companies are now established offering an n-of-1 trial service to HMOs so that cost-effectiveness studies can be established in individual patients seeking long-term medical treatment. Barriers to the wider dissemination and implementation of n-of-1 trials include a lack of intellectual and administrative experience. The effort of setting up an n-of-1 trial service in primary care is substantial: this includes the time and cost of paperwork and consent forms, arranging identical placebobs from a pharmacy, and printing and distribution of patient diaries. Collaboration with pharmacy colleagues and funding and administrative experience from primary care organisations (PCOs) will be essential. Despite these barriers, we should remember that n-of-1 trials are at the top of the hierarchy of strength of evidence for treatment decisions. If we are truly interested in patient-centred care and shared decision making, we should invest in n-of-1 trials placing them firmly in the area of usual patient care.

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Hormone replacement therapy after the menopause — where are we now?

The Million Women Study1 generated a renewed concern about the use of hormone therapy, and it is now timely to review the current role of hormone replacement therapy (HRT) for women around and after the menopause. While therapy may result in improved quality of life, recent studies have provided some clarification of potential risks. Some have even questioned whether such therapy should be prescribed at all, but, assuming that it is still suitable, the recent concerns have implications on what we should prescribe, to whom, and for how long.

The Million Women Study was a large, observational study that recruited women involved in the UK breast screening programme. The study showed that HRT is associated with a duration-dependent increase in the risk of breast cancer. The increase associated with combined oestrogen-progestogen HRT is significantly higher (relative risk = 2.0 compared with no use) than for oestrogen-only therapy (relative risk = 1.30) and for tibolone (relative risk = 1.45). HRT also increases breast density, delaying the diagnosis of breast cancer. There was no difference in the risk of breast cancer with the type of oestrogen or progestogen used or sequential or continuous combined regimens. When therapy is stopped, the risk decreases — and after 5 years cessation reaches the same level as in women who have never taken the treatment. Interestingly, the authors contrast the estimated cumulative incidence of breast and endometrial cancer in women in developed countries, comparing oestrogen-only and combined hormone therapy. They imply that unopposed oestrogen should be preferred, even in women with a uterus, even though there is a consequent small increased risk of endometrial cancer.

The Million Women Study confirmed what was already known about the overall risk of breast cancer with HRT. In addition, the study emphasised the significantly higher risk of breast cancer associated with combined preparations compared to oestrogen-only preparations. It went on to document the surprising and not previously reported fact that tibolone is also associated with an increased risk of breast cancer, and that the longer a patient takes HRT, the higher the risk. The Women’s Health Initiative (WHI), a large randomised controlled trial, reported similar risks for breast cancer with combined hormone therapy,1 but no increased risk with unopposed oestrogen when taken for 7 years.3

The WHI study involved healthy postmenopausal women who were randomly assigned to combined oestrogen-progestogen, oestrogen-only or placebo, with the study endpoints being the number of women who died of coronary causes or who had a nonfatal myocardial infarction. The final results
showed that combination treatment and oestrogen alone do not confer cardiac protection, and may actually increase the risk of coronary heart disease — especially during the first year of use.²

The Women’s Estrogen–Progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial (WELLHART)³ also showed that there was no significant effect of HRT on the progression of atherosclerosis, but in contrast to previous trials,²⁵⁶ there was no increase in coronary events in the first year of treatment.

These studies confirm that in healthy postmenopausal women, HRT should not be used to prevent cardiovascular disease, or if established, its progression.

However, the WELLHART findings conflict with those from Estrogen in the Prevention of Atherosclerosis Trial (EPAT).⁴ This study used carotid artery wall thickness as an index of subclinical, asymptomatic atherosclerosis, whereas in the WELLHART study, coronary angiography was used to evaluate later stages of symptomatic atherosclerosis (although one must be aware that EPAT used surrogate markers rather than cardiovascular events or death). Oestrogen was found to reduce the extent of atherosclerosis if initiated close to the menopause, but appears to have little effect on established atherosclerosis. This may explain the discrepancies between previous observational data⁵⁻⁷ and more recent randomised controlled trials (for example WHI and WELLHART) that investigated older women. However, further analysis of WHI data shows that the increased risk of coronary heart disease was only found in women who were more than 20 years postmenopause, and that treatment with unopposed oestrogen may in fact be beneficial.

The effects of HRT on the brain are unclear. It may be that if treatment is started early (around the time of the menopause) — and before the pathological processes of amyloid deposition around the neurones or atheromatous coronary artery plaque formation have started — there may be a beneficial effect. If started later, there is no benefit.⁸

Nevertheless, these recent publications do have implications for prescribing. Most women who request HRT do so for relief of menopausal symptoms that can be extremely distressing and substantially affect their quality of life. One large survey⁹ found that 84% of women experience classic menopausal symptoms, such as hot flushes and night sweats, with 45% finding them to be a significant problem. However, women need to be aware that no hormonal treatments are without risk. Symptomatic women should be offered treatment, which some suggest should be for no longer than 5 years.¹⁰ It would be prudent for women who have had breast cancer to avoid HRT, although there is no evidence to suggest that their prognosis will be affected.¹¹ Women at risk of thromboembolism may be more suited to non-oral treatment.¹² Further, patients who have experienced premature ovarian failure should not be denied replacement oestrogen, as there is no evidence that the risks and duration effects of treatment for postmenopausal women apply, and the ‘clock’, with regard to risk, should not begin until 50 years of age.

With reference to women who have been taking long-term HRT for symptom relief and/or bone protection, the editorial commentary alongside the Million Women Study advised that they should discontinue use as soon as possible.¹³ This was alarmist, unwarranted and unhelpful. Women should be made aware of the long-term benefits, namely decreased risk of osteoporosis,¹⁴ fractures¹⁵ and colorectal cancer;² and the increased risks, namely breast cancer¹⁶ and venous thromboembolic disease.²³ But risks and benefits need to be put into perspective. Relative risk is difficult to understand — WHI data indicates that a 24% increased risk of breast cancer actually means only 8 extra cases per 10 000 women per year (Table 1).

Some women will elect to continue taking the therapy as it will protect their bones for as long as they take it. For the early postmenopausal women with hypoeostrogenic symptoms, HRT is the most appropriate agent, but others may consider changing to a bisphosphonate, selective oestrogen receptor modulator, calcium or vitamin D for bone protection. Despite the effectiveness of HRT in preventing osteoporosis, the Committee on Safety of Medicines concluded that HRT should no longer be recommended as first-line therapy for preventing osteoporosis, but made no distinction between oestrogen alone and combined treatments.⁳²

So, what type of HRT should be prescribed? Oestrogen–progestogen combinations appear to confer the greatest risk of breast cancer and venous thromboembolic disease.¹⁸ Oestrogen alone, even in women who have a uterus, is a possible therapeutic option, but goes against the basic dictum of ‘first do no harm’ when we know that there is a small chance it may produce endometrial hyperplasia/carcinoma.¹ There would also be more abnormal bleeding — which would require investigation and possibly hysterectomy — at a time when the hysterectomy rate is decreasing. One option would be to give oestrogen, by any route, with a progestogen-releasing intrauterine device to protect the endometrium.³³

The effect on the breast of using an intrauterine device with oestrogen is

| Table 1. Relative and absolute risks/benefits after hormone replacement therapy²,³ |
|-----------------------------------------------|-------------------------------|
| 5 years of CEE and MPA | 7 years of CEE |
| Relative risk (%) | Extra annual cases per 10 000 women | Relative risk (%) | Extra annual cases per 10 000 women |
| Breast cancer | 26 | 8 | -23 | -7¹ |
| Myocardial infarction | 29 | 7 | -9 | -5² |
| Stroke | 41 | 8 | 39 | 12 |
| Venous thromboembolic disease | 200 | 18 | 33 | 7 |
| Colon cancer | -37 | -6 | No significant effect |
| Hip fractures | -33 | -5 | 39 | -6 |
| Endometrial cancer | -19 | -1 |

CEE = Conjugated equine estrogens (0.625 g/day). MPA = Medroxyprogesterone acetate (2.5 mg/day). ¹Reduction in risk is not statistically significant.
unknown, but as the progestogen is delivered locally to the endometrium, it is likely that the effect would be less than by other routes. The Million Women Study has shown for the first time that tibolone is associated with breast cancer risk.1 This is an unexpected finding, as previous data suggested that tibolone is less stimulating to and does not increase the density of the breast.24,25 It is possible that participants in the Million Women Study were put on or switched to tibolone because of these benefits,26 but there is no information on the previous use of HRT in these women. It remains an option for relieving symptoms, protecting against bone loss and improving libido.

After the WHI findings were published, there was a worldwide reduction in the prescribing of HRT. This was followed in the subsequent months by women returning to their GPs, accepting the increased risk of breast cancer, and asking to recommence therapy.27 Many women cannot function at premenopausal level without the treatment. It is worth noting that both WHI and the Heart and Estrogen/Progestin Replacement Study (HERS) examined women with a mean age of 63 years, who had neither oestrogen deficient symptoms nor osteoporosis. This is significantly older than the majority of women who request HRT to improve their quality of life. Older women with symptoms of urogenital atrophy will benefit from long-term use of low-dose local oestrogen preparations with no evidence of risk.14

The key issue for menopausal women remains unchanged: a significant proportion feel better on HRT, and take it to improve and maintain their quality of life.15 The prescribing decision must be made after weighing up the risks and benefits with a fully informed patient. From the recent studies concerning the breast, it would appear that, for long-term therapy, oestrogen and tibolone may be safer than oestrogen-progestogen preparations, and if oestrogen is given alone, an intrauterine device could protect the endometrium.

For many women, HRT will not be suitable, not be wanted and will be unlikely to be of benefit — advice about lifestyle measures may be all that is needed. HRT is not a panacea for all postmenopausal women, but is still appropriate — if used selectivity and under regular review — to improve quality of life, and, for some, to prevent osteoporosis.

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British Journal of General Practice, March 2005
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