy (RRBSO) to prevent ovarian cancer. Reviews on the effect of hormone therapy on breast cancer in women with BRCA mutations and hormone therapy after RRBSO highlight several good quality observational studies showing that estrogen alone may be neutral to beneficial in reducing breast cancer risk, whereas studies showed no to small absolute increases in risk with estrogen-progestogen use compared with women with RRBSO not taking hormones, dependent on duration of use.[174] Using hormone therapy until the average age of menopause offers substantial cardiovascular, bone, and other benefits with minimal increase in absolute risk of cancer, thus warranting consideration.[175]

History of gynecologic cancer

For patients with a history of gynecologic cancer, oncologists should be included in shared decision making. NAMS and the joint European Menopause

and Andropause Society and International Gynecologic Cancer Society position statements from 2022 and 2020 agree that hormone therapy is likely safe for women with treated stage I endometrial cancer, non-serous and epithelial ovarian cancer, and non-hormone responsive cervical, vaginal, and vulvar cancers; however, high quality evidence is limited.[13 176 177] Neither systemic nor topical hormone therapy is recommended for women with a history of serous or granulosa cell tumors, high grade or advanced stage endometrial cancers, endometrial stromal sarcomas, or leiomyosarcomas.

History of thrombophilia

For women with a history of treated, provoked venous thromboembolism, their risk may have returned to the population average. Those with known clotting disorders such as factor V Leiden and antiphospholipid syndrome should avoid estrogen and the prothrombotic progestins. If all non-hormonal treatment options fail to treat symptoms, use of low dose transdermal estradiol with micronized progesterone could be considered, as could possibly starting anticoagulation in consultation with a hematologist.[178 179]

History of migraine

Migraine is not a contraindication to hormone therapy use, and physiologic estradiol dosing for menopausal symptoms is not associated with increased risk of stroke among women with migraine with aura.[180] Although data in this population are limited, using the lowest dose and transdermal route may mitigate any risks not captured by studies. For migraines triggered by hormonal fluctuations, using continuous estrogen and progestogens is preferred.

People of diverse genders

The main consideration for gender diverse people is to provide sensitive, individualized care, using the patient's own gender and anatomic terms. People born with ovaries taking masculinizing hormones may experience hypoestrogenic symptoms and amenorrhea within several months of starting treatment. Some choose to undergo hysterectomy and others will also undergo bilateral salpingo-oophorectomy. The treatments discussed above should be offered, noting that estrogen and progestogen use may be less desirable if incongruent with the patient's thoughts about hormones and gender. For people born with testes on feminizing therapy, testosterone reduction and increased estrogen can cause unwanted side effects. This can be more pronounced in those who undergo orchiectomy. If hormones are stopped at any point, withdrawal symptoms and bone loss are common.

Guidelines

The most recent and comprehensive guidelines on treating menopausal symptoms and signs come from NAMS in 2022. Table 10 also includes subspecialty specific and international guidelines that used high quality evidence in their recommendations and applied appropriate caveats when evidence was lacking. The guidelines generally agree on core principles. Hormone therapy is recommended for treatment of signs and symptoms of menopause but not prevention of cardiovascular disease. That said, the British and Korean guidelines suggest starting hormone therapy early, as it may reduce the risk of cardiovascular disease. This is an open area of research.

Emerging treatments

Vasomotor symptoms

Before menopause, estrogen binds to and inhibits activity in the kisspeptin, neurokinin B, and dynorphin (KNDy) neurons. With menopausal loss of estrogen, KNDy neurons can stimulate the hypothalamic thermoregulatory center inappropriately, causing vasomotor symptoms. A novel class of non-hormonal neuromodulators includes the recently approved fezolinetant, and several under investigation, such as elinzanetant and Q-122.

Fezolinetant is an oral neurokinin-3 receptor antagonist under FDA review. The phase 3 trial randomized women aged 40-65 and averaging seven or more moderate-to-severe hot flashes a day 1:1:1 to placebo, fezolinetant 30 mg, or fezolinetant 45 mg. At week 12, the difference in the least squares mean frequency of vasomotor symptoms for fezolinetant 30 mg compared with placebo was −2.39 (standard error 0.44) hot flashes (P<0.001) and −2.55 (0.43) hot flashes (P<0.001) for fezolinetant 45 mg compared with placebo. Severity also decreased significantly. The most frequent adverse effects were headache and nausea.[187]

Elinzanetant is an oral neurokinin-1 and neurokinin-3 receptor antagonist undergoing phase 3 trials. The phase 2 trial randomized 152 postmenopausal women to four different doses of elinzanetant versus placebo and showed reduced frequency of VMS for those taking elinzanetant 120 mg at four and 12 weeks and elinzanetant 160 mg at four weeks only. Significant reduction in least squares mean severity was found only for women taking elinzanetant 160 mg at week 12 (0.27 (0.13); P=0.048).[188]

Q-122 is a twice daily oral KNDy neuron modulator that targets the C-X-C chemokine receptor type 4. A phase 2 clinical trial in 131 women with breast cancer taking tamoxifen or aromatase inhibitor therapy found that Q-122 produced a statistically significant improvement in the self-reported Vasomotor Symptom Severity Score compared with placebo at 28 days. Adverse effects included hot flashes, diarrhea, and UTIs.[189]

Genitourinary syndrome of menopause

Vulvovaginal energy based devices may work by creating microtrauma in the vaginal mucosa, thereby stimulating collagen growth and thickening of the epithelium.[12] These devices are not FDA approved for treatment of GSM. In a 2017 systematic review and

meta-analysis of 14 low to very low quality studies on the effect of laser therapy on GSM, laser therapy improved symptoms and quality of life and restored vaginal mucosa.[190] A 2022 systematic review of vaginal lasers on GSM included 64 studies (10 RCTs, seven observational studies, and 47 pre-post studies without a control group). It found improvements in Female Sexual Function Index, the vaginal health index, and symptoms on the visual analog scale. However, studies were not high quality and under-reported safety data. Further clinical trials with sham control groups are needed.[191]

Hypoactive sexual desire disorder

According to the 2019 global consensus position statement on testosterone therapy (not FDA approved) in women, testosterone has sufficient efficacy and safety data to be indicated for postmenopausal women with HSDD.[192] In the 2021 International Society for the Study of Women's Sexual Health (ISSWSH) clinical practice guideline on systemic testosterone for HSDD in women, RCTs consistently show testosterone to be more effective than placebo in improving sexual desire, arousal, orgasm frequency, genital responsiveness, frequency of satisfying sexual events, and self-image when given with or without hormone therapy.[193]

Short term safety data are encouraging, but long term data are lacking. A meta-analysis of seven trials of transdermal testosterone 300 µg patch daily versus placebo with or without hormone therapy for 24 weeks showed that common adverse effects were acne and hair growth, with no alopecia, clitoromegaly, or voice deepening.[194] Lipid profiles, cardiometabolic markers, and liver and kidney function were unchanged. Short term studies showed no increase in breast cancer or cardiovascular events, but long term safety data beyond two years are limited and inconclusive.[193]

Because studies have focused on postmenopausal women, insufficient data are available to endorse testosterone use in perimenopausal women.[195] That said, in this typically younger and healthier population, fewer underlying risks should exist beyond the need to ensure contraception, so its consideration is reasonable.

Testosterone should be delivered via transdermal route and monitored according to the ISSWSH practice guideline (fig 4). Compounded transdermal testosterone from reliable compounding pharmacies can be considered, as no government approved transdermal formulation is available for women outside of Australia. Sublingual, intramuscular, oral, and pellet formulations are more likely to yield dangerous supraphysiologic concentrations and permanent adverse effects, and thus are not recommended.[192 194 196-198]

Conclusions

Symptoms of low and fluctuating sex hormones are common and bothersome for many women during the menopause transition and postmenopause. In perimenopause, contraception must be considered. Postmenopause, hormone therapy is the most effective treatment for most symptoms and should include a progestogen for women with a uterus. Risks vary by hormone formulation, dose, and route of administration. Consideration of individualized cardiovascular and oncologic risks is essential for informed, shared decision making. Non-hormonal

GLOSSARY OF ABBREVIATIONS

- AACE—Association of Clinical Endocrinologists
- ACOG—American College of Obstetrics and Gynecology
- BMD—bone mineral density
- CBT—cognitive behavioral therapy
- CEE—conjugated equine estrogen
- CGHFBC—Collaborative Group on Hormonal Factors in Breast Cancer
- CHC—combined hormonal contraceptives
- CHD—coronary heart disease
- DEXA—dual energy x ray absorptiometry
- ERAA—estrogen receptor agonist-antagonist
- FDA—Food and Drug Administration
- FMP—final menstrual period
- GSM—genitourinary syndrome of menopause
- HSDD—hypoactive sexual desire disorder
- ISSWSH—International Society for the Study of Women's Sexual Health
- KNDy—kisspeptin, neurokinin B, and dynorphin
- NAMS—North American Menopause Society
- RCT—randomized controlled trial
- RRBSO—risk reducing bilateral salpingo-oophorectomy
- SHBG—sex hormone binding globulin
- SNRI—serotonin-norepinephrine reuptake inhibitor
- SSRI—selective serotonin reuptake inhibitor
- SWAN—Study of Women's Health Across the Nation
- UTI—urinary tract infection
- WHI—Women's Health Initiative

QUESTIONS FOR FUTURE RESEARCH

- What are the risks of breast cancer, cardiovascular disease, and other chronic disease outcomes with estradiol (via various routes of administration) and micronized progesterone?
- What are the long term effects of extended use of hormone therapy?
- What role should bone health have in decision making about initiation, dosing, and duration of hormone therapy?
- Are the cardiovascular and oncologic risks of hormone therapy the same in perimenopausal women as in postmenopausal women?
- How does age at initiation of hormone therapy influence risk of breast cancer and cardiovascular disease, apart from duration?
- What are the risks of incidence and recurrence of breast cancer with local low dose vaginal estradiol and dehydroepiandrosterone?

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

We asked menopausal women from our clinical practices, some of whom are involved in large scale support groups, to review our proposed outline and provide input on important aspects of their experience that should be included. Input included:

- Know the symptoms and that not all women experience hot flashes
- One patient stated: "I really was shocked that I was so unaware that it was happening or happened. I spent years complaining to specialists... yet, without the tell-tale symptom of hot flashes, it never occurred to me or my previous physicians that these problems could be the result of perimenopause and menopause"
- It is important for women to be educated on the menopause transition and menopause and to have awareness of their body and the changes that are happening
- Women should discuss the menopause transition and menopause with healthcare providers, relatives, and friends
- Don't settle for your care. Find a clinician who listens to your concerns and symptoms; these can be found at www.menopause.org

pharmacologic, complementary, alternative, and behavioral treatments are available, with varied efficacy and safety. New frontiers include neurokinin modulating therapy for vasomotor symptoms, testosterone for HSDD, and novel treatments for GSM. Women should receive education about the symptoms of menopause and be aware that menopause can present in various ways. Ample treatment options are available; clinicians should provide anticipatory guidance and engage women about their symptoms early and regularly.

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Web appendix: Supplementary tables