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Hormone therapy for first-line management of menopausal symptoms: Practical recommendations

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Abstract

Hormone therapy use has undergone dramatic changes over the past 20 years. Widespread use of hormone therapy in the 1980s and 1990s came to an abrupt halt in the early 2000s after initial findings of the Women's Health Initiative trial were published and the study was terminated. Since then, much has been learned about the characteristics of women most likely to benefit from hormone therapy. There is general agreement that women younger than 60 years or who initiate hormone therapy within 10 years of menopause onset gain short-term benefit in terms of symptomatic relief and long-term benefit in terms of protection from chronic diseases that affect postmenopausal women. Despite accumulating evidence in support of hormone therapy for symptomatic menopausal women, the slow response by the medical community has led to a 'large and unnecessary burden of suffering' by women worldwide. Greater efforts are clearly needed to educate physicians and medical students about the pathophysiology of menopause and the role of hormone therapy in supporting women through the transition. This article provides a brief historical perspective of events that led to the backlash against hormone therapy, explores the current position of guideline groups, and provides practical recommendations to guide first-line management of symptomatic menopausal women.

Keywords

breast cancer, guidelines, hormone therapy, menopause, venous thromboembolism, women's health

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Introduction

Menopausal hormone therapy (HT) has undergone major changes during the past 20 years. Prior to 2000, HT was widely used to treat menopausal symptoms such as hot flushes and vulvovaginal atrophy.[1] In the late 1990s, the Women's Health Initiative (WHI) trial was undertaken to determine whether HT provided protection from certain chronic diseases (e.g. coronary heart disease (CHD)) that affect women after menopause. Interim analyses raised concerns about associated adverse outcomes, mainly an increased risk of breast cancer in the combined oestrogen + progestin arm,[2] and an increased risk of stroke in the oestrogen-only arm.[3] Investigators concluded that the risk–benefit profile of HT did not support its use for primary prevention of chronic diseases in postmenopausal women and the study was terminated. Intense media coverage followed which led to a dramatic and persistent decline in the use of HT worldwide.[4]

Over the next several years, extensive re-analysis and assessment of the WHI data cast doubt about the validity of the original conclusions. Notably, age-stratified data indicated that absolute excess risk of adverse outcomes,

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including all-cause mortality, was low in women aged 50–59 years at the start of treatment,[5,6] and that benefits in this age group were maintained during a cumulative follow-up of 18 years. Conversely, no beneficial effects were observed in women aged 60–69 or 70–79 years at the start of treatment.[6]

In 2016, to atone for the turmoil caused by the inappropriately communicated findings of the WHI trials, two WHI investigators published a request for forgiveness:

> Reluctance to treat menopausal symptoms has derailed and fragmented the clinical care of midlife women, creating a large and unnecessary burden of suffering. Clinicians who stay current regarding hormonal and non-hormonal treatments can put menopause management back on track by helping women make informed treatment choices. In addition, we must train and equip the next generation of health care providers with the skills to address the current and future needs of this patient population.[7]

Over the past few years, several guidelines and position statements have been updated to reflect the current approach to menopause management.[8–12] There is general agreement among guideline groups that HT has a favourable risk–benefit ratio in women who initiate treatment between 50 and 59 years of age or within 10 years of menopause onset. In this population, HT is highly effective for relief of vasomotor and urogenital symptoms, and can prevent bone loss and fracture. Symptom relief provides additional benefits such as improved sexual function and overall quality of life (QoL). A recent systematic review which examined the 'timing hypothesis' of HT indicated that beginning treatment at a younger age (<60 years) may protect against all-cause mortality, cardiac mortality and CHD events.[13] Nevertheless, despite accumulating evidence and widespread support for use of HT in younger symptomatic menopausal women, the medical community has been slow to respond, with little to no change in prescribing practices.

The aim of this article is to provide a concise and practical overview of the current approach to first-line treatment of symptomatic menopausal women. Recommendations are based on international guidelines of HT and the expert opinion (clinical experience and expertise) of the authors.

Box 1. Menopausal symptoms and signs.[8,11]

Central nervous system:
- Vasomotor symptoms (hot flushes, night sweats)
- Mood disturbances (anxiety, depression)
- Cognitive function (memory loss, cognitive difficulties)
- Sleep disturbances (delayed onset, frequent wakenings)

Genitourinary tract:
- Vulvovaginal atrophy, dyspareunia
- Sexual dysfunction
- Urgency, stress incontinence
- Urinary frequency

Musculoskeletal system:
- Joint/muscle pain
- Loss of muscle mass (sarcopenia)
- Loss of bone mass (osteopenia, increased risk for fractures)

Box 2. Pathophysiological significance of hot flushes.

Hot flushes are more than simply 'feeling hot'. They are a red alert, signifying an early neurovegetative disrupted response to fluctuations/loss of oestrogens on whole brain health.
Hot flushes are thought to be endocrine and/or thermoregulatory events that originate in the hypothalamus due to a decrease in secretion of ovarian hormones[14]
Hot flushes predict an increasing risk of:
- Affective symptoms rooted in the limbic and visceral brain (e.g. depression and anxiety)
- Cognitive symptoms rooted in the cognitive, cholinergic part of the brain, with mental deterioration up to and including Alzheimer's disease
- Motor symptoms rooted in the basal ganglia and dopaminergic system

The earlier that menopause occurs, the worse is the impact on brain health, especially iatrogenic menopause due to early mono- or bilateral ovariectomy[17]
Adequate management of hot flushes may provide protection from pathological aging of the whole brain

Certain statements reflect the clinical experience and expertise of the authors.

Therapeutic approach

Menopause is a normal physiological event associated with an age-related reduction in hormone secretion from the ovaries. Menopausal symptoms and signs (Box 1) affect about 80% of women, 20% of them severely.[8,11]

Since moderate-to-severe menopausal symptoms can negatively impact a woman's well-being and health expectancy, treatment is indicated. Hot flushes, for example, are more than a nuisance, but may be a signal of future chronic conditions such as cardiovascular disease, osteoporosis and cognitive impairment (Box 2), and should be treated accordingly.[14] Recently, a nationwide case-control study from Finland suggested a small increase in the absolute risk of Alzheimer's disease associated with long-term (>10 years) exposure to systemic HT,[15] but this finding requires corroboration before any conclusions can be drawn. Although evidence does not support use of HT solely for primary prevention of chronic diseases,[8,12] symptomatic women who begin HT in early menopause may gain protection from certain chronic conditions.[13,16]

Importantly, HT is part of an overall management strategy for menopausal women that includes lifestyle measures aimed at promoting and maintaining good health, which include smoking cessation (if relevant), a diet low in sugar and fat, regular physical activity (e.g. brisk walking), moderate alcohol consumption, and weight management (body mass index (BMI) < 30 mg/m^2).[8,11]

Table 1. Recommendations for use of hormone therapy in symptomatic menopausal women with risk factors, based on international guidelines,[8–12] clinical literature[18–20] and expert opinion (clinical experience and expertise) of the authors.

Age >60 years or more than 10 years since onset of menopause:
• For current users of HT with an established reduction/disappearance of symptoms and improved quality of life, HT can be continued at an appropriate dose (lowest effective dose) for an appropriate time if no new contraindications emerge
• For never-users of menopausal HT due to inadequate communication of risks and benefits, for whom HT is indicated, and in the absence of major contraindications, treatment with transdermal oestradiol (either 25 mcg patch or gel, 1 puff per day) and vaginal progesterone (either 100 mg in the evening continuously or 200 mg in the evening for 14 days a month) is preferred. If other risk factors are present, vaginal treatment with oestradiol or oestriol is preferred
Obesity (body mass index > 30 mg/m^2):
• As elevated oestrone production from adipose tissue increases the risk of proliferative endometrial lesions,[18] protecting the endometrium with progesterone or progestogens (e.g. levonorgestrel or dienogest intrauterine system) is a priority
• The opportunity to add low-dose transdermal oestradiol should be considered on an individual basis, balancing symptom intensity with risk
• The woman's willingness to make lifestyle improvements should be empowered
Insulin resistance:
• Oestradiol is a master regulator of body and brain bioenergetics. Specifically, oestradiol facilitates the action of insulin, whereas menopausal loss of oestradiol increases insulin resistance[19]
• Menopausal HT should be recommended to women with type 2 diabetes, or a family history of diabetes, as it reduces progression and delays the appearance[20]
Hypertension:
• Menopausal HT can improve recent-onset hypertension, with enhanced response to antihypertensive drugs
• In women with aggressive postmenopausal hypertension, the option to start transdermal HT should be discussed with a cardiologist
Smoking:
• Women who smoke should be counselled to quit while also increasing daily aerobic exercise in order to improve endothelial function, reduce hypertension and, if relevant, reduce the risk of weight gain
• For women who choose not to quit, vaginal HT is preferred. In selected cases, systemic HT may be considered, but only if the woman is fully aware of the higher independent cardiovascular risk due to smoking
Dyslipidemia:
• Transdermal menopausal HT is preferred in women with dyslipidemia
• In women with severe dyslipidemia, menopausal HT can be considered for highly symptomatic patients who have inadequate response to alternative treatments, in collaboration with the internal medicine specialist and administered concomitantly with antihyperlipidemic agents
Venous thromboembolism: personal or familial:
• Vaginal HT with oestradiol or oestriol or prasterone is preferred

HT: hormone therapy.

The therapeutic approach to managing women transitioning through menopause has a dual but continuous aim: to address the initial symptoms/complaints and to reduce long-term postmenopausal adverse outcomes. Since the relative importance of these aims will vary depending on the phase of menopause, treatment must be personalized. Before prescribing HT, it is important to evaluate for co-existing risk factors to determine whether HT is appropriate for the patient. The presence of risk factors does not necessarily preclude use of HT and can inform treatment selection (Table 1).[8–12,18–20] Main risk factors for HT use include older age (>60 years), obesity (BMI > 30 kg/m^2), insulin resistance, increased cardiovascular risk (e.g. dyslipidaemia, hypertension, diabetes mellitus, smoking) and a personal or family history of venous thromboembolism (VTE). Contraindications/cautions to use of HT include undiagnosed abnormal vaginal bleeding, active thromboembolic disorder or acute-phase myocardial infarction, suspected or active breast or endometrial cancer or ovarian cancer, active liver disease with abnormal liver function tests and porphyria cutanea tarda. Some useful questions to ask and examinations/investigations to perform to assess risk are outlined in Box 3. Women receiving HT must also assume personal responsibility for minimizing any risk factors to ensure continued suitability for use. As certain risk factors (e.g. presence of metabolic diseases) may require additional concomitant therapeutic interventions, the responsibility of managing a menopausal patient should be shared among relevant specialties.

Good communication between physician and patient is essential to treatment success. HT is not a 'lifestyle option' but, rather, is a validated therapeutic strategy that can enhance women's health and well-being.[21] Physicians have a key role in supporting, counselling and assuring a woman that she is making a suitable and safe therapeutic choice. To facilitate informed choice, clinicians must

Box 3. Evaluating risk factors for hormone therapy in candidate patients.

Questions to ask:

- Age
- Menstruation status
- Menopausal symptoms
- Past and current medical history
- Family history
- Lifestyle factors (e.g. smoking, alcohol use, exercise)
- Concurrent medications

Examinations/investigations to perform:

- Body weight
- Waist circumference
- Blood pressure
- Blood tests if indicated by responses to questioning
- Imaging (e.g. ultrasound, bone density) if indicated by responses to questioning
- Mammography if not performed within previous year
- Bone densitometry (dual-energy x-ray absorptiometry) if patient at risk for osteoporosis

understand the basic concepts of relative risk and communicate them in a clear and comprehensible manner that balances the benefits of HT with any potential adverse consequences, and include comparisons of HT with other therapies as appropriate.

HT

HT encompasses several different drug classes including oestrogens, progestogens, oestrogen + progestogen combinations, tibolone, raloxifene and a combination of conjugated oestrogen and bazedoxifene, a selective oestrogen receptor modulator (SERM), that is, tissue-selective oestrogen complex (TSEC).[12] Treatment options are available in a wide range of doses and are formulated for oral, transdermal or vaginal administration. HT does not exhibit a class effect per se with regard to side effects or adverse events; each product has its own risk–benefit profile. Understanding the attributes of available treatment options is key to optimizing therapy in individual patients.

Oestrogens

Oestrogen is the primary active component of HT and is the recognized 'gold standard' for treating menopausal symptoms, especially vasomotor symptoms. Oestrogens used for HT include conjugated equine estrogens (CEEs), synthetic conjugated estrogens, micronized 17β-oestradiol, oestriol, oestradiol valerate and oestradiol hemihydrate.[12] Although there appears to be relatively minor differences in efficacy among oestrogen products, their risk–benefit profiles differ.[12] With regard to choice of oestrogen, patients are advised to follow their clinician's advice based on international recommendations.[8–12]

Progestogens

Endogenous progesterone plays an essential role in the menstrual cycle, inducing secretory transformation of the endometrium and maintaining pregnancy. Since chronic unopposed exposure of the endometrium to oestrogen increases the risk of endometrial hyperplasia and cancer,[22] progestogens are a part of systemic HT in menopausal women with an intact uterus.[23] Progestogens include the natural progestogen, progesterone and a range of synthetic compounds (collectively known as progestins) structurally related to progesterone or testosterone which have varying potential beneficial effects on cardiovascular and nervous systems, breast and bone.[24] Although selecting the 'best' progestogen for use in an individual patient requires further clarification, there is evidence to suggest that dydrogesterone and micronized progesterone have better risk profiles than medroxyprogesterone acetate (MPA),[25] and are associated with a lower risk of breast cancer compared with other progestogens.[26–28]

Combined oestrogen + progestogen

Recommendations for use of combined oestrogen + progestogen HT should be based on current national and international guidelines.[8–12] The dose and duration of progestogen per cycle depends on the type and dose of oestrogen being administered, and should be aligned with the endometrial effectiveness of the progestogen as assessed in clinical studies involving endometrial biopsies.[25] The metabolic and tolerability profiles of available progestogens should also be considered, as well as patient-specific factors including potential risk factors for HT.

Cyclical or sequential HT involves daily administration of oestrogen, with the addition of progestogen for 10–14 days a month (monthly bleeds) or for 10–14 days every 13 weeks (bleeds every 3 months). This regimen minimizes the endometrial cancer risk associated with unopposed oestrogen.[29] Another approach involves continuous administration of both oestrogen and progestogen, but at a lower progestogen dose which may minimize associated breast cancer risk; this regimen eliminates withdrawal bleeding and promotes amenorrhea.

In perimenopausal women, sequential HT should consist of a comparatively low oestrogen dose and higher progestogen dose, as endogenous ovarian oestradiol production can remain relatively high during this phase.[30,31] Sequential HT typically causes regular progestogen withdrawal bleeds, which may be of value for patients new to HT who have been experiencing irregular bleedings due to their perimenopausal stage. Any irregular bleeding and/or spotting that occurs in addition to regular progestogen withdrawal bleeds can be managed by increasing the oestrogen dose as this stabilizes the endometrium. Although sequential HT can be used in postmenopausal women, it

can cause regular progestogen withdrawal bleeds to an older age (up to 60 years) which is largely undesirable. At the point where withdrawal bleeds become weak and/or short-term, or no longer occur, a change to continuous combined HT is possible, with the aim of achieving amenorrhea within 4–6 months. Continuous combined HT should be used only in women who are at least 2 years past their last menstrual period as it can cause irregular bleeding in perimenopausal women due to the unpredictable residual production of oestradiol by remaining primordial ovarian follicles.

Based on a woman's individual clinical profile, progestogen-free therapeutic alternatives such as tibolone (synthetic steroid),[32] raloxifene for postmenopausal osteoporosis[33] and TSEC (conjugated oestrogens + bazedoxifene) to prevent bone loss[34] may be appropriate for use.

Starting and stopping HT

International guidelines recommend that HT be started as soon as menopausal signs or symptoms appear which, in most women, is between 45 and 55 years of age.[8–12] Women with primary ovarian insufficiency require earlier and continued use of HT (at least until the normal age of menopause) to protect against associated postmenopausal chronic diseases.[35]

Current users of HT can remain on treatment indefinitely (lifelong if indicated), or at least until such time as the patient asks to stop. However, regular monitoring of HT is advised, with adjustments made to type, dosage and/or route of administration according to a patient's changing circumstances and treatment goals, which range from symptom relief to prevention of intermediate/late signs and degenerative consequences of menopause.[19]

Dose and route of administration

The most appropriate dose of HT depends on the woman's phase of life, age and general health status. Guideline recommendations provide a useful starting point,[8,12] after which the dose can be tailored to the individual patient. A useful approach may be to start HT at a low dose, then titrate upwards to the lowest effective dose that is consistent with the woman's treatment goals.

The route of administration of HT depends on a woman's individual circumstances, including the presence of risk factors (Table 1).[8–12,18–20] The first priority in selecting a regimen is safety, followed by preference. In women >60 years, transdermal HT or an ultra-low-dose oral product may be more appropriate than conventional-dose systemic HT. In obese women, the transdermal route is preferred. Oral oestradiol has greater positive impact than transdermal HT on insulin resistance and is the option of choice in non-obese patients with impaired glucose tolerance. Although evidence is insufficient to recommend any one route of HT over another in patients with increased cardiovascular risk (e.g. dyslipidemia, hypertension, diabetes, etc), there is some evidence to support use of transdermal HT in women with increased cerebrovascular risk.[36,37]

Natural products

There is limited evidence for the efficacy of natural products such as isoflavones in menopause management, and safety data are inadequate.[38] As such, there are currently no official recommendations to support the use of natural products for managing menopausal symptoms.

Risk management

The potential relationship between HT use and breast cancer is controversial. In the WHI trial, the apparent increase in breast cancer risk with CEE + MPA versus placebo was no longer significant after adjusting for confounding variables.[39] Excess risk of HT-associated breast cancer appears to relate to use of combined therapy (oestrogen + progestogen) and duration of treatment.[40] However, actual risk is low, estimated at <1 case per 1000 women-years among HT users, which is lower than the risk associated with endogenous factors such as increased breast density or lifestyle factors such as obesity, physical inactivity and alcohol consumption.[23,41] Current thought is that HT is unlikely to cause breast cancer per se, but may have a promoter effect on existing tumours. In other words, in a small number of women receiving HT (approximately 8 in 10,000), HT may increase the possibility of being diagnosed with a presumed pre-existing breast cancer.[12] Interestingly, an analysis of postmenopausal breast cancer patients reported higher survival rates among users versus never-users of HT.[42]

The main risk associated with HT use is VTE (deep vein thrombosis and pulmonary embolism), although again the actual incidence is low, estimated at one or two cases per 1000 woman-years among HT users.[11] VTE is rare in otherwise low-risk women aged <60 years, but the incidence increases with advancing age as age is a major risk factor for VTE.[11] Other established risk factors for VTE include obesity, smoking and thrombophilia.[11,23] VTE risk appears to be greatest in the period soon after initiation of oral HT, but reverts to basal risk level for non-HT users after treatment discontinuation.[43] HT regimens which include a progestogen, and progestogen type, may also impact on VTE risk.[23] Dydrogesterone and micronized progesterone are considered safer progestogens with an acceptable metabolic profile and are preferred over MPA.[25] Observational studies suggest that transdermal HT is less thrombogenic than oral HT,[44] although this requires confirmation in randomized controlled trials.[23,45]

Mitigating HT risk

In women with risk factors for VTE or breast cancer (e.g. family history, obesity, smoking, physical inactivity, genetic factors, older age), the risk–benefit balance of HT must be considered carefully before prescribing. Choice of formulation may mitigate some risk. In women without risk factors including normal weight, the risk profiles of oral and transdermal HT appear to be equivalent. In women at increased risk for VTE, transdermal HT is preferred over oral therapy as it may attenuate risk by avoiding first-pass metabolism.[23,45] In terms of breast cancer risk, there appears to be no difference between oral and transdermal routes of administration, although high-quality evidence across the range of HT formulations is limited.[23]

Use of HT in postmenopausal >60 years

HT use in women aged >60 years or >10 years since menopause onset requires distinguishing between those who are continuing or initiating HT. Healthy women who began treatment before age 60 can continue to use HT indefinitely provided that they undergo regular objective assessment of the benefits and risks.[23] If symptoms appear many years after menopause onset, it must be determined whether they relate to reduced oestrogen production or other causes (e.g. insulin resistance, hypertensive peaks, alcohol consumption during the evening). Evidence is insufficient to recommend initiating HT in women aged >60 years to prevent CHD or fractures.[23] Moreover, in view of the increased risk of VTE events soon after initiation of oral HT, use of oral HT in women with a higher basal risk for VTE merits careful consideration.[23] Vaginal treatment may be more appropriate in this population, with adjustments made to dose and/or application frequency to maintain symptom relief.

Psychological issues associated with use of HT

Aside from concerns about risks of breast cancer or VTE, psychological factors can also influence beliefs and attitudes towards HT. Despite enhanced well-being and improved QoL associated with relief of menopausal symptoms, a woman may also have feelings of insecurity/confusion or even shame due to the lingering social stigma surrounding HT use. The willingness of the public and healthcare professionals to accept HT as a legitimate treatment for moderate-to-severe menopausal symptoms has been slow, with many continuing to view it as a lifestyle measure. For HT users, feeling the need to hide use from friends and family, or feeling inadequately supported by healthcare professionals, can cause significant stress at a vulnerable time of life. Moreover, undertreatment of menopausal symptoms continues to deny many women the opportunity for a better QoL and protection from age-related diseases.

Greater efforts are required to educate practising physicians and medical students about the pathophysiology of menopause and the role of HT in supporting symptomatic women through the transition. Empowered by knowledge of the benefits of HT, and a clearer understanding of the risks, prescribing physicians can acquire the confidence to assume responsibility for first-line treatment of menopausal women.

Future trends

More than 15 years after the mass hysteria that followed publication of the WHI preliminary findings, the tide appears to be turning. More scientific and robust assessment of the WHI findings has shown the benefits of HT in appropriate patients. Looking ahead, an accumulating body of evidence in support of HT might be expected to resolve any remaining uncertainties about its risks and benefits in women traversing menopause. The future should include gaining greater insight into the relative merits of the different HT regimens with respect to dosage, route of administration and treatment duration. Although not all menopausal women require HT for symptomatic relief, all menopausal women are entering a phase of life when age-related diseases (cardiovascular, metabolic, cognitive, cancer, osteoporosis) are beginning to appear. A potential role for HT, in combination with lifestyle measures such as diet and exercise, for primary prevention of some of these diseases has been proposed.[45] This is clearly an important area of future research since these diseases represent the major causes of morbidity and mortality in the older female population.

The move towards personalized medicine involving diagnostic tools that can identify patient characteristics at the gene/molecular level may direct future treatment approaches in menopausal women and improve the risk–benefit balance of HT. It is already possible to better identify risks for breast cancer and cardiovascular disease in women receiving HT.[45] Expanding this research across the menopausal spectrum may bring a net result of marked improvement in women's overall health. The importance of lifestyle measures as part of the overall strategy for menopause management cannot be underestimated and needs to be continually reinforced by the healthcare provider.

In addition to gaining a better understanding of the pathophysiological changes that occur during menopause and optimizing use of available HT regimens, the development of receptor-specific targeted therapies is likely to be an avenue for future research.

Conclusion

In our experience of treating menopausal women, we recognize the wide range of benefits associated with use of HT. HT reduces or eliminates hot flushes and improves

sleep quality, mood and memory; it reduces the symptoms/signs of genitourinary syndrome of menopause, improving vaginal dryness, reducing dyspareunia and alleviating symptoms of urgency and post-coital cystitis; it reduces joint pain and delays the progression of menopausal osteoarthritis; it reduces age-related loss of muscle mass, optimizes peripheral insulin use and reduces the risk and progression of type 2 diabetes. In synergy with a healthy lifestyle, HT improves symptoms and signs of menopause and promotes longevity in a state of health.

It is unfortunate that the benefits of HT on health and health expectancy in menopausal women were overshadowed by misinformation extrapolated from women mainly unsuited to receive HT. That time has passed, however, and HT is currently accepted as an effective and safe option for healthy symptomatic women younger than 60 years of age or within 10 years of onset of menopause who have no contraindications/cautions for its use. It is hoped that the practical points presented in this article can serve to guide physicians in the first-line treatment of women with menopausal symptoms.

Declaration of conflicting interests

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