

EDITORIAL

Long-term hormone replacement therapy

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Introduction

The risks and benefits of taking hormone replacement therapy (HRT) for more than five years are uncertain. There are no large long-term randomised placebo-controlled trials to guide the duration of therapy. Large trials are expensive, difficult to run and can only examine a limited number of regimens and routes of HRT.

Until the results of large trials (see box on facing page) are reported we can only guess at the potential primary effect of HRT on major postmenopausal morbidity and mortality from the much weaker designs of observational studies (cohort and case control). These trials are not randomised and are open to bias and confounding. When the results of observational trials are expressed as relative risk, there is generally less chance of a result being due to bias or confounding if the relative risk is more than halved (<0.5) or more than doubled (>2.0). The increased relative risk of lung cancer in smokers is 43.0 and thus the association is very strong. Hot flushes are reduced by HRT to a relative risk of 0.2. Both results suggest the findings are likely to be causally related. A relative risk of 1.0 suggests no effect either way.

In this issue...

Hormone replacement therapy is good at relieving menopausal symptoms, but Alastair MacLennan explains why more research is needed about its long-term effects. Consumers will be particularly interested in the adverse effects of treatment, according to Helen Hopkins, Tony Wade and Derek Weir.

Adverse reactions may not be the focus of a visit from a pharmaceutical detailer, but these representatives of the pharmaceutical industry usually have a lot of useful information. Ric Day advises us on how to get the most from a detailer's visit.

Drug company representatives rarely discuss old drugs such as digoxin. Although digoxin is no longer a first-line drug in the treatment of heart failure, Daniel Ninio tells us that it still has a role in atrial fibrillation.

Breast cancer

A reanalysis of the data from 51 observational studies showed a relative risk of 1.023 (95% CI* 1.01–1.04) for each year of HRT use. The relative risk for HRT use of five years or longer (average 11 years) was 1.35 (95% CI 1.21–1.49).¹ These small increases in relative risk (i.e. under 2.0) could be due to detection bias, for example the HRT users could have had more breast examinations and mammograms. HRT users also have more independent risk factors, such as higher social class, Western diet, fewer pregnancies, later first pregnancy, and a higher alcohol intake, which could also account for small changes in the relative risk of breast cancer. However, if the increased risk is real it would equate to an extra two detected breast cancers per 1000 women who use HRT for five years. Paradoxically, most observational studies show a significant reduction in deaths from breast cancer in HRT users. Selection and detection bias can confound all these results.

There is no good evidence that HRT users with a family history of breast cancer further increase their risk compared to non-users with a similar history. Women taking HRT do not need to have mammography more often than other women.

Recent observational studies on the role of added cyclical and continuous progestogens given with oestrogen therapy have not clarified if these regimens have any effect on breast cancer rates.^{2,3} The relative risks were again small in both studies with overlap of the confidence intervals for oestrogen alone versus oestrogen/progestogen regimens. Thus, no recommendations can yet be made as to whether added progestogens influence breast cancer risk.

Bowel cancer

The most recent meta-analysis of 23 observational trials suggests that in postmenopausal women who have ever taken HRT the relative risk is 0.80 (95% CI 0.72–0.92).⁴ This is a 20% reduction in colorectal cancer, however this result is open to the biases of non-randomisation. The effect needs to be confirmed in long-term randomised placebo-controlled trials.

Endometrial cancer

The relative risk that taking unopposed oestrogen for 10 years causes endometrial cancer is 9.5 (95% CI 7.40–

* CI = confidence interval

New randomised placebo-controlled long-term trials

Two large randomised controlled trials have recently commenced. The Women's Health Initiative includes 27 000 American women who will receive HRT or placebo treatment. It is a nine-year study which started two years ago with funding of nearly US\$1 billion. The other primary prevention study of HRT is the Women's International Study of long Duration Oestrogen after Menopause (WISDOM). It is a placebo-controlled study of women taking oestrogen, or oestrogen and progestogen for 10 years with a further 10-year follow-up of clinical end-points such as fracture, cardiac events, cancer, dementia, thromboembolism, quality of life and death. WISDOM will enrol 36 200 women internationally. In the UK, WISDOM is funded for 22 000 entrants, and funding for a cohort of 2000 Australian women is currently being sought to contribute to this important trial. This collaboration will help validate the extrapolation of the results of WISDOM to the Australian population.

12.30) and so this is likely to be a true effect. Additional progestogen greatly reduces this risk, but the degree of this protection is not accurately known. Currently the recommended regimen for women with a uterus is to take oestrogen and cyclical progestogens before the menopause and for 1–2 years after menopause. Continuous combination therapy can be introduced after four years of cyclical therapy or when the woman is definitely postmenopausal. This reduces the amount of initial bleeding that is normally seen for several months when commencing a combined continuous HRT regimen.

Thromboembolism

Current observational studies suggest that although this is a relatively rare potential complication, the absolute risk rises from 1 in 10 000 to 3 in 10 000 in HRT users (relative risks in four studies ranged from 2.1–6.9). A past history of thromboembolism before the menopause is not an absolute contraindication to postmenopausal HRT, but might prompt the prescriber to consider testing for thrombophilia.⁵

Cardiovascular disease

Observational and animal studies suggest a potential benefit for HRT. A recent meta-analysis of these epidemiological studies reports a relative risk of 0.70 (95% CI 0.65–0.75) for oestrogen therapy alone and 0.66 (0.53–0.84) for combined HRT.⁶ However, many researchers argue that the studies have the potential bias of a 'healthy user' effect. A three-year randomised placebo-controlled trial (PEPI)⁷ has suggested a potential benefit in the primary prevention of ischaemic heart disease. Secondary prevention studies do not suggest that HRT can reverse the early risk of established ischaemic heart disease.⁸ Currently HRT may be offered to women with risk factors as a potential (but not established) primary

cardioprotective agent to complement other established drug therapies and lifestyle changes.

Stroke

HRT was not consistently associated with a change in the relative risk of stroke in observational studies.

Osteoporosis

Short-term randomised controlled trials consistently show that HRT improves low bone density, and when used prophylactically it inhibits loss of bone after the menopause. However, long-term randomised trials are still needed to show that improved bone density results in a major reduction in osteoporotic fractures, particularly at the hip. Improvements in surrogate end-points suggest that a reduced risk of fractures will be one of the main benefits of taking oestrogen for many years.

All therapies for osteoporosis require long-term compliance to achieve their effect. In South Australia in 1997 the median length of use in all women on HRT was five years with 70% continuance rate at five years. In women with a diagnosis of osteoporosis the median length of use was six years.⁹

Alzheimer's dementia

A meta-analysis of 10 observational studies showed a reduction of this dementia in HRT users. The relative risk was 0.71 (CI 0.52–0.98).¹⁰ Although there are plausible neuroprotective mechanisms for HRT, long-term randomised placebo-controlled trials are awaited to see if HRT has a primary preventative role in this disease which is becoming more common with increasing longevity. A recent secondary prevention trial does not suggest that HRT can reverse established disease.¹¹

Other risks and benefits

Potential long-term risks still need to be defined by long-term randomised controlled trials. They include increased risks of gall bladder and uterine surgery.

Other potential benefits may include a reduction in tooth loss, dry eyes, dry skin, arthritic symptoms, urge incontinence, frequency, nocturia, urinary tract infections, dry vagina, dyspareunia, memory loss and possibly some types of depression. All of these need to be assessed in large trials, but if a woman experiences sustained symptom relief from HRT then long-term therapy may be appropriate to maintain her quality of life.

Current options for length of HRT use

With all the caveats about the weaknesses of observational data, these data are all we can use when advising a woman about the potential risks and benefits of long-term HRT. Until the results of the Women's Health Initiative and WISDOM are available it is not possible to make general recommendations for the duration of treatment. Probably, for menopausal

symptom control, up to five years therapy is appropriate, with the option of another five years if still symptomatic when weaned off HRT. Longer therapy would be necessary for other potential indications such as the prevention of cardiovascular disease, dementia, some urological problems and osteoporosis. Phytoestrogens have yet to be shown in published rigorous scientific trials to be of greater benefit for menopausal symptoms than a placebo or to prevent osteoporotic fractures and cardiovascular events.

A woman's informed choice for long-term HRT should be based on unbiased information, explanation of the current data and its limitations and an understanding of her individual needs, risks and preferences. It should not be based on myth, selected information, vested interests in HRT or other products for the menopause and especially not on the lack of skill or knowledge of the adviser.

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Self-test questions

The following statements are either true or false (answers on page 111)

1. Hormone replacement therapy increases the risk of stroke.
2. Women taking hormone replacement therapy should have mammography more often than other women.

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