

## Therapeutic choices for menopausal symptoms

Oestrogen-based hormone replacement therapy (HRT) effectively treats menopausal symptoms, but fear of long-term harms can limit use. Discussions about treating menopausal symptoms should be informed by the evidence, the woman's individual circumstances and a realistic appraisal of the alternatives.

### HRT is the most effective treatment for menopausal symptoms

Oestrogen, with or without a progestogen, is the most effective proven treatment for menopausal symptoms<sup>1-3</sup> (see Box 1), decreasing hot flushes by 17–20 episodes per week more than placebo.<sup>4</sup> HRT reduces fracture risk and helps maintain bone density.<sup>2</sup>

Large clinical trials initiating HRT in older postmenopausal women have not shown benefits for cardiovascular disease, mortality, cognition or dementia.<sup>3</sup>

#### Box 1: Benefits of HRT<sup>3,5,6</sup>

HRT reduces	
Menopausal symptoms	Other effects
Hot flushes/night sweats	Osteoporotic fracture risk
Urogenital symptoms	Colorectal cancer risk
Sleep problems*	(oestrogen plus progestogen HRT only)
Arthralgia (oestrogen plus progestogen HRT)	Diabetes risk†
Sexual problems	

\* Sleep may be improved because of reduced vasomotor and urogenital symptoms<sup>3</sup>

† Self-reported diagnosis of diabetes in a subgroup of participants of the Women's Health Initiative study, with glucose measured in a small subsample

### Consider potential benefits and harms for individuals

Most risk estimates come from the Women's Health Initiative (WHI) study, but this population was not typical of women considering HRT for menopausal symptoms (see WHI inset, next page). Risks for women using HRT around menopause may be lower than popularly perceived (see Box 2).

The balance of benefits and potential harms for each woman depends on individual factors, including:

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

NPS is an independent, non-profit organisation for Quality Use of Medicines, funded by the Australian Government Department of Health and Ageing.

National Prescribing Service Limited

ABN 61 082 034 393 | Level 7/418A Elizabeth Street Surry Hills NSW 2010 | PO Box 1147 Strawberry Hills NSW 2012  
Phone: 02 8217 8700 | Fax: 02 9211 7578 | email: info@nps.org.au | web: www.nps.org.au

## Type of HRT

Combined HRT (oestrogen plus progestogen) is used for women with an intact uterus, to reduce risk of endometrial cancer, while unopposed oestrogen is used for women without a uterus. With this treatment approach, risks with oestrogen-only HRT were lower than for combined HRT for most outcomes in the WHI trials (except stroke).<sup>7</sup>

Observational data suggest a lower VTE risk with transdermal compared with oral HRT; however, long-term randomised trials have not been conducted.<sup>1,8</sup> Transdermal preparations may be more appropriate for women with hard-to-control hypertension, hypertriglyceridaemia, increased risk of cholelithiasis, significant liver disease, bowel dysfunction and inadequate control on oral therapy.<sup>1,2</sup>

## Age

Women in their 50s have a lower age-related risk of most events — such as stroke and coronary heart disease — than older postmenopausal women (> 60 years), so any increased risk with HRT is likely to be small (see Box 2).<sup>7</sup> As women age, their background risk of some events will increase and the balance of risks and benefits may change.

## Duration of therapy

The risks of breast cancer (with combined HRT) and endometrial cancer (with unopposed oestrogen in women with a uterus) increase with duration of therapy. The risk of VTE is greatest in the first 1–2 years of use, especially for obese women and those with thrombophilia.<sup>7,9</sup> Determine the appropriate length of therapy individually; general recommendations cannot be made.<sup>7,10</sup> Treatment durations greater than 5 years with combined HRT are thought to increase risk, but a risk-free treatment interval cannot be determined from available evidence, even below 5 years.<sup>7,10</sup>

## Breast cancer risk

**Oestrogen plus progestogen HRT:** Breast cancer risk increases with duration of therapy and declines 2–3 years after stopping.<sup>7,11,14</sup> The size of the increased risk in WHI was an extra 8 cases per 10,000 person years (or 4 per 1000 women taking combined HRT for 5 years).<sup>11,12</sup> Using Australian data on breast cancer incidence, the NHMRC estimated a baseline risk of 11 breast cancers per 1000 non-HRT-users, increasing to 15 breast cancers per 1000 women using combined HRT for 5 years.<sup>15</sup>

Increased risk was mainly in women who had used HRT before the study. Nonetheless, all participants had an increased risk over time of breast cancer.<sup>16</sup>

**Oestrogen-only HRT:** Oestrogen-only HRT did not increase breast cancer risk after 7 years in the WHI trial in women without a uterus, with unexpectedly fewer cases with oestrogen than placebo (statistically significant after adherence adjustment).<sup>13,17</sup> Some observational studies suggest increased risk with oestrogen only<sup>7</sup>, but after much longer treatment durations (e.g. 20 years).<sup>18</sup> Observational studies are prone to bias and confounding and randomised data provide the best evidence.

## Abnormal mammography

Both combined and oestrogen-only HRT increase breast density and abnormal mammography, which may concern women, even if breast cancer is not diagnosed.<sup>3,11,13</sup>

## Coronary heart disease (CHD)

CHD risk may be elevated in the first year of treatment in older postmenopausal women starting combined HRT.<sup>5,12</sup> In the WHI trials, 85% of CHD events were in women over 60 across both treatment regimens.<sup>19</sup> Some data suggest that starting HRT in older women several years after menopause increases vascular risk, while women closer to menopause may benefit because of differences in the vasculature after menopause.<sup>2,7</sup> This 'timing hypothesis' is under debate and remains speculative until specific randomised data are available.<sup>7</sup> The hypothesis does not relate to all outcomes (stroke, VTE, cancer).

### The Women's Health Initiative trials (WHI)<sup>20</sup> dramatically altered HRT prescribing worldwide

Trial populations: older women (average age 63 years) 13–14 years post menopause — not typical of women likely to start HRT for symptom management.

2 large-scale randomised controlled trials looking for CHD-prevention benefits seen in observational studies.

**Trial 1:** Combined HRT trial: conjugated equine oestrogens 0.625 mg with medroxyprogesterone 2.5 mg daily vs placebo (in women with a uterus)

Stopped early — with no cardiovascular benefits after 5 years, the benefit-to-harm ratio for women in the trial was unacceptable. The global harm index (including breast cancer, CHD, stroke, pulmonary embolism, death) exceeded the pre-specified boundary and was not offset by benefits in prespecified outcomes.

**Trial 2:** Oestrogen-only trial: conjugated equine oestrogens 0.625 mg daily vs placebo (in women without a uterus)

Stopped after 7 years because there was no CHD benefit and an elevated risk of stroke — but the global index of harms was not exceeded.

## Box 2: Potential harms of HRT (based on data from older postmenopausal women in the WHI study)<sup>6</sup>

Event	Increased risk per 10,000 women per year using HRT (instead of placebo)*	
	Oestrogen-only	Oestrogen and progestogen HRT
Stroke	12 extra strokes	8 extra strokes
VTE	8 extra VTEs <sup>†</sup>	18 extra VTEs
Coronary heart disease	No increase	6 extra CHD events
Breast cancer	No increase	8 extra cases
Endometrial cancer	Increased risk <sup>‡</sup>	No increased risk

\* Annualised incidence based on 6.8 years (for oestrogen-only) + 5.2 years' data (for oestrogen + progestogen).

<sup>†</sup> Statistically significant only for deep vein thrombosis.

<sup>‡</sup> From observational studies. The WHI oestrogen-only group all had prior hysterectomy.

### CASE REVIEW: Marjorie's story

Marjorie is 51, active and married. Her periods have been irregular for about 6 months and she feels tired, irritable and has 3 or 4 hot flushes a day. Her uterus is intact. She's heard that HRT causes breast cancer and wants to discuss her treatment options. *Is HRT an option? What information will help her decide?*

Your discussion with Marjorie could include:

- Typical experiences of menopause and midlife.
- Informing Marjorie how HRT will help her symptoms. Advise that short-term use of low-dose HRT (3–5 years) is often appropriate and the risks relatively small in her age group. Consider her risk factors such as age, personal and family medical history and cardiovascular and thrombotic risk.
- Telling Marjorie about the potential risks of combined HRT (see Box 2). Mention that risk declines after stopping treatment (but only after 2–3 years for breast cancer).
- Advise that the duration of therapy varies from woman to woman but you will discuss ongoing need and any change in risks and benefits annually.

## When can HRT be used?

HRT is recommended for moderate to severe menopausal symptoms, using the lowest effective dose for the shortest necessary duration (up to 5 years).<sup>2,3,21</sup> Some women may need longer treatment.

When using HRT:

- start with a low dose — it may take 2 or 3 visits over the first 6 months to tailor the dose, route and regimen to the individual
- low and ultra-low doses reduce vasomotor symptoms, with fewer short-term adverse effects than standard

doses (e.g. breast tenderness and bleeding)<sup>2</sup>; while it is not known if low doses reduce fracture risk, they help maintain BMD<sup>22</sup>

- vasomotor symptoms often need 2–5 years of treatment, and symptoms may recur after stopping (see below)
- review any change in the woman's risk profile annually and consider if therapy is still needed.<sup>7,21,23</sup>

Observational studies suggest that using HRT in women with premature or surgical menopause, reduces cardiovascular disease and osteoporotic fracture<sup>3</sup> but there are no randomised data. Being younger, their risk of other events is relatively low. Consider early specialist review.

### Advise women that symptoms may return after stopping HRT

Symptoms recur after stopping HRT in 30% to 50% of women (including vasomotor symptoms, pain or stiffness and vaginal dryness).<sup>10,24</sup> Small unblinded trials suggest little difference in rebound symptoms between gradually and abruptly stopping HRT.<sup>25,26\*</sup>

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.<sup>2</sup> Women who experience a return of symptoms may wish to extend their duration of therapy beyond 5 years; advise about the specific risks and benefits for the woman and her HRT regimen.<sup>2</sup>

### Consider intravaginal oestrogens for predominantly vaginal symptoms

#### Marjorie's story

It becomes apparent that Marjorie is most worried about her vaginal symptoms.

- Advise using water-based lubricants (Sylk, KY Jelly) and polycarbophil-based vaginal moisturiser (Replens). If these are insufficient, use topical vaginal oestrogens.
- Inform her that local oestrogen will not reduce non-vaginal symptoms.

Local vaginal oestrogens are useful if non-hormonal lubricants and moisturisers are insufficient, when moderate to severe vaginal symptoms (such as dryness) predominate.<sup>27</sup> A local oestrogen can be added if women continue to experience vaginal symptoms on low-dose systemic HRT. Symptoms can take 4–6 weeks to improve, or longer for dyspareunia.<sup>1,27</sup> Low-dose vaginal oestrogen does not reduce vasomotor symptoms or fracture risk.<sup>27</sup>

The effects of HRT on urinary tract infections are unclear<sup>27,28</sup> but urinary incontinence may be worsened by oral HRT.<sup>29</sup>

Vaginal oestrogens are considered safer than systemic HRT because there is little systemic absorption, although this can still occur.<sup>1,27</sup> Use the lowest effective dose and advise

\* The dose was tapered over 2 weeks (alternate days) in one trial<sup>26</sup> and reduced by 1 day per month over 6 months in another.<sup>25</sup>

women about correct dosing and application. Rarely, breast tenderness may indicate systemic absorption and possible overdosing.<sup>27</sup>

There is a lack of safety data beyond 1 year of use<sup>27</sup> but some women may need long-term therapy. If vaginal preparations are used long term, a 12-day course of progestin every 6–12 months can be considered to protect the endometrium<sup>2</sup>, although some experts consider this unnecessary, citing a lack of evidence.<sup>27,30</sup>

Topical oestrogens available in Australia include creams (Ovestin) and pessaries (Vagifem, Ovestin Ovula). None has been shown to be better than any other — consider patient preference.<sup>31</sup>

## What are the alternatives to HRT?

### Non-pharmacological changes

Lifestyle modifications such as regular light exercise, light clothing and reducing stress may help manage symptoms. Sleeping in a cooler room, relaxation therapy and sleep hygiene may help with sleep problems. Advise women to avoid possible triggers such as caffeine, smoking, alcohol and spicy foods.<sup>23</sup> Smoking is a risk factor for many conditions after menopause (e.g. osteoporosis): advise women to quit.

### Tibolone

Tibolone has oestrogenic, progestogenic and androgenic activity.<sup>1</sup> It improves vaginal dryness, vasomotor symptoms, and libido<sup>34</sup> and reduces fracture risk.<sup>35</sup> In trials it increased stroke risk in older women but not younger women.<sup>35</sup> Avoid use in older women and those with cardiovascular risk factors.

Tibolone increased the risk of breast cancer recurrence in women receiving adjuvant therapy and it is contraindicated in women with a history of breast cancer.<sup>2,36</sup> Effects on breast cancer risk in women without breast cancer and on the endometrium are uncertain.<sup>34,37</sup> Tibolone may be unsuitable in perimenopausal women because it increases breakthrough bleeding.<sup>2</sup> There is insufficient evidence to determine if tibolone is safer than HRT.

### Testosterone: long-term adverse effects are unknown

The use of testosterone (and dehydroepiandrosterone [DHEA]) in postmenopausal women is controversial; no products are TGA approved for this use in Australia. Small trials suggest that testosterone with oestrogen moderately improves sexual function compared with oestrogen alone.<sup>38</sup> Other than for surgical menopause, clinical guidelines recommend caution in using testosterone for the menopause because of

### Women using hormonal contraception

HRT preparations use much lower hormone doses than oral contraceptives but do not protect against conception in women with evidence of ovulation.<sup>2</sup>

Low-dose oral contraceptives are sometimes suggested for menopausal symptoms in non-smoking women requiring contraception.<sup>32</sup> Although there is little evidence, it can be assumed that combined oral contraceptives have similar risks to oral hormone replacement therapy for this age group.<sup>33</sup> (See *NPS News 54: Hormonal contraceptives* about appropriate hormonal contraception for women older than 40 years).

#### Marjorie's story

Marjorie has talked with friends, family, her doctor, her pharmacist and health shop workers. She's heard there are alternatives to HRT, some prescribed and some not.

- Ask which therapies Marjorie is considering, in a non-judgmental manner, and what she expects from treatment
- Advise about lifestyle changes, as a first step
- Use the information on pages 4–5 to help you discuss the alternatives to HRT, including complementary medicines.

limited understanding about its role, the diagnosis and treatment of androgen deficiency, and a lack of long-term safety data (e.g. for cardiovascular health and cancer risk).<sup>1,39</sup> (See insert on compounded and 'bioidentical' hormone therapy.)

### Selective serotonin reuptake inhibitors (SSRIs) may be an option in breast cancer

Trials of SSRIs and venlafaxine for hot flushes in menopausal women and women with breast cancer have had mixed results, with at best a reduction of 1 hot flush per day.<sup>40</sup> Trials in women with breast cancer using tamoxifen or other selective oestrogen-receptor modulators more often showed a benefit.<sup>34,40</sup>

Venlafaxine or paroxetine may be useful for women with breast cancer and severe flushes<sup>2</sup> or for those who do not wish to use HRT and understand the limited benefit of an antidepressant.<sup>41</sup> For most menopausal women the benefit-to-harm ratio is probably unfavourable; use is off-label in Australia.

**Bioidentical hormone therapy has no evidence of efficacy and may be harmful — see insert.**

## Complementary medicines are used, but evidence is still lacking

Despite more research, the evidence for complementary medicines is still inconclusive. Most have little efficacy and poor quality safety data. 'Natural' alternatives can provide a sense of wellbeing<sup>42</sup>, but they have financial costs and may not improve symptoms.<sup>41</sup>

Bear in mind that:

- hot flushes improve by up to 60% with placebo, partly due to natural fluctuation in symptoms<sup>43</sup>; anecdotal and uncontrolled reports of effectiveness are unreliable
- 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.

**Efficacy:** The evidence for red clover, soy isoflavones and black cohosh do not show a significant treatment effect. Some poor-quality trials indicate benefits, but these are usually clinically insignificant (e.g. 1 less hot flush per day), and are no greater than the placebo effect in HRT trials.<sup>44–46</sup> (See insert for details on efficacy and safety of commonly used complementary medicines.)

**Safety:** Hepatotoxicity requiring liver transplant has been reported for black cohosh.<sup>47</sup> Short-term studies of soy isoflavones, black cohosh and red clover do not show adverse effects on the endometrium, breast density or lipids<sup>41,44</sup>, although one 5-year study of a daily high-dose soy isoflavone extract in older women found a 3% increase in endometrial hyperplasia.<sup>48</sup> Dietary soy is probably safe.<sup>1,41</sup> There are few safety data for dong quai, chasteberry or wild yam.<sup>49</sup> Natural 'progesterone' creams may not protect the endometrium.<sup>40</sup>

### Marjorie's story

Marjorie mentions that friends have recommended black cohosh or red clover, which are natural and don't have side effects. She is keen to try them.

- Advise Marjorie that these alternative medicines don't have convincing evidence for helping hot flushes.
- Discuss possible severe liver toxicity with black cohosh and lack of efficacy data for red clover.
- Encourage Marjorie to let her health professionals know about any OTC medicines she may choose to take.

### Expert reviewers

Professor Alastair H. MacLennan  
Head of Discipline of Obstetrics & Gynaecology  
School of Paediatrics & Reproductive Health  
The Women's and Children's Hospital,  
University of Adelaide

Clinical Professor Bronwyn Stuckey  
Keogh Institute for Medical Research  
Department of Endocrinology and Diabetes  
Sir Charles Gairdner Hospital  
School of Medicine and Pharmacology  
University of Western Australia.

### References

1. Cobin RH, et al. *Endocr Pract* 2006;12:315-37.
2. Endocrinology Expert Group. *Therapeutic Guidelines: Endocrinology*. Version 4. Melbourne: Therapeutic Guidelines Ltd, 2009.
3. Australian Government National Health and Medical Research Council. *Hormone replacement therapy: A summary of the evidence*. Canberra: NHMRC, 2005.
4. Nelson HD. *JAMA* 2004;291:1610-20.
5. Vickers MR, et al. *BMJ* 2007;335:239.
6. Prentice
7. 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).
8. Canonico M, et al. *BJ* 2008;336:1227-31.
9. Curb JD, et al. *Arch Intern Med* 2006;166:772-80.
10. July 2008 position statement of The North American Menopause Society. *Menopause* 2008;15:584-602.
11. Chlebowski RT, et al. *JAMA* 2003;289:3243-53.
12. Farquhar CM, et al. *Cochrane Database Syst Rev* 2005;CD004143.
13. Stefanick ML, et al. *JAMA* 2006;295:1647-57.
14. Chlebowski RT, et al. *N Engl J Med* 2009;360:573-87.
15. Australian Government National Health and Medical Research Council. *Making Decisions: Should I use hormone replacement therapy? (HRT)*. 2005. [http://www.nhmrc.gov.au/publications/synopses/\\_files/wh37.pdf](http://www.nhmrc.gov.au/publications/synopses/_files/wh37.pdf) (accessed 23 June 2009).
16. Anderson GL, et al. *Maturitas* 2006;55:103-15.
17. Anderson GL, et al. *JAMA* 2004;291:1701-12.
18. Chen WY, et al. *Arch Intern Med* 2006;166:1027-32.
19. Rossouw JE, et al. *JAMA* 2007;297:1465-77.
20. Anderson GL, et al. *Clin Trials* 2007;4:207-17.
21. Royal Australian and New Zealand College of Obstetricians and Gynaecologists. *Hormone Therapy Advice*. 2007. <http://www.ranzog.edu.au/womenshealth/hormonetherapy.shtml> (accessed 17 March 2009).
22. 2006 position statement of The North American Menopause Society. *Menopause* 2006;13:340-67.
23. CKS. *Menopause - Management*. Clinical Knowledge Summaries. 2009. <http://cks.library.nhs.uk/menopause> (accessed 17 March 2009).
24. Ockene JK, et al. *JAMA* 2005;294:183-93.
25. Haimov-Kochman R, et al. *Menopause* 2006;13:370-6.
26. Aslan E, et al. *Maturitas* 2007;56:78-83.
27. 2007 position statement of The North American Menopause Society. *Menopause* 2007;14:355-69.
28. Moehrer B, et al. *Cochrane Database Syst Rev* 2003;CD001405.
29. Hendrix SL, et al. *JAMA* 2005;293:935-48.
30. MacLennan AH, Sturdee DW. *Climacteric* 2006;9:321-2.
31. Suckling J, et al. *Cochrane Database Syst Rev* 2006;CD001500.
32. Birkhauser MH, et al. *Climacteric* 2008;11:108-23.
33. ACOG Committee on Practice Bulletins-Gynecology. *Obstetrics & Gynecology* 2006;107:1453-72.
34. *Menopausal Symptoms*. Clinical Evidence 2007. <http://clinicalevidence.BMJ.com/ceweb/conditions/woh/0804/0804.jsp> (accessed 17 March 2009).
35. Cummings SR, et al. *New England Journal of Medicine* 2008;359:697-708.
36. Kenemans P, et al. *Lancet Oncol* 2009;10:135-46.
37. *Australian Medicines Handbook*. Adelaide: Australian Medicines Handbook Pty Ltd, 2008.
38. Sombonporn W, et al. *Testosterone for peri- and postmenopausal women*. CD004509. *Cochrane Database of Systematic Reviews* 2005. [http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD004509/pdf\\_standard\\_fs.html](http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD004509/pdf_standard_fs.html) (accessed 23 July 2009)
39. Wierman ME, et al. *J Clin Endocrinol Metab* 2006;91:3697-710.
40. Nelson HD, et al. *JAMA* 2006;295:2057-71.
41. *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).
42. Williamson M, et al. *Information use and needs of complementary medicines users*. 2008. [http://www.nps.org.au/\\_data/assets/pdf\\_file/0010/66619/Complementary\\_Medicines\\_Report\\_-\\_Consumers.pdf](http://www.nps.org.au/_data/assets/pdf_file/0010/66619/Complementary_Medicines_Report_-_Consumers.pdf) (accessed 17 March 2009).
43. MacLennan AH, et al. *Cochrane Database Syst Rev* 2004;CD002978.
44. Nedrow A, et al. *Arch Intern Med* 2006;166:1453-65.
45. Lethaby AE, et al. *Cochrane Database Syst Rev* 2007;CD001395.
46. Howes LG, et al. *Maturitas* 2006;55:203-11.
47. *Adverse Drug Reactions Advisory Committee*. *Aust Adv Drug Reactions Bull* 2006;25.

## Erratum: NPS News 61: Topical issues in dermatology

Table 1: Topical therapies for solar keratoses from the December 2008 issue of *NPS News* has been amended to clarify the limited evidence for the efficacy of 5-fluorouracil and to help provide a more reliable estimate of efficacy.

Topical treatment options for solar keratoses include photodynamic therapy, 5-fluorouracil, diclofenac and imiquimod (see Table 1). The table below presents a summary of their reported efficacy and possible side effects. Studies have not assessed whether topical therapies for solar keratoses prevent invasive skin cancer.

Differences between trials, such as in patient populations and outcome assessment, mean that it is not possible to reliably compare results presented for different therapies. Studies directly comparing the efficacy of topical therapies are few in number and often of poor quality.

When deciding on the most appropriate treatment approach, consider the site, number and thickness of lesions as well as individual patient factors (i.e. age, comorbidity, preference and treatment cost).<sup>1</sup> Refer to *NPS News 61 Topical issues in dermatology* for more information about considerations in selecting topical therapies for solar keratoses.

**Table 1: Topical therapies for solar keratoses**

Topical therapy	Reported efficacy	Possible side effects
<b>5-fluorouracil</b> 5%(Efudix)	Systematic review suggests an average complete clearance in about 50%* of patients (range 0%–96%). <sup>2</sup> This result should be interpreted with caution because of the poor quality of studies, many of which were unblinded, had unclear allocation concealment and did not account for dropouts.	Pain, burning, redness, itching, hyperpigmentation, blistering and cracking of the skin in the treated area. <sup>3</sup>
<b>Imiquimod 5%</b> (Aldara)	45% to 84%* complete clearance of lesions (2–8 weeks after the end of treatment). <sup>4–7</sup>	Local skin reactions (itching, burning, pain, erythema, flaking, scaling, dryness, scabbing, crusting, erosion and ulceration) are common and can be severe. <sup>5,8</sup> In 1 trial, 4% of imiquimod treated patients withdrew because of local skin reactions, 41% of patients required at least one rest period but most resumed treatment thereafter. <sup>5</sup> Systemic flu-like symptoms may occur (e.g. malaise, fever, nausea, myalgia). <sup>8</sup>
<b>Photodynamic therapy</b> using methyl aminolevulinate (Metvix)	69% to 91% <sup>†</sup> complete response in short-term comparative trials (3–6 months of follow-up). <sup>9–12</sup> Cryotherapy may be more suitable for thicker lesions <sup>9,12</sup> and those in less cosmetically sensitive areas. <sup>10,11,13</sup>	Temporary pain, burning, erythema, itching, oedema and crusting. <sup>14</sup> Pain is sometimes severe and may require analgesia and/or local anaesthesia, or rarely, treatment cessation. <sup>15</sup>
<b>Diclofenac</b> (Solaraze 3% gel)	50%* complete clearance vs 20% with placebo (30 days follow-up after the end of treatment). <sup>16</sup>	Contact dermatitis, erythema, rash, inflammation, irritation, pain, itching, tingling or blistering in the treated area. <sup>17</sup>

\* Percentage of patients with complete clearance of all treated lesions

<sup>†</sup> Percentage of treated lesions cleared completely

### References

- Therapeutic Guidelines Limited. Therapeutic Guidelines: Dermatology; Version 3. 2009
- Askew DA, et al. *Int J Dermatol* 2009;48:453-63.
- Valeant Pharmaceuticals Australasia Pty Ltd. 1 June 2008.
- Lebwohl M, et al. *J Am Acad Dermatol* 2004;50:714-21.
- Korman N, et al. *Arch Dermatol* 2005;141:467-73.
- Szeimies RM, et al. *J Am Acad Dermatol* 2004;51:547-55.
- Stockfleth E, et al. *Arch Dermatol* 2002;138:1498-502.
- iNova Pharmaceuticals (Australia) Pty Limited. 2 April 2009.
- Szeimies RM, et al. *J Am Acad Dermatol* 2002;47.
- Kaufmann R, et al. *Br J Dermatol* 2008;158:994-9.
- Morton C, et al. *Br J Dermatol* 2006;155:1029-36.
- Freeman M, et al. *J Dermatolog Treat* 2003;14:99-106.
- de Berker D, et al. *Br J Dermatol* 2007;156:222-30.
- Galderma Australia Pty Ltd. 1 August 2008.
- Australian Medicines Handbook, 2009.
- Wolf JE Jr, et al. *Int J Dermatol* 2001;40:709-13.
- CSL Limited. 12 December 2008.

*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.*



National Prescribing Service Limited

## Compounded and 'bioidentical' hormone therapy — claims and uncertainties<sup>1-7</sup>

What is claimed	What is known
<ul style="list-style-type: none"> <li>'Bioidentical' hormones are promoted as being identical to those produced by a woman's body (e.g. oestriol), rather than 'synthetic'.</li> </ul>	<p>Bioidentical hormones may contain oestradiol, oestriol, oestrone, progesterone, testosterone and dehydroepiandrosterone (DHEA), formulated in various combinations in buccal trouches, lozenges and topical creams. The formulations 'triest' and 'biest' are commonly used, in which oestriol is the principal component.</p> <p>In reality 'bioidentical hormones' may be from plant, animal or synthetic sources.</p>
<ul style="list-style-type: none"> <li>Compounded bioidentical hormone therapy can be 'tailored' or 'customised' to the woman's hormone needs, sometimes using salivary measures of hormone levels.</li> </ul>	<p>There are no peer-reviewed data of appropriate salivary levels required for a clinical response, and salivary measures are unreliable hormone assays.<sup>4</sup></p>
<ul style="list-style-type: none"> <li>Promoted as being safer, gentler and more natural than pharmaceutical HRT.</li> </ul>	<p>Some substances used in bioidentical hormone therapy are available in conventional HRT; for example, many conventional HRT products contain oestradiol, an oestrogen that naturally occurs in the body.</p> <p>Any oestrogenic compound with similar benefits to those of conventional HRT may also have the same risks. There is a further risk of inadequate endometrial protection, with 3 reported cases of endometrial cancer in women taking bioidentical hormones (including progesterone, dose unknown) for several years.<sup>5</sup> Testosterone and DHEA 'bioidenticals' may cause high testosterone levels, with unknown safety.<sup>6</sup></p>
<ul style="list-style-type: none"> <li>Claim to be supported by evidence.</li> </ul>	<p>Compounded products have not been shown to be effective in randomised trials.</p> <p>Safety claims are based on animal studies and trials with oestriol using inadequate doses.<sup>7</sup></p> <p>There are medicolegal concerns about the prescription of unproven, non-TGA-approved bioidentical hormones.</p>

## Evidence for efficacy and safety of complementary medicines available for menopausal symptoms

Efficacy for hot flushes and menopausal symptoms	Safety
<b>Black cohosh — equivocal, inconsistent evidence of benefit</b>	
<ul style="list-style-type: none"> <li>3 of 6 trials reported improvements on a menopausal symptom severity score.<sup>8,9</sup></li> <li>The best quality 1-year publicly funded study found no benefit.<sup>10,11</sup> The extract in this study was a non-proprietary product, similar to marketed products. Women were aged 45–55, with an average of 6.5 hot flushes per day.<sup>10,11</sup></li> </ul>	<ul style="list-style-type: none"> <li>Hepatotoxicity has occurred.<sup>12</sup> Advise people to report liver symptoms.</li> <li>No short-term adverse effects identified in small studies up to 1 year.</li> <li>Gastrointestinal upset may occur rarely.</li> <li>Effects on breast have not been studied<sup>13</sup></li> <li>No endometrial thickening seen after 3 months<sup>13</sup></li> <li>No long-term data</li> </ul>
<p>Quality of evidence<sup>†</sup></p> <p>Evidence reviewed: systematic reviews of 6 trials, in 1170 peri- or postmenopausal women. 217 women with breast cancer risk or history.<sup>8</sup></p> <p>Quality: fair–poor, with only one good-quality study.<sup>8</sup> Average duration: 3 months, one 12-month study.</p>	
<b>Phytoestrogens/isoflavones</b>	
<b>Red clover extract — treatment effects range from small to none in systematic reviews<sup>14-16</sup></b>	
<ul style="list-style-type: none"> <li>At best, 1 fewer hot flush per day in women experiencing 5–9 flushes per day.<sup>16</sup></li> <li>A good-quality 12-week study in mostly postmenopausal women found no benefit.<sup>17</sup> In this study, symptoms were reduced by 35% to 40% in both placebo and 2 red clover study groups (Promensil and Rimostil). Despite this, women in all three groups were still experiencing more than 5 hot flushes per day after 12 weeks.<sup>17</sup></li> </ul>	<ul style="list-style-type: none"> <li>No serious short-term adverse effects were identified.</li> <li>No effects on breast density, lipids, endometrial thickness or bone were found in a 3-year study in women with a family history of breast cancer. 320 of the 401 women were premenopausal; may not generalise to postmenopausal women.<sup>18</sup></li> <li>2 trials reported no effect on endometrial thickness, 2 reported a decrease in endometrial thickness.<sup>14</sup></li> <li>Red clover extracts may contain coumarins and can affect INR.</li> </ul>
<p>Quality of evidence</p> <p>Evidence reviewed: systematic reviews of 6 placebo-controlled trials, all of the brand Promensil; including about 300 women.<sup>13</sup> Average duration: 12-16 weeks.</p> <p>Quality: fair–poor, with 1 good-quality study.<sup>8,14</sup></p>	

(Continued overleaf)



National Prescribing Service Limited

National Prescribing Service Limited (NPS) is an independent, non-profit organisation for Quality Use of Medicines. We provide accurate, balanced, evidence-based information and services to help people choose if, when and how to use medicines to improve their health and wellbeing. We are member-based and work in partnership with health professionals, government, pharmaceutical industry and consumers. NPS is funded by the Australian Government Department of Health and Ageing.

## Evidence for efficacy and safety of complementary medicines available for menopausal symptoms (continued)

Efficacy for hot flushes and menopausal symptoms	Safety
<b>Soy isoflavones</b>	
<b>Dietary soy (flour, powder or beverages) — no evidence of an effect on hot flush frequency or severity<sup>14,15</sup></b>	
<ul style="list-style-type: none"> <li>• 7 of 9 studies found no differences in hot flushes.<sup>14</sup></li> <li>• 1 good-quality trial found no difference from placebo after 12 weeks 90 mg/day.<sup>8</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Short-term effects include unpleasant taste and gastrointestinal effects (bloating, weight gain).</li> <li>• No data to assess longer term adverse effects.</li> </ul>
<p>Quality of evidence</p> <p>Evidence reviewed: systematic reviews of 10–11 trials.<sup>8,14</sup> Average duration: 12–24 weeks, 1 trial of 96 weeks.<sup>8</sup> Quality: most poor to fair. 1 good-quality trial.<sup>8</sup></p>	
<b>Soy isoflavone extracts (usually tablets) — mixed results, with no consistent evidence of benefit, in mostly poor-quality trials</b>	
<ul style="list-style-type: none"> <li>• 5 of 9 trials reported significant differences in frequency or severity of hot flushes<sup>14</sup></li> <li>• At best, 1 less hot flush per day.<sup>15</sup></li> </ul>	<ul style="list-style-type: none"> <li>• 5 trials evaluated endometrial thickness and found no difference during course of trial (longest trial 1 year).<sup>15</sup></li> <li>• Short term effects include bloating, nausea, weight gain, concerns about bowel function.<sup>14</sup></li> <li>• Studies measuring effects on vaginal pH and vaginal maturation indices had mixed results.<sup>14</sup></li> <li>• One poor quality trial found increased endometrial hyperplasia in older postmenopausal women taking a soy extract for 5 years compared with placebo.<sup>19</sup></li> </ul>
<p>Quality of evidence</p> <p>Evidence reviewed: 3 systematic reviews of 9–11 trials<sup>14,15,16</sup>, including around 1200 women. 1 systematic review included around 600 women with breast cancer.<sup>15</sup> Average duration: 12–24 weeks, one 2-year study. Quality: Fair–poor.<sup>14,15</sup></p>	
<b>Other interventions</b>	
<b>Dong quai — no effect on number of hot flushes or the Kupperman Index<sup>20†</sup></b>	
	<ul style="list-style-type: none"> <li>• May have oestrogenic effects and has shown in-vitro proliferation of breast-cancer cells — do not use in breast cancer and other oestrogen-sensitive conditions.<sup>21</sup></li> <li>• One small trial found no effect on endometrial thickness, or vaginal maturation indices.</li> <li>• Contains coumarins and can increase INR.<sup>21</sup></li> <li>• Has antiplatelet and anticoagulant effects.</li> </ul>
<p>Quality of evidence: 1 poor-quality trial of 71 postmenopausal women.<sup>20</sup></p>	
<b>Wild yam, progesterone topical creams — no effect on hot flushes<sup>8</sup></b>	
	<ul style="list-style-type: none"> <li>• Wild yam is incorrectly believed to be a natural progesterone, but it cannot be converted to progesterone in the body and does not oppose oestrogen.<sup>22</sup></li> <li>• Do not use as the progestogen component of HRT.<sup>22</sup></li> </ul>
<p>Quality of evidence: 2 poor-quality trials in 80 women using wild yam for 12 weeks.<sup>8</sup></p>	
<b>Ginseng — no effect on menopausal symptoms including mood, psychological wellbeing and cognition</b>	
	<ul style="list-style-type: none"> <li>• May interact with warfarin to reduce INR.<sup>23</sup></li> </ul>
<p>Quality of evidence: 2 trials (6–16 weeks); 1 trial used a standardised ginseng extract, the other panax ginseng with ginkgo.<sup>23</sup></p>	
<b>Vitamin E — no differences in hot flushes or severity with 800 units daily<sup>8</sup></b>	
	<ul style="list-style-type: none"> <li>• Doses of vitamin E &gt; 400 units per day have been associated with increased mortality in observational data.<sup>13</sup></li> </ul>
<p>Quality of evidence: 1 fair-quality trial in 125 women with previous breast cancer<sup>8</sup></p>	

\* In randomised, blinded clinical trials

† Indicators of quality were adequacy of randomisation, allocation concealment, blinding, power, intention-to-treat analysis (the least-biased, most conservative method; results are analysed according to randomisation regardless of dropouts).<sup>8,14</sup>

‡ A scale rating severity of symptoms, including hot flushes, numbness/tingling, insomnia, arthralgia, nervousness, weakness, depression, vertigo, headache, palpitations and formication.<sup>23</sup>

### References

1. US Food and Drug Administration. Bio-Identicals: Sorting myths from facts. 2008. (accessed 23 June 2009).
2. Australian Menopause Society. Bioidentical hormones for menopausal symptoms. Buderim: Australian Menopause Society, 2007.
3. Monash University. "Bioidentical" hormones. 2009. (accessed 23 June 2009).
4. MacLennan AH, Sturdee DW. Climacteric 2006;9:1–3.
5. Eden JA, et al. Med J Aust 2007;187:244–5.
6. Testosterone therapy for women. Jean Hailes Foundation for Women's Health. May 2008. (accessed 17 March 2009).
7. Cirigliano, M. J Womens Health (Larchmt) 2007;16:600–31.
8. Nedrow A, et al. Arch Intern Med 2006;166:1453–65.
9. Borrelli F, Ernst E. Pharmacol Res 2008;58:8–14.
10. Reed SD, et al. Menopause 2008;15:51–8.
11. Newton KM, et al. Ann Intern Med 2006;145:869–79.
12. Aust Adv Drug Reactions Bull 2006;25(2). (accessed 23 June 2009)8.
13. Alternatives to HRT for management of symptoms of the menopause. Scientific Advisory Committee Opinion paper 6. Canberra: Royal College of Obstetricians and Gynaecologists, 2006. (accessed 17 March 2009).
14. Lethaby AE, et al. Cochrane Database Syst Rev 2007;CD001395.
15. Nelson HD, et al. JAMA 2006;295:2057–71.
16. Howes LG, et al. Maturitas 2006;55:203–11.
17. Tice JA, et al. JAMA 2003;290:207–14.
18. Powles TJ, et al. Menopause Int 2008;14:6–12.
19. Unfer V, et al. Fertil Steril 2004;82:145–8.
20. Hirata JD, et al. Fertil Steril 1997;68:981–6.
21. Dong Quai. Natural Medicines Comprehensive Database.
22. Australian Medicines Handbook, 2009.
23. Herbal medicines for menopausal symptoms. Drug Ther Bull 2009;47:2–6.