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Maintaining postreproductive health: A care pathway from the European Menopause and Andropause Society (EMAS)

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ABSTRACT

This position statement from the European Menopause and Andropause Society (EMAS) provides a care pathway for the maintenance of women's health during and after the menopause. It is designed for use by all those involved in women's health. It covers assessment, screening for diseases in later life, treatment and follow-up. Strategies need to be optimised to maintain postreproductive health, in part because of increased longevity. They encompass optimising diet and lifestyle, menopausal hormone therapy and non-estrogen-based treatment options for climacteric symptoms and skeletal conservation, personalised to individual needs.

1. Introduction

Life expectancy has increased remarkably in recent years and women live longer than men. Life expectancy at birth in the European Union in 2013 was 83.3 years for women and 77.8 years for men [1]. Between 2002 (the first year for which data are available for all EU Member States) and 2013, life expectancy increased by 2.4 years for women. The UK's Office for National Statistics found that in 2011–2013 women aged 65 years had an average of 20.7 years of life remaining [2]. Worldwide, the number of postmenopausal women is estimated to reach 1.1 billion in 2025 [3].

Ageing populations are naturally more vulnerable to health disorders and their medical care is burdening national economies. Primary care providers should manage the individual needs of most midlife women, with the aim of preventing the development or delaying the progress of menopause-related health disorders. The purpose of this care pathway is to provide guidance to optimise healthcare for midlife women, from assessment to management options. Drugs in development are also detailed.

The care pathway is based mainly on the evidence presented in the following recent documents: EMAS position statements and clinical guides, published in *Maturitas* between 2010 and 2016 [see for example 4], a guideline from the UK National Institute for Health and Care Excellence (NICE) [5], a clinical practice guideline from the Endocrine Society [6], a practitioner's toolkit for managing the menopause [7] and the recommendations for the clinical care of midlife women produced by the North American Menopause Society [8].

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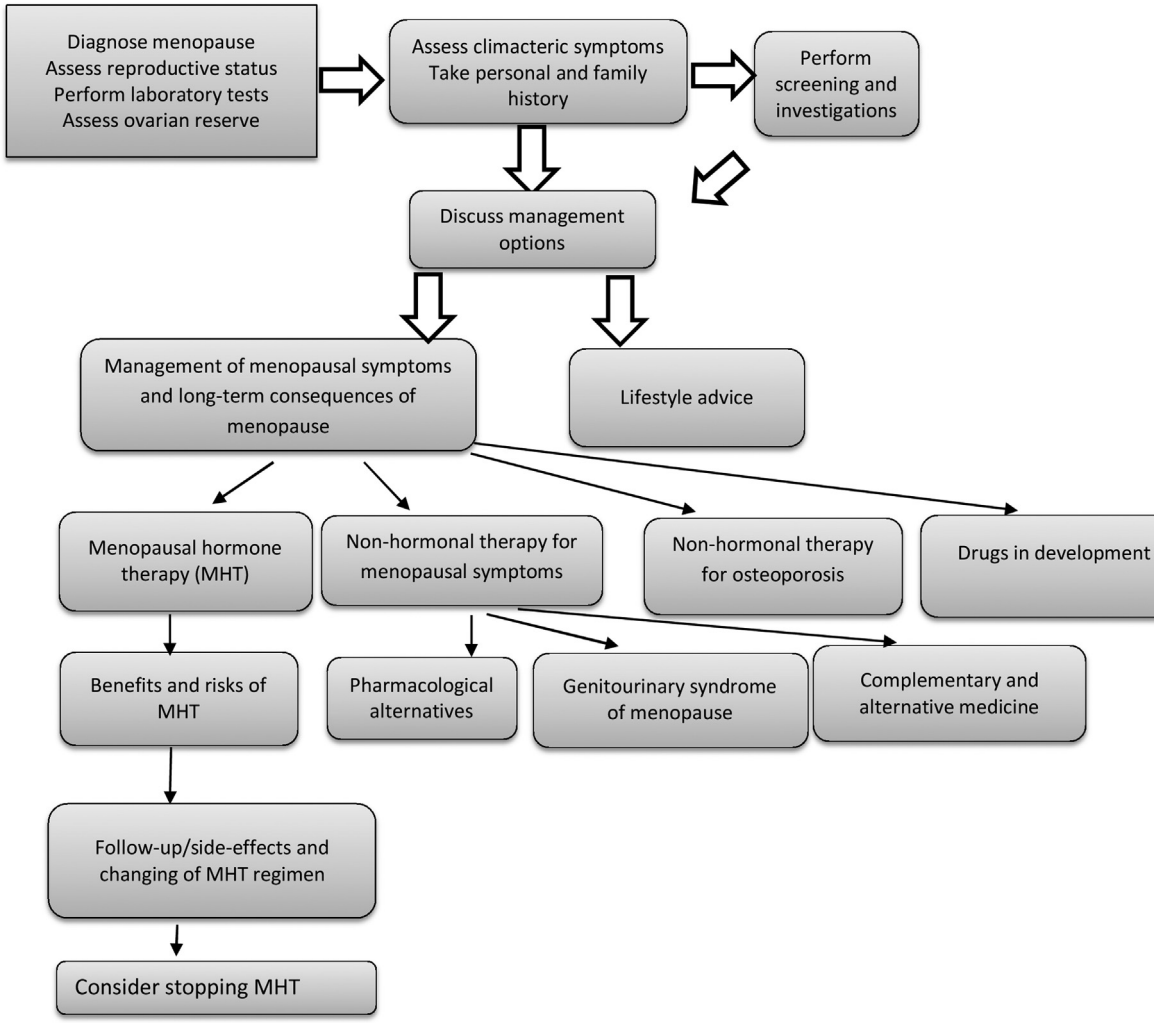

Fig. 1. A care pathway for the maintenance of women's postreproductive health.

The first step is to assess climacteric symptoms and diagnose menopause (Fig. 1). The consultation can also be an opportunity to assess the risk of disorders in later life such as cardiovascular disease and osteoporosis and to encourage women to take part in national screening programmes for cervical, breast and colon cancer. If the woman is troubled by menopausal symptoms, the management options should be discussed. These will include lifestyle advice as well as pharmacological interventions (hormonal and non-hormonal).

2. Diagnose menopause

For most women the menopause is a natural and inevitable process due to ovarian ageing and which usually occurs in their late 40s or early 50s [9,10]. Spontaneous menopause is recognised retrospectively after 12 months of amenorrhoea and occurs at an average age of 52. However, it can be induced earlier by medical intervention, such as bilateral oophorectomy or iatrogenic ablation of ovarian function by chemotherapy, radiotherapy or treatment with gonadotrophin-releasing hormone analogues. In the absence of surgery, induced premature ovarian failure may be permanent or temporary. The following terms are used:

* **Early menopause** describes menopause in women aged 40–45 years.
* **Premature menopause** denotes definitive loss of ovarian function (e.g. through bilateral oophorectomy) before the age of 40.
* **Premature ovarian insufficiency (POI)** describes transient or permanent loss of ovarian function in women before the age of 40. A substantial proportion of these women have spontaneous resumption of ovulation, menstruation and successful spontaneous pregnancy.
* **Menopause transition** is the time when there are changes to the menstrual cycle and endocrine levels. According to STRAW + 10 the transition begins with variation in the length of the menstrual cycle and ends with the final menstrual period [10].

3. Investigations and assessment of ovarian reserve

3.1. Endocrine investigations

Where it is deemed helpful, the following blood investigations may be used.

3.1.1. Follicle stimulating hormone (FSH)

There is no need to measure FSH levels to diagnose menopause in otherwise healthy women (who are not using hormonal contraception) over the age of 45 who have not had a period for at least 12 months or in perimenopausal women with vasomotor symptoms and irregular periods. Nor should FSH levels be used to diagnose menopause in hysterectomised women with menopausal symp-

toms. However, FSH and E2 measurements should be undertaken in younger women and considered in those with polycystic ovary syndrome (PCOS), endometrial ablation or in women needing a differential diagnosis of amenorrhoea [5].

3.1.2. Thyroid function tests

Symptoms of thyroid dysfunction can often mimic those of menopause. Thyroid function should therefore be checked when the relevant signs and symptoms are present or when there is a lack of response to menopausal hormone therapy.

3.1.3. Exclusion of other causes of amenorrhoea

Pregnancy and hyperprolactinaemia need to be excluded, especially in women under the age of 45

3.2. Assessment of premature ovarian insufficiency (POI)

In women with suspected POI, FSH, luteinising hormone (LH), estradiol, prolactin and testosterone levels and thyroid stimulating hormone (TSH), as a marker of thyroid function, should be checked. The diagnosis of POI is confirmed by two elevated FSH levels drawn at least 1 month apart. As POI can be associated with genetic abnormalities and autoimmune disease, additional evaluation should include a karyotype and testing for a fragile X premutation, thyroid peroxidase antibodies, adrenal antibodies, fasting glucose, and serum calcium and phosphorus levels.

3.3. Assessment of ovarian reserve

Serum anti-Mullerian hormone (AMH) and antral follicle count can be helpful to assess ovarian reserve, especially for women with POI seeking fertility treatments. However, there are concerns about the lack of standardised AMH assays [11–13].

4. Assessment of climacteric symptoms, personal and family history

4.1. Climacteric symptoms

4.1.1. Vasomotor symptoms

Vasomotor symptoms are the main menopausal complaints. They can greatly reduce quality of life and last for many years in some women [10]. Persistent vasomotor symptoms are associated with certain factors like ethnicity, younger age at menopause, current smoking, weight gain and lower educational level [14,15].

4.1.2. Complaints related to the urogenital tract

Complaints related to the urogenital tract occur mainly in the late menopausal period [10]. Direct enquiry about these symptoms should be made, since women are often embarrassed to discuss them, even though they can compromise quality of life and sexual health [10,16]. Recently described as 'the genitourinary syndrome of the menopause' (GSM), symptoms of urogenital atrophy include: dyspareunia, genital dryness, irritation/burning/itching of vulva or vagina, post-coital bleeding, decreased sexual desire and reduced lubrication with sexual activity as well as frequent or urgent urination [16,17].

4.1.3. Sleep problems

Sleep problems such as insomnia can be associated with vasomotor symptoms especially if there is a sweating component [18], but sleep disturbance can be an independent symptom. They can adversely affect quality of life.

4.1.4. Cognitive dysfunction and mood disorders

Cognitive dysfunction and mood disorders are frequently encountered in peri- and early postmenopausal women. Women complain about poor concentration, impaired memory, difficulties in performing multiple tasks, as well as symptoms of depression and anxiety. Other common psychological symptoms include mood swings and irritability. Health professionals should ask about their presence. Somatic symptoms such as muscle and joint pains and headaches may be related to negative mood symptoms and these should also be the subject of enquiry [19].

4.2. Personal history

This should include the following information:

4.2.1. Lifestyle

Lifestyle parameters, including smoking habits, alcohol consumption, exercise and nutrition

4.2.2. Medical history

Medical history, including in particular cardiovascular disease, hypertension, diabetes mellitus, venous thromboembolic disease, breast disease, cancer, osteoporosis, thyroid dysfunction, autoimmune disorders, migraine, mental health problems and current medication.

4.2.3. Gynaecological history

Gynaecological history, including presenting symptoms, age of menarche and menopause, type of menopause (natural or iatrogenic), disturbances in the length or duration of the menstrual cycle, history of benign or malignant gynaecological problems, signs of androgen excess, history of premenstrual syndrome, as well as details of any gynaecological surgery.

4.2.4. Obstetric history

Obstetric history, including number of pregnancies, miscarriages or abortions, complications of pregnancy (e.g. gestational diabetes or pre-eclampsia), infertility, as well as total duration of lactation.

4.3. Family history

This should include information about dyslipidaemia, osteoporosis, diabetes mellitus, cardiovascular disease, venous thromboembolism, cancer and dementia, as well as other major comorbidities.

5. Screening and investigations

5.1. Cardiovascular assessment

Evaluation of anthropometric indices, measurement of blood pressure and estimation of cardiovascular risk should be performed in accordance with national and international guidelines.

5.1.1. Anthropometric indices

Records of weight, height, waist and hip circumference should be kept for reference and comparison with follow-up data. Body mass index (BMI) and waist-to-hip ratio (WHR) should be calculated according to standard formulae: BMI = body weight (kg)/height^2 (m^2) and WHR = waist circumference (cm)/hip circumference (cm) [20,21].

5.1.2. Blood pressure

Blood pressure should be measured twice during a clinic visit and the average value of systolic and diastolic blood pressure should be recorded [22].

5.1.3. Estimation of cardiovascular risk

Estimation of cardiovascular risk may be undertaken using traditional algorithms of cardiovascular risk stratification such as the Systemic Coronary Risk Evaluation (SCORE) risk charts of the European Society of Cardiology (http://www.heartscore.org) or the Framingham score in the USA (http://cvdrisk.nhlbi.nih.gov) [23,24]. Classification in the following categories is used in the European guidelines [23]: low risk, moderate risk, high risk and very high risk. A therapeutic intervention is warranted for women at moderate or greater risk.

5.2. Gynaecological assessment

In general, pelvic assessment (physical examination and ultrasound) in asymptomatic women should be restricted to those at high risk of endometrial or ovarian cancer [4,25]. Abnormal bleeding in the perimenopause or in users of menopause hormone therapy (MHT) and postmenopausal bleeding require evaluation to diagnose or exclude pelvic pathology [25,26].

Women should be encouraged to take part in national screening programmes for cervical cancer [see for example 27–29]. However, taking cervical smears (the Pap test) after the menopause may not only cause pain and discomfort but also lead to an unsatisfactory smear for assessment or result in a false-positive diagnosis of a cytological abnormality. There is limited evidence that use of topical estrogens may reduce the likelihood of an atrophic smear. In some countries one of the indications for topical estriol includes preparation for cervical smears [30].

5.3. Breast assessment

Screening programmes vary throughout the world, with different recommendations regarding the age at which screening is started and stopped, as well as regarding the screening interval. Breast screening should be carried out according to local guidelines [31–34]. For women at increased risk of breast cancer there are specific recommendations such as those produced by the NICE in the UK [35]. EMAS has proposed that screening should be individualised because of the limitations of population-based screening, in particular overdiagnosis [36].

In general, more frequent mammography is not recommended in MHT users and the evidence from current randomised controlled trials does not support stopping MHT before mammography to reduce recall rates [36]. Estrogen-based MHT, but not tibolone, increases mammographic density. Greater mammographic density is associated with increased breast cancer risk and reduced sensitivity of screening mammography. However, the clinical significance of MHT-induced changes is uncertain, as the increase in mammographic density found with unopposed estrogen in the Women's Health Initiative (WHI) study was accompanied by a reduction in breast cancer risk [37].

5.4. Assessment of osteoporosis and fracture risk

In general, population screening for osteoporosis is not advised and instead selective examination of high-risk women should be undertaken [38,39]. Two individualised web-based calculation tools for fracture risk are the FRAX algorithm and the Garvan fracture risk calculator. These tools integrate bone mineral density (BMD) and clinical risk factors for fracture risk calculation in the individual patient in daily practice. QFracture is a web-based calculation tool developed for use in the UK which integrates more clinical risk factors than the previous two, but not BMD [40]. The FRAX tool has been developed by the World Health Organization (WHO) to evaluate fracture risk in men and women. The FRAX algorithms give the 10-year probability of hip fracture and of a major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture). The risk of fracture can be calculated on clinical risk factors alone or with femoral neck BMD in addition. Although all three fracture risk calculation tools include straightforward risk factors, such as age, sex, previous fractures and body weight, they differ in several respects, for example the inclusion of other clinical risk factors, BMD and fall risks.

Dual-energy X-ray absorptiometry (DXA) is the most widely validated technique used to assess BMD. DXA is usually applied to sites of biological relevance, such as the hip, spine and forearm [41]. DXA gives measurements of BMD that predict fracture at the specific site, with an increase in fracture risk of approximately 1.5 per standard deviation (SD) decrease in BMD (termed the gradient of risk). The highest gradient of risk is provided by DXA at the femoral neck for hip fracture prediction, where the risk of fracture increases 2.6-fold for every SD decrease in BMD. Guidelines regarding the use of DXA vary worldwide. For example, the National Osteoporosis Foundation recommends BMD assessment in all women aged 65 years or more, regardless of risk factors [42].

5.5. Assessment of muscle strength and mass

Sarcopenia, defined as low muscle mass plus low muscle strength or decreased physical performance, is a consequence of ageing. While muscle strength in postmenopausal women can be evaluated by handgrip strength, specialist referral is required for detailed assessment [43].

6. Discuss management options

The following approach is advised [5,6]:

- Provide information about the long- and short-term consequences of the menopause.
- Give advice about lifestyle and pharmacological interventions, detailing benefits and risks.
- Provide information on contraception to perimenopausal women.
- Decide together with the woman what is the most appropriate therapeutic intervention, taking lifestyle and individual needs into account.

7. Lifestyle advice

Lifestyle factors such as smoking cessation, maintaining a healthy diet, moderate to vigorous physical activity and moderation of alcohol consumption need to be discussed [44].

7.1. Diet

Recommended diet plans include encouraging consumption of:

- mono- and polyunsaturated rather than saturated fats;
- complex carbohydrates derived from fruits, beans, legumes, rice and whole-grain cereals;
- proteins derived from fish, plants, poultry or skimmed dairy products [44].

Calcium and vitamin D intake need to be optimised [45,46].

7.2. Physical activity

Women should be encouraged to take aerobic exercise, at least 150 min per week of moderate intensity or at least 75 min per week of vigorous intensity. In addition, at least 2 days per week of muscle-strengthening activities will be beneficial [47]. Women who cannot achieve these levels of exercise should nevertheless be as active as possible. However, evidence from randomised controlled trials shows that exercise does not improve vasomotor symptoms [48].

8. Management of menopausal symptoms and long-term consequences of menopause

Administration of systemic MHT has a favourable risk–benefit profile for women under the age of 60 years or within 10 years after menopause for menopausal symptoms and osteoporosis (see Section 9) [4,5,49,50]. MHT at very low doses or non-estrogen-based therapies should be considered for older women. Symptoms due to the genitourinary syndrome of the menopause can be managed with low-dose topical estrogens or non-hormonal therapies [17]. Prevention and management of cardiovascular disease should be undertaken in accordance with international and national guidelines [see for example 22–24]. MHT should not be used primarily for the primary or secondary prevention of cognitive decline or dementia.

9. Menopausal hormone therapy (MHT) types

The main components of MHT are estrogens and progestogens. Estrogen alone is given to hysterectomised women. Progestogens and the selective estrogen receptor modulator bazedoxifene are added in regimens for non-hysterectomised women to reduce the increased risk of endometrial hyperplasia and carcinoma which occurs with unopposed estrogen [51]. Tibolone is a synthetic steroid compound that is in itself inert, but whose metabolites have estrogenic, progestogenic and androgenic actions. It is classified as MHT [52]. 'Bio-identical hormones' is a term used to describe medications which are plant-derived and modified to be structurally identical to endogenous human hormones such as estradiol and progesterone, just like most approved MHT products. The US Food and Drug Administration (FDA) is concerned about the claims for safety, effectiveness and superiority of bio-identical preparations that are made in 'compounding pharmacies' [53]. Different routes of administration can be used for individual hormones. The routes of administration are oral, transdermal (patches and gels), subcutaneous (implants) and vaginal.

The estrogens used in MHT include:

- 17β estradiol (17β E2)
- estriol
- conjugated estrogens (equine or plant-based) (CEE)
- promestriene.

While most are given orally, estradiol can be given transdermally, subcutaneously or vaginally. Estriol can be given vaginally.

The types of progestogens [54] are detailed in Table 1, apart from the native molecule progesterone, which can be used in MHT in combination with estrogens:

Most progestogens are given orally, although norethisterone and levonorgestrel are available in transdermal patches combined with estradiol, and levonorgestrel can be delivered directly to the uterus with an intrauterine device. Progesterone is formulated as tablets for oral or vaginal use or as a vaginal gel.

Bazedoxifene, a selective estrogen receptor modulator (SERM) approved for the treatment of postmenopausal women at risk of fracture, antagonises the effects of estrogen on the endometrium. The combination of conjugated estrogens with bazedoxifene as a novel tissue-selective estrogen complex (TSEC) can be used in postmenopausal women.

9.1. Individualising MHT dose

Anecdotally, young women, especially those who have had a premature surgical menopause with a sudden fall in estrogen levels, may need initially higher doses of estrogen to alleviate menopausal symptoms than their older counterparts. Women with premature surgical menopause often become testosterone deficient and may need testosterone supplementation to achieve vasomotor symptom control with estrogen, and also for hypoactive sexual desire disorder. There is increasing evidence that ultra-low estrogen doses – as low as 0.5 or 0.25 mg oral or 14 μg transdermal estradiol – can control hot flushes and prevent bone loss, but most studies have been undertaken in women in their 40s or 50s [55,56]. Given the scarce data, however, regarding the effect of ultra-low dose MHT on fracture risk, women with premature or early menopause may benefit more from treatment with standard-dose MHT, at least regarding fracture risk.

9.2. Benefits and risks of MHT

9.2.1. The main benefits of MHT

The main benefits of MHT can be summarised as follows [4–6,49]:

- MHT is the most effective treatment for vasomotor symptoms.
- Systemically administered MHT and topical estrogens are effective in the management of symptoms of vulvar and vaginal atrophy.
- MHT prevents postmenopausal bone loss.
- MHT may aid in the management of low mood that results from menopause.
- Standard-dose estrogen-alone MHT may decrease coronary heart disease and all-cause mortality in women younger than 60 years of age and within 10 years of menopause.

9.2.2. The main risks of MHT

The main risks of MHT can be summarised as follows [4–6,49]:

- Estrogen-alone MHT increases the risk of endometrial cancer.
- Oral, but not transdermal, estrogens increase the risk of venous thromboembolism.
- Combined MHT, but not estrogen-alone MHT, may be associated with an increased risk of breast cancer; this risk seems to be lost when MHT is discontinued.
- MHT may confer a small increased risk of stroke: there is a suggestion that transdermal preparations have less impact on the risk of stroke than oral preparations
- MHT use over the age of 65 may cause deterioration in cognitive function.
- Initiation of standard-dose oral MHT in women over the age of 60 who have established atherosclerosis may not result in a decreased risk of coronary heart events.

9.3. Follow-up, side-effects and changing of MHT regimen

- After starting MHT, women should receive their first follow-up appointment within 2–3 months, to review the efficacy of treatment and to discuss possible side-effects [4]. They should have an annual consultation thereafter to assess efficacy, dose, type, route

Table 1
Classification of progestogens.

Structurally related to progesterone		
Pregnane derivatives	Acetylated	MPA, megestrol acetate, chlormadinone acetate, cyproterone acetate
	Non-acetylated	Dydrogesterone, medrogestone
19-norpregnane derivatives	Acetylated	Nomegestrol acetate, nesterone
	Non-acetylated	Demegestone, promegestone, trimegestone
Structurally related to testosterone		
Ethinylated	Estranes	Norethindrone, norethindrone acetate, ethynodiol diacetate, norethynodrel, lynestrenol, tibolone
	13-ethylgonanes	Levonorgestrel, desogestrel, norgestimate, gestodene
Nonethinylated		Dienogest, drospirenone

of administration and need for continued treatment. Changes in the balance of benefits and risks need to be ascertained.
- Women with premature ovarian failure may need more frequent visits because of the adverse health consequences of untreated menopause and should be seen until the average age of the natural menopause.
- For women who have bothersome side-effects such as breast tenderness, bloating, fluid retention, headaches and mood swings, the options include reducing the dose of estrogen, changing the type of progestogen, using bazedoxifene or altering the route administration (e.g. transdermal rather than oral).
- Women with persistent breakthrough bleeding (more than 6 months) require gynaecological assessment [25].

9.4. Duration of use and stopping MHT

- In women with premature ovarian failure, systemic estrogen-based MHT is recommended at least until the average age of the natural menopause, unless it is contraindicated [4,5,49].
- The routine discontinuation of systemic MHT at age of 65 is not recommended – decisions need to be individualised [57].
- Vaginal estrogen may be continued long term, since the genitourinary syndrome of the menopause is a chronic condition. Endometrial pathology is rarely encountered following one year of use. Detailed recommendations differ between preparations; however, annual review is prudent [30].

- The limited evidence available shows no advantage of either tapering down or stopping systemic MHT abruptly [58].
- Women who wish to stop MHT should be advised about the possibility of a return of menopausal symptoms and in this light should be informed about the non-estrogen-based treatments for vasomotor symptoms and osteoporosis. They should also be cautioned about a possible increased risk of CHD and stroke in the first year after stopping MHT [59].

10. Non-hormonal therapies for menopausal symptoms

10.1. Pharmacological alternatives for vasomotor symptoms

Several options are available for women who do not wish to take or who have a contraindication to MHT, but few studies have compared their efficacy with that of MHT [60,61].

10.1.1. Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs)

Paroxetine, citalopram, escitalopram, venlafaxine and desvenlafaxine have been found to be effective for the treatment of hot flushes in several studies. In 2013 the US Food and Drug Administration approved paroxetine (7.5 mg daily) to treat moderate to severe hot flushes (vasomotor symptoms) associated with menopause [62]. No other SSRI or SNRI is approved for the treatment of hot flushes. Some SSRIs and SNRIs are potent cytochrome P450 2D6 (CYP2D6) inhibitors and decrease the metabolism of tamoxifen and may reduce its anti-cancer effect. Thus paroxetine should be avoided in tamoxifen users and venlafaxine is the preferred antidepressant in this population, with desvenlafaxine as an alternative, given that its metabolism also does not involve CYP2D6 [63].

10.1.2. Gabapentin

Gabapentin is a gamma-aminobutyric acid analogue indicated for epilepsy and neuropathic pain, but it also reduces hot flushes [64], although it is not currently approved for this indication. It does not inhibit cytochrome P450 and thus can be used in women taking tamoxifen.

10.1.3. Clonidine

Clonidine is a centrally acting alpha-adrenoceptor agonist that was developed for the treatment of hypertension. It is licensed for the treatment of hot flushes in some countries [60].

10.1.4. Stellate ganglion blockade (SGB)

Stellate ganglion blockade (SGB) was originally investigated as a treatment for hot flushes due to the similarity of these symptoms and those with hyperhidrosis, a neurological condition of excessive sweating, for which the procedure is effective. The current body of evidence, which includes that from a randomised controlled trial, shows marked variability in the magnitude of benefit of SGB on hot flushes [65,66].

10.2. Hypoactive sexual desire and vulvovaginal atrophy

10.2.1. Flibanserin

Flibanserin was approved for the management of hypoactive sexual desire disorder in premenopausal women in 2015 by the US Food and Drug Administration and could be considered after the menopause [67].

10.2.2. Ospemifene

Ospemifene, administered orally, is a selective estrogen receptor modulator approved for the treatment of moderate to severe vulvovaginal atrophy in women who are not candidates for local vaginal estrogens [68]. It is approved for use in both Europe and the USA.

10.2.3. Vaginal bio-adhesive moisturisers and lubricants

Vaginal bio-adhesive moisturisers and lubricants can alleviate symptoms of vaginal dryness [17]. Moisturisers are typically used on a regular basis, rather than episodically (usually associated with sexual activity). Lubricants are typically used episodically to correspond to sexual activity.

10.2.4. Laser therapy

Laser therapy for vulvovaginal atrophy is a new approach, but larger, long-term studies are required to explore its efficacy and safety data before definite conclusions can be drawn [69].

11. Alternative and complementary therapies

These are less effective than estrogen and need further evaluation in randomised controlled trials [59]. They include phytoestrogens (i.e. isoflavones, coumestans, lignans and stilbenes), meditation, cognitive behavioural therapy, relaxation and controlled breathing, acupuncture and homeopathic medicine. They are examined in more detail in the EMAS position statement 'Non-hormonal management of menopausal vasomotor symptoms' [60].

12. Non-hormonal therapy for osteoporosis

An overview of the non-estrogen-based treatments of osteoporosis is presented in Table 2.

12.1. Calcium and vitamin d

Calcium and vitamin D play a key role in bone metabolism, and correction of nutritional deficiencies is therefore advised as part of osteoporosis management. It is probably safer to achieve adequate calcium levels through dietary modification rather than using supplements because of the risk of renal stones and cardiovascular disease found with supplements [46]. Vitamin D supplementation can be undertaken with either vitamin D2 (ergocalciferol) or vitamin D3 (cholecalciferol). In some countries guidelines aim to increase supplement use to prevent vitamin D deficiency among at-risk groups, including people aged over 65 [45].

12.2. Selective estrogen receptor modulators (SERMS)

Selective estrogen receptor modulators (SERMS) (raloxifene and bazedoxifene) are approved for the prevention and treatment of postmenopausal osteoporosis, since they decrease the risk of vertebral fractures. However, the effect of both raloxifene and bazedoxifene in reducing non-vertebral fractures is limited to high-risk populations. Raloxifene reduces the risk of primary breast cancer in women with osteoporosis and has the same effect as tamoxifen in the prevention of breast cancer in high-risk women. Both SERMS may increase the frequency of hot flushes and the risk of venous thromboembolism [70].

12.3. Bisphosphonates

Bisphosphonates are first-line anti-osteoporotic medications because of their generally favourable safety profile and low cost [71]. To avoid prolonged suppression of bone turnover, a 'drug-holiday' of 1–3 years after 5 years of continuous treatment may be advised [72]. Side-effects include upper gastrointestinal irritation and acute phase reactions (oral and intravenous preparations, respectively) and less commonly osteonecrosis of the jaw, atrial fibrillation, oesophageal cancer and atypical femoral fracture.

12.4. Denosumab

Denosumab is an antiresorptive agent, with a generally favourable safety profile, which has been approved for the treatment of osteoporosis in high-risk women [73]. It is a human monoclonal antibody against RANKL, an osteoclast-stimulating cytokine. The medicine is administered as a subcutaneous injection every 6 months. Side-effects include rash, dermatitis, eczema and, rarely, cellulitis, while sporadic cases of osteonecrosis of the jaw and atypical femur fractures have also been reported. Bone loss resumes within 6 months after discontinuation of denosumab, implying the need for an alternative treatment for continued skeletal conservation.

12.5. Strontium ranelate

Strontium ranelate reduces bone resorption and promotes bone formation to a lesser extent. It reduces the risk of vertebral fractures, as well as of non-vertebral and hip fractures in high-risk patients [74,75]. Mild and self-limited side-effects include nausea and vomiting. Strontium ranelate has been associated with a higher risk of venous thromboembolism, and with a rare hypersensitivity reaction (DRESS syndrome: drug rash with eosinophilia and systemic symptoms). Concerns about its cardiovascular safety have limited its use to the treatment of severe osteoporosis in postmenopausal women who are unable to receive alternative medications [76]. The medicine should not be administered to patients with known cardiovascular or cerebrovascular disease or uncontrolled hypertension.

12.6. Parathyroid hormone (PTH)

Parathyroid hormone (PTH) is an anabolic therapy. The intact molecule of PTH (amino acids 1–84) as well as the 1–34 N-terminal fragment (teriparatide) are administered in the form of daily subcutaneous injections for a maximum of 24 months. Long-term animal studies have indicated a link between PTH use and the development of osteosarcoma. Although this finding has not been confirmed in humans, the use of PTH for the treatment of osteoporosis is limited to 2 years. Simultaneous administration of PTH and antiresorptive agents is not advised because the latter attenuate the effect of the former. However, this recommendation may not apply in cases of antiresorptive preparations with an extended time interval of administration, like denosumab or zoledronic acid. Stopping anabolic treatment should be followed by administration of an antiresorptive agent, to prevent the ensuing bone loss [74,77].

13. Drugs in development

The following estrogen and non-hormonal therapies are in development for the management of menopausal symptoms and osteoporosis and will increase the therapeutic armamentarium in future years.

- Vaginal estrogen preparations for the treatment of vulvovaginal atrophy [78]: TX-004HR is a softgel capsule [79] and WC-3011 a cream [80].
- An oral estradiol/progesterone combination capsule for vasomotor symptoms (TX-001HR) [78,81].
- Dehydroepiandrosterone (DHEA) combined with acolbifene for vasomotor symptoms in postmenopausal women [78,82].
- Cathepsin K inhibitors (e.g. odanacatib and ONO-5334) [83] and sclerostin antibodies (e.g. romosozumab and blosozumab) for osteoporosis [84].

14. Summary

* For most women the menopause is a natural and inevitable process due to ovarian ageing that usually occurs in their late 40s or early 50s. It can cause bothersome, disrupting symptoms in some women.
* Conditions affecting postreproductive health include osteoporosis, cardiovascular disease, cognitive decline and dementia.
* Assessment should be holistic and include menopausal symptoms, personal and family history, cardiovascular and osteoporotic risk factors as well as gynaecological and breast health.
* Strategies to maintain postreproductive health encompass optimising diet and lifestyle, menopausal hormone therapy and

Table 2
Non-estrogen-based treatment options for osteoporosis.

Medication	Efficacy: vertebral fractures	Efficacy: non-vertebral fractures	Side-effects	Clinical indications/recommendations
SERMS	30–50% reduction		• Hot flushes • Venous thromboembolism	• Women at risk of breast cancer (raloxifene decreases the risk of primary breast cancer) • Women at risk of vertebral fractures • Women with upper gastrointestinal problems
Bisphosphonates	Up to 50% reduction	Up to 30–40% reduction in hip fractures	• Upper gastrointestinal irritation • Acute phase reactions • Osteonecrosis of the jaw • Atrial fibrillation • Oesophageal cancer • Atypical fractures	• Most cost-effective treatment • Non-compliant women (because intravenous preparations are available) • Consider a drug holiday after prolonged treatment (>5 years)
Denosumab	Up to 68% reduction	Up to 40% reduction in hip fractures	• Skin reactions (rash, eczema, dermatitis) • Cellulitis • Osteonecrosis of the jaw • Atypical fractures	• Older women at high risk of vertebral fractures or hip fracture • Women not wishing daily, weekly or monthly regimens • Non-compliant or institutionalised women • Intolerance to bisphosphonates • Renal insufficiency • Consider a drug holiday after prolonged treatment (> 5 years)
Strontium ralenate	Up to 40% reduction	Up to 16%	• Vomiting and diarrhoea • Venous thromboembolism • DRESS syndrome (drug rash with eosinophilia and systemic symptoms) • Cardiovascular disease	• Second-line therapy when other anti-osteoporotic treatments are not indicated or tolerated • Should not be used in women at high risk of cardiovascular disease or uncontrolled hypertension
Teriparatide/recombinant PTH	Up to 70% reduction	Up to 50% decrease	• Hypercalcaemia • Nausea • Vomiting • Dizziness • Hypercortisolism • Osteosarcoma in animals	• Women with prevalent fractures or spine deformity • Women with extremely low T-scores (<−3.5) • Women who fracture or markedly decrease bone mass density while on antiresorptive therapy

non-estrogen-based options for climacteric symptoms. Skeletal conservation should be personalised to individual needs.

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