BMJ Best Practice

Menopause

Straight to the point of care

Last updated: Dec 04, 2024

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Summary

The diagnosis of menopause is clinical, based on the absence of menses for 12 months, and does not require further testing for appropriately presenting patients.

Estrogen therapy is an effective treatment for the management of menopausal symptoms including hot flashes, night sweats, and urogenital symptoms.

For women with an intact uterus, a progestin must be co-administered with an estrogen to protect against endometrial hyperplasia and cancer.

Arbitrary limits should not be placed on the duration of use of hormone therapy (HT); all patients require individualized decision-making. Reassessment should occur at least annually. Transdermal administration of estradiol is associated with a lower risk of stroke and venous thromboembolism than oral administration of estradiol and is unlikely to increase the risk of stroke and venous thrombosis above that of non-users.

Nonhormonal interventions may help women who have a contraindication to, or cannot tolerate, HT. However, they are less effective than HT in controlling menopausal symptoms.

Definition

Onset of menopause is heralded by the cessation of menses for at least 12 consecutive months, without some other reason for amenorrhea (such as pregnancy, hormone therapy, or other medical condition). No further testing is indicated for amenorrhea in an appropriate clinical context or symptoms of menopause in a woman without a uterus.[1]

Permanent cessation of ovarian function may occur surgically by removal of both ovaries (surgical menopause) or medically, usually due to chemotherapy or radiation therapy (treatment-induced menopause).

The perimenopause includes the years before and after the cessation of menses in an ovulating woman and is marked by irregular menses and menopausal symptoms. Management of menopause symptoms requires individualization based on each woman's clinical circumstance.

THEORY

Epidemiology

The average age of menopause in the developed world is 51 years, a benchmark useful for counseling women in the perimenopause (also called menopausal transition or climacteric).[2] Hot flashes (vasomotor symptoms [VMS]) are the most common menopausal symptom: moderate to severe hot flashes were reported by 24% of women ages 50 to 54 years in the Women's Health Initiative.[3] Prevalence decreased rapidly with age, from 15% in women ages 55 to 59 years to 6% in the 60- to 69-year age group and only 3% in women ages >70 years.[3] The Study of Women's Health Across the Nation (SWAN), a multi-ethnic observational study of menopausal transition among 3302 women, found that the median total of VMS duration was 7.4 years.[4] Among the women who had a specific final menstrual period, the median length of VMS was lower at 4.5 years, but women who reported first hot flashes when they were premenopausal or early on in perimenopause had the longest median total duration of >11.8 years. African-American women reported a median 10.1 years of VMS, the longest of any ethnicity in the study. Longer duration of VMS occurred in patients of younger age, lower educational level, greater perceived stress, and with higher depressive symptoms and anxiety.[4]

Etiology

Women are born with a set number of oocytes. As this supply of oocytes becomes depleted during their early 40s, ovarian production of progesterone, estradiol, and testosterone begins to decline. Fertility also significantly declines.

Before menopause, estradiol is the predominant estrogen. Serum estradiol levels vary throughout the menstrual cycle but average about 100 picograms/mL (367 picomol/L). After menopause, estrone, which is derived from estradiol metabolism in the liver and peripheral conversion of androstenedione in adipose tissue, becomes the dominant estrogen. Serum estrone levels average about 30 to 50 picograms/mL (110-184 picomol/L). Symptoms of menopause, such as hot flashes and urogenital atrophy, are closely related to decreasing estradiol levels.[5]

Pathophysiology

The menopausal state has a number of different pathognomonic signs and symptoms, each of which is tied to decreasing ovarian hormone production.

The precise pathophysiology of vasomotor symptoms is currently unknown. The combination of biochemical changes in hormone levels, alterations in the central thermoregulatory zone, alterations in several neurotransmitter systems (serotonergic, noradrenergic, opioid, adrenal, and autonomic), genetic predisposition, and social or cultural factors all contribute to an individual’s perception and complaint of hot flashes.

Declining estradiol levels are associated with symptomatic urogenital atrophy in about 40% of postmenopausal women.[6] There may be vaginal epithelial thinning, decreased secretions, reduction in vaginal elasticity, and increase in the pH of vaginal fluid (>6). Vaginal symptoms include dryness, itching, discharge, and painful intercourse. Thinning of the vaginal and vulvar epithelium can lead to tears and bleeding with intercourse. Changes visible on exam include pallor, loss of rugae, shrinkage of the clitoris and labia minora, loss of fat padding in the labia majora, and shrinkage of the vagina. These factors can lead to significant dyspareunia with attendant declines in self-esteem, quality of life, and sexual function.

In the menopause transition, bone resorption accelerates, resulting in an average decline in bone density of 10% to 12% in the spine and hip.[7] This, combined with other factors such as deconditioning and corticosteroid use, increases the risk of fractures with activities of daily living or falls.[8]

The risk of mortality from cardiovascular disease increases with the onset of menopause, regardless of the reason for menopause onset.[9] This is primarily driven by changes associated with aging, including increase in fat mass, insulin resistance, and modified lipid profile, with an increase in low-density lipoprotein and triglycerides and a decrease in high-density lipoprotein.[10] [11]

Classification

Terminology

Menopause:

- In healthy women, menopause is a natural event that usually occurs between 40 and 60 years of age (average 51 years).[2] This represents the permanent cessation of menstruation and ovulatory function.

Premature menopause:

- Menopause before the age of 40 years is considered premature and may occur spontaneously or because of surgery (such as bilateral oophorectomy), radiation of the pelvis, chemotherapy, autoimmune disease, fragile X syndrome, or unknown causes (idiopathic).

Primary ovarian insufficiency:

- Refers to amenorrhea, hypoestrogenic status, and elevated gonadotropins due to a decline of ovarian function before the age of 40.

Perimenopause:

- The transition from cyclic menstrual bleeding to a total cessation of menses happens over several years; duration is variable. Perimenopause is marked by menstrual irregularity and periods of amenorrhea due to declining progesterone and estradiol levels, and ends 12 months after the final menstrual period.

Case history

Case history #1

A 50-year-old white schoolteacher presents complaining of night sweats and difficulty sleeping. She has also noticed a decrease in her libido and discomfort during intercourse. Her family complains that she is more irritable. She is worried about a 6 pound 10 ounce (3 kg) weight gain since her last visit 1 year ago. She has not had her period for 12 months; immediately prior to that her periods were lighter and shorter. On pelvic exam, the labia minora appear thin and the vaginal mucosa is slightly pale, but the rest of the physical exam is unremarkable.

THEORY

Other presentations

Women who enter premature menopause before age 40, have a hysterectomy with bilateral ovarian removal, or have radiation therapy or chemotherapy that may affect the ovaries may experience more abrupt onset of symptoms than women in natural menopause.

Approach

The diagnosis of menopause is a clinical one, made retrospectively after the absence of menses for 12 months in a patient of an appropriate age for menopause (e.g., >45 years).[1]

History

Sixty or more days of amenorrhea during the previous year has sensitivity of 94% and specificity of 91% for predicting menopause within 2 years.[27] Hot flashes and menstrual irregularity are not helpful for predicting the onset of menopause, because these symptoms may precede menopause by years. It is important to remember the possibility of late-life pregnancy in a woman with amenorrhea. Heavy bleeding carries the possibility of endometrial pathology, and increasing menstrual symptoms of any kind require further investigation.

Exam

There are no consistent characteristic findings in early menopause. Some patients may display thinning of the labia minora or pallor of the vestibule. On speculum exam, there may be loss of rugae and mild pallor to the vaginal mucosa. Generally these changes will occur well after the onset of menopause.

Tests

Menopause is a clinical diagnosis, based on the absence of menses for 12 months.

Serum follicle-stimulating hormone (FSH) is recommended for diagnosis in women under 40 years of age, and may be helpful in women ages 40 to 45 years.[1] [28] An elevated FSH level may be predictive of impending menopause after several months of amenorrhea. Measurement of serum FSH is not recommended in women over 45 years of age. Testing for FSH early in perimenopause is usually not helpful because of variability in levels from day to day and during the menstrual cycle.[29]

Serum estradiol testing is not usually indicated.

History and exam

Key diagnostic factors

amenorrhea (common)

- Sixty or more days of amenorrhea during the previous year has sensitivity of 94% and specificity of 91% for predicting menopause within 2 years.[27]
- It is important to remember the possibility of late-life pregnancy in a woman with amenorrhea.

irregular menstrual cycle (common)

- Irregularity in the menstrual cycle during the late 40s marks the entry into perimenopause. Other causes of infrequent/reduced menstrual bleeding (such as polycystic ovarian syndrome) should also be evaluated in the proper clinical context.

hot flashes and night sweats (common)

- Vasomotor symptoms (VMS) may begin several years before menopause. A multi-ethnic observational study of menopausal transition among 3302 women found that the median total VMS duration was 7.4 years.[4] Among the women who had a specific final menstrual period, the median length of VMS was 4.5 years, but women who reported hot flashes when they were premenopausal or in early perimenopause had a median total duration of >11.8 years.[4] African-American women reported a median 10.1 years of VMS, the longest of any ethnicity in the study.[4]
- Up to 15% of women continue to have hot flashes years after menopause.[30]

vaginal symptoms (common)

- Dryness, itching, and dyspareunia are consistently associated with menopause transition and are related to decreased circulating levels of estrogen, which leads to urogenital atrophy. Vaginal symptoms may affect up to 45% of menopausal women.[31] Pale, dry vaginal mucosa with decreased rugae is often found on pelvic exam and may cause pruritus or dyspareunia and lead to urinary tract infections.

mood changes (common)

- Irritability and mood swings, which range from sadness and crying for no reason to withdrawal from social interaction, are not uncommon.

Other diagnostic factors

sleep disturbance (common)

- These symptoms are commonly associated with menopause transition and are worsened by nocturnal hot flashes.

mild memory impairment (common)

- Minor memory lapses are usually not predictive of developing dementia, and may be related to variable hormone levels and poor sleep (due to hot flashes).

heavy menstrual bleeding (uncommon)

- Approximately 25% of women have at least one episode of heavy menstrual bleeding in the perimenopause, usually before the onset of infrequent/reduced menstrual bleeding. The annual rate of presentation to health services with heavy menstrual bleeding increases from around 2% per year to between 4% and 5% in women >40 years of age, and peaks in women ages between 45 and 49 years.[32]
- Menstrual bleeding that is heavier, longer, or more frequent may be indicative of problems such as endometrial polyps, fibroids, or malignancy.

Risk factors

Strong

age 40 to 60 years

- In healthy women living in the developed world, menopause is a natural event that usually occurs between 40 and 60 years of age, following a normal distribution pattern. The median age at

menopause in Europe ranges from 50.1 to 52.8 years, in North America from 50.5 to 51.4 years, in Latin America from 43.8 to 53 years, and in Asia from 42.1 to 49.5 years.[2] [12]

cancer treatment

- Chemotherapy and pelvic radiation may destroy ovarian follicles and result in abrupt menopause. The risk varies with chemotherapeutic agent, dose, and age at the time of treatment. It is higher with alkylating agents, which can result in primary ovarian insufficiency in approximately 40% of treated cases.[13] Risk attributable to radiation therapy is dependent on the site exposed to radiation, dose, and age at the time of treatment.

smoking

- Smokers undergo menopause about 2 years earlier than nonsmokers and have more hot flashes.[14]

ovarian surgery

- Removal of the ovaries for any reason will immediately precipitate menopause. It is commonly done during treatment for malignancy of the pelvic organs, such as ovarian cancer. Bilateral oophorectomy is less commonly performed in younger women at the time of hysterectomy, but can be part of a treatment program for severe endometriosis. Premenopausal women who are carriers of the BRCA gene mutation may undergo risk-reducing surgery, including prophylactic oophorectomy.[15]

Weak

mother's age at menopause

- The mother's age at onset of menopause is not a strong predictor for her daughters.

Tests

1st test to order

Test	Result
pregnancy test • Indicated in sexually active women with amenorrhea. A negative urine human chorionic gonadotropin (hCG) test reliably excludes pregnancy. • Quantitative blood tests for hCG should be reserved for special clinical circumstances, such as following a possible ectopic pregnancy.	**negative**

Other tests to consider

Test	Result
follicle-stimulating hormone (FSH) • Recommended for diagnosis in women under 40 years of age, and may be helpful in women ages 40 to 45 years.[1][28] An elevated FSH level may be predictive of impending menopause after several months of amenorrhea. • Not recommended in women over 45 years of age; testing for FSH early in perimenopause is usually not helpful because of variability in levels from day to day and during the menstrual cycle.[29]	**elevated >30 IU/L**
serum estradiol • Testing is not usually indicated. • Estradiol is the predominant estrogen before menopause. Serum estradiol levels vary throughout the menstrual cycle but average about 100 picograms/mL (367 picomol/L). • After menopause, estrone, which is derived from estradiol metabolism in the liver and peripheral conversion of androstenedione in adipose tissue, becomes the dominant estrogen.	**<30 picograms/mL (<110 picomol/L)**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Pregnancy	• Amenorrhea with breast tenderness, fatigue, nausea, and an enlarging abdomen may be pregnancy.	• Urine human chorionic gonadotropin (hCG) level >25 IU/L is considered positive for pregnancy. • Urine hCG level <5 IU/L is considered negative for pregnancy.
Polycystic ovary syndrome	• Common features include hirsutism, acne, and scalp hair loss; irregular and infrequent periods (often <8 per year); weight gain; and infertility. • Sweating or oily skin may occur.	• Serum total and free testosterone elevated; serum dehydroepiandrosterone sulfate (DHEAS) elevated. • Symptoms typically begin at the time of puberty.
Hyperthyroidism	• Menstrual irregularity, hot flashes,[33] tachycardia, tremor, hair loss, anorexia, and weight loss.	• Thyroid-stimulating hormone levels may be suppressed (<0.01 IU/L).
Hypothyroidism	• Heavy bleeding, infrequent or reduced menstrual bleeding/amenorrhea. Other symptoms are fatigue, hair loss, dry skin, constipation, and weight gain.	• Thyroid-stimulating hormone levels may be elevated (>10 IU/L).
Anorexia	• Patients with onset of anorexia later in life may also have amenorrhea, vaginal dryness, and sleep disturbance but usually will also be underweight and may have electrolyte disturbance, anemia, and bradycardia (or other cardiac arrhythmia). They do not experience hot flashes. It is normally possible to differentiate an eating disorder from premature menopause by taking a careful history of eating habits and measuring follicle-stimulating hormone (FSH).	• FSH levels will be low to normal (c.f., high in menopause). There may be electrolyte disturbance, anemia, and bradycardia in severe cases of anorexia nervosa. • Ovarian reserve tests (anti-Mullerian hormone, antral follicle count) are likely to be normal.
Adverse effects of medications such	• Tamoxifen and raloxifene (selective estrogen receptor	• Consider a trial of withholding the pertinent therapy if possible, to see if

Condition	Differentiating signs / symptoms	Differentiating tests
as nitrates, niacin, raloxifene, or tamoxifen	modifiers) can cause hot flashes. • Niacin, prescribed to raise high-density lipoprotein cholesterol levels, can also cause hot flashes. • The medication history should include herbal and alternative preparations.	the hot flashes are primarily medication-induced. • Consider nonhormonal treatments (e.g., clonidine, venlafaxine, gabapentin).
Carcinoid syndrome	• Symptoms of carcinoid syndrome include diarrhea and flashes. • Other clinical features include wheeze, palpitations, telangiectasia, and abdominal pain.	• CBC, serum chromogranin A/B, and 24-hour urinary 5-hydroxyindoleacetic acid (5-HIAA) may be elevated. • Imaging studies to identify location of primary tumor.

Screening

For patients with the correct clinical presentation, no testing is needed to establish a diagnosis of menopause.

There are no menopause-specific screening recommendations. Age-appropriate screening is continued through menopause. Cervical cytology may be discontinued at age 65 years in women with a documented history of normal recent cytology tests in the proper clinical circumstance.[34] Screening for breast cancer is age-dependent, and recommendations regarding when to begin vary somewhat between different professional organizations.[35]

Osteoporosis

Bone mass density should be evaluated in all women who meet any of the following criteria:[8]

- Age 65 years and older
- History of fracture after menopause (with the exception of skull, facial bone, ankle, finger, or toe)
- Medical causes of bone loss including >3 months of systemic glucocorticoid therapy.

Bone mass density testing should be considered for postmenopausal women younger than 65 years if one or more of the following risk factors is present:[8]

- Discontinued estrogen with additional risk factors for fracture (e.g., any of those listed below)
- Body weight <127 lb (57.7 kg) or BMI <21 kg/m²
- History of hip fracture in a parent
- Current smoker
- Excessive alcohol intake
- Long-term use of medications associated with bone loss including prednisone or aromatase inhibitors.

In the US, dual-energy x-ray absorptiometry (DXA) is the preferred technique for assessment of bone mass density.[8] Risk assessment and DXA screening policy for primary prevention of osteoporosis may vary regionally.

Approach

Treatment is indicated if menopausal symptoms interfere with a woman's daily functioning and quality of life. The prevailing symptoms should be clarified, and lifestyle changes and drug therapy options (with benefits and risks) explained.

Hormone therapy should be given at the lowest dose and for the shortest time possible, while retaining the benefit of symptom relief. Since duration of symptoms cannot be predicted, there is no predetermined maximum duration of hormone therapy; all patients require individualized decision making. Reassessment should occur at least annually.

Management of hot flashes

Hot flashes can be treated with pharmacologic (hormonal and nonhormonal) or nonpharmacologic (lifestyle and alternative) approaches, or a combination of both.

Lifestyle changes

Despite limited evidence, certain lifestyle changes can improve symptom tolerance. Women should be encouraged to lose weight (where appropriate) and to exercise more.[11] Both have cardiovascular and bone health benefits and can improve overall wellbeing, but may not have a specifically identifiable impact on hot flashes and cannot improve bone density.[8]

Other self-care measures include avoidance of spicy foods, alcohol, caffeine, warm environments, and stress. Alcohol and caffeine intake are associated with worsening vasomotor symptoms (VMS). Wearing layered clothing and use of hand-held fans, drinking cold water, and mist bottles may be helpful. One qualitative review of randomized controlled trials (RCTs) and meta-analyses found that yoga is moderately effective in the short term for psychological symptoms, but has no impact on somatic, vasomotor, or urogenital symptoms.[37]

Oral combination estrogen/progestin therapy

Hormonal therapy for a woman with a uterus comprises an estrogen, and a progestin to protect against endometrial hyperplasia and cancer.[17] Estrogens are the most effective treatment for VMS, reducing hot flashes by 80% to 90%.[38]

Combination regimens include:

- Continuous combined regimens: an estrogen and a progestin are taken daily
- Sequential regimens: a progestin is added cyclically for 10 to 14 days each month.

The continuous combined regimen is indicated in women who have had amenorrhea for more than 12 months. It is easy to follow and continues the amenorrhea of menopause. If the woman has breakthrough bleeding after the first 6 months on the continuous combined regimen, endometrial assessment (pelvic ultrasound ± endometrial biopsy) is required and consideration should be given to switching to a sequential regimen so that she can have a predictable bleeding pattern.

In a sequential regimen, a progestin is added to an estrogen for the last 10 to 14 days of the cycle. Sequential hormone therapy (HT) may be preferred by perimenopausal women, but may also be indicated in postmenopausal women.[36] [39]

Hormone therapy with an estrogen alone

Women without a uterus can take an estrogen alone if they do not have contraindications for systemic estrogen therapy.[17]

Transdermal administration of an estrogen

A transdermal formulation of estrogen (usually estradiol) is preferable to an oral estrogen in women who have a higher thrombotic risk (including body mass index >30), are taking other medications, have borderline triglyceride levels, are at risk for gallstones, or have difficulty adhering to a daily pill-taking regimen. Because there is no first-pass effect, a transdermal estrogen formulation may reduce the risk of thromboembolism compared with an oral estrogen, but this has not been studied in an RCT.[22] [23] It might also have a lower incidence of nausea. Long-term complications of transdermal estrogen formulations are probably the same as those of oral estrogens, although these were not specifically studied in the Women's Health Initiative. According to UK National Institute for Health and Care Excellence recommendations, a transdermal estrogen formulation at standard therapeutic doses does not increase the risk of venous thromboembolism compared with baseline population risk, nor is it likely to increase the risk of stroke.

Transdermal estradiol is available in patch, metered-dose spray, or gel formulations, all of which are applied to the skin. One 12-week, multicenter RCT found that, compared with placebo, transdermal estradiol gel significantly reduced the frequency and severity of hot flashes at weeks 4 and 12 in healthy menopausal women who had moderate to severe hot flashes.[40] Headache, infection, breast pain, nausea, and insomnia were the most frequently reported side effects. A network meta-analysis found no difference in efficacy between an estradiol transdermal patch and an estradiol transdermal spray for vasomotor symptoms.[41]

Women with an intact uterus require protection with a progestin. A combination of an estrogen and a progestin is available in a single transdermal patch. Transdermal combined sequential HT preparations are also available.

Stopping estrogen therapy

There is insufficient evidence to recommend one method of stopping estrogen therapy over another. There is no standard age for discontinuation of HT. Each individual should be assessed on a regular basis (e.g., annually) to determine the extent of benefit from HT. For women who derive minimal benefit from HT, a reasonable discussion of treatment cessation may take place at any age.

Conjugated estrogens with bazedoxifene

Conjugated estrogens/bazedoxifene (a selective estrogen receptor modulator) has been approved by the Food and Drug Administration for the treatment of VMS and osteoporosis prevention in women with an intact uterus.[8] [42] Compared with conjugated estrogens/medroxyprogesterone, women treated with conjugated estrogens/bazedoxifene experienced significantly fewer adverse events. Women taking conjugated estrogens/bazedoxifene should not take a progestin.

Bazedoxifene has a favorable (anti-estrogenic) effect on breast tissue.[43] Further research is required.

Bioidentical hormones

Bioidentical hormone therapy (BHT) preparations are simply an estrogen (with or without a progestin) in a custom compounded base. Unregulated compounded BHT has been touted as "natural" and safer than conventional HT, but these claims are unsubstantiated.

One systematic review concluded that BHT is more effective than placebo for treating moderate to severe menopausal hot flashes (low to moderate quality evidence), but with higher rates of adverse effects.[44] There is no long-term safety data relating to outcomes such as myocardial infarction, stroke, and breast cancer.[44]

Advisory bodies such as the North American Menopause Society, the American College of Obstetricians and Gynecologists, the US National Academies of Sciences, Engineering, and Medicine, and the British Menopause Society do not generally recommend compounded estrogen/progestin therapy due to the lack of standardized purity and potency with the attendant risks of over- or under-dosing.[17][39] [45] [46] Similarly, the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) do not recommend BHT due to the lack of proven benefit and the potential for poor quality control.[23] For most women, licensed (regulated) HT provides appropriate therapy without the risks of custom preparations.

Regulated preparations containing estradiol and micronized progesterone (an estrogen similar to, and a progestogen equivalent to, those produced by the ovaries) should be used in preference to compounded preparations by women considering more natural preparations. The 2017 AACE/ACE position statement recommends that when the use of progesterone is necessary, micronized progesterone is considered the safer alternative to a synthetic progestin.[23] Micronized progesterone may be taken by the oral or vaginal route, but transdermal micronized progesterone does not protect the endometrium.[47]

Bioidentical progesterone cream is available over the counter, but only one of three published RCTs showed some efficacy compared with placebo in reducing VMS.[48]

Risks of hormone therapy

It is important to provide information on the benefits and risks of HT, to help women make an informed choice about which, if any, treatment to use for menopausal symptoms.

Risk associated with HT use varies between women depending upon dose, duration, route of administration, age at initiation of therapy, and whether a progestogen is included in the regimen. The benefit-risk ratio of HT appears favorable for the management of VMS and the prevention of bone loss or fracture among women (without contraindications) who are under 60 years of age or are within 10 years of the menopause onset.[8] [17]

During 18 years of follow-up, all-cause mortality among the pooled cohort of postmenopausal women who received 5 to 7 years of HT in the two Women's Health Initiative trials did not differ between the HT and placebo groups (27.1% versus 27.6%, respectively; hazard ratio [HR] 0.99, 95% confidence interval [CI] 0.94 to 1.03]).[49] Neither estrogen alone (HR 0.94, 95% CI 0.88 to 1.01) nor estrogen plus progestin (HR 1.02, 95% CI 0.96 to 1.08) were associated with increased risk of all-cause mortality.[49]

Heart disease, stroke, and venous thromboembolism

- HT is not currently recommended for the primary prevention of cardiovascular disease.[17][18] [19] [20] Further research is required to evaluate the impact of timing of HT initiation on coronary heart disease risk and mortality.

Difference in coronary heart disease incidence per 1000 menopausal women over 7.5 years (95% confidence interval) [1]	Current HT users	Treatment duration below 5 years	Treatment duration 5 to 10 years	More than 5 years since stopping treatment
Women on an estrogen alone - RCT estimate[2]	6 fewer (-10 to 1)	No available data	No available data	6 fewer (-9 to -2)
Women on an estrogen alone - observational estimate[3]	6 fewer (-9 to -3)	No available data	No available data	No available data
Women on an estrogen + a progestin - RCT estimate[2]	5 more (-3 to 18)	No available data	No available data	4 more (-1 to 11)
Women on an estrogen + a progestin - observational estimate[3]	No available data	No available data	No available data	No available data

HT, hormone replacement therapy; RCT, randomized controlled trial

[1] Results from Weiner et al (Menopause. 2008;15:86-93) were used for the baseline population risk estimation.

[2] For women aged 50–59 years at entry to the RCT.

[3] Observational estimates are based on cohort studies with several thousand women.

Absolute rates of coronary heart disease for different types of hormone therapy (HT) compared with no HT (or placebo), different durations of HT use, and time since stopping HT for menopausal women.
National Institute for Health and Care Excellence. Menopause: diagnosis and management. Dec 2019

- The risk of venous thromboembolism and ischemic stroke increases with oral HT, but the absolute risk of stroke in women under 60 years of age is very low.[1] [50] [51] Observational studies and a meta-analysis indicate that transdermal estrogens are associated with a lower risk of venous thromboembolism and stroke than oral estrogens.[1] [17][50] [51] Patients at high risk for cardiovascular complications should have a careful assessment of the risks and benefits of HT, and may be candidates for a trial of non-HT.[11]

Difference in stroke incidence per 1000 menopausal women over 7.5 years (95% confidence interval)[1]	Current HT users	Treatment duration below 5 years	Treatment duration 5 to 10 years	More than 5 years since stopping treatment
Women on an estrogen alone - RCT estimate[2]	0 (-5 to 10)	No available data	No available data	1 more (-4 to 9)
Women on an estrogen alone - observational estimate[3]	3 more (-1 to 8)	No available data	No available data	No available data
Women on an estrogen + a progestin - RCT estimate[2]	6 more (-2 to 21)	No available data	No available data	4 more (-1 to 13)
Women on an estrogen + a progestin - observational estimate[3]	4 more (1 to 7)	No available data	No available data	No available data

HT, hormone replacement therapy; RCT, randomized controlled trial

1 Results from Weiner et al (Menopause. 2008;15:86-93) were used for the baseline population risk estimation.

2 For women aged 50–59 years at entry to the RCT.

3 Observational estimates are based on cohort studies with several thousand women.

Absolute rates of stroke for different types of hormone therapy (HT) compared with no HT (or placebo), different durations of HT use, and time since stopping HT for menopausal women.

National Institute for Health and Care Excellence. Menopause: diagnosis and management. Dec 2019

Breast and ovarian cancer

- HT with an estrogen alone is associated with little or no change in the risk of breast cancer.[1] An estrogen prescribed in combination with a progestin is associated with a small increase in the risk of breast cancer.[1] [50] [51] [Evidence C] The increased risk is related to duration of treatment, and likely recedes after treatment is stopped.[1] [50] [51] The UK Medicines and Healthcare products Regulatory Agency has published a table summarizing the risk of breast cancer for women currently receiving hormone therapy and post treatment from age of menopause up to age 69 years.[52]

	Risks over 5 years use (with no use or 5 years current HRT use)		Total risks up to age 69 (after no use or after 5 years HRT use†)		Risks over 10 years (with no use or 10 years current HRT use)		Total risks up to age 69 (after no use or after 10 years HRT use†)	
	Cases per 1000 women with no HRT use	**Extra cases per 1000 women using HRT**	Cases per 1000 women with no HRT use	**Extra cases per 1000 women using HRT**	Cases per 1000 women with no HRT use	**Extra cases per 1000 women using HRT**	Cases per 1000 women with no HRT use	**Extra cases per 1000 women using HRT**
Risks associated with **combined estrogen-progestogen HRT**								
Breast cancer	13	**+8**	63	**+17**	27	**+20**	63	**+34**
Sequential HRT	13	**+7**	63	**+14**	27	**+17**	63	**+29**
Continuous combined HRT	13	**+10**	63	**+20**	27	**+25**	63	**+40**
Endometrial cancer	2	-	10	-	4	-	10	-
Ovarian cancer	2	**+ <1**	10	**+ <1**	4	**+1**	10	**+1**
Venous thromboembolism (VTE)§	5	**+7**	26	**+7**	8	**+13**	26	**+13**
Stroke	4	**+1**	26	**+1**	8	**+2**	26	**+2**
Coronary heart disease (CHD)	14	-	88	-	28	-	88	-
Fracture of femur	1.5	-	12	-	1	-	12	-
Risks associated with **estrogen-only HRT**								
Breast cancer	13	**+3**	63	**+5**	27	**+7**	63	**+11**
Endometrial cancer	2	**+4**	10	**+4**	4	**+32**	10	**+32**
Ovarian cancer	2	**+ <1**	10	**+ <1**	4	**+1**	10	**+1**
Venous thromboembolism (VTE)§	5	**+2**	26	**+2**	10	**+3**	26	**+3**
Stroke	4	**+1**	26	**+1**	8	**+2**	26	**+2**
Coronary heart disease (CHD)	14	-	88	-	28	-	88	-
Fracture of femur	0.5	-	12	-	1	-	12	-

Summary of HRT risks and benefits during current use and current use plus post-treatment from age of menopause up to age 69 years, per 1000 women with 5 years or 10 years use of HRT.#Key: *Menopausal symptom relief is not included in this table, but is a key benefit of HRT and will play a major part in the decision to prescribe HRT. †Best estimates based on relative risks of HRT use from age 50. For breast cancer this includes cases diagnosed during current HRT use and diagnosed after HRT use until age 69 years; for other risks, this assumes no residual effects after stopping HRT use. § Latest evidence suggests that transdermal HRT products have a lower risk of VTE than oral preparations*

Medicines and Healthcare products Regulatory Agency. Hormone replacement therapy (HRT): further information on the known increased risk of breast cancer with HRT and its persistence after stopping. Aug 2019 [internet publication]; used with permission

- There is evidence to suggest that HT increases breast tissue density.[1] This can make tumor detection more difficult, and may result in some women being recalled for repeat mammography and/or further evaluation.

- A meta-analysis of 52 epidemiologic studies analyzed the risks of ovarian cancer in 12,110 postmenopausal women, 55% of whom had used HT for some period of time.[53] The meta-analysis suggested that 5 years of HT use, starting at age 50 years, would result in one extra ovarian cancer per 1000 users.[53]
- One 2019 meta-analysis of prospective studies found HT use for more than 1 year in postmenopausal women to be associated with an increased risk of breast cancer.[54] Risk increased with longer duration of HT use, and persisted after HT was stopped. Risk was higher with combined estrogen-progestogen compared with estrogen-only preparations, but there was no increased risk with topical vaginal estrogens. Current advice is unchanged - that HT should be used for the shortest time that it is needed, and patients should be vigilant for signs of breast cancer and encouraged to attend regular breast cancer screening.[52] [55] The risks and benefits of HT should be discussed with patients during shared decision making before commencing HT.[1] [56]

Nonhormonal medications for vasomotor symptoms

A systematic review and meta-analysis of 43 trials of nonhormonal therapies found that estrogen replacement was significantly more effective than nonhormonal alternatives.[57] However, nonhormonal alternatives may benefit women who are unable to take an estrogen because of risk factors or inability to tolerate HT.[58]

Selective serotonin-reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs)

- SSRIs and SNRIs are effective for treating VMS in women unable to take HT.[59] [60] [61]
- Some evidence suggests that escitalopram may be more effective than other SSRIs at reducing hot flashes.[61] Only paroxetine is approved for the treatment of moderate to severe VMS associated with menopause.[38] [62]
- In an 8-week RCT of 339 perimenopausal and postmenopausal women with bothersome VMS, venlafaxine (an SNRI) reduced the frequency of symptoms by 1.8 more per day than placebo (P=0.005).[63] Low-dose estradiol appeared to be more effective (2.3 fewer VMS per day than placebo), but it was not compared directly with venlafaxine in this study.[63] Venlafaxine may be a reasonable alternative for women unable to take an estrogen.
- Compared with placebo, desvenlafaxine (an SNRI) reduced the frequency and severity of moderate to severe hot flashes over a 12-month period in an RCT of 365 postmenopausal women with bothersome VMS.[64] Subsequent to concerns regarding the safety of desvenlafaxine in this patient population, a discrete safety analysis found no evidence for an increased risk of cardiovascular, cerebrovascular, or hepatic events associated with desvenlafaxine (compared with placebo) for the treatment of menopausal VMS.[65]

Gabapentin

- Studies indicate that gabapentin is moderately effective for the treatment of hot flashes.[36] [66] However, drowsiness, dizziness, and unsteadiness are commonly reported adverse effects.[66] Gabapentin may result in intolerable lethargy when used during the day.[36] Side effects can be mitigated by dosing only at night, or by using a dose escalation regimen.

Clonidine

- Clonidine, an antihypertensive agent, reduces hot flashes but may be less effective than SSRIs/SNRIs and gabapentin.[36] Hypotension may be a treatment-limiting adverse effect.[67] Blood

pressure should be monitored during therapy and for rebound after discontinuation. Transdermal patches result in stable blood levels and are preferred to oral clonidine preparations.[36]

Symptoms of urogenital atrophy

Low-dose vaginal estrogen preparations can be considered in women with symptoms of urogenital atrophy.[17]

A review of Medline and Cochrane databases showed that vaginal estrogens are more effective than placebo for improving dryness and decreasing dyspareunia, urinary urgency, and urinary frequency.[68] Rates of urinary tract infections also declined with vaginal estrogen use. Serum estradiol levels remained within postmenopausal norms, except for those who used high-dose vaginal estrogen cream.[68]

In women without a history of hormone-dependent cancer, vaginal estrogens can be continued for symptom relief, and there is no evidence to recommend endometrial surveillance.[31] In the Women's Health Initiative observational study, the risk of cardiovascular disease, invasive breast cancer, and endometrial cancer did not differ between women who were vaginal estrogen users and those who were not.[69]

Vaginal estrogens do not require progestin replacement.

Vaginal estradiol tablets do not result in significant systemic absorption and can be used long-term as required. However, in October 2019, the European Medicines Agency recommended limiting the use of high-strength estradiol vaginal creams (containing estradiol 100 micrograms/g or 0.01%) to a single treatment period of up to 4 weeks. This is because levels of estradiol in the blood were found to be higher than normal postmenopausal levels and could result in similar adverse effects to those seen with systemic (oral or transdermal) HT (e.g., venous thromboembolism, stroke, endometrial cancer, breast cancer). This formulation should not be used in patients already on HT.[70] Therefore, other vaginal estrogen formulations (e.g., conjugated estrogen cream, estradiol intravaginal tablets and rings) may be preferred. There is no evidence to suggest that any one vaginal estrogen preparation is more efficacious than another.[71]

Ospemifene is a selective estrogen receptor modulator indicated for the treatment of dyspareunia in postmenopausal women. In a phase 3 trial, ospemifene increased the percentage of superficial cells and reduced dyspareunia compared with placebo.[72] Hot flashes were the most frequently reported adverse event (ospemifene 7% versus placebo 4%).[72] [73]

Breast and gynecologic cancer survivors

Consensus recommendations for the management of menopausal symptoms after breast cancer include:[74] [75]

- Generally avoiding treatment with systemic menopausal hormone therapy or vaginal estrogen*
- Implementing lifestyle measures (e.g., healthy diet, regular physical activity, smoking cessation, weight loss, limiting or avoiding alcohol, maintaining adequate levels of vitamin D and calcium)
- Nonhormonal, pharmacologic therapy (e.g., selective serotonin/noradrenaline reuptake inhibitors), and/or cognitive behavioral therapy.

*There are data to suggest that HT does not increase risk of recurrence in women who do not have an estrogen-dependent malignancy.[76] [77] One review suggested that short-term use of HT may result in improvement of menopausal vasomotor and genitourinary symptoms in patients with gynecologic

cancer who do not have an estrogen-dependent malignancy.[76] The use of estrogens in women with non-estrogen-dependent malignancy must be tailored to the patient's situation.

Polycarbophil gel, a vaginal moisturizer, can also be offered as an effective treatment for symptoms of vaginal atrophy, including dryness and dyspareunia.[78] [79] Dyspareunia is common in breast cancer survivors due to atrophy and dryness from lack of estrogen. In a small trial, lidocaine reduced tenderness in the vulvar vestibule of postmenopausal breast cancer survivors with dyspareunia (median coital pain score 8 on a 10-point scale) compared with normal saline.[78] Intravaginal dehydroepiandrosterone (DHEA) and oral ospemifene are approved for the management of dyspareunia, but safety following breast cancer has not been established.[74]

Reduced libido

Women with distressing low sexual desire and tiredness should be counseled that androgen supplementation is an option, particularly if an estrogen with or without a progestin has not been effective.

The Endocrine Society recommends against diagnosing androgen deficiency in healthy menopausal women because there is a lack of a well-defined syndrome and data correlating androgen levels with specific signs or symptoms are not available.[80] See Sexual dysfunction in women .

Urinary stress incontinence

Pelvic floor rehabilitation may be useful for urinary stress incontinence.[81] In one study, 73.4% of postmenopausal women randomized to a combination of intravaginal estriol and pelvic floor rehabilitation for 6 months experienced subjective improvement in stress urinary incontinence compared with only 9.71% of women in the control (estriol-only) group.[82] Both groups reported improvement in signs and symptoms of urogenital atrophy.

Sleep disturbance and mood symptoms

Difficulty sleeping or nocturnal restlessness and awakening are common problems during menopause. Insomnia is often associated with hot flashes (other factors, such as depression or sleep apnea, may also be involved). But no studies have shown a direct physiologic link.

Some women report improved sleep while taking HT.[17] [83] In one systematic review of 11 studies of varying quality, progesterone improved VMS and sleep quality.[84]

Data suggest that short-term use of HT may improve mood and depressive symptoms during the menopausal transition and in the early menopause, but study results are inconsistent.[85] [86] There is evidence to suggest that cognitive behavioral therapy (CBT) may have a beneficial role in the management of low mood and anxiety in women with menopausal symptoms after breast cancer treatment.[87] There is a lack of good quality evidence relating to CBT specifically in women with depression related to early menopause but given the low risk of harms and strong evidence base for treating depression in the general population it is a reasonable option in women who are perimenopausal with depression.[88]

While HT or other alternatives may improve sleeping patterns, an assessment should be made for other underlying factors that may require targeted treatment. Mood disorders, notably depression, often improve with HT, although conventional antidepressants may be more effective.[89] Women with symptoms of severe depression should be referred for mental health assessment.

Alternative or herbal therapies

A Cochrane review of 43 RCTs involving phytoestrogens found that there was a large placebo effect (from 1% to 59%) in most of the trials.[90] This, and other reviews, have found no conclusive evidence that phytoestrogens, including isoflavones, are effective for the management of menopausal VMS.[38] [90] [91]

Acupuncture and reflexology have not been shown to significantly improve VMS compared with placebo.[38]

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute			(summary)
initial presentation with mild vasomotor symptoms			
	1st	**lifestyle changes**	

Ongoing (summary)

women with a uterus, moderate to severe hot flashes, with/without reduced libido		
▪ amenorrhea >12 months	1st	continuous combined regimen
▪ menstrual irregularity and periods of amenorrhea (perimenopause)	1st	sequential regimen
	2nd	conjugated estrogens/bazedoxifene
	3rd	selective serotonin-reuptake inhibitor (SSRI)/serotonin-norepinephrine reuptake inhibitor (SNRI)
	4th	gabapentin
	5th	clonidine
women without a uterus or with levonorgestrel-releasing intrauterine device fitted in the last 5 years, moderate to severe hot flashes, with/without reduced libido		
	1st	estrogen alone
	2nd	selective serotonin-reuptake inhibitor (SSRI)/serotonin-norepinephrine reuptake inhibitor (SNRI)
	3rd	gabapentin
	4th	clonidine
urogenital atrophy only		
	1st	vaginal estrogen ± vaginal moisturizer
	2nd	ospemifene ± vaginal moisturizer
urinary stress incontinence only		
	1st	pelvic floor rehabilitation

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

initial presentation with mild vasomotor symptoms

1st **lifestyle changes**

» Despite limited evidence, certain lifestyle changes can improve symptom tolerance. Women may be encouraged to lose weight (where appropriate) and to exercise more.[11] Both have cardiovascular and bone health benefits and can improve overall wellbeing, but may not have a specifically identifiable impact on hot flashes and cannot improve bone density.[8]

» Other self-care measures include avoidance of spicy foods, alcohol, caffeine, warm environments, and stress. Alcohol and caffeine intake are associated with worsening vasomotor symptoms.

» Wearing layered clothing and use of hand-held fans, drinking cold water, and mist bottles may be helpful.

» One qualitative review of randomized controlled trials and meta-analyses found that yoga is moderately effective in the short term for psychological symptoms, but has no impact on somatic, vasomotor, or urogenital symptoms.[37]

Ongoing

women with a uterus, moderate to severe hot flashes, with/without reduced libido

amenorrhea >12 months **1st** **continuous combined regimen**

Primary options

» estrogens, conjugated/medroxyprogesterone: 0.3/1.5 mg to 0.625/5 mg orally once daily (dose depends on brand used)

OR

» estradiol/norethindrone acetate transdermal: 0.05/0.14 mg patch twice weekly

Secondary options

» medroxyprogesterone: 2.5 mg orally once daily

--AND--

» estrogens, conjugated: 0.3 to 1.25 mg orally once daily
-or-
» estrogens, esterified: 0.3 to 1.25 mg orally once daily
-or-
» estradiol transdermal: dose depends on brand of patch, spray, or gel; consult product literature for guidance on dose

» Hormonal therapy for a woman with a uterus comprises an estrogen, and a progestin to protect against endometrial hyperplasia and cancer.[17] Estrogens are the most effective treatment for vasomotor symptoms, reducing hot flashes by 80% to 90%.[38]

» The continuous combined regimen is indicated in women who have had amenorrhea for more than 12 months. It is easy to follow and continues the amenorrhea of menopause.

» If the woman has breakthrough bleeding after the first 6 months on the continuous combined regimen, endometrial assessment (pelvic ultrasound ± endometrial biopsy) is required and consideration should be given to switching to a sequential regimen so that she can have a predictable bleeding pattern.

» A transdermal estrogen formulation (usually estradiol) is preferable to an oral estrogen for women who have a higher thrombotic risk

Ongoing

(including body mass index >30), are taking other medications, have borderline triglyceride levels, are at risk for gallstones, or have difficulty adhering to a daily pill-taking regimen. Because there is no first-pass effect, a transdermal estrogen formulation may reduce the risk of thromboembolism compared with an oral estrogen, but this has not been studied in a randomized controlled trial (RCT). It might also have a lower incidence of nausea.[22] [23]

» Long-term complications of transdermal estrogen formulations are probably the same as those of oral estrogens, although these were not specifically studied in the Women's Health Initiative. According to UK National Institute for Health and Care Excellence recommendations, a transdermal estrogen formulation at standard therapeutic doses does not increase the risk of venous thromboembolism compared with baseline population risk.[1]

» Transdermal estradiol is available in patch, metered-dose spray, or gel formulations, all of which are applied to the skin. One 12-week, multicenter RCT found that, compared with placebo, transdermal estradiol gel significantly reduced the frequency and severity of hot flashes at weeks 4 and 12 in healthy menopausal women who had moderate to severe hot flashes.[40] Headache, infection, breast pain, nausea, and insomnia were the most frequently reported side effects. A network meta-analysis found no difference in efficacy between an estradiol transdermal patch and an estradiol transdermal spray for vasomotor symptoms.[41]

» A combination of an estrogen and a progestin is available in a single transdermal patch in most countries.

» Hormone replacement preparations are available in different combinations. A few examples of regimens are outlined above.

menstrual irregularity and periods of amenorrhea (perimenopause)

1st

sequential regimen

» Hormonal therapy for a woman with a uterus comprises an estrogen, and a progestin to protect against endometrial hyperplasia and cancer.[17] Estrogens are the most effective treatment for vasomotor symptoms, reducing hot flashes by 80% to 90%.[38]

» In a sequential regimen, a progestin is added to an estrogen for the last 10 to 14 days of the cycle. Sequential hormone therapy (HT)

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is primarily used by perimenopausal women, but may also be indicated in postmenopausal women.

» A transdermal estrogen formulation (usually estradiol) is preferable to an oral estrogen for women who have a higher thrombotic risk (including body mass index >30), are taking other medications, have borderline triglyceride levels, are at risk for gallstones, or have difficulty adhering to a daily pill-taking regimen. Because there is no first-pass effect, a transdermal estrogen formulation may reduce the risk of thromboembolism compared with an oral estrogen, but this has not been studied in a randomized controlled trial (RCT). It might also have a lower incidence of nausea.[22] [23]

» Long-term complications of transdermal estrogen formulations are probably the same as those of oral estrogens, although these were not specifically studied in the Women's Health Initiative. According to UK National Institute for Health and Care Excellence recommendations, a transdermal estrogen formulation at standard therapeutic doses does not increase the risk of venous thromboembolism compared with baseline population risk.[1]

» Transdermal estradiol is available in patch, metered-dose spray, or gel formulations, all of which are applied to the skin. One 12-week, multicenter RCT found that, compared with placebo, transdermal estradiol gel significantly reduced the frequency and severity of hot flashes at weeks 4 and 12 in healthy menopausal women who had moderate to severe hot flashes.[40] Headache, infection, breast pain, nausea, and insomnia were the most frequently reported side effects. A network meta-analysis found no difference in efficacy between an estradiol transdermal patch and an estradiol transdermal spray for vasomotor symptoms.[41]

» Hormone replacement preparations are available in different combinations. Transdermal combined sequential HT preparations are available.

2nd **conjugated estrogens/bazedoxifene**

Primary options

» estrogens, conjugated/bazedoxifene: 0.45/20 mg orally once daily

» Conjugated estrogens/bazedoxifene (a selective estrogen receptor modulator) has been

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approved by the Food and Drug Administration for the treatment of vasomotor symptoms and osteoporosis prevention in women with an intact uterus.[8] [42]

» Compared with conjugated estrogens/medroxyprogesterone, women treated with conjugated estrogens/bazedoxifene experienced significantly fewer adverse events. Women taking conjugated estrogens/bazedoxifene should not take a progestin.

» Bazedoxifene has a favorable (anti-estrogenic) effect on breast tissue.[43] Further research is required.

3rd **selective serotonin-reuptake inhibitor (SSRI)/serotonin-norepinephrine reuptake inhibitor (SNRI)**

Primary options

» paroxetine: 7.5 mg orally once daily

OR

» escitalopram: 10-20 mg orally once daily

OR

» desvenlafaxine: 100 mg orally once daily

OR

» venlafaxine: 37.5 to 75 mg orally (extended-release) once daily

Secondary options

» fluoxetine: 10-20 mg orally once daily

OR

» citalopram: 10-30 mg orally once daily

» SSRIs and SNRIs are effective for treating vasomotor symptoms (VMS) in women unable to take hormone therapy.[59] [60] [61]

» Some evidence suggests that escitalopram may be more effective than other SSRIs at reducing hot flashes.[61] Only paroxetine is approved for the treatment of moderate to severe VMS associated with menopause.[38] [62]

» In an 8-week randomized controlled trial (RCT) of 339 perimenopausal and postmenopausal women with bothersome VMS, venlafaxine (an

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SNRI) reduced the frequency of symptoms by 1.8 more per day than placebo (P=0.005).[63] Low-dose estradiol appeared to be more effective (2.3 fewer VMS per day than placebo), but it was not compared directly with venlafaxine in this study.[63] Venlafaxine may be a reasonable alternative for women unable to take an estrogen.

» Compared with placebo, desvenlafaxine (an SNRI) reduced the frequency and severity of moderate to severe hot flashes over a 12-month period in an RCT of 365 postmenopausal women with bothersome VMS.[64] Subsequent to concerns regarding the safety of desvenlafaxine in this patient population, a discrete safety analysis found no evidence for an increased risk of cardiovascular, cerebrovascular, or hepatic events associated with desvenlafaxine (compared with placebo) for the treatment of menopausal VMS.[65]

4th **gabapentin**

Primary options

» gabapentin: 300 mg orally once daily initially, increase to 300 mg three times daily if required, increase gradually according to response if required, maximum 2400 mg/day

» Studies indicate that gabapentin is moderately effective for the treatment of hot flashes.[36] [66] However, drowsiness, dizziness, and unsteadiness are commonly reported adverse effects.[66]

» Gabapentin may result in intolerable lethargy when used during the day.[36] If night sweats are the primary bothersome symptom of menopause, gabapentin may be taken only at night. For daytime hot flashes, a dose escalation regimen may be used if other pharmacologic options are not available.

5th **clonidine**

Primary options

» clonidine transdermal: 0.1 mg/24 hour patch once weekly

Secondary options

» clonidine: 0.05 to 0.2 mg orally (immediate-release) once or twice daily

» Clonidine, an antihypertensive agent, reduces hot flashes but may be less effective than selective serotonin-reuptake inhibitors/

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serotonin-norepinephrine reuptake inhibitors and gabapentin.[36]

» Hypotension may be a treatment-limiting adverse effect.[78] Blood pressure should be monitored during therapy and for rebound after discontinuation.

» Transdermal patches result in stable blood levels and are preferred to oral clonidine preparations.[36]

women without a uterus or with levonorgestrel-releasing intrauterine device fitted in the last 5 years, moderate to severe hot flashes, with/without reduced libido

1st **estrogen alone**

Primary options

» estradiol transdermal: dose depends on brand of patch, spray, or gel; consult product literature for guidance on dose

Secondary options

» estrogens, conjugated: 0.3 to 1.25 mg orally once daily

OR

» estrogens, esterified: 0.3 to 1.25 mg orally once daily

» Women without a uterus can take an estrogen alone if they do not have contraindications for systemic estrogen therapy.[17] Estrogens are the most effective treatment for vasomotor symptoms, reducing hot flashes by 80% to 90%.[38]

» A transdermal estrogen formulation (usually estradiol) is preferable to an oral estrogen for women who have a higher thrombotic risk (including body mass index >30), are taking other medications, have borderline triglyceride levels, are at risk for gallstones, or have difficulty adhering to a daily pill-taking regimen. Because there is no first-pass effect, a transdermal estrogen formulation may reduce the risk of thromboembolism compared with an oral estrogen, but this has not been studied in a randomized controlled trial (RCT). It might also have a lower incidence of nausea.[22] [23]

» Long-term complications of transdermal estrogen formulations are probably the same

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as those of oral estrogens, although these were not specifically studied in the Women's Health Initiative. According to UK National Institute for Health and Care Excellence recommendations, a transdermal estrogen formulation at standard therapeutic doses does not increase the risk of venous thromboembolism compared with baseline population risk.[1]

» Transdermal estradiol is available in patch, metered-dose spray, or gel formulations, all of which are applied to the skin. One 12-week, multicenter RCT found that, compared with placebo, transdermal estradiol gel significantly reduced the frequency and severity of hot flashes at weeks 4 and 12 in healthy menopausal women who had moderate to severe hot flashes.[40] Headache, infection, breast pain, nausea, and insomnia were the most frequently reported side effects. A network meta-analysis found no difference in efficacy between an estradiol transdermal patch and an estradiol transdermal spray for vasomotor symptoms.[41]

2nd **selective serotonin-reuptake inhibitor (SSRI)/serotonin-norepinephrine reuptake inhibitor (SNRI)**

Primary options

» paroxetine: 7.5 mg orally once daily

OR

» escitalopram: 10-20 mg orally once daily

OR

» desvenlafaxine: 100 mg orally once daily

OR

» venlafaxine: 37.5 to 75 mg orally (extended-release) once daily

Secondary options

» fluoxetine: 10-20 mg orally once daily

OR

» citalopram: 10-30 mg orally once daily

» SSRIs and SNRIs are effective for treating vasomotor symptoms (VMS) in women unable to take hormone therapy.[59] [60] [61]

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» Some evidence suggests that escitalopram may be more effective than other SSRIs at reducing hot flashes.[61] Only paroxetine is approved for the treatment of moderate to severe VMS associated with menopause.[38] [62]

» In an 8-week randomized controlled trial (RCT) of 339 perimenopausal and postmenopausal women with bothersome VMS, venlafaxine (an SNRI) reduced the frequency of symptoms by 1.8 more per day than placebo (P=0.005).[63] Low-dose estradiol appeared to be more effective (2.3 fewer VMS per day than placebo), but it was not compared directly with venlafaxine in this study.[63] Venlafaxine may be a reasonable alternative for women unable to take an estrogen.

» Compared with placebo, desvenlafaxine (an SNRI) reduced the frequency and severity of moderate to severe hot flashes over a 12-month period in an RCT of 365 postmenopausal women with bothersome VMS.[64] Subsequent to concerns regarding the safety of desvenlafaxine in this patient population, a discrete safety analysis found no evidence for an increased risk of cardiovascular, cerebrovascular, or hepatic events associated with desvenlafaxine (compared with placebo) for the treatment of menopausal VMS.[65]

3rd **gabapentin**

Primary options

» gabapentin: 300 mg orally once daily initially, increase to 300 mg three times daily if required, increase gradually according to response if required, maximum 2400 mg/day

» Studies indicate that gabapentin is moderately effective for the treatment of hot flashes.[36] [66] However, drowsiness, dizziness, and unsteadiness are commonly reported adverse effects.[66]

» Gabapentin may result in intolerable lethargy when used during the day.[36] If night sweats are the primary bothersome symptom of menopause, gabapentin may be taken only at night. For daytime hot flashes, a dose escalation regimen may be used if other pharmacologic options are not available.

4th **clonidine**

Primary options

» clonidine transdermal: 0.1 mg/24 hour patch once weekly

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Secondary options

» clonidine: 0.05 to 0.2 mg orally (immediate-release) once or twice daily

» Clonidine, an antihypertensive agent, reduces hot flashes but may be less effective than selective serotonin-reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors and gabapentin.[36]

» Hypotension may be a treatment-limiting adverse effect.[67] Blood pressure should be monitored during therapy and for rebound after discontinuation.

» Transdermal patches result in stable blood levels and are preferred to oral clonidine preparations.[36]

urogenital atrophy only

1st **vaginal estrogen ± vaginal moisturizer**

Primary options

» estrogens, conjugated vaginal: (0.625 mg/g cream) insert 0.5 to 2 g into the vagina once daily for 21 days, followed by no treatment for 7 days, then repeat; or insert 0.5 g into the vagina twice weekly

OR

» estradiol vaginal: (intravaginal tablets) 10 micrograms (1 tablet) into the vagina once daily for 2 weeks, followed by 10 micrograms (1 tablet) twice weekly thereafter; (intravaginal ring) 1 ring (7.5 micrograms/24 hours or 50-100 micrograms/24 hours) inserted into the vagina and replaced every 3 months, dose depends on brand used; (0.01% or 100 micrograms/g cream) insert 2-4 g (200-400 micrograms) into the vagina once daily for 1-2 weeks, then taper dose gradually over 1-2 weeks to maintenance dose of 1 g (100 micrograms) once to three times weekly
Use of estradiol 0.01% (100 micrograms/g) cream should be limited to a single treatment period of up to 4 weeks.[70]

» Low-dose vaginal estrogen preparations can be considered in women with symptoms of urogenital atrophy.[17]

» A review of Medline and Cochrane databases showed that vaginal estrogens are more

Ongoing

effective than placebo for improving dryness and decreasing dyspareunia, urinary urgency, and urinary frequency.[68] Rates of urinary tract infections also declined with vaginal estrogen use. Serum estradiol levels remained within postmenopausal norms, except for those who used high-dose vaginal estrogen cream.[68]

» In women without a history of hormone-dependent cancer, vaginal estrogens can be continued for symptom relief, and there is no evidence to recommend endometrial surveillance.[31] In the Women's Health Initiative observational study, the risk of cardiovascular disease, invasive breast cancer, and endometrial cancer did not differ between women who were vaginal estrogen users and those who were not.[69]

» Vaginal estrogens do not require progestin replacement.

» Vaginal estradiol tablets do not result in significant systemic absorption and can be used long-term as required. However, in October 2019, the European Medicines Agency recommended limiting the use of high-strength estradiol vaginal creams (containing estradiol 100 micrograms/g or 0.01%) to a single treatment period of up to 4 weeks due to the risk of adverse effects usually associated with systemic (oral or transdermal) hormone therapy (HT). This formulation should not be used in patients already on HT.[70] Therefore, other vaginal estrogen formulations (e.g., conjugated estrogen cream, estradiol intravaginal tablets and rings) may be preferred. There is no evidence to suggest that any one vaginal estrogen preparation is more efficacious than another.[71]

» Polycarbophil gel, a vaginal moisturizer, can also be offered for symptoms of vaginal atrophy, including dryness and dyspareunia.[78] [79]

2nd **ospemifene ± vaginal moisturizer**

Primary options

» ospemifene: 60 mg orally once daily

» Ospemifene is a selective estrogen receptor modulator indicated for the treatment of dyspareunia in postmenopausal women. In a phase 3 trial, ospemifene increased the percentage of superficial cells and reduced dyspareunia compared with placebo.[72] Hot flashes were the most frequently reported

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		adverse event (ospemifene 7% versus placebo 4%).[72] [73] » Polycarbophil gel, a vaginal moisturizer, can also be offered for symptoms of vaginal atrophy, including dryness and dyspareunia.[78] [79]
urinary stress incontinence only		
	1st	**pelvic floor rehabilitation** » Pelvic floor rehabilitation may be useful for urinary stress incontinence.[81] In one study, 73.4% of postmenopausal women randomized to a combination of intravaginal estriol and pelvic floor rehabilitation for 6 months experienced subjective improvement in stress urinary incontinence compared with only 9.71% of women in the control (estriol-only) group.[82] Both groups reported improvement in signs and symptoms of urogenital atrophy.

Emerging

Dehydroepiandrosterone (DHEA)/prasterone

DHEA, an androgen precursor to testosterone and estrogen, is approved for the treatment of postmenopausal dyspareunia due to vulvovaginal atrophy based on a placebo-controlled 12-week trial.[92] A review of 18 trials concluded that DHEA may slightly improve sexual function compared with placebo.[93] However, it is associated with androgenic side effects, mainly acne, and its role remains uncertain.[93]

Stellate ganglion block

Stellate ganglion block, typically employed in the management of pain syndromes and vascular insufficiency, may be effective in the management of hot flashes in women who cannot take estrogen-based therapy.[94] Further research is required.[95]

Tibolone

Tibolone is a steroid derived from yams that has mixed estrogen-, progesterone-, and testosterone-like effects on multiple tissues. One Cochrane review concluded that tibolone is more effective than placebo, but less effective than hormone therapy, at reducing vasomotor symptoms.[96] It is not recommended in women with a history of breast cancer, and may increase the risk of stroke in older women.[36][97] Tibolone is available in Europe, but not the US.

Fezolinetant

Fezolinetant is a neurokinin 3 (NK3) receptor antagonist. The NK3 receptor has a role in the brain's regulation of body temperature. The drug is approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of moderate-to-severe vasomotor symptoms (hot flushes) associated with menopause.

Primary prevention

The US Preventive Services Task Force (USPSTF) recommends against the use of hormone therapy (HT) for primary prevention of chronic conditions in postmenopausal women because the overall risks outweigh the benefits.[16] Potential primary prevention endpoints include a moderately decreased fracture risk, and a small decrease in the risk of developing diabetes or depression.[1][17] These are more than offset by the increased risk of venous thromboembolism and a moderate increased risk of cardiovascular disease.[18] [19] In primary prevention trials, the risk of invasive breast cancer decreased with estrogen-only treatment but increased in the combined estrogen with progestin group. In particular, HT is not currently recommended for the primary prevention of cardiovascular disease.[17][18] [19][20] Further research is required to evaluate the impact of timing of HT initiation on coronary heart disease risk and mortality, but there may be some benefit if HT is started early (ages <60 years).[21]

Primary prevention must be made distinct from treatment of symptoms at the onset of menopause. For patients with significant symptoms, the benefits of therapy are likely to outweigh the risks.[17]

With greater awareness of the effect of declining estrogen levels on cardiovascular and bone health, women should be advised about diet and lifestyle factors that can help to reduce early menopausal symptoms and improve later health. Such factors include maintaining healthy weight, smoking cessation, adequate calcium and vitamin D intake, increasing exercise, and reducing alcohol and caffeine.

In the absence of contraindications, HT is an effective therapeutic intervention for the prevention of osteoporosis in women under the age of 60 years and women within 10 years of menopause onset.[8] [17] Women with an intact uterus should receive combined estrogen/progestin therapy to protect against endometrial hyperplasia and cancer, whereas women without a uterus should receive estrogen alone.[8] There are no data to suggest greater efficacy of oral versus transdermal estrogen; however, risk of venous

thromboembolism may be lower with transdermal estrogen due to the absence of the first-pass effect.[8] [22] [23] [24] Younger women, particularly those <40 years, may require higher doses of HT than older women to effectively prevent against bone loss.[8] Benefit is maintained during treatment, but decreases once treatment stops.[1] [8] Upon stopping, the benefit of HT may persist for longer in women who took HT for longer.[1] Bisphosphonates may be appropriate to prevent bone loss in women with early menopause when estrogen is contraindicated, or when HT is discontinued.[8] Regarding nonpharmacologic interventions, regular low-intensity physical activity, such as walking, bowling, and golf, has been shown to lower hip fracture risk in postmenopausal women.[25]

Guidelines recommend systemic HT for women who undergo risk-reducing bilateral salpingo-oophorectomy before the natural menopause.[17][26] A progestin is required if the uterus is preserved. HT may be continued until the time the natural menopause would have been expected; menopausal symptoms occurring when HT is stopped are managed in the same way as symptoms of natural menopause.[26]

Patient discussions

Relaxation training may be appropriate for some patients and has been shown to moderately decrease hot flashes.

Where appropriate, encourage women to lose weight and to exercise more.[11] Other self-care measures include avoidance of spicy foods, alcohol, hot drinks, warm environments, and stress. To manage hot flashes, advise use of layered clothing and cooling methods such as hand-held fans, drinking cold water, and mist bottles. However, there is no good research evidence to support any of these approaches.

In general, patients should be advised to follow a well-balanced nutritious diet, take nutritional supplements (calcium and vitamin D), and exercise at least 30 minutes most days of the week.

FOLLOW UP

Monitoring

Monitoring

Women should be monitored to ensure they receive adequate benefit from their treatment, and counseled appropriately about individual risks. Arbitrary limits should not be placed on the duration of use of hormone therapy (HT); all patients require individualized decision making. Reassessment should occur at least annually.

Complications

Complications	Timeframe	Likelihood
hormone therapy-related vaginal bleeding	**short term**	**medium**
Vaginal bleeding is common in the first 4 to 6 months with estrogen and progestogen therapy. If necessary, more progestogen may be added to a continuous estrogen-progestogen regimen. Changing to a cyclic combination regimen results in the woman having monthly withdrawal bleeding. Persistent postmenopausal vaginal bleeding requires further investigation.		
hormone therapy-related breast tenderness	**short term**	**medium**
This is a complication of estrogen treatment. The dose of estrogen should be decreased. Persistent symptoms require further investigation.		
cardiovascular disease	**long term**	**medium**
The menopause transition is a period of accelerated cardiovascular disease risk.[21] [105] Women with premature or early menopause (before age 40 or 45 years, respectively) have an increased risk of cardiovascular disease.[105] [106]		
hormone therapy-related venous thromboembolism	**variable**	**low**
Observational studies and a meta-analysis indicate that transdermal estrogens are associated with a lower risk of venous thromboembolism (VTE) than oral estrogens.[1][50] [51] The risk of VTE is higher if hormone therapy is initiated after age 60 years or more than 10 years from menopause onset.[17]		
hormone therapy-related breast cancer	**variable**	**low**
Hormone therapy with an estrogen alone is associated with little or no change in the risk of breast cancer.[1] An estrogen prescribed in combination with a progestin is associated with a small increase in the risk of breast cancer.[1][50] [51] [Evidence C] The increased risk is related to duration of treatment, and likely recedes after treatment is stopped.[1][50] [51]		
hormone therapy-related stroke	**variable**	**low**
The risk of venous thromboembolism and ischemic stroke increases with oral hormone therapy, but the absolute risk of stroke in women under 60 years of age is very low.[1][50] [51] Data on the risk of hemorrhagic stroke in women using hormone therapy are inconsistent and lacking.[20] Observational studies and a meta-analysis indicate that transdermal estrogens are associated with a lower risk of venous thromboembolism and stroke than oral estrogens.[1][17][50] [51]		
urinary tract infections	**variable**	**low**
Vaginal and urogenital epithelial thinning occurs with menopause and can lead to increased susceptibility to urinary tract infections. Vaginal (or systemic) estrogen replacement can improve the thickness and health of the perineal epithelium and lower the rate of recurrent urinary tract infections.		

FOLLOW UP

Prognosis

Menopause is a physiologic event and its timing may be determined genetically. The endocrine changes are permanent, but hot flashes usually resolve in most women within 5 to 10 years. In an observational study, the median total vasomotor symptom duration was 7.4 years, but this varied by ethnicity.[4] African-American women reported the longest total vasomotor symptom duration (median, 10.1 years).[4] Urogenital atrophy may stay the same or worsen.

Diagnostic guidelines

International

Clinical practice for the diagnosis and treatment of menopause (https://www.endocrinepractice.org/article/S1530-891X(20)43264-1/fulltext) [33]

Published by: American Association of Clinical Endocrinologists **Last published:** 2011

Treatment of symptoms of the menopause (https://www.endocrine.org/clinical-practice-guidelines) [36]

Published by: The Endocrine Society **Last published:** 2015

Menopause: diagnosis and management (https://www.nice.org.uk/guidance/ng23) [1]

Published by: National Institute for Health and Care Excellence (UK) **Last published:** 2019

Treatment guidelines

International

Nonhormone therapy position statement (https://www.menopause.org/publications/professional-publications/position-statements-other-reports) [98]

Published by: North American Menopause Society **Last published:** 2023

The hormone therapy position statement (https://www.menopause.org/publications/professional-publications/position-statements-other-reports) [17]

Published by: North American Menopause Society **Last published:** 2022

Osteoporosis in menopause (https://www.jogc.com/article/S1701-2163(21)00749-0/fulltext) [99]

Published by: Society of Obstetricians and Gynaecologists of Canada **Last published:** 2022

Management of osteoporosis in postmenopausal women: the position statement (https://www.menopause.org/publications/professional-publications/position-statements-other-reports) [8]

Published by: North American Menopause Society **Last published:** 2021

The genitourinary syndrome of menopause position statement (https://www.menopause.org/publications/professional-publications/position-statements-other-reports) [100]

Published by: North American Menopause Society **Last published:** 2020

Clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis (https://pro.aace.com/clinical-guidance/2020-clinical-practice-guidelines-diagnosis-and-treatment-postmenopausal) [101]

Published by: American Association of Clinical Endocrinologists; American College of Endocrinology **Last published:** 2020

Position statement on menopause (https://pubmed.ncbi.nlm.nih.gov/28703650) [23]

Published by: American Association of Clinical Endocrinologists; American College of Endocrinology **Last published:** 2017

ACOG practice bulletin no 141: management of menopausal symptoms (https://www.acog.org/clinical/clinical-guidance/practice-bulletin) [38]

Published by: American College of Obstetricians and Gynecologists **Last published:** 2014 (reaffirmed 2024)

International

Management of symptomatic vulvovaginal atrophy (https://www.menopause.org/publications/professional-publications/position-statements-other-reports) [31]

Published by: North American Menopause Society **Last published:** 2013

Clinical practice for the diagnosis and treatment of menopause (https://www.endocrinepractice.org/article/S1530-891X(20)43264-1/fulltext) [33]

Published by: American Association of Clinical Endocrinologists **Last published:** 2011

Recommendations on women's midlife health and menopause hormone therapy (https://www.imsociety.org/ims_recommendations.php) [102]

Published by: The International Menopause Society **Last published:** 2016

Treatment of symptoms of the menopause (https://www.endocrine.org/clinical-practice-guidelines) [36]

Published by: The Endocrine Society **Last published:** 2015

Stroke in women: management of menopause, pregnancy and postpartum (https://eso-stroke.org/guidelines/eso-guideline-directory) [20]

Published by: European Stroke Organisation **Last published:** 2022

Optimising the menopause transition (https://journals.sagepub.com/doi/10.1177/20533691221104882) [103]

Published by: British Menopause Society; Royal College of Obstetricians and Gynaecologists; Society for Endocrinology **Last published:** 2022

Menopause: guidance for nurses, midwives and health visitors (https://www.rcn.org.uk/Professional-Development/publications/rcn-menopause-guidance-for-nurses-midwives-and-health-visitors-uk-pub-009326) [104]

Published by: Royal College of Nursing (UK) **Last published:** 2020

Recommendations on hormone replacement therapy in menopausal women (https://thebms.org.uk/publications/consensus-statements) [39]

Published by: The British Menopause Society; Women's Health Concern **Last published:** 2020

EVIDENCE TABLES

Evidence tables

What are the effects of hormone replacement therapy (HRT) administered for menopausal symptoms on the risk of developing breast cancer?[1]

This table is a summary of the analysis reported in a guideline (underpinned by a systematic review) that focuses on the above important clinical question.

View the full source guideline (https://www.nice.org.uk/guidance/ng23/evidence)

Evidence C * Confidence in the evidence is very low or low where GRADE has been performed and there may be no difference in effectiveness between the intervention and comparison for key outcomes. However, this is uncertain and new evidence could change this in the future.

Population: Peri- and post-menopausal women up to 65 years
Intervention: HRT
Comparison: No HRT

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
Breast cancer [a]	No statistically significant difference	Very Low
Breast cancer (estrogen plus progesterone)	See note [b]	See note [b]
Breast cancer (estrogen only)	No statistically significant difference	Low
Breast cancer (estrogen plus progesterone versus estrogen only)	No statistically significant difference	Very Low
Randomized controlled trials with post-intervention follow-up [c]		
Breast cancer (current HRT user, 10-year follow-up) [a]	No statistically significant difference	Very Low
Breast cancer (estrogen plus progesterone, 8.2 years post-intervention follow-up)	Favors comparison	Low
Breast cancer (estrogen, 6.6 years post-intervention follow-up)	No statistically significant difference	Low

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
Breast cancer (estrogen, 10.6 years post-intervention follow-up)	No statistically significant difference	Very Low

Recommendations as stated in the source guideline

The results in this table are underpinned by randomized controlled trial (RCT) evidence, but the recommendations made by the guideline development group also take into account observational cohort evidence included in the guideline, stating that women around the age of natural menopause should be advised of the following:

- The baseline risk of breast cancer for women around menopausal age varies from one woman to another according to the presence of underlying risk factors
- HRT with an estrogen alone is associated with little or no change in the risk of breast cancer
- HRT with an estrogen and a progestogen can be associated with an increase in the risk of breast cancer
- Any increase in the risk of breast cancer is related to treatment duration and reduces after stopping HRT.

Following surveillance for new evidence, this guideline is in the process of being updated. In the interim, NICE have added the MHRA risk table and recommend referring to this during discussions with women about HRT (https://assets.publishing.service.gov.uk/media/5d680409e5274a1711fbe65a/Table1.pdf).

Note

[a] Results for this outcome are included in one RCT which evaluates HRT (estradiol and estradiol plus norethisterone for women with uterus; estradiol only for women without uterus) versus no treatment.

[b] Results are presented in two RCTs separately with low and very low quality evidence reporting no statistically significant difference between treatment groups.

[c] The guideline development group notes that the duration of HRT treatment ranged from 11.9 months to 14 years. They also note that post-intervention follow-up was reported in some trials ranging from 8 to 10 years which did not necessarily account for the full length of time participants were exposed to HRT, given that some women had previously used HRT.

* Evidence levels

The Evidence level is an internal rating applied by BMJ Best Practice. See the EBM Toolkit (https://bestpractice.bmj.com/info/evidence-tables/) for details.

Confidence in evidence

A - High or moderate to high

B - Moderate or low to moderate

C - Very low or low

† Effectiveness (BMJ rating)

Based on statistical significance, which demonstrates that the results are unlikely to be due to chance, but which does not necessarily translate to a clinical significance.

‡ Grade certainty ratings

High	The authors are very confident that the true effect is similar to the estimated effect.
Moderate	The authors are moderately confident that the true effect is likely to be close to the estimated effect.
Low	The authors have limited confidence in the effect estimate and the true effect may be substantially different.
Very Low	The authors have very little confidence in the effect estimate and the true effect is likely to be substantially different.

BMJ Best Practice EBM Toolkit: What is GRADE? (https://bestpractice.bmj.com/info/toolkit/learn-ebm/what-is-grade/)

Key articles

- Barnabei VM, Cochrane BB, Aragaki AK, et al. Menopausal symptoms and treatment-related effects of estrogen and progestin in the Women's Health Initiative. Obstet Gynecol. 2005 May;105(5 Pt 1):1063-73. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15863546?tool=bestpractice.bmj.com)
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Images

Difference in coronary heart disease incidence per 1000 menopausal women over 7.5 years (95% confidence interval) [1]	Current HT users	Treatment duration below 5 years	Treatment duration 5 to 10 years	More than 5 years since stopping treatment
Women on an estrogen alone - RCT estimate[2]	6 fewer (-10 to 1)	No available data	No available data	6 fewer (-9 to -2)
Women on an estrogen alone - observational estimate[3]	6 fewer (-9 to -3)	No available data	No available data	No available data
Women on an estrogen + a progestin - RCT estimate[2]	5 more (-3 to 18)	No available data	No available data	4 more (-1 to 11)
Women on an estrogen + a progestin - observational estimate[3]	No available data	No available data	No available data	No available data

HT, hormone replacement therapy; RCT, randomized controlled trial

[1] Results from Weiner et al (Menopause. 2008;15:86-93) were used for the baseline population risk estimation.

[2] For women aged 50–59 years at entry to the RCT.

[3] Observational estimates are based on cohort studies with several thousand women.

Figure 1: Absolute rates of coronary heart disease for different types of hormone therapy (HT) compared with no HT (or placebo), different durations of HT use, and time since stopping HT for menopausal women.

National Institute for Health and Care Excellence. Menopause: diagnosis and management. Dec 2019

Difference in stroke incidence per 1000 menopausal women over 7.5 years (95% confidence interval)[1]	Current HT users	Treatment duration below 5 years	Treatment duration 5 to 10 years	More than 5 years since stopping treatment
Women on an estrogen alone - RCT estimate[2]	0 (-5 to 10)	No available data	No available data	1 more (-4 to 9)
Women on an estrogen alone - observational estimate[3]	3 more (-1 to 8)	No available data	No available data	No available data
Women on an estrogen + a progestin - RCT estimate[2]	6 more (-2 to 21)	No available data	No available data	4 more (-1 to 13)
Women on an estrogen + a progestin - observational estimate[3]	4 more (1 to 7)	No available data	No available data	No available data

HT, hormone replacement therapy; RCT, randomized controlled trial

1 Results from Weiner et al (Menopause. 2008;15:86-93) were used for the baseline population risk estimation.

2 For women aged 50–59 years at entry to the RCT.

3 Observational estimates are based on cohort studies with several thousand women.

Figure 2: Absolute rates of stroke for different types of hormone therapy (HT) compared with no HT (or placebo), different durations of HT use, and time since stopping HT for menopausal women.

National Institute for Health and Care Excellence. Menopause: diagnosis and management. Dec 2019

	Risks over 5 years use (with no use or 5 years current HRT use)		Total risks up to age 69 (after no use or after 5 years HRT use†)		Risks over 10 years (with no use or 10 years current HRT use)		Total risks up to age 69 (after no use or after 10 years HRT use†)	
	Cases per 1000 women with no HRT use	**Extra cases per 1000 women using HRT**	Cases per 1000 women with no HRT use	**Extra cases per 1000 women using HRT**	Cases per 1000 women with no HRT use	**Extra cases per 1000 women using HRT**	Cases per 1000 women with no HRT use	**Extra cases per 1000 women using HRT**
Risks associated with **combined estrogen-progestogen HRT**								
Breast cancer	13	**+8**	63	**+17**	27	**+20**	63	**+34**
Sequential HRT	13	**+7**	63	**+14**	27	**+17**	63	**+29**
Continuous combined HRT	13	**+10**	63	**+20**	27	**+25**	63	**+40**
Endometrial cancer	2	-	10	-	4	-	10	-
Ovarian cancer	2	**+ <1**	10	**+ <1**	4	**+1**	10	**+1**
Venous thromboembolism (VTE)§	5	**+7**	26	**+7**	8	**+13**	26	**+13**
Stroke	4	**+1**	26	**+1**	8	**+2**	26	**+2**
Coronary heart disease (CHD)	14	-	88	-	28	-	88	-
Fracture of femur	1.5	-	12	-	1	-	12	-
Risks associated with **estrogen-only HRT**								
Breast cancer	13	**+3**	63	**+5**	27	**+7**	63	**+11**
Endometrial cancer	2	**+4**	10	**+4**	4	**+32**	10	**+32**
Ovarian cancer	2	**+ <1**	10	**+ <1**	4	**+1**	10	**+1**
Venous thromboembolism (VTE)§	5	**+2**	26	**+2**	10	**+3**	26	**+3**
Stroke	4	**+1**	26	**+1**	8	**+2**	26	**+2**
Coronary heart disease (CHD)	14	-	88	-	28	-	88	-
Fracture of femur	0.5	-	12	-	1	-	12	-

Figure 3: Summary of HRT risks and benefits during current use and current use plus post-treatment from age of menopause up to age 69 years, per 1000 women with 5 years or 10 years use of HRT.#Key: *Menopausal symptom relief is not included in this table, but is a key benefit of HRT and will play a major part in the decision to prescribe HRT. †Best estimates based on relative risks of HRT use from age 50. For breast cancer this includes cases diagnosed during current HRT use and diagnosed after HRT use until age 69 years; for other risks, this assumes no residual effects after stopping HRT use. § Latest evidence suggests that transdermal HRT products have a lower risk of VTE than oral preparations*

Medicines and Healthcare products Regulatory Agency. Hormone replacement therapy (HRT): further information on the known increased risk of breast cancer with HRT and its persistence after stopping. Aug 2019 [internet publication]; used with permission

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Please note that recommended formulations and doses may differ between drug databases drug names and brands, drug formularies, or locations. A local drug formulary should always be consulted for full prescribing information.

Treatment recommendations in BMJ Best Practice are specific to patient groups. Care is advised when selecting the integrated drug formulary as some treatment recommendations are for adults only, and external links to a paediatric formulary do not necessarily advocate use in children (and vice-versa). Always check that you have selected the correct drug formulary for your patient.

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Regardless of the language in which the content is displayed, numerals are displayed according to the original English-language numerical separator standard. For example 4 digit numbers shall not include a comma nor a decimal point; numbers of 5 or more digits shall include commas; and numbers stated to be less than 1 shall be depicted using decimal points. See Figure 1 below for an explanatory table.

BMJ accepts no responsibility for misinterpretation of numbers which comply with this stated numerical separator standard.

This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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// Acknowledgements:

Dr Heather Currie, Dr Haitham Hamoda, and Dr Bradford W. Fenton would like to gratefully acknowledge Dr Rebekah Wang-Cheng, a previous contributor to this topic.
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DISCLOSURES: MW has received research funding from Ferring and Pfizer Wyeth; has acted as an advisory board consultant for Pfizer Wyeth, QuatRx, and Yoplait; and is on the speakers' bureau of Amgen, Upsher Smith, and Warner Chilcott. MW is also an author of a reference cited in this topic.