



Australian Government

National Health and Medical Research Council

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Hormone Replacement Therapy:

A SUMMARY OF THE EVIDENCE

for General Practitioners and other Health Professionals

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IN BRIEF

Main benefits of HRT

HRT reduces the incidence or risk of:

- hot flushes
- urogenital symptoms
- sleep problems
- osteoporotic fracture
- colorectal cancer (combined HRT)

Main risks of HRT

HRT increases the risk of:

- DVT, PE
- stroke
- breast cancer (combined HRT)
- endometrial cancer (oestrogen-only HRT)
- ovarian cancer (oestrogen-only HRT)

No change in risk

HRT does not appear to affect:

- weight gain
- headache, migraine
- breast cancer (oestrogen-only HRT)
- colorectal cancer (oestrogen-only HRT)

Insufficient evidence

It is not clear whether HRT affects:

- other menopausal symptoms
- coronary artery disease
- ovarian cancer (combined HRT)
- cognition, dementia

This summary sets out the risks and benefits associated with use of hormone replacement therapy (HRT) in women around the time of menopause. It is based on a comprehensive review of the evidence, interpreted by an expert NHMRC working party. The NHMRC website, www.nhmrc.gov.au includes the commissioned literature review.

Women need to be active partners in deciding about HRT. The evidence relates to populations, not to individual women, and each woman's individual history and circumstances need to be taken into account.

Other NHMRC resources to support this decision making are:

- *Hormone Replacement Therapy: Exploring the Options for Women*, a booklet providing information on HRT; and
- *Making decisions: Should I use hormone replacement therapy? (HRT)* a resource to help the individual woman weigh up the pros and cons of combined HRT for her.

KEY FINDINGS

- **Symptoms:** HRT is an effective proven therapy for the management of hot flushes and some other menopausal symptoms.
- **Osteoporotic fracture:** HRT reduces the rate of osteoporotic fracture, but any benefit depends on continued use.
- **Breast cancer:** For oestrogen-only HRT, current evidence indicates little or no effect. Combined HRT increases the risk of breast cancer. Risk increases with duration of use.
- **Endometrial cancer:** Risk is increased with oestrogen therapy, but not with continuous combined HRT.
- **Coronary artery disease:** HRT does not appear to provide primary or secondary prevention. An increase in risk with HRT cannot be ruled out.
- **Stroke:** HRT increases the risk of stroke.
- **Venous thromboembolism (Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE)):** HRT increases the risk, especially in the first year of use.
- **Tibolone and Raloxifene:** Tibolone is an effective therapy for menopausal symptoms, and Raloxifene for osteoporosis: Risk-related evidence is very limited, especially on long-term risk. Research has focused on areas of their anticipated usefulness and side effects.
- **Complementary and alternative medicines (CAMs), “natural” hormones:** No evidence-based statement can be made about the benefits or risks of any of these.
- **Premature menopause:** There is no clear evidence on risks and benefits of HRT for younger women with premature or surgical menopause.

CONCERNS AND QUESTIONS WOMEN MAY RAISE

ABOUT SYMPTOMS:

- hot flushes, night sweats
- vaginal dryness, painful sex
- urinary incontinence, infections
- loss of libido
- depression, anxiety, irritability, mood swings
- memory loss, difficulty concentrating
- headaches, migraine
- dry, itchy skin
- muscle and joint pain
- tiredness, disturbed sleep
- quality of life/wellbeing

ABOUT HRT SIDE-EFFECTS (PERCEIVED OR POTENTIAL):

- bleeding
- migraine/headache
- nausea/vomiting
- weight gain
- breast tenderness
- fluid retention
- hair loss/gain
- high blood pressure

ABOUT POTENTIAL HEALTH RISKS AND BENEFITS OF HRT:

- bone mineral density, osteoporosis, fracture
- breast cancer
- endometrial cancer
- colorectal cancer
- heart disease
- stroke
- venous thromboembolism

- gallbladder disease
- mammography interpretation

ABOUT OTHER POTENTIAL APPROACHES:

- lifestyle approaches to disease prevention
- complementary, alternative and “natural” therapies

NHMRC Levels of evidence

Level I:

Evidence from a systematic review of all relevant randomised controlled trials.

Level II:

Evidence from at least one properly designed randomised controlled trial.

Level III-1:

Evidence from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).

Level III-2:

Evidence from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies, or interrupted time series with a control group.

Level III-3:

Evidence from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group.

RELIEF OF MENOPAUSE SYMPTOMS

EFFECT OF HRT ON SYMPTOMS OF MENOPAUSE

Vasomotor Systems: HRT including tibolone (see page 7) is effective in treating hot flushes in postmenopausal women (Level I & II evidence). The benefits appear to be present across the Australian-approved dose regimens of combined oestrogen/progesterone therapy, and oestrogen-only therapy.

Urogenital Symptoms: HRT (including tibolone) relieves urogenital symptoms associated with menopause (Level I & II evidence). Vaginal preparations are as effective as oral HRT in alleviating vaginal symptoms.

Sleep: HRT improves sleep (Level II evidence). It is unclear whether this is because of, or independent of, the improvements in vasomotor and urogenital symptoms.

Psychological Wellbeing, General Quality of Life: The impact on these issues is less clear. Women reporting a decrease in psychological wellbeing or quality of life fall within the normal range experienced by non-menopausal women. Level I, II & III-2 evidence suggests a possible slight effect.

Other Symptoms: There is insufficient evidence to draw conclusions about the efficacy of HRT to improve other symptoms reported by women.

UNWANTED SIDE-EFFECTS OF HRT

Bleeding: Level I evidence indicates more frequent irregular bleeding with oral HRT compared to placebo, for both oestrogen-only and combined (particularly continuous) HRT; and for transdermal oestrogen-only, other than low dose (25 µg). No studies were available for transdermal combined HRT. Tibolone causes less bleeding than HRT, provided it is not started until one year after the last period (Level I & II evidence).

Weight Gain: Level I & II evidence shows no effect of HRT on weight gain.

Other Unwanted Side Effects: HRT increases the likelihood of breast tenderness, but not fluid retention or migraine/headache (Level I & II evidence). There is insufficient evidence to draw conclusions on the relationship between HRT or tibolone and other symptoms reported by women.

UNWANTED SIDE-EFFECTS OF HRT

OTHER POTENTIAL HEALTH BENEFITS OF HRT

EFFECT OF HRT ON COLORECTAL CANCER

Oestrogen-only HRT: There is no evidence of a protective effect. One large RCT (Level II evidence) suggests there is no effect.

Combined HRT: There is consistent Level II evidence of a small protective effect. Based on this evidence and Australian incidence figures, HRT can be expected to prevent one case of colorectal cancer per 1000 women in their 50s who take this therapy for 5 years (a decrease from 3 to 2 per 1000 women).

EFFECT OF HRT ON OSTEOPOROTIC FRACTURE

Note: The Literature Review looked at evidence relating to fracture, rather than osteopaenia/osteoporosis as indicated by bone mineral density.

Good quality level I, II & III-2 evidence suggests a reduced risk of fracture with HRT, with observational evidence indicating reduced risk across all fracture sites. Whilst the evidence suggests that HRT with progestogen confers greater protection, direct comparison may not be appropriate due to the different study populations. The only study to report fracture risk by duration of HRT use (Level III-2 evidence) found a benefit only with >2 years of use.

The recent large WHI trial¹ (Level II evidence) showed a significant reduction in fractures at hip, vertebrae and wrist. The HERS study^{2,3} (Level II evidence), which looked specifically at HRT in women with established heart disease, showed an overall protective effect but no statistically significant reduction in fracture at any specific site.

Any protective benefit appears to depend on continued use. Evidence from past users shows that risk reduction is not maintained beyond 5 years after stopping HRT (Level II evidence).

Vaginal administration of oestrogens does not appear to offer a protective effect (Level III-2 evidence).

Raloxifene: Level I & II evidence indicates that raloxifene decreases risk of new vertebral fractures in osteoporotic women, but has no effect on risk of non-vertebral fractures (see Raloxifene box on page 8 for other risk-related information).

EFFECT OF HRT ON COGNITION/DEMENTIA

Women in General: Interpreting the evidence is difficult as the women studied and tests used vary across studies. On balance, the systematic reviews (Level I evidence) and subsequent studies do not show a consistent benefit on cognition, although isolated studies show a positive effect.

Women with Dementia: There is little good quality evidence. The highest quality systematic review (Level I evidence) reports inconsistent findings on HRT and cognition in women with dementia.

EFFECT OF HRT ON BREAST CANCER

Oestrogen-only HRT: Current Level I, II & III-2 evidence shows little or no effect of oestrogen-only HRT on breast cancer risk.

Combined HRT: High quality systematic reviews (Level I evidence), plus recent RCTs and observational studies (Level II & III-2 evidence), confirm an increased risk of breast cancer with combined HRT. Based on this research and Australian incidence figures, 4 excess cancers can be expected per 1000 women in their 50s using this therapy for 5 years (an increase from 11 to 15 per 1000 women). The magnitude of the increased risk should be considered in the context of the absolute risk of breast cancer in this population. The risk appears to diminish with increasing time since cessation of HRT.

- 1 Cauley JA, Robbins J, Chen Z et al. 2003, Effects of estrogen plus progestin on risk of fracture and bone mineral density, *Journal of the American Medical Association*, 290: 1729-1738.
- 2 Hulley S, Furberg C, Barrett-Connor E et al. 2002, Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II), *Journal of the American Medical Association*, 288(1): 58-66.
- 3 Hulley S, Grady D, Bush T et al. 1998, Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women, *Journal of the American Medical Association*, 280(7):605-613.

EFFECT OF HRT ON BREAST CANCER continued

Women with Previous Breast Cancer: A recent trial⁴ was stopped because HRT was associated with increased risk of recurrence. (This study was published after completion of the NHMRC literature review.)

MAMMOGRAPHY AND HRT

Recent Level III evidence^{5,6} (published after completion of the NHMRC literature review) indicates HRT (combined or oestrogen-only) increases the risk of false positive mammographic findings, in both current and past users. Women recalled for investigation following a false positive mammogram may experience inconvenience and anxiety, and may be less likely to accept subsequent invitations to screening.

EFFECT OF HRT ON ENDOMETRIAL CANCER

Oestrogen-only HRT: For women with an intact uterus, oestrogen-only HRT increases endometrial cancer risk (Level I, II & III-2 evidence). The increase in risk is closely related to the duration of oestrogen-only use. Elevated risk persists whether women discontinue HRT or switch to combined oestrogen/progestogen HRT. Some, but not all, studies suggest that the risk may diminish over time.

Combined HRT: High quality RCT evidence (Level II) shows no increased risk with continuous combined HRT (this assumes a sufficient dose of progestogen with standard doses of oestrogen: ≥ 2.5 mg medroxy progesterone acetate, or equivalent doses of other progestogens). The protective effect of progestogen is dose- and duration-dependent.

Evidence from observational studies (Level III-2) is less consistent. Some small case-control studies report an elevation in risk with longer duration combined HRT (continuous or sequential). Nevertheless, any increase in risk with oestrogen/progestogen HRT is smaller than the increase with oestrogen alone.

EFFECT OF HRT ON OVARIAN CANCER

Oestrogen-only HRT: Level III-2 evidence suggests an increased risk of ovarian cancer, with risk increasing with longer duration of therapy.

Combined HRT: A high quality RCT (Level II evidence) provides insufficient evidence to draw conclusions on the risk of ovarian cancer.

EFFECT OF HRT ON CORONARY ARTERY DISEASE

Oestrogen-only HRT: There is insufficient evidence from RCTs (Level II evidence) to draw conclusions on the effect of oestrogen-only HRT on CAD.

Combined HRT: Recent high quality trials (Level II evidence) indicate that combined HRT does not provide primary protection against CAD. An increase in risk cannot be ruled out.

Women with Existing Cardiovascular Disease: Level II evidence shows no effect of HRT on risk of Myocardial Infarction (MI) or Chronic Heart Disease (CHD) death.

- 4 Holmberg L, Anderson H. 2004. "HABITS (hormonal replacement therapy after breast cancer – is it safe?), a randomised comparison: trial stopped", *The Lancet*, published online February 3. <http://image.thelancet.com/extras/03let12260web.pdf>
- 5 Banks E, Reeves G, Beral V, Bull D, Crossley B, Simmonds M, Hilton E et al. 2004. Impact of use of hormone replacement therapy on false positive recall in the NHS breast screening programme: results from the million women study. *British Medical Journal*, 328: 1291-1292
- 6 Chlebowski RT, Hendrix SL, Langer RD, Stefanick ML, Gass M, Lane D, Rodabough RJ et al. 2003. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women. The Women's Health Initiative randomized trial. *Journal of the American Medical Association*, 289: 3243-3253.

EFFECT OF HRT ON STROKE

There is consistent evidence from RCTs and observational studies (Level II & III-2 evidence) of an increase in risk of stroke with HRT (both combined and oestrogen-only). Based on this research and Australian incidence figures, 2 excess strokes can be expected per 1000 women in their 50s who use HRT for 5 years (an increase from 4 to 6 per 1000 women).

The WHI oestrogen-only study⁷ (Level II evidence, published after completion of the NHMRC literature review) was stopped because of an increase in stroke.

There is insufficient evidence from RCTs to distinguish stroke type.

There is some Level III evidence indicating that any risk increase is dose-dependent with respect to oestrogen.

VENOUS THROMBOEMBOLISM (DVT AND PE)

Oestrogen-only HRT: There is insufficient evidence (Level II) from RCTs to draw conclusions on risk.

Combined HRT: Systematic reviews and a large, high quality RCT (Level I & II evidence) indicate a substantially increased risk of DVT and PE for women on combined HRT. Based on this research and Australian incidence figures, 5 excess venous thromboembolisms can be expected per 1000 women using HRT for 5 years (an increase from 3 to 8 per 1000 women). Level III evidence suggests that the risk may be greatest especially within the first year of HRT use.

Women with existing cardiovascular disease are at similar risk to women without existing CVD.

CHOLECYSTITIS/CHOLECYSTECTOMY

A recent high quality RCT (Level II evidence) showed a slight increase, of borderline statistical significance, for risk of gallbladder disease and biliary tract surgery with combined oestrogen/progestogen HRT.

TIBOLONE AND RALOXIFENE

These are sometimes regarded as different from conventional oestrogen/progestogen HRT. Although they both act on oestrogen receptors (sometimes called selective estrogen receptor modulators), they have differing effects on different tissues (see below).

Vasomotor and Urogenital Symptoms: Consistent Level I & II evidence shows tibolone to be more effective than placebo or no treatment, and equal in efficacy to HRT.

Sleep Disturbance: There is limited and conflicting Level II evidence that tibolone has an effect.

Quality of Life: There is limited Level II evidence that tibolone improves global quality of life, but no evidence on its effectiveness according to menopause-specific global symptom scales.

Bleeding: Level I & II evidence suggests that while tibolone does cause bleeding, particularly in the early stages of treatment, it is associated with a lower incidence of bleeding than either oestrogen or continuous combined HRT.

Breast Cancer, Osteoporotic Fracture, Other Health Conditions: There is insufficient evidence to determine the impact of tibolone on risk.

7 The Women's Health Initiative Steering Committee. 2004. "Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative Randomized Controlled Trial". *Journal of the American Medical Association* 291(14), 1701-12

TIBOLONE AND RALOXIFENE continued

Osteoporotic Fracture: Level I & II evidence indicates that raloxifene decreases the risk of new vertebral fractures in osteoporotic women, but has no effect on risk of non-vertebral fractures.

Venous Thromboembolism: Level II evidence indicates that raloxifene significantly increases risk.

Endometrial Cancer: Level II evidence indicates that raloxifene has no effect on risk.

Breast Cancer: There is Level II evidence that raloxifene decreases risk.

Cardiovascular Events: There is some Level II evidence that raloxifene decreases risk in women with existing increased cardiovascular risk, but has no effect on cardiovascular event rates in women in general.

Vaginal Bleeding: There is Level II evidence that Raloxifene does not appear to increase vaginal bleeding.

SOY AND SOY PRODUCTS

Recent Level I evidence⁸ (published after completion of the NHMRC literature review) shows no significant impact on hot flushes, global menopausal symptoms or quality of life scales.

Limited Level II evidence suggests soy protein has no effect on sleep disturbance.

BLACK COHOSH

There is a paucity of good quality evidence on the efficacy of black cohosh against hot flushes, and no evidence on its effect on sleep disturbances.

OTHER SUBSTANCES INCLUDING DONG QUAI, EVENING PRIMROSE OIL, GINSENG, RED CLOVER AND CHINESE HERBS

Level II evidence indicates that dong quai, evening primrose oil, ginseng and a Chinese herb mixture have no effect on hot flushes.

Recent Level 1 evidence⁹ (published after completion of the NHMRC literature review) indicates that red clover (promensil) has no significant impact on hot flushes.

Limited Level II evidence indicates that dong quai has no effect on urogenital symptoms.

There is no evidence on the effect of these herbs on sleep disturbances.

NHMRC RESOURCES

Available online at www.nhmrc.gov.au

Hormone Replacement Therapy: Exploring the Options for Women, 2005

Making Decisions: Should I use hormone replacement therapy? (HRT) 2005

Hormone Replacement Therapy for Women At or After the Menopause: a comprehensive literature review, 2004

HRT Evidence Summary Table: Effects and Levels of Evidence, 2005

A Guide to the Development, Implementation and Evaluation of Clinical Practice Guidelines, 1999

8 Krebs EE, Ensrud KE, MacDonald R, Wilt TJ. 2004. Phytoestrogens for treatment of menopausal symptoms: a systematic review. *Obstetrics and Gynaecology*, 104: 824-836.

9 ibid