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EVIDENCE SYNTHESIS

Evidence-based review of therapies at the menopause

Alastair H MacLennan MD FRANZCOG

Discipline of Obstetrics and Gynaecology, School of Paediatrics and Reproductive Medicine, The University of Adelaide, Adelaide, South Australia, Australia

Abstract

Background and Objective The highest level of scientific evidence available for each therapy for menopausal symptoms was sought, for example, systematic reviews of randomised controlled trials (RCTs).

Results There is reasonable evidence that some symptoms are modified by lifestyle, for example, cessation of smoking, exercise, reduction of alcohol, diet and alleviation of psychosocial stress.

No complementary medicine, for example, phytoestrogens, black cohosh, herbal or homeopathic medicines or complementary therapies, for example, acupuncture, yoga, chiropractic manipulation, reflexology or magnetic devices have a greater effect than the usual placebo effect seen in quality blinded RCTs. Some have potential side-effects. So-called 'bioidentical hormones' have no evidence-base and potential for harm. None of the above therapies have evidence of efficacy and long-term safety.

Selective serotonin and noradrenaline re-uptake inhibitors ameliorate vasomotor symptoms and sometimes menopausal depression better than placebo.

The most effective therapy for menopausal (oestrogen) deficiency symptoms is oestrogen which is the main component of hormone replacement therapies (HRT). Compared with placebo HRT is highly effective in relieving hot flushes, night sweats, dry vagina and dyspareunia. It also improved joint pains, sexuality and sleeplessness and reduced subsequent fractures in RCTs. The increased risk of oral HRT for thromboembolism is small around menopause, for those without thrombotic risk factors, and is not elevated with non-oral routes. Cardiovascular disease may be reduced when HRT is initiated near menopause. Breast cancer risk increases after several years with the use of oral HRT containing progestogens at an annual rate of 8/10 000 (<0.1%). No increase in breast cancer risk was seen with oestrogen-only HRT.

Key words: complementary therapy, evidence-based review, hormone replacement therapy, menopause.

Introduction

Readers of the scientific journal *Evidence-Based Healthcare* hardly need reminding of the levels of scientific evidence and the limitations of each method of data collection and assessment, but it is a lack of understanding of the quality, reliability and applicability of each type of study that has created worldwide lay and medical confusion about the value and safety of interventions around and after the menopause. These interventions include lifestyle, complementary/alternative therapies and pharmaceutical treatments. This review assesses the safety and efficacy of all the commonly used menopausal therapies by the top level of evidence available in the scientific literature. Evidence was sought from the Cochrane library systematic reviews, Pub Med, EMBASE, Scopus and BMJ Clinical Evidence databases.

The review will document the level of evidence or lack of evidence for the many therapeutic options faced by symptomatic menopausal woman. From best to worst evidence, the levels are systematic reviews of quality placebo controlled randomised trials, a large placebo controlled randomised trial, observational studies, for example, cohort and case–control studies, uncontrolled series of cases, and the anecdotal case (Table 1).[1] Two further unofficial and lower levels of evidence that often influence the management of the menopause are non-expert opinion and vested-interest opinion. The latter sometimes is associated with

Correspondence: Professor Alastair MacLennan, Discipline of Obstetrics and Gynaecology, The University of Adelaide, The Women's and Children's Hospital, 72 King William Road, North Adelaide, SA 5006, Australia. Email: alastair.maclennan@adelaide.edu.au

Competing interests: Alastair MacLennan was until recently Editor-in-Chief of *Climacteric*, The Journal of the International Menopause Society. Through the University of Adelaide he has received research funds and travel expenses from a variety of pharmaceutical companies.

Table 1 Australian National Health and Medical Research Council levels of evidence[1]

1	Evidence obtained from a systematic review of all relevant randomised controlled trials.
2	Evidence obtained from at least one properly designed randomised controlled trial.
3-1	Evidence obtained from well designed pseudo-randomised controlled trials.
3-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case–control analytic studies, or interrupted time series with a control group.
3-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group.
4	Evidence obtained from case series, either post-test or pre-test and post-test.

the pharmaceutical industry but much more often with the almost unregulated alternative medicine industry.

Some or all of the common symptoms of the menopause are experienced by up to 80% of women around menopause. The main four groups of symptoms are vasomotor (e.g. hot flushes, night sweats), psychological (e.g. anxiety, irritability), locomotor (e.g. joint pains, backache) and uro-genital (vaginal dryness, urinary frequency). Symptoms can begin several years before the last menstrual period and contrary to common belief can last for many years and sometimes into old age. A recent large observational study has reported that the mean duration of vasomotor symptoms was 5.5 years.[2] Menopausal symptoms are common in all cultures but vary in individual frequency with joint pains being the most common symptom in Asia. These symptoms can reduce quality of life and around 60% of women self-medicate and seek alternative therapies to alleviate their symptoms and 20–30% between age 50–60 use HRT.[3,4] The longer-term consequences of the loss of ovarian function at the menopause and a decrease in oestrogen levels seen in observational studies are increasing risk of cardiovascular disease, osteoporotic fractures and diminished cognitive function and dementia. This review, however, will explore the evidence for the therapeutic options for the control of menopausal symptoms and, where data are available, the potential to influence long-term disease or disability.

Lifestyle factors

These are part of normal preventative medicine and are mostly common sense. Most have an influence on menopausal symptoms, quality of life and on the main morbidities of aging.

Smoking

A systematic review has confirmed a clear association between smoking and earlier menopause.[5] Smokers experience menopause 2–3 years earlier than non-smokers and may have more severe symptoms than non-smokers owing to the anti-oestrogenic effect of hydrocarbons.

Exercise

Physical exercise reduces hot flushes more than the effect of a placebo in sedentary women.[6] Exercise also improves quality of life as measured on the SF-36 score. Regular exercise may also slow postmenopausal bone loss and reduce the risk of falls by improving balance.

Maintenance of optimal weight

The US longitudinal observational study of Women's Health across the Nation (SWAN) showed that women on average experience a cumulative increase in fat mass of 3.4 kg with an increase in the waist circumference of 5.7 cm.[7] Regular aerobic exercise of at least 30 min a day and an appropriate diet are required to help reduce this metabolic side-effect of the menopause. Menopausal weight gain is not associated with HRT use as the same gain is consistently noted in the placebo control groups of blinded trials.[8]

Alcohol

Some, but not all, observational studies have suggested that alcohol may minimally delay menopause.[9] Alcohol consumption may cause transient increases in oestrogen and the subsequent fluctuation in oestrogen levels trigger hot flushes. More than two standard drinks per day is associated in observational studies with an increased risk of breast cancer (RR 1.4).[10]

Calcium and vitamin D

Calcium requirements are increased after menopause and women then need around three portions of calcium containing foods, for example, milk, yogurt, cheese to slow the 1–2% per year bone loss that begins near menopause and can lead to osteoporotic fractures.[11] Many women have a poor dietary intake of calcium and should consider a 600 mg daily calcium supplement. Vitamin D supplements may also be required in women with low vitamin D levels who may not be exposed to daily sunlight.[11]

Psychosocial stress and sexual dysfunction

There are many observational studies showing the influence of stressful factors at middle age, for example, elderly parents, adolescent children, marital problems, changing body image, changing role in the family, re-employment and general health and fitness.[12,13] Interventions for these factors cannot easily be tested in RCTs but observational studies suggest benefit in addressing these issues around menopause.[14] Low libido is a very common complaint after menopause. Sexual counselling and hormone therapies as discussed below may be helpful for some individuals.

Complementary and alternative medicines (CAMs) and alternative therapies

The alternative medicine industry targets menopausal women in advertisements and industry sponsored media

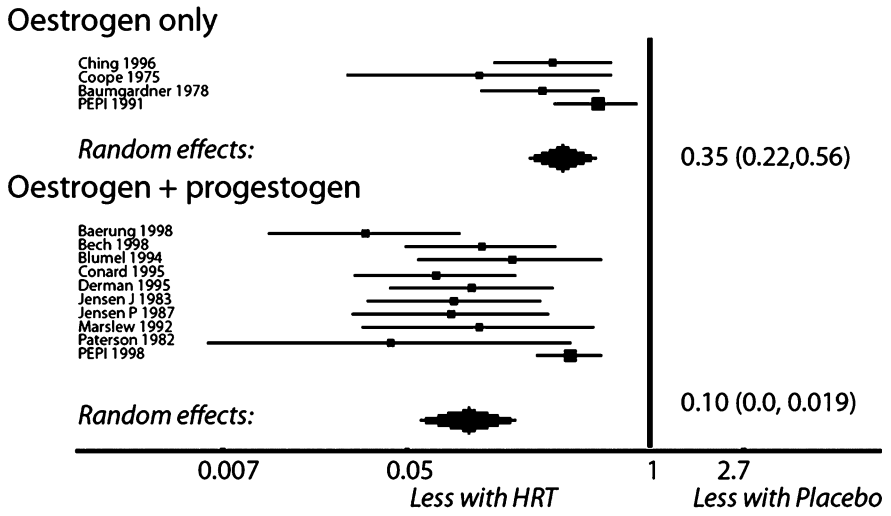

Figure 1 Cochrane systematic review of quality randomised placebo controlled trials of HRT versus placebo and their effect on vasomotor symptoms.[15]

reports. Approximately 60% of women aged 45–55 use CAMs and 30% attend alternative practitioners usually before seeking medical advice and trying evidence-based therapies.[3]

Commonly used CAMs are phytoestrogens, black cohosh products, herbal and homeopathic medicines. Alternative therapies include chiropractic, naturopathy, acupuncture, iridology and aromatherapy. Systematic reviews of published data on all these medications and therapies for menopausal symptoms show that they have no greater efficacy than the placebo effect normally seen in quality randomised trials, occasional side-effects and drug interactions and no long-term safety data.[15,16] Many countries have double legislative standards for CAMs and pharmaceutical/medical therapies. Rather than all medicines being treated equally and having the same high standards of quality control, efficacy, safety and advertising claims CAMs are hugely under-regulated and protected by dubious legislation, the underfunding of regulatory agencies and the powerful lobby of a large alternative medicine industry.[17]

It is very important to differentiate the common temporary placebo effect of most unproven therapies for menopausal symptoms from the prolonged and statistically and clinically better results of truly effective therapies. Also no CAMs have long-term cardioprotective, neuroprotective and fracture preventative effects that may be associated with proven therapies. In a systematic Cochrane review of quality double-blind randomised control trials the placebo effect on the frequency of hot flushes and night sweats was 58% compared with the 90% of combined HRT (Fig. 1).[18] This degree of placebo effect should be the yard stick of assessing the putative effect of other therapies for vasomotor symptoms. The quality of studies for CAMs at the menopause are often poor and a 50% effect may be claimed without a comparative placebo group or where a placebo group shows comparatively minimal change, small numbers or unblinding of the placebo treatment may explain the statistically significant but clinically dubious claim.

Phytoestrogens

Systematic reviews of phytoestrogens supplements or diets do not show that they have efficacy in placebo controlled randomised trials.[15,16] As seen in Figure 2 the apparent modest effect seen in short-term trials of products such as *Promensil* is no better than the expected placebo effect. In a few of these small trials the placebo groups showed only a small response compared with the phytoestrogen group suggesting a small effect. However, this could reflect different populations being studied, statistical error owing to small sample size or unblinding. Unblinded or uncontrolled studies of any therapy claiming an early effect size on vasomotor symptoms of under 60% are unconvincing.

Black cohosh

Products containing black cohosh such as *Remifemin* also have effects not significantly better than the expected placebo effect seen in HRT trials and there have been case reports of liver damage following the use of black cohosh.[19,20] Although the reported incidence of liver disease may be relatively rare considering the wide use of this heavily marketed product there are serious concerns about the recognition and underreporting of side-effects from the use of all types of alternative medicines. Less than half the public inform their doctors of their use and most of the public are unaware of the potential for harm or drug interaction from CAMs.[3]

Herbal medicines

There have been reports of adulteration of Chinese herbal medicines and neither Chinese or Western herbal mixtures beat the double-blind placebo test.[15,21] A wide range of side-effects and drug interactions have been described for

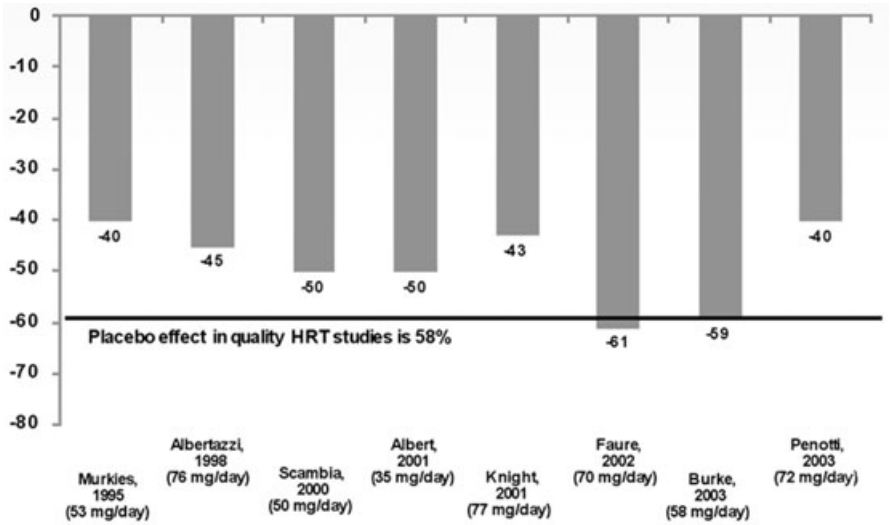

Figure 2 Results of published trials of isoflavones do not show a greater effect than the average placebo effect of 58% seen in quality randomised trials of HRT (Fig. 1). In some of the trials of isoflavones smaller effects in their placebo groups were described.

many herbal products including *St John's Wort* where there is evidence of a mild antidepressant effect which is outweighed by the lack of standardisation of dose and quality and the potential for side-effects and drug interactions.

Homeopathic medicines

Homeopathy lacks any rational scientific basis and hundreds of trials have failed to deliver significant or convincing evidence to support the use of homeopathy for the treatment of any particular ailment including menopausal symptoms.[16] Again it fails the placebo test.

Acupuncture

A systematic review of acupuncture for the treatment of menopausal hot flushes found six randomised trials versus sham acupuncture.[22] The review failed to show a specific effect of acupuncture for the control of hot flushes.

Yoga

In a non-blinded 8 week controlled trial little effect was seen on hot flushes in the normal exercise control group and a significantly better effect was seen in the group practising yoga.[23] However, again the size of the treatment effect was no better than the standard placebo effect in blinded studies of HRT. Yoga, meditation and relaxation techniques appear to have temporary positive effects to the extent of placebos.

Other body-based therapies

There are no supporting quality data for the use of chiropractic or osteopathic manipulation, reflexology or magnetic devices in the treatment of the menopause.[15]

'Bioidentical hormones'

This new and mostly unregulated alternative industry purports to deliver 'natural' hormones for menopausal complaints without any of the risks of conventional HRT. However, some of them contain the same hormones, for example, oestrogen but in untested doses and mixtures that may contain other hormones not registered for use in women, for example, growth hormone, melatonin and dehydroepiandrosterone (DHEA). Some dispensing therapists, without evidence, logic or disease association, diagnose a 'progesterone deficiency' state that requires treatment with their concocted '*progesterone cream*'. There is no published peer reviewed quality evidence that so-called 'bioidentical hormones', privately mixed by compounding pharmacists are better or safer in any way than the same oestrogens in registered and tested products.[24,25] These untested imported hormonal mixtures give the buyer no proven advantage over carefully tested HRT, and are not approved by The Therapeutic Goods Administration in Australia or the Federal Drugs Administration in the USA. They do not protect against endometrial cancer that can be induced by unopposed oestrogen in women with a uterus. Claims that 'bioidentical hormones' can be tailored to suit each woman's hormonal needs by measuring hormones in their saliva are completely unsubstantiated, are pseudoscientific and lead to inappropriate prescription. The major menopause and endocrine scientific societies decry the unregulated and unwarranted prescription for profit of these dubious and potentially dangerous products.

In a wide-ranging detailed book on the scientific assessment of the value of alternative medicines in all medicine Professor Edzard Ernst, the world's first professor of complementary medicine, and science writer Simon Singh concluded that 'the market is being misled over and over again, often by misguided therapists and sometimes by exploitative charlatans'. They called for 'the tricks to stop, and for real treatments to take priority and for scientific standards, evaluation and regulation to be applied to all types of medicine. If such standards are not applied to the alternative health sector then homeopaths, acupuncturists, chiropractors, herbalists and other alternative therapists will continue to prey on the most desperate and vulnerable in society,

raiding their wallets, offering false hope, and endangering their health'.[16]

It is often argued by those with vested interests that the public should have the freedom to self-medicate with 'harmless' therapies. What is not explained are the 'four harms of harmless therapies' which are (i) the waste of health resources (currently estimated at AUD $4 billion in Australia and in the USA at US$100 billion per year in the USA); (ii) the underestimated side-effects and drug interactions; (iii) the cost of delay or lost opportunity for effective therapy; and (iv) the disappointment, disillusionment and possible depression from successive alternative therapies that fail to help.[26]

Evidence-based therapies at the menopause

Non-hormonal therapies

Selective serotonin or noradrenaline re-uptake inhibitors, for example, venlalaxine and desvenlaflaxine

Double-blind randomised controlled trials mostly show that these therapies are marginally but statistically better than placebo in reducing vasomotor symptom frequency and severity.[27,28] They also significantly reduce mean depression scores in low doses compared with placebo in some trials.[29,30] Common side-effects are nausea, dry mouth somnolence and dizziness which may reduce with time or be lessened by starting at low doses.

Clonidine and gabapentin have both been shown to be slightly better than placebo in reducing vasomotor symptoms but have frequent minor side-effects that make long-term compliance poor.[27,31,32]

Other non-hormonal therapies

The above therapies do not help other menopausal symptoms such as joint pains or urinary frequency or vaginal dryness. If hormonal treatment is contraindicated, for example, because of concurrent adjuvant therapy for breast cancer, these oestrogen deficiency symptoms may respond to non-specific symptomatic therapy with non-steroidal anti-inflammatory agents, anti-cholinergics and vaginal moisturisers respectively.

Hormonal therapies (HRT)

Ovarian hormone therapies generally referred to as hormone replacement therapy (HRT), are the best researched and most effective management of both menopausal symptoms and the longer-term consequences of oestrogen deficiency. HRT has been available for over 60 years but has only recently been subjected to long-term placebo controlled randomised controlled trials such as the Women's Health Initiative (WHI) and the Women's International Study of long Duration Oestrogen after Menopause (WISDOM).[33–36] Long-term quality observational studies currently extend up to nearly 30 years, for example, The Nurses Health Study.[37]

Cochrane systematic reviews clearly show the efficacy of HRT in reducing both vasomotor symptoms (Fig. 1) by up to 90% and in reducing urogenital symptoms such as vaginal dryness and painful intercourse which are increasingly common symptoms after menopause.[18,38] Both WHI and WISDOM showed a significant reduction in joint pains in the HRT groups compared with placebo and WISDOM also showed a reduction in sleeplessness and improved sexuality in the HRT group.[36] Overall health-related quality of life was also improved on HRT in the WISDOM trial.[36]

To understand the recent controversy about longer-term HRT and to understand that it is usually possible to choose an HRT regimen with maximum benefit and minimum risk for symptomatic women near menopause it is very important to understand the relevance and the limitations of the various trials and studies to date. WHI and WISDOM did not study the normal users of HRT. These trials mostly studied women without major menopausal symptoms who commenced HRT 13–14 years on average after menopause in the hope that HRT would reduce major morbidities such as cardiovascular disease in later life. At the time of the design of these major trials, it was not appreciated that there is a probable 'window of therapeutic opportunity' for cardioprotection near menopause, where oestrogen therapy can help reduce the acceleration in atherosclerosis seen after menopause but it may disrupt established atherosclerotic plaques if given for the first time later in postmenopausal life.[39–42] Thus, increasing the risk of cardiovascular events when initiated in this older group.

Before 2002, and the publication of the first results of a long-term Level 2 RCT, that is, WHI, Level 3 observational studies (using the Australian National Health & Medical Research Council levels of evidence) were mostly of women who commenced HRT near menopause for symptom control. These studies had mostly suggested that long-term therapy conveyed cardiovascular and fracture benefit but increased thromboembolism and that combined (oestrogen and progestogen) HRT increased the risk of breast cancer. The initial results of the combined HRT arm of WHI showed that after 5 years of combined therapy there was a significant reduction in fractures but no overall cardiovascular benefit in this population and an increase in thromboembolism and breast cancer.[33] The adverse media reaction to this first view of early WHI data encouraged up to two-thirds of HRT users to stop therapy, often without medical consultation.[43] Various advisory bodies rapidly issued strongly worded guidance, to the effect that HRT should be used at the lowest dose for the shortest possible time and only in severely symptomatic women.[44] Recent analyses of new data from WHI, other RCTs and observational and animal studies have now unified much of the HRT data, changed the risk: benefit ratio for the large majority of women who commence HRT for symptom control around menopause and given cause for the guidelines to be reviewed and changed. The new data are mostly good news for the 99% of women who commence HRT near menopause and before age 60 and are quite different from first published WHI risks and benefits seen in its unvalidated 'global index' for all women aged 50–79 at trial entry (Figs 3–6).[33]

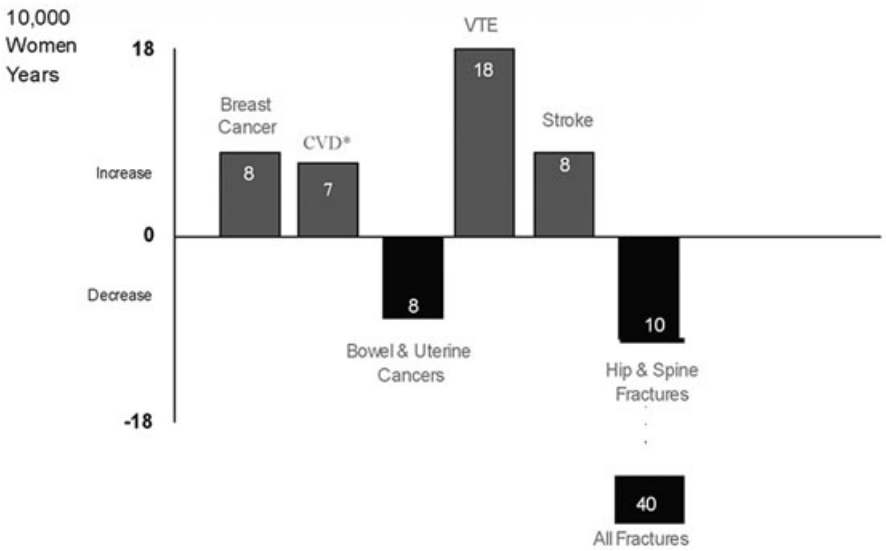

Figure 3 The original 'global index' of selected risks and benefits published in 2002 for all women in the combined oestrogen and progestogen arm of the WHI trial.[2] These mostly asymptomatic and often elderly women initiated therapy in the trial between ages 50 and 79 years and on average 13–14 years after menopause. *Not statistically significant.

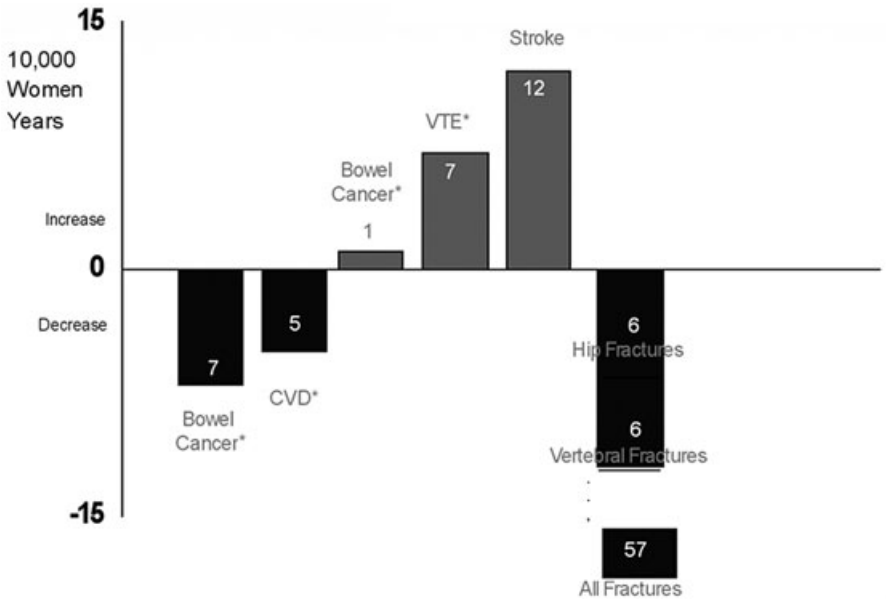

Figure 4 The original 'global index' of selected risks and benefits published in 2004 for all women in the oestrogen-only arm of the WHI trial.[3] These mostly asymptomatic and often elderly women who had had a hysterectomy initiated therapy in the trial between ages 50 and 79 years and on average 13–14 years after menopause. *Not statistically significant.

Cardiovascular disease

There are now strong data in support of the 'critical therapeutic window' hypotheses that oestrogen is cardioprotective if initiated around menopause when there are still vascular oestrogen receptors responsive to exogenous oestrogen.[37,39,45] HRT administered around menopause appears to reduce the progression of atherosclerotic plaque but if HRT is administered many years after menopause, it is not beneficial and may sometimes disrupt established plaque with adverse effects. In WHI the increase in cardiovascular events only reached statistical significance in the 70- to 79-year-old group on oral combined HRT (Fig. 7).

A meta-analysis of RCTs (Level 1 evidence) shows a statistically and clinically significant 39% reduction in cardiac events compared with placebo control groups when HRT is initiated under the age of 60 years [odds ratio (OR) 0.68; 95% confidence interval (CI) 0.48–0.96]. However, this cardioprotective effect was not seen in older women initiating HRT after the age of 60 years (OR 1.03; 95% CI 0.91–1.16).[42] When combined HRT is initiated many years after menopause there is an increase in cardiac events during the first year of therapy (HR 1.47; 95% CI 1.12–1.92).[42]

Subsequent cardiac morbidity is reduced after 2 years of HRT in these older women (HR 0.79; 95% CI 0.67–0.93).[42] All-cause mortality in younger HRT users compared with placebo is also significantly reduced (HR 0.61; 95% CI 0.39–0.95).[41]

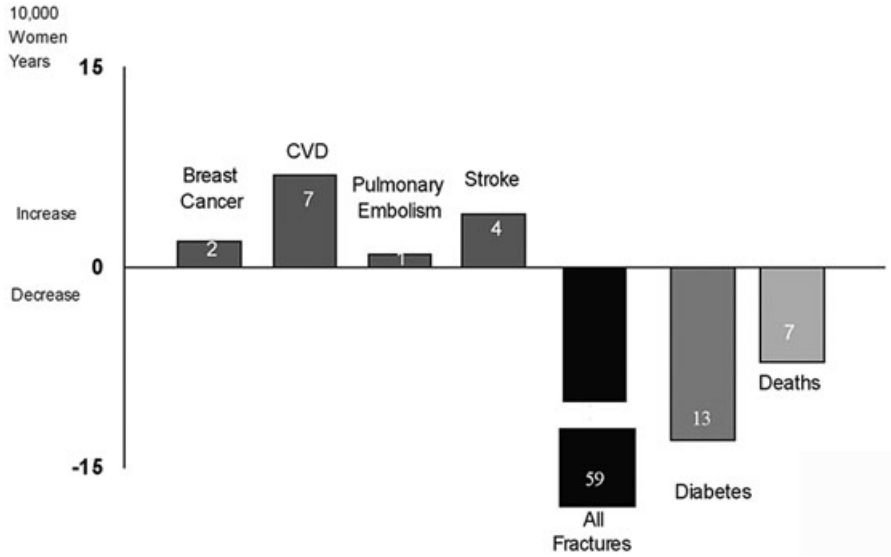

Figure 5 Data from WHI of combined oestrogen and progestogen HRT risks and benefits (excluding symptom control and quality of life measurements) for women commencing therapy under age 60.

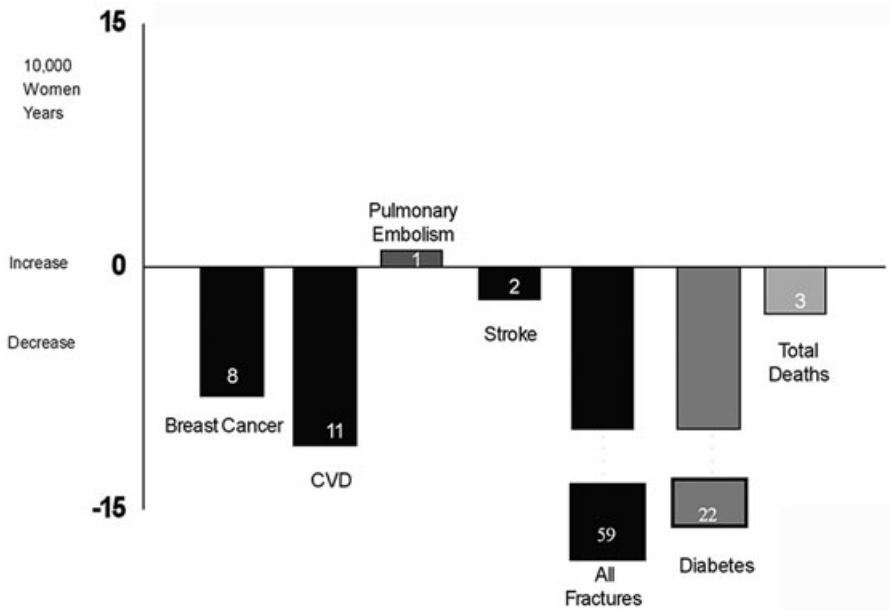

Figure 6 Data from WHI of oestrogen-only HRT risks and benefits (excluding symptom control and quality of life measurements) for women commencing therapy under age 60.

Currently data from Level II trials near menopause suggest that oestrogen-only regimens may offer greater cardioprotection than some combined regimens but more research is needed on the timing and type of progestogen therapy.

The two long-term RCTs of HRT (WHI and WISDOM) studied the initiation of HRT in women many years after menopause (average 13–14 years) because the outcomes being measured were more prevalent in later age and a 30-year trial from menopause was not practical. The populations in these two trials were unrepresentative of symptomatic women who initiate HRT near menopause. Although WHI alone was not powered for sub-analyses of cardiac events, in the 8832 women under the age of 60 years in the two HRT trial arms, the combined RCT data now indicate cardioprotection in women initiating HRT near menopause, especially when oestrogen-only regimens are used (Fig. 7).[37,40,42,45] A recent paper from the WHI investigators reported on coronary artery calcification, which reflects calcified atheroma and total plaque burden, in the oestrogen-only arm of WHI, 8.7 years after randomisation.[46] In those who were 80% or more compliant, there was 61% less atherosclerotic plaques in women whose mean age was 55 years at baseline, as compared with the placebo group ($P = 0.004$).

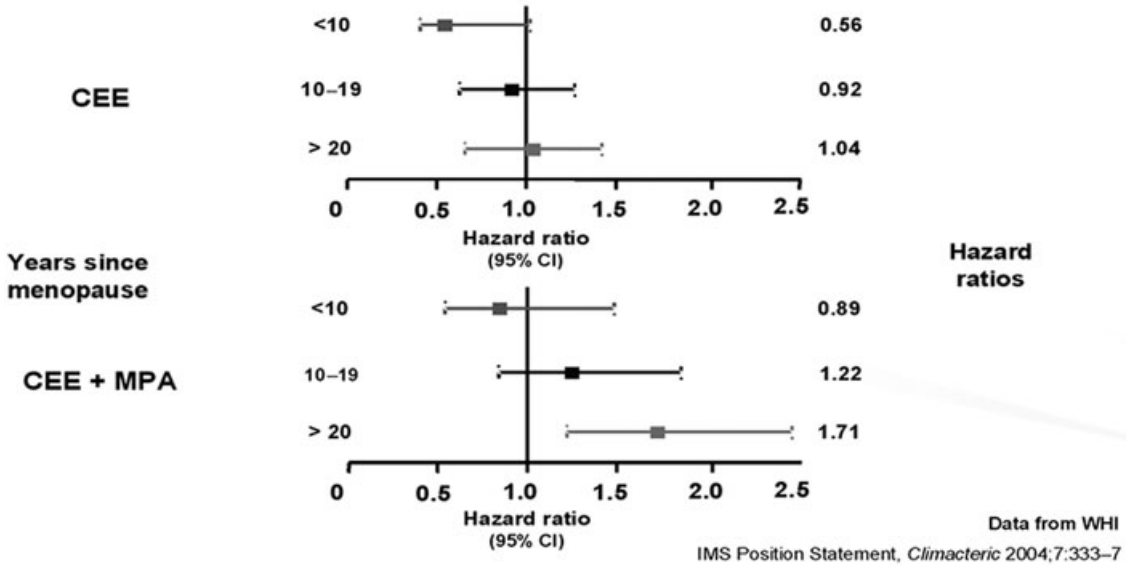

Figure 7 Hazard ratios and 95% confidence intervals for cardiovascular events seen in the oestrogen-only and combined HRT arms of the WHI trial according to years from menopause at the time of HRT initiation.

Breast cancer

Before WHI, observational studies (Level 3 evidence) had suggested an increased relative risk of breast cancer with long-term combined HRT of 1.53 after a median of 8 years.[47] WHI actually reported a relative risk of 1.26 (adjusted 95% CI 0.83–1.92) after 5.6 years of cHRT.[2] However, the media often highlighted the relative risk without explaining the absolute risk. The absolute increased risk of breast cancer with combined HRT in WHI was eight per 10 000 women years or less than 0.1% per annum after 5 years of therapy.[33] Level 1 systematic reviews of all higher level data now suggest an increased risk of breast cancer on combined HRT of four per 10 000 women years, that is, two per 1000 women after 5 years.[48–50] Some epidemiological groups have preferred to use worst scenario statistics that are derived from observational data including the Million Women's Study (Level 3-3).[51] A few of these groups continue to fuel alarmist media reports with low level data and without clarifying the absolute risk associated with combined and oestrogen-only regimens published in RCTs. These cancer-orientated groups, using selected observational data, generally have no clinical responsibility for the clinical care of menopausal women and do not put cancer risk into perspective with the overall benefits and risks of HRT that vary with each individual and regimen. Thus, media, medical and public confusion about HRT has continued since 2002.

Observational data may inflate the real risk (owing to selection and detection biases, etc.) and intention to treat analyses of RCTs may reduce the real risk owing to non-compliance with therapy. Both methodologies have their merits and demerits but when similar populations are being compared RCTs usually trump observational studies.

Another way to counsel about risk is to compare the increased relative risk seen in WHI for breast cancer, which was 1.26 (1.00–1.59) to other common risk factors. Thus, this relative risk is similar to a late menopause at age 55 years or more (RR 1.22), three alcoholic drinks per day (RR 1.4) or nulliparity (RR 1.67).[10] Later analysis of the WHI data showed that there was no significant increase in breast cancer among those who initiated combined HRT for the first time during the 7 years of WHI.[52]

Even better news from WHI came when the oestrogen-only arm showed an almost significant reduction in breast cancer by 7.1 years compared with placebo therapy in this hysterectomised group (HR 0.77; 95% CI 0.59–1.01).[34] Significance was reached in a sub-analysis of those who were compliant with the oestrogen-only therapy. Observational data (Level 3) has suggested that more than 20 years of oral oestrogen-only therapy may increase breast cancer rates.[53]

These results challenge many of the beliefs about oestrogen and breast cancer but may incriminate added systemic progestogen. The breast cancer risks of long-term combined oral HRT as quantitated above are strongly evidence-based and are not disputed in this review. However, HRT research is not static and new regimens to avoid the risk of systemic progestogens, for example, tibolone, intrauterine progestogen and systemic oestrogen and the replacement of the progestogen with a selective oestrogen or progestogen receptor modulator are now available but will also require long-term Level 2 trials.

Ovarian cancer

Data from Level 3-3, observational studies such as the Million Women's Study show a non-significant increase in ovarian cancer after 5 years of combined HRT but a significant increase after 5 years of unopposed oestrogen-only therapy.[54,55] The increased absolute risk in the Million Women's Study was estimated as one in 2500.[55] This risk is

mostly seen in women who have had a hysterectomy with ovarian conservation and take oestrogen for more than 5 years. This group is about 8% of HRT users. In this group, the reduction in breast cancer seen in WHI would balance the mortality associated with both cancers. Tibolone use was not associated with a rise in ovarian cancer.

Thromboembolism

This remains the main short-term serious risk of HRT. The risk of thromboembolism on oral HRT appears to be greatest in the first year or two of use and is highest in those with thrombophilia and/or obesity.[56] The absolute risk varies with individual risk factors for thromboembolism. Risk varies with age at initiation and overall the increased risk is about one in 10 000 at the age of 50 years and increases with age at onset of therapy.[57] In the future, genetic screening for thrombophilia may become a cost-effective proposition. Currently, clinical risk factors may merit screening. Non-oral routes of oestrogen, adding micronised progesterone or pregnane-derived progestogens when a uterus is present and tibolone, have not been associated with thromboembolic risk (Level II and III evidence). However, these have not been studied in long-term randomised trials. Nevertheless, those requiring HRT despite an increased risk of thromboembolism should take HRT by a non-oral route.[57]

Fractures

The expected one-third reduction of fractures (hip, spine and overall) seen in observational studies was confirmed by WHI (RR 0.66).[33,34] Importantly, this statistically significant reduction was seen in a population not screened for osteoporosis and is equivalent to the reduction in fractures seen with the main treatments for osteoporotic fractures in high risk groups. HRT remains a cost-efficient and relatively safe option for the prevention of fractures when initiated before the age of 60 years in osteoporotic women who are often also symptomatic. Such women may have few other cost-efficient therapeutic options and this indication for HRT needs to be revisited in light of the recalculated risks of HRT (especially low-dose oestrogen-only regimens).[58]

Cognitive function and dementia

The effect of HRT on the brain is likely to remain controversial because a very long-term trial from menopause will probably be impossible. Observational studies (Level 3) support the 'critical window hypothesis' where HRT use from near menopause shows more cognitive benefit than commencing HRT many years after menopause.[59] WHI studied only women commencing HRT over the age of 65 years and, like its cardiovascular data, suggested detriment in this older group.[60] Brain atrophy was most evident in the women over age 65 experiencing cognitive deficits before initiating HRT.[61] Thus, hormone therapy does not reverse established cognitive decline. The Cache County observational study noted a 59% reduction in dementia in early menopausal users who took therapy for more than 10 years.[62] Other Level 3 studies, which have not distinguished between early or late initiation of HRT, have not seen consistent cognitive benefit.

Stroke

In WHI, no effect of combined HRT on stroke was seen in the first year of therapy. The risk ratios increased to 1.72 over the next 4 years and decreased to 0.66 in year 6. Yearly confidence intervals have not been published but, in the elderly WHI population, the overall absolute increased risk was eight per 10 000 per annum (0.08%). The final hazard ratio (HR) for stroke was 1.31 (adjusted 95% CI 0.93–1.84).[63] In the oestrogen-only arm of WHI, the HR was 1.39 (adjusted 95% CI 0.97–1.99).[63] Again the prevalence of stroke is age-dependent and the numbers under the age of 60 years were small and too small to test the critical window hypotheses for stroke. An increased risk of transient ischaemic attacks and strokes must currently be presumed as likely in women initiating HRT many years after menopause.

Bowel and uterine cancers

In the combined HRT arm of WHI, a small decrease in these cancers was seen of around eight per 10 000 per annum.[33] Oestrogen-only therapy had no effect on bowel cancer in WHI.[34]

Revised risk/benefit ratios for HRT

Figures 3 and 4 show the overall main morbidities assessed initially in the overall WHI population who were an average age of 63–64 years and had a high prevalence of cardiovascular risk factors on entry to the trial.[64] These mostly asymptomatic women were *not* representative of HRT users who usually start HRT near menopause. In contrast, recent data from WHI allow compilation of a very different morbidity profile for women in the combined arm and the oestrogen-only arm who commenced therapy under the age of 60 years (Figs 5,6).[64] Although WHI was underpowered to study women under the age of 60 years, the 8832 women in WHI under the age of 60 years are the largest number in a single randomised placebo-controlled trial.

Importantly, these risk/benefit charts, however, do not include the main benefit and indication for the use of HRT in symptomatic women and that is improved quality of life from the alleviation of debilitating menopausal symptoms.

Menopausal symptom control and quality of life

Symptom control and improved quality of life are often achieved with appropriate tailoring of HRT to the individual symptomatic woman. This is the main reason for the commencement of HRT and for high continuation rates. Vasomotor symptoms, urogenital symptoms, sexuality, sleeplessness and joint pains are all significantly improved in quality trials.[18,36,38]

The international media scare in 2002 prompted medical review and cessation of long-term HRT in some users who had no further indication for its use. However, many more women inappropriately stopped therapy or never started HRT without medical advice because of media and medical

perception of the risks of HRT. Ironically many women who experienced menopause after 2002 may have missed a therapeutic window for cardioprotection and possible cognitive benefit and also suffered unnecessary menopausal symptoms if they avoided, or their advisors denied them, the option of HRT. Many women have reported that their doctor, pharmacist or alternative therapist has said that HRT was 'too dangerous' and they should use non evidence-based complementary therapies.[43] As discussed above no complementary therapy has a greater effect than the placebo effect seen in well-designed and blinded randomised control trials.

Tibolone

Although not a traditional HRT, tibolone is a steroid with oestrogenic, progestogenic and androgenic properties and currently has a good safety profile in short-term RCTs up to 4 years.[65] It is an all-in-one single dose oral postmenopausal therapy with a moderately effective action on menopausal and urogenital symptoms, libido and bone. Tibolone does not stimulate breast cell proliferation or increase breast tissue density. Randomised controlled trials up to 3 years do not show any increase in breast cancer rates. However, tibolone is not recommended after breast cancer in women on adjuvant therapy because of potential reduction in the efficacy of these therapies.[66] There is a question mark about a small increased risk of stroke seen in one trial of elderly women with osteoporosis but this result was confounded by unusually low numbers of stroke in the placebo group.[67] Similarly the Million Women's Study (Level 3-3) showed an association with breast cancer that may have been confounded by the selection of women with breast cancer for tibolone therapy.[51] This finding has been contradicted by other observational studies and by all RCTs to date.

Early side-effects of HRT

In the Level 1 Cochrane systematic review of RCTs of HRT for vasomotor symptoms, the two significantly increased side-effects were breast tenderness and start-up bleeding on combined continuous HRT in women with a uterus.[18] Breast tenderness may be transient in the first month or can usually be reversed with oestrogen dose reduction. Diminishing bleeding for several months is normal on continuous combined regimens especially if started near the menopause when a cyclical progestogen and continuous oestrogen may be a better initial option. The key to successful HRT and patient adherence is to tailor their therapy and to consider non-oral routes when oral oestrogen absorption may be compromised by irritable bowel syndrome, malabsorption syndromes, increased liver metabolism, and drug interactions, for example, H2 antagonists and complementary medicines such as St John's Wort. Doses should be the lowest that are effective and length of therapy to avoid ongoing symptoms is usually for years rather than months.[2] One option is to cease HRT every 4–5 years with an expectation that about half will note a loss of quality of life warranting possible recommencement of therapy and half will not wish further therapy.

Conclusion

It is morally wrong and scientifically and medically unsound to advocate and purvey therapies that at best only have a placebo effect. This policy will eventually cause distrust in the doctor–patient relationship, may lead to unexpected or unrecognised side-effects, will delay the use of effective therapies, exploits the gullible, wastes the health dollar and will not have long-term benefits.

In contrast, there are evidence-based effective non-hormonal and hormonal options for the modern management of the menopause. Oestrogen therapy is clearly the best therapy for oestrogen deficiency symptoms and if given from near menopause and in the likely therapeutic window of benefit may have long-term advantages. The risks of HRT have been inflated by the popular press and those purveying alternative therapies. However, there are potential side-effects and risks from HRT that can be reduced by individualising and tailoring the therapy. Emerging data suggest fewer side-effects with lower HRT doses, minimising or limiting systemic progestogens, the use of non-oral routes in some women and the use of HRT in symptomatic women from near menopause. HRT can be offered to informed women for as long as they have debilitating symptoms but the data are not yet strong enough to advocate it for chronic disease prevention, except for osteoporosis prevention near menopause or after premature menopause with the option of other effective fracture prevention treatments at a later age. The systematic reviews of HRT show that the main two start-up side-effects are irregular uterine bleeding which is normal during the first few months of combined HRT and breast tenderness when excessive oestrogen is used. The message is that the latest data on HRT do not warrant the fear and ultra-conservative approach adopted in 2002.[68] Longer-term therapy is appropriate for women with longer-term symptoms who are aware of the potential risks of their regimen in their personal circumstances. Individualised regimens can reduce the incidence of adverse outcomes. When HRT is initiated near menopause for symptom control and subsequent improved quality of life, there may be additional bone, heart and possible cognitive benefits that outweigh the risks that are not significantly raised under the age of 60 years.[69] After this age, women can try stopping therapy to see if their quality of life continues without therapy. However, some women have continuing symptoms even into their seventh decade and they need not be denied HRT if their therapy and risks are individualised, understood and not exaggerated.

New menopausal regimens are moving towards non-oral routes that may avoid increased thromboembolism, the avoidance of systemic progestogens to minimise breast cancer risk through the use of local intrauterine progestogen delivery systems, for example, *Mirena* and the substitution of progestogens with selective oestrogen receptor modulators, for example, *bazedoxifene*.

Ultra low doses of oestrogen are being tested for the prevention of osteoporosis and testosterone continues to be assessed for selected women with low libido, menopausal

depression and tiredness but is not yet registered in Australia for these indications and lacks long-term safety trials. As well as potentially safer regimens the lesson has been learnt to select potentially safer women for therapy and this means initiating therapy during the 'window of therapeutic opportunity' which means the years near menopause.

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