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Menopause and MHT in 2024: addressing the key controversies – an International Menopause Society White Paper

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ABSTRACT

The vision of the International Menopause Society (IMS) is that all women across the world will have easy and equitable access to evidence-based knowledge and health care, empowering them to make fully informed midlife health choices. The aim of this White Paper is to provide a well-balanced educational narrative of the menopause and menopause hormone therapy (MHT) from IMS experts, leading into World Menopause Day 2024. This is achieved by exploring the anthropology and history of menopause, the principles and controversies of prescribing MHT, and by placing this into regulatory and menopause society contexts. The White Paper also lays the groundwork for the forthcoming updated IMS recommendations on menopause and will act as a blueprint for the future ethical management of menopause from practical and aspirational perspectives. An important section of the paper is 'The 5Ws of prescribing MHT': WHO is MHT for; WHAT types and doses of MHT; WHEN should MHT be started and stopped; WHY is MHT important; WHERE can MHT be accessed? A key points summary of this information is provided for healthcare professionals and the public. The summary provides 'easy to access' advice regarding several recent controversial MHT prescribing issues in the healthcare and media spotlights.

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Introduction

The aim of this 2024 White Paper is to provide an International Menopause Society (IMS) position statement about menopause and menopause hormone therapy (MHT), and in particular to address some of the key controversies. The paper's purpose is to act as a blueprint upon which to base the future ethical management of menopause from both practical and aspirational perspectives.

The mission of the IMS is to work globally to promote and support access to best-practice health care for women through their menopause transition and post-reproductive years, enabling them to achieve this with optimal health and well-being. Through effective communication and evidence-based education about menopause, women can be empowered to make informed personalized choices aligned with their individual goals.

After many years of neglect, we have finally seen long overdue unprecedented attention given to menopause in the popular media, empowering women to seek care for menopause symptoms. Yet the media and even academic literature present polarized views on its management. These contrasting views often leave women feeling confused and disempowered rather than supported through their menopause transition and susceptible to unproven marketed products.

Very few therapeutic medical interventions have generated as much controversy, and very few have waxed and waned in popularity as much as MHT. Opinions about MHT appear to be driven as much by the sociocultural climate as they are by the emerging evidence from clinical trials. These sociocultural factors include demographics, education, religion, beliefs, values, social classes, sexuality and attitudes.

The search for a well-balanced narrative of the menopause momentum continues [1]. This paper serves to lay the groundwork for this well-balanced narrative by defining the history and current context of menopause and MHT.

This aim of this White Paper is not to provide a comprehensive toolkit of therapeutic options and evidence for efficacy and safety; this is well covered by recommendations, guidelines and consensus statements. The paper is primarily intended to explore the following:

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Laying the groundwork for a well-balanced narrative of the menopause momentum by exploring its history, principles of prescribing and professional/societal/regulatory contexts
This article has been republished with minor changes. These changes do not impact the academic content of the article.

- key anthropological, evolutionary, historical, sociodemographic and cultural issues which have influenced the perception of whether menopause is a natural life stage or a modern disease;
- the expectation that menopause should be treated and how it should be treated;
- expectations as to how effective and safe this treatment should be;
- factors that have led to disappointment amongst women and confusion amongst healthcare professionals (HCPs);
- what can be done going forward to avoid polarization of views to achieve a well-balanced narrative on MHT that is empowering to both HCPs and women in midlife and menopause.

Anthropological and evolutionary perspectives on menopause

Menopause and MHT continue to be topics of considerable controversy and debate to the detriment of many women and society as a whole. The perspectives and attitudes toward menopause driving this controversy can be understood from anthropological, evolutionary, historical and modern medicine perspectives.

The stages of the menopause have been well defined by the Stages of Reproductive Aging Workshop (STRAW)+10 group [2], primarily being classified according to menstrual regularity, with hormonal markers of secondary importance. Although the mean age of natural menopause is often quoted in some regions such as Europe at 51 years, meta-analyses of global data indicate that the mean age at natural menopause is actually 48.8 years [3]. Studies such as the US Study of Women's Health Across the Nation (SWAN) [4] and from other regions, for example sub-Saharan Africa [5], show that this age varies according to many socioeconomic and other factors such as HIV and can also occur early and prematurely in a significant proportion of the population [3–5].

Distressing symptoms typically start in the perimenopause, and often even before women enter the perimenopause as defined by the STRAW+10 criteria. Yet government-regulated therapies are approved for postmenopausal women, with no specific approved therapies for perimenopausal women. Menopause healthcare systems and treatments that are more 'symptom-focused' rather than 'stage-focused' can better meet women's needs [6].

Better still, a 'life course approach' can identify individuals at risk of early menopause and premature ovarian insufficiency, which are associated with osteoporosis, cardiovascular disease and cognitive problems. For instance, smoking in childhood and early adulthood is correlated with early menopause, while regular exercise and minimal alcohol consumption correlate with reduced risk of early menopause [7].

In many women 50% of life is now spent in a postmenopausal state, and given that we generally have an aging population globally it is expected that by 2025 more than one billion women globally will be in a perimenopausal or postmenopausal age group.

It is therefore imperative that health strategies are put into place to optimize the health and quality of life of women at this stage of life. Menopause is a key factor contributing to non-communicable diseases in women, including cardiovascular, bone and cognitive health. It is therefore necessary that the menopause is taken into account in this United Nations Decade of Healthy Aging [8, 9].

Is menopause entirely unique to the human species?

Three characteristics make 'natural' menopause unique to the human female. Menopause occurs universally among individuals living into later years, occurs halfway through the maximum lifespan of our species and is quite age specific, albeit that there is some variation across populations and geographical regions, with the mean age of natural menopause ranging from 46 to 52 years [3].

Reproductive senescence (biological aging) is not unique to humans in the animal kingdom. Some rhesus and macaque monkeys stop menstruating 1–2 years before their maximum lifespan, and there are sporadic cases of menopause described in some apes late in their lifespan such as the pygmy chimpanzee (Pan Troglodytes), the bonobo (Pan Paniscus) and also in some whale species [10, 11]. The key difference is in the timing, with reproductive senescence occurring at the end of the maximum lifespan in chimpanzees and whales compared to the middle of the lifespan in humans.

One of the key questions is whether menopause has a purpose in humans (*Homo sapiens*). There are a number of hypotheses to explain human menopause [12, 13], and the following are among the most widely recognized:

- Grandmother hypothesis: evolution of a lengthy postreproductive period with a focus on grandmothers nurturing their daughters' offspring rather than producing further offspring of their own. This allows their daughters to have more children, and grandmothers therefore pass on their longevity genes to more descendants, who have longer adult lifespans as a result of their genetic advantage. This hypothesis explains the adaptive value of menopause but does not explain the origins of the trait [14].
- Pleiotropy (from Greek *pleio* ['many'] and *tropic* ['affecting']) (natural selection) hypothesis: features with a high adaptive value early in the life course are naturally selected, such as egg production and storage. This may be the best design to optimize the quality of reproduction, and an approximate 50-year limit is inherent in all mammalian reproduction [15].
- Epiphenomenon (non-selectionist) hypothesis: menopause may merely be a by-product of our increasing maximum lifespan over the last few centuries, especially through the reduced incidence of infectious diseases [16].

Historical perspectives on menopause and its treatment

The cessation of menstruation and women's ability to conceive was described as far back as the fifth century BC by Hippocrates, but no particular treatment of menopause was proposed.

The ancient Chinese Medical text *Huangdi Neijing* (黄帝内经, 475–221 BC), also known as Yellow Emperor's Inner Canon, describes 7-year life cycles for women. The fifth cycle which is at age 35 years is where skin complexion declines and frequent miscarriages are experienced, and the seventh cycle which is at age 49 years is where there is cessation of menses leading to inability to bear children and hence the menopausal stage. In the first century AC under the Roman Empire, the narration of Pliny the Elder in his *Natural History* fostered the idea that menstruation was attached to some specific properties significantly contributing to the menstrual taboo [17].

In the Middle Ages it was thought that the disorderly uterus rose or descended and committed actions difficult to endure, leading to faintness of the heart, tightness of the chest, breathlessness, hiccups and troublesome accidents [18].

Menopause became a medical entity in the early nineteenth century and was increasingly linked to pathology and disease. The boundaries were blurred between menopause and the effects of aging, and physicians identified a series of unpleasant, even fatal complaints, associated with the 'condition'. Menopause was associated with various diseases that warranted treatment according to the male physicians of the time using various strategies including medicines, bloodletting with leeches and surgery.

After diagnosis of menopause, Dr Edward John Tilt, a Victorian physician, recommended carbonated soda, opium and a large belladonna plaster placed at the pit of the stomach, and vaginal injections with a solution of acetate of lead followed by prescriptions of hydrochlorate of morphine, chloric ether and distilled water [19].

It was not until 1923 that the scientists Edgar Allen and Edward A. Doisy first isolated estrogenic steroids [20], and in 1942 Premarin (pregnant mare's urine) was first patented. In 1966 in his book *Feminine Forever*, Robert Wilson recommended estrogen as a 'cure' for the 'tragedy of the menopause'.

In 1968, one of the most eminent obstetricians and gynecologists of her time, Dame Josephine Barnes touched on hormonal changes during the menopause transition in *Women's Hour*, a popular radio program in the UK. It was deemed by some as 'acutely embarrassing' to hear about hot flushes at 2 o'clock in the afternoon! However, by 1970 feminists began to challenge the orthodox medical model of menopause and viewed it as a positive transformation.

Its medicalization was perceived as a conspiracy by the gerontocracy 'to produce a submissive female patient who could be treated with drugs'. In her book *The Change*, Germaine Greer stated that 'menopause is a time for mourning. The menopausal woman should be allowed her quiet time and her melancholy' [21].

In her publication *Hot Flushes, Cold Science* in 2010, Louise Foxcroft stated that current attitudes to menopause have been reached through the filter of thousands of years of rampant chauvinism, collusion, trial, error and secrecy [22].

The controversy and polarization of views about management of the menopause and MHT deepened even further following publication of major MHT trials at the turn of the new millennium.

Impact of the major MHT studies

The initial reports from the Women's Health Initiative (WHI) study in the USA in 2002 [23] and The Million Women Study (MWS) in the UK in 2003 [24] resulted in a significant decline in the use of MHT (by 80%) due to concerns about the reported risks of cardiovascular events and breast cancer.

The reporting of these two studies came as a shock to conventional wisdom. Prior to this, MHT was viewed extremely positively because of the favorable findings of observational studies, which led to women being regularly counseled about use of MHT for preventive reasons, as well as for symptom relief [25].

Although the absolute risks of MHT on health outcomes in the WHI were rare to very rare by common standards, the data were alarmingly presented as percentage changes rather than absolute numbers by the media, and the risks were said to apply across all age groups. The fall in prescribing, especially in primary care, resulted in many women 'suffering in silence' and seeking other solutions for their symptoms.

Numerous subsequent WHI publications following the initial report demonstrated that the problems were mainly in the older age groups [26], and probably due to the particular types and doses of hormone therapy used in the WHI. Yet many women and their prescribers were still too anxious to return to use of MHT.

Further randomized clinical trials such as the Kronos Early Estrogen Prevention Study (KEEPS) [27], the Early versus Late Intervention Trial with Estradiol (ELITE) [28] and the Danish Osteoporosis Prevention Study (DOPS) [29], focusing on the use of MHT in women at the usual age of menopause transition with more modern types of MHT, showed that there were few risks in this age group. Unfortunately, these studies were not of the scale of the WHI, and therefore could not definitively assess the impact on major outcome measures such as cardiovascular events, fractures and dementia.

Other MHT studies showed findings contradicting the WHI but were not included in influential guidelines. For example, major observational studies such as the French E3N Cohort Study [30] demonstrated lower breast cancer risks with conventional body-identical MHT [31], but these data were excluded from the latest analysis by the Collaborative Group on Hormonal Factors in Breast Cancer [32]. Instead, the Collaborative Group emphasized breast cancer risks over the benefits of MHT, and excluded the majority of the data from MHT studies containing micronized progesterone rather than progestins.

Some recent guidelines present perspectives that contrast, particularly on the issue of primary prevention, with findings of the gold-standard Cochrane meta-analyses. For example, a Cochrane review showed that those who started MHT less than 10 years after the menopause had lower mortality (relative risk 0.70, 95% confidence interval [CI] 0.52–0.95; moderate quality evidence) and coronary heart disease (composite of death from cardiovascular causes and non-fatal myocardial infarction) (relative risk 0.52, 95% CI 0.29–0.96; moderate quality evidence), although they were still at increased risk of venous thromboembolism (VTE) (relative risk 1.74, 95% CI

1.11–2.73; high quality evidence) compared to placebo or no treatment [33].

Given the ongoing controversy, there is clearly a need for a definitive long-term randomized clinical trial where conventionally regulated bioidentical/biosimilar MHT is started in women at the usual age of menopause and followed for long enough and in sufficient numbers to assess major outcome measures such as cardiovascular and breast cancer events. Unfortunately, the costs of such a trial would be prohibitive, making unbiased recommendations based on the current literature all the more critical. Continued collection of high-quality, prospective observational registry data may be the best compromise solution.

Menopause specialists should now strive to achieve a coordinated approach to the gathering and amalgamation of data. Societies such as the IMS could coordinate this data 'trawl'. This important venture could be funded by the IMS Endowment for Education and Research (EER) and the IMS could act as a global repository for this information. This would also facilitate the dissemination of information to HCPs and the public that could be used to influence clinical practice in a positive way. In the meantime, comprehensive systematic reviews and meta-analyses will be performed in connection with the update of the 2016 IMS recommendations on MHT [34].

Rationale for menopause management

It is well recognized that although part of a natural life-course progression, menopause can be associated with distressing symptoms which impact on personal, social and professional quality of life. Although the classic symptoms of menopause are vasomotor symptoms (VMS) such as hot flushes and night sweats, and genitourinary symptoms (vulval, vaginal and urinary), there are numerous other symptoms which can occur at this time of the life course. These may be caused or exacerbated by the loss of estrogen but may also depend on other associated factors, for example genetic/epigenetic, just as genetic variation at the $TACR_3$ locus is associated with VMS [35]. For Asian women, physical symptoms such as body aches and joint pains as well as psychological symptoms are recognized to be more prevalent than VMS [36]. A recent systematic review and meta analysis of prevalence data globally found that joint and muscular discomfort were the most prevalent menopause related symptoms at 65.43% (95% CI 62.51–68.29) [37].

There has been considerable controversy regarding what constitutes a genuine menopause symptom, which has resulted in inconsistency as to what outcomes and best measurements should be assessed in clinical trials. This has led to the recent development of a Core Outcome Set for vasomotor and genitourinary symptoms associated with menopause in the COMMA global initiative [38, 39].

There is also now good evidence that women predisposed to severe VMS also have a higher incidence of cardiovascular disease [40]. Although it is yet unknown whether this association is causal, it is important that VMS and heart health are assessed in a 'menopause check', which is an opportunity for screening, and can be routinely conducted using standardized protocols and algorithms in primary care such as those proposed in an IMS toolkit [41].

The variety of menopause-related symptoms can impact significantly on individuals' physical, mental and cognitive health as well as their personal and professional relationships. More recently, there has been growing recognition that these symptoms can have a profound impact on performance in the workplace, leading to reduced individual and corporate productivity, loss of efficiency and even loss of employment [42].

A proportion of women will go through menopause with few or no symptoms and as such will not require treatment from this perspective. However, the widespread dissemination of misinformation and disinformation may encourage some of these women to request MHT from their HCPs purely to maintain skin, nail and hair quality and/or for potential primary prevention benefits such as cardiovascular and brain health, for which there is not currently an indication. This has been one of the key issues which has caused recent controversy given that MHT is not currently recommended solely for primary prevention, although in a number of countries there is also a license for prevention of osteoporosis.

Use of MHT should not be considered an anti-aging strategy. This highlights the need for women to receive trusted information about why, and for what purpose, MHT can or cannot be provided.

Holistic management adopting a biopsychosocial approach during this key milestone in a women's life allows optimization of health for a better quality of life. This approach includes primary prevention of chronic disease through healthy eating, active lifestyle and preventive immunization (e.g. pneumococcal, shingles), timely and appropriate screening for chronic disease and cancers, avoiding harmful substances such as cigarette smoking, avoiding excessive alcohol, staying social engaged and focusing on mental wellness.

This may be all that is required, or all that is available in some countries and regions, to achieve healthy aging, and women making this choice should not feel under pressure to medicalize their menopause, as described in a recent review of menopause management [43]. However, it is equally important that the distressing symptoms and potential sequalae of menopause are also not trivialized [1].

Menopause can also be effectively managed with evidence-based cognitive behavioral therapies, hypnotherapy and non-hormonal pharmacological medicines, all of which women should be made aware of. These options should be made more readily accessible given the growing evidence for benefit, particularly for those who cannot, or choose not to, use MHT [41, 43–45].

Numerous complementary therapies are currently accessed by women as first-line treatments for managing menopause before professional help is sought, but often with little evidence for effectiveness and safety. Whilst these preparations are unlikely to cause harm, they can occasionally be associated with significant adverse effects and often lack efficacy. Ongoing research on complementary therapies is warranted given that there are some favorable data from small clinical trials, but proper regulation of the sale of these products is vital to ensure ethical, safe and cost-effective management of menopause [44, 45].

The 5Ws of prescribing MHT

The aim of this section of the White Paper is to interrogate some of the key controversial issues which have arisen over the last few years and have led to much confusion amongst HCPs and women seeking treatment for menopause-related problems. The aim is not to replicate recent practical prescribing guidance of MHT which can already be found in various toolkits and position statements [34, 41, 46], and which will also be available in updated guidelines from the IMS, and in a subsequent planned update of the global consensus of societies [47].

Who is MHT for?

MHT is conventionally indicated for women with natural and surgical menopause who are experiencing distressing vasomotor and/or vulvovaginal symptoms.

Should women without symptoms be prescribed MHT?

There has been considerable controversy as to whether women who are asymptomatic should be prescribed MHT. Although MHT is primarily indicated for the relief of distressing menopause symptoms, it is often incorrectly promoted to women as an 'elixir of youth'.

There is good evidence that MHT reduces the incidence of osteoporosis and risk of osteoporosis-related fractures, and in some countries – for example, in the USA and Australia – this is also a primary indication for MHT.

There are also good data supporting its use for reducing the risk of cardiovascular disease, thereby having a positive impact on life expectancy, but MHT is not currently licensed anywhere globally for these indications.

There are many other women who might benefit from MHT for whom it is not indicated according to the label. For example, women with premature ovarian insufficiency and early menopause who may require MHT for symptomatic relief, but should also receive it for primary prevention purposes.

However, the research findings regarding the impact of MHT on cognition and dementia are considerably less reliable and require further research.

These issues have all been comprehensively reviewed in the last four World Menopause Day IMS White Papers on premature ovarian insufficiency [48], bone health [49], cognitive health [50] and cardiovascular health [51].

Should medically high-risk women be prescribed MHT?

As always in such situations, the benefits of treating bothersome symptoms on a woman's quality of life must be weighed against the potential risks associated with MHT. The definition of 'acceptable risk' can vary considerably among HCPs and patients.

For example, MHT is conventionally contraindicated in women with hormone receptor-positive breast cancer and endometrial cancer. However, depending on the degree of impact on quality of life, and the efficacy and tolerability of non-hormonal alternatives, some women may be willing to accept the risk of using, or going back to using, MHT, particularly in those treated for early-stage cancer [52].

In women with a past history of VTE, MHT may be considered if it had been provoked by certain circumstances, for example major surgery or prolonged immobility, and use of a concomitant anticoagulant for VTE prophylaxis could be considered.

There are ongoing projects to develop medical eligibility criteria for MHT, as per the World Health Organization (WHO) guidance on contraception, to provide specific graded guidance for a variety of different clinical case scenarios. These medical eligibility criteria guidelines are likely to be helpful in the future but are still in development and require universal consensus and application [53, 54].

What types and doses of MHT?

Factors which determine the type and dose of MHT typically prescribed by HCPs include the following:

- patient preference;
- uterine presence or absence;
- contraceptive needs;
- symptom type and severity;
- comorbidities.

Prescribing algorithms in recently published toolkits [41] very clearly guide HCP prescribing with regards to these factors.

The aim of this section is to critically examine some of the controversies which have arisen recently with regards to the recommended type and dose of MHT.

Is the type of estrogen important?

There are four types of estrogens which occur naturally in human beings; estrone, estradiol, estriol and estetrol. There are some claims, particularly among those promoting compounded bioidentical hormone therapy, that replacement of these estrogens in the correct proportions is important to optimize the efficacy and safety of MHT. This claim has not been proven and remains one of many concerns about the safety and efficacy of compounded bioidentical hormone therapy.

Regulated systemic MHT has conventionally contained conjugated equine estrogens (CEE), estradiol and estradiol valerate. More recently, estetrol has been investigated as a treatment for VMS in clinical trials and is likely to be brought to market, as it has been for contraception. Vaginal MHT typically contains estradiol, estriol or, more recently, dehydroepiandrosterone (prasterone).

A systemic oral selective estrogen receptor modulator (ospemifene) and a CO_2 and erbium laser have also been marketed for symptoms of vulvovaginal atrophy (VVA)/Genitourinary Syndrome of Menopause (GSM) symptoms. Despite encouraging findings from observational and uncontrolled studies, controlled randomized clinical trials of laser therapy for VVA/GSM have not yet confirmed the benefits compared to sham laser.

There are very few head-to-head studies evaluating whether one type of commonly used systemic or local

estrogen in MHT, such as Conjugated Equine Estrogens (CEE) versus estradiol, is superior to another in alleviating menopause symptoms. Estrone and estriol are biologically weaker estrogens than CEE and estradiol, but these are not typically marketed for systemic MHT.

The recent move toward use of transdermal estradiol (patches/gels/sprays) is supported by evidence from observational and case-controlled studies of reduced risk of VTE [55]. However, there are often considerable variations in serum concentrations of estradiol in women treated with the same transdermal preparation (which may vary by a factor of 10), and large inter-individual differences. A woman's response to the same dose can therefore be difficult to predict.

The efficacy of transdermal MHT is based on sufficient permeability of the steroid through the skin. Diet, alcohol, drug consumption, smoking, physical activity and stress may all cause rapid and transitory changes in peripheral blood flow, absorption and metabolism. There may also be circadian variations in dermal blood flow with higher levels in the evenings enhancing absorption [56].

In view of all these variables, a transdermal preparation may not always be the best option for an individual. If there are no particular risk factors (e.g. obesity, history of VTE) there is little reason why oral estrogen could not be prescribed. Patient-informed choice should always prevail.

Are the types of progestogen important?

There is now considerable evidence that micronized progesterone and biologically similar progestogens (e.g. dydrogesterone) appear to have metabolic and possibly breast advantages over androgenic progestogens [30, 55, 57, 58]. Although this is not yet reflected in regulatory guidance or in prescription leaflets, it can make a considerable difference in the individualization of therapy.

The choice of progestogen can also be particularly important from a psychological standpoint in women with a past history of premenstrual syndrome (PMS)/premenstrual dysphoric disorder (PMDD) who often have progestogen intolerance [59]. In these patients it may also be necessary to reduce the dose and duration of micronized progesterone, for example, 7–10 days per month at 100 mg (rather 200 mg) in sequential MHT regimens. However, for progestogen-intolerant women on these suboptimal doses and regimens, regular monitoring with ultrasonography and/or endometrial biopsy is critical to exclude endometrial hyperplasia or carcinoma [60].

Vaginal administration of micronized progesterone may be even better tolerated by 'progestogen-sensitive' patients but is off-label in most countries for MHT. Other options include the uterine delivery of progestogen (levonorgestrel) from an intrauterine device and the oral tissue-selective estrogen complex (TSEC) (CEE/bazedoxifene), although the latter is only licensed in a few countries currently.

Are the doses of estrogen and progestogen important?

Estrogen. There have recently been an increasing number of concerning case reports of women being prescribed doses of estrogen well outside the licensed dose range. It has not been unusual to see three to four times the maximum recommended dosage of systemic estradiol patches and gels, sometimes used in combinations of routes of delivery.

Whilst there is some evidence that higher doses are required in order to achieve endogenous cycle stabilization and suppression in women with PMS/PMDD and perimenopausal depression [61, 62], or where absorption is poor, it is important to adhere to the principle of prescribing at the minimum fully effective dose where possible. Higher doses of estrogen are also typically required in women with premature ovarian insufficiency (POI) and early menopause in order to achieve full symptom relief and optimal bone mineralization [48].

The doses of estradiol required to achieve adequate conventional vasomotor symptom relief and bone protection are actually quite low (1–2 mg of estradiol orally, 25–50 µg patches or 1–2 pumps of estrogen gel), and whilst there is a dose–response effect for both VMS and bone density, benefits can even be achieved with ultra-low-dose MHT formulations containing 0.5 mg of estradiol orally, or 14 µg transdermally [63–65].

The rationale supporting the principle of using lower doses of MHT to achieve adequate benefits is the lower likelihood of adverse estrogen effects (e.g. breast tenderness, bloating, bleeding problems), including a lower risk of VTE with oral estrogen, and of stroke, even with transdermal estrogen [66]. Whilst the risk of hormone-dependent breast cancer has not been proven to be dose-dependent, excessive use of MHT could potentially increase risk. The absence of evidence is not necessarily evidence of absence.

Supraphysiological levels of estrogen also confer a risk of a sudden decrease in treatment effectiveness 'tachyphylaxis', due to estrogen receptor insensitivity. Whilst not common, this can occur even with high doses of transdermal estrogen [67], as well as with implanted estrogen pellets. This risk can be mitigated by prescribing estrogen at the minimum (fully) effective doses. Estrogen pellets are unlicensed and require better regulation, but with cautious monitoring of estrogen levels can be an option in some countries for the few women whose symptoms do not respond to oral and transdermal preparations.

Progestogen. It is important to reiterate that the dose of progestogen used provides adequate endometrial protection according to standard guidelines [41], unless it is absolutely necessary to reduce the dose in progestogen-intolerant women [68]. This is particularly important with sequential combined MHT regimens where the incidence of hyperplasia tends to be higher with long-term usage, even with standard dose regimens [69]. Typical doses used with standard doses of estrogen in MHT include 200 mg of micronized progesterone/10 mg of dydrogesterone for 12–14 days in a sequential regimen, or 100 mg of progesterone/5 mg dydrogesterone in continuous regimens.

The levonorgestrel intrauterine device is another way of providing effective endometrial protection as well as contraception, although it is not licensed for endometrial protection in all countries. Other possible options for avoiding or minimizing progestogen intolerance include the TSEC containing a combination of CEE/bazedoxifene [70], and the selective tissue estrogenic activity regulator (STEAR) tibolone [71]. Unfortunately, despite the need for more options to personalize MHT, these products are licensed in only a few countries.

Recent findings from the ELITE study indicate that there may be an increased risk of endometrial hyperplasia with sequential vaginal progesterone gel, even with a relatively low dose of estradiol of only 1 mg [72]. Although vaginal progesterone gel is no longer licensed for endometrial protection, if progesterone is administered vaginally, whatever the formulation, similar doses to oral progesterone should be used and monitoring of any unscheduled bleeding should be instituted promptly as previously described.

If the dose of estrogen is increased it is important that the dose of progestogen is also increased proportionately to provide sufficient endometrial protection, although there is little evidence from women using higher doses outside the product license [73]. More research is needed to guide the correct dosing of progesterone when higher doses of estrogen are used, such as in women with POI.

Monitoring of MHT doses

The prescribing principle here is that we should 'first treat the patient, not the result'. As such, if a patient with menopause at the usual age is using MHT purely for symptom relief, and they achieve full relief of their symptoms without any adverse effects, then it is unnecessary to routinely check their hormone levels.

The situations where a hormone profile might be helpful to 'monitor MHT' are as follows:

- inadequate symptom relief after 6–12 weeks of commencing MHT;
- persistent adverse effects after 6–12 weeks of commencing MHT;
- use of MHT in women with POI and early menopause (particularly with one or both of the aforementioned issues, or if there are concerns about inadequate bone mineralization on a dual-energy X-ray absorptiometry scan).

It is important to note that estradiol levels are best interpreted with transdermal preparations as oral estrogen is metabolized partly to estrone. Mass spectrometry is the best method for measuring estradiol levels but may not always be available.

Why are women still turning to compounded bioidentical MHT in some countries?

The alarming manner in which the risks of MHT in the WHI and other studies were publicly reported resulted in women turning to other options to manage their distressing menopause symptoms, even though in the WHI women were on average more than 10 years past the usual age of menopause when they were recruited (average age 63 years) [23].

One of these options was compounded bioidentical hormone therapy, which has been marketed as being substantially different and more natural compared to conventionally regulated MHT and promoted by various media celebrities and functional medicine physicians.

Promotion of these unlicensed preparations often focuses on the notion that they could be precisely personalized in dose and variety through the prior testing of serum and salivary levels of various hormones. That notion is not supported by empirical research which shows that a woman's ovarian hormone levels, particularly in the perimenopause, can vary substantively across a menstrual cycle [74]. In addition to this, the accuracy and reliability of salivary testing of sex steroids has not been established.

Despite recently improved confidence in conventionally regulated hormone therapy, prescription of compounded varieties continues in a number of countries, especially the USA, the UK, South Africa and Australia.

The revised global consensus statement on MHT states that 'the use of custom-compounded hormone therapy is not recommended because of lack of regulation, rigorous safety and efficacy testing, batch standardization, and purity measures' [47,p.314].

More recently, the Scientific Statement by the Endocrine Society and the National Academies of Sciences, Engineering and Medicine found that that there was no rationale for routine prescribing of unregulated, untested and potentially harmful custom compounded bioidentical hormone therapies, and cases of endometrial cancer having been reported due to inadequate progestogen [75–77].

It is therefore important that regulators, medical societies and HCPs inform women that the potential benefits of compounded varieties of MHT can be achieved with conventionally regulated varieties of body-identical MHT, which have been rigorously tested for efficacy and safety.

Has the prescribing of testosterone in women become overzealous?

Until relatively recently, testosterone was regarded exclusively as a male hormone, even though it is also produced endogenously in women, and was not recommended for female usage.

In fact, there were no preparations licensed for female usage in menopause until very recently when the Therapeutic Goods Administration in Australia licensed the use of a 1% testosterone cream for women with hypoactive sexual desire disorder (HSDD), distressing low libido.

Most prescribing of testosterone in women globally is still off-label, with titration of male testosterone preparations into female doses, typically 1/10th designed to achieve total testosterone levels within the female physiological range.

There are now good data for the efficacy and safety of treatment of HSDD with testosterone in natural and surgical menopause, both with and without 'standard E + P MHT' from a number of randomized controlled trials and systematic reviews and meta-analyses [78, 79].

Although there is evidence for the safety and efficacy of testosterone used alone in menopause, it is generally recommended that conventional MHT is commenced before testosterone is considered for persistent HSDD symptoms to ensure that women are well estrogenized, especially vaginally, before their libido is enhanced. The global consensus statement on testosterone for women recommends following a biopsychosocial approach in deciding whether prescribing testosterone is indicated [80].

However, there is still a dearth of evidence for the potential benefits of testosterone in women with other menopause-associated problems such as cognition, mood, energy and general quality of life, even though these are also promoted by the media as potential benefits of testosterone [81]. Whilst we await the data from properly designed studies to better evaluate these outcomes, the primary indication for testosterone in women should remain for HSDD, and any other benefits which occur should be regarded as secondary [82].

When should MHT be started and stopped?

Timing of MHT commencement is also a controversial issue in menopause care. MHT has been primarily researched in women who are either postmenopausal (i.e. usually 12 months after the final menstrual period) or, in some studies, in late perimenopause (i.e. after 6 months of amenorrhea with significantly elevated FSH levels).

Should MHT be started before the menopause?

Starting up to 10 years or more before the final menstrual period, perimenopause is a frequently neglected and poorly managed phase of a woman's life course. Perimenopausal women often experience the co-occurrence of various menopause and cycle-related symptoms, which can begin in the mid-30s with the reduction of ovarian reserve. A recent survey showed that women experiencing symptoms 'off-time', that is, perimenopause-related menstrual cycle changes or symptoms in a timeframe before a person expects them, can lead to worse ratings on measures of stress, satisfaction and health [83].

Prescribing MHT in the perimenopause can be difficult because the fluctuations in hormone levels can result in episodes of estrogen deficiency rapidly followed by episodes of estrogen excess. Increases in estradiol and cycle irregularities during the menopause transition may be due to luteal-out-of-phase events which appear to be triggered by prolonged high follicular phase follicle stimulating hormone (FSH) levels with recruitment of multiple follicles simultaneously [84].

MHT remains an option for these women if they are symptomatic, recognizing that MHT is off-label in this phase of life. Considerably more research is needed to determine optimum MHT regimens for perimenopausal women. Sequential therapies are preferred but even these may cause irregular bleeding.

Another option in perimenopausal women who do not have contraindications is the conventional ethinyl estradiol-based combined oral contraceptive, or the newer estradiol or estetrol-based combined oral contraceptives. The levonorgesterel intrauterine device is another very useful option at this time, and can be used in combination with estrogen if MHT is required.

A further option could be to combine a gonadotrophin releasing hormone (GnRH) agonist or antagonist to suppress residual ovarian activity with 'add back' MHT. Such combined products already exist for treating bleeding problems associated with fibroids and endometriosis, although individual components could also be administered [85].

Non-hormonal alternatives, for example neurokinin (NK) receptor antagonists, could in theory be considered but these have yet to be researched in perimenopausal women and would not address menstrual cycle irregularities or the need for contraception.

Should MHT be initiated in older women well past the menopause transition?

Most society recommendations advise caution when it comes to prescribing MHT de novo in women 60 years of age or older [34, 46]. This advice has arisen from studies such as the WHI where women initiating MHT in their 60s and, particularly, their 70s were found to have a higher incidence of cardiovascular and venous thromboembolic events, stroke and breast cancer compared to women in their 50s [23].

Most women in this older age group have few or no VMS and any VVA/GSM symptoms can be effectively treated with vaginal estrogen therapies. At the same time, is important to recognize that up to 30–40% of women in their 60s and 10–15% in their 70s report bothersome VMS [86, 87]. New-onset VMS in these age groups should be investigated according to clinical presentation, to exclude etiologies such as hyperthyroidism and phaeochromocytoma.

Some women unconventionally seek treatment for osteoporosis with MHT in the over 60s age category because they wish to avoid non-hormonal bone-sparing preparations due to their adverse effects; in making an informed decision, the benefit–risk balance of all preparations should be carefully weighed [49].

Problems particularly arise when women who may or may not be symptomatic ask their HCPs to commence MHT because they feel they missed the opportunity to use MHT in their 50s, because of the concerns raised by the WHI/MWS studies or because they had their MHT discontinued 'prematurely' by their HCPs.

Such women should be counseled that commencing MHT de novo is not conventionally recommended. However, if MHT is to be initiated, it is important that very low doses are prescribed, ideally with transdermal estrogen, in order to avoid adverse effects; for example, 25 µg estradiol patches, 1 pump of estradiol gel or 1 estradiol spray transdermally, with micronized progesterone 100 mg or dydrogesterone 5 mg for endometrial protection.

When should MHT be stopped?

Most regulatory authorities such as the Medicines and Healthcare products Regulatory Agency (MHRA), European Medicines Agency (EMA) or US Food and Drug Administration (FDA) still advise that MHT should be used at the lowest dose for the shortest duration needed to relieve symptoms, because MHT may increase the risk of some cancers, VTE and stroke, and because the risks increase the longer MHT is used.

However, there is now universal agreement amongst national and international menopause societies that arbitrary limits should not be placed on the duration of use of MHT [34, 46, 47].

The IMS governing principles on MHT state 'There are no reasons to place mandatory limitations on the duration of MHT'. 'Whether or not to continue therapy should be decided at the discretion of the well-informed woman and her HCP, dependent upon the specific goals and an objective estimation of ongoing individual benefits and risks' [34,p.111].

Thus, the modern management of menopause should include personalization regarding the duration of MHT usage.

Why is MHT important?

Are we overmedicalizing the menopause?

Menopause per se does not require treatment but the distressing symptoms and conditions that can be associated with it do warrant treatment. The current indication for use of MHT is treatment of VMS and VVA/GSM. It is estimated that 80% of women experience VMS, 25% of women will suffer with severe VMS and the median duration of symptoms is 8–10 years (meaning half of women will experience those symptoms for longer than 8–10 years) [88]. MHT also has a second-line indication for treatment of osteoporosis in some countries, and by the age of 80 years up to 50% of women will have osteoporosis if left untreated.

It is important to counsel women from the outset that menopause symptoms such as VMS and sleep disturbances [89], mood swings and brain fog will usually improve with time and may not require treatment [50]. The difficulty is knowing when these symptoms will improve, and it is important not to let women suffer indefinitely if a conservative approach is adopted.

It is well recognized that the menopause transition can often be associated with a number of other distressing symptoms such as low energy and musculoskeletal aches and pains, and that MHT can also have a positive impact on these symptoms. Prior to prescribing, the predominant symptoms should be identified, and realistic goals set as to the degree of improvement expected, and also over what timeline a response to treatment is expected. The ultimate goal is to empower women with evidence-based information to make an individualized choice that is right for them.

Should we be recommending non-hormonal alternatives instead of or in addition to MHT?

The wider the armamentarium of treatment options, the easier it is to individualize/personalize treatment. As previously mentioned, any medical treatments should be underpinned by optimization of lifestyle, diet, exercise, minimizing alcohol and avoiding or stopping smoking.

Women presenting with distressing menopause-related issues should all be offered evidence-based, safe, effective non-hormonal as well as hormonal options as part of the treatment toolkit [41]. The options should be tailormade to the individual's wishes and medical history – some women may wish to avoid hormone therapies or may be contraindicated to them.

The difficulty is the lack of licensed non-hormonal therapeutic options resulting in off-label use of treatments such as anti-depressants for VMS. The 2015 NICE guideline made it very clear that selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors should not be used as first-line treatments of VMS in women who have no contraindications to MHT [90].

Recent research has resulted in a new class of drugs, the NK receptor antagonists, which are already licensed in some countries for the treatment of VMS [91,92]. This provides another licensed option for targeting menopause symptoms, thereby facilitating personalization of therapy.

Therapeutic areas of unmet need for MHT

There continue to be significant areas of unmet need in menopause medicine where MHT could be of great benefit, either because the subjects are regarded as taboo or because research and development has not been focused in these areas:

- VVA/GSM/sexual health: whilst there are numerous products now available for the management of VVA/GSM symptoms, there is still considerable reluctance for women to come forward to have these symptoms treated, because of embarrassment of the patient, reluctance of the HCP to open the conversation and trivialization of the impact of these symptoms [93]. Equally important is the management of sexual health issues such as HSDD and the provision of adequate expertise and resources to manage these issues using a biopsychosexual approach with androgenic products licensed for female use where required [94].
- POI/early menopause: these remain areas of concern because of lack of awareness of the public and amongst general HCPs about the impact these conditions can have, not only on quality of life but also on long-term health. In the past, women with POI were referred to as 'the lost tribes'. It is imperative that women who may have POI/early menopause problems are encouraged to present early so that they can be diagnosed and managed effectively with MHT unless medically contraindicated. White Papers and updated guidelines are important but only effective if there is adequate dissemination and translation of the information globally. The European Society of Human Reproduction and Embryology (ESHRE) POI guideline is currently being updated and will be disseminated soon [95].
- Perimenopause: although this has already been addressed it is important to emphasize that, in addition to menopause-related symptoms, this period of a woman's life can also be associated with distressing menstrual disturbances, PMS/PMDD and challenging sexual health issues that require well-considered treatment regimens [96].
- Iatrogenic menopause due to:
  - Benign causes/non-hormone-dependent cancers – it is concerning that many women who could use MHT after benign or non-hormone dependent, iatrogenic menopause are still not being offered it. The short-term and long-term risks of POI and

early menopause on quality of life, multimorbidity and mortality are now well recognized, particularly after bilateral oophorectectomy [97]. For too long, the focus of cancer treatment has been solely on improving longevity. Whilst longevity is important, it means very little without optimal general and sexual quality of life [98].

- Hormone-dependent cancers – research into treatment options that can be used after hormone-dependent malignancy is long overdue [98]. It is encouraging that research is now being conducted with some non-hormonal therapeutic options, for example NK receptor antagonists that can potentially be used in women with a past history of hormone receptor-positive malignancy who are contraindicated for use of MHT.

Where can MHT be accessed?

Women in low and middle-income countries have limited or no access to MHT – what can be done?

Much of what is written about MHT presumes that it is universally accessible, which it is certainly not. In a number of countries, few or no MHT options are available. Even where MHT is available, expertise is often lacking to prescribe it effectively, safely and ethically. As such, it is important that pragmatic, region/country/culture-sensitive approaches to managing menopause are employed [99].

National and international menopause societies play an important role in providing training in MHT and menopause care. The IMS currently has outreach to 64 affiliated menopause societies through the Council of Affiliated Menopause Societies (CAMS) and members in 90 countries who can advise on optimal approaches that can be used in national and regional settings to manage menopause.

The CAMS offers an innovative Toolkit for Starting a Menopause Society as well as a Holding Hands Program in which small societies are supported by larger societies. Monthly 'Menopause Hour' webinars provide education in local languages on issues of national and regional importance. These programs have provided critical guidance for the formation and continued growth of menopause societies across the globe.

Menopause societies are now starting up in regions of the world such as Africa and the Middle East where few or no menopause societies existed. The continued growth of menopause societies across the globe is vitally important to address the critical unmet need for training of HCPs in menopause care and for educating midlife women on the impact of menopause on their health and well-being.

Are influencers (medical, political and social) creating unrealistic expectations, or restoring the balance to where it should be?

There has been a recent 'renaissance' in menopause management in a number of countries, particularly in the UK, where recognition of the potential impact of menopause has finally been brought to the attention of the public, HCPs and, most importantly, policymakers.

In the UK, menopause and MHT political 'Tzars' and women's health ambassadors have been appointed to oversee the availability of MHT to ensure that this is equitably distributed at a fair cost to the public.

Whilst this empowerment of women to seek assistance for their menopause has largely been a positive development, there have been some unexpected consequences which are less desirable. These include the following:

- unrealistic expectations of what can be achieved with the currently available treatment options including MHT;
- disappointment if MHT does not achieve the desired effect on symptom alleviation, particularly for mood and cognition-related problems;
- disappointment if there are unexpected adverse effects;
- difficulty in accessing MHT or interruption of MHT supplies;
- difficulty in accessing primary or secondary-level menopause healthcare either due to lack of resources or lack of expertise;
- commercialization of menopause management which risks over-investigation and overtreatment;
- unregulated advice and support from self-appointed experts with little or no training

Overall, these consequences have partly arisen because this 'renaissance' has been driven by the public and media celebrities rather than government departments of health. It is therefore important that coordinated approaches to managing the menopause are fully developed by health departments to ensure adequate clinical and educational resources, and equitable access to evidence-based advice, MHT and alternatives.

Potential conflicts of interest

The issue of potential conflicts of interest and the role of the pharmaceutical industry has been a particularly vexed issue in menopause medicine – perhaps more so than in many other fields of medicine. The influence of pharmaceutical companies in menopause care is particularly difficult to accept among those with the view that menopause is a natural stage in a woman's life course and does not require treatment per se, and even among those who accept that distressing symptoms associated with menopause do warrant treatment.

Whilst it is understandable why some might view collaboration with the pharma industry as being unethical, realistically government health departments and research agencies cannot support the costs of all randomized trials. A considerable amount of medicine research and development and non-promotional education would not happen if it was not for the pharma industry.

The view of the IMS and most menopause societies is that collaboration with the pharma industry can be ethical as long as the primary objectives are as follows:

- the primary beneficiary of the collaboration is the woman/patient/public;
- any collaboration is entirely transparent with all potential conflicts of interest declared;
- drug research and development addresses unmet therapeutic needs, and is not purely designed to boost financial profits;
- the direction of any educational support is unrestricted, non-promotional and developed by menopause societies not pharma.

If there is to be less reliance on the support of for-profit organizations it is of course imperative that government departments of health globally provide adequate resources for independent investigator-led research and development, and for the education of HCPs in managing menopause-related problems, particularly in low and middle-income countries. Equivalent ethical standards must of course also be followed in government-funded studies [100].

Role of the regulators

The primary role of regulatory agencies such as the EMA (Committee for Medicinal Products for Human Use), FDA and MHRA is to protect and improve public health. Whilst acting as safety gatekeepers for the introduction of novel medicinal products, it is important that they have, or avail themselves, of sufficient expertise to be able to make balanced judgments on the products they assess.

It would therefore be greatly advantageous if these authorities routinely collaborated with the national and international menopause societies that represent the HCPs who look after the women for whom these products are designed to benefit.

Examples of where this collaboration could benefit menopause medicine include the following:

- the proliferation of compounded bioidentical hormone prescribers/clinics in some countries, despite the availability of conventionally regulated MHT;
- the refusal to remove 'standard' black box warning labels in some countries (e.g. cardiovascular disorders/dementia/breast cancer/endometrial cancer) from low-dose local estrogen therapies despite the absence of any evidence of harm;
- the inconsistent approach of regulators globally to granting of product licenses, for example the levonorgestrel intrauterine device is not licensed as part of MHT in the USA and Canada;
- the reluctance to license testosterone for female usage, which is currently only licensed in Australia;
- the tendency to focus on one aspect of risk with MHT, for example breast cancer, whilst not taking into consideration the overall benefit–risk balance [101]. Unless there are specific reasons why there should be national/regional differences, a consistent approach to these and other issues globally is important to instill confidence and facilitate universal access to safe and effective products, without geographic or ethnic discrimination.

Importance of the IMS and other menopause societies

Menopause societies play an important role in advancing the understanding, treatment and management of menopause and midlife women's health. The work of these societies includes:

- the advancement of research;
- the development and dissemination of education for HCPs, women and communities;
- advocacy for government policies and funding;
- promotion of equitable inclusion and access to treatment;
- addressing misinformation and stigma.

There are national and regional societies that focus on local issues and delivery, and the IMS, as the only global menopause society, brings them together via the CAMS to support the delivery of its vision.

As CAMS members, societies are working together to develop resources, share information and promote each other so that their vital work is a benefit to HCPs and women beyond the boundaries of their nations/regions. The IMS, via the CAMS Holding Hands program, is working with HCPs to establish menopause societies in areas where there are none.

The IMS, in partnership with CAMS members, creates state-of-the-art educational resources and events. Developed and supported by the world's leading experts on menopause and midlife women's health, these resources ensure that the latest science and emerging trends from across the world are promoted and made accessible to HCPs and women.

This extensive portfolio of events and educational resources, translated into multiple languages and many of them available for free, increase knowledge, foster awareness between cultures and enhance accessibility in underserved areas. MHT is a key topic across this portfolio which includes the following:

- a biennial World Congress on Menopause;
- World Menopause Day;
- the society's bimonthly journal *Climacteric*;
- IMPART, a free online course for HCPs;
- an expert review of key scientific papers (Menopause Live);
- a monthly webinar series;
- a monthly interview series;
- a monthly CAMS webinar;
- The Clinical Colloquium series – topical roundtable discussions between menopause experts of the future and leading experts;
- an update of the IMS recommendations on women's midlife health and menopause, following which a further revision of the global consensus statement on MHT will be published;
- a partnership of the IMS with the ESHRE, American Society for Reproductive Medicine (ASRM) and Monash Centre for Health Research and Implementation (MCHRI), which has facilitated a recent update of the ESHRE POI guideline;

- Menopause Info, providing evidence-based and reliable information for women.

It is essential that all menopause societies and health organizations at national and global levels work in partnership to address polarized views on menopause that often leave women feeling confused and disempowered. The only way to develop and promote future ethical management of menopause, from both practical and aspirational perspectives, is to work together as one menopause community.

Future hopes for menopause care

We have come a long way since the first commercially available estrogens and progestogens. At present, conventionally licensed body-identical MHT appears to offer some advantages over conjugated estrogens and synthetic androgenic progestogens. It is disappointing that regulatory guidance does not recognize the differences in biological and clinical effects with more 'natural' types of conventionally regulated MHT. Expanded funding of menopause research is critical to further evaluate the benefits and safety of modern types of MHT and to develop and identify novel treatment options that minimize adverse effects and maximize benefits. A key priority in research is critically evaluating the notion perpetrated by some agencies and media that all types of MHT have an identical impact on menopause related health issues.

Through research partnership with the pharma industry, TSECs and selective estrogen receptor modulators have been developed as treatment approaches that maintain benefits whilst minimizing adverse effects. Continued research and development of complementary, cognitive and licensed non-hormonal approaches for women who cannot, or who choose not to, use MHT is crucial. Another example of collaboration with industry is the improved understanding of the hypothalamic pathophysiological processes leading to the genesis of distressing menopause symptoms. These collaborations have resulted in novel therapeutic options such as the NK receptor antagonists that can be used by women who either choose not to use MHT or have a contraindication to MHT, and pending results from ongoing trials, also for women with a history of hormone-sensitive malignancies who arguably have the greatest need.

Improved understanding of pharmacogenetics will facilitate truly individualized therapeutic options for management of menopause-related symptoms and also change the benefit–risk ratio in favor of primary prevention in women deemed to be at risk of the long-term complications of natural menopause. Advisory bodies such as the United States Preventive Services Taskforce (USPSTF) do not currently recommend MHT for primary prevention [102] despite the favorable evidence for bone and cardiovascular benefits, and long-standing juxtaposed criticism from menopause experts [103, 104].

Conclusions

Menopause is an important stepping stone on the path of a woman's life course and may have evolutionary significance in *Homo sapiens*. Although a recognized stage from the time of Hippocrates, menopause has taken on more importance because it has become a midlife stage for many women and therefore should not be regarded as being just a part of the aging process.

Whilst the recent focus has been on empowering women to proactively manage their distressing menopause symptoms, it is also important to promote a positive view of menopause as a natural stage in a woman's life and an opportunity to re-evaluate and address current and future health concerns.

The cessation of ovarian activity can liberate women from distressing cycle-related symptoms such as PMS/PMDD, menstrual migraine and painful heavy menstruation [105]. It is also an opportunity to be liberated from concerns about pregnancy, offering women the opportunity to explore new opportunities in their life course.

Globally, there is a critical unmet need for easy access to evidence-based information and safe and effective treatment options for those needing treatment. Continued progress in the training of healthcare providers and the education of midlife women will optimize not only individual, but also societal, health and productivity, and reduce the burden of non-communicable diseases which are a major health concern in the twenty-first century.

Advancing menopause care and education globally can also help to dispel misconceptions and lower stigma about menopause and female aging more generally, and thereby encourage more women to seek the care they need to optimize their health at midlife and beyond. Healthcare providers worldwide have a duty to provide a supportive, informative environment where women can freely discuss menopause as it affects them individually, express their concerns and priorities and receive personalized care to optimize their health and well-being in the second half of their lives.

Key note

Whilst the majority of personal experiences with menopause relate to cisgender women (who were born female and identify as female), transgender men and some people who identify as neither men nor women also experience menopause. This White Paper refers to 'women' in alignment with the available data, which does not routinely identify gender identity.

There is a paucity of readily-available data on trans and gender diverse experiences of menopause. Trans and gender diverse people have unique age-related health needs that clinicians should consider, including referral to specialist services when necessary [106].

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Appendix 1. Key Points Summary of the Principles of Prescribing Menopause Hormone Therapy (MHT) – the 5Ws

1) **Who is MHT for?**
   - Usual indications for MHT
     - Distressing vasomotor (VMS) and vulvovaginal atrophy/genitourinary syndrome of menopause (VVA/GSM) symptoms
     - Osteoporosis prevention (first line in some countries, second line in others)
   - Asymptomatic women
     - MHT is primarily indicated for symptomatic women
     - MHT should not be regarded as an 'elixir of youth'
     - MHT is not currently indicated for primary prevention of cardiovascular disease or dementia in women at usual age of menopause but is important preventive therapy for women with primary ovarian insufficiency (POI)/ early menopause, even if asymptomatic
   - High-risk women
     - Careful counseling of benefit–risk balance required as with any other medication
     - Definition of 'acceptable risk' will vary – personalization of prescribing required
     - Ongoing development of medical eligibility criteria will be useful (as with contraception)

2) **What types and doses of MHT?**
   - Type of estrogen
     - There is no evidence that replicating the precise ratio of the four human estrogens (estrone, estradiol, estriol, estetrol) is required
     - Most types of estrogen will alleviate VMS and VVA/GSM if used in sufficient doses
     - Despite biological differences between estrogen types in MHT there is little evidence of clinically significant differences in efficacy and safety
     - Route of delivery (i.e. oral versus non-oral) has cardiometabolic significance (e.g. no venous thromboembolism [VTE] risk with transdermal estrogen)
     - Healthy women at usual age of menopause can have oral MHT if they prefer, or if they cannot absorb or are allergic to transdermal estrogen
   - Type of progestogen
     - Primary indication for progestogens in MHT is to prevent endometrial hyperplasia/cancer
     - Most progestogens achieve this if used in a sufficient dose/duration
     - There are differences in tolerance and safety of progestogens that should be considered when prescribing MHT
     - Body-identical progesterone and body similar progestogens (e.g. dydrogesterone) have less adverse impact on cardiometabolic and breast risk markers than androgenic progestogens
   - Doses of estrogen and progestogen
     - Prescribing of MHT should be at minimum fully effective doses, to achieve maximum benefits with minimal adverse effects
     - If the dose of estrogen is increased in non-fixed dose MHT formulations, the dose of progestogen should also be increased to maintain adequate endometrial protection
     - In women with progestogen intolerance, lower dose and duration may be required – endometrial surveillance is mandatory with ultrasound ± hysteroscopy ± endometrial biopsy
     - Other options (may be off license/unavailable in some countries) include vaginal progesterone, intrauterine levonorgestrel and oral tissue selective estrogen complex (TSEC) (conjugated equine estrogens [CEE]/bazedoxifene)
   - Monitoring of MHT
     - Routine hormone profiles are not required to initiate or monitor MHT in women at the usual age of menopause
     - Hormonal profiles may be useful in the following circumstances, especially if a regimen change has already been attempted:
       - Inadequate symptom relief after 12 weeks of commencing/switching MHT
       - Persistent adverse effects after 12 weeks of commencing/switching MHT
       - Use of MHT in POI/early menopause especially if efficacy issues/adverse effects, or concern about osteopenia/osteoporosis
       - NB: estradiol levels are most representative of effect on transdermal estrogen therapy, measured by mass spectrometry techniques where available
   - Compounded bioidentical hormone therapy
     - Custom compounded bioidentical hormone therapy is not recommended because of concerns about regulation, rigorous safety and efficacy testing, batch standardization and purity measures
     - Potential benefits of compounded bioidentical hormone therapy can be achieved with conventionally regulated body-identical MHT which has been rigorously tested for efficacy and safety
   - Testosterone
     - Testosterone is an important female hormone the levels of which naturally decline through a woman's life course
     - The primary indication for testosterone replacement in women is hypoactive sexual desire disorder (HSDD) – distressing low libido
     - Benefits for other symptoms (e.g. cognition, mood) are not established based on current trial data and should not be a primary indication for prescribing
     - A biopsychosocial approach should be followed for diagnosis of HSDD and prescribing according to the global consensus statement
     - Testosterone preparations remain off license for women in most countries, requiring down-titration of male preparations such as gels (typically 1/10th of male dose)

3) **When should MHT be started and stopped?**
   - Premature ovarian insufficiency/early menopause
     - Hormone therapy (MHT or combined oral contraceptives [COCs]) should be commenced as early as possible following diagnosis of POI/early menopause unless contraindicated
     - Early institution of treatment restores quality of life and reduces the risk of long-term health risks (osteoporosis/cardiovascular disease/dementia)
     - Treatment should be continued at least until the usual age of menopause and personalized continuation of MHT considered after this based on benefit–risk assessment
   - Premenopause/perimenopause
     - MHT is currently indicated for women in menopause/late perimenopause
     - Menopause-associated symptoms often commence in premenopause or early perimenopause
     - MHT can be used off-label in these women but there may be a higher incidence of adverse effects due to intermittent endogenous estrogen production

- COCs can be used in women who do not have contraindications other than age; newer estradiol and estetrol COCs may have less VTE risk
- Research of novel treatment approaches in premenopause/perimenopause is urgently required

◦ Older postmenopausal women (≥60 years)
- Routine initiation of MHT from age 60 years onwards is not recommended due to potentially increased risks (e.g. VTE with oral MHT, stroke)
- Use of MHT to treat/prevent osteoporosis in women ≥60 years is not recommended as a first-line option
- Personalized prescribing based on the benefit–risk assessment is acceptable, especially in women with persistent VMS
- Treatment of VVA/GSM symptoms with topical estrogen is recommended in this age group and is not contra-indicated

◦ When should MHT be stopped
- Arbitrary limits (e.g. 5 years) should not be placed on duration of MHT use
- A personalized approach should be employed, empowering women to make an evidence based individual decision
- Ongoing use of MHT rather than Initiation of MHT in women ≥60 years may be associated with a more favorable risk–benefit profile for cardiovascular/VTE events

4) **<u>Why</u> is MHT important?**

◦ Is menopause being over-medicalized?
- Menopause does not necessarily require treatment beyond optimization of lifestyle, diet, exercise, etc.
- However, distressing menopause-associated symptoms and risks should be proactively identified and addressed by healthcare providers
- Treatment with MHT and medicinal alternatives should always be underpinned by health optimization measures and talking therapies if indicated
- Provision of a routine 'menopause check' globally could help to reduce suffering and reduce the incidence of non-communicable diseases by identifying problems early through screening, especially as VMS are linked with an increased risk of cardiovascular disease
- The vision of the International Menopause Society (IMS) is that all women across the world will have easy and equitable access to evidence-based knowledge and health care, empowering them to make fully informed mid-life health choices

◦ Role of non-hormonal options
- The wider the armamentarium of treatment options, the easier it is to individualize management of menopause
- Women choosing not to use hormone therapies or who have insufficient relief of symptoms/persistent symptoms into later life/adverse effects/contraindications to MHT should be able to choose evidence-based non-hormonal options
- Selective serotonin reuptake inhibitors (SSRIs)/serotonin and norepinephrine reuptake inhibitors (SNRIs) should not be used routinely to treat VMS in women who do not have contraindications to MHT
- Access to talking therapies, for example cognitive behavioral therapy/hypnotherapy, needs to be improved in most countries
- Ongoing development of, and access to, non-hormonal options with an indication for VMS, for example neurokinin (NK) receptor antagonists, is imperative to widen therapeutic choices

◦ Therapeutic areas of unmet need
- Areas of unmet need remain despite improved awareness of menopause. These include:
- VVA/GSM – symptoms affect more than 50% of the postmenopause population and yet only the minority receive topical MHT, leaving women 'suffering in silence'
- POI/early menopause – higher prevalence than originally thought (POI up to 4% especially in low and middle-income countries [LMICs]); many still present too late, or not at all, by which stage preventable complications have arisen and cause more of a problem
- Perimenopause – symptoms are common and distressing, but hormone therapy is more challenging due to fluctuating hormone levels, and is therefore not attempted even though it could be
- Iatrogenic menopause due to:
  - Benign causes/non-hormone-dependent cancer – MHT can usually be prescribed but is often neglected resulting in suffering and needless non-communicable diseases (NCDs)
  - Hormone-dependent cancer – benefit–risk balance of MHT and non-hormonal options should be discussed proactively

5) **<u>Where</u> can MHT be accessed?**

◦ Access to MHT in low and middle-income countries
- Women in many countries, especially in LMICs, have little or no access to MHT and alternative options for menopause management – this situation needs to improve
- National and international menopause societies play a vital role in improving awareness and providing education about menopause and MHT – this can be achieved through translated guidelines/online educational tools/apps/Artificial Intelligence (AI), etc.
- Improved menopause healthcare provision is essential in view of global aging and the pandemic of non-communicable diseases in this United Nations Decade of Healthy Aging

◦ Impact of 'social and political influencers' on MHT
- Misinformation and disinformation in social and other media can lead to confusion and disempowerment of women about the menopause and MHT
- Expectations about the potential benefits and risks of MHT often do not match reality and can lead to disappointment for MHT users
- Governments, healthcare professionals (HCPs) and society in general have a duty of care to fully inform women about menopause to empower them to make a choice that is right for them
- Appropriate menopause/MHT advice will have societal as well as personal benefits through:
  - Reduction of the societal healthcare burden
  - Improved efficiency and productivity in the workplace

Notes:

(1) Please see full manuscript for greater detail regarding MHT types, doses, regimens, references, etc.
(2) Link to IMS (https://imsociety.org) and Menopause Info (https://menopauseinfo.org) websites.
(3) Progestogens = progesterone and synthetic progestins.