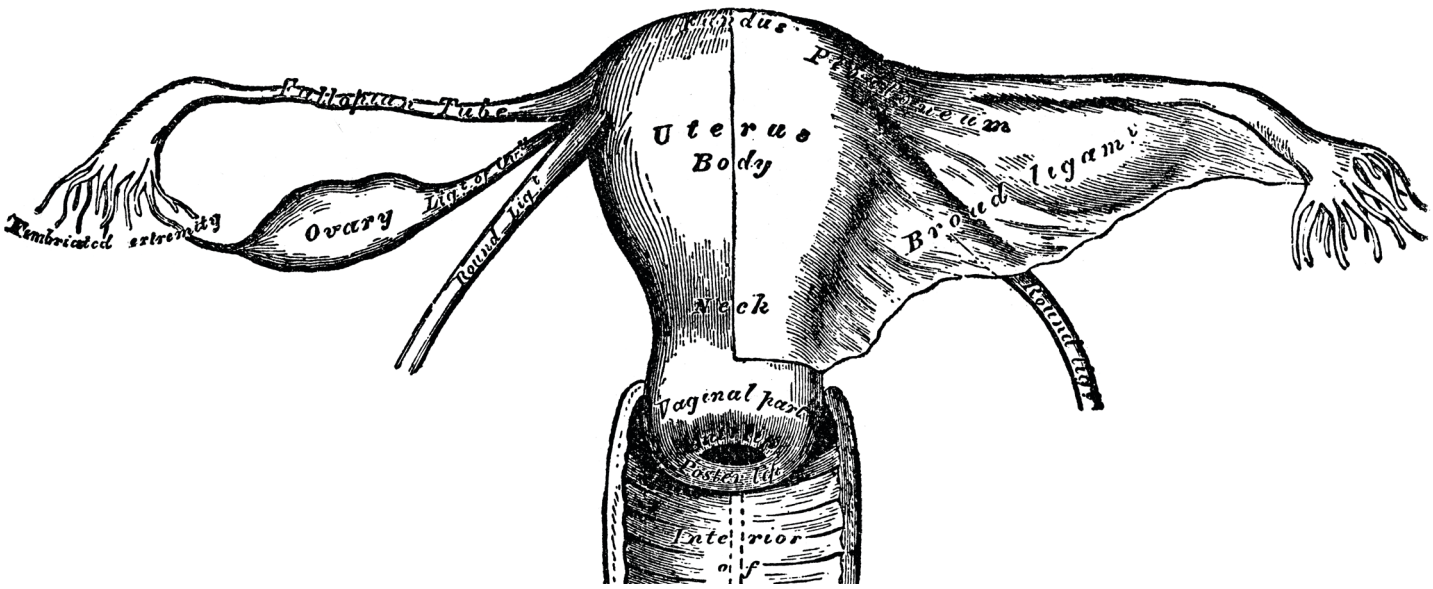
M EXPERT MONOGRAPH ISSUE 21

Myths and Misconceptions Regarding Menopause and Menopausal Hormonal Therapy



CLINICAL A/PROFESSOR AMANDA VINCENT

MBBS, BMed Sci, PhD, FRACP

Adjunct Clinical Associate Professor Amanda Vincent is a clinician researcher working as a Consultant endocrinologist at Monash Health, Melbourne working in the Menopause clinic (including the Early Menopause clinic), Osteoporosis and Clinical Nutrition clinics. She is also a Senior Research Fellow at Monash Centre for Health Research and Implementation, Monash University. Her research interests include women's health, particularly early/ premature menopause, and health professional/consumer education. She is the President of the Australasian Menopause Society.

This article discusses the outcome of research concerning menopause and menopausal hormonal therapy.

Introduction

Menopausal Hormonal Therapy (MHT) is the most effective therapy for improving quality of life in menopausal women and it was widely used until the publication of the Women's Health Initiative (WHI) studies in 2002 and 2004. There was a subsequent decline in the use of MHT, amid concern and confusion on the part of women and clinicians regarding its risks and benefits. This decline was paralleled with a rise in the use of complementary and alternative therapies for menopausal symptoms.[5]

The subsequent reappraisal of the WHI has been combined with more recent data regarding other oestrogen and progestogen preparations and also non-hormonal therapies. This has led to clarification, and consequently, a better understanding of the risks and benefits of MHT. As a result, there has been an improvement in the tailoring of menopause management to the individual woman.

This article expands on myths and misconceptions related to menopause and MHT as identified in previous research[6,7] and, anecdotally, in the Monash Health Menopause Clinic.

Take Home Messages

- Subsequent WHI reports indicated only a small or no significant increase in breast cancer risk in women aged 50 to 59 years, or within ten years of menopause taking MHT after 13 years cumulative follow-up[1]…and no increase in mortality.[2]
- In women aged 50 to 59 years, or who had commenced MHT within ten years of menopause, there was no increase in cardiovascular disease with MHT and evidence of a reduction in both cardiovascular disease mortality and non-fatal myocardial infarction.
- For healthy women aged over forty-five years and who have menopausal symptoms, the diagnosis of perimenopause or menopause is a clinical one. Laboratory and other tests are not required.[3,4]
- Scientific, clinical and regulatory bodies in women's health advise against the use of 'compounded bio-identical hormone therapy'.[3]

1. Misconception: MHT causes weight gain

Weight gain in women at midlife is primarily a consequence of aging; women characteristically gain 0.5kg per year.[3] Risk factors for obesity in middle-aged women include lower education levels; urbanisation of their environment; inactivity; higher parity; a family history of obesity; sleep disruption; depression; early menarche and possibly early menopause.[3] However, menopause is associated with an altered body composition, with an increased fat mass, decreased lean body mass and increased visceral adiposity. There is a transition from a gynoid to an android pattern of fat distribution.[4] This altered body composition has adverse metabolic implications, including insulin resistance, dyslipidaemia and increased risk of diabetes mellitus and cardiovascular disease.[4] A Cochrane review[8] (involving 28 randomised controlled trials and including 28,559 women), found no significant difference in weight gain or increased body mass index (BMI) between women using MHT and non-users of MHT. Indeed, MHT may assist in maintaining lean body mass and prevent android fat distribution.[3]

2. Myth: Breast cancer is the commonest cause of death in post-menopausal women.

Women believe that they are more likely to die from breast cancer than cardiovascular disease, when actually, the converse is true. More Australian women (27%) perceived breast cancer as a health risk, compared to 11%, who perceived cardiovascular disease as a health risk.[7] Actual mortality figures for the two conditions are 4% and 31% respectively.[9] Australian clinicians reported that a woman's fear of breast cancer was the main barrier to prescribing MHT.[6]

3. Misconception: 26% of women who take MHT get breast cancer

Newspaper publication of results of the WHI study (e.g. The Daily Telegraph, 10th July 2002), carried headlines reporting that combined MHT increased the risk of breast cancer by 26%. It was interpreted by some reporters as 26% of women taking MHT would be diagnosed with breast cancer and that women should cease their MHT. There followed a significant decline in MHT sales.[5]

Fifteen years later, amid much controversy, the understanding of the risks and benefits of MHT, as investigated by the WHI, is much clearer. The WHI randomised controlled trial[10] involved 27,347 women aged 50 to 79 years (mean age 63 years, so much older than the peak age of 50-59 years for MHT use[5]). These women were randomised to (i) combined MHT with conjugated combined equine oestrogen (CEE) plus medroxyprogesterone acetate (MPA), or placebo (n=16608) in women with an intact uterus and (ii) CEE alone, or placebo in hysterectomised women (n=10739). The primary efficacy and safety outcomes for the trial were cardiovascular disease and breast cancer respectively.

ADVERTISEMENT

Addressing relief for vaginal atrophy[1-4]

Ovestin® oestriol

Refer to primary advertisement on page 5 for PBS listing and Product Information (PI). Review PI before prescribing.

Aspen Australia. St.Leonards, NSW 2065.Prepared: February 2017.

The combined MHT study was ceased prematurely after 5.2 years due to concerns about an increased risk of breast cancer. In comparison to placebo, the relative risk of invasive breast cancer reported in all MHT users was 1.26 (95% confidence interval [CI] 1.00-1.59),[10] hence the description of a 26% increase in risk. However, the overall absolute risk of breast cancer, indicating the actual number of breast cancer cases in combined MHT users (166) versus placebo (124) during the study, was an additional eight to nine breast cancer cases per 10,000 women per year.[1,10]

There was no significant increase in breast cancer risk with use of CEE alone after 7.2 years [hazard ratio 0.82, 95% CI 0.50-1.34] and a non-significant five fewer breast cancer cases/10,000/ year in the CEE alone group, compared to placebo (Table 1).[1] Subsequent WHI reports indicated no significant increase in breast cancer risk in women aged 50 to 59 years, or within 10 years of menopause in either women taking combined MHT or CEE alone[1] during the intervention phase, and no increase in mortality[2] (Table 1).

Extended follow-up of the WHI indicated a small increased risk of breast cancer after 13 years (nine additional cases per 10,000 women per year; hazard ratio 1.34; 95% CI 1.03-1.75; see Table 1), with combined MHT.[1] This is consistent with that observed in observational studies. However, at 18 years' cumulative follow-up of the WHI, breast cancer mortality was not significantly increased with combined MHT, and a significant reduction in mortality (hazard ratio 0.55; 95%CI 0.33-0.92) was reported with CEE alone.[2] A study assessing modifiable breast cancer risk factors indicated that the level of alcohol consumed and an increased BMI conferred a greater attributable risk than did MHT.[11]

4. Misconception: MHT increases the risk of heart disease.

The initial WHI report in July 2002 described a 29% increase in the relative risk of coronary artery disease respectively with combined MHT;[10] however, this has not been sustained in further re-analyses

of the WHI (Table 1) and a Cochrane systematic review of the role of MHT in primary and secondary prevention of cardiovascular disease.[12] The Cochrane systematic review and meta-analyses of 19 randomised clinical trials (involving 40,410 women) concluded that there was no increase in cardiovascular disease mortality, non-fatal myocardial infarction, angina or revascularisation with MHT, relative to placebo in healthy women or women with pre-existing cardiovascular disease.[12]

In women who had commenced MHT within 10 years of menopause, there was evidence of a reduction in both cardiovascular disease mortality and non-fatal myocardial infarction (eight fewer cases per thousand women; relative risk 0.52; 95% CI 0.29-0.96).[12] The stroke risk was increased in the total group (six additional cases per 1000 women; relative risk 1.24; 95% CI 1.10-1.41), but not in those who commenced MHT within 10 years of menopause (relative risk 1.37; 95% CI 0.80-2.34).[12]

An increased risk of venous thromboembolism is the consistent significant risk associated with oral MHT, regardless of age, or time since MHT was initiated after menopause. There were five to 10 more cases per 1000 women relative to placebo (relative risk 1.92; 95% CI 1.24-2.99 overall, versus 1.74; 95% CI 1.11-2.73, in women within 10 years of menopause.[12]

5. Myth: A blood test is necessary to diagnose menopause

For healthy women aged over 45 years and who have menopausal symptoms, the diagnosis of perimenopause or menopause is a clinical one. Laboratory and other tests (e.g. Follicle Stimulating Hormone [FSH] Anti-Mullerian Hormone [AMH], oestradiol, inhibin B, antral follicle count on ultrasound) are not required.[3,4]

For healthy women aged over 45 years and who have menopausal symptoms, the diagnosis of perimenopause or menopause is a clinical one. Laboratory and other tests are not required.[3,4]

A woman is considered postmenopausal when she is over the age of 45 and has had at least 12 months' amenorrhoea.[4] Laboratory testing may be required in the setting of younger women, for atypical clinical presentations and for women who have had a previous hysterectomy or endometrial ablation.[4] Laboratory and ultrasound testing is necessary in women under 40 years of age, when a diagnosis of premature menopause or premature ovarian insufficiency (POI) is suspected. The diagnostic criteria for POI is greater than four months' oligomenorrhoea or amenorrhoea in a woman under the age of 40, along with elevated FSH levels in the menopausal range, documented on two occasions four to six weeks apart.[3]

Hormonal testing should not be performed on women currently taking the combined oral contraceptive pill, as the results are uninterpretable. Although AMH levels are a useful marker of ovarian reserve, the use of AMH to diagnose or predict when menopause might occur is not supported currently.[4]

6. Myth: Complementary therapies are as effective as MHT and safer.

Whilst there has been a decline in MHT use post-publication of the WHI, there has been a concomitant rise in the use of complementary and alternative therapies (CAMs) by women to manage menopausal symptoms.[5] A study of 10,011 Australian menopausal women aged 59 to 64 years found that 75% used at least one self-prescribed CAM, and 12% used MHT.[13] Women may not disclose CAM use to their doctor and often have little knowledge of the quality, safety and efficacy of CAM.[7,14] Recommendations for use of non-hormonal therapies, including CAM, are summarised in Table 2.

A meta-analysis of randomised controlled trials with mixed results suggested that soy isoflavones (but not red clover isoflavones) may be an effective botanical therapy,[15] although safety in women who have or have had breast cancer is unclear. A Cochrane review reported no significant difference in frequency of hot flushes between black cohosh and placebo, and there were concerns regarding potential hepatotoxicity with black cohosh.[16]

Clinical trials of cognitive behavioural therapy in women who have or have not had breast cancer demonstrated a reduction in ratings for problematical vasomotor symptoms, but not for frequency.[16] Two clinical trials of hypnosis indicated a significant reduction in frequency of hot flushes compared to placebo.[3, 16]

Randomised controlled trials of acupuncture versus sham acupuncture show no difference in frequency of hot flushes.[17]

7. Myth: Compounded bio-identical hormone therapy is safer than conventional MHT.

Marketing and media promotion of 'compounded bio-identical hormone therapy' as a safe and effective alternative to conventional MHT, plus concern and confusion following publication of the WHI results, have led to an increase in the popularity of these products. Compounded bio-identical hormones may contain various oestrogens (oestriol, oestradiol, and oestrone), pregnenolone, testosterone, DHEA and progesterone.[3]

The phrase 'bio-identical hormone therapy' has been recognised by the US Federal Drug Administration and medical societies as

a marketing term, and not one based on scientific evidence. Bio-identical hormones are those chemically or structurally identical to those produced by the body, and thus conventional transdermal oestradiol and micronised progesterone both fulfil this definition.

Evidence is lacking to support claims that compounded bioidentical hormone therapy is superior to conventional MHT. Similar adverse events have been reported with compounded bioidentical hormone therapy, including endometrial cancer.[18]

Problems arise with compounded hormonal therapy due to the lack of:

i. Regulatory oversight;
ii. Manufacturing standards;
iii. Clinical testing of quality, pharmacokinetics, efficacy and safety;
iv. The use of unsubstantiated salivary hormone testing to titrate doses.

Scientific, clinical and regulatory bodies in women's health advise against the use of 'compounded bio-identical hormone therapy'.[3]

8. Misconception: All progestogens have the same risks.

The term 'progestogen' includes both progesterone (naturally occurring in humans) and progestins (synthetic versions of progesterone that also bind to the progesterone receptor and exert a similar effect on the endometrium).

A progestogen is prescribed with oestrogen therapy in women with an intact uterus to protect against endometrial hyperplasia and carcinoma.[3]

Progesterone has poor bioavailabilty when taken orally unless it is micronised (a recent development), and therefore a number of synthetic progestins have been created. All progestogens bind to the progesterone receptor, thus mediating the protective effect on the endometrium. However, differences exist between different progestogens related to pharmacokinetics, metabolism and binding to other receptors (androgen, glucocorticoid, mineralocorticoid) translating into potentially different risk and benefit profiles.[19]

Levonorgestrel, norethisterone and MPA all bind to the androgen receptor; MPA and promegestone bind to the glucocorticoid receptor and drospirenone has anti-mineralocorticoid and anti-androgenic activity.[19]

Although the WHI study indicated that use of CEE plus MPA was associated with an increased breast cancer risk compared with placebo (see above), a recent systematic review[20] concluded that combined MHT using micronised progesterone was associated with a lower breast cancer risk compared with synthetic progestins (relative risk 0.67; 95% CI 0.55-0.81).

The effect of newer progestins (e.g. drospirenone, dienogest, gestodene) on breast cancer risk is unclear. The risk of venous thromboembolism is increased with the use of oral (but not transdermal) oestrogen.[3] However, the choice of progestin may also influence venous thromboembolism risk. An increased risk is observed with norpregnane derivatives (e.g. nomegestrol and promegestone), but not with micronised progesterone.[19,21]

Progestins with androgenic or glucocorticoid activity attenuate or reverse the beneficial effects of oestrogen on surrogates of cardiovascular disease risk factors, including insulin resistance, lipid metabolism, blood pressure and endothelial function.[19] Drospirenone, in contrast, has anti-mineralocorticoid effects and is more beneficial regarding blood pressure. How these effects on surrogate markers translate into differences in overall cardiovascular mortality and morbidity is unclear.

9. Misconception: Non-hormonal pharmacological therapies are as effective as MHT for vasomotor symptoms.

Non-hormonal pharmacological therapies for vasomotor symptoms include certain antidepressants, gabapentinoids (gabapentin and pregabalin) agents and clonidine (Table 2). Almost 50% of 745 Australian endocrinologists, general practitioners and gynaecologists reported that they had limited knowledge and needed to learn more about non-hormonal therapies.[6]

There are few head-to-head studies comparing oestrogen to non-hormonal pharmacological therapies, however, evidence suggests that these agents are not as effective as oestrogen. Venlafaxine and gabapentin have a similar efficacy to 0.5mg oestradiol in reducing vasomotor symptoms.[3]

The only non-hormonal pharmacological agent for hot flushes approved by the Therapeutic Goods Administration is clonidine, and use of other classes of drugs for this indication in Australia is considered 'off-label'. Low-dose paroxetine is approved for this use in the USA.

Declaration

A/Prof Amanda Vincent was commissioned by Healthed for this article. The ideas, opinions and information presented are solely those of the author. The advertiser does not necessarily endorse or support the views expressed in this article.

The author's competing interests statement can be viewed at www.healthed.com.au/monographs.

ADVERTISEMENT

Addressing relief for vaginal atrophy[1-4]

Ovestin® oestriol

only about 25% of women suffering from vaginal atrophy symptoms actually volunteer the information to their health-care professional[5]

Before prescribing please review full Product Information available on request from Aspen Australia or at www.aspenpharma.com.au/products

PBS Information: Ovestin Cream and Ovestin Ovula are listed on the PBS as an oestrogen. Ovestin Tablet is not listed on the PBS.

Minimum Product Information – Ovestin (oestriol) Tablets, Cream and Ovula - INDICATIONS: Tablets: Short-term treatment of menopausal syndrome. Cream and Ovula: Vulvo-vaginal complaints due to oestrogen deficiency associated with the climacteric and postmenopause or after ovariectomy; atrophic vaginitis; pruritus vulvae; dyspareunia due to vulvo-vaginal atrophy; auxiliary therapy in the treatment of vaginal infections; pre-operative therapy for vulvo-vaginal surgery and during subsequent convalescence; ulcers in cases of prolapse of the uterus or vagina; to avoid misinterpretation of a cytological smear. **CONTRAINDICATIONS:** Pregnancy (Cat. B1); lactation; known, past or suspected breast cancer; known or suspected oestrogen-dependent malignant tumours; undiagnosed genital bleeding; previous or current active VTE (DVT, pulmonary embolism); known thrombophilic disorders; history of recurrent VTE or known thrombophilic disease in a patient who is not already on anticoagulant treatment; active or recent arterial thromboembolic disease; current or history of thrombophlebitis; history during pregnancy or previous use of steroids of a manifestation or deterioration of otosclerosis; endometriosis; untreated endometrial hyperplasia; porphyria; severe liver dysfunction or history of liver disease; disturbed lipid metabolism; hypersensitivity to ooestriol or any excipients (see full PI). **PRECAUTIONS:** leiomyoma; history of or risk factors for thromboembolic disorders; risk factors for oestrogen dependent tumours; hypertension; liver disorders; diabetes mellitus; cholelithiasis; migraine or severe headache; systemic lupus erythematosus; history of endometrial hyperplasia; epilepsy; asthma; otosclerosis; severe pruritus; cholestatic jaundice; herpes gestationis; coronary artery disease; smoking; ischaemic stroke; ovarian cancer; fluid retention; cardiac or renal dysfunction; gall bladder disease; uterine fibroids; epilepsy; asthma; fibrocystic mastopathy; metabolic bone disease; dementia; lactation (see full PI). **INTERACTIONS:** corticosteroids; succinylcholine; theophyllines; troleandomycin; oral anticoagulants; inducers of drug-metabolizing enzymes e.g. anticonvulsants, barbiturates, anti-infectives, antiretroviral agents, St John's wort (see full PI). **ADVERSE EFFECTS:** Tablets: fluid retention; nausea; breast discomfort and pain; postmenopausal spotting; cervical discharge; flu-like symptoms. Cream and Ovula: local irritation or itching (see full PI). **DOSAGE AND ADMINISTRATION:** Tablets: Swallow with food at the same time each day. Initially up to 4mg daily for 5-7 days then 1-2mg daily thereafter as maintenance. Cream: For intravaginal administration at night using a calibrated applicator (each application-dose is 0.5g of Ovestin cream containing 0.5mg ooestriol). *Vulvo-vaginal complaints associated with menopause:* Initially, one application-dose per day for 3 weeks then one application twice weekly thereafter as maintenance (discontinue therapy every 2-3 months for 4 weeks to review need for further treatment). *Pre-surgery therapy:* one application-dose per day beginning 2 weeks before operation. *Suspect cytological smear:* one application-dose per day for 7 days before re-evaluating. Ovula: For intravaginal administration, at night. *Vulvo-vaginal complaints associated with menopause:* initially one pessary daily for 2-3 weeks, then one pessary once or twice a week thereafter as maintenance (discontinue every 2-3 months for 4 weeks to assess need for further treatment). *Pre-surgery therapy:* one pessary daily, beginning 2 weeks before operation. *Suspect cytological smear:* one pessary daily for 7 days before re-evaluation (See full PI for full instructions on administration, missed doses and switching from HRT). (Based on PI last amended: 06/07/2016)

References: 1. Ovestin Cream Approved Product Information 6 July 2016 **2.** Ovestin Pessaary Approved Product Information 6 July 2016 **3.** Ovestin Tablets Approved Product Information 6 July 2016 **4.** Suckling et al. 2006, Local oestrogen for vaginal atrophy in postmenopausal women (review). Cochrane Collaboration **5.** Sturdee DW, Panay N. Recommendations for the management of postmenopausal vaginal atrophy – on behalf of the International Menopause Society Writing Group.Climacteric 2010;Early Online, 1-14

All sales and marketing requests to: **Aspen Pharmacare Australia Pty Ltd**, ABN 51 096 236 985, 34-36 Chandos Street, St Leonards, NSW 2065
Tel +61 2 8436 8300 aspen@aspenpharmacare.com.au www.aspenpharma.com.au

Aspen Australia is comprised of Aspen Asia Pacific Pty Ltd (ABN 75 146 444 484) and its subsidiaries, including Aspen Pharmacare Australia Pty Ltd (ABN 51 096 236 985), Aspen Pharma Pty Ltd (ABN 88 004 118 594), Aspen Nutritionals Australia Pty Limited ACN 160607509, Orphan Holdings Pty Ltd (ABN 50 115 816 209), Orphan Australia Pty Ltd (ABN 11 067 189 342) and Aspen Products Pty Ltd (ABN 17 003 144 170). Prepared: February 2017. AF01649 ASP1562

aspen AUSTRALIA

Table 1: Risks and Benefits of MHT in Women Aged 50 to 59 Years as Reported in the Women's Health Initiative. Adapted from [1,22]

A. Combined Conjugated Equine Estrogen plus Medroxyprogesterone Acetate

Outcome	Hazard Ratio (95% CI)	Absolute risk versus placebo (Difference per 10000 person-year)	Statistically significant
Intervention phase (5.6 years follow-up)			
Coronary heart disease	1.34 (0.82-2.19)	5 more	No
Breast cancer	1.21 (0.81-1.80)	6 more	No
All cancer	0.97 (0.76-1.23)	1 fewer	No
Stroke	1.51 (0.81-2.82)	5 more	No
Deep vein thrombosis	**3.01 (1.36-6.66)**	**10 more**	**Yes**
Hip fracture	0.17 (0.02-1.45)	3 fewer	No
Vertebral fracture	**0.38 (0.25-0.97)**	**6 fewer**	**Yes**
All-cause Mortality	0.67 (0.43-1.04)	10 fewer	No
Cumulative phase (13 years follow-up)			
Coronary heart disease	1.27 (0.93-1.74)	5 more	No
Breast cancer	**1.34 (1.03-1.75)**	**9 more**	**Yes**
All cancer	1.07 (0.92-1.24)	7 more	No
Stroke	1.37 (0.89-2.11)	4 more	No
Deep vein thrombosis	1.17 (0.76-1.82)	2 more	No
Hip fracture	0.57 (0.31-1.04)	4 fewer	No
Mortality	0.88 (0.94-1.24)	5 fewer	No

B. Conjugated Equine Oestrogen Alone

Outcome	Hazard Ratio (95% CI)	Absolute risk versus placebo (Difference/10000-year)	Statistically significant
Intervention phase (7.2 years follow-up)			
Coronary heart disease	0.60 (0.35-1.04)	11 fewer	No
Breast cancer	0.82 (0.50-1.34)	5 fewer	No
All cancer	0.89 (0.66-1.19)	8 fewer	No
Stroke	0.99 (0.53-1.85)	1 fewer	No
Deep vein thrombosis	1.66 (0.75-3.65)	5 more	No
Hip fracture	5.01 (0.59-42.91)	3 more	No
Vertebral fracture	0.50 (0.17-1.47)	4 fewer	No
All-cause Mortality	0.70 (0.46-1.09)	11 fewer	No
Cumulative follow-up (13 years follow-up)			
Coronary heart disease	**0.65 (0.44-0.96)**	**11 fewer**	**Yes**
Breast cancer	0.76 (0.52-1.11)	7 fewer	No
All cancer	**0.80 (0.64-0.99)**	**18 fewer**	**Yes**
Stroke	0.96 (0.60-1.55)	1 fewer	No
Deep vein thrombosis	0.79 (0.47-1.75)	3 more	No
Hip fracture	0.88 (0.36-2.17)	0	No
Mortality	0.78 (0.59-1.03)	12 fewer	No

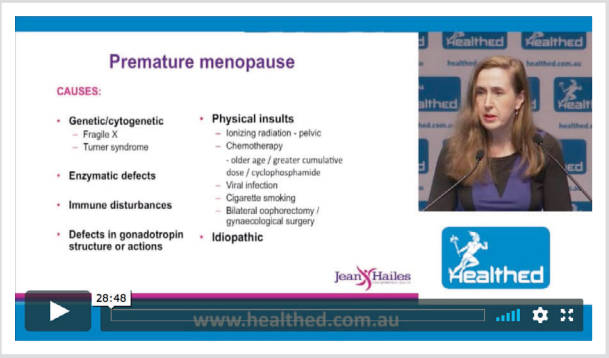
Table 2: Non-hormonal therapies for vasomotor symptoms

*Derived from North American Menopause Society 2015 Position statement[16] and systematic review/meta-analysis[15]

Therapy	Hot flush reduction#	Level of evidence*
RECOMMENDED for reduction of vasomotor symptoms		
Medications		
SSRIs and SNRIs Venlafaxine 75-150 mg/day Desvenlafaxine 100-150 mg/day Escitalopram 10-20mg/day Paroxetine 10-20mg/day	-1.13 (-1.70 to -0.57)	I
Gabapentin 300-900 mg/day in divided doses	-2.05 (-2.80 to -1.30)	I
Pregabalin 75-150mg bd		II
Clonidine 50-75mcg bd	-0.95 (-1.4 to -0.47)	II
Mind-Body Techniques		
Clinical hypnosis		I
Cognitive behavioural therapy		I
RECOMMEND WITH CAUTION for vasomotor symptoms		
Lifestyle		
Weight loss		II
Mind-Body technique		
Mindfulness stress reduction		II
Dietary/ supplement		
Soy isoflavones	-1.22 (-2.0 to -0.42)	II
Other		
Stellate ganglion blockade		II
DO NOT RECOMMEND for vasomotor symptoms		
Mind-Body technique		
Yoga		I
Paced respiration		I
Relaxation		II
Dietary/supplements		
Herbal and other supplements		I-V
Other		
Acupuncture		I
Chiropractic		III
Homeopathy		III
Calibration of neural oscillations		III

#Mean difference in number of daily hot flushes versus placebo (95% confidence interval).[15] Oestrogen-containing therapy reduced hot flushes by approximately 2.40 to 3.20 flushes per day.[23] *Level of evidence:[16] **Level I**: high quality randomised controlled trials (RCTs) or meta-analyses. **Level II:** lesser quality RCTs, systematic reviews of level II studies, inconsistent results of Level I studies. **Level III:** uncontrolled trials, case-control studies, systematic reviews of level III studies. **Level IV:** case series/ case-control studies. **Level V:** expert opinion.

Video Resources



Premature Menopause with Dr Sonia Davison

Indications of HRT with Dr John Eden

Watch full lectures on the Healthed website. Visit www.healthed.com.au/video

References

1. Manson JE, Chlebowski RT, Stefanick ML, Aragaki AK, Rossouw JE, Prentice RL, et al. *Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials.* JAMA. 2013 Oct; 310(13): 1353-68.
2. Manson JE, Aragaki AK, Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, et al. *Menopausal hormone therapy and long-term all-cause and cause-specific mortality: The women's health initiative randomized trials.* JAMA. 2017 Sep; 318(10): 927-38.
3. Baber RJ, Panay N, Fenton A, Group IMSW. *2016 IMS Recommendations on women's midlife health and menopause hormone therapy.* Climacteric. 2016 Apr; 19(2): 109-50.
4. Davis S, Lambrinoudaki I, Lumsden MA, Mishra GD, Pal L, Rees M, et al. *Menopause*. Nat Rev Dis Primers. 2015 Apr; 1: 1-19.
5. MacLennan AH, Gill TK, Broadbent JL, Taylor AW. *Continuing decline in hormone therapy use: population trends over 17 years.* Climacteric. 2009 Apr; 12(2): 122-30.
6. Yeganeh L, Boyle J, Teede H, Vincent A. *Knowledge and attitudes of health professionals regarding menopausal hormone therapies.* Climacteric. 2017 Aug; 20(4): 348-55.
7. Deeks A, Zoungas S, Teede H. *Risk perception in women: a focus on menopause.* Menopause. 2008 Mar-Apr; 15(2): 304-9.
8. Kongnyuy EJ, Norman RJ, Flight HKI, Rees MC. *Oestrogen and progestogen hormone replacement therapy for peri-menopausal and post-menopausal women: weight and body fat distribution.* Cochrane Database Syst Rev. 2011; (4).
9. Foundation H. Australian Heart Disease statistics 2015: Australian Heart Foundation, 2015.
10. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. *Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial.* JAMA. 2002 Jul; 288(3): 321-33.
11. Maas P, Barrdahl M, Joshi AD, Auer PL, Gaudet MM, Milne RL, et al. *Breast Cancer Risk From Modifiable and Nonmodifiable Risk Factors Among White Women in the United States.* JAMA Oncol. 2016 Oct; 2(10): 1295-302.
12. Boardman Henry MP, Hartley L, Eisinga A, Main C, Roqué i Figuls M, Bonfill Cosp X, et al. *Hormone therapy for preventing cardiovascular disease in post-menopausal women.* Cochrane Database Syst Rev. 2015 Mar; (3): CD002229. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002229.pub4/abstract.
13. Peng W, Adams J, Hickman L, Sibbritt DW. *Complementary/alternative and conventional medicine use amongst menopausal women: Results from the Australian Longitudinal Study on Women's Health.* Maturitas. 2014 Nov; 79(3): 340-2.
14. Byard RW, Musgrave I, Maker G, Bunce M. *What risks do herbal products pose to the Australian community?* Med J Aust. 2017 Feb; 206(2): 86-90.
15. Nelson HD, Vesco KK, Haney E, Fu R, Nedrow A, Miller J, et al. *Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis.* JAMA. 2006 May; 295(17): 2057-71.
16. *Nonhormonal management of menopause-associated vasomotor symptoms: 2015 position statement of The North American Menopause Society.* Menopause. 2015 Nov; 22(11): 1155-72; quiz 73-4.
17. Ee C, Xue C, Chondros P, Myers SP, French SD, Teede H, et al. *Acupuncture for Menopausal Hot Flashes: A Randomized Trial.* Ann Intern Med. 2016 Feb; 164(3): 146-54.
18. Eden JA, Hacker NF, Fortune M. *Three cases of endometrial cancer associated with 'bioidentical' hormone replacement therapy.* Med J Aust. 2007 Aug; 187: 244-5.
19. Stanczyk FZ, Hapgood JP, Winer S, Mishell DR Jr. *Progestogens used in postmenopausal hormone therapy: differences in their pharmacological properties, intracellular actions, and clinical effects.* Endocr Rev. 2013 Apr; 34(2): 171-208.
20. Asi N, Mohammed K, Haydour Q, Gionfriddo MR, Vargas OL, Prokop LJ, et al. *Progesterone vs. synthetic progestins and the risk of breast cancer: a systematic review and meta-analysis.* Syst Rev. 2016 Jul; 5(1): 121.
21. Mueck AO. *Postmenopausal hormone replacement therapy and cardiovascular disease: the value of transdermal estradiol and micronized progesterone.* Climacteric. 2012 Apr; 15 Suppl 1: 11-7.
22. Baber R. *Hormone therapy and menopause. A protracted misunderstanding explained.* Medicine Today. 2017; 18(2): 23-6.
23. Nelson HD. *Commonly used types of postmenopausal estrogen for treatment of hot flashes: scientific review.* JAMA. 2004 Apr; 291(13): 1610-20.