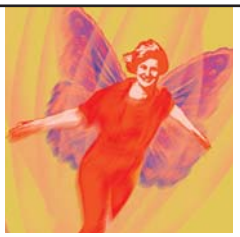

Hormone therapy

Weighing up the evidence

BACKGROUND Hormone therapy (HT) use is well established for menopausal symptom relief, but its use is not currently considered justified for the prevention of disease.

OBJECTIVE This article reviews the recent literature on the risks and benefits of HT in postmenopausal women.

DISCUSSION Menopausal symptoms are severe in around 20% of Australian women and HT effectively relieves these symptoms. Controversy still surrounds the risk profile of HT in women at the time of the menopausal transition, although risks are likely to be small. Recent literature has demonstrated that the role of HT in disease prevention is limited, based primarily on the lack of preventive benefits rather than on the small but present adverse effects of HT use. Historically, the HT literature holds many salient lessons for clinicians. These include the shortcomings of animal data, observational human data, and human trials focussing on intermediate end-points in guiding clinical practice. The HT story also reinforces the principle that health prevention strategies in low risk primary prevention settings should be lifestyle based. Pharmacological therapy, with its inherent risks, even if small, should be reserved for high risk settings.

Effects of hormone therapy

Short term – menopausal symptom relief

A Cochrane systematic review of randomised controlled trials evaluated the effects of hormone therapy (HT) on menopausal symptoms.[1] Hormone therapy decreased hot flush frequency by 77% and severity by 87% compared to placebo.[1] Side effects were not significantly greater than placebo therapy. No other therapies have similar efficacy. While HT is effective in midlife women with significant symptoms (and the serious adverse effects described in older postmenopausal women are likely to be very infrequent), no adequately powered studies in this age group exist and results from existing trials in older women cannot be extrapolated.[2]

Cardiovascular and cerebrovascular disease

Cardiovascular and cerebrovascular disease (CVD) is uncommon in younger and midlife women; it increases exponentially with age and is the leading cause of female death in western societies. Overwhelmingly, observational data suggested that HT was cardioprotective, however, these studies were affected by significant bias. Animal and human interventional studies demonstrating that oestrogen had a plethora of potentially beneficial effects on the cardiovascular system did not assess the net clinical effect of HT.[3] Randomised controlled trials have now evaluated the effects of oral oestrogen and progestin HT (combined HT) and oestrogen alone on CVD when initiated in older postmenopausal women (*Table 1*).[4–6]

The first, the 'HERS' study, did not show a benefit of oral combined HT over placebo (*Table 1*).[4] In women with CVD, HT significantly increased early cardiovascular events and venous thromboembolism (VTE).[4] The open labelled extension of HERS failed to demonstrate benefit of HT on CVD.[5] This is important as HT was ineffective in a high risk population, the secondary pre-

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vention setting where pharmacological therapy (as opposed to lifestyle intervention) is most likely to result in a favourable benefit/risk profile.[5]

The first arm of the Women's Health Initiative (WHI), a chronic disease prevention trial using combined oestrogen plus progestin (E+P), addressed the effects of oral E+P on long term disease prevention in older postmenopausal women (*Table 1*).[6] The study was stopped prematurely as invasive breast cancer exceeded the stopping boundary and the global index suggested the risks of HT use exceeded the benefits (*Figure 1*).[6] There was a small increase in the risk of CVD and stroke or cerebrovascular accident (CVA) with E+P use (*Table 1, Figure 1*). There have been criticisms of the WHI, however this was a large, adequately powered study with important results. The salient message was that HT had minimal preventive benefits; yet the media and lay public focussed on the small, increased risk of adverse events, many of which did not reach significance (*Table 1*). Importantly, analysis of the data from the oestrogen alone WHI arm (E arm), was released earlier this year (*Table 1*).[7] Oestrogen did not increase CVD although it

Table 1. Randomised controlled trials of HT in postmenopausal women (focussing on hard clinical endpoints)

Study title/year published	Participant numbers, characteristics, duration of trial	Comments	Preparation given
HERS: Heart and Estrogen/ Progestin Replacement Study JAMA 1998[4]	2763 women with established CVD, 4.1 years, mean age 66.7 years	Secondary prevention trial in high risk women	CEE 0.625 mg + Provera 2.5 mg continuously or placebo
Heart and Estrogen/Progestin I Replacement Study I HERS II JAMA 2002[5]	Unblinded open label follow up of HERs 93% follow up	Extension of trial did not confirm trend toward lower CVD	CEE 0.625 mg + Provera 2.5 mg continuously or placebo
WHI: Women's Health Initiative Combined E+P arm JAMA 2002[4]	Primary prevention Mean age 63 years, mean duration 5.2 years 200 had HT use before study	Women had CVRF (42%) High rate of HT drop outs 4200 at baseline had HT in past (group where breast cancer was higher)	CEE 0.625 mg + Provera 2.5 mg continuously or placebo
WHI: Women's Health Initiative Estrogen alone JAMA 2004[5]	Primary prevention trial in 10 739 women past hysterectomy 50–79 years, mean duration 6.8 years	Women had CVRF, but generally were representative of the older western female population	CEE 0.625 mg continuously or placebo
WHIMS: WHI memory study JAMA 2004 E+P and E[13]	Sub-study within WHI in women >65 years, mean age 72 years	Women were older, cannot distinguish effects of earlier postmenopausal use of HT	CEE 0.625 mg + Provera 2.5 mg cont or CEE 0.625 mg alone or placebo

Footnote: CI=confidence intervals, all stated are 95% CI, must not include 1.00 to be significant, nominal CI describes the variability in risk estimates that would apply in a trial with only one outcome and is unadjusted (only legitimate in WHI for CHD and breast cancer as these were primary end-points). Adjusted CI are variability of risk estimates corrected for multiple comparisons. CEE=conjugate equine estrogen, P=Provera 2.5 mg continuously, CHD=coronary heart disease, CVA=stroke or cerebrovascular accident, VTE=venous thromboembolism, MCI=mild cognitive impairment, CVRF=cardiovascular risk factors

did increase stroke similarly to E+P.[7]

Essentially, HT use does not prevent CVD when commenced in older postmenopausal women. Diligence in screening for risk factors, emphasis on lifestyle interventions and use of other proven preventive therapies remain very important in reducing the risk of CVD. These trials cannot answer questions regarding the cardiovascular effects of HT in perimenopausal or prematurely menopausal women. The effects in these groups are as yet unknown with further research required.

Fracture prevention

Osteoporosis is a significant cause of morbidity and mortality in postmenopausal women, a risk in part attributable to accelerated postmenopausal bone loss in women.[8] Both the combined E+P and the oestrogen (E) arm of the WHI have demonstrated that HT reduces hip and total fractures (*Table 1*).[6-8] While there is no clear consensus, there may be a role for HT in fracture prevention in women with menopausal symptoms in their 50s who are at high fracture risk (t-score –3.5 without fractures or –2 with fractures) as the initial step in a life long fracture prevention program with subse-

in disease prevention

Outcome measures CI (*nominal*) CI (adjusted for analysis of multiple variables)				**Attributable risk from HT per 10 000 women on HT/year above risk in placebo group**	
CHD 0.99 (0.8–1.22)					
CHD 1.09 (0.71–1.66) year 5 0.99 (0.73–1.35) year 6–8					
CHD	1.29	(*1.02–1.63*)	(0.85–1.97)	CVD	7
CVA	1.41	(*1.07–1.85*)	(0.86–2.31)	CVA	8
Breast cancer	1.26	(*1.00–1.59*)	(0.83–1.92)	Breast cancer	8
VTE	2.11	(*1.58–2.82*)	(1.26–3.55)	VTE	18
Colon cancer	0.63	(*0.43–0.92*)	(0.32–1.24)	Colon cancer	–6
Hip fracture	0.66	(*0.45–0.98*)	(0.33–1.33)	Hip fracture	–5
All fracture	0.76	(*0.69–0.85*)	(0.63–0.92)	All fracture	–44
CHD	0.91	(*0.75–1.12*)	(0.72–1.15)	CVD	5
CVA	1.39	(*1.10–1.77*)	(0.97–1.99)	CVA	12
Breast cancer	0.77	(*0.59–1.01*)	(0.57–1.06)	Breast cancer	–7
VTE	1.33	(*0.99–1.79*)	(0.86–2.08)	VTE	7
Colon cancer	1.08	(*0.75–1.55*)	(0.63–1.86)	Colon cancer	1
Hip fracture	0.61	(*0.41–0.91*)	(0.33–1.11)	Hip fracture	–6
All fracture	0.70	(*0.63–0.79*)	(0.59–0.83)	All fracture	–56
Dementia					
E	1.49	(*0.83–2.66*)		Dementia	12
E+P	2.05	(*1.21–3.48*)		Dementia	23
Mild cognitive impairment (MCI)					
E	1.38	(*1.01–1.89*)		MCI	27
E+P	1.44	(*1.04–1.99*)		MCI	35

quent evolution to other effective agents within 5 years. However, for the large majority of women in their 50s, using HT will have fracture protection only when risks for both falls and fractures are generally low. Once HT is stopped, bone loss resumes.[8] The median age of hip fracture is 79 years and therefore, fracture protection from HT would require continuing for decades or starting later in life when fracture risk is highest.[8] In this age group, adherence is poor and the side effect profile greater, significantly limiting the practical use of HT. Smaller HT doses or newer compounds including selective oestrogen receptor modulators (eg. raloxifene) as well as estro-progestins (eg. tibolone), may be more appropriate, however, this is not yet known. In the majority of cases, other therapies that have established fracture prevention efficacy (including bisphosphonates and selective oestrogen receptor modulators) should be used in preference to HT for first line treatment of women with osteoporosis who are at a high fracture risk.

Breast cancer

The lifetime risk of developing breast cancer in Australia is high, and the rate increases with age. A review of observational data involving 52 000 women with breast cancer and 108 000 controls, showed no significant increase in breast cancer for women who take HT for less than 5 years.[9] For women who used HT for more than 5 years, a relative risk of 1.35 was reported. This was similar to the rate of increase in breast cancer risk seen in the E+P WHI study (*Table 1*)[6] where those primarily affected were women on HT before participating in WHI (4200 women, mean use >5.2 years). Oestrogen alone did not increase the risk of breast cancer (*Table 1*).[7]

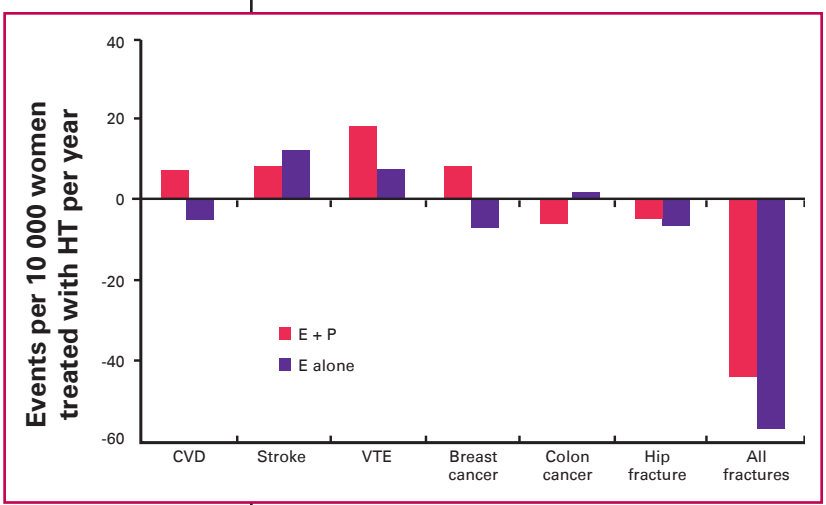

Figure 1. The attributable risk of combined oestrogen and progestin (E+P) and oestrogen alone (E) compared to placebo from the WHI studies per 10 000 women treated with HT per year

The effect of HT in women with a history of breast cancer has also been trialed. The HABITS trial (Hormonal Replacement Therapy After Breast Cancer – is it safe?) was an open randomised trial addressing the safety of 2 years of HT in women with previous breast cancer; mean age was 55 years.[10] It was recently reported that the trial had been terminated because, of the 345 women recruited, 26/174 on HT and 7/171 not on HT had a new breast cancer event after a median of 2.1 years. A similar concurrent trial in Sweden had a statistically different hazard ratio (HABITS 3.3 [95% CI; 1.5–7.4], Swedish study 0.82 [95% CI; 0.35–1.9], pooled data 1.79 [95% CI; 1.03–3.10]).[10] The results of the Swedish study are yet to be separately published and the results will then require further evaluation to understand the reasons for the discrepancies noted. The HABITS investigators concluded that even short term use of HT poses an unacceptably high risk of breast cancer[10] although this conclusion remains controversial. Potentially, in restricted circumstances where other measures have been unsuccessful and quality of life is severely compromised, HT may still be an option in specialist hands.

The Million Women Study (MWS)[11] was an observational study of women having mammography looking retrospectively at HT use and subsequent breast cancer. The study was large and did look at types and regimens of HT used. However, it was not a randomised trial and had significant weaknesses including potential bias with a short follow up and extrapolation of the data to 10 years. The control population was not ideal and duration of HT use was inaccurate and misleading as this data was only collected at baseline. The MWS did confirm an increased adjusted relative risk of breast cancer with HT including E alone 1.30 (1.21–1.40), E+P 2.00 (1.88–2.12) and tibolone 1.45 (1.25–1.68).[11] Importantly, the data is inconsistent with randomised trials[6,7] (*Table 1*) and results should be viewed with some scepticism.

Summary

Oestrogen and progestin use induces a small (1.35 fold) increased risk of breast cancer in women using therapy for more than 5 years (*Table 1*).[6] Women using E alone do not appear to have an increased risk, with a trend toward risk reduction (*Table 1*).[7] We await randomised data on tibolone use. Hormone therapy use

with a past history of breast cancer is difficult to justify.

Thrombosis

Oral oestrogens activate coagulation.[3] In the clinical setting this manifests as a 2–4 fold increased risk of VTE based on both epidemiological and randomised interventional studies.[3,6,7] Most events occur during the first 2 years of HT and the increased VTE risk appears to be independent and multiplicative with other risks of VTE,[12] with the relevant clinical issue being the baseline risk of VTE before HT. Overall, HT is not ideal in high risk women (prior VTE, thrombophilias, immobility or leg fractures), especially with factor V Leiden mutation where there is a specific interaction with HT. Screening for clotting abnormalities before HT is not routinely recommended unless there is a family or personnel history of thrombosis.

To minimise the risk of thrombosis, consideration should be given to withdrawal of HT with temporary acquired risk factors including lower limb fracture or significant surgery. Aspirin may also be protective as the incidence of DVT was 50% lower in women on aspirin in the HERS trial.[4] Finally, transdermal oestrogen therapy may be less procoagulant than oral HT, as it does not have a hepatic first pass effect on coagulation proteins in the liver, a theory recently supported by the case control Estrogen and Thromboembolism Risk Study (ESTHER).[13]

Dementia

Dementia and cognitive impairment were expected to improve with HT from prior basic science and observational data. However, the recently reported Women's Health Initiative Memory study (WHIMS) (*Table 1*) has demonstrated there is a small increase in the risk of dementia when HT is commenced in older women (average age 72 years).[14] There were some weaknesses in the study, however, this data is consistent across both E+P and E alone and fits with the lack of benefit of HT in those with established dementia demonstrated to date. It does not address the effects of HT used around the menopausal transition.

Ongoing controversies

Despite significant investment and multiple large trials on HT, there are many controversies remaining. These are primarily in four main areas.

- What are the risks of serious adverse effects of HT use in younger symptomatic women during the menopausal transition? This is not actually known.[2,15] It appears that these risks were not significantly increased in the WHI in the younger women, however, the studies were not designed nor powered to establish this.[2] Even if the hazard ratio (HR) were similar in younger women to those in the WHI, this equates to very few actual HT attributable events as baseline risks are low. For example, CVD risk is around 5.3/10 000 in the 50–54 years age group. A HR of 1.26 or a 26% increase noted in the WHI would increase this to 6.8 or one CVD event per 10 000 women treated with HT per year.[2,6] To support this, a recent report of 4065 women involved in two randomised trials of conjugated equine oestrogens (CEE) +/- provera in women of mean age around 53 years did not demonstrate any CV events during 1 year of HT in women on HT or placebo during the menopausal transition.[5]
- What are the long term risks of HT use using preparations other than oral CEE and provera? We do not know this at present and although many theories abound it is unlikely we will have randomised controlled trials to clarify this in the near future.
- What are the preventive effects of HT if commenced at the time of menopause for long term use? The Women's International Study of long Duration Oestrogen after Menopause (WISDOM) trial using HT in younger women for disease prevention was ceased after the WHI study reported. It is unlikely to be repeated. Any trials here would need to be prohibitively large and long to be adequately powered to detect changes in diseases that are otherwise very uncommon in this age group.
- What is the role and ideal duration of HT used in premature menopause? We have little on which to base clinical practice here.

Conclusion

Hormone therapy use has well established efficacy in relieving menopausal symptoms during the menopausal transition. Serious adverse effects in this relevant age group are not defined, but are likely to be low. However, benefits of long term HT for chronic disease prevention are small and occur in the presence of small but significant adverse effects of HT. These adverse effects are more relevant in the older woman and generally HT should not be used for disease prevention.

Summary of important points

- HT effectively relieves moderate to severe menopausal symptoms with few associated risks.
- HT does not appear to prevent CVD. It does cause a small increased risk and it should be avoided in women with existing cardiovascular or thromboembolic cerebrovascular disease. Other proven, effective, yet underutilised therapies, are more appropriate for prevention.
- In women at high fracture risk, HT use reduces fractures but only while therapy is continued. This is of limited clinical relevance as high fracture risk is uncommon at the onset of menopause when HT is otherwise indicated, well tolerated and potentially safer. With age, the fracture preventive value of HT increases, but so does the absolute number of significant adverse HT events rendering alternative agents more appropriate.
- Breast cancer increases with E+P use, but not with E use alone. Counselling on this risk is appropriate. Combined HT use is rarely appropriate with a history of breast cancer except perhaps under specialist supervision in women with severe symptoms not amenable to other interventions.
- HT is associated with an independent and multiplicative 2–4 fold increase in risk of VTE. The individual's underlying baseline risk is important here. Withholding therapy or taking concomitant aspirin is appropriate for women with temporary acquired thrombotic risk.
- Women need to be educated on the facts to allow them to make an educated choice on their personal use of HT.

Conflict of interest: none.

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