



National Prescribing Service Limited



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Dr Sam Sample
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Prescribing
Practice Review

No. 47
Therapeutic
choices for
menopausal
symptoms

Dear Dr Sample,

This issue of the *Prescribing Practice Review* outlines the key evidence for choosing how to treat the symptoms of menopause.

Use of oestrogen and progestogen for hormone replacement therapy (HRT) dropped dramatically after the publication of the Women's Health Initiative study in 2002. Most women have now heard that HRT involves risks, and may be reluctant to consider it.

Nonetheless, oestrogens with or without a progestogen remain the most effective treatment for menopausal symptoms. To make an informed decision, women need to know the extent of benefits and potential harms that apply to their individual situations.

As well as examining how the risks of adverse effects and magnitude of benefits of conventional HRT vary from woman to woman, this *Prescribing Practice Review* looks at the alternatives, including compounded bioidentical hormone therapy, non-hormonal treatments and complementary and alternative medicines.

Yours sincerely,

Dr Janette Randall
Chair, National Prescribing Service

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Therapeutic choices for menopausal symptoms

KEY MESSAGES

- Discuss a woman's goals and concerns about menopause and her treatment preferences
- Oestrogen with or without progestogen is the most effective treatment for women with menopausal symptoms
- Consider potential benefits and harms and assess cardiovascular risk
- Tailor the dose and duration of therapy according to individual symptoms and existing risks
- Inform women about the limited efficacy and safety data on complementary and alternative medicines

Discuss a woman's treatment goals and concerns about menopause

Enquire about each woman's particular goals or concerns about menopause and her attitude towards taking HRT and other therapies

Oestrogen-based hormone replacement therapy (HRT) has benefits and harms that vary significantly from woman to woman. Providing personalised information can help women to make informed choices.

Individualise the decision to use HRT based on:

- symptom severity

- age and background risk (e.g. cardiovascular, venous thromboembolism [VTE], stroke, breast cancer)
- years since menopause at treatment initiation
- type of therapy (oestrogen only or combined oestrogen plus progestogen)
- dose
- route of administration
- duration of therapy
- personal choice.

Oestrogen with or without progestogen is the most effective treatment

HRT decreases hot flushes by about 18 episodes per week more than placebo¹

The primary indication for systemic HRT is to reduce moderate to severe menopausal symptoms, including hot flushes, night sweats, urogenital symptoms, sexual problems and, with oestrogen plus progestogen, arthralgia.^{2,3}

Oestrogen-based HRT reduces fracture risk and helps to maintain bone density², but other agents are first line for preventing fractures in women at high risk.⁴

Consider intravaginal oestrogens for predominantly vaginal symptoms

Women who have moderate to severe, predominantly vaginal symptoms and who do not respond to non-hormonal lubricants and moisturisers may wish to consider local intravaginal oestrogens instead of other forms of HRT.⁵ Symptoms can take 4–6 weeks to improve, or longer for dyspareunia.^{2,5} Low dose vaginal oestrogen does not reduce vasomotor symptoms or fracture risk.⁵

Vaginal oestrogens are considered safer than oral, transdermal or implant HRT because there is little systemic absorption.^{2,5} Rarely, breast tenderness may indicate systemic absorption and possible overdosing.⁵

Consider potential benefits and harms and assess cardiovascular risk

Provide written information to assist in decision-making

Written information can help women understand the range of potential benefits and harms, and to decide whether to try HRT.

The NHMRC booklet *Hormone replacement therapy: exploring the options for women* is intended to help women make decisions about HRT and also includes some information about complementary and alternative medicines (available at www.nhmrc.gov.au/publications/synopses/wh35syn.htm).

Bear in mind that risks may be calculated and reported in different ways.

The absolute risks of HRT may increase with age

The major harms of oestrogen with or without progestogen found in the Women's Health Initiative (WHI) study are summarised in Table 1.

As women age, their background risk of some events will increase and the balance of risks and benefits may change. Many non-smoking women in their 50s taking HRT are likely to experience only small absolute increases in risk, because of their low background risk.⁶

Unlike other risks that may increase over time, the risk of VTE is greatest in the first 1–2 years of use after which it remains relatively constant.⁶

Breast cancer risk increases with the duration of combined oestrogen and progestogen therapy

Oestrogen plus progestogen: Breast cancer risk was increased with 5 years of oestrogen plus progestogen HRT.^{7,8} Breast cancer risk increases with duration of therapy and declines within a few years of stopping.^{6,7,9}

Oestrogen alone: There was no increase in breast cancer risk with up to 7 years of oestrogen-only HRT in women without a uterus.¹⁰

Both combined and oestrogen-only HRT increase the proportion of abnormal mammograms.^{7,10} This can cause concern even when breast cancer is not diagnosed.

Assess cardiovascular risk when initiating therapy in women over 60 years

In women in their 60s or older, coronary heart disease (CHD) risk may be elevated from the first year after starting oestrogen with progestogen therapy.⁸ Starting oestrogen-based HRT several years after menopause may have a greater vascular risk, while women closer to menopause may benefit.^{6,11} However, this 'timing hypothesis' remains speculative.⁶ Time since menopause is not thought to affect stroke, VTE or cancer risk.

Table 1. Evidence from the Women's Health Initiative study on harms of oestrogen with or without progestogen^{12*}

Harms	Oestrogen + progestogen (compared with placebo)		Oestrogen alone (compared with placebo)	
	Hazard ratio (95% confidence interval)	Absolute risk difference per 10 000 patient-years [†]	Hazard ratio (95% confidence interval)	Absolute risk difference per 10 000 patient-years
Venous thromboembolism (VTE) [‡]	2.06 (1.57 to 2.70)	+18	1.32 (0.99 to 1.75)	+8
Stroke	1.31 (1.02 to 1.68)	+8	1.37 (1.09 to 1.73)	+12
Coronary heart disease	1.24 (1.00 to 1.54)	+6	0.95 (0.79 to 1.15)	
Breast cancer	1.24 (1.01 to 1.54)	+8	0.80 (0.62 to 1.04)	
Endometrial cancer	0.81 (0.48 to 1.36)		N/A	

* Based on an average follow up of 5.6 years for oestrogen plus progestogen and 7.1 years for oestrogen alone. Women started therapy at an average age 63–64 and 13–14 years post menopause.

[†] Absolute risk difference estimates indicate the number of extra cases per 10 000 women on treatment for 1 year, compared with women who took a placebo.

[‡] Observational data suggest a lower VTE risk with transdermal compared to oral HRT, however, long-term randomised trials have not been conducted.⁶

See NPS News 64 for:

- a description of the Women's Health Initiative trial and its findings
- further details of the data on breast cancer risk
- an insert covering the claims and uncertainties about 'bioidentical' hormone therapy
- a tabular summary of evidence for efficacy and safety of complementary medicines for menopausal symptoms.

Tailor the dose and duration of therapy according to individual symptoms and existing risks

Start with a low dose

Breast tenderness and vaginal bleeding are very common with medium-dose oestrogen with progestogen.³ Low and ultra-low doses reduce vasomotor symptoms, with fewer short-term adverse effects.¹¹ Oestrogen without progestogen should only be prescribed to women who have had a hysterectomy.

It may take 2–3 visits over the first 6 months to tailor the dose, route and regimen to suit the individual. Inform women that adverse effects may resolve after 3 months or so of treatment or after adjusting therapy.¹³

See www.nps.org.au/tools for a table of HRT products and regimens.

A risk-free treatment interval has not been identified

Determine the appropriate length of therapy individually. There are insufficient data to estimate how long oestrogen with progestogen can be

taken before risk of breast cancer increases and general recommendations about the appropriate length of therapy cannot be made.^{6,14}

Review any change in the woman's risk profile annually and consider if therapy is still needed⁶

Small, unblinded trials suggest little difference in rebound symptoms between gradually and abruptly stopping HRT.^{15,16} Some guidelines suggest gradually tapering the dose in equal steps over 6 weeks for women whose symptoms were mild initially, and up to 6 months gradual reduction for those with initially severe symptoms.¹¹

Menopausal symptoms may recur in 30% to 50% of women after stopping HRT.^{14,17} If symptoms return persistently, review the risks and benefits before prescribing a further course. Vasomotor symptoms mostly need 2–3 years of treatment, but some women may need longer.¹³

Other pharmacological treatment options

Bioidentical hormone therapy has no evidence of efficacy and may be harmful

The safety and efficacy of compounded hormone products — often marketed as 'bioidentical', 'customised' or 'natural' therapy — have not been evaluated in randomised trials. Claims of superior safety are based on animal studies and trials with oestriol using inadequate doses.¹⁸ Compounded products are not subject to the same Therapeutic Goods Administration regulation as conventional prescription medicines, and there are medico-legal concerns about prescribing them.

Any oestrogenic compound with similar benefits to oestrogen-based HRT is likely to have the same risks. In addition, these formulations may contain too little progestogen to offer adequate endometrial protection; there have been 3 reported cases of endometrial cancer in women taking bioidentical hormones for several years.^{19,20} Furthermore, testosterone and DHEA 'bioidenticals' may result in undesirably high levels of testosterone.²¹

Low-dose oral contraceptives are sometimes suggested for menopausal symptoms in non-smoking women requiring contraception. Although there is little evidence, combined oral contraceptives are likely to have at least similar risks to oral hormone replacement therapy.²²

Tibolone may be as effective as oestrogen with progestogen for vasomotor symptoms²³

Tibolone also improves vaginal dryness and libido, and reduces fracture risk.^{23,24}

Avoid tibolone in older women and those at increased risk of stroke.²⁵ In one placebo-controlled trial with older women, tibolone increased stroke risk, but not in another trial with younger women.^{24,26} There is insufficient evidence to determine if tibolone is safer than oestrogen-based HRT. Tibolone may be unsuitable in perimenopausal women because it increases breakthrough bleeding.¹¹

Selective serotonin reuptake inhibitors (SSRIs) are an option in breast cancer-related hot flushes¹¹

Trials of SSRIs and venlafaxine for hot flushes in menopausal women and women with breast cancer have had mixed results.²⁷ Trials in women who had breast cancer treated with selective oestrogen receptor modulators were more likely to show a benefit.^{23,27}

Inform patients about the limited efficacy and safety data on complementary and alternative medicines

Complementary medicines are widely used, but evidence is lacking

Most complementary medicines have little evidence of efficacy and poor quality safety data. Anecdotal evidence is particularly unreliable, as hot flushes improve by up to 60% with placebo, partly due to natural fluctuation in symptoms.¹

The data for red clover, soy isoflavones and black cohosh do not support a significant treatment effect. The benefits found in some trials were mostly not clinically significant.^{28–30}

Adverse events have occurred with some complementary medicines

The sheer size of the WHI study (over 26 000 women) allowed very small risks to be identified.

There are no equivalent data for HRT alternatives and therefore their relative safety is uncertain.

Hepatotoxicity has been reported for black cohosh, with cases needing liver transplantation.³¹ One 5-year study of a high dose soy isoflavone extract in older women found a 3% increase in endometrial hyperplasia.³² However, other short-term studies of soy isoflavones, black cohosh or red clover have not found adverse effects on the endometrium or breast density when these were assessed.^{30,33} There are few safety data for dong quai, chasteberry or wild yam.³⁴

Natural 'progesterone' creams lack proven efficacy and may not protect the endometrium sufficiently when used in combination with oestrogenic therapies.

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References

1. MacLennan AH, et al. *Cochrane Database Syst Rev* 2004;CD002978.
2. Cobin RH, et al. *Endocr Pract* 2006;12:315–37.
3. Welton AJ, et al. *BMJ* 2008;337:a1190.
4. Osteoporosis Australia. Prevent the next fracture: GP guide. 2008. http://www.osteoporosis.org.au/files/internal/oa_fracture_gp.pdf (accessed 21 July 2009).
5. *Menopause* 2007;14:355–69.
6. Medicines and Healthcare products Regulatory Agency. UK Public Assessment Report. Hormone replacement therapy: safety update. 2007. <http://www.mhra.gov.uk/home/groups/pl-p/documents/websitesresources/con2032228.pdf> (accessed 23 June 2009).
7. Chlebowski RT, et al. *JAMA* 2003;289:3243–53.
8. Farquhar CM, et al. *Cochrane Database Syst Rev* 2009;CD004143.
9. Chlebowski RT, et al. *N Engl J Med* 2009;360:573–87.
10. Stefanick ML, et al. *JAMA* 2006;295:1647–57.
11. Therapeutic Guidelines: Endocrinology. Version 4. Melbourne: Therapeutic Guidelines Ltd, 2009.
12. Prentice RL, Anderson GL. *Annu Rev Public Health* 2007;29:131–50.
13. Menopause - Management. Clinical Knowledge Summaries. 2009. <http://cks.library.nhs.uk/menopause> (accessed 17 March 2009).
14. Utian WH, et al. *Menopause* 2008;15:584–602.
15. Aslan E, et al. *Maturitas* 2007;56:78–83.
16. Haimov-Kochman R, et al. *Menopause* 2006;13:370–6.
17. Ockene JK, et al. *JAMA* 2005;294:183–93.
18. Cirigliano M. *J Womens Health (Larchmt)* 2007;16:600–31.
19. Eden JA, et al. *Med J Aust* 2007;187:244–5.
20. MacLennan AH, Sturdee DW. *Climacteric* 2006;9:1–3.
21. Jean Hailes Foundation for Women's Health. Testosterone therapy for women. May 2008. <http://www.managingmenopause.org.au/content/view/124/143/> (accessed 24 July 2009).
22. ACOG Committee on Practice Bulletins-Gynecology. *Obstetrics Gynecol* 2006;107:1453–72.
23. Menopausal Symptoms. *Clinical Evidence* 2007. <http://clinicalevidence.bmj.com/ceweb/conditions/woh/0804/0804.jsp> (accessed 17 March 2009).
24. Cummings SR, et al. *N Engl J Med* 2008;359:697–708.
25. Australian Medicines Handbook. 2009.
26. Kenemans P, et al. *Lancet Oncol* 2009;10:135–46.
27. Nelson HD, et al. *JAMA* 2006;295:2057–71.
28. Howes LG, et al. *Maturitas* 2006;55:203–11.
29. Lethaby AE, et al. *Cochrane Database Syst Rev* 2007;CD001395.
30. Nedrow A, et al. *Arch Intern Med* 2006;166:1453–65.
31. Medicines and Healthcare products Regulatory Agency. Black Cohosh. UK Public Assessment Report. <http://www.mhra.gov.uk/home/groups/es-herbal/documents/websitesresources/con2024279.pdf> (accessed 17 March 2009).
32. Unfer V, et al. *Fertil Steril* 2004;82:145–8.
33. Alternatives to HRT for management of symptoms of the menopause. Scientific Advisory Committee Opinion paper 6. 2006. <http://www.rcog.org.uk/womens-health/clinical-guidance/alternatives-hrt-management-symptoms-menopause> (accessed 17 March 2009).
34. *Drug Ther Bull* 2009;47:2–6.

The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.



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