ARTICLE

Management of menopause

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SUMMARY

During perimenopause and after menopause, women may experience diverse symptoms.

All women require a comprehensive assessment of their current health and risks for future disease, appropriate screening, and promotion of a healthy lifestyle.

Menopausal hormone therapy is the most effective treatment for menopausal symptoms. It can be offered to symptomatic patients with no contraindications following an individualised discussion about the risk of harms versus benefits.

Menopausal hormone therapy is recommended for women with premature ovarian insufficiency (menopause occurring before 40 years of age) regardless of symptoms, unless contraindicated.

Nonhormonal medications may improve symptoms for women who have contraindications to, or do not wish to take, menopausal hormone therapy.

Introduction

The average age of menopause in Australian women is 51 years. Perimenopause typically lasts several years before menopause, during which fluctuating ovarian function and hormone concentrations affect the menstrual cycle.[1] Box 1 lists definitions related to menopause.

Menopause can occur spontaneously, be induced by medical treatments (e.g. chemotherapy, radiotherapy) or by surgical removal of the ovaries. Approximately 75% of women experience symptoms during perimenopause and after menopause, with 25% experiencing moderate to severe symptoms affecting their quality of life.[3] Multiple symptoms typically occur (see Box 2), including vasomotor symptoms (e.g. hot flushes, night sweats), joint and muscle pains, mood changes, sleep disturbance, low libido and genitourinary symptoms. Menopause is also associated with an increased risk of osteoporosis and cardiovascular disease.[4]

Box 1 Definitions related to menopause

menopause—the final menstrual period or the permanent cessation of ovarian function

early menopause—menopause occurring at 40 to 44 years of age

premature ovarian insufficiency—menopause occurring before 40 years of age; women may experience oligomenorrhoea and amenorrhoea during this time[2]

perimenopause—from when the menstrual cycle starts changing until 12 months after menopause

postmenopause—from 12 months after menopause

In this article, the term 'women' only refers to cisgender women. Trans- and gender-diverse people may also experience menopausal symptoms and may benefit from appropriately tailored health services.

Management for menopausal symptoms

The management of menopausal symptoms (see Box 2) includes an assessment of the patient's:

- general health, current symptoms and concerns
- risks of cardiovascular disease and osteoporosis
- need for screening and preventive activities.

During perimenopause, a menstrual bleeding history should be documented, noting any abnormal bleeding

Box 2 Common perimenopausal or menopausal symptoms

menstrual cycle changes in length (longer or shorter) and flow (heavier or lighter)

vasomotor symptoms (hot flushes, night sweats)

mood changes

cognitive concerns ('brain fog')

sleep disturbance

musculoskeletal symptoms

low libido

formication (sensation of insects crawling under the skin)

genitourinary symptoms (vaginal dryness, dyspareunia, urinary urgency, urinary frequency, recurrent urinary tract infections)

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that requires investigation, before considering systemic menopausal hormone therapy (MHT).

Depending on individual symptoms, management may include nonpharmacological and pharmacological (including hormonal and nonhormonal) therapies, which are discussed below.

Any ongoing need for contraception should be determined.[5]

Premature ovarian insufficiency (see Box 1) can be associated with increased health risks to women. Women with premature ovarian insufficiency require comprehensive assessment and management. MHT is recommended regardless of symptoms (unless contraindicated) until the usual age of menopause, to reduce the risks of osteoporosis and cardiovascular disease.[6]

MHT is the most effective treatment for menopausal symptoms.[4] It can be offered to symptomatic patients with no contraindications following individualised discussions about risk of harms versus benefits and other therapies available.

Other established benefits of MHT include improved quality of life, and prevention of osteoporosis and, potentially, cardiovascular disease.[4,7,8] Estrogen therapy is suitable for the management of osteoporosis or low bone density in women younger than 60 years of age.[9]

Useful resources to assist practitioners in assessing and managing menopause include:

- A Practitioner's Toolkit for the Management of the Menopause from the Women's Health Research Program at Monash University
- Menopause health professional tool from Jean Hailes for Women's Health.

Nonpharmacological treatments for menopausal symptoms

Lifestyle modifications such as exercise, weight loss and reducing alcohol consumption may be helpful for some women. These measures may not reduce the severity of symptoms but may make them more manageable and improve overall wellbeing.

Cognitive behavioural therapy can reduce the impact of vasomotor symptoms and alleviate sleep disturbance.[10,11]

Menopausal hormone therapy for menopausal symptoms

Menopausal hormone therapy (MHT) is indicated for treatment of menopausal symptoms. It is highly effective for alleviating vasomotor symptoms and may improve sleep disturbance, mood changes, cognitive concerns and musculoskeletal symptoms.[4]

Regimens used for MHT include:

- **estrogen-only for women who have had a total hysterectomy**; unopposed estrogen is associated with endometrial hyperplasia and potential malignancy
- **combined estrogen plus progestogen for women with a uterus:**
  - cyclic combined MHT—continuous estrogen with a progestogen given cyclically (e.g. for 12 to 14 continuous days of a calendar month)
  - continuous combined MHT—continuous estrogen and progestogen
- **tibolone for women more than one year after menopause**, particularly those with low libido.

Women starting on MHT must be warned about adverse effects, including nausea and breast tenderness. Women should be reviewed after 6 to 12 weeks of starting MHT to evaluate ongoing menopausal symptoms and any adverse effects. At this review, dosage or formulation adjustments can be made; for example, if vasomotor symptoms remain problematic, the estrogen dose can be increased. Annual reassessment is recommended to ensure health screening is up to date and to review the need for ongoing treatment.

Women prescribed cyclic MHT should expect a regular vaginal bleed at the end of the progestogen phase. Some women may have irregular bleeding and spotting when starting cyclic MHT, and adjusting therapy can help (e.g. increasing the progestogen dose or duration). For both cyclic and continuous combined regimens, bleeding and spotting often settles over months, but if it persists beyond 6 months, or becomes heavy or prolonged, it should be investigated.

There is no maximal duration of MHT defined. Many women wish to stop MHT after some time to assess whether their symptoms still warrant treatment. Some may elect to continue MHT indefinitely. This latter group must be counselled about the potential long-term harms of MHT (see below).

For a complete list of MHT formulations available in Australia, refer to the Guide to MHT/HRT doses from the Australasian Menopause Society.

Estrogen

Estrogen is the primary component of MHT. Most formulations contain either estradiol or conjugated equine estrogens.[12] Estradiol is preferred because it is structurally similar to 17-beta-estradiol, the commonest naturally occurring estrogen in premenopausal women. Various estradiol

preparations are available (e.g. oral tablets or capsules, transdermal patch or gel). Systemic estrogen should be started at a low-to-medium dose and adjusted according to symptoms.

Estrogen is effective for treating genitourinary symptoms (e.g. vaginal dryness, urinary frequency, recurrent urinary tract infections).[13] Genitourinary symptoms often improve in women taking systemic MHT, but some require additional topical vaginal estrogen.

Topical vaginal estrogen is only appropriate for managing genitourinary symptoms. Low-dose vaginal estrogen (estradiol or estriol)[12] is available as vaginal tablets, pessaries or creams and does not require the addition of a progestogen.

Progestogens and combination preparations

Progestogens are required for women with a uterus who are prescribed estrogen-containing MHT.

For perimenopausal women, cyclic MHT is used, where a progestogen is given cyclically with estrogen (e.g. for 12 to 14 continuous days of a calendar month). For postmenopausal women, continuous combined MHT is used, where a progestogen is given continuously with estrogen.

If continuous combined MHT is used by perimenopausal women, irregular bleeding frequently occurs; cyclic MHT is recommended to minimise irregular bleeding. Once a woman has been using cyclic MHT for 12 months, a trial of continuous combined MHT can take place.

Several progestogens are available for use in MHT (e.g. micronised progesterone, dydrogesterone, drospirenone, norethisterone, medroxyprogesterone acetate). Their properties vary—for example, some are more androgenic while others exert anti-mineralocorticoid effects. No randomised controlled trial data are available to guide choice.[14] Micronised progesterone and dydrogesterone (which is structurally similar to natural progesterone) may have a lower breast cancer risk than older synthetic progestogens[15] and, for most women, are considered first line.

Most progestogens are given orally as tablets or capsules, either in a fixed-dose combination product with estrogen, or as separate preparations. Transdermal patches contain a combination of estradiol and norethisterone. A progestogen-releasing intrauterine device (IUD), the 52 mg levonorgestrel-releasing IUD, can be used for up to 5 years in combination with estrogen. It has the added benefit of providing contraception and managing heavy menstrual bleeding.

Women younger than 50 years of age, without contraindications, can use combined hormonal contraception such as a combined oral contraceptive pill for MHT. This has the benefit of providing symptomatic relief, menstrual-cycle control, and contraception.

Tibolone

Tibolone is a synthetic steroid that is metabolised into components with estrogenic, progestogenic and androgenic actions. It is useful for postmenopausal women, particularly those with low libido. The usual dose is 2.5 mg orally, daily.

Clinical trials have demonstrated low-dose tibolone (e.g. 1.25 mg orally, daily) may reduce both vertebral and nonvertebral fractures. It can also be used to treat low bone density.[16]

Tibolone should only be prescribed to women who are more than one year after menopause as it can cause vaginal bleeding. Women with a history of breast cancer should not be prescribed tibolone. Tibolone is associated with increased risk of stroke in women older than 60 years of age.[16]

Cardiovascular disease risk and MHT

Menopause is also associated with an increased risk of cardiovascular disease.[4]

Women who start MHT younger than 60 years of age, or within 10 years of menopause, have reduced all-cause mortality and risk of coronary heart disease. These women also have fewer cardiac events on long-term follow up.[17] These findings support the 'timing hypothesis',[18] where women who start MHT close to menopause experience a cardiovascular benefit, whereas those who start MHT several years after menopause do not experience this benefit.[19] At present there is no role for MHT in the primary prevention of cardiovascular disease; however, in women with premature ovarian insufficiency, MHT may reduce the risk of cardiovascular disease and should be used until the usual age of menopause.

Contraindications to MHT

Strong contraindications to MHT include undiagnosed vaginal bleeding, and a history of breast or endometrial cancers, or acute cardiovascular or thromboembolic events. Other contraindications to prescribing MHT are listed in Box 3.

Transdermal estrogen (rather than oral) may be recommended for women with:

- a history of atherosclerotic heart disease or stroke
- a history of migraine with aura
- treated cardiovascular disease risk factors (e.g. hypertension, dyslipidaemia)
- increased risk of venous thromboembolism
- hepatobiliary disease.

Risk of harms associated with MHT

For most women younger than 60 years, or within 10 years of menopause, the risks of MHT are low and outweighed by the benefits.[4] Estrogen-only MHT is associated with endometrial hyperplasia and potential malignancy due to unopposed estrogenic effects, and therefore use is limited to women who have had a total hysterectomy. For conditions where caution is recommended when prescribing MHT, see Box 3.[20]

Breast cancer

The Women's Health Initiative trials found the combination preparation of conjugated equine estrogens+medroxyprogesterone acetate was associated with an increased incidence of breast cancer.[8] Women taking conjugated equine estrogens alone had a reduced risk of breast cancer,[21] highlighting the role of progestogens. The risk of breast cancer has been linked to the duration of MHT.[14] Observational data suggest that micronised progesterone and dydrogesterone may confer a lower risk of breast cancer than older synthetic progestogens.[15]

Thromboembolic disease

Oral estrogen undergoes first-pass metabolism in the liver and alters the hepatic production of coagulation factors. This is associated with a 2- to 3-fold increase in venous thromboembolism, but the absolute risk remains low. Estradiol and estetrol theoretically have lower risks of venous thromboembolism, though strong evidence for this is lacking. Transdermal estrogen does not carry this risk and is the preferred option for women with risk factors for venous thromboembolism or cardiovascular disease.[22,23]

Nonhormonal drugs and other preparations for menopausal symptoms

Table 1 lists typical doses of nonhormonal drugs used for vasomotor symptoms of menopause. Nonhormonal drugs may be useful for women with contraindications to MHT (see Box 3) or who do not wish to take MHT. Generally, nonhormonal drugs are less effective than MHT and do not confer the bone- or cardiovascular-protective benefits of estrogen. Most of the drugs have limited use because of their adverse effects.[10]

Selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) have modest effects on vasomotor symptoms and may improve sleep and mood.

Box 3 Precautions for menopausal hormone therapy (MHT)

Contraindications to MHT

- hormone-dependent cancers including breast and endometrial [NB1]
- undiagnosed vaginal bleeding
- acute cardiovascular event
- acute venous thromboembolism [NB2]
- porphyria cutanea tarda
- severe liver disease

Conditions where caution is recommended with MHT

- past myocardial infarction, transient ischaemic attack or stroke [NB3] [NB4]
- high risk of venous thromboembolism [NB3]
- active liver disease [NB3]
- migraine with aura [NB3]
- hypertriglyceridaemia [NB3]
- hepatobiliary disease [NB3]
- high risk of breast cancer
- age older than 65 years and no prior use of MHT

NB1: MHT is generally safe to use in patients with treated stage 1 endometrial malignancy.
NB2: Consider transdermal estrogen for MHT if the patient is anticoagulated.
NB3: Exercise caution with oral estrogen; transdermal estrogen is preferred for MHT.
NB4: Treated hypertension is not a contraindication to MHT use.
Adapted from reference 20.

Gabapentin and oxybutynin may reduce the frequency and severity of vasomotor symptoms. The North American Menopause Society no longer recommends clonidine or pregabalin for treatment of vasomotor symptoms because of their adverse effects; however, they are still used in some instances in Australia.[10]

Unlike vasomotor symptoms, genitourinary symptoms do not improve with time. Nonhormonal lubricants can be helpful for vaginal dryness.

Complementary therapies and herbal preparations (e.g. black cohosh, phytoestrogens) have insufficient evidence of benefit, can cause adverse effects, and are not recommended.[20,24] Custom-compounded, bioidentical hormone therapy is also not recommended because of limited dose regulation and lack of safety data.[4]

Emerging treatments

Emerging options for the treatment of menopausal symptoms include estetrol, an estrogen found in the fetal liver, and neurokinin 3 receptor antagonists.[20] Estetrol may provide some safety advantages through reduced effects on liver and breast tissue.[25] Neurokinin 3 receptor antagonists are promising nonhormonal treatments for vasomotor symptoms.[20,26] A 2023 randomised placebo-controlled trial reported the neurokinin 3 receptor antagonist, fezolinetant, was effective and well tolerated for the treatment of vasomotor symptoms.[27]

Table 1 Nonhormonal drugs for vasomotor symptoms

Drug [NB1]	Dosage	Adverse effects
serotonin and noradrenaline reuptake inhibitors		
desvenlafaxine	25 to 150 mg orally daily	dizziness, nausea, sexual dysfunction
venlafaxine	37.5 to 150 mg orally daily	
selective serotonin reuptake inhibitors		
citalopram	10 to 20 mg orally daily	dizziness, nausea, sexual dysfunction
escitalopram	5 to 20 mg orally daily	
paroxetine [NB2]	10 to 25 mg orally daily	
other drugs		
clonidine [NB3]	25 to 75 micrograms orally twice daily	dizziness, drowsiness, constipation
gabapentin	100 to 900 mg orally daily in up to 3 divided doses	drowsiness, dizziness, possible withdrawal symptoms
oxybutynin [NB4]	2.5 to 5 mg orally twice daily	dry mouth, drowsiness, blurred vision

NB1: All drugs listed in the table, except clonidine, are not registered by the Therapeutic Goods Administration for treating vasomotor symptoms.

NB2: Paroxetine should not be co-administered with tamoxifen; co-administration can cause inhibition of cytochrome P450 2D6 and reduce the efficacy of tamoxifen.

NB3: Clonidine may be used but is no longer recommended because of its adverse effects.[10]

NB4: Oxybutynin may help symptoms of overactive bladder; however, it may cause adverse effects, particularly cognitive decline in older people.[10]

Conclusion

MHT is highly effective for the relief of symptoms associated with menopause. For most women within 10 years of menopause or younger than 60 years of age, the benefits are likely to outweigh the risk of harms. The benefits of MHT are not only limited to symptom control, but also good evidence supports its role in prevention of osteoporosis and cardiovascular disease. Local vaginal preparations can be used for genitourinary symptoms only. Women should be counselled on their therapeutic options and prescribed a regimen tailored to their individual needs. <

Conflicts of interest: Karen Magraith has received honoraria for presentations from Mylan, Jean Hailes for Women's Health, and the Australasian Menopause Society.

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