EMAS Consensus Statement

Menopause, wellbeing and health: A care pathway from the European Menopause and Andropause Society

Irene Lambrinoudaki [a,*], Eleni Armeni [a], Dimitrios Goulis [b], Silvia Bretz [c], Iuliana Ceausu [d], Fatih Durmusoglu [e], Risto Erkkola [f], Ivan Fistonic [g], Marco Gambacciani [h], Marije Geukes [i], Haitham Hamoda [j], Caiomhe Hartley [k], Angelica Lindén Hirschberg [l,m], Blazej Meczekalski [n], Nicolas Mendoza [o], Alfred Mueck [p,q], Antonina Smetnik [r], Petra Stute [s], Mick van Trotsenburg [t], Margaret Rees [u]

[a] Second Department of Obstetrics and Gynecology, National and Kapodistrian University of Athens, Greece
[b] Unit of Reproductive Endocrinology, First Department of Obstetrics and Gynecology, Medical School, Aristotle University of Thessaloniki, Greece
[c] Clinica Silvia Bretz, Rio de Janeiro, Brazil
[d] Department of Obstetrics and Gynecology I, "Carol Davila" University of Medicine and Pharmacy, "Dr. I. Cantacuzino" Clinical Hospital, Bucharest, Romania
[e] Istanbul Medipol International School of Medicine, Istanbul, Turkey
[f] Department of Obstetrics and Gynecology, University Central Hospital, Turku, Finland
[g] Institute for Women's Health, Zagreb, Croatia
[h] Menopause and Osteoporosis Unit, San Rossore Clinical Center, Pisa, Italy
[i] Department of Obstetrics and Gynecology, Ziekenhuisgroep Twente (Hospital Group Twente), Post Box 7600, 7600 SZ Almelo, the Netherlands
[j] Department Gynaecology, King's College Hospital, Denmark Hill, London SE5 9RS, UK
[k] Menopause Health Clinic, Dublin, Ireland
[l] Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden
[m] Department of Gynecology and Reproductive Medicine, Karolinska University Hospital, Stockholm, Sweden
[n] Department of Gynecological Endocrinology, Poznan University of Medical Sciences, Poznan, Poland
[o] Department of Obstetrics and Gynecology, University of Granada, Spain
[p] Department of Women's Health, University Hospital Tuebingen, Germany
[q] Beijing OB/GYN Hospital, Capital Medical University, China
[r] Department of Gynecological Endocrinology, National Medical Research Centre for Obstetrics, Gynecology and Perinatology, Ministry of Healthcare of the Russian Federation, Moscow, Russia
[s] Department of Obstetrics and Gynecology, University Clinic Inselspital, Bern, Switzerland
[t] Department of Obstetrics and Gynecology, University Hospital St. Poelten-Lilienfeld, Austria
[u] Women's Centre, John Radcliffe Hospital, Oxford OX3 9DU, UK

ARTICLE INFO

ABSTRACT

This care pathway from the European Menopause and Andropause Society (EMAS) provides an updated pathway for monitoring and guidance of women at midlife, focusing on those approaching the end of the reproductive life-cycle, going through the menopausal transition and beyond. The care pathway is written by professionals involved in women's health and provides a stepwise individualized approach, stratified according to needs, symptoms and reproductive stage. Furthermore, the pathway provides details on screening for chronic diseases related to menopause and ageing. Treatment options for climacteric symptoms range from menopausal hormone therapy to non-hormonal alternatives and lifestyle modifications. Therapy should be tailored to personal needs and wishes. The pathway aims to offer a holistic, balanced approach for monitoring middle-aged women, aiming to control health problems effectively and ensure healthy ageing.

1. Introduction

Life expectancy has considerably increased since 1970 [1], and now >50% of women are expected to break the 90-year barrier by 2030 [2]. Growing older rather than old means spending almost half of life after the menopause, challenging the concept of healthy ageing [3]. Iatrogenic menopause may be induced by cancer treatment or bilateral salpingo-oophorectomy for benign disease and may occur before the average age of natural menopause, which is around the age of 50 [4,5]. The sudden fall in estrogen levels with iatrogenic menopause may lead to rapid onset of vasomotor symptoms [4]. Approximately 1% of women of reproductive age worldwide have premature ovarian insufficiency (POI) and approximately 2–7.6% of women experience early menopause between the ages of 40 and 45 years, which requires prompt diagnosis and management to ensure long-term health [6,7].

Quality of life after menopause can decline due to bothersome menopausal symptoms (e.g. hot flushes and night sweats, sleep problems, muscle and joint pain, anxiety, depression, low libido), symptoms of vulvovaginal atrophy (e.g. vaginal dryness and dyspareunia) and chronic conditions related to ageing. The perception of ageing can be affected by factors such as the age and type of menopause, ethnicity, life course, socioeconomic factors, social support, childhood abuse, workplace, type of employment, level of education, religion and individual cultural beliefs [8]. Health care professionals managing women transitioning through menopause should assess and guide women towards healthy ageing, address symptoms and provide primary prevention advice for chronic conditions such as osteoporosis and cardiovascular disease [5]. Furthermore, women should be offered prevention plans linked with national screening programmes for breast, colon and cervical cancer [9].

This care pathway updates the EMAS statement published in 2016. It is based on EMAS Care Online [3], position statements and clinical guides published by EMAS during the last five years [10–14], recommendations of the International Menopause Society (IMS) on menopausal hormone therapy [15], the IMS white paper on premature ovarian insufficiency [16], British Menopause Society guidelines [17], North American Menopause Society guidelines on the management of the genitourinary syndrome of menopause (GSM) [18] and postmenopausal osteoporosis [19] as well as its position statement on menopausal hormone therapy [20], European guidance on the diagnosis and management of osteoporosis in postmenopausal women [21] and the Endocrine Society guideline on the pharmacological management of osteoporosis in postmenopausal women [22].

2. Diagnosing reproductive status

The first aim in the diagnostic approach is to assess the reproductive status of the woman who presents with irregular cycles or amenorrhoea.

The accurate diagnosis of the reproductive status is based on the following points [23]:

- **Spontaneous menopause** is usually defined retrospectively, after 12 months of amenorrhoea, typically at 50–51 years [15,24]. The age of spontaneous menopause varies between ethnic groups. According to data retrieved from 21 studies and 10 countries, the youngest age at menopause has been described as 48 years for women living in South Asia, the oldest as 52 years in Japanese women, and an intermediate age of 50 years for Caucasian women [24].
- **The menopausal transition** usually starts with variability in the length of the menstrual cycle and ends with the last menstrual period [25].
- **Induced menopause** is defined as cessation of ovarian function following an intervention (e.g. oophorectomy or chemotherapy) [3,16].

Subsequent classification of menopause is related to the age at which

menstruation ceases [3]: POI is diagnosed when menses stop before the age of 40 years, while early menopause occurs between 40 and 45 years of age (Fig. 1). The term "perimenopause" denotes the period between the beginning of menstrual irregularities and 12 months after the last menstrual period. After this time, the woman enters the postmenopausal phase [23].

3. Investigations and assessment of ovarian reserve

3.1. Endocrine investigations

3.1.1. Follicle-stimulating hormone

Measurement of serum concentrations of follicle-stimulating hormone (FSH) is not required for formal confirmation of menopausal stage for women over the age of 45. FSH assessment is indicated in women aged 40–45 years who report a change in their menstrual cycle and menopausal symptoms [26]. Women aged <40 years in whom menopause is suspected should be assessed to explore possible POI [5,16,26].

3.1.2. Exclusion of other causes of amenorrhoea

Other causes of amenorrhoea or menstrual disturbances need to be explored, especially in women aged <45 years. These include thyroid dysfunction [27], pituitary hormone disorders (e.g. hyperprolactinaemia or hypopituitarism), hypercortisolaemia, polycystic ovarian syndrome, functional hypothalamic amenorrhoea or eating disorders [16].

3.2. Assessment of premature ovarian insufficiency

The first step in the diagnosis of POI is to determine whether there is a personal history of oligo-amenorrhoea or amenorrhoea of at least 4 months in a woman younger than 40 years. If so, FSH should be assessed to confirm the diagnosis. There is a discordance between national and international societies regarding the appropriate threshold in FSH concentrations to diagnose POI. The European Society of Human Reproduction and Embryology (ESHRE) guideline suggests a threshold of >25 IU/L [28], while the UK National Institute for Health and Care Excellence (NICE) guideline suggests FSH concentrations >30 IU/L [26]. In any case, FSH concentrations >40 IU/L, measured on at least two occasions (4–6 weeks apart), are diagnostic of POI [15,29,30].

Investigation for causes of POI includes: personal and family history, exclusion of secondary causes (e.g. autoimmune disorders, genetic disorders, iatrogenic factors, infections like mumps or tuberculosis), and evaluation of ovarian hormones combined with a pituitary hormone profile [16]. Further blood tests should also measure levels of luteinizing hormone (LH), sex hormone-binding globulin (SHBG), estradiol (E_2), testosterone (T), thyroid stimulating hormone (TSH) and prolactin [5,16].

3.3. Assessment of ovarian reserve

Ovarian reserve can be assessed by measuring several markers, with serum anti-Müllerian hormone (AMH) being the preferred one. A limitation in comparing AMH assays is the lack of international standards [31,32]. Although serum AMH estimation is useful in predicting reproduction outcomes, it has no clinical use in predicting age at menopause onset [31]. Another marker of ovarian reserve is the antral follicle count (AFC), but it does not have any added value in predicting age of menopause [33,34].

| 40 years | | 45 years | 50–51 years |

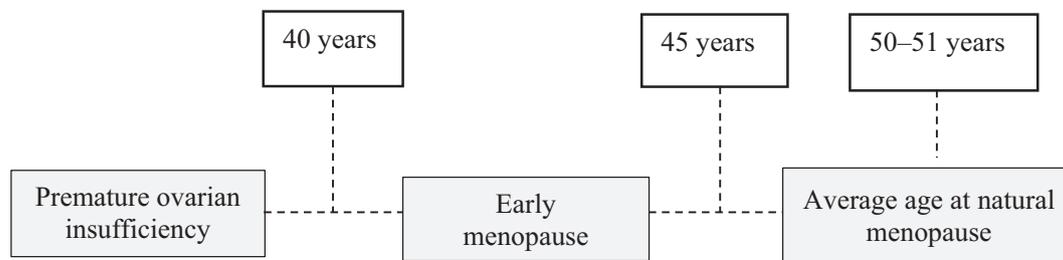| Premature ovarian insufficiency | Early menopause | Average age at natural menopause |

Fig. 1. The final menstrual period defines the menopause. The average age at natural menopause is approximately 50.5 years (95% CI: 50.2 to 50.8) [24]. Women with premature ovarian insufficiency experience ovarian senescence before the age of 40 years. Termination of menses at an age >40 years but under 45 years is defined as early menopause.

4. Assessment of menopausal symptoms, personal and family history

4.1. Menopausal symptoms

4.1.1. Vasomotor symptoms

Vasomotor symptoms consist mainly of hot flushes and chronically disturbed sleep, which can lead to fatigue, insomnia and irritability and have a major impact on daily activities. They are mainly attributed to dilatation and constriction of blood vessels in the skin, allowing heat loss due to a sudden increase in blood flow [35]. Hot flushes begin in the perimenopause and usually persist for 4–5 years after menopause, but they might continue for up to 10 years or even more in up to 25% of women [36]. Apart from affecting quality of life, the severity of vasomotor symptoms is associated with an increased risk of both cardiovascular disease and diabetes mellitus [37–39].

4.1.2. Sleep problems

Sleeping patterns at midlife can be disrupted by bothersome vasomotor symptoms with or without insomnia [40,41]. The severity of symptoms is related to ethnicity, pre-existing depressive symptoms and body mass index (BMI) before the menopausal transition [42].

4.1.3. Cognitive dysfunction and mood disorders

Peri- or postmenopausal women frequently report impaired memory, poor concentration or difficulties in multi-tasking. Moreover, they can present with feelings of anxiety and depression, mood swings and irritability. Chronically disturbed sleep can lead to irritability, fatigue, concentration problems as well as muscle and joint ache [43].

4.1.4. Genitourinary syndrome of the menopause

The term genitourinary syndrome of menopause (GSM) is used to describe a wide range of symptoms affecting the vagina, vulva, urethra and bladder due to estrogen deficiency. These symptoms include irritation, dryness, burning, urinary frequency and urgency, recurrent urinary tract infections and symptoms of pain and dryness during intercourse [18]. GSM usually becomes apparent towards the late perimenopausal stage, but can also be prevalent in pre- or early perimenopause [25,44]. Signs and symptoms related to the urogenital system have been estimated to affect up to 50% of postmenopausal women. These symptoms respond to treatment with low-dose and ultra-low-dose vaginal estrogens, which do not result in significant systemic absorption and can be administered long term if required [3]. Many women tend to regard these signs and symptoms as an age-related phenomenon or a complication of iatrogenic interventions (i.e., surgery or chemotherapy) which they have to live with and hence avoid discussing them [18,45]. Direct questions are often needed to explore and discuss the extent of GSM-related symptoms and offer treatment choices [18].

4.2. Personal history

The personal history should include the following items.

4.2.1. Lifestyle

Details on lifestyle should be collected, through questions related to smoking, alcohol consumption, nutritional patterns, physical activity and sedentary time, as well as weight and BMI.

4.2.2. Medical history

Health care professionals should enquire about a history of cardiovascular disease, hypertension, diabetes mellitus, cancer, benign breast disorders, venous thromboembolism and pulmonary embolism, osteoporosis, thyroid dysfunction, autoimmune disorders, sleep pattern, migraine and mental health disorders. Details of current medication, as well as complementary and alternative therapies, should be documented, as should details of any previous surgery.

4.2.3. Gynaecological history

Gynaecological history should include details on age at menarche and menopause, presenting symptoms, type of menopause (spontaneous or induced), history of disturbances in the duration or length of the menstrual cycle, polycystic ovarian syndrome, history of premenstrual syndrome, symptoms suggestive of androgen excess, history of malignant or benign gynaecological conditions and any gynaecological surgery. Current or previous use of hormonal and non-hormonal contraceptives, as well as possibility of pregnancy, should also be documented [46].

4.2.4. Obstetric history

Obstetric history should include details on parity and number of pregnancies or infertility, history and total duration of breastfeeding, and pregnancy-related complications such as pre-eclampsia or gestational diabetes.

4.3. Family history

Family history should include details about first-degree relatives on cardiovascular disease, diabetes, hypertension, dyslipidaemia, venous thromboembolism, cancer, osteoporosis, dementia, cognitive disorders and other age-related comorbidities.

5. Screening and investigations

Different risk assessment tools are available to estimate the patient's risk of lung, colorectal and breast cancer, as well as the risk of osteoporosis [45]. In addition, a "core set" for the assessment of problems in functioning related to the climacteric is being developed based on the International Classification of Functioning, Disability and Health [47].

5.1. Cardiovascular assessment

The four major predictors of cardiovascular risk in women, in order of significance, are the following: smoking status, history of diabetes mellitus, blood pressure and levels of cholesterol [48]. These parameters can be used for an estimation of the overall risk of future cardiovascular events as per national and international guidelines.

5.1.1. Anthropometric indices

Bodyweight, height and waist and hip circumference should be assessed as needed based on individual cardiometabolic risk. The results can be used to calculate the body mass index (BMI) and the waist-to-hip ratio (WHR), which are useful in predicting the risk of metabolic syndrome as well as cardiometabolic risk [49]. For remote consultations, using telemedicine, women should be encouraged to monitor their weight.

5.1.2. Blood pressure

Visits should include two measurements of blood pressure, and the average reading should be documented [49].

5.1.3. Estimation of cardiovascular risk

The risk of cardiovascular events can be stratified using electronic algorithms such as the US Framingham score (http://cvdrisk.nhlbi.nih.gov) [50,51]. The European Society of Cardiology (ESC) offers an equivalent algorithm (SCORE – Systematic Coronary Risk Evaluation), which quantifies risk of cardiovascular events in the general population [52].

The ESC published the updated SCORE2 risk prediction algorithm, calibrated and validated to predict the 10-year risk of a first-onset cardiovascular event in European populations, stratifying participants by gender [48]. This tool is expected to provide an individualized risk estimation, taking the gender-specific risk factors into account. The SCORE2-OP toolkit estimates the 5- and 10-year risk of cardiovascular events in individuals aged >70 years. This tool provides gender-stratified results, and it has been validated for four different geographical regions, representing countries with different levels of cardiovascular risk [53]. Beyond the widely used cardiovascular risk stratification algorithms, women-specific risk factors, such as a history of hypertensive disease of pregnancy or radiation therapy for breast cancer, should also be considered [54].

Cardiovascular risk stratification should be taken into consideration at the time of the discussion of treatment options, especially menopausal hormone therapy (MHT) [55].

✓ Women with very high cardiovascular risk (SCORE ≥ 10%) should receive only topical estrogen treatment (vaginal) in combination with secondary prevention for the management of cardiovascular risk factors (CRFs).
✓ Women with high cardiovascular risk (SCORE 5% to <10%) can receive topical hormone replacement in combination with primary or secondary prevention strategies for CRFs. If systemic MHT is needed, transdermal regimens can be offered on an individual basis.
✓ Women with moderate cardiovascular risk (≥1% up to <5%) can be offered any type of systemic MHT, with or without primary prevention strategies for the management of CRFs.
✓ Women with low cardiovascular risk (<1%) can be offered any type of MHT.

5.2. Gynaecological assessment

The frequency of pelvic assessment (gynaecological examination and transvaginal ultrasound) depends on the individual's risk of pelvic (cervical, endometrial or ovarian) cancer.

● Asymptomatic women at moderate-high risk of pelvic cancer should be encouraged to participate in the national screening programmes. Policies on the incorporation of screening for human papilloma virus vary worldwide [56–59].
● Women presenting with abnormal bleeding will require evaluation to exclude pelvic pathology [59].
  ✓ Initial evaluation of women with abnormal uterine bleeding (such as perimenopausal intermenstrual or postcoital bleeding or breakthrough bleeding in MHT users) or postmenopausal bleeding (PMB) should consist of a pelvic examination followed by transvaginal ultrasound, for estimation of endometrial thickness (ET) and assessment of other pathologies such as fibroids, endometrial polyps and ovarian cysts. If ET is >4 mm in women with PMB not taking MHT, further evaluation is required, as per the national guidelines. Subsequently, further management can involve hysteroscopy or endometrial sampling [60,61]. Combined cyclic hormone therapy is almost always associated with regular uterine bleeding, and continuous combined therapy with amenorrhoea, but both may lead to unscheduled bleeding at initiation [61,62]. Persistent unscheduled bleeding beyond 4–6 months after commencing MHT warrants investigation with ultrasound scan and/or hysteroscopy with endometrial biopsy [61,62].
  ✓ The risk of endometrial cancer in MHT users with unscheduled bleeding is lower than that in non-users with postmenopausal bleeding, especially in women who had not been experiencing bleeding before commencing therapy and who are taking combined estrogen and progestogen therapy. For the majority of MHT users with unscheduled bleeding, modifying progestogen intake (type, dose, duration and route of administration) will often control the bleeding, but it is important to first exclude pelvic pathology.
  ✓ If the bleeding continues, transvaginal ultrasound should be performed, and further investigation with endometrial sampling and hysteroscopy may be required.

5.3. Breast assessment

Screening programmes for breast cancer in the general population, as well as for women with a family history of breast cancer, vary worldwide. Recommendations differ regarding the age at which screening is started and stopped, and regarding screening interval [63–71]. The main points of breast assessment are summarized below:

✓ Screening should be individualized to reduce the burden of overdiagnosis due to population-based assessment [72].
✓ Individual risk of breast cancer will determine the optimum frequency of mammographic screening, which differs between women with average [64] and higher-than-average risk [63].
✓ MHT users do not require more frequent mammographic screening. MHT may increase breast tissue density, slightly reducing the sensitivity of mammography [73].
✓ Women with POI or early menopause should adhere to the national or international breast cancer screening programmes [16].

5.4. Assessment of osteoporosis and fracture risk

● Population screening for osteoporosis is not advised [4,74–77]. Perimenopausal and postmenopausal women should be stratified according to their risk of fracture into the groups of high, intermediate or low risk with the aid of Internet-based algorithms, such as the FRAX calculator [19,77] or the Garvan [78] and the Q-Fracture® (approved for use in the UK) [77,79], prior to bone mineral density (BMD) assessment. These tools calculate the individual's probability of a future fracture using clinical risk factors (e.g. age, smoking, obesity, use of alcohol or long-term use of steroids) [77,80]. Unlike the Garvan tool, FRAX and Q-Fracture® do not account for the

previous history of falls [81], details of which should be carefully documented to guide individualized treatment options. Moreover, these algorithms do not explore possible comorbidities, knowledge of which will improve the prediction of future fracture risk, such as osteoarthritis, heart disease, chronic obstructive pulmonary disease, multiple sclerosis, Parkinson disease and so on [82]. The use of FRAX is recommended for women aged 40 years or above [83].

• Dual-energy X-ray absorptiometry (DEXA) is the established gold standard non-invasive method for the quantitative measurement of BMD and prediction of fracture risk, with good reproducibility [84]. This technique is used at sites of clinical relevance, namely the lumbar spine and the femoral neck in posterior-anterior views [84]. BMD assessment predicts the gradient of fracture risk, which is the increase in the relative risk of fracture attributed to a decrease in BMD by 1 SD [85]. The highest gradient of risk is described for hip fractures, for which the risk increases by 2.6 per 1-SD decrease in femoral neck BMD [86,87]. DEXA measurements can also be applied at the forearm, in hyperparathyroidism, in severe states of obesity and in cases where BMD at the traditional sites cannot be measured or interpreted [84].

• Guidelines for BMD assessment with DEXA differ between countries. According to the European guidance and the guidelines from the UK National Institute for Health and Care Excellence (NICE) on the management of osteoporosis after the menopause, all post-menopausal women >65 years of age should be screened [21,88]. BMD should be assessed in women aged 50 to 65 years of age in the presence of specific risk factors for osteoporosis, such as hypogonadism, premature menopause, hyperparathyroidism, hyperthyroidism, hyperprolactinaemia, diabetes mellitus, Cushing's disease, coeliac disease, chronic liver disease or pancreatitis, inflammatory bowel disease, rheumatoid arthritis, haematological disorders, homocystinuria, chronic kidney disease, immobility, a history of falls or fragility fracture, use of oral or systemic glucocorticoids, smoking, heavy alcohol intake (>14 units per week) and low BMI (<18.5 kg/m^2) [88]. For younger postmenopausal women, BMD evaluation is appropriate only if the assessment would influence subsequent management [21].

• Women with POI should undergo baseline BMD assessment at the time of diagnosis and then be followed up at intervals specified by the care providers to ensure that MHT maintains bone health [5,28].

5.5. Assessment of muscle strength and mass

The European Working Group on Sarcopenia in Older People defined sarcopenia as an acute or chronic, progressive and generalized loss of muscle mass and loss of muscle strength (quality/quantity) which may result in low physical performance [89]. The age-related decline in muscle strength/mass and decreased physical performance affect older postmenopausal women [90].

• Evaluation of handgrip strength is a useful indicator of muscle strength [90].
• Evaluation of sarcopenia can be done easily by measuring gait speed or using the SARC-F questionnaire [90]. The questionnaire is a useful tool for assessing the individual prior to referring to the specialist clinic and includes the following components: strength, rise from a chair, falls, climb stairs, need for assistance with walking [91]. Patients with suspected sarcopenia need specialist referral [90].

6. Discuss management options

Management should include:

• Provision of information about the consequences of menopause.
• Discussion of lifestyle changes.
• Discussion of contraception needs in perimenopausal women.

• Making a shared decision with the woman on the most appropriate therapeutic intervention, considering benefits and risks, the personal needs and lifestyle.

7. Lifestyle advice

Advice on healthy living at midlife and beyond is presented in Fig. 2 (adapted from [92–96]).

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

• For women experiencing menopause after the age of 45 years, MHT is the first-line treatment for managing bothersome menopausal symptoms, either during perimenopause or after the menopausal transition [15,17,97,98]. Women experiencing symptoms of vulvovaginal atrophy can be treated only with low-dose topical estrogen preparations or vaginal dehydroepiandrosterone (DHEA) [10].
• MHT should be provided to all women experiencing menopause at a younger age, unless contraindicated, at least until the age of natural menopause [16,17].
• MHT can be considered for managing postmenopausal osteoporosis, especially if menopausal symptoms and clinical risk factors for osteoporosis are present. MHT has a favourable benefit/risk balance in perimenopausal or postmenopausal women within 10 years of the last menstrual period [17,19,99,100].
• MHT initiated before the age of 60 years or within 10 years since menopause is associated with reduced progression of atherosclerosis. MHT should not be used for primary or secondary prevention of cardiovascular disease. Prevention strategies should be guided by national and international guidelines [101–103].
• MHT is unlikely to increase the risk of dementia or to have a detrimental effect on cognitive function if initiated before the age of 60 years. MHT should not be used to attempt to prevent cognitive decline or dementia as epidemiological evidence remains inconsistent [17,104,105]. A study published in 2021 using data from a large sample found that MHT use does not appear to increase the risk of developing dementia overall, but slightly increases the risk of developing Alzheimer's disease among long-term users of estrogen-progestogen therapies [106].

9. MHT types

MHT consists of two main components, estrogens and progestogens [15]. Estrogens are needed to control symptoms of estrogen loss [17,98]. The progestogens are added to estrogen treatment in women with an intact uterus to counteract the hyperplastic effect of estrogen on the endometrium [15,17,97,98].

Bazedoxifene is a selective estrogen receptor modulator (SERM), which can be used in combination with estrogen treatment for endometrial protection in postmenopausal women who have contraindications to or cannot tolerate progestogens [107,108].

Tibolone is a synthetic steroid compound that has metabolites with estrogenic, progestogenic and androgenic activity [109–111]. It is indicated for mitigating vasomotor symptoms and osteoporosis in postmenopausal women, independently of hysterectomy status [17]. Available data suggest that even a low dose of tibolone (1.25 mg daily; the standard dose is 2.5 mg) has been shown to be effective in decreasing the rates of vertebral and non-vertebral fracture in postmenopausal women aged 60–85 years [112]. On the other hand, treatment with tibolone increases the risk of stroke in women over the age of 60 years and is also associated with a higher risk of breast cancer recurrence [111,113].

Testosterone replacement can be offered to women with low sexual desire and administered together with MHT [17].

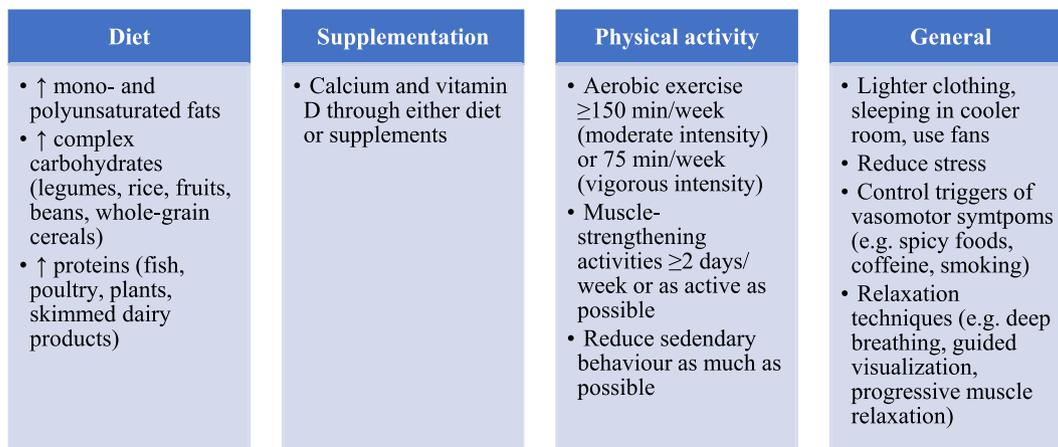Compounded bioidentical hormones are structurally modulated to

Diet	Supplementation	Physical activity	General
• ↑ mono- and polyunsaturated fats • ↑ complex carbohydrates (legumes, rice, fruits, beans, whole-grain cereals) • ↑ proteins (fish, poultry, plants, skimmed dairy products)	• Calcium and vitamin D through either diet or supplements	• Aerobic exercise ≥150 min/week (moderate intensity) or 75 min/week (vigorous intensity) • Muscle-strengthening activities ≥2 days/week or as active as possible • Reduce sedentary behaviour as much as possible	• Lighter clothing, sleeping in cooler room, use fans • Reduce stress • Control triggers of vasomotor symtpoms (e.g. spicy foods, coffeine, smoking) • Relaxation techniques (e.g. deep breathing, guided visualization, progressive muscle relaxation)

Fig. 2. Lifestyle advice for the management of menopausal symptoms and for prevention of chronic disease associated with ageing and the menopause.

resemble the hormones produced by the human ovary. Although E_2 and progesterone formulations are similar to the regulated MHT regimens, there are concerns about safety and efficacy when manufacture is unregulated [114]. Long-term safety data are still missing [115]. MHT regimens classified according to hormone type, dose and route of administration are presented in Table 1. The availability of the individual hormonal preparations varies worldwide.

9.1. Individualizing MHT dose

Women experiencing POI or early menopause should, in principle, receive treatment with estrogen doses which are higher than the doses given to women with natural menopause, aiming to restore hormone concentrations to the premenopausal state (mean, 120 pg/mL; follicular phase, 20–350 pg/mL; midcycle peak, 150–750 pg/mL; luteal phase, 30–450 pg/mL) [116]. Circulating estradiol levels vary between women, and depend on the type of hormones, the dose, the route of administration, metabolization and steady state [28,117]. Transdermal or oral administration of E_2 at the doses used in MHT is associated with better BMD response compared with oral contraceptives [118,119].

Low-dose MHT effectively controls symptoms in perimenopausal and postmenopausal women [120,121]. For women >45 years commencing MHT to manage menopausal symptoms, the dose of MHT should be adjusted to the lowest that remains effective [94,120]. Treatment, however, should be individualized, with no arbitrary dose or duration limits. Low-dose MHT is associated with improvements in BMD, although fracture data are missing [19]. Low-dose tibolone (1.25 mg) has been shown to decrease the risk of vertebral and non-vertebra fractures in older postmenopausal women [112].

In postmenopausal women with low libido in the context of hypoactive sexual desire disorder (HSDD), testosterone treatment can be offered using appropriate approved female preparations, or approved male formulations as an off-licence use, to provide the recommended female replacement doses. In the latter case, the dose should be customized to result in serum testosterone concentrations approximating those in premenopausal women [122].

9.2. Benefits and risks of MHT

9.2.1. The main benefits of MHT
These can be summarized as follows [15,17,97,98,100,105,123–125]:

- Management of vasomotor symptoms.
- Management of symptoms of vulvovaginal atrophy.
- Prevention of bone loss and osteoporotic fractures.

Table 1
Menopausal hormone therapy regimens.

Regimen	Route of administration	Dose
Estrogens		
17-Beta-estradiol	Tablet, patch, gel, transdermal spray, vaginal cream or ring	Standard dose: 2–4 mg (oral) or 50–100 μg (transdermal) Low dose: 1 mg (oral) or 25 μg (transdermal) Ultra-low dose: 0.25–0.5 mg (oral) or 14 μg (transdermal)
CEE	Oral tablet	Standard dose: 0.625–1.25 mg Low dose: 0.300–0.400 mg
Estriol	Vaginal gel, cream or ring	0.5–1 mg cream 0.03 mg per pessary 7.5 μg over 24 h per ring
Promestriene	Vaginal cream or tablets	10 mg
Progestogens		
Micronized progesterone	Oral or vaginal tablet	100–200 mg orally or vaginally
Levonorgestrel	Oral tablet or transdermal patch or intrauterine system device	30–40 μg (orally) 150 μg (transdermally) 14–20 mg (intrauterine device)
Dydrogesterone	Oral tablet	2.5–20 mg
Norethisterone acetate	Oral tablet or patch	0.5–1.0 mg (orally) or 125–250 μg (transdermally)
Drospirenone	Oral tablet	1–2 mg
Medroxyprogesterone acetate	Oral tablet	2.5–10 mg
Norgestrel	Oral tablet	0.25–0.5 mg
Chlormadinone acetate	Oral tablet	2 mg
Nomegestrol acetate	Oral tablet	2.5–5 mg
Promegestone	Oral tablet	2.5–10 mg
Trimegestone	Oral tablet	0.25 mg
Norgestimate	Oral tablet	0.5 mg
Dienogest	Oral tablet	3–4 mg
Other		
Ospemifene (SERM)	Oral tablet	60 mg
Bazedoxifene (SERM)	Oral tablet combined with CEE	10 mg or 20 mg or 40 mg and 0.45 mg or 0.625 mg
Tibolone	Oral tablet	1.25–2.5 mg
DHEA (prasterone)	Vaginal tablet	6.5 mg

CEE: conjugated equine estrogens; DHEA: dehydroepiandrosterone.

- Improved mood and wellbeing.
- Reduced risk of new-onset diabetes mellitus.
- If initiated early after the menopausal transition, MHT may reduce the risk of cardiovascular disease.
- MHT improves risk factors of cognitive decline. If initiated early after menopause, it may prevent cognitive decline.

9.2.2. The main risks of MHT

These can be summarized as follows [15,17,97,98,100,123–129]:

- The increased risk of breast cancer in women over 50 years taking MHT is primarily associated with the addition of a progestogen to estrogen therapy and with duration of use. It also varies according to the type of progestogen. It is lower with progesterone and dydrogesterone than with other progestogens. The risk of breast cancer attributable to MHT is small and decreases after treatment is stopped.
- Oral but not transdermal MHT is associated with an increase in venous thromboembolism.
- MHT may confer a small risk of stroke, which is more common in women treated with oral rather than transdermal estrogen.
- MHT initiated in women > 60 years of age or >10 years after menopause does not have cardiovascular benefits but also does not cause harm.
- MHT does not appear to increase the risk of cognitive decline overall but may increase the risk of dementia in older women, if initiated after the age of 65 years.

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

- Following initiation of treatment, women should be offered an initial follow-up assessment after 2–3 months to review the efficacy of treatment and discuss adverse effects [98,130].
- Subsequent follow-up appointments should be offered based on individual needs, to discuss possible adverse effects of treatment and ensure compliance. Women with POI or early menopause are likely to require more frequent clinic visits to explore possible problems related to hormone deficiency at an early stage [16]. Women should be reminded of the benefit of participating in national screening programmes for breast and cervical cancer screening. Blood tests should be recommended according to clinical need [98,130].
- Changing the MHT regimen is appropriate for women with bothersome side effects such as bloating, breast tenderness, mood swings, fluid retention or irregular bleeding [131]. Symptoms are expected to improve by adjusting the dose of estrogen or changing the route of administration from oral to transdermal. Bazedoxifene is an alternative for women intolerant of progestogens [131,132]. Alternatively, endometrial protection can be achieved with the use of a levonorgestrel-containing intra-uterine device, which will also provide contraception in the perimenopause [133]. The combination of conjugated estrogen with bazedoxifene seems to be more neutral to breast tissue, but is not readily available worldwide and further data are required [134].
- HSDD can be a persistent complaint of women taking estrogen-based MHT. Here, addition of testosterone treatment to MHT can be considered, provided symptoms of vulvovaginal atrophy are appropriately treated first [122].

9.4. Duration of use and stopping MHT

The duration of treatment should be individualized, taking into account the needs of the woman, her wishes and possible risks of ongoing treatment [17,97,98]. There is no need for annual gynaecological follow-up in asymptomatic women with no abnormal vaginal bleeding or those women not at increased risk of gynaecological cancer [3].

Low-dose vaginal estrogens can be continued long term, as long as symptoms of GSM persist [10,18,98], as their use is not associated with a higher risk of breast or endometrial cancer [17].

Women with POI and early menopause should continue MHT until the age of natural menopause (51–52 years) [17,28,97,98,135]. Women aged >45 years commencing MHT for symptom control should continue MHT as long as symptoms persist and MHT has a favourable benefit/risk balance for them. As it is impossible to predict the duration of symptoms in individual women, trials of either tapering or stopping MHT can be undertaken. After stopping MHT, women at high clinical risk of fracture should be offered a non-hormonal medication for bone health [17,100,121].

10. Non-hormonal therapies for menopausal symptoms

10.1. Pharmacological alternatives for vasomotor symptoms

Non-hormonal management of menopausal hot flushes and night sweats is suggested for women who do not wish to initiate MHT or who are not eligible for it [4,136].

10.1.1. Selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors

Selective serotonin reuptake inhibitors (SSRIs) like paroxetine, citalopram or escitalopram and serotonin-norepinephrine reuptake inhibitors (SNRIs) like venlafaxine or desvenlafaxine are effective for the management of hot flushes [137–140], but should be considered as second-line treatment options in women for whom MHT is not contraindicated. SSRIs are effective in reducing the frequency of menopausal hot flushes, by 40–50% for paroxetine at a dose of 7.5-25 mg, by 45–47% for citalopram at a dose of 10-20 mg, and by 30–45% for escitalopram at a dose of 10-20 mg. SNRIs are also an effective alternative for reducing the frequency of bothersome hot flushes, by 22–55% for venlafaxine at a dose of 75-100 mg and by 60–70% for desvenlafaxine at a dose of 100-150 mg [141]. Caution is advised in prescribing paroxetine or fluoxetine for women with breast cancer treated with tamoxifen, as these types of SSRIs are known to inhibit P450 cytochrome activity, interfering with tamoxifen metabolism [139].

10.1.2. Gabapentin and pregabalin

Gabapentin is as effective as venlafaxine in controlling hot flushes but seems to be less popular [139]. Daily doses of 300–900 mg reduce the severity of symptoms by 40–45% [141]. Concerns about gabapentin and pregabalin misuse and dependence need to be taken into consideration before their use for vasomotor symptoms [3].

10.1.3. Clonidine

This centrally active alpha-2 adrenergic agonist, which is also an antihypertensive, is moderately effective – reducing vasomotor symptoms by 20–35% [141]. It is recommended for breast cancer survivors by both NAMS and NICE [139,141].

10.1.4. Oxybutinin

This anticholinergic agent has also been shown to decrease the severity of vasomotor symptoms compared with placebo (5 mg dose vs 2.5 mg dose vs placebo: 86% vs 70% vs 29%) as well as the frequency of hot flushes (5 mg dose vs 2.5 mg dose vs placebo: 77% vs 60% vs 27%) [142]. Oxybutinin use is associated with side-effects such as constipation, dry mouth and higher risk of dementia. However, it could be considered in women unable to take estrogen [141,142].

10.2. Hypoactive sexual desire and genitourinary syndrome of menopause

10.2.1. Flibanserin

Flibanserin acts as a full agonist at postsynaptic serotonin 5HT-1A receptors and as an antagonistic at postsynaptic 5HT-2A receptors. A dose of 100 mg at bedtime improves HSDD symptoms [143].

10.2.2. Ospemifene

A selective estrogen receptor modulator, ospemifene exerts an agonistic effect on vaginal tissues, improving GSM symptoms. Daily treatment with 60 mg orally improves vaginal dryness and dyspareunia. Safety data are available on its administration for 12 months [144–146].

10.2.3. Vaginal bio-adhesive moisturizers and lubricants

Symptoms of vulvovaginal atrophy can be eased with over-the-counter vaginal moisturizers and lubricants. Products with pH and osmolality similar to those of vaginal secretions are recommended. Moisturizers require frequent use for effective symptom control, while lubricants can be used less frequently and as needed in sexual activity [10,18,147].

10.2.4. Laser therapy

Energy-based therapies include fractional CO_2 laser or erbium YAG laser and radiofrequency devices; however, none of these approaches has received FDA approval due to safety concerns [18]. Although clinical studies have shown benefit and safety [148–150], recent experimental data and data from randomized controls trials question the efficacy of laser treatment [151,152].

11. Alternative and complementary therapies

Alternative and complementary therapies are less effective than MHT for the control of climacteric symptoms. They include phytoestrogens, yoga, acupuncture, homoeopathic medicine, mindfulness-based stress reduction, clinical hypnosis and paced respiration [4,15,136,153]. These therapies have modest effects on menopausal symptoms; the evidence is limited by the quality and heterogeneity of studies [154]. Health care providers should take into consideration possible interactions with standard medicines such as anticancer therapies, anticoagulants and antiepileptics.

Cognitive behavioural therapy (CBT), originally developed for patients suffering from depression and anxiety, has recently been considered as an effective treatment for the control of health problems like chronic pain, insomnia as well as vasomotor symptoms [46,121,155]. The CBT protocols MENOS 1 and MENOS 2 have been recommended for the treatment of depression and anxiety during the menopausal transition and postmenopause [156,157]. CBT can be accessed in a variety of ways: self-help books, phone and online as well as face to face [158]. The MENOS 4 trial showed that women with breast cancer experiencing hot flushes can benefit from CBT delivered by trained specialist nurses [159,160].

12. Non-hormonal therapy for osteoporosis

12.1. Calcium and vitamin D

Calcium and vitamin D are crucial for bone mineralization, hence their intake should be adequate [95]. A daily calcium intake of 800–1200 mg and vitamin D intake of 600 IU are recommended to maintain skeletal health after menopause. Calcium supplements are advisable if the dietary intake is below the recommended target. Vitamin D supplementation is advisable for women with very little sunlight exposure, which is more likely during the winter months [95]. Recommended daily allowance of vitamin D is increased to 800 IU for women aged over 71 years [3,21,161].

12.2. Selective estrogen receptor modulators

Raloxifene is indicated for women at risk of osteoporosis. Treatment with 60 mg daily reduces the risk of vertebral and secondary fractures by 30% and 40% respectively, compared with women not on any anti-osteoporosis treatment, while increasing BMD at the femoral neck [162]. In addition, raloxifene reduces the risk of invasive breast cancer in women at high risk [163,164]. Nevertheless, raloxifene treatment has not been associated with a meaningful reduction in the risk of non-vertebral fractures [165]. Adverse effects include a slight increase in the risk of venous thromboembolism, vaginal dryness, leg cramps and an increase in severity of hot flushes [163,164].

Bazedoxifene is a newer SERM approved for the treatment of osteoporosis. It reduces the risk of vertebral fractures by 39% [166] and the risk of secondary fractures by 34% [162], and increases spine BMD, as assessed at 3 and 7 years of treatment [167]. Adverse effects include a slight increase in the risk of venous thromboembolism and an increase in vasomotor symptoms [163,164].

12.3. Bisphosphonates

Bisphosphonates are first-line medications for women over the age of 60 years at increased risk of fragility fractures. There are no robust data to explore the effects of bisphosphonates in younger postmenopausal women with osteoporosis or premenopausal women with low BMD [168]. Oral bisphosphonates include alendronate (70 mg once weekly), risedronate (150 mg monthly, as two 75 mg doses taken on consecutive days) and ibandronate (150 mg monthly, as a single dose) [19,21]. Ibandronate can also be administered as an intravenous injection (3 mg once every three months). Zoledronic acid is administered as a 5 mg intravenous infusion annually [19].

The efficacy of bisphosphonates in reducing the risk of fracture can be summarized as follows [19]:

- The risk of vertebral fractures is reduced by alendronate (up to 43%), risedronate (up to 39%), ibandronate (up to 33%) and zoledronic acid (up to 62%) [166].
- The risk of non-vertebral fractures is reduced by risedronate and zoledronic acid.
- The risk of hip fractures is reduced by alendronate, risedronate and zoledronic acid.

Adverse effects include upper gastrointestinal irritation (oral preparations) and acute-phase reaction (intravenous preparation). Recently, gastro-resistant formulations have become available, which are associated with fewer, less severe side-effects and thus better compliance [169]. Less common adverse effects include atrial fibrillation, atypical femoral fracture, osteonecrosis of the jaw (ONJ) and oesophageal cancer [3]. The incidence of ONJ among patients treated with bisphosphonates is estimated to be 0.001% to 0.01%, which is only marginally higher than that in the general population (<0.001%) [170]. Risk factors for ONJ include poor oral hygiene, diabetes mellitus, ill-fitting dentures, chronic inflammation, glucocorticoid use and malignancy [170]. Control of oral disease prior to initiation of treatment and maintenance of good oral hygiene can help to prevent ONJ [170].

The decision to continue or stop treatment should be reviewed every 3–5 years. There is limited evidence to guide the decision to continue treatment after 10 years [21].

12.4. Denosumab

Denosumab, a human monoclonal antibody with potent anti-resorptive activity, acts by inhibiting the receptor activator of the nuclear factor kappa-B ligand (RANKL). Denosumab is indicated for women at high risk of fragility fractures and is administered as a 60 mg subcutaneous injection every 6 months. It increases BMD at all sites, and reduces the risk of vertebral fractures by 68% and hip fractures by 40% [3]. Discontinuation of denosumab is associated with rebound accelerated bone loss and increased risk of vertebral fractures; therefore, a bisphosphonate should be used after denosumab withdrawal to inhibit bone loss. Adverse effects after short-term use include skin reactions. Sporadic cases of osteonecrosis of the jaw and atypical femoral fractures have been described in patients on long-term use [3,19,21].

12.5. Calcitonin

This antiresorptive agent is available as an intramuscular injection or intravenous infusion, for the short-term treatment of patients with acute bone loss due to sudden immobilization, hypercalcaemia due to cancer or Paget's disease, but not for osteoporosis [171].

12.6. Parathyroid hormone

Agents with the potential to activate the parathyroid hormone (PTH) receptor, such as teriparatide (daily subcutaneous injection 20 μg) and abaloparatide (daily subcutaneous injection 80 μg), reduce the risk of vertebral and non-vertebral fractures significantly (teriparatide by 59% and 38%, and abaloparatide by 86% and 49%, respectively) [19,166]. Abaloparatide is more potent than teriparatide in improving BMD at the hip, but no agent has been shown to decrease the risk of hip fracture in pivotal trials, possibly because of power limitations. Adverse effects include postural hypotension, at least after the first doses of treatment, and hypercalcaemia [19]. Treatment should not be offered to patients at high risk of osteosarcoma or bone metastases. The total duration of teriparatide treatment is two years cumulatively within a patient's lifetime. The FDA in November 2020 allowed this to be extended in patients who remain at very high risk of fracture after the 2 years of treatment [19]. Treatment with abaloparatide is approved by the FDA but not the EMA due to concerns for cardiovascular safety, mainly arrhythmias [3,19,21,172].

12.7. Romosozumab

Romosozumab is a human monoclonal antibody which inhibits sclerostin, a glycoprotein that regulates bone turnover. Romosozumab inhibits bone resorption and stimulates bone formation. It is administered as two subcutaneous injections totalling 210 mg per month. It is approved by the FDA and the EMA [173]. Romosozumab reduces the rates of vertebral, non-vertebral and hip fractures by 67%, 33% and 56%, respectively [3,166]. It is indicated for women at very high risk of fragility fractures, namely those with previous fractures or multiple risk factors for fracture and women who lose BMD or sustain a fracture while on anti-resorptive therapy [3,19].

Adverse effects include mild injection site reactions and hypersensitivity. Another adverse event is the higher risk of major cardiovascular events compared with alendronate. Therefore, romosozumab should not be administered to women at high risk of cardiovascular disease [19].

13. Drugs in development

Neurokinin-3 receptor antagonists are promising agents in the control of menopause-associated vasomotor symptoms. Hypothalamic neurokinin B (NKB) signalling, and its interaction with the thermoregulatory centre through the related neurokinin 3 receptor, are shown to control thermoregulation, hence NK3 receptor antagonists have an important therapeutic potential in the management of hot flushes. In the postmenopausal environment of estrogen deficiency, NKB signalling and the ensuing overstimulation of kisspeptin-NKB-dynorphin neurons in the thermoregulatory centre activate heat dissipation effectors [174]. Investigational drugs belonging to this category include fezolinetant, elinzanetant, MLE4901 and pavinetant [174–177].

14. Summary

Menopause, or the cessation of menstruation, is the inevitable result of normal ovarian ageing due to the depletion of ovarian follicles, occurring in the late 40s or early 50s. The decline in estrogen concentrations is associated with menopausal symptoms, especially hot flushes and night sweats, sleep problems, mood imbalance, muscle and joint pain, and symptoms of vulvovaginal atrophy. Spontaneous or iatrogenic POI or early menopause requires MHT at least until the typical age of spontaneous menopause. Post-reproductive health is further affected by problems related to ageing and menopause, like osteoporosis, cardiovascular disease and cognitive decline. The management of women transitioning to menopause should be individualized, considering their risk profile and their wishes and needs.

Contributors

Irene Lambrinoudaki, Eleni Armeni and Dimitrios Goulis prepared the initial draft, which was circulated to all other named authors, EMAS board members and advisors for comments and approval; production was coordinated by Irene Lambrinoudaki and Margaret Rees.

Provenance and peer review

This article is an EMAS care pathway and was not externally peer reviewed.

Declaration of competing interest

1. Irene Lambrinoudaki: None declared.
2. Eleni Armeni: None declared.
3. Dimitrios G. Goulis: None declared.
4. Silvia Bretz: None declared.
5. Iuliana Ceausu: None declared.
6. Fatih Durmusoglu: None declared.
7. Risto Erkkola: None declared.
8. Ivan Fistonic: has received consulting fees in the past 3 years from Fotona Inc.
9. Marco Gambacciani: has received speaker and consulting fees in the past 3 years from MSD, Theramex and Bayer.
10. Marije Geukes: None declared.
11. Haitham Hamoda: None declared.
12. Caiomhe Hartley: None declared.
13. Angelica Lindén Hirschberg in the past 3 years has received grant support from ITF Research Pharma for the "Blissafe" study.
14. Blazej Meczekalski: None declared.
15. Nicolas Mendoza in the past 3 years has received grant support from Astellas Pharma.
16. Alfred Mueck: None declared.
17. Antonina Smetnik: none declared.
18. Petra Stute has received speaker and consulting fees in the past 3 years from Besins Healthcare, Jenapharm GmbH & Co. KG, Labatec Pharma SA, Effik SA, Astellas Pharma AG and Viatris.
19. Mick van Trotsenburg: None declared.
20. Margaret Rees: None declared.

References

[1] G.B.D. M. Collaborators, Global, regional, and national under-5 mortality, adult mortality, age-specific mortality, and life expectancy, 1970-2016: a systematic analysis for the Global Burden of Disease Study 2016, Lancet (London, England) 390 (2017) (2016) 1084–1150, https://doi.org/10.1016/S0140-6736(17)31833-0.

[2] V. Kontis, J.E. Bennett, C.D. Mathers, G. Li, K. Foreman, M. Ezzati, Future life expectancy in 35 industrialised countries: projections with a Bayesian model ensemble, Lancet (London, England) 389 (2017) 1323–1335, https://doi.org/10.1016/S0140-6736(16)32381-9.

[3] M. Rees, D. Goulis, P. Lopes, EMAS Care Online: The Essential Guide to Women's Health in Midlife and Beyond, European Menopause and Andropause Society, Geneva, 2020.

[4] M. Rees, R. Angioli, R.L. Coleman, R. Glasspool, F. Plotti, T. Simoncini, C. Terranova, European Menopause and Andropause Society (EMAS) and International Gynecologic Cancer Society (IGCS) position statement on managing the menopause after gynecological cancer: focus on menopausal symptoms and osteoporosis, Maturitas. 134 (2020) 56–61, https://doi.org/10.1016/j.maturitas.2020.01.005.

[5] I. Lambrinoudaki, S.A. Paschou, M.A. Lumsden, S. Faubion, E. Makrakis, S. Kalantaridou, N. Panay, Premature ovarian insufficiency: a toolkit for the primary care physician, Maturitas. 147 (2021) 53–63, https://doi.org/10.1016/j.maturitas.2020.11.004.

[6] C.B. Coulam, S.C. Adamson, J.F. Annegers, Incidence of premature ovarian failure, Obstet. Gynecol. 67 (1986) 604–606.

[7] G.D. Mishra, N. Pandeya, A.J. Dobson, H.-F. Chung, D. Anderson, D. Kuh, S. Sandin, G.G. Giles, F. Bruinsma, K. Hayashi, J.S. Lee, H. Mizunuma, J.E. Cade, V. Burley, D.C. Greenwood, A. Goodman, M.K. Simonsen, H.-O. Adami, P. Demakakos, E. Weiderpass, Early menarche, nulliparity and the risk for premature and early natural menopause, Hum. Reprod. 32 (2017) 679–686, https://doi.org/10.1093/humrep/dew350.

[8] H.P.G. Schneider, M. Birkhäuser, Quality of life in climacteric women, Climacteric. 20 (2017) 187–194, https://doi.org/10.1080/13697137.2017.1279599.

[9] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 68 (2018) 394–424, https://doi.org/10.3322/caac.21492.

[10] A.L. Hirschberg, J. Bitzer, A. Cano, I. Ceausu, P. Chedraui, F. Durmusoglu, R. Erkkola, D.G. Goulis, L. Kiesel, P. Lopes, A. Pines, M. van Trotsenburg, I. Lambrinoudaki, M. Rees, Topical estrogens and non-hormonal preparations for postmenopausal vulvovaginal atrophy: an EMAS clinical guide, Maturitas. 148 (2021) 55–61, https://doi.org/10.1016/j.maturitas.2021.04.005.

[11] E. Russo, M. Caretto, A. Giannini, J. Bitzer, A. Cano, I. Ceausu, P. Chedraui, F. Durmusoglu, R. Erkkola, D.G. Goulis, L. Kiesel, I. Lambrinoudaki, A. L. Hirschberg, P. Lopes, A. Pines, M. Rees, M. van Trotsenburg, T. Simoncini, Management of urinary incontinence in postmenopausal women: an EMAS clinical guide, Maturitas. 143 (2021) 223–230, https://doi.org/10.1016/j.maturitas.2020.09.005.

[12] P. Anagnostis, J. Bitzer, A. Cano, I. Ceausu, P. Chedraui, F. Durmusoglu, R. Erkkola, D.G. Goulis, A.L. Hirschberg, L. Kiesel, P. Lopes, A. Pines, M. van Trotsenburg, I. Lambrinoudaki, M. Rees, Menopause symptom management in women with dyslipidemias: an EMAS clinical guide, Maturitas. 135 (2020) 82–88, https://doi.org/10.1016/j.maturitas.2020.03.007.

[13] R. Slopien, E. Wender-Ozegowska, A. Rogowicz-Frontczak, B. Meczekalski, D. Zozulinska-Ziolkiewicz, J.D. Jaremek, A. Cano, P. Chedraui, D.G. Goulis, P. Lopes, G. Mishra, A. Mueck, M. Rees, L.M. Senturk, T. Simoncini, J. C. Stevenson, P. Stute, P. Tuomikoski, S.A. Paschou, P. Anagnostis, I. Lambrinoudaki, Menopause and diabetes: EMAS clinical guide, Maturitas. 117 (2018) 6–10, https://doi.org/10.1016/j.maturitas.2018.08.009.

[14] F.A. Trémollieres, I. Ceausu, H. Depypere, I. Lambrinoudaki, A. Mueck, F. R. Pérez-López, Y.T. van der Schouw, L.M. Senturk, T. Simoncini, J.C. Stevenson, P. Stute, M. Rees, Osteoporosis management in patients with breast cancer: EMAS position statement, Maturitas. 95 (2017) 65–71, https://doi.org/10.1016/j.maturitas.2016.10.007.

[15] R.J. Baber, N. Panay, A. Fenton, 2016 IMS Recommendations on women's midlife health and menopause hormone therapy, Climacteric. 19 (2016) 109–150, https://doi.org/10.3109/13697137.2015.1129166.

[16] N. Panay, R.A. Anderson, R.E. Nappi, A.J. Vincent, S. Vujovic, L. Webber, W. Wolfman, Premature ovarian insufficiency: an International Menopause Society White Paper, Climacteric. 23 (2020) 426–446, https://doi.org/10.1080/13697137.2020.1804547.

[17] H. Hamoda, N. Panay, H. Pedder, R. Arya, M. Savvas, Medical Advisory Council of the British Menopause Society, The British Menopause Society & Women's Health Concern 2020 recommendations on hormone replacement therapy in menopausal women, Post Reprod. Health 26 (2020) 181–209, https://doi.org/10.1177/2053369120957514.

[18] NAMS, The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society, Menopause. 27 (2020) 976–992, https://doi.org/10.1097/GME.0000000000001609.

[19] NAMS, Management of osteoporosis in postmenopausal women: the 2021 position statement of The North American Menopause Society, Menopause. 28 (2021) 973–997, https://doi.org/10.1097/GME.0000000000001831.

[20] NAMS, The 2017 hormone therapy position statement of The North American Menopause Society, Menopause. 24 (2017) 728–753, https://doi.org/10.1097/GME.0000000000000921.

[21] J.A. Kanis, C. Cooper, R. Rizzoli, J.-Y. Reginster, European guidance for the diagnosis and management of osteoporosis in postmenopausal women, Osteoporos. Int. 30 (2019) 3–44, https://doi.org/10.1007/s00198-018-4704-5.

[22] D. Shoback, C.J. Rosen, D.M. Black, A.M. Cheung, M.H. Murad, R. Eastell, Pharmacological management of osteoporosis in postmenopausal women: an Endocrine Society guideline update, J. Clin. Endocrinol. Metab. 105 (2020), https://doi.org/10.1210/clinem/dgaa048.

[23] M. Rees, K. Abernethy, G. Bachmann, S. Bretz, I. Ceausu, F. Durmusoglu, R. Erkkola, I. Fistonic, M. Gambacciani, M. Geukes, D.G. Goulis, A. Griffiths, H. Hamoda, C. Hardy, C. Hartley, A.L. Hirschberg, A. Kydd, S. Marshall, B. Meczekalski, N. Mendoza, A. Mueck, E. Persand, K. Riach, A. Smetnik, P. Stute, M. van Trotsenburg, N. Yuksel, R. Weiss, I. Lambrinoudaki, The essential menopause curriculum for healthcare professionals: a European Menopause and

[24] InterLace, Variations in reproductive events across life: a pooled analysis of data from 505 147 women across 10 countries, Hum. Reprod. 34 (2019) 881–893, https://doi.org/10.1093/HUMREP/DEZ015.

[25] S.D. Harlow, M. Gass, J.E. Hall, R. Lobo, P. Maki, R.W. Rebar, S. Sherman, P. M. Sluss, T.J. De Villiers, Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging, Fertil. Steril. 97 (2012) 843–851, https://doi.org/10.1016/j.fertnstert.2012.01.128.

[26] NICE, National Institute for Health and Care Excellence (NICE) menopause: diagnosis and management. www.nice.org.uk/guidance/ng23, 2015.

[27] G.E. Krassas, K. Poppe, D. Glinoer, Thyroid function and human reproductive health, Endocr. Rev. 31 (2010) 702–755, https://doi.org/10.1210/er.2009-0041.

[28] L. Webber, M. Davies, R. Anderson, J. Bartlett, D. Braat, B. Cartwright, R. Cifkova, S. De Muinck Keizer-Schrama, E. Hogervorst, F. Janse, L. Liao, V. Vlaisavljevic, C. Zillikens, N. Vermeulen, ESHRE Guideline: management of women with premature ovarian insufficiency, Hum. Reprod. 31 (2016) 926–937, https://doi.org/10.1093/humrep/dew027.

[29] S. Vujovic, M. Brincat, T. Erel, M. Gambacciani, I. Lambrinoudaki, M.H. Moen, K. Schenck-Gustafsson, F. Tremollieres, S. Rozenberg, M. Rees, EMAS position statement: managing women with premature ovarian failure, Maturitas. 67 (2010) 91–93, https://doi.org/10.1016/j.maturitas.2010.04.011.

[30] NICE, Premature menopause (premature ovarian insufficiency) | information for the public | menopause: diagnosis and management | guidance, NICE, 2015. https://www.nice.org.uk/guidance/ng23/ifp/chapter/premature-menopause-premature-ovarian-insufficiency#diagnosis. (Accessed 20 March 2022).

[31] L.M.E. Moolhuijsen, J.A. Visser, Anti-Müllerian hormone and ovarian reserve: update on assessing ovarian function, J. Clin. Endocrinol. Metab. 105 (2020) 3361–3373, https://doi.org/10.1210/clinem/dgaa513.

[32] R. Punchoo, S. Bhoora, Variation in the measurement of anti-Müllerian hormone - what are the laboratory issues? Front. Endocrinol. (Lausanne) 12 (2021), 719029 https://doi.org/10.3389/fendo.2021.719029.

[33] C. Kim, J.C. Slaughter, E.T. Wang, D. Appiah, P. Schreiner, B. Leader, R. Calderon-Margalit, B. Sternfeld, D. Siscovick, M. Wellons, Anti-Müllerian hormone, follicle stimulating hormone, antral follicle count, and risk of menopause within 5 years, Maturitas. 102 (2017) 18–25, https://doi.org/10.1016/j.maturitas.2017.04.018.

[34] S. Iliodromiti, R.A. Anderson, S.M. Nelson, Technical and performance characteristics of anti-Müllerian hormone and antral follicle count as biomarkers of ovarian response, Hum. Reprod. Update 21 (2015) 698–710, https://doi.org/10.1093/humupd/dmu062.

[35] N. Santoro, C. Roeca, B.A. Peters, G. Neal-Perry, The menopause transition: signs, symptoms, and management options, J. Clin. Endocrinol. Metab. 106 (2021) 1–15, https://doi.org/10.1210/clinem/dgaa764.

[36] N.E. Avis, S.L. Crawford, G. Greendale, J.T. Bromberger, S.A. Everson-Rose, E. B. Gold, R. Hess, H. Joffe, H.M. Kravitz, P.G. Tepper, R.C. Thurston, Duration of menopausal vasomotor symptoms over the menopause transition, JAMA Intern. Med. 175 (2015) 531–539, https://doi.org/10.1001/jamainternmed.2014.8063.

[37] K.E. Gray, J.G. Katon, E.S. LeBlanc, N.F. Woods, L.A. Bastian, G.E. Reiber, J. C. Weitlauf, K.M. Nelson, A.Z. LaCroix, Vasomotor symptom characteristics: are they risk factors for incident diabetes?, in: Menopause Lippincott Williams and Wilkins, 2018, pp. 520–530, https://doi.org/10.1097/GME.0000000000001033.

[38] T. Muka, C. Oliver-Williams, V. Colpani, S. Kunutsor, S. Chowdhury, R. Chowdhury, M. Kavousi, O.H. Franco, Association of vasomotor and other menopausal symptoms with risk of cardiovascular disease: a systematic review and meta-analysis, PLoS One 11 (2016), e0157417, https://doi.org/10.1371/journal.pone.0157417.

[39] D. Zhu, H.-F. Chung, A.J. Dobson, N. Pandeya, D.J. Anderson, D. Kuh, R. Hardy, E.J. Brunner, N.E. Avis, E.B. Gold, S.R. El Khoudary, S.L. Crawford, G.D. Mishra, Vasomotor menopausal symptoms and risk of cardiovascular disease: a pooled analysis of six prospective studies, Am. J. Obstet. Gynecol. 223 (2020) 898. e1–898.e16, https://doi.org/10.1016/j.ajog.2020.06.039.

[40] A. Vahratian, Sleep duration and quality among women aged 40-59, by menopausal status, NCHS Data Brief (2017) 1–8.

[41] H.M. Kravitz, I. Janssen, J.T. Bromberger, K.A. Matthews, M.H. Hall, K. Ruppert, H. Joffe, Sleep trajectories before and after the final menstrual period in the Study of Women's Health Across the Nation (SWAN), Curr. Sleep Med. Rep. 3 (2017) 235–250, https://doi.org/10.1007/s40675-017-0084-1.

[42] K.A. Matthews, Y. Chang, M.M. Brooks, S.L. Crawford, I. Janssen, H. Joffe, H. M. Kravitz, R.C. Thurston, S.R. El Khoudary, Identifying women who share patterns of reproductive hormones, vasomotor symptoms, and sleep maintenance problems across the menopause transition: group-based multi-trajectory modeling in the Study of Women's Health Across the Nation, Menopause. 28 (2020) 126–134, https://doi.org/10.1097/GME.0000000000001663.

[43] P. Monteleone, G. Mascagni, A. Giannini, A.R. Genazzani, T. Simoncini, Symptoms of menopause - global prevalence, physiology and implications, Nat. Rev. Endocrinol. 14 (2018) 199–215, https://doi.org/10.1038/nrendo.2017.180.

[44] A. Cagnacci, A. Xholli, M. Sclauzero, M. Venier, F. Palma, M. Gambacciani, Vaginal atrophy across the menopausal age: results from the ANGEL study, Climacteric. 22 (2019) 85–89, https://doi.org/10.1080/13697137.2018.1529748.

[45] S.S. Faubion, L.C. Larkin, C.A. Stuenkel, G.A. Bachmann, L.A. Chism, R. Kagan, A. M. Kaunitz, M.L. Krychman, S.J. Parish, A.H. Partridge, J.V. Pinkerton, T. S. Rowen, M. Shapiro, J.A. Simon, S.B. Goldfarb, S.A. Kingsberg, Management of

genitourinary syndrome of menopause in women with or at high risk for breast cancer: consensus recommendations from The North American Menopause Society and The International Society for the Study of Women's Sexual Health, Menopause. 25 (2018) 596–608, https://doi.org/10.1097/GME.0000000000001121.

[46] NICE, Overview | menopause: diagnosis and management | guidance, NICE, 2019. https://www.nice.org.uk/guidance/NG23. (Accessed 23 March 2022).

[47] M. Zangger, C. Weber, P. Stute, Developing an ICF core set for climacteric syndrome based on the International Classification of Functioning, Disability and Health (ICF), Maturitas. 143 (2021) 197–202, https://doi.org/10.1016/j.maturitas.2020.10.014.

[48] ESC, SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe, Eur. Heart J. 42 (2021) 2439–2454, https://doi.org/10.1093/eurheartj/ehab309.

[49] B. Williams, G. Mancia, W. Spiering, E. Agabiti Rosei, M. Azizi, M. Burnier, D. L. Clement, A. Coca, G. de Simone, A. Dominiczak, T. Kahan, F. Mahfoud, J. Redon, L. Ruilope, A. Zanchetti, M. Kerins, S.E. Kjeldsen, R. Kreutz, S. Laurent, G.Y.H. Lip, R. McManus, K. Narkiewicz, F. Ruschitzka, R.E. Schmieder, E. Shlyakhto, C. Tsioufis, V. Aboyans, I. Desormais, ESC/ESH Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH), Eur. Heart J. 39 (2018) (2018) 3021–3104, https://doi.org/10.1093/eurheartj/ehy339.

[50] L. Jahangiry, M.A. Farhangi, F. Rezaei, Framingham risk score for estimation of 10-years of cardiovascular diseases risk in patients with metabolic syndrome, J. Health Popul. Nutr. 36 (2017) 36, https://doi.org/10.1186/s41043-017-0114-0.

[51] C. Andersson, M. Nayor, C.W. Tsao, D. Levy, R.S. Vasan, Framingham Heart Study: JACC Focus Seminar, 1/8, J. Am. Coll. Cardiol. 77 (2021) 2680–2692, https://doi.org/10.1016/j.jacc.2021.01.059.

[52] R.M. Conroy, K. Pyörälä, A.P. Fitzgerald, S. Sans, A. Menotti, G. De Backer, D. De Bacquer, P. Ducimetière, P. Jousilahti, U. Keil, I. Njølstad, R.G. Oganov, T. Thomsen, H. Tunstall-Pedoe, A. Tverdal, H. Wedel, P. Whincup, L. Wilhelmsen, I.M. Graham, The S. Project Group, Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project, Eur. Heart J. 24 (2003) 987–1003, https://doi.org/10.1016/S0195-668X(03)00114-3.

[53] SCORE2-OP risk prediction algorithms: estimating incident cardiovascular event risk in older persons in four geographical risk regions, Eur. Heart J. 42 (2021) 2455–2467, https://doi.org/10.1093/eurheartj/ehab312.

[54] A.H.E.M. Maas, G. Rosano, R. Cifkova, A. Chieffo, D. van Dijken, H. Hamoda, V. Kunadian, E. Laan, I. Lambrinoudaki, K. Maclaran, N. Panay, J.C. Stevenson, M. van Trotsenburg, P. Collins, Cardiovascular health after menopause transition, pregnancy disorders, and other gynaecologic conditions: a consensus document from European cardiologists, gynaecologists, and endocrinologists, Eur. Heart J. 42 (2021) 967–984, https://doi.org/10.1093/eurheartj/ehaa1044.

[55] A.H.E.M. Maas, Hormone therapy and cardiovascular disease: benefits and harms, Best Pract. Res. Clin. Endocrinol. Metab. 35 (2021), 101576, https://doi.org/10.1016/j.beem.2021.101576.

[56] E.T.H. Fontham, A.M.D. Wolf, T.R. Church, R. Etzioni, C.R. Flowers, A. Herzig, C. E. Guerra, K.C. Oeffinger, Y.-C.T. Shih, L.C. Walter, J.J. Kim, K.S. Andrews, C. E. DeSantis, S.A. Fedewa, D. Manassaram-Baptiste, D. Saslow, R.C. Wender, R. A. Smith, Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society, CA Cancer J. Clin. 70 (2020) 321–346, https://doi.org/10.3322/caac.21628.

[57] D. Evans, S. Goldstein, A. Loewy, A.D. Altman, No. 385-indications for pelvic examination, J. Obstet. Gynaecol. Can. 41 (2019) 1221–1234, https://doi.org/10.1016/j.jogc.2018.12.007.

[58] ACOG, ACOG Committee opinion no. 754: the utility of and indications for routine pelvic examination, Obstet. Gynecol. 132 (2018) e174–e180, https://doi.org/10.1097/AOG.0000000000002895.

[59] E. Dreisler, L.G. Poulsen, S.L. Antonsen, I. Ceausu, H. Depypere, C.T. Erel, I. Lambrinoudaki, F.R. Pérez-López, T. Simoncini, F. Tremollieres, M. Rees, L. G. Ulrich, EMAS clinical guide: assessment of the endometrium in peri and postmenopausal women, Maturitas. 75 (2013) 181–190, https://doi.org/10.1016/j.maturitas.2013.03.011.

[60] J. Morrison, J. Balega, L. Buckley, A. Clamp, E. Crosbie, Y. Drew, L. Durrant, J. Forrest, C. Fotopoulou, K. Gajjar, R. Ganesan, J. Gupta, J. Hughes, T. Miles, E. Moss, M. Nanthakumar, C. Newton, N. Ryan, A. Walther, A. Taylor, British Gynaecological Cancer Society (BGCS) uterine cancer guidelines: recommendations for practice, Eur. J. Obstet. Gynecol. Reprod. Biol. 270 (2022) 50–89, https://doi.org/10.1016/j.ejogrb.2021.11.423.

[61] NICE, Heavy menstrual bleeding: assessment and management NICE guideline. www.nice.org.uk/guidance/ng88, 2018. (Accessed 20 March 2022).

[62] Management of endometrial hyperplasia. Green-top guideline no. 67. RCOG/BSGE joint guideline | February 2016. https://www.rcog.org.uk/media/knmjbj5c/gtg_67_endometrial_hyperplasia.pdf.

[63] D.L. Monticciolo, M.S. Newell, L. Moy, B. Niell, B. Monsees, E.A. Sickles, Breast cancer screening in women at higher-than-average risk: recommendations from the ACR, J. Am. Coll. Radiol. 15 (2018) 408–414, https://doi.org/10.1016/j.jacr.2017.11.034.

[64] M.A. Helvie, T.B. Bevers, Screening mammography for average-risk women: the controversy and NCCN's position, J. Natl. Compr. Cancer Netw. 16 (2018) 1398–1404, https://doi.org/10.6004/jnccn.2018.7081.

[65] H.J. Schünemann, D. Lerda, C. Quinn, M. Follmann, P. Alonso-Coello, P.G. Rossi, A. Lebeau, L. Nyström, M. Broeders, L. Ioannidou-Mouzaka, S.W. Duffy, B. Borisch, P. Fitzpatrick, S. Hofvind, X. Castells, L. Giordano, C. Canelo-Aybar, S. Warman, R. Mansel, F. Sardanelli, E. Parmelli, A. Gräwingholt, Z. Saz-Parkinson, Breast cancer screening and diagnosis: a synopsis of the European Breast Guidelines, Ann. Intern. Med. 172 (2020) 46–56, https://doi.org/10.7326/M19-2125.

[66] European Commission, European guidelines on breast cancer screening and diagnosis. https://healthcare-quality.jrc.ec.europa.eu/european-breast-cancer-guidelines/screening-ages-and-frequencies, 2021.

[67] National Institute for Health and Care Excellence, Familial breast cancer: classification and care of people at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer, Clin. Guidel. 164 (2013). https://pubmed.ncbi.nlm.nih.gov/25340237/. (Accessed 23 March 2022).

[68] NHS, Breast screening (mammogram), NHS. https://www.nhs.uk/conditions/breast-screening-mammogram/. (Accessed 23 March 2022) (n.d.).

[69] CDC, What is breast cancer screening?. https://www.cdc.gov/cancer/breast/basic_info/screening.htm, 2021. (Accessed 23 March 2022).

[70] NHS, Cervical screening. https://www.nhs.uk/conditions/cervical-screening/, 2020. (Accessed 23 March 2022).

[71] ABS, Breast Cancer Screening Guidelines. https://www.cancer.org/cancer/breast-cancer/screening-tests-and-early-detection/american-cancer-society-recommendations-for-the-early-detection-of-breast-cancer.html, 2022. (Accessed 23 March 2022).

[72] H. Depypere, J. Desreux, F.R. Pérez-López, I. Ceausu, C.T. Erel, I. Lambrinoudaki, K. Schenck-Gustafsson, Y.T. van der Schouw, T. Simoncini, F. Tremollieres, M. Rees, EMAS position statement: individualized breast cancer screening versus population-based mammography screening programmes, Maturitas. 79 (2014) 481–486, https://doi.org/10.1016/j.maturitas.2014.09.002.

[73] R.T. Chlebowski, G. Anderson, M. Pettinger, D. Lane, R.D. Langer, M.A. Gilligan, B.W. Walsh, C. Chen, A. McTiernan, Estrogen plus progestin and breast cancer detection by means of mammography and breast biopsy, Arch. Intern. Med. 168 (2008) 370–377, https://doi.org/10.1001/archinternmed.2007.123 (quiz 345).

[74] J. Compston, A. Cooper, C. Cooper, N. Gittoes, C. Gregson, N. Harvey, S. Hope, J. A. Kanis, E.V. McCloskey, K.E.S. Poole, D.M. Reid, P. Selby, F. Thompson, A. Thurston, N. Vine, UK clinical guideline for the prevention and treatment of osteoporosis, Arch. Osteoporos. 12 (2017) 43, https://doi.org/10.1007/s11657-017-0324-5.

[75] J.A. Kanis, C. Cooper, R. Rizzoli, J.-Y. Reginster, Executive summary of the European guidance for the diagnosis and management of osteoporosis in postmenopausal women, Calcif. Tissue Int. 104 (2019) 235–238, https://doi.org/10.1007/s00223-018-00512-x.

[76] R. Eastell, C.J. Rosen, D.M. Black, A.M. Cheung, M.H. Murad, D. Shoback, Pharmacological management of osteoporosis in postmenopausal women: an Endocrine Society* clinical practice guideline, J. Clin. Endocrinol. Metab. 104 (2019) 1595–1622, https://doi.org/10.1210/jc.2019-00221.

[77] C. Cooper, K. Javaid, M. Elliott, D. Stephens, N. Tanna, UK consensus guideline on the management of patients at low, high, and very high risk of osteoporotic fracture. https://www.guidelines.co.uk/download?ac=8295, 2020.

[78] A. Agarwal, W.D. Leslie, T.V. Nguyen, S.N. Morin, L.M. Lix, J.A. Eisman, Predictive performance of the Garvan Fracture Risk Calculator: a registry-based cohort study, Osteoporos. Int. (2021), https://doi.org/10.1007/s00198-021-06252-3.

[79] J. Hippisley-Cox, C. Coupland, Derivation and validation of updated QFracture algorithm to predict risk of osteoporotic fracture in primary care in the United Kingdom: prospective open cohort study, BMJ. 344 (2012), e3427, https://doi.org/10.1136/bmj.e3427.

[80] J.A. Kanis, N.C. Harvey, C. Cooper, H. Johansson, A. Odén, E.V. McCloskey, A.B. of the N.O.G. Group, A systematic review of intervention thresholds based on FRAX: a report prepared for the National Osteoporosis Guideline Group and the International Osteoporosis Foundation, Arch. Osteoporos. 11 (2016) 25, https://doi.org/10.1007/s11657-016-0278-z.

[81] J.P.W. van den Bergh, T.A.C.M. van Geel, W.F. Lems, P.P. Geusens, Assessment of individual fracture risk: FRAX and beyond, Curr. Osteoporos. Rep. 8 (2010) 131–137, https://doi.org/10.1007/s11914-010-0022-3.

[82] J.D. Dorfman, A. Wyman, G. FitzGerald, T.A. Emhoff, F.A. Anderson, H.P. Santry, Risks factors for significant injury after geriatric falls, Int. J. Aging Res. 2 (2019) 30, https://doi.org/10.28933/ijoar-2018-12-2305.

[83] E.S. Siris, S. Baim, A. Nattiv, Primary care use of FRAX: absolute fracture risk assessment in postmenopausal women and older men, Postgrad. Med. 122 (2010) 82–90, https://doi.org/10.3810/PGM.2010.01.2102.

[84] C.P. Wong, L.U. Gani, L.R. Chong, Dual-energy X-ray absorptiometry bone densitometry and pitfalls in the assessment of osteoporosis: a primer for the practicing clinician, Arch. Osteoporos. 15 (2020) 135, https://doi.org/10.1007/s11657-020-00808-2.

[85] P. Paper, J.A. Kanis, E.V. McCloskey, H. Johansson, C. Cooper, R. Rizzoli, J.-Y. Reginster, European guidance for the diagnosis and management of osteoporosis in postmenopausal women, Osteoporos. Int. 24 (2013) 23–57, https://doi.org/10.1007/s00198-012-2074-y.

[86] F. Cosman, S.J. de Beur, M.S. LeBoff, E.M. Lewiecki, B. Tanner, S. Randall, R. Lindsay, N.O. Foundation, Clinician's guide to prevention and treatment of osteoporosis, Osteoporos. Int. 25 (2014) 2359–2381, https://doi.org/10.1007/s00198-014-2794-2.

[87] D. Marshall, O. Johnell, H. Wedel, Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures, BMJ. 312 (1996) 1254–1259, https://doi.org/10.1136/bmj.312.7041.1254.

[88] NICE, Guidance | osteoporosis: assessing the risk of fragility fracture | guidance, NICE, 2017. https://www.nice.org.uk/guidance/cg146/chapter/1-guidance. (Accessed 22 March 2022).

[89] A.J. Cruz-Jentoft, G. Bahat, J. Bauer, Y. Boirie, O. Bruyère, T. Cederholm, C. Cooper, F. Landi, Y. Rolland, A. Aihie, S.S.M. Schneider, C.C. Sieber, E. Topinkova, M. Vandewoude, M. Visser, M. Zamboni, Sarcopenia: revised European consensus on definition and diagnosis European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2, Age Ageing 48 (2019) 16–31, https://doi.org/10.1093/ageing/afy169.

[90] E. Dent, J.E. Morley, A.J. Cruz-Jentoft, H. Arai, S.B. Kritchevsky, J. Guralnik, J. M. Bauer, M. Pahor, B.C. Clark, M. Cesari, J. Ruiz, C.C. Sieber, M. Aubertin-Leheudre, D.L. Waters, R. Visvanathan, F. Landi, D.T. Villareal, R. Fielding, C. W. Won, O. Theou, F.C. Martin, B. Dong, J. Woo, L. Flicker, L. Ferrucci, R. A. Merchant, L. Cao, T. Cederholm, S.M.L. Ribeiro, L. Rodríguez-Mañas, S. D. Anker, J. Lundy, L.M. Gutiérrez Robledo, I. Bautmans, I. Aprahamian, J.M.G. A. Schols, M. Izquierdo, B. Vellas, International Clinical Practice Guidelines for Sarcopenia (ICFSR): screening, diagnosis and management, J. Nutr. Health Aging 22 (2018) 1148–1161, https://doi.org/10.1007/s12603-018-1139-9.

[91] T.K. Malmstrom, D.K. Miller, E.M. Simonsick, L. Ferrucci, J.E. Morley, SARC-F: a symptom score to predict persons with sarcopenia at risk for poor functional outcomes, J. Cachexia. Sarcopenia Muscle 7 (2016) 28–36, https://doi.org/10.1002/jcsm.12048.

[92] I. Lambrinoudaki, I. Ceasu, H. Depypere, T. Erel, M. Rees, K. Schenck-Gustafsson, T. Simoncini, F. Tremollieres, Y.T. van der Schouw, F.R. Pérez-López, EMAS position statement: diet and health in midlife and beyond, Maturitas 74 (2013) 99–104, https://doi.org/10.1016/j.maturitas.2012.10.019.

[93] A. Cano, S. Marshall, I. Zolfaroli, J. Bitzer, I. Ceausu, P. Chedraui, F. Durmusoglu, R. Erkkola, D.G. Goulis, A.L. Hirschberg, L. Kiesel, P. Lopes, A. Pines, M. van Trotsenburg, I. Lambrinoudaki, M. Rees, The Mediterranean diet and menopausal health: an EMAS position statement, Maturitas. 139 (2020) 90–97, https://doi.org/10.1016/j.maturitas.2020.07.001.

[94] NICE, Scenario: management of menopause, perimenopause, or premature ovarian insufficiency | management | menopause | CKS, NICE, 2020. https://cks.nice.org.uk/topics/menopause/management/management-of-menopause-perimenopause-or-premature-ovarian-insufficiency/#information-lifestyle-advice. (Accessed 9 October 2021).

[95] A. Cano, P. Chedraui, D.G. Goulis, P. Lopes, G. Mishra, A. Mueck, L.M. Senturk, T. Simoncini, J.C. Stevenson, P. Stute, P. Tuomikoski, M. Rees, I. Lambrinoudaki, Calcium in the prevention of postmenopausal osteoporosis: EMAS clinical guide, Maturitas 107 (2018) 7–12, https://doi.org/10.1016/j.maturitas.2017.10.004.

[96] R.U. Erkkola, T. Vasankari, R.A. Erkkola, Opinion paper: exercise for healthy aging, Maturitas 144 (2021) 45–52, https://doi.org/10.1016/j.maturitas.2020.10.012.

[97] NAMS, The 2017 hormone therapy position statement of the North American Menopause Society, Menopause. 25 (2018) 1362–1387, https://doi.org/10.1097/GME.0000000000001241.

[98] E. Armeni, I. Lambrinoudaki, I. Ceausu, H. Depypere, A. Mueck, F.R. Pérez-López, Y.T.V. Der Schouw, L.M. Senturk, T. Simoncini, J.C. Stevenson, P. Stute, M. Rees, Maintaining postreproductive health: a care pathway from the European Menopause and Andropause Society (EMAS), Maturitas 89 (2016) 63–72, https://doi.org/10.1016/j.maturitas.2016.04.013.

[99] P.M. Camacho, S.M. Petak, N. Binkley, D.L. Diab, L.S. Eldeiry, A. Farooki, S. T. Harris, D.L. Hurley, J. Kelly, E.M. Lewiecki, R. Pessah-Pollack, M. McClung, S. J. Wimalawansa, N.B. Watts, American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines for the diagnosis and treatment of postmenopausal osteoporosis-2020 update, Endocr. Pract. 26 (2020) 1–46, https://doi.org/10.4158/GL-2020-0524SUPPL.

[100] S. Rozenberg, N. Al-Daghri, M. Aubertin-Leheudre, M.-L. Brandi, A. Cano, P. Collins, C. Cooper, A.R. Genazzani, T. Hillard, J.A. Kanis, J.-M. Kaufman, I. Lambrinoudaki, A. Laslop, E. McCloskey, S. Palacios, D. Prieto-Alhambra, J.-Y. Reginster, R. Rizzoli, G. Rosano, F. Trémollieres, N.C. Harvey, Is there a role for menopausal hormone therapy in the management of postmenopausal osteoporosis? Osteoporos. Int. 31 (2020) 2271–2286, https://doi.org/10.1007/s00198-020-05497-8.

[101] F.L.J. Visseren, F. Mach, Y.M. Smulders, D. Carballo, K.C. Koskinas, M. Bäck, A. Benetos, A. Biffi, J.-M. Boavida, D. Capodanno, B. Cosyns, C. Crawford, C. H. Davos, I. Desormais, E. Di Angelantonio, O.H. Franco, S. Halvorsen, F.D. R. Hobbs, M. Hollander, E.A. Jankowska, M. Michal, S. Sacco, N. Sattar, L. Tokgozoglu, S. Tonstad, K.P. Tsioufis, I. van Dis, I.C. van Gelder, C. Wanner, B. Williams, 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice, Eur. J. Prev. Cardiol. (2021), https://doi.org/10.1093/eurjpc/zwab154.

[102] P.H. England, Health matters: preventing cardiovascular disease. https://www.gov.uk/government/publications/health-matters-preventing-cardiovascular-disease/health-matters-preventing-cardiovascular-disease, 2019 (n.d.).

[103] C. for D.C. and Prevention, Best Practices for Cardiovascular Disease Prevention Programs: A Guide to Effective Health Care System Interventions and Community Programs Linked to Clinical Services. https://www.cdc.gov/dhdsp/pubs/docs/Best-Practices-Guide-508.pdf, 2017 (Atlanta, GA).

[104] C.E. Gleason, N.M. Dowling, W. Wharton, J.E. Manson, V.M. Miller, C.S. Atwood, E.A. Brinton, M.I. Cedars, R.A. Lobo, G.R. Merriam, G. Neal-Perry, N.F. Santoro, H.S. Taylor, D.M. Black, M.J. Budoff, H.N. Hodis, F. Naftolin, S.M. Harman, S. Asthana, Effects of hormone therapy on cognition and mood in recently postmenopausal women: findings from the randomized, controlled KEEPS-Cognitive and Affective Study, PLoS Med. 12 (2015), e1001833, https://doi.org/10.1371/journal.pmed.1001833 (discussion e1001833).

[105] P. Stute, J. Wienges, A.-S. Koller, C. Giese, W. Wesemüller, H. Janka, S. Baumgartner, Cognitive health after menopause: does menopausal hormone therapy affect it? Best Pract. Res. Clin. Endocrinol. Metab. 35 (2021), 101565 https://doi.org/10.1016/j.beem.2021.101565.

[106] Y. Vinogradova, T. Dening, J. Hippisley-Cox, L. Taylor, M. Moore, C. Coupland, Use of menopausal hormone therapy and risk of dementia: nested case-control studies using QResearch and CPRD databases, BMJ. 374 (2021), n2182, https://doi.org/10.1136/bmj.n2182.

[107] J.V. Pinkerton, J.A. Harvey, R. Lindsay, K. Pan, A.A. Chines, S. Mirkin, D. F. Archer, Effects of bazedoxifene/conjugated estrogens on the endometrium and bone: a randomized trial, J. Clin. Endocrinol. Metab. 99 (2014) E189–E198, https://doi.org/10.1210/jc.2013-1707.

[108] J.V. Pinkerton, W.H. Utian, G.D. Constantine, S. Olivier, J.H. Pickar, Relief of vasomotor symptoms with the tissue-selective estrogen complex containing bazedoxifene/conjugated estrogens: a randomized, controlled trial, Menopause. 16 (2009) 1116–1124, https://doi.org/10.1097/gme.0b013e3181a7df0d.

[109] H.J. Kloosterboer, Historical milestones in the development of tibolone (Livial®), Climacteric. 14 (2011) 609–621, https://doi.org/10.3109/13697137.2011.580639.

[110] H.J. Kloosterboer, Tissue-selectivity: the mechanism of action of tibolone, Maturitas. 48 (Suppl. 1) (2004) S30–S40, https://doi.org/10.1016/j.maturitas.2004.02.012.

[111] G. Formoso, E. Perrone, S. Maltoni, S. Balduzzi, J. Wilkinson, V. Basevi, A. M. Marata, N. Magrini, R. D'Amico, C. Bassi, E. Maestri, Short-term and long-term effects of tibolone in postmenopausal women, Cochrane Database Syst. Rev. 10 (2016), CD008536, https://doi.org/10.1002/14651858.CD008536.pub3.

[112] S.R. Cummings, B. Ettinger, P.D. Delmas, P. Kenemans, V. Stathopoulos, P. Verweij, M. Mol-Arts, L. Kloosterboer, L. Mosca, C. Christiansen, J. Bilezikian, E.M. Kerzberg, S. Johnson, J. Zanchetta, D.E. Grobbee, W. Seifert, R. Eastell, The effects of tibolone in older postmenopausal women, N. Engl. J. Med. 359 (2008) 697–708, https://doi.org/10.1056/NEJMoa0800743.

[113] P. Sismondi, R. Kimmig, E. Kubista, N. Biglia, J. Egberts, R. Mulder, J. Planellas, G. Moggio, M. Mol-Arts, P. Kenemans, Effects of tibolone on climacteric symptoms and quality of life in breast cancer patients—data from LIBERATE trial, Maturitas. 70 (2011) 365–372, https://doi.org/10.1016/j.maturitas.2011.09.003.

[114] F.Z. Stanczyk, H. Matharu, S.A. Winer, Bioidentical hormones, Climacteric. 24 (2021) 38–45, https://doi.org/10.1080/13697137.2020.1862079.

[115] Y. Liu, Y. Yuan, A.J. Day, W. Zhang, P. John, D.J. Ng, D. Banov, Safety and efficacy of compounded bioidentical hormone therapy (cBHT) in perimenopausal and postmenopausal women: a systematic review and meta-analysis of randomized controlled trials, Menopause. 29 (2022) 465–482, https://doi.org/10.1097/GME.0000000000001937.

[116] K. Pagana, T. Pagana, T. Pagana, Mosby's Diagnostic & Laboratory Test Reference, 14th ed., Elsevier, 2019.

[117] F. Fruzzetti, G. Palla, M. Gambacciani, T. Simoncini, Tailored hormonal approach in women with premature ovarian insufficiency, Climacteric. 23 (2020) 3–8, https://doi.org/10.1080/13697137.2019.1632284.

[118] B. Cartwright, J. Robinson, P.T. Seed, I. Fogelman, J. Rymer, Hormone replacement therapy versus the combined oral contraceptive pill in premature ovarian failure: a randomized controlled trial of the effects on bone mineral density, J. Clin. Endocrinol. Metab. 101 (2016) 3497–3505, https://doi.org/10.1210/jc.2015-4063.

[119] D. Cintron, R. Rodriguez-Gutierrez, V. Serrano, P. Latortue-Albino, P.J. Erwin, M. H. Murad, Effect of estrogen replacement therapy on bone and cardiovascular outcomes in women with turner syndrome: a systematic review and meta-analysis, Endocrine. 55 (2017) 366–375, https://doi.org/10.1007/s12020-016-1046-y.

[120] T.J. de Villiers, J.E. Hall, J.V. Pinkerton, S.C. Pérez, M. Rees, C. Yang, D. D. Pierroz, Revised global consensus statement on menopausal hormone therapy, Maturitas. 91 (2016) 153–155, https://doi.org/10.1016/j.maturitas.2016.06.001.

[121] NAMS, The North American Menopause Society statement on continuing use of systemic hormone therapy after age 65, Menopause. 22 (2015) 693, https://doi.org/10.1097/GME.0000000000000492.

[122] S.R. Davis, R. Baber, N. Panay, J. Bitzer, S.C. Perez, R.M. Islam, A.M. Kaunitz, S. A. Kingsberg, I. Lambrinoudaki, J. Liu, S.J. Parish, J.A. Pinkerton, J. Rymer, J. A. Simon, L. Vignozzi, M.E. Wierman, Global consensus position statement on the use of testosterone therapy for women, Maturitas. 128 (2019) 89–93, https://doi.org/10.1016/J.MATURITAS.2019.07.001.

[123] V.A. Flores, L. Pal, J.E. Manson, Recommended hormone therapy in menopause: concepts, controversies and approach to treatment, Endocr. Rev. (2021), https://doi.org/10.1210/endrev/bnab011.

[124] R. Slopien, E. Wender-Ozegowska, A. Rogowicz-Frontczak, B. Meczekalski, D. Zozulinska-Ziolkiewicz, J.D. Jaremek, A. Cano, P. Chedraui, D.G. Goulis, P. Lopes, G. Mishra, A. Mueck, M. Rees, L.M. Senturk, T. Simoncini, J. C. Stevenson, P. Stute, P. Tuomikoski, S.A. Paschou, P. Anagnostis, I. Lambrinoudaki, Menopause and diabetes: EMAS clinical guide, Maturitas. 117 (2018) 6–10, https://doi.org/10.1016/j.maturitas.2018.08.009.

[125] A.H.E.M. Maas, G. Rosano, R. Cifkova, A. Chieffo, D. Van Dijken, H. Hamoda, V. Kunadian, E. Laan, I. Lambrinoudaki, K. Maclaran, N. Panay, J.C. Stevenson, M. Van Trotsenburg, P. Collins, Cardiovascular health after menopause transition, pregnancy disorders, and other gynaecologic conditions: a consensus document from European cardiologists, gynaecologists, and endocrinologists, Eur. Heart J. 00 (2020) 1–18, https://doi.org/10.1093/eurheartj/ehaa1044.

[126] H. Lyytinen, E. Pukkala, O. Ylikorkala, Breast cancer risk in postmenopausal women using estradiol-progestogen therapy, Obstet. Gynecol. 113 (2009) 65–73, https://doi.org/10.1097/AOG.0b013e31818e8cd6.

[127] NIHR, NIHR evidence - risk of breast cancer with HRT depends on therapy type and duration - informative and accessible health and care research. https://evidence.nihr.ac.uk/alert/risk-of-breast-cancer-with-hrt-depends-therapy-type-and-duration/, 2021. (Accessed 20 March 2022).

[128] A. Fournier, F. Berrino, F. Clavel-Chapelon, Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study, Breast Cancer Res. Treat. 107 (2008) 103–111, https://doi.org/10.1007/s10549-007-9523-x.

[129] A. Fournier, A. Fabre, S. Mesrine, M.-C. Boutron-Ruault, F. Berrino, F. Clavel-Chapelon, Use of different postmenopausal hormone therapies and risk of histology- and hormone receptor-defined invasive breast cancer, J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 26 (2008) 1260–1268, https://doi.org/10.1200/JCO.2007.13.4338.

[130] R.M. Islam, R.J. Bell, S. Green, M.J. Page, S.R. Davis, Safety and efficacy of testosterone for women: a systematic review and meta-analysis of randomised controlled trial data, Lancet Diabetes Endocrinol. 7 (2019) 754–766, https://doi.org/10.1016/S2213-8587(19)30189-5.

[131] M. Jewson, P. Purohit, M.A. Lumsden, Progesterone and abnormal uterine bleeding/menstrual disorders, Best Pract. Res. Clin. Obstet. Gynaecol. 69 (2020) 62–73, https://doi.org/10.1016/j.bpobgyn.2020.05.004.

[132] T.J. de Villiers, A.A. Chines, S. Palacios, P. Lips, A.Z. Sawicki, A.B. Levine, C. Codreanu, N. Kelepouris, J.P. Brown, Safety and tolerability of bazedoxifene in postmenopausal women with osteoporosis: results of a 5-year, randomized, placebo-controlled phase 3 trial, Osteoporos. Int. 22 (2011) 567–576, https://doi.org/10.1007/s00198-010-1302-6.

[133] S.M.R. Hardman, A.E. Gebbie, The contraception needs of the perimenopausal woman, Best Pract. Res. Clin. Obstet. Gynaecol. 28 (2014) 903–915, https://doi.org/10.1016/j.bpobgyn.2014.05.006.

[134] J.V. Pinkerton, E.A. Conner, Beyond estrogen: advances in tissue selective estrogen complexes and selective estrogen receptor modulators, Climacteric. 22 (2019) 140–147, https://doi.org/10.1080/13697137.2019.1568403.

[135] G. Mishra, R. Hardy, D. Kuh, Are the effects of risk factors for timing of menopause modified by age? Results from a British birth cohort study, Menopause. 14 (2007) 717–724, https://doi.org/10.1097/GME.0b013e31802f3156.

[136] G. Mintziori, I. Lambrinoudaki, D.G. Goulis, I. Ceausu, H. Depypere, C.T. Erel, F. R. Pérez-López, K. Schenck-Gustafsson, T. Simoncini, F. Tremollieres, M. Rees, EMAS position statement: non-hormonal management of menopausal vasomotor symptoms, Maturitas. 81 (2015) 410–413, https://doi.org/10.1016/j.maturitas.2015.04.009.

[137] G. Riemma, A. Schiattarella, M. La Verde, G. Zarobbi, S. Garzon, G. Cucinella, G. Calagna, D. Labriola, P. De Franciscis, Efficacy of low-dose paroxetine for the treatment of hot flushes in surgical and physiological postmenopausal women: systematic review and meta-analysis of randomized trials, Medicina (Kaunas) 55 (2019), https://doi.org/10.3390/medicina55090554.

[138] R.J. Orleans, L. Li, M.-J. Kim, J. Guo, M. Sobhan, L. Soule, H.V. Joffe, FDA approval of paroxetine for menopausal hot flushes, N. Engl. J. Med. 370 (2014) 1777–1779, https://doi.org/10.1056/NEJMp1402080.

[139] J. Woyka, Consensus statement for non-hormonal based treatments for menopausal symptoms, Post Reprod. Health 26 (2020) 137–141, https://doi.org/10.1177/2053369120930508.

[140] C.A. Stuenkel, Managing menopausal vasomotor symptoms in older women, Maturitas. 143 (2021) 36–40, https://doi.org/10.1016/j.maturitas.2020.08.005.

[141] H. Hirsch, J.E. Manson, Menopausal symptom management in women with cardiovascular disease or vascular risk factors, Maturitas. 161 (2022) 1–6, https://doi.org/10.1016/j.maturitas.2022.01.016.

[142] R.A. Leon-Ferre, P.J. Novotny, E.G. Wolfe, S.S. Faubion, K.J. Ruddy, D. Flora, C.S. R. Dakhil, K.M. Rowland, M.L. Graham, N. Le-Lindqwister, T.J. Smith, C. L. Loprinzi, Oxybutynin vs placebo for hot flashes in women with or without breast cancer: a randomized, double-blind clinical trial (ACCRU SC-1603), JNCI Cancer Spectr. 4 (2020) pkz088, https://doi.org/10.1093/jncics/pkz088.

[143] J.A. Simon, A.H. Clayton, N.N. Kim, S. Patel, Clinically meaningful benefit in women with hypoactive sexual desire disorder treated with flibanserin, Sex. Med. 10 (2022), 100476, https://doi.org/10.1016/j.esxm.2021.100476.

[144] D.F. Archer, J.A. Simon, D.J. Portman, S.R. Goldstein, I. Goldstein, Ospemifene for the treatment of menopausal vaginal dryness, a symptom of the genitourinary syndrome of menopause, Expert. Rev. Endocrinol. Metab. 14 (2019) 301–314, https://doi.org/10.1080/17446651.2019.1657008.

[145] V. Di Donato, M.C. Schiavi, V. Iacobelli, O. D`oria, E. Kontopantelis, T. Simoncini, L. Muzii, P. Benedetti Panici, Ospemifene for the treatment of vulvar and vaginal atrophy: a meta-analysis of randomized trials. Part I: evaluation of efficacy, Maturitas. 121 (2019) 86–92, https://doi.org/10.1016/j.maturitas.2018.11.016.

[146] V. Di Donato, M.C. Schiavi, V. Iacobelli, O. D`oria, E. Kontopantelis, T. Simoncini, L. Muzii, P. Benedetti Panici, Ospemifene for the treatment of vulvar and vaginal atrophy: a meta-analysis of randomized trials. Part II: evaluation of tolerability and safety, Maturitas. 121 (2019) 93–100, https://doi.org/10.1016/j.maturitas.2018.11.017.

[147] N. Potter, N. Panay, Vaginal lubricants and moisturizers: a review into use, efficacy, and safety, Climacteric. 24 (2021) 19–24, https://doi.org/10.1080/13697137.2020.1820478.

[148] Y. Khamis, A.M. Abdelhakim, K. Labib, B.A. Islam, S.A. Nassar, A.O.A. Motaal, D. M. Saleh, H. Abdou, A.M. Abbas, E.M. Mojahed, Vaginal CO2 laser therapy versus sham for genitourinary syndrome of menopause management: a systematic review and meta-analysis of randomized controlled trials, Menopause. 28 (2021) 1316–1322, https://doi.org/10.1097/GME.0000000000001845.

[149] E. Mension, I. Alonso, M. Tortajada, I. Matas, S. Gómez, L. Ribera, S. Anglès, C. Castelo-Branco, Vaginal laser therapy for genitourinary syndrome of menopause - systematic review, Maturitas. 156 (2022) 37–59, https://doi.org/10.1016/j.maturitas.2021.06.005.

[150] M. Gambacciani, M. Cervigni, A. Gaspar, A. Novakov Mikić, J. Gaviria, N. Koron, Z. Vizintin, Safety of vaginal erbium laser: a review of 113,000 patients treated in the past 8 years, Climacteric. 23 (2020) S28–S32, https://doi.org/10.1080/13697137.2020.1813098.

[151] K. Mackova, A.M. Mazzer, M. Mori Da Cunha, L. Hajkova Hympanova, I. Urbankova, A.W. Kastelein, E. Vodegel, K. Vander Linden, H. Fehervary, Z. Guler, J.P. Roovers, L. Krofta, J. Verhaeghe, J. Deprest, Vaginal Er:YAG laser application in the menopausal ewe model: a randomised estrogen and sham-controlled trial, BJOG. 128 (2021) 1087–1096, https://doi.org/10.1111/1471-0528.16558.

[152] F.G. Li, S. Maheux-Lacroix, R. Deans, E. Nesbitt-Hawes, A. Budden, K. Nguyen, C. Y. Lim, S. Song, L. McCormack, S.D. Lyons, E. Segelov, J.A. Abbott, Effect of fractional carbon dioxide laser vs sham treatment on symptom severity in women with postmenopausal vaginal symptoms: a randomized clinical trial, JAMA. 326 (2021) 1381–1389, https://doi.org/10.1001/jama.2021.14892.

[153] V. Djapardy, N. Panay, Alternative and non-hormonal treatments to symptoms of menopause, Best Pract. Res. Clin. Obstet. Gynaecol. (2021), https://doi.org/10.1016/j.bpobgyn.2021.09.012.

[154] N. Panay, E. Kalu, Management of premature ovarian failure, Best Pract. Res. Clin. Obstet. Gynaecol. 23 (2009) 129–140, https://doi.org/10.1016/j.bpobgyn.2008.10.008.

[155] M.S. Hunter, Cognitive behavioral therapy for menopausal symptoms, Climacteric. 24 (2021) 51–56, https://doi.org/10.1080/13697137.2020.1777965.

[156] B. Ayers, M. Smith, J. Hellier, E. Mann, M.S. Hunter, Effectiveness of group and self-help cognitive behavior therapy in reducing problematic menopausal hot flushes and night sweats (MENOS 2): a randomized controlled trial, Menopause. 19 (2012) 749–759, https://doi.org/10.1097/gme.0b013e31823fe835.

[157] E. Mann, M.J. Smith, J. Hellier, J.A. Balabanovic, H. Hamed, E.A. Grunfeld, M. S. Hunter, Cognitive behavioural treatment for women who have menopausal symptoms after breast cancer treatment (MENOS 1): a randomised controlled trial, Lancet Oncol. 13 (2012) 309–318, https://doi.org/10.1016/S1470-2045(11)70364-3.

[158] E. Stefanopoulou, M.S. Hunter, Telephone-guided Self-Help Cognitive Behavioural Therapy for menopausal symptoms, Maturitas. 77 (2014) 73–77, https://doi.org/10.1016/j.maturitas.2013.09.013.

[159] D. Fenlon, T. Maishman, L. Day, J. Nuttall, C. May, M. Ellis, J. Raftery, L. Turner, J. Fields, G. Griffiths, M.S. Hunter, Effectiveness of nurse-led group CBT for hot flushes and night sweats in women with breast cancer: results of the MENOS4 randomised controlled trial, Psychooncology. 29 (2020) 1514–1523, https://doi.org/10.1002/pon.5432.

[160] NICE, 2021 Exceptional Surveillance of Menopause: Diagnosis and Management (NICE Guideline NG23), 2021.

[161] F.R. Pérez-López, M. Brincat, C.T. Erel, F. Tremollieres, M. Gambacciani, I. Lambrinoudaki, M.H. Moen, K. Schenck-Gustafsson, S. Vujovic, S. Rozenberg, M. Rees, EMAS position statement: vitamin D and postmenopausal health, Maturitas. 71 (2012) 83–88, https://doi.org/10.1016/j.maturitas.2011.11.002.

[162] Y.-Z. Jin, J.H. Lee, B. Xu, M. Cho, Effect of medications on prevention of secondary osteoporotic vertebral compression fracture, non-vertebral fracture, and discontinuation due to adverse events: a meta-analysis of randomized controlled trials, BMC Musculoskelet. Disord. 20 (2019) 399, https://doi.org/10.1186/s12891-019-2769-8.

[163] S. Palacios, M. Brincat, C.T. Erel, M. Gambacciani, I. Lambrinoudaki, M.H. Moen, K. Schenck-Gustafsson, F. Tremollieres, S. Vujovic, M. Rees, S. Rozenberg, EMAS clinical guide: selective estrogen receptor modulators for postmenopausal osteoporosis, Maturitas. 71 (2012) 194–198, https://doi.org/10.1016/j.maturitas.2011.11.010.

[164] J.H. Liu, Selective estrogen receptor modulators (SERMS): keys to understanding their function, Menopause. 27 (2020) 1171–1176, https://doi.org/10.1097/GME.0000000000001585.

[165] B. Ettinger, D.M. Black, B.H. Mitlak, R.K. Knickerbocker, T. Nickelsen, H. K. Genant, C. Christiansen, P.D. Delmas, J.R. Zanchetta, J. Stakkestad, C.C. Glüer, K. Krueger, F.J. Cohen, S. Eckert, K.E. Ensrud, L.V. Avioli, P. Lips, S.R. Cummings, Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators, JAMA. 282 (1999) 637–645, https://doi.org/10.1001/jama.282.7.637.

[166] P. Barrionuevo, E. Kapoor, N. Asi, F. Alahdab, K. Mohammed, K. Benkhadra, J. Almasri, W. Farah, M. Sarigianni, K. Muthusamy, A. Al Nofal, Q. Haydour, Z. Wang, M.H. Murad, Efficacy of pharmacological therapies for the prevention of fractures in postmenopausal women: a network meta-analysis, J. Clin. Endocrinol. Metab. 104 (2019) 1623–1630, https://doi.org/10.1210/jc.2019-00192.

[167] L. Peng, Q. Luo, H. Lu, Efficacy and safety of bazedoxifene in postmenopausal women with osteoporosis: a systematic review and meta-analysis, Medicine (Baltimore) 96 (2017), e8659, https://doi.org/10.1097/MD.0000000000008659.

[168] J. Pepe, J.-J. Body, P. Hadji, E. McCloskey, C. Meier, B. Obermayer-Pietsch, A. Palermo, E. Tsourdi, M.C. Zillikens, B. Langdahl, S. Ferrari, Osteoporosis in premenopausal women: a clinical narrative review by the ECTS and the IOF, J. Clin. Endocrinol. Metab. 105 (2020), https://doi.org/10.1210/clinem/dgaa306.

[169] F. Thomasius, S. Palacios, A. Alam, M. Boolell, F. Vekeman, G. Gauthier, Fracture rates and economic outcomes in patients with osteoporosis prescribed risedronate gastro-resistant versus other oral bisphosphonates: a claims data analysis, Osteoporos. Int. 33 (2022) 217–228, https://doi.org/10.1007/s00198-021-06108-w.

[170] A.A. Khan, A. Morrison, D.A. Hanley, D. Felsenberg, L.K. McCauley, F. O'Ryan, I. R. Reid, S.L. Ruggiero, A. Taguchi, S. Tetradis, N.B. Watts, M.L. Brandi, E. Peters, T. Guise, R. Eastell, A.M. Cheung, S.N. Morin, B. Masri, C. Cooper, S.L. Morgan, B. Obermayer-Pietsch, B.L. Langdahl, R. Al Dabagh, K.S. Davison, D.L. Kendler, G. K. Sándor, R.G. Josse, M. Bhandari, M. El Rabbany, D.D. Pierroz, R. Sulimani, D. P. Saunders, J.P. Brown, J. Compston, Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus, J. Bone Miner. Res. 30 (2015) 3–23, https://doi.org/10.1002/jbmr.2405.

[171] EMA, Calcitonin. https://www.ema.europa.eu/en/medicines/human/referrals/calcitonin#:~:text=Calcitonin-containing medicines have been available in the EU,most EU countries, 2012. Why were calcitonin-containing medicines reviewed%3F.

[172] EMA, Refusal of the marketing authorisation for Eladynos (abaloparatide). https://www.ema.europa.eu/en/documents/smop-initial/questions-answers-refusal-marketing-authorisation-eladynos-abaloparatide_en.pdf, 2018.

[173] EMA, Approval of the marketing authorization for Evenity (romosozumab). https://www.ema.europa.eu/en/documents/medicine-qa/questions-answers-approval-marketing-authorisation-evenity-romosozumab_en.pdf#:~:text=EMA%2F565564%2F2019 EMEA%2FH%2FC%2F004465, 2019. Approval of the marketing authorisation for,medicine Evenity for the treatme.

[174] S.J. Menown, J.A. Tello, Neurokinin 3 receptor antagonists compared with serotonin norepinephrine reuptake inhibitors for non-hormonal treatment of menopausal hot flushes: a systematic qualitative review, Adv. Ther. 38 (2021) 5025–5045, https://doi.org/10.1007/s12325-021-01900-w.

[175] M. Modi, W.S. Dhillo, Neurokinin 3 receptor antagonism: a novel treatment for menopausal hot flushes, Neuroendocrinology. 109 (2019) 242–248, https://doi.org/10.1159/000495889.

[176] N. Santoro, A. Waldbaum, S. Lederman, R. Kroll, G.L. Fraser, C. Lademacher, L. Skillern, J. Young, S. Ramael, Effect of the neurokinin 3 receptor antagonist fezolinetant on patient-reported outcomes in postmenopausal women with vasomotor symptoms: results of a randomized, placebo-controlled, double-blind, dose-ranging study (VESTA), Menopause. 27 (2020) 1350–1356, https://doi.org/10.1097/GME.0000000000001621.

[177] J.K. Prague, R.E. Roberts, A.N. Comninos, S. Clarke, C.N. Jayasena, P. Mohideen, V.H. Lin, T.P. Stern, N. Panay, M.S. Hunter, L.C. Webber, W.S. Dhillo, Neurokinin 3 receptor antagonism rapidly improves vasomotor symptoms with sustained duration of action, Menopause. 25 (2018) 862–869, https://doi.org/10.1097/GME.0000000000001090.