

Review

Menopause—Biology, consequences, supportive care, and therapeutic options

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SUMMARY

Menopause is the cessation of ovarian function, with loss of reproductive hormone production and irreversible loss of fertility. It is a natural part of reproductive aging. The physiology of the menopause is complex and incompletely understood. Globally, menopause occurs around the age of 49 years, with geographic and ethnic variation. The hormonal changes of the menopause transition may result in both symptoms and long-term systemic effects, predominantly adverse effects on cardiometabolic and musculoskeletal health. The most effective treatment for bothersome menopausal symptoms is evidence-based, menopausal hormone therapy (MHT), which reduces bone loss and may have cardiometabolic benefits. Evidence-based non-hormonal interventions are also available for symptom relief. Treatment should be individualized with shared decision-making. Most MHT regimens are not regulator approved for perimenopausal women. Studies that include perimenopausal women are needed to determine the efficacy and safety of treatment options. Further research is crucial to improve menopause care, along with research to guide policy and clinical practice.

INTRODUCTION

Menopause is a biological event that women who live past midlife experience. In this review, we use the term “women” to comport with the menopausal literature—however, we acknowledge that some transgender men and non-binary or gender diverse people might also experience menopause and that although transgender women do not experience menopause, some might experience menopausal symptoms when decreasing the dose of or stopping hormone therapy.

Traditionally defined as the time of a woman's last menstrual bleed, this definition of the menopause does not apply to women with irregular periods or amenorrhea due to a variety of causes prior to their natural menopause transition. Therefore, a more broadly applicable definition of the menopause is the final cessation of ovarian function comprising loss of reproductive hormone production and irreversible loss of fertility.

Menopause is perceived and experienced differently by individuals in the same community and across cultures. Although some women may be profoundly disabled by their menopause-associated symptoms, for others, the hormonal changes are a minor inconvenience.^{1–3} Recognition that menopause, for most women, is a natural biological event, does not exempt the use of interventions to alleviate symptoms. Furthermore, irrespective of symptoms, menopause-associated hormonal changes add to the genetic, lifestyle, and environmental risk factors that influence

an individual's risk of developing chronic non-communicable diseases (NCDs), which increasingly emerge from the sixth decade of life. Although menopausal hormone therapy (MHT) may reduce the impact of the menopause on the development of NCD, overall, menopause offers an opportune time for the prevention of NCDs through identification and management of recognized risk factors.

This review summarizes the biology and consequences of menopause, the role of supportive care, and the menopause-specific therapeutic options available to women.

TERMINOLOGY USED TO DESCRIBE THE MENOPAUSE

Women who have both ovaries removed before the onset of their spontaneous or natural menopause are said to have experienced surgical menopause. A hysterectomy alone is not surgical menopause. In Western countries, where the median age of menopause is approximately 50–51 years,⁴ “early menopause” is defined as occurring between the ages of 40 and 45 years, and complete loss of ovarian function before the age of 40 years is termed premature ovarian insufficiency or POI. Although these chronologic definitions of early menopause and POI are not appropriate for all countries, such as India, where the average age of natural menopause is 46 years,⁵ region-specific definitions of these terms remain lacking.

BIOLOGY OF THE MENOPAUSE AND DIAGNOSTIC APPROACHES

By convention, menopause has been defined as an entire year without a menstrual period due to depletion of oocytes. This definition does not apply to women who have infrequent cycles or are amenorrheic immediately prior to menopause, including women who have had a hysterectomy, endometrial ablation, or intrauterine hormonal contraception, or women who are using contraception that suppresses ovulation.

The physiological stages of reproductive aging have been defined with reasonable accuracy using menstrual-cycle-based criteria and have been reported and refined.⁶ This classification system, described by the Stages of Reproductive Aging Workshop +10 (STRAW+10), profiles menopause specifically in women who transition from regular menstrual cycles through to postmenopausal amenorrhoea.⁶ A small proportion of individuals will go on to have another bleeding event after what is considered to be their final menstrual period (FMP), but these are unlikely to be ovulatory.⁷ Therefore, menopause, or the FMP, is a retrospective diagnosis that takes a year to define in previously menstruating women.

The process of oocyte depletion is exponential and begins in fetal life.^{8–10} Some confusion pertaining to menopause stems from the associated terminology. Although there are subtle changes in reproductive hormones and menstrual cyclicity that precede “the menopause transition,” for most women, the onset of the transition is marked by a missed menstrual period. Missing at least one menstrual period within the past 3 months or a variation in menstrual cycle length of 7 days or more defines the early menopause transition.⁶ This is thought to represent a “threshold” of oocytes below which normal ovarian function cannot be maintained. This threshold appears to reflect an overall loss of the follicle cohort. Although the term “menopause transition” is often used interchangeably with the perimenopause, the latter extends beyond the menopause transition and includes the first 12 months beyond the final menstrual bleed (Figure 1).⁶ Consequently, the perimenopause and the early postmenopause overlap, as a woman is considered to be postmenopausal from the time of her last menstrual period, which can only be retrospectively identified.⁶

The earliest hormonal changes are a decrease in the ovarian production of inhibin, which is responsible for restraining pituitary follicle stimulating hormone (FSH) secretion, specifically inhibin B in the follicular phase and inhibin A in the luteal phase.¹¹ With the decline in inhibin, there is a monotropic rise in FSH throughout the cycle but most prominent in the early follicular phase. This FSH rise, in turn, leads to a shortening of the follicular phase and an accelerated process of follicle maturation.^{12,13} In some cases, FSH remains elevated in the luteal phase, leading to recruitment of a new follicle before the prior cycle has ended, the so called “luteal-out-of-phase” (LOOP) phenomenon.¹⁴ At this point in the menopause transition, women do not consistently experience decreased estradiol levels. However, some symptoms may emerge at this point, including mild hot flashes and perimenstrual sleep disruption.^{15,16} The early transition is very variable in duration and can last for 5 years or longer.¹⁷

As the follicle pool further dwindles, women experience longer duration of amenorrhea. Once a woman has gone 60 days or longer without a menstrual period, she has entered the late menopause transition, and the prevalence of more classic menopausal symptoms increases. These include worsening vasomotor symptoms (VMSs) (hot flashes and night sweats), vaginal dryness, worsening sleep, and adverse mood (low mood and anxiety).^{6,18,19} The late transition has a better defined duration than the early transition lasting for a median of about 4 years.¹⁷ Hormone production by the ovary is erratic during this period of life, and it appears that both low estradiol levels, as well as variable estradiol levels, contribute to the symptom experience. Although menstrual cyclicity occurs intermittently, there is a relative decrease in luteal phase progesterone production.²⁰

In women who undergo menopause before the age of 45 years, whose symptoms are atypical and not clearly related to menopause, or who are weighing a decision about whether to initiate long-acting contraception or undergo a surgical procedure that would not be necessary if they were postmenopausal, it may be desirable to predict the onset of the FMP or to confirm that the menopause transition is underway. For example, a woman with a known fibroid uterus and menorrhagia with chronic anemia may wish to know when her FMP is likely to occur to decide whether to have a hysterectomy versus waiting for menopause to end the problem. In other cases, the diagnosis of menopause may be in doubt, and it is important not to miss other diagnoses such as hyperprolactinemia. Measurement of prolactin and thyroid function tests should be performed when clinically appropriate. It is rarely necessary to measure gonadotropins (FSH and luteinizing hormone [LH]). However, measurement is sometimes helpful to distinguish between amenorrhea due to menopause and amenorrhea due to conditions such as polycystic ovarian syndrome or hypothalamic causes.

Blood concentrations of anti-müllerian hormone (AMH), made by developing ovarian follicles, reflect the ovaries' follicle reserve.²¹ Consequently, there has been interest in AMH as a potential predictor of when menopause might occur. AMH varies only minimally across the menstrual cycle and therefore can be assessed regardless of the timing within the menstrual cycle or presence of amenorrhea.²² AMH is, however, suppressed in women using combined hormonal contraception or depot medroxyprogesterone acetate (MPA) and can yield a falsely low result. A systematic review of the published literature concluded that AMH lacks precision in predicting age at menopause when menopause is not imminent.²² Nonetheless, a very low AMH value in women aged less than 45 years was found to suggest an increased risk of early menopause or POI²² and was identified as a better predictor than an elevated early follicular phase FSH.²³ In a US study, undetectable AMH (<10 pg/mL) was 81%–92% predictive of the FMP occurring within the next 24 months in those aged 48 or older. In contrast, the likelihood that a woman aged less than 48 years with undetectable AMH levels would have her FMP within the next 12 months was only 51%.²³ Conversely, a high AMH (≥ 100 pg/mL) was highly predictive of the FMP not occurring within 48 months in two studies.^{23,24}

For women aged at least 45 years and menstruating prior to their menopause, the diagnosis of menopause should be made

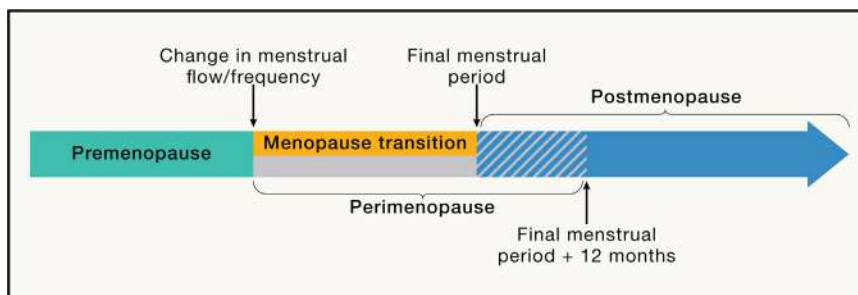


Figure 1. A summary of life stages around the menopause

FMP, final menstrual period.

on clinical grounds, including symptoms.^{25–27} However, FSH should be measured to confirm the diagnosis of early menopause and POI, optimally with raised FSH and low estradiol on at least 2 occasions, 4 weeks apart, and optimally at least 4 weeks after cessation of any contraceptive hormones.^{25–27} AMH may be indicative but is not diagnostic of menopause, even in the context of POI.^{22,23} Measurement of FSH and estradiol is uninterpretable in women using contraceptives and other treatments that suppresses ovulation.

TIMING OF THE MENOPAUSE

The timing of the menopause is moderately consistent across geographical areas and ethnic groups, occurring around the age of 49.⁴ The basis of this common pattern is due to complex genetic traits that are largely unidentified.²⁸ Familial predisposition to early or late menopause is commonly encountered, which supports the hypothesis of a genetic programming of ovarian failure.²⁹ A relevant mechanism that determines age at menopause is the rate of oocyte loss throughout life. Beginning in utero from mid-gestation, the number of oocytes in the ovaries is subject to a continuous and progressive decrease due to apoptosis. This process starts during fetal life and continues throughout infancy, adolescence, and adult reproductive life, independent of reproductive events or hormones.³⁰ This continuous loss is quantitatively far more important than follicle consumption due to ovulatory activity and is the primary determinant of ovarian exhaustion leading to loss of fertility and cessation of menses at midlife.⁴

An additional mechanism explaining the progressive loss of ovarian function is the decreased sensitivity of ovarian follicular cells (granulosa and theca cells) to pituitary gonadotrophins (FSH and LH) that is observed in the later premenopausal years.³¹ The loss of coordinated production of estrogen and progesterone by follicular cells, along with the reduced response of theca cells to the mid-cycle LH surge, drive altered ovulation and menstrual irregularities. Other ovarian-derived hormones, such as inhibin B and AMH, decline with age because their synthesis depends on the number of follicles.³¹ This progressive global hormonal change alters the feedback between the ovaries and the hypothalamic nuclei producing gonadotrophin releasing hormone (GnRH), contributing to the cycle disturbances that characterize the perimenopause.³²

There is evidence that, before menopause, the hypothalamus undergoes independent functional modifications that impact the

pattern of LH release at mid-cycle shows the most prominent alteration, with less frequent but lengthier pulses, leading to disrupted ovulation, thereby decreasing fertility and causing menstrual irregularities.¹² These observations suggest that some yet unidentified controller of reproductive aging might reside in the central nervous system and contribute to the events that precipitate ovarian failure at midlife.^{4,33}

SYMPTOMS ARISING FROM THE MENOPAUSE TRANSITION

The road to menopause is not difficult for all, but for some, symptoms may be severe or even disabling and disruptive to work and family. The core menopausal symptoms are VMS, sleep disruption, anxiety and low mood, and urogenital changes, all of which may impact sexual desire.^{25,26} Although women expect menopausal symptoms to start in their 50s, symptoms often emerge in the early menopausal transition, with ethnic variations in timing and symptom burden. VMS are not uncommon prior to the menopause transition. Nighttime VMS have been reported as occurring in 35% of women while pregnant and 29% postpartum.³⁴ However, the prevalence of VMS more than doubles with age, increasing from 32% of premenopausal women to 66% of perimenopausal women (Figure 2).¹ Other symptoms are reported as emerging during the late premenopausal years. However, whether such symptoms are due to hormonal changes that precede the perimenopause or psychosocial and environmental factors remains uncertain.^{35,36}

The prevalence of any menopause-related VMS varies from 53% to 80% worldwide.^{1,37–40} An Australian longitudinal study described four VMS trajectories that included a severe VMS profile from the early transition peaking during the perimenopause, a late onset severe VMS profile peaking up to 4 years postmenopause with a slow decline thereafter, a moderate severe profile with an earlier peak and offset than the late onset severe profile, and a mild VMS profile with a slight peak around the FMP.² The US Study of Women's Health Across the Nation (SWAN) study also identified a severely symptomatic group whose VMS started well before their FMP and continued well into the postmenopause.⁴¹

VMS are not the cardinal symptoms of menopause in all countries. Although the 28% prevalence of moderate to severe VMS in postmenopausal women in Bangladesh, a low-income country,⁴² matches the 28% prevalence reported for Australia, a high-income country,¹ postmenopausal women in Bangladesh

are, as in other Asian countries,³⁹ more likely to report moderate to severe new onset joint pain (40%) than troublesome VMS.⁴² Overweight and obesity, smoking, and lower socioeconomic status are independently associated with a greater likelihood of VMS.^{1,43} Moderate to severe VMS are independently associated with impaired sleep, poorer concentration, depressive symptoms, impaired psychological and general well-being, and lower overall quality of life.^{44–47}

The duration of menopausal VMS is mixed. In the SWAN study, the median duration of VMS was 7.4 years but varied by race and ethnicity, with African-American women reporting a greater median duration of 10.1 years compared with women of European ancestry (6.5 years).⁴⁸ Although the SWAN study reported that women with VMS that occur earlier in their menopause transition appear more likely to have a longer symptom duration,⁴⁸ this has not been a consistent finding. In the Australian Longitudinal Study of Women's Health, women with later onset and severe VMS were most likely to have the longest symptom duration.² Other Australian studies have reported that 42% of women aged 60–64 years¹ and 33% of women aged 65–79 years⁴⁹ continue to experience VMS.

From the early menopausal transition, women report increased frequency of sleep disturbance, including sleep maintenance, sleep initiation, and early morning awakenings, worsening across the menopause transition and worse for those with surgical menopause.⁵⁰ Almost three out of four postmenopausal women suffer from fatigue, and two out of three have difficulty sleeping.⁴⁶ However, sleep disruption is multifactorial, involving hormonal changes, bothersome VMS, mood disorders, stress, poor health, obesity, or preexisting sleep disorders.⁵¹ Sleep disturbances appear to increase as women progress through the menopause transition.^{52,53} Low estrogen levels have been associated with greater difficulty of falling asleep and frequent waking.⁵⁰ Objectively measured VMS occur during early sleep, preceding or simultaneous with waking episodes, with increased VMS frequency correlating with worsening sleep disturbance indices.⁵⁴

Mood change is a recognized menopausal symptom.²⁵ However, preexisting anxiety and depressive symptoms are often incorrectly partially or fully attributed to the onset of menopause. Anxiety symptoms increase with progression through the menopause transition, peaking in the late perimenopause.⁵⁵ Counterintuitively, women who have high anxiety when they enter the menopause transition have been observed to have lessening of their anxiety as they progress toward postmenopause.⁵⁵ With respect to low mood, the reporting of depressive symptoms varies according to the instrument used and the cutoff applied to classify women as having depressive symptoms. Nonetheless, an increased likelihood of women experiencing depressive symptoms, peaking during the perimenopause and associated with VMS, has been consistently reported.^{45,56} Variable and fluctuating estrogen levels appear responsible for mood issues rather than lower absolute levels of estrogen.^{57,58} Other risk factors for depressive symptoms include poor sleep, stressful or negative life events, employment status, age, and race.⁵⁷ The likelihood that a woman will experience a major depressive episode increases in the perimenopause.⁵⁹ The risk of a major depressive episode has been observed to be greatest for women

with a prior history of major depression, psychotropic medication use, higher body mass index, and very upsetting life events, but not VMS frequency.⁵⁹

Postmenopausal hypoestrogenism leads to the thinning of the vaginal epithelium, a decreased number of superficial epithelial cells, and decreased glycogen production. Glycogen is an essential energy source for lactobacilli, which dominate the healthy vaginal microbiota, maintain a low vaginal pH, and provide a protective barrier against infection.⁶⁰ Therefore, reduced vaginal tissue glycogen changes the vaginal microbiome, resulting in an alkaline pH.⁶⁰ Hypoestrogenism decreases fibroblastic activity and local collagen production.⁶¹ These microstructural changes lead to alterations in both anatomy and function. The epithelium thins and becomes pale, elasticity decreases, and vaginal narrowing and shortening may occur along with constriction of the introitus, regression of the labia minora, and urethral prominence.⁶² The resultant urogenital atrophy is a common and under reported chronic, progressive condition, and bothersome symptoms require long-term treatment. The prevalence of bothersome symptoms has been estimated at approximately 70%.⁶³

The most prevalent vulvovaginal atrophy (VVA) symptoms are dryness, irritation, and discharge⁶⁴ and are a major cause of sexual dysfunction.⁶⁵ Other urogenital symptoms include urinary frequency, nocturia, urgency, incontinence, and recurrent urinary tract infections.⁶⁴ The symptoms are primarily related to estrogen deficiency in the vagina, vulva, and lower urinary tract.⁶⁶ These urogenital symptoms may appear early in the transition,^{18,19} are typically progressive, unlikely to improve without treatment, and relapse when treatment is ceased. Urogenital menopausal symptoms are underdiagnosed and undertreated.^{63,67,68} Women may be hesitant to report these symptoms, possibly because they believe such symptoms are expected with aging.⁶⁷

LIFE CONSEQUENCES OF THE MENOPAUSE

Research has highlighted that the menopausal transition is associated with cardiovascular, bone, and mood effects and may impact future health risks in postmenopausal women.^{1,32} During the menopause transition and beyond, women should be encouraged to keep up with routine healthcare screenings, including screening for cervical cancer, breast cancer, and colon cancer, as well as for any identified health risks, such as excess weight gain, abdominal adiposity, prediabetes and diabetes, hypertension, hyperlipidemia, risks for depression and mood disorders, cardiovascular disease (CVD), and osteoporosis. Comprehensive care of postmenopausal women involves lifestyle optimization. This includes optimizing nutrition, avoiding being sedentary and increasing physical activity, adding strength and resistance exercise or training, getting adequate sleep, reducing stress, decreasing alcohol consumption, and avoiding smoking.⁶⁹

SILENT HEALTH CONSEQUENCES OF THE MENOPAUSE TRANSITION

The majority of women do not experience severe menopausal symptoms, and some experience little or no bothersome

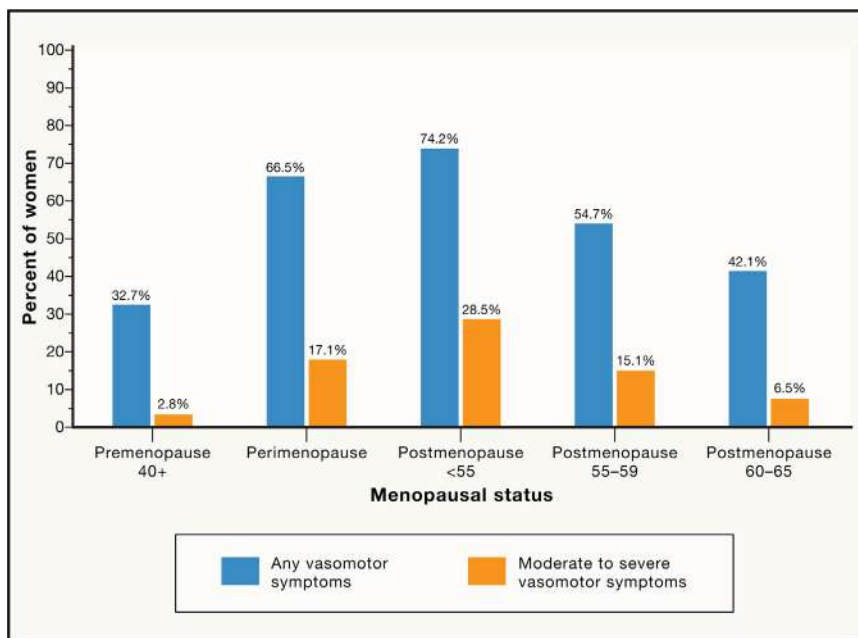


Figure 2. Prevalence of vasomotor symptoms according to the menopausal stage in Australian women

VMSs, vasomotor symptoms. Data from Gartoulla et al.¹

symptoms.^{1,39} Yet, irrespective of symptoms, the hormonal changes at menopause have systemic effects, increasing the risk of CVD, diabetes mellitus, cancers associated with central adiposity, and bone loss and fragility fracture.

Changes in body composition and disease risk

Compared with men, women are more vulnerable to traditional CVD risk factors, such as hypertension, diabetes, and smoking.⁷⁰ In addition to this gender-specific vulnerability, menopause prompts important detrimental changes in the metabolic system. An increase in body fat, particularly visceral fat, is commonly seen at the menopausal transition.³² The cause is not completely understood, but new research has linked daily energy expenditure with fat-free mass.⁷¹ Decreased physical activity is frequently observed in women at midlife, and the related muscle atrophy, or sarcopenia, is implicated in decreased energy expenditure and impaired insulin sensitivity.⁷² These bodily and lifestyle changes have relevant cardiometabolic implications because they favor insulin resistance⁷³ and a more adverse lipoprotein profile, with increased blood triglycerides and a reduction in high-density lipoprotein cholesterol (HDL-C).⁷⁴ Visceral fat accumulation leads to increased production of adipocytokines and other fat-derived inflammatory molecules that contribute to insulin resistance and vascular endothelial dysfunction.⁷⁵ Visceral fat accumulation is associated with increased risks of breast,⁷⁶ endometrial,⁷⁷ and colon cancer.⁷⁸

How, and if, this modified energy balance at midlife is associated with estrogen withdrawal or with the functional modifications in the hypothalamus is unclear.⁷⁹ Fat redistribution toward the abdominal and subcutaneous regions coincides with the menopause transition, but long-term cohort observations show that this process starts well before.⁸⁰ Early or surgical menopause are associated with increased weight gain⁸¹ and women

who use MHT tend to accrue less abdominal fat compared with non-users.⁸² Decreased SHBG concentration, presumed to be due to hypoestrogenism, is associated with fat redistribution toward the abdomen and increased peripheral resistance to insulin.⁸³

Animal and human studies have revealed that estrogen has an important role in tissue insulin sensitivity. In premenopausal women, insulin uptake by skeletal muscle is more efficient than in men.⁸⁴ However, insulin-mediated glucose disposal in muscle is diminished in postmenopausal women compared with premenopausal women.⁸⁵ Studies of estrogen receptor α (ER α) knockout mice have shown that estrogen plays a

critical role in muscle insulin uptake mediated by this receptor⁸⁶ and has favorable effects on pancreatic beta cell function.⁸⁷ These are further mechanisms by which estrogen protects against insulin resistance and type 2 diabetes.

Menopause-related estrogen loss is an established cause of vascular endothelial dysfunction, a condition characterized by decreased synthesis of vasodilatory and anti-inflammatory compounds, such as nitric oxide.^{88,89} This phenomenon is most responsible for the acceleration of atherosclerotic disease in women after the menopause and translates into structural and functional modifications of small resistance arteries, as well as of larger conduit vessels.⁷³

Overall, estrogens are protective against CVD and diabetes,⁹⁰ whereas menopause and its related metabolic modifications are associated with increased risk of myocardial infarction and cerebrovascular events.⁹¹

Menopause and musculoskeletal health

The shared embryogenesis of bone and skeletal muscle, combined with the positive association between muscle mass and bone mineral content throughout life, has led to the recognition of the importance of the bone-muscle unit. Muscle proteins modulate bone turnover, whereas bone proteins exert anabolic effects on muscle.⁹² Furthermore, the mechanical load exerted by muscle on bone influences bone remodeling. Low muscle mass and function not only increase the risk of falls but are also intimately related to low bone mineral density (BMD) and therefore osteopenia and osteoporosis, both of which increase a woman's risk of fracture.

With respect to bone loss, the drop in estrogen at menopause causes accelerated bone resorption that exceeds bone formation.⁹³ Receptor activator of nuclear factor kappa ligand (RANKL), produced by osteoblastic cells and T- and

B-lymphocytes in bone, stimulates bone-reabsorbing cell (osteoclast) differentiation and increases their activity and life span.⁹³ At menopause, there is insufficient estrogen to adequately suppress RANKL, leading to increased osteoclast numbers, activation, and longevity and hence increased bone resorption.⁹³ Estrogen also inhibits the production of the bone-reabsorbing cytokines, interleukin-1, and tumor necrosis factor- α .⁹⁴ Loss of the protective effect of estrogen against cytokine-mediated bone resorption, similarly, contributes to menopause-associated bone loss.

These effects are seen from the onset of the menopause transition in naturally menopausal women and peak at about 2 years after the FMP.⁹⁵ Vertebral bone loss from 1 year before through to 2 years after the FMP measured by radiological BMD is, on average, 7.4%, with an average loss of 5.8% at the femoral neck.⁹⁵ Although the absolute loss of BMD is less in obese women,⁹⁵ the association between bone health and obesity is complex, such that obesity should not be assumed to protect against fragility fracture.⁹⁶ Ethnic differences in bone resorption changes were found to be attenuated, but not eliminated, by adjustment for BMI.⁹⁷ Together with the age-associated decline in intestinal calcium absorption, vitamin D deficiency, and impaired renal synthesis of active 1,25-dihydroxy vitamin D₃,⁹⁸ these changes over time lead to osteoporosis and increased likelihood of fragility fracture.⁹³

Estrogen insufficiency may contribute to the pathogenesis of sarcopenia through direct and indirect pathways. Acting via ER β in skeletal muscle stem cells, known as satellite cells, estrogen is believed to stimulate satellite cell proliferation in response to muscle damage, an effect diminished with the decline in estrogen at menopause.⁷² Added to this, the menopause-associated increase in visceral fat leads to increased production of proinflammatory cytokines, which have deleterious effects on skeletal muscle function and regeneration.⁷² ER α has been implicated as having a critical role in the maintenance of muscle mitochondrial and metabolic health. In a mouse model, ER α deletion results in impaired insulin signaling and glucose disposal and increased inflammation and fat infiltration.⁸⁶ Thus, the adverse metabolic effects of estrogen insufficiency are integrally and bidirectionally associated with adverse skeletal muscle effects.⁹⁹

Estrogen treatment, with or without a progestogen, protects against postmenopausal vertebral and nonvertebral fractures, with the protective effects seen in women with and without normal BMD.^{100,101} Evidence that estrogen protects against sarcopenia is lacking. The present mainstay of prevention of sarcopenia is quality nutrition, with adequate protein, and regular physical, including resistance, exercise.

Cognition and menopause

Cognitive symptoms are common among women transitioning through the menopause, such as trouble with word finding, poor short-term memory, and impaired problem solving.¹⁰² Although these symptoms have been well documented, women without underlying health conditions continue to function within the range of normal cognitive performance.¹⁰² Objectively measured VMS frequency has been positively associated with changes in cognitive performance.¹⁰³ Disrupted sleep is also a recognized menopausal complaint,²⁵ and sleep deprivation adversely affects attention and

working memory.¹⁰⁴ Furthermore, inadequate sleep duration at midlife has been associated with a significantly greater likelihood of dementia, independent of sociodemographic, behavioral, cardiometabolic, and mental health variables.¹⁰⁵ Therefore, the extent to which cognitive symptoms are a direct consequence of the decline in estrogen or are secondary to poor quality sleep and mood change is uncertain.¹⁰²

Concern about cognition has been raised for women who have an early menopause. Observational data indicate that bilateral oophorectomy before the age of 46 years is associated with a 2-fold greater likelihood of mild cognitive impairment in women after the age of 50 years.¹⁰⁶ Estrogen therapy was not observed to reduce this risk in this case-control and cross-sectional analysis. The authors suggest a longitudinal study with serial cognitive testing over a long follow-up period to better answer this question.¹⁰⁶ Greater understanding of the impact of sex hormone depletion on cognitive performance following early surgical menopause is needed, including the impact of androgen insufficiency in this context.

As highlighted in an International Menopause Society White paper, cognitive changes at menopause should not be seen as the harbinger of dementia.¹⁰² Reassuringly, most studies suggest that the dip in cognitive performance during the natural menopause transition is transient and followed by recovery postmenopause.^{105,107} Robust clinical trials have not shown a benefit of MHT on cognitive function in postmenopausal women,^{108–111} but similar studies of estrogen therapy's effects on cognitive performance during the perimenopause are needed. Best practice guidelines recommend against the use of MHT solely for cognitive concerns or for the prevention of dementia.^{25–27,102}

SUPPORTIVE CARE

Menopause experience in the workplace is shaped by menopausal symptoms along with physical, psychosocial, and cultural characteristics of the workplace environment.¹¹² The more severe the VMS, the more that daily activities are impacted.¹¹² Early menopause health risks and perimenopausal migraines, menorrhagia, and mood issues bring additional health concerns to the workplace.

Moderately to severely bothersome VMS are associated with impaired psychological and general well-being in midlife women⁴⁴ and may adversely affect work performance.^{113,114} Studies from the UK, the Netherlands, Australia, and the US show that moderate-severe VMS are associated with decreased work ability (overall occupational and health competence to perform work tasks¹¹⁵), with lower symptom reporting when there is full-time employment, supervisor support, and workplace temperature control.^{114,116,117} A Mayo Clinic survey found that women with more symptoms had increased adverse work outcomes.¹¹⁸ A small subanalysis in this study found higher rates for Black, followed by Hispanic, women compared with White women.¹¹⁸

Poorer work ability has been independently associated with being unpartnered, obese or overweight, smoking, being a caregiver, and having insecure housing, but not with age.¹¹³ A UK survey found that women who struggled with menopausal symptoms in relation to their work were more likely to have financial

deprivation, poorer self-rated health, depression, and adverse psychosocial occupational factors but not greater work-place physical demands.¹¹⁶

An emerging body of research demonstrates associations between menopause, work related issues, and economic outcomes. Direct costs include medical and pharmacy costs, time away for appointments and testing, and the need for therapies. In contrast, indirect costs include lower work productivity, higher absenteeism, and activity impairment.^{118,119}

Improved access to evidence-based medical evaluation and treatment and more supportive workplace environments are needed. However, as an array of non-menopause-related factors contribute to the impact of menopause on work,^{116,117,120} supportive care in the workplace needs to be holistic rather than menopause centric. Furthermore, most research to date has focused on those employed outside the home, studies of the impact of menopause on women in voluntary and caregiving roles and working from home are needed.

CURRENT THERAPEUTIC OPTIONS

Not all women need treatment for their menopause-associated symptoms. Care options include lifestyle optimization and attention to NCD risk factors. It is understandable that many women seek non-prescription remedies for initial symptom relief with variable results. However, over 85% of women in high-income countries do not receive effective, regulator-approved treatment for their menopausal symptoms.^{68,121} The proportions of highly symptomatic women not receiving treatment in low- and middle-income countries have not been systematically documented. Prescription therapy for symptom relief includes sex hormone therapy, compounds that are not strictly sex hormones but act via sex hormone receptors, and novel molecules that modulate brain neural pathways involved in the generation of VMS.

Complementary and alternate medicines

Complementary and alternate medicines (CAMs) for menopausal symptoms have been frequently touted, are widely advertised, and have an overall dismal track record of efficacy when subjected to rigorous scientific study. The best studied of these are phyto (plant) estrogen supplements and black cohosh (*Cimicifuga racemosa*). Systematic reviews of phytoestrogens do not support benefits in the relief of VMS.^{122,123} In numerous trials, black cohosh, not to be confused with blue cohosh, which has known liver toxicity, has been shown to be safe with limited efficacy in some single-site clinical trials. However, the HALT study, which was the most rigorous and comprehensive clinical trial to date, consisting of 351 participants, demonstrated no improvement with black cohosh over placebo among perimenopausal women experiencing VMS.¹²⁴ The dilemma that black cohosh poses to the clinician is a common one when dealing with herbal remedies or “nutriceuticals” for menopausal symptoms. On the one hand, these treatments do not result in improvements beyond what is achieved with placebo. On the other hand, they are typically inexpensive and have low potential for harm. Acupuncture appears no more effective than placebo in well-controlled trials, whereas cognitive behavioral therapy has been shown to significantly reduce bothersome VMS and might

have added benefits for sleep and mood.¹²⁵ Consideration of over-the-counter remedy use should include a shared decision-making plan to perform intermittent monitoring of liver and renal function because such therapies are not regulated by most national regulating bodies and have been shown to contain doses that differ from that on the label and occasional impurities that could cause harm.

Non-hormonal prescription therapy

There are a variety of non-hormonal medications that have demonstrated efficacy against VMS. Virtually all of these medications have been discovered incidentally, when patients who had been taking them for their primary purpose and who also had VMS noted that their VMS improved on the medication. This serendipitous discovery of non-hormonal treatments underscores the overall lack of knowledge of the fundamental pathophysiology of VMS, which has only recently been elucidated leading to new and better targeted treatments.

The selective serotonin reuptake inhibitors/selective norepinephrine reuptake inhibitors (SSRI/SNRIs) are among the first non-hormonal agents to have been studied systematically in multiple randomized, placebo-controlled clinical trials. Their relative efficacy is shown in Table 1 along with gabapentin and clonidine. The MSFLASH clinical trial network also tested combinations of venlafaxine and estradiol,¹²⁶ as well as individual SNRIs.¹²⁷ These medications have long formed the mainstay of treatment for women with significant menopausal symptoms for whom hormone therapy is contraindicated, such as those with breast cancer or a personal history of thromboembolism. Although these non-hormonal treatments can offer some relief for many women, none are as effective as MHT, and side effects such as sexual dysfunction are not uncommon.

A breakthrough in the understanding of the origin of VMS occurred with the discovery of co-localization of the neurotransmitters kisspeptin, neurokinin 3B (NK3B), and dynorphin in what are called KNDy neurons in the infundibular nucleus of the hypothalamus.¹⁴¹ Linkage of variants in the tachykinin gene, which encodes NK3B, to VMS in postmenopausal women¹⁴² was followed by experiments in oophorectomized rodents in which blocking the neurokinin receptor on KNDy neurons appeared to eliminate coolness seeking behavior.¹⁴³ These experiments led to the development of NK3B antagonists for clinical use. Clinical trial results have shown a reduction in VMS significantly greater than placebo therapy.¹⁴⁴ The first NK3B antagonist, fezolinetant, was approved in May 2023 by the US Food and Drug Administration as an oral medication for the treatment of moderate to severe menopausal VMS. Dual agents are agents that target both the NK1B and NK3B receptor¹⁴⁵ and/or address multiple inflammatory pathways, such as G-CSF and the transient receptor potential melastatin 8 (TRPM8) channel¹⁴⁶ are also in development and show promise for treating VMS.

Most recently, the non-hormonal compound Que-122, which targets the chemokine receptor CXCR4,¹⁴⁷ has been shown in a phase 2 trial to significantly reduce VMS in women taking either estrogen antagonist therapy or aromatase inhibitor therapy after breast cancer,¹⁴⁸ with the effect, compared with placebo, similar to that seen with NK3B antagonist fezolinetant.¹⁴⁹

Table 1. Prescription non-hormonal options for menopausal vasomotor symptoms

Medication	Usual daily oral doses	% Reduction in VMS	Side effects
Citalopram ¹²⁸	20–40 mg qd	50%	nausea, somnolence or insomnia, dry mouth, and dyspepsia
Desvenlafaxine ¹²⁹	100–150 mg	60%	nausea, dry mouth, insomnia/somnolence, constipation, high blood pressure, and sexual dysfunction
Escitalopram ¹³⁰	10–20 mg	50%	nausea, insomnia, headache, sexual dysfunction
Fluoxetine ¹³¹	10–20 mg	50%	nausea, insomnia, headache, and sexual dysfunction
Paroxetine mesylate ^{a,132}	7.5 mg	30%	nausea, insomnia, and headache
Venlafaxine ¹³⁰	37.5–150 mg	60%	nausea/vomiting, anorexia, dry mouth, sexual dysfunction, and high blood pressure
Clonidine ¹³¹	transdermal: 0.1–0.2 mg; oral: 0.1–0.3 mg	24%–44%	dry mouth, orthostatic hypotension, dizziness, and constipation
Gabapentin ^{131,133,134}	100–900 mg	45%	drowsiness, dizziness, and weight
Pregabalin ^{135,136}	150–300 mg	65%–71%	somnolence and dizziness
Oxybutynin ^{137–139}	2.5–15 mg/day	~80% with extended release formulation	anticholinergic side effects increase with higher doses; cognitive decline; caution if over 65 years of age
Fezolinetant ¹⁴⁰	45 mg/day	55%–65%	headaches, abdominal pain, diarrhea, insomnia, back pain, hot flush, and reversible elevated hepatic transaminase

^acontraindicated in women taking tamoxifen

Sex hormone therapy

The mainstay of MHT is estrogen, prescribed alone for women who have had a hysterectomy but with a progestogen in non-hysterectomized women to protect against endometrial stimulation that can lead to hyperplasia and malignant transformation (Table 2).¹⁵⁰

Systemic estrogen therapy can be oral, or as a transdermal patch, gel, or spray. Subcutaneous implants are available but not regulated, and intranasal estrogen is no longer available. All regulated non-oral estrogen preparations contain estradiol, the primary circulating estrogen during the premenopausal years. Oral preparations include conjugated estrogens (CEs; a mix of several different estrogens), micronized estradiol, piperazine estrone sulfate, estradiol valerate, and estriol. Estetrol, an estrogen produced by the fetal liver, is available as a combined oral contraceptive (COC) and is being studied as a potential estrogen for MHT.¹⁵¹

Oral estrogen preparations are metabolized in the small intestine and liver to estradiol, estrone, and estrone sulfate, which results in blood levels of estrone sulfate 5- to 10-fold greater than estradiol.¹⁵² Estrone sulfate has a long plasma half-life and slow clearance rate and thus acts as a reservoir for the formation of estradiol and estrone in target tissues.¹⁵² This allows for once-a-day dosing or oral estrogen. Oral estrogen has favorable lipid effects, lowering total and low-density lipoprotein cholesterol (LDL-C) and increasing HDL-C.¹⁵³ However, oral therapy may increase blood triglycerides.¹⁵³ Oral estrogen also causes perturbations in coagulation protein production, leading to a 2- to 3-fold increase in the risk of venous thromboembolic

events (VTEs), which is further increased with greater body weight.^{154,155} Other direct hepatic effects of oral estrogen include increases in thyroid and cortisol binding globulins and sex hormone binding globulin (SHBG) and an increased risk of cholelithiasis.³ In contrast, non-oral estrogen delivery avoids first past hepatic metabolism, and circulating estradiol and estrone sulfate are approximately in a 1 to 1 ratio.³ The hepatic effects of oral estrogen can occur with supraphysiological non-oral estradiol therapy.¹⁵⁶

Women who have not had a hysterectomy require concurrent progestogen therapy to prevent endometrial hyperplasia when treated with estrogen, and several progestogens are available for this purpose.³ Progestogens include progesterone, as made in humans but not in plants, and synthetic progestogens, also known as progestins. Wild yam contains the phyto-steroid diosgenin, which does not act as a progesterone in humans but is used to synthesize progesterone and other steroids.¹⁵⁷ Because of this, wild yam cream should not be used as a progesterone cream. The progestins most often used in MHT include dydrogesterone, which is structurally similar to progesterone, norethisterone acetate (NETA; also known as norethindrone), drospirenone, levonorgestrel (LNG), and MPA.³ All progestogens protect the endometrium, but their clinical profiles differ according to their binding to other receptors. For example, drospirenone binds mineralocorticoid and androgen receptors (ARs), resulting in weak diuretic and anti-androgenic effects, respectively.³ Some progestogens, including progesterone, are limited to oral preparations, whereas NETA and LNG have been incorporated into a transdermal patch with estradiol. A

Table 2. Prescription menopausal hormone therapies for vasomotor and other menopausal symptomsStandard estrogen doses (with sequential or continuous progestogen/alone in hysterectomized women)^a

Conjugated estrogens	0.3–1.25 mg
17 β estradiol	0.5–2 mg
Estradiol valerate	0.5–2 mg
Transdermal estradiol hemihydrate patch	releases 25–100 mcg
Estradiol hemihydrate gel	0.5–1.5
Estradiol gel	0.75/pump (1–4 pumps/day)
Estradiol hemihydrate skin spray	1.53 mg/spray (1–3 sprays/day)
Estriol	1–2 mg

Sequential progestogens (daily dose for 12–14 days per month)

Dydrogesterone	5–10 mg
Micronized progesterone	200 mg
Medroxyprogesterone acetate	5–10 mg
Norethisterone acetate	0.5–2.5 mg ^b
Transdermal norethisterone acetate (with estradiol) patch	releases 140–250 mcg

Continuous progestogens (daily dose)

Dydrogesterone	5–10 mg
Drospirenone	2 mg
Micronized progesterone	100 mg
Medroxyprogesterone acetate	2.5–5 mg
Norethisterone acetate	0.5–1 mg
Transdermal norethisterone acetate (with estradiol) patch	releases 140–250 mcg
Levonorgestrel (with estradiol) patch	releases 15 mcg/day
Levonorgestrel intrauterine device	initially releases 20 mcg/day

Other

Tibolone	1.25–2.5 mg
Conjugated estrogens plus bazedoxifene	0.45 mg/20 mg

^aOral unless specified; availability of menopausal hormone therapies and approved prescribing indications by regulatory bodies vary between countries.^bAn ultra-low dose oral combination of norethisterone 0.1 mg with 0.5 mg estradiol is available in some countries.

LNG impregnated intrauterine device (LNG-IUD) provides endometrial protection for approximately 8 years, with minimization of systemic side effects.¹⁵⁸

The benefit to risk ratio of hormone therapy has been the subject of extensive debate. Although some guidelines do not consider well-managed CVD risk factors to be a contraindication to estrogen therapy,²⁵ others consider high CVD risk¹⁵⁹ or known coronary heart disease a contraindication.¹⁶⁰ A consistent recommendation, however, is that non-oral estrogen is the preferred option for women at increased VTE and CVD risk, including women who are smokers, have obesity, or diabetes.^{26,159,161} Primate research suggests that MPA, but not progesterone, opposes favorable vascular effects of estrogen,¹⁶² and this has led to some recommendations that progesterone is the optimal progestogen in the setting of increased CVD risk.^{26,159}

The impact of MHT on breast cancer risk remains controversial. The Women's Health Initiative (WHI) studies demonstrated that oral CE with MPA increased breast cancer risk,¹⁶³ an effect not seen with oral CE-only therapy.¹⁶⁴ Generalization of these findings to women of all ages and all MHT options is limited because the WHI studies only included predominantly asymp-

tomatic women aged 50–79 years, with 25% being past or current MHT users at recruitment who used a specific MHT regimen.¹⁶³ Whether non-oral MHT regimens, either as estrogen-only or estrogen plus progesterone therapy, influence the risk of breast cancer has not been determined in large clinical trials. Observational studies suggest progesterone and dydrogesterone may offer a better breast safety profile over NETA and MPA,^{165,166} with little data for drospirenone. However, robust randomized clinical trial evidence that one progestogen is safer than another in terms of breast cancer risk is lacking. It is uncertain whether the use of the LNG-IUD in postmenopausal women with concurrent estrogen therapy is associated with increased breast cancer risk, as the available data are limited to observational studies with methodological issues.¹⁶⁷ MHT should not be initiated in women with estrogen-dependent cancer, including breast cancer.

Tibolone is a synthetic steroid with estrogenic, progestogenic, and androgenic effects.¹⁶⁸ It has wide international availability, excluding the US. Taken orally, tibolone alleviates VMS, with efficacy marginally less than standard estrogen therapy.¹⁶⁹ Improvements in mood and sleep have been demonstrated.^{169,170}

The progestogenic effects of tibolone abrogate the need for concurrent progestogen therapy, and the likelihood of unscheduled bleeding is lower than with continuous combined estrogen-progestogen therapy.¹⁷¹ Improvements in sexual desire, arousal, and responsiveness with tibolone have been attributed to its androgenic effects along with estrogenic effects treating vaginal atrophy symptoms.¹⁷² Tibolone does not increase mammographic density¹⁷³ and has not been associated with increased breast cancer risk in women with no history of breast cancer.¹⁶⁹ Tibolone is not associated with an increased risk of VTE¹⁶⁹ and has a neutral CVD risk profile in women aged less than 60 years at commencement.¹⁷⁴ A small increase in ischemic stroke, but not cardiac events, was seen in a clinical trial of women at high risk of fragility fracture commencing tibolone, aged 60 years and older.¹⁷⁵ This study also demonstrated a 45% reduction in vertebral fracture risk and a 26% reduction in nonvertebral fracture compared with placebo over 3 years at a dose of 1.25 mg/day.¹⁷⁵

Bazedoxifene, is a selective estrogen receptor modulator (SERM), which has been shown to provide adequate endometrial protection when combined with low dose CE therapy.¹⁷⁶ A combined CE-bazedoxifene formulation is available in some countries for the treatment of VMS in non-hysterectomized women.

Women who have had a hysterectomy can commence estrogen-only therapy or tibolone from the onset of their symptoms. Management of the perimenopause is more complicated in other women because the ovaries continue to function during this phase, albeit intermittently. Therefore, consideration needs to be given to menstrual cycle predictability and contraception, as well as symptom relief. Perimenopausal hormonal management options vary globally according to availability and acceptability of therapies. In many countries, women can continue the COC with a risk assessment well into their early fifties, with preference often given to low dose ethinylestradiol COCs, estradiol-containing COCs, and, possibly, the estetrol-containing COC. An LNG-IUD can be used to manage bleeding and contraception with concurrent systemic estrogen for symptoms, and where available, a progestin-only oral contraceptive at a dose that suppresses ovulation can be used in a similar manner. Estrogen-progestogen therapy in the perimenopause should be sequential (progestogen for 12–14 days/month) to induce a monthly bleed. This therapy does not provide contraception. Continuous combined MHT including tibolone can be commenced 12 months after the known, or estimated, FMP.

Following the analysis of the 13-year-follow up of WHI study,¹⁷⁷ it was suggested that MHT was an option for women up to the age of 59 years or within 10 years of menopause and healthy women bothered by moderate to severe menopausal symptoms.¹⁷⁸ This led to the widespread recommendation that the initiation of MHT be limited to women aged less than 60 years or within 10 years of menopause onset.²⁶ This recommendation resulted in confusion. For example, it was problematic for women who experienced menopause in their mid to late fifties and presented with symptoms in their early sixties, still within 10 years of menopause.

In the WHI analyses by age and years after menopause, a greater risk for coronary heart disease was only seen for women more than 20 years post menopause on CE plus MPA; yet, women of this age benefited most in terms of having the greatest risk reduction in hip fracture with MHT.¹⁷⁷ The risk of stroke was

not statistically significantly different from placebo in WHI for women aged 50–59 and 70–79 years at commencement for CE plus MPA and CE alone.¹⁷⁷ For women aged 60–69, there was a greater stroke risk compared with placebo, but this was only seen in the treatment phase and was no longer significant when the risk was examined from randomization through to long-term follow up.¹⁷⁷ After 18 years of follow up, all-cause, CVD, and cancer mortality did not differ between the hormone therapy and placebo arms in both WHI studies.¹⁷⁹ Furthermore, the WHI data pertains specifically to oral estrogen therapy, with or without MPA, in predominantly asymptomatic women.^{163,164} Evidence to justify applying these age and years-since-menopause limits to the initiation of non-oral estrogen therapy for symptomatic women, or for fracture prevention, is lacking. These blanket recommendations urgently need review.

It is recommended that women with POI or early surgical menopause take MHT until the natural age of menopause, at which point, a re-evaluation should determine the risks and benefits of continuing.¹⁸⁰

Immediately following the publication of the first WHI study analyses, recommendations were to use the lowest effective dose of MHT for the shortest duration¹⁸¹ and then to limit MHT use to approximately 5 years.¹⁸² However, these recommendations have been revised in more recent guidelines, which advise that the duration of therapy should be based on each individual's symptoms and personal benefit-risk evaluation.^{25,26,159,160} Extended duration therapy might also be considered when other options are not suitable to prevent bone loss. For women who need to continue or initiate hormone therapy over age 60 or more than 10 years from menopause onset, consideration should be given to transdermal estrogen therapy because of the lower VTE risk. Ongoing therapy requires regular review of each individual's benefits and risks.

SERMs

SERMs are synthetic, non-steroidal hormones with variable or mixed ER agonist or antagonist properties depending on the specific target tissues.^{183,184} Hence, the distinctive effects of different SERMs on bone, breast, lipids, endometrium, vagina, and brain allow targeted use for menopause management. SERMs with more favorable ER activity include raloxifene, bazedoxifene alone and paired with CEs, and ospemifene.

Raloxifene, a second-generation benzothiophene, has partial ER agonist activity in bone, ER antagonist activity in breast and endometrium, with neutral effects in the vagina. Raloxifene reduces bone resorption and turnover, increases vertebral and hip BMD, and significantly decreases the risk of vertebral, but not non-vertebral, fractures.¹⁸⁵ It has been shown to reduce estrogen-sensitive breast cancers by 72% after 4 years, and by 76% after 8 years.¹⁸⁶ In another study, invasive, but not pre-invasive breast cancers, were reduced.¹⁸⁷ Approved to prevent and treat osteoporosis and, in the US, to prevent breast cancer, raloxifene is primarily used to treat postmenopausal women at increased risk of estrogen-sensitive breast cancer with bone loss. Side effects include VMS, leg cramps, and VTE, limiting use in symptomatic perimenopausal and postmenopausal women. Although overall stroke incidence was not increased by raloxifene, more fatal strokes occurred in women at high risk of CVD.¹⁸⁸

Bazedoxifene, an indole-based, third-generation SERM, has ER agonist effects in bone.¹⁸³ Bazedoxifene is associated with reduced vertebral but not nonvertebral fractures and improved BMD in postmenopausal women with osteoporosis.^{176,189} Potential side effects include VMS and VTE. ER antagonist effects in breast tissue and the endometrium allow pairing with CE as combined MHT to relieve VMS and protect against bone loss without a progestogen, with no increase in bleeding or breast tenderness, compared with placebo.¹⁸³

Ospemifene has ER agonist effects in vaginal tissues with slight estrogenic endometrial effects.¹⁹⁰ Initially developed for osteoporosis, improvements in vaginal maturation index and sexual well-being were found with relief of vulvovaginal dryness and dyspareunia.¹⁹¹

Postmenopausal androgen therapy

Androgens are 19-carbon steroid hormones traditionally associated with the induction of male secondary sexual characteristics. The precursors for production of testosterone, which is considered the primary human androgen, are androstenedione and dehydroepiandrosterone (DHEA)—these are classified as pre-androgens. After menopause, testosterone is mainly produced in non-ovarian tissues from these pre-androgens.¹⁹² In addition to having direct androgenic effects, testosterone acts indirectly through aromatization to estradiol.

Research into testosterone in women has been compromised by insensitivity and imprecision of conventional immunoassays to measure testosterone at the low concentrations that occur in women. Despite increased availability of liquid/gas chromatography with tandem mass spectrometry (LC/GCMS), which more precisely measures testosterone, caution is warranted when making assumptions regarding blood testosterone concentrations and clinical outcomes. This is because testosterone is partly synthesized in target tissues from pre-androgens,¹⁹² and tissue response is modulated by AR density, coactivators and corepressors, and the influence of other sex steroids.¹⁹³ Therefore, testosterone blood levels may not equate to tissue levels or target tissue response.

Available data indicate that testosterone is anabolic in musculoskeletal tissues, acting through both ERs and ARs.¹⁹⁴ But musculoskeletal outcomes from clinical trials of testosterone are inconclusive due to their small size, short duration, and heterogeneous outcome measures.¹⁹⁵ Similar limitations apply to studies of testosterone and cognitive function.¹⁹⁵ Thus, although there is evidence for neuroprotective and anti-inflammatory effects of testosterone in the brain,¹⁹⁶ whether there are any benefits of testosterone on cognition is not known. Published clinical trials have not shown that testosterone therapy improves mood or well-being¹⁹⁵ or improves major clinical depression.¹⁹⁷ With respect to cardiovascular function, available data do not support adverse effects of endogenous testosterone on lipids, vascular function, or CVD risk in postmenopausal women.¹⁹⁵ No increased risk of breast cancer has been seen in clinical trials of up to 2 years duration that have used postmenopausal transdermal testosterone therapy in doses that result in blood concentrations similar to those of premenopausal women.¹⁹⁵ Studies of longer duration are needed.

The only evidence-based, and agreed upon, indication for judicious testosterone supplementation is for postmenopausal women assessed as having low sexual desire with associated personal distress, also known as hypoactive sexual desire dysfunction (HSDD).¹⁹⁸ An international task force concluded that there is insufficient evidence to support the use of testosterone therapy for any other symptoms, clinical condition, or disease prevention, or for use in premenopausal women with HSDD.¹⁹⁸ The task force recommended that when a regulator-approved female-specific testosterone formulation is unavailable, a fractionated dose of an approved male formulation can be used to treat women with HSDD.¹⁹⁸ There was a strong recommendation against the use of individually compounded testosterone therapy due to concerns of safety and efficacy.¹⁹⁸

Although an important precursor for postmenopausal testosterone production, DHEA given systemically has not been shown to improve sexual function or mood, or alleviate VMS, in postmenopausal women in randomized, placebo-controlled, clinical trials.^{199,200}

OVARIAN TISSUE PRESERVATION AND TRANSPLANTATION

Fertility preservation has made significant steps forward in the recent past, allowing women in need of gonadotoxic treatments to retain the chance of future pregnancies.²⁰¹ Cryopreservation of ovarian tissue for future reimplantation is a technique that is used when a rapid collection of gonadal tissue is warranted to allow a quick initiation of cancer treatment or when oocyte retrieval is impossible or contraindicated.²⁰² With this approach, the cryopreserved ovarian tissue can be laparoscopically reimplanted into the ovaries once clinical conditions allow. Resumption of estrogen and progesterone synthesis, along with ovulation and menstrual cycles, have been observed following this technique.²⁰³ Hence, a new chance for pregnancy is offered to the recipients.

More recently, ovarian tissue cryopreservation for later transplantation has been proposed for other clinical applications, including delaying menopause in women with a family history of POI or even for spontaneous menopause happening at a normal age range, so as to obtain a more “natural” hormonal treatment as opposed to standard menopause hormone therapy.²⁰⁴ These applications have stimulated a yet unsettled debate on the ethical implications and balance between benefits and risks (and costs) of these complex procedures.²⁰⁵

More recently, research on the ovarian microenvironment has pinpointed the relevance of growth and differentiating factors and of gonadal stem cells as important modulators of follicular development and ovulatory function.²⁰⁶ Based on these observations, strategies aimed at “rejuvenating” the ovaries have been attempted, either by injecting platelet-rich plasma, a preparation enriched in growth factors, into the ovaries, or alternatively stem cells derived from different sources, such as autologous fat tissue, bone marrow, or even menstrual blood.^{207,208} All these approaches are at best experimental and have relevance mostly for fertility applications. The potential role of these strategies for the hormonal management of premature or physiological menopause is uncertain and contentious.

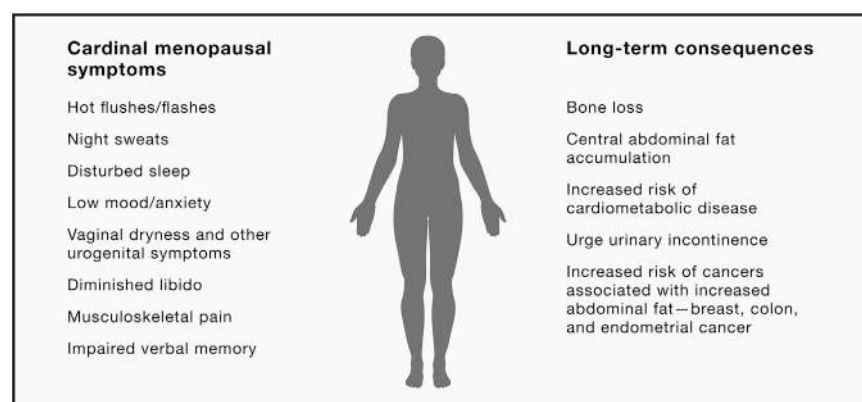


Figure 3. Cardinal symptoms and consequences of menopause

Treatment needs to be daily, with a vaginal insert containing 6.5 mg of DHEA to improve signs and symptoms of VVA in women with dyspareunia.²¹¹ Effects are superior to placebo and comparable to vaginal estrogens, although head-to-head studies are lacking.²¹¹ When application is reduced to twice a week, as recommended for vaginal estrogen therapy, the beneficial effects are lost.²¹⁸ No adverse endometrial effects

SPECIFIC TREATMENT OF UROGENITAL ATROPHY

Urogenital atrophy symptoms adversely affect sexual well-being, relationships, quality of life, self-esteem, and social interaction.^{63,209} Mild VVA symptoms of dryness and dyspareunia may respond to non-hormonal vaginal moisturizers.²¹⁰ Vaginal estrogen alleviates vaginal dryness, vulvar itching, atrophic vaginitis, and dyspareunia, as well as urinary urgency, and prevents recurrent urinary tract infections.⁶⁵ Due to the high affinity of estrogen for ERs, only a low dose is needed for vaginal effects. Estrogen therapies used for VVA include estradiol as a vaginal tablet, cream, soft gel insert, or vaginal ring, estriol as a vaginal cream or pessary, and CE in a vaginal cream. A DHEA vaginal pessary is also available.²¹¹ This is a pro-hormone with local conversion to testosterone, which may then be aromatized to estradiol in vaginal tissues.¹⁹² All of these therapies alleviate symptoms, normalize vaginal pH, and restore vaginal tissue integrity in most women.²¹² Low dose vaginal estrogen has not been found to increase the risk of breast or endometrial cancer, VTE, or CVD.²¹³ However, a systematic review of adverse occurrences with vaginal estrogen highlighted that available data are mostly limited to 52 weeks of therapy or less.²¹⁴

Vaginal estrogen therapies vary in their systemic absorption, depending on potency of the estrogen, frequency, and duration of use, and whether the vagina is atrophic (greater absorption) or estrogenized (little-no absorption).²¹⁵ Systemic absorption is low with vaginal tablets or soft gel inserts containing 10 mcg of estradiol or less and vaginal creams with doses of 0.5 mg of CE and 0.5 mg of estradiol.²¹⁵ Estriol, a short-acting estrogen with short receptor occupancy and the lowest ER affinity of all estrogens, is effective in treating symptomatic VVA²¹⁶ and protects against urinary tract infections.²¹⁷

Concurrent progestogen therapy is not recommended for endometrial protection with low dose vaginal estrogen therapy based on safety data collected in trials of over 1 year. However, longer term safety data are needed regarding long-term endometrial safety.²¹⁴ All postmenopausal spotting or bleeding should be evaluated with transvaginal ultrasound, endometrial sampling, or both.¹⁶⁰

Vaginal DHEA therapy (prasterone) is approved in several countries for the treatment of postmenopausal dyspareunia.²¹¹

or meaningful changes in the serum estradiol or DHEA-derived steroids have been observed in studies for up to 52 weeks.²¹⁹

Ospemifene, a SERM with estrogenic effects in vaginal tissues, is approved in some countries for the treatment of dyspareunia and vaginal dryness.¹⁹¹ Increased endometrial thickness and polyps have been reported after 12 months of treatment but not endometrial cancer or hyperplasia.²²⁰ Reported side effects include VMS, and less often muscle cramps, headache, and vaginal discharge.

Intravaginal testosterone has been explored as a potential treatment of VVA due to the role of androgens in vaginal health.²²¹ Studies suggesting that intravaginal testosterone might restore vaginal integrity are mostly limited by inadequate size, duration, lack of placebo, or inconsistent reporting of systemic hormone concentrations.²²² A small, placebo-controlled study of intravaginal testosterone in women on aromatase inhibitor therapy demonstrated improvement in VVA symptoms.²²³

Energy-based therapies for VVA include fractional CO₂ laser or erbium YAG laser and radiofrequency devices. Although small clinical studies suggest benefit and safety,²²⁴ data from two recent randomized controlled trials (RCTs), one for postmenopausal women with VVA²²⁵ and one of breast cancer survivors on aromatase inhibitors,²²⁶ reported no benefit over sham therapy.

For women with estrogen-sensitive cancers, lubricants and vaginal moisturizers are recommended as first line therapy. Tamoxifen, as a partial ER agonist, results in a lower likelihood of vaginal dryness than aromatase inhibitors.²²⁷ Although the safety of intravaginal estrogen, prasterone, and oral ospemifene in breast cancer survivors has not been established, treatment may be considered for women with severe symptoms by shared decision-making with open discussion of the benefits and risks and inclusion of a breast cancer specialist.²²⁸

KNOWLEDGE GAPS AND RESEARCH DIRECTIONS

Despite decades of research pertaining to menopause, more work is needed to document the contemporary age of menopause onset, the age of early menopause and POI, and symptom prevalence and health impacts outside high-income countries. Similarly, robust observational studies are needed to better understand the impact of menopause on employment engagement

in workplaces, working from home, and on care-providers and volunteers.

Although an array of MHT formulations is available to alleviate symptoms, information about the long-term efficacy and safety of MHT is limited to the preparations used in the WHI studies conducted in the US. There is an urgent need for longer term studies to establish the efficacy of non-oral estradiol on cardiometabolic and cognitive outcomes, and dose optimization of oral progesterone and other progestogens for endometrial protection. Equally needed are studies of the safety of these preparations with respect to breast cancer, VTE, and CVD risk. These studies need to be multi-national to ensure that the findings have global applicability. Meanwhile, the dogma around limiting the initiation of MHT by age, or years since menopause onset, should be relaxed because available data suggest that non-oral estrogen therapy may not confer the risks of oral CE that led to the introductions of these constraints. Guidance regarding when to initiate MHT must be evidence based, formulation specific, and unambiguous. Therapy should be individualized depending on age and health risks to provide the most appropriate therapy, formulation, and duration of use, recognizing that health risks may increase with age. When uncertainty exists as to risks, the role of compassionate use of hormone therapy, despite potential risks, needs to be considered.

Studies to optimize perimenopausal well-being are challenging because this life stage is difficult to define for research purposes. Hence, most MHT regimens are not regulator approved for use in perimenopausal women. Nonetheless, studies of perimenopausal women are needed to determine the efficacy and safety of treatment options in this population.

There are sufficient data to justify a trial of testosterone therapy for postmenopausal women with HSDD. Adequately powered RCTs are also warranted to determine the efficacy of testosterone therapy for premenopausal women with HSDD and whether postmenopausal testosterone offers any benefit for musculoskeletal health or cognitive function. Until better data are available, the therapeutic use of testosterone should be limited to postmenopausal women with HSDD.

Ideally, future studies in this field will use a standardized set of symptom measures or Core Outcome Sets identified for VMS and urogenital symptoms to best reflect the joint priorities of menopausal women, clinicians, and researchers. This will ensure reporting of standardized outcomes that will enable findings from different studies to be compared and combined.^{229,230}

Conclusions

Optimizing health at menopause is the gateway to healthy aging for women. Although not all women will experience bothersome menopause-related symptoms, the silent effects of the menopause transition may be substantial, such as bone loss increasing future fragility fracture risk and adverse effects on blood lipids and cardiometabolic disease risk. Therefore, all women should have access to a general health assessment at the time of menopause transition to maximize their physical well-being, including their cardiometabolic and musculoskeletal health, and their psychological and sexual well-being. Women with bothersome menopausal symptoms should be counseled on treatment op-

tions and offered evidence-based therapies, such as MHT. This requires knowledgeable healthcare providers who are equipped with the skills to provide evidence-based care. Further research, including studies of perimenopausal women, is needed to close knowledge gaps and achieve better care (Figure 3).

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DECLARATION OF INTERESTS

S.R.D. reports honoraria from Besins Healthcare, Mayne Pharma, Health Ed, BioSynt, Lawley Pharmaceuticals, and Que Oncology. She has served on advisory boards for Mayne Pharma, Astellas Pharmaceuticals, Theramex, and Gedeon Richter and has been an institutional investigator for Que Oncology and Ovoca Bio.

J.P. is PI for a Multicentre Trial sponsored by Bayer, Fees to UVa, serves on the editorial board for OBG Management, and is an author for Up To Date and Merck.

N.S. is a study investigator and member of the scientific advisory board and consultant for Astellas; is a member of the scientific advisory board for Amazon (Project Ember), MenoGenix Inc., and Que Oncology; and is a consultant for Ansh Labs. She has served as the president of the Society for Reproductive Investigation in the past.

T.S. has received consulting fees from Abbott, Astellas, Gedeon Richter, Mitsubishi Tanabe, Sojournix, Estetra, Mithra, Actavis, Medtronic, Shionogi, and Applied Medical and speaker's honoraria from Abbott, Shionogi, Gedeon Richter, Intuitive Surgical, Applied Medical, Theramex.

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