Sex hormone prescribing in postmenopausal women

Hormone replacement or hormone therapy and what are the alternatives?

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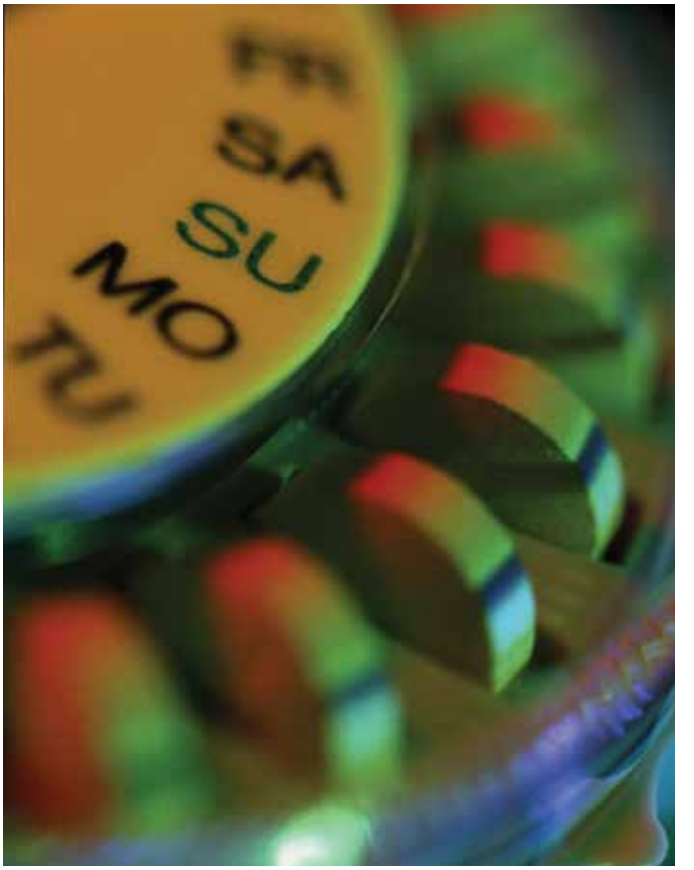

A personalised approach to managing menopausal symptoms in women is needed in which the decision to use menopausal hormonal therapy, or alternatives, requires assessment and discussion of the woman's individual risk and benefit profile with ongoing review.

Publication of the Women's Health Initiative (WHI) study in 2002 was associated with a 40% decrease in the prescribing of menopausal hormone therapy (MHT) in Australia.[1] Highlighting this issue, a recent study of Australian women observed that only 12% of postmenopausal women aged below 55 years with moderate to severe vasomotor symptoms (VMS) were taking MHT.[2] A decade since the WHI, reappraisal of the evidence in relation to the 50- to 59-year-old woman, the main user of MHT, has helped to clarify the benefits and risks of this treatment.

MHT has generally replaced the term 'hormone replacement therapy' (HRT). MHT includes oestrogens and progestogens in differing formulations and also tibolone. The term 'HRT' could best be applied to sex steroid therapy for women with early (before 45 years of age) or premature (before 40 years of age) menopause in which treatment is directed at replacing the abnormal oestrogen deficiency.

Recent US data indicate that VMS persist for longer than has been appreciated previously, with a median duration of 7.4 years, although more than 30% of women report a VMS duration of 14 years.[3] Greater duration of symptoms was associated with a younger age at onset of symptoms, smoking, higher body mass index, African-American ethnicity and greater negative affect.[3] These findings may have implications for the duration and type of treatment.

Current management of menopause involves lifestyle strategies,

Key points

- **Oestrogen is the most effective therapy for menopausal symptoms, including vasomotor and genitourinary symptoms.**
- **Many postmenopausal symptomatic women are not receiving treatment.**
- **The main risk of oral oestrogen-containing menopausal hormone therapy in healthy women aged below 59 years or within 10 years of menopause is thromboembolism. Use of transdermal oestrogen minimises this risk.**
- **Certain antidepressants and anticonvulsants and also clonidine are effective nonhormonal alternatives for management of vasomotor symptoms.**
- **Limited evidence supports the use of acupuncture, yoga, soy isoflavones, cognitive behavioural therapy and stellate ganglion blockade for relief of vasomotor symptoms.**
- **Hormone therapy should be instituted early and continued until the usual age of natural menopause in women with premature menopause (menopause at age <40 years), unless contraindicated.**

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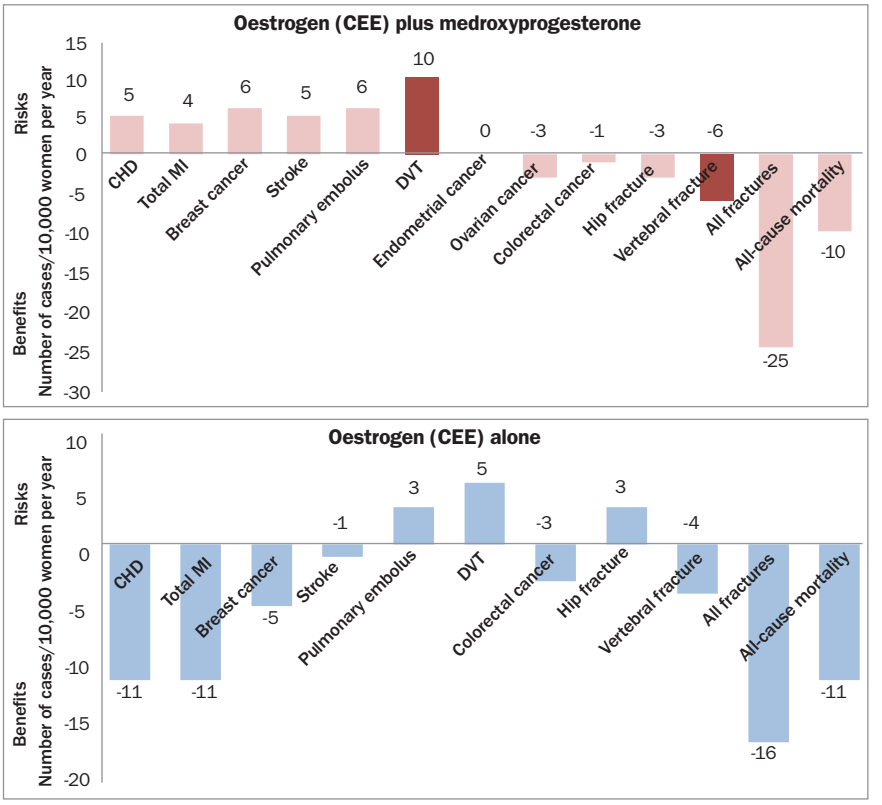

Figures 1a and b. Risks and benefits of menopausal hormone therapy for women aged 50 to 59 years as reported in the Women's Health Initiative (WHI).[9]

The WHI comprised two studies. The first study used conjugated equine oestrogen (CEE) plus medroxyprogesterone acetate in nonhysterectomised women who were randomised to oral 0.625 mg CEE plus continuous 2.5 MPA (n = 8506) or placebo (n = 8102) with median follow up of 5.6 years (a, top). The second used CEE alone in hysterectomised women who were randomised to oral 0.625 mg CEE (n = 8506) or placebo (n = 8102) with median follow up of 7.2 years (b, bottom). The absolute risks and benefits for primary and selected secondary outcomes are shown as the difference between treatment and placebo per 10,000 women per year. Each number represents the excess/risk (positive) or fewer/benefit (negative) cases compared with placebo. In women aged 50 to 59 years, the only statistically significant risk (shown in dark red) for women taking hormonal treatment compared with placebo was an increased risk of DVT and a statistically significant benefit in relation to decreased vertebral fractures.

Abbreviations: CEE = conjugated equine oestrogen; CHD = coronary heart disease; DVT = deep vein thrombosis; MI = myocardial infarction.

individualisation of MHT and consideration of nonhormonal agents or complementary and alternative medicine (CAM).

Menopausal hormone therapy

Benefits and risks of systemic MHT

Menopausal symptoms are the main reason why women seek treatment, and systemic oestrogen therapy is the most effective treatment for VMS.[4] Beneficial effects of oestrogen therapy are also observed for sleep disturbance, genitourinary symptoms, sexual function, mood and quality of life.[5] Both consumers and healthcare professionals have knowledge gaps related to MHT with confusion regarding the interpretation of relative versus absolute risks.[6,7] Consultations concerning the menopause and MHT involve complex decision making, often in the face of uncertainty, and most women prefer evidence-based, individualised risk information and shared decision making leading to informed choices.[8]

The benefits and risks of systemic MHT differ in younger versus older women and with:

- time since menopause
- formulation used (oral versus transdermal)
- type (oestradiol versus conjugated equine oestrogen) and dose of oestrogen
- the addition and type of progestogen used for endometrial protection.

Tibolone, a synthetic steroid with oestrogenic, progestogenic and androgenic activity, and tissue-specific oestrogen complex (TSEC) are alternative forms of MHT with individual risk and benefit profiles. The levonorgestrel intrauterine device is an alternative progestogen preparation with little systemic absorption, providing endometrial protection, contraception and control of menstrual bleeding problems in the symptomatic perimenopausal woman.

The benefits and risks of MHT for women aged 50 to 59 years as observed in the WHI are shown in Figures 1a and b.[9] The timing hypothesis proposes that oestrogen therapy is cardioprotective, with reduced plaque formation, when commenced around the time of menopause in the setting of no or minimal atherosclerosis.[9] In contrast, MHT initiated in older women long past menopause with established atherosclerosis is associated with attenuation and reversal of the beneficial effects, an increased risk of plaque erosion and rupture, and an increased risk of cardiovascular disease (CVD). This hypothesis is supported by the findings of observational studies and randomised controlled trials, with a recently published Cochrane review indicating reduced CVD risk (but not stroke) with MHT use in women aged less than 60 years and less than 10 years postmenopause.[10,11] Increased risk of venous thromboembolism with use of oral MHT is seen in women of all ages, with greatest risk in the first year of treatment.[10]

The relation between MHT and breast cancer is complex and controversial with evidence that longer duration of MHT and addition of a progestin is associated with an increased risk of breast cancer, although the absolute risk is small and decreases following cessation of MHT.[11] The risk of breast cancer may be reduced with the use of micronised progesterone or dydrogesterone as the progestogen.[5] Thromboembolic risks and hepatic effects are minimised with the use of transdermal oestrogen.[12]

Prevention of bone loss and fracture is an added benefit of MHT in symptomatic women.

Oestrogen-containing MHT is contraindicated in the setting of oestrogen-dependent cancer. Nonoral MHT (or a nonhormonal alternative) should be used with caution in women with a previous thromboembolism, at high risk of CVD, and in those with known CVD, breast cancer, thromboembolism, migraine with aura, liver disease, hypertriglyceridaemia or gall bladder disease. Oral MHT is contraindicated in these circumstances.

International guidelines recommend the use of MHT for moderate to severe menopausal symptoms for up to five years in healthy women initiating treatment prior to age 60 years or within 10 years of menopause. Continued use beyond that time is based on a woman's individual risk profile and continuing symptoms.[13]

Women with premature menopause

Women with premature menopause (including spontaneous premature ovarian insufficiency and bilateral oophorectomy) may experience longer duration and more severe menopausal symptoms. Observational studies report an increased risk of CVD, osteoporosis, cognitive dysfunction and dementia with spontaneous or surgical menopause before age 45 years.[14] However, these studies indicate that use of MHT until at least the age of 45 years diminishes these risks. Current guidelines recommend initiating MHT at diagnosis and continuing (in women without contraindications) until the average age of natural menopause.[5,13]

Genitourinary syndrome and vaginal oestrogen

Genitourinary syndrome of menopause (GSM) refers to vulvovaginal and urinary tract atrophy secondary to oestrogen deficiency.[15] GSM symptoms, including vaginal dryness, dyspareunia, pruritus and recurrent urogenital infections, are common. However, surveys reveal that only a minority of women with these symptoms seek help or are offered assistance by healthcare professionals.[15] Vaginal oestrogen preparations are effective for the management of GSM,[16] with minimal systemic absorption, and are not considered to be associated with the same risks as systemic MHT.

Table 1. Nonhormonal pharmacological agents effective in reducing VMS[22]

Therapy	Dose per day	Reduction in VMS frequency compared with baseline*
Selective serotonin reuptake inhibitors		
Citalopram	10 to 30 mg	40 to 60%
Escitalopram	10 to 20 mg	
Paroxetine†	7.5 to 20 mg	
Serotonin and noradrenaline reuptake inhibitors		
Desvenlafaxine	100 mg	60%
Venlafaxine, extended release	37.5 to 150 mg	
Other		
Clonidine‡	0.1 to 0.15 mg	26 to 49%
Gabapentin	300 to 900 mg in divided doses	44 to 80%
Pregabalin	150 to 300 mg in divided doses	60%

* Oestrogen therapy is associated with a reduction in frequency of VMS of 85 to 90%.
† Paroxetine is a cytochrome P450 2D6 inhibitor and should not be used in women also taking tamoxifen due to potential inhibition of tamoxifen bioactivation.
‡ Only clonidine has regulatory approval in Australia for use in women with hot flushes and use of all the other agents should be considered off label. Abbreviation = vasomotor symptoms.

Other hormone therapies

Combined oral contraceptive pill

The low-dose combined oral contraceptive pill may be considered as an alternative to MHT for women with premature menopause or if contraception is required for the perimenopausal woman. The usual contraindications apply.

Tissue-specific oestrogen complex

Clinical trials of a TSEC, in which conjugated equine oestrogen is combined with bazedoxifene (a serum oestrogen receptor modulator), demonstrated endometrial protection, menopausal symptom relief and increased bone mineral density in short-term studies.[17] The results of long-term studies in regards to the risk of breast cancer and CVD are awaited. This agent is not yet available in Australia.

Nonhormonal pharmacological therapies

For women who are reluctant or have contraindications to use of MHT, meta-analyses and systematic reviews of randomised controlled trials have provided some guidance regarding effective nonhormonal pharmacological therapies for improving VMS (Table 1).[18-22] Importantly, complete resolution of VMS may not be necessary to achieve meaningful benefit, with 1.64 fewer moderate to severe hot flushes each day identified as the treatment satisfaction threshold in a randomised controlled trial of desvenlafaxine.[23] This is consistent with the 0.93 to 2.05 reduction in hot flushes each day versus placebo reported as significant in meta-analyses of nonhormonal therapies for VMS.[19,20] In contrast, oestrogen therapy is associated with a 2.4 to 3.2 reduction in the number of hot flushes each day.[4,24]

A recent meta-analysis suggested that escitalopram is the most effective of the selective serotonin reuptake inhibitors.[20] Commencing at a low dose and titrating upwards has been suggested to minimise side effects and maximise response.[25] It is important to note that studies of nonhormonal therapies were of eight to 52 weeks' duration and long-term efficacy of these agents is unknown.

Table 2. Complementary and alternative medicines for vasomotor symptoms (VMS)

Therapy	Effect on VMS
Mind-body therapies	
Acupuncture	Limited evidence of reduction in VMS
Cognitive behavioural therapy	Reduction in VMS problem rating but not frequency. Improved sleep, sexual function and mood
Paced respiration	No effect
Yoga	Limited evidence of reduction in VMS
Herbal therapies	
Black cohosh	Inconsistent evidence of reduction in VMS and concern regarding potential hepatotoxicity
Dong quai	No effect
Evening primrose oil	No effect
Multibotanical	No effect
Phyto-oestrogen topical cream	No effect
Red clover	No effect
Soy isoflavone	Limited evidence of reduction in VMS
St John's wort	No effect
Other	
Dehydroepiandrosterone (DHEA)	No effect
Folic acid	No effect
Homeopathy	No effect
Magnesium supplements	No effect
Magnetic therapy	No effect
Omega-3 fatty acids	No effect
Stellate ganglion blockade	Limited evidence of a reduction VMS
Vitamin E	No effect

Complementary and alternative medicines

As MHT use has declined, there has been an increase in use of CAM, defined as biologically-based botanicals, vitamins, minerals, fatty acids, compounded 'bioidentical' hormone therapy, probiotics, whole diets, functional foods, and mind-body, energy, manipulative and body-based therapies.[26] In a study of Australian women aged 45 to 65 years, 53% had consulted a CAM practitioner and/or used a CAM.[27]

Recommended reading and resources

A practitioner's toolkit for the management of the menopause
www.imsociety.org/downloads/menopause_toolkit.pdf

Davis SR, et al. Menopause. Nature Reviews Disease Primers 2015; 1: 1-19. Available online at:
www.nature.com/articles/nrdp20154

de Villiers TJ, et al. Updated 2013 International Menopause Society recommendations on menopausal hormone therapy and preventive strategies for midlife health. Climacteric 2013; 16: 316-337.
www.imsociety.org

Manson JE, et al. Algorithm and mobile app for menopausal symptom management and hormonal/nonhormonal therapy decision-making: a clinical decision-support tool from The North American Menopause Society. Menopause 2015; 22: 247-253. Available as Apple and Android apps

Australasian Menopause Society
www.menopause.org.au

Jean Hailes for Women's Health
www.jeanhailes.org.au

However, there is limited evidence to support the use of CAM in women for the management of menopausal symptoms (Table 2).[19,22,26] Bioidentical hormones are defined as compounds with a similar chemical structure to hormones secreted by the ovaries and adrenal glands.[5] This term could apply to oestradiol used in conventional MHT; however, in the lay literature compounded 'bioidentical' hormone therapy (CBHT) refers to preparations of various hormones (including oestrogens, progesterone and testosterone) prepared by a compounding pharmacist. Although CBHT has been promoted as safer than conventional MHT, there is no evidence to suggest that this is true. Inconsistencies in purity and quality of CBHT have been identified and cases of endometrial cancer associated with the use of CBHT have been reported.[28,29] CBHT is not recommended by international and national menopause, gynaecological or endocrine societies.

Conclusion

Menopausal symptoms are common with significant adverse effects on quality of life (see the Box for a list of recommended reading and resources). The most common risk associated with MHT in women aged 50 to 59 years is thromboembolism. Management of menopause requires personalised medicine where the decision to use MHT (or alternatives) requires assessment and discussion of the woman's individual risk and benefit profile with ongoing review. **ET**

References

A list of references is included in the website version (www.medicinetoday.com.au) of this article.

COMPETING INTERESTS: None.

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References

1. Main P, Robinson M. Changes in utilisation of hormone replacement therapy in Australia following publication of the findings of the Women's Health Initiative. Pharmacoepidemiol Drug Saf 2008; 17: 861-868.
2. Gartoulla P, Worsley R, Bell RJ, Davis SR. Moderate to severe vasomotor and sexual symptoms remain problematic for women aged 60 to 65 years. Menopause 2015; 22: 694-701.
3. Avis NE, Crawford SL, Greendale G, et al. Duration of menopausal vasomotor symptoms over the menopause transition. JAMA Intern Med 2015; 175: 531-539.
4. MacLennan Alastair H, Broadbent JL, Lester S, Moore V. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. Cochrane Database Syst Rev 2004; (4): CD002978.
5. Santen RJ, Allred DC, Ardoin SP, et al. Postmenopausal hormone therapy: an Endocrine Society scientific statement. J Clin Endocrinol Metab 2010; 95(7 Suppl 1): S1-S66.
6. Tao M, Teng Y, Shao H, Wu P, Mills EJ. Knowledge, perceptions and information about hormone therapy (HT) among menopausal women: a systematic review and meta-synthesis. PLoS One 2011; 6: e24661.
7. Sturmberg JP, Pond DC. Impacts on clinical decision making – changing hormone therapy management after the WHI. Aust Fam Physician 2009; 38: 249-251.
8. Walter FM, Emery JD, Rogers M, Britten N. Women's views of optimal risk communication and decision making in general practice consultations about the menopause and hormone replacement therapy. Patient Educ Couns 2004; 53: 121-128.
9. Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. JAMA 2013; 310: 1353-1368.
10. Boardman Henry MP, Hartley L, et al. Hormone therapy for preventing cardiovascular disease in post-menopausal women. Cochrane Database Syst Rev 2015; CD02229
11. Mirkin S, Archer DF, Pickar JH, Komm BS. Recent advances help understand and improve the safety of menopausal therapies. Menopause 2015; 22: 351-360.
12. Canonico M, Plu-Bureau G, Lowe GDO, Scarabin P-Y. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. BMJ 2008; 336: 1227-1231.
13. de Villiers TJ, Pines A, Panay N, et al. Updated 2013 International Menopause Society recommendations on menopausal hormone therapy and preventive strategies for midlife health. Climacteric 2013; 16: 316-337.
14. Vincent A, Farrell E. Premature menopause. In: Dvornyk V, editor. Current topics in menopause: Sharjah, United Arab Emirates: Bentham Science Publishers; 2013. p. 414-441.
15. Portman DJ, Gass ML. Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and the North American Menopause Society. Menopause 2014; 21: 1063-1068.
16. Suckling JA, Kennedy R, Lethaby A, Roberts H. Local oestrogen for vaginal atrophy in postmenopausal women. Cochrane Database Syst Rev 2006 (4); CD001500.
17. Harvey JA, Lindsay R, Pan K, et al. Effects of bazedoxifene/conjugated estrogens on the endometrium and bone: a randomized trial. J Clin Endocrinol Metab 2014; 99: E189-E198.
18. Rada G, Capurro D, Pantoja T, et al. Non-hormonal interventions for hot flushes in women with a history of breast cancer. Cochrane Database Syst Rev 2010 (9); CD004923.
19. Nelson HD, Vesco KK, Haney E, et al. Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. JAMA 2006; 295: 2057-2071.
20. Shams T, Firwana B, Habib F, et al. SSRIs for hot flashes: a systematic review and meta-analysis of randomized trials. J Gen Intern Med 2014; 29: 204-213.
21. L'Esperance S, Frenette S, Dionne A, Dionne JY. Pharmacological and non-hormonal treatment of hot flashes in breast cancer survivors: CEPO review and recommendations. Support Care Cancer 2013; 21: 1461-1474.
22. Vincent AJ. Management of menopause in women with breast cancer. Climacteric 2015; Feb 24: 1-39.
23. Wyrwich KW, Spratt DI, Gass M, Yu H, Bobula JD. Identifying meaningful differences in vasomotor symptoms among menopausal women. Menopause 2008; 15: 698-705.
24. Nelson HD. Commonly used types of postmenopausal estrogen for treatment of hot flashes: scientific review. JAMA 2004; 291: 1610-1620.
25. Richardson MK. Alternatives to hormone therapy for hot flashes: many choices but science is lacking. Menopause 2013; 20: 980-982.
26. Nedrow A, Miller J, Walker M, Nygren P, Huffman LH, Nelson H. Complementary and alternative therapies for the management of menopause-related symptoms: a systematic evidence review. Arch Intern Med 2006; 166: 1453-1465.
27. van der Sluijs CP, Bensoussan A, Liyanage L, Shah S. Women's health during mid-life survey: the use of complementary and alternative medicine by symptomatic women transitioning through menopause in Sydney. Menopause 2007; 14: 397-403.
28. The Endocrine Society position statement: bio-identical hormones 2006. Available online at: www.endo-society.org (accessed July 2015).
29. Eden JA, Hacker NF, Fortune M. Three cases of endometrial cancer associated with 'bioidentical' hormone replacement therapy. Med J Aust 2007; 187: 244-245.