

I INTRODUCTION

The menopause is a normal biological phenomenon that is accompanied by profound hormonal changes. It signifies the end of the reproductive phase of a woman's life and is also associated with accelerated ageing. Menopause can be natural (thought to be associated with the depletion of ovarian follicles) or surgical (where the ovaries are surgically removed). As ovarian follicles produce oestrogen and progesterone, the follicle depletion results in lower circulating levels of these hormones. In turn, multiple body tissues appear to be affected, some acutely and some over the longer-term.

In the case of natural menopause, the transition from normal menstrual function to amenorrhoea is gradual. In contrast, surgically-induced menopause is abrupt.

While the nature and severity of menopause symptoms vary considerably amongst women, the most common is the hot flush. Estimates of the incidence of hot flushes range from 25% to 85% of menopausal women (Kronenberg, 1990). Other short term symptoms such as urogenital changes, sleep disturbances and emotional changes may also prove problematic. Replacement of oestrogen has an accepted role in the alleviation of short term menopause symptoms; however up until recently it had also been promoted to diminish the potential consequences of depleted circulating oestrogen upon bone and the cardiovascular system.

The practice of prescribing oestrogen for the treatment of menopausal-related symptoms has commonly been termed hormone replacement therapy (HRT). A more correct term, however, is hormone therapy. For the majority of women, the depletion of oestrogen which occurs during menopause does not need to be 'replaced'; oestrogen is only required for women who have significant menopausal symptoms. However, as HRT is such a well known and accepted term, it will be used throughout this review to describe oestrogen-containing therapies.

Other non-oestrogen containing therapies exist which are used to relieve menopausal symptoms. Those evaluated in this review include tibolone, raloxifene and various other therapies grouped under the term complementary and alternative medicines (CAMs) which are not prescription medicines, but are widely used by women.

The aim of the current review is to systematically present the evidence relating to both the benefits and risks associated with the therapies commonly used at or after the menopause.

1.1 USE OF MENOPAUSAL THERAPIES IN AUSTRALIA

The following section provides a brief description of each of the menopausal therapies to be considered in this review, as well as an estimate of their use in Australia (where available).

The public reimbursement of prescription medicines via the Pharmaceutical Benefits Schedule (PBS) provides a reasonable estimate of the volume of prescription drug use as there is minimal use of non-PBS funded prescription medicines in Australia. National statistics are available quantifying the annual volume of prescriptions by PBS item number. Therefore, where possible, PBS statistics will be used to estimate use of menopausal therapies in Australia.

1.1.1 HRT

HRT involves the administration of exogenous oestrogen. Oestrogens used in HRT include oestradiol valerate, conjugated equine oestrogens and piperazine oestrone sulfate.

In women with an intact uterus, oestrogen alone (ERT) has the potential to cause proliferation of endometrial cells and hence increases the risk of developing endometrial cancer. For this reason, it is advised that women with an intact uterus be given a progestogen also (EPRT). The progestogen can be given either continuously throughout the cycle, or can be given sequentially for part of the cycle (ie, for at least 12-14 days). Progestogens used in HRT include norethisterone acetate and medroxyprogesterone acetate.

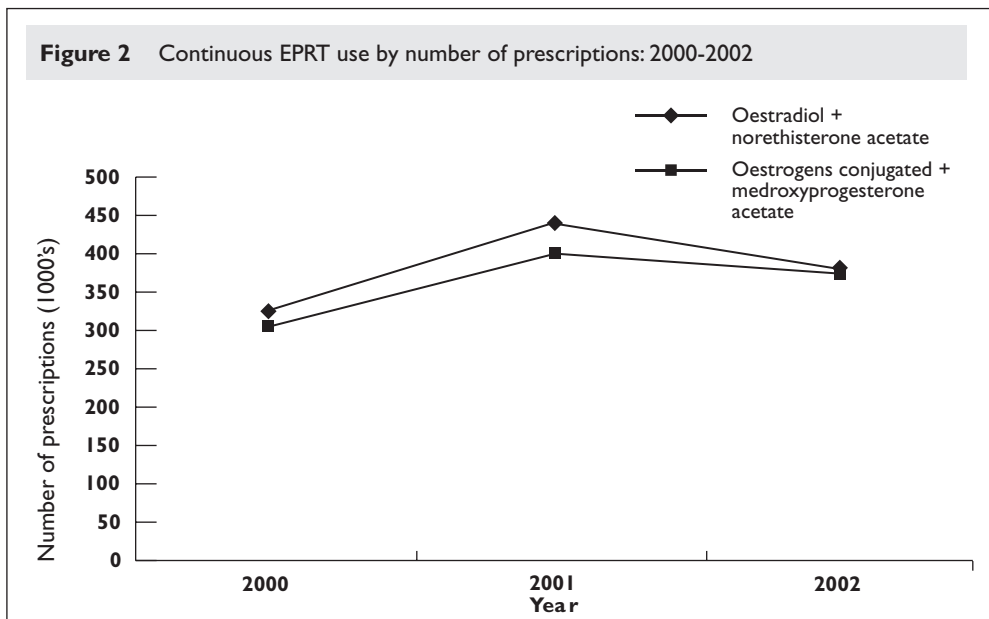
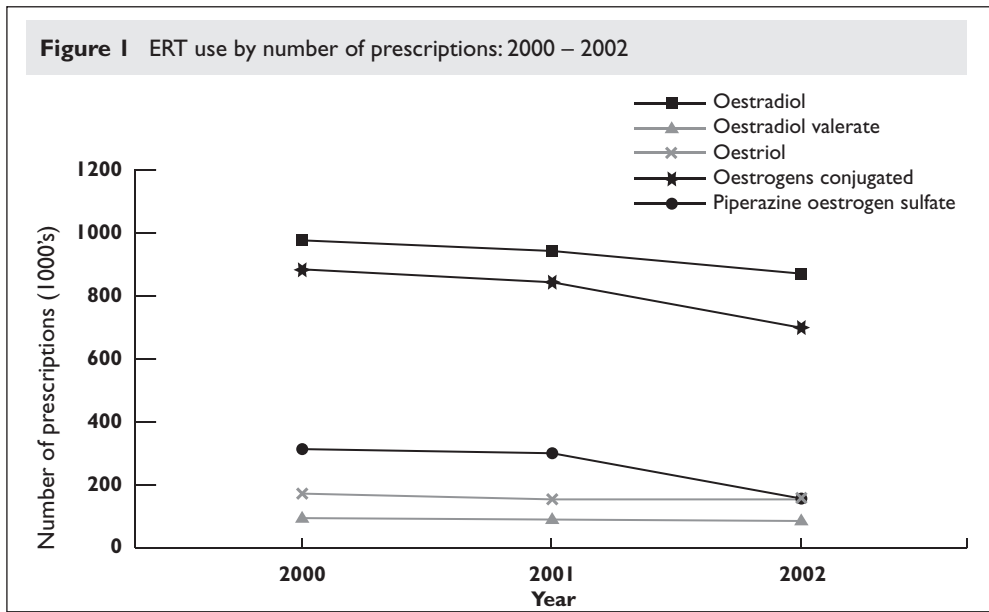
Table 1 includes a list of the oestrogen-only and combination therapies available on the PBS.

TABLE I PBS LISTING OF HRT

Generic name	Mode of administration	Dose		Proprietary name
		Oestrogen	Progestogen	
Oestrogens				
<i>Natural and semisynthetic oestrogens</i>				
Oestradiol	Oral tablet	2 mg	–	Zumenon
	Vaginal tablet	25 µg	–	Vagifem
	Transdermal gel ^a	1 mg	–	Sandrena
	Transdermal patch ^a	various	–	Estraderm, Climara, Femtran, Dermestril, Menorest
Oestradiol valerate	Oral tablet	1 mg, 2 mg	–	Progynova
	Injection	10 mg in 1 mL	–	Primogyn Depot
Oestriol	Oral tablet	1 mg	–	Ovestin
	Pessaries	500 µg	–	Ovestin, Ovula
	Vaginal cream	1 mg/g	–	Ovestin
Oestrogens-conjugated	Oral tablet	300 µg, 600 µg	–	Premarin
Piperazine oestrone sulfate	Oral tablet	730 µg, 1.46 µg	–	Genoral, Ogen
Progestogens and oestrogens in combination				
<i>Continuous preparations</i>				
Oestradiol with norethisterone acetate	Oral tablets	1 mg	500 µg	Kliovance
	Oral tablets	2 mg	1 mg	Kliogest
	Transdermal patch ^a	various	various	Estalis
	Oral tablets	625 µg	5 mg	Provelle
Oestrogens-conjugated with medroxyprogesterone acetate	Oral tablets	625 µg	2.5 mg, 5 mg	Premia continuous
<i>Sequential preparations</i>				
Oestradiol and oestradiol with dydrogesterone	Oral tablet	2 mg	10 mg	Femoston
Oestradiol and oestradiol with norethisterone acetate	Oral tablets	2 mg/1 mg, 4 mg/1 mg	1 mg	Trisequens Trisequens Forte
	Transdermal patch ^a	various	various	Estalis sequi, Estracombi
Oestradiol valerate and oestradiol valerate with cyproterone acetate	Oral tablets	2 mg	1 mg	Climen
Oestrogens conjugated and oestrogens conjugated with medroxyprogesterone acetate	Oral tablets	625 µg	5 mg, 10 mg	Premia

^a Available as a restricted benefit

Figure 1, Figure 2 and Figure 3 provide an estimate of the annual number of prescriptions for oestrogen only, continuous oestrogen/progestogen, and sequential oestrogen/progestogen products that are currently available on the PBS in Australia. Oestradiol and conjugated oestrogens are the most commonly used oestrogen-only therapies in Australia. The two available continuous combined regimens are used in similar quantities while oestradiol/ oestradiol + norethisterone is the most commonly used sequential therapy used.



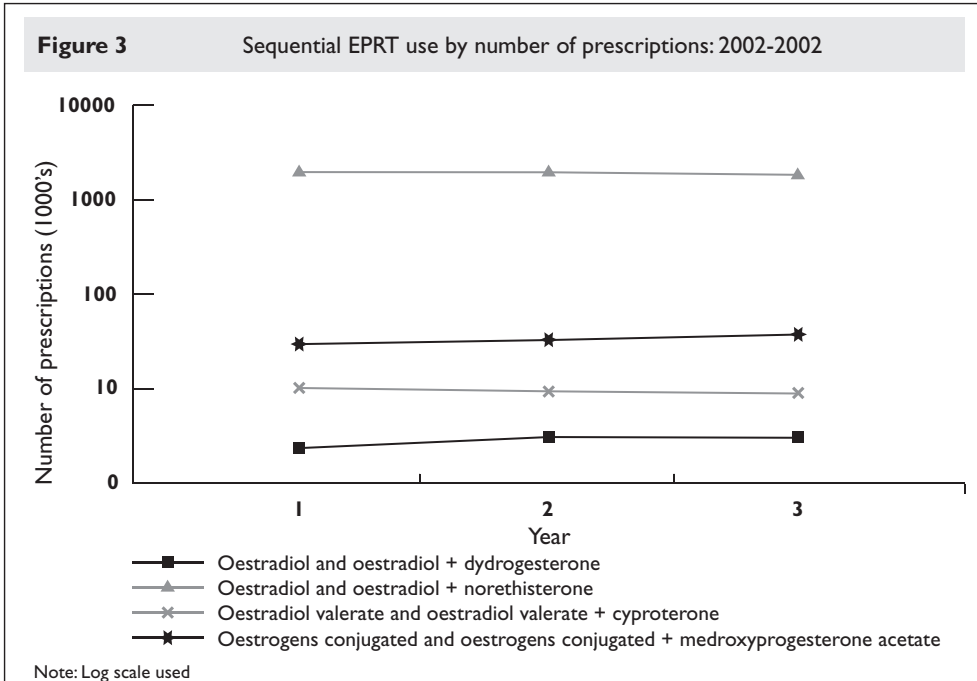
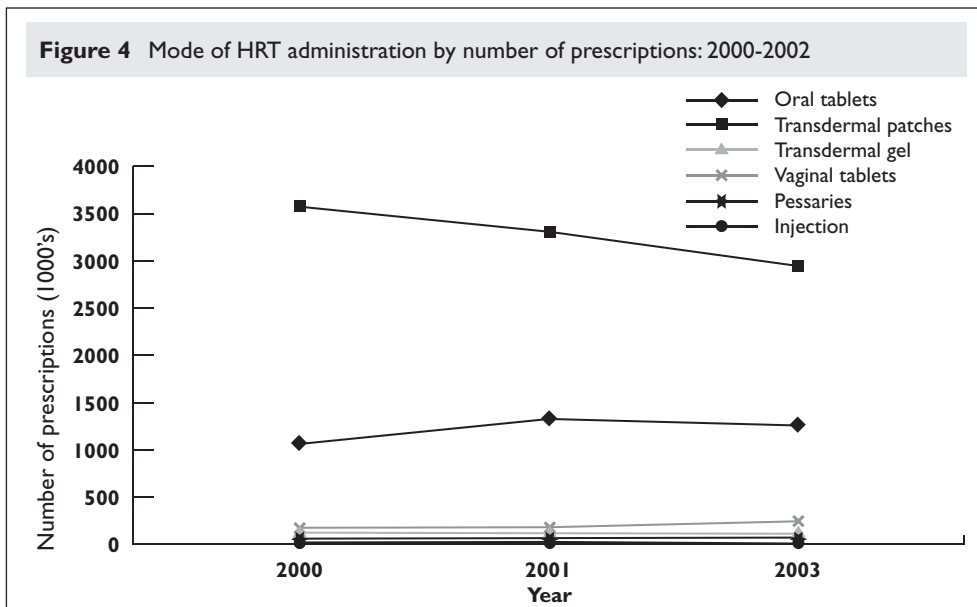


Figure 4 displays the annual number of prescriptions according to the mode of administration for hormone replacement products that are currently available on the PBS in Australia. They show that oral administration of HRT is by far the most common. This is most likely because the public reimbursement of transdermal HRT is restricted to women who cannot tolerate oral therapy.



1.1.2 TIBOLONE

Tibolone (Livial®) is a synthetic steroid which has differential effects on different tissues. Tibolone is metabolised into three different isomers, two of which have predominantly oestrogenic effects, and one which has both progestogenic and androgenic effects. The oestrogenic effects occur on the vagina, bone and thermoregulatory system, while the progestogenic (and anti-oestrogenic) effects occur in the breast. Androgenic effects occur in the metabolic and haematologic systems.

Tibolone is indicated for the treatment of symptoms resulting from the natural or surgical menopause and prevention of postmenopausal bone mineral density loss. As tibolone does not cause bleeding it is often favoured by women who are > 1 year past their last period. It should be noted that tibolone should not be used until at least 12 months after the last natural menstrual bleed as, if taken soon sooner than this, the frequency of irregular bleeding may be increased.

While tibolone is available as a prescription drug, it is not currently listed on the PBS. Therefore, it is not possible to obtain any accurate data regarding its use. However, given that it is not reimbursed it is not likely to be widely used.

1.1.3 RALOXIFENE

Raloxifene (Evista®) is a selective oestrogen receptor modulator (SERM); it displays differential effects at different oestrogen receptors. It has been shown to act as an agonist on bone and lipid receptors (thereby having a positive effect) and antagonistic effects at other oestrogen receptors including those on the breast and uterus (thus theoretically having less potential to cause breast or uterine cancer compared with conventional oestrogens).

Raloxifene is indicated for use in the prevention and treatment of osteoporosis in postmenopausal women and is currently listed on the PBS (see Table 2) with the following Authority Required listing:

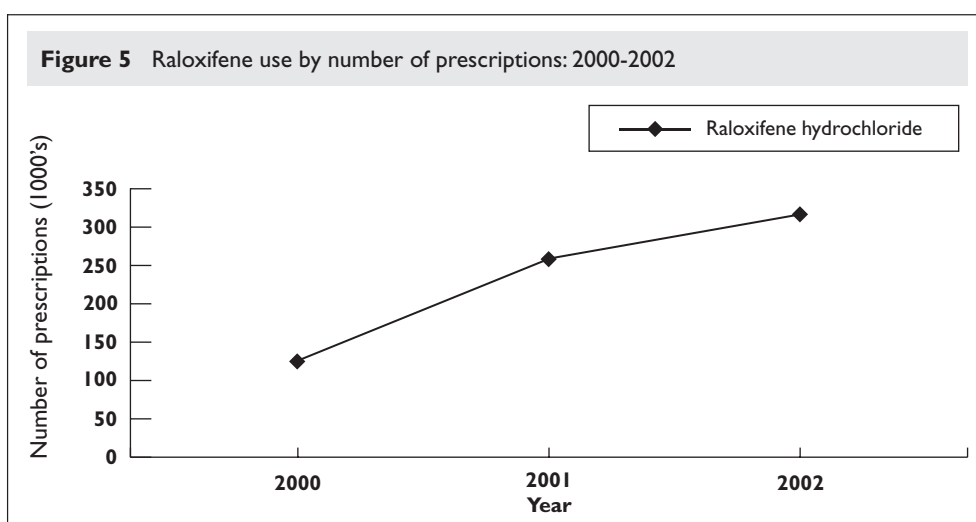
Initial treatment for established post-menopausal osteoporosis in patients with fracture due to minimal trauma. The fracture must have been demonstrated radiologically and the year of plain x-ray or CT-scan or MRI scan must be included in the authority application. A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body; Continuing treatment for established post-menopausal osteoporosis in patients with fracture due to minimal trauma, where the patient has previously been issued with an authority prescription for this drug.

TABLE 2 PBS LISTING FOR RALOXIFENE

Generic name	Mode of administration	Dose		Proprietary name
		Oestrogen	Progestogen	
Raloxifene hydrochloride ^a	Oral tablets	60 mg		Evista

^a Authority required.

The use of raloxifene has increased substantially over the last few years. Figure 5 shows the number of prescriptions for raloxifene filled during the period 2000-2002.



1.1.4 CAMS

Complementary and alternative medicines (CAMs) are therapies that are either not a part of the conventional medical system, or are based on non-Western teachings of physiology (ACOG, 2001). There are many therapies used as alternatives to HRT including plant oestrogens, herbs, vitamins and minerals and unconventional hormones and steroids. Some of the CAMs most commonly used during the menopause include the following: (i) soy and soy products, which contain isoflavones, a type of 'phytoestrogen'; (ii) red clover which contains phytoestrogens called coumestans; (iii) black cohosh which has been suggested to have oestrogenic-like actions; and (iv) dong quai, a traditional Chinese medicine which is said to have oestrogenic activity (ACOG, 2001).

While it is difficult to accurately estimate the numbers of women in Australia using CAMs for menopause, a study conducted by the North American Menopause Society estimates that at least 30% of North American women use phytoestrogens, herbal supplements, natural oestrogens or acupuncture (Kaufert *et al.*, 1998). It is likely that this number may have increased since 2002 as a result of the controversy surrounding conventional HRT since the interim results of the Women's Health Initiative (WHI) study were published (Rossouw *et al.*, 2002).

2 METHODS

2.1 RESEARCH QUESTIONS

The clinical question to be answered by this review was defined by the HRT Working Party in conjunction with the reviewers. The Patient Intervention Comparator Outcomes (PICO) criteria (Scott *et al.*, 1995) were used to help determine the key elements of the clinical question. In general, the aim of this review was to evaluate the effect of HRT upon patient relevant outcomes (both benefits and risks). For this reason, surrogate outcomes (such as lipid levels for cardiovascular risk and bone mineral density for osteoporosis) were not included. The exception was the effect of HRT on blood pressure in women with existing hypertension.

The primary research questions addressed by this review were:

1. What is the efficacy and safety of HRT in postmenopausal women?
2. What is the efficacy and safety of raloxifene in treating osteoporotic fracture in postmenopausal women?
3. What is the efficacy and safety of tibolone in the treatment of the symptoms of menopause?
4. What is the efficacy and safety of selected complementary and alternative medicines in the treatment of the symptoms of menopause?

For the review of HRT, a number of more detailed questions are to be answered including the effect of the following on each of the outcomes:

- type of HRT used
- duration of HRT
- time since last therapy
- mode of HRT administration.

As the objective of this review was to inform Australian clinical practice, the review is limited to therapies approved for and available for use in Australia. For CAMs, the most commonly used therapies are assessed.

2.2 LITERATURE SEARCH

A search of the literature was undertaken in the MEDLINE and EMBASE databases using EMBASE.com. In addition, the Cochrane Database of Systematic Reviews (CDSR) and the Database of Abstracts of Reviews of Effects (DARE) were searched to help identify existing systematic reviews. Due to the availability of recent systematic reviews, searches were limited to publications from 1992 onwards. Searches were also limited to English-language publications.

2.2.1 HRT

The HRT search was undertaken in a stepped approach. First, the brand names of the hormone replacement preparations currently funded on the Pharmaceutical Benefits Schedule (PBS) in Australia were searched. Subsequent searches included MeSH terms and textwords relating to oestrogen together with those relating to menopause. These were then combined with terms relating to study type (RCTs, cohorts, case-control). For systematic reviews more general hormone terms were combined with terms for reviews and meta-analysis. The search strategy used and the resulting number of citations are outlined in Table 3.

The search was conducted in May 2003. Therefore, studies published after May were not eligible for inclusion in the systematic review. However, additional results of a number of key studies including the Women's Health Initiative and the Million Women Study have been published subsequent to the literature search. A summary of the characteristics and results of these studies will be included in Addendum B.

TABLE 3 HRT: SEARCH STRATEGY

Search no.	Database	Date searched	Search terms	Citations
1	MEDLINE EMBASE	<1966 – May 2003	Brand name search (kiovance or klogest or estalis or provelle or premia or femostan or trisequens or estracombi or climen or zumenon or vagifem or sandrena or estraderm or climara or femtran or dermestril or menorest or progynova or primogyn or ovestin or premarin or genoral or ogen) and menopause, in english	540
2	MEDLINE EMBASE	1992-May 2003	Keyword search (RCTs) (‘estradiol’/exp or ‘estrogen’/exp or ‘conjugated estrogen’/exp or ‘estrogen therapy’/exp or ‘estrone’/exp or ‘estradiol plus norethisterone acetate’/exp or ‘gestagen’/exp or ‘hormone substitution’/exp or ‘hormonal therapy’/exp or ‘hormone deficiency’/exp or ‘estrogen blood level’/exp) and (‘menopause’/exp or ‘postmenopause’/exp or ‘postmenopause osteoporosis’/exp or ‘aged’/exp) and (‘comparative study’/exp or ‘randomized controlled trial’/exp or ‘crossover procedure’/exp or ‘double blind procedure’/exp or ‘parallel design’/exp or ‘single blind procedure’/exp or ‘placebo’/exp), in english	2837
3	MEDLINE EMBASE	1992-May 2003	Textword search (RCTs) ((estrogen* or oestrogen* or estradiol or oestradiol or estrone* or oestrone* or gestagen or ‘hormone *4 therapy’ or ‘hormonal *4 therapy’ or ‘hormone *4 replacement’ or ‘hormonal *4 replacement’):ab,ti and (menopaus* or postmenopaus* or perimenopaus* or climacter*):ab,ti and (english):la) and (randomi* or ‘double blind’ or ‘single blind’ or placebo or controlled or ((single or double) and dummy)):ab,ti, in english	1955
4	MEDLINE EMBASE	1992-May 2003	Textword search (cohort/case-control) (cohort or ‘case control’ or ‘case control’):ab,ti and ((estrogen* or oestrogen* or estradiol or oestradiol or estrone* or oestrone* or gestagen or ‘hormone *4 therapy’ or ‘hormonal *4 therapy’ or ‘hormone *4 replacement’ or ‘hormonal *4 replacement’):ab,ti and (menopaus* or postmenopaus* or perimenopaus* or climacter*):ab,ti and (english):la),	644
5	MEDLINE EMBASE	1992-May 2003	Systematic review search (hormone or hormonal) and therapy and (‘meta analysis’ or meta and analysis or review), restricted to Title (ti), between 1992 and 2003	93
TOTAL	<i>Non duplicate citations (including CDSR and DARE)</i>			3397

Abbreviations: CDSR, Cochrane Database of Systematic Reviews; DARE, Database of Abstracts of Reviews of Effectiveness.

In total, 3397 non-duplicate citations were identified. One reviewer assessed the eligibility of all abstracts and a random sample of ten percent was independently assessed by a second reviewer. Where discrepancy existed, this citation was discussed in detail by three reviewers. After applying the inclusion/exclusion criteria, 365 citations were potentially eligible for inclusion in the review. After review of the full paper of potentially eligible articles, 128 studies were available for inclusion in the

review. The reasons for exclusion of citations were noted (see Table 4) and a list of excluded citations and the reason for exclusion of each citation is included in Appendix A.

TABLE 4 HRT: REASONS FOR EXCLUSION

Reason for exclusion	Description	Number of exclusions	
		Title/abstract	Full paper
<i>Total number of citations</i>		3397	365
Not a clinical study	Citation does not describe the results of a systematic review, randomised controlled trial, cohort study or case-control studies. Narrative reviews, case reports, letters, <i>in vitro</i> studies and animal studies were excluded.	928	3
Not HRT	Citation did not assess the effect of HRT (defined as a therapy including an oestrogen and either progesterone or testosterone).	786	3
Not for menopause	Citation was not assessing the risks or benefits use of HRT in menopausal women.	23	2
Wrong outcomes	Citation did not describe a study assessing one of the included outcomes or assessed only surrogate measurement of one of the included outcomes (with the exception of blood pressure in hypertensive women).	952	34
Not in English	Due to time constraints, only English-language articles were eligible for inclusion in the review.	14	0
Wrong comparator	Randomised controlled trials without a no-HRT arm (ie, placebo, calcium, vitamin D, no therapy).	168	13
Wrong study type	Non-randomised trial, non-comparative or case series.	130	19
Study too small	For the majority of outcomes, where there were sufficient studies available, the minimum sample size allowed was 50/arm. For adverse events the minimum sample size allowed was 20/arm.	28	16
Duplicate data	Multiple publications of the same data.	4	15
Other	Citations which described methodology of studies only, type/dose/regimen of HRT not available/used in Australia, insufficient methodology reported; included in existing systematic review, not adjusted for other risk factors, no comparator results presented, data not systematically collected.	6	18
Systematic review	Included in or published prior to an included existing systematic review.	-	117
<i>Total remaining citations</i>		368	128

2.2.2 TIBOLONE

The tibolone search was conducted in September 2003 and included terms for tibolone only. The search strategy used is outlined in Table 5.

TABLE 5 TIBOLONE SEARCH STRATEGY

Search no.	Database	Date searched	Search terms	Citations
I	Embase.com (MEDLINE EMBASE)	<1966 – September 2003	(tibolone or livial), in english between 1992 and 2003	534
TOTAL	Non duplicate citations (including CDSR and DARE)			473

Abbreviations: CDSR, Cochrane Database of Systematic Reviews; DARE, Database of Abstracts of Reviews of Effectiveness.

In total, 473 non-duplicate citations were identified. One reviewer assessed the eligibility of all abstracts. After applying the inclusion/exclusion criteria, 16 citations were potentially eligible for inclusion in the review. After review of the full paper of potentially eligible articles, eight studies were available for inclusion in the review. The reasons for exclusion of citations were noted (see Table 6) and a list of excluded citations and the reason for exclusion of each citation is included in Appendix A.

TABLE 6 TIBOLONE: REASONS FOR EXCLUSION

Reason for exclusion	Description	Number of exclusions	
		Title/abstract	Full paper
<i>Total number of citations</i>		473	16
Not a clinical study	Citation does not describe the results of a systematic review, randomised controlled trial, cohort study or case-control studies. Narrative reviews, case reports, letters, <i>in vitro</i> studies and animal studies were excluded.	311	3
Not tibolone	Citation did not assess the effect of tibolone.	4	2
Not for menopause	Citation was not assessing the risks or benefits use of tibolone in menopausal women.	14	0
Wrong outcomes	Citation did not describe a study assessing one of the included outcomes or assessed only surrogate measurement of one of the included outcomes (with the exception of blood pressure in hypertensive women).	101	0
Not in English	Due to time constraints, only English-language articles were eligible for inclusion in the review.	0	0
Wrong comparator	Randomised controlled trials without a placebo or HRT arm.	0	1
Wrong study type	Non-randomised trial, non-comparative or case series.	6	1
Study too small	For tibolone the minimum sample size allowed was 20/arm.	6	0
Systematic review	Included in or published prior to the primary existing systematic review.	13	-
Other	Other reasons.	2	1
Total remaining citations		16	8

2.2.3 RALOXIFENE

The raloxifene search was conducted in September 2003 and included terms for raloxifene and menopause. The search strategy used is outlined in Table 7.

TABLE 7 RALOXIFENE SEARCH STRATEGY

Search no.	Database	Date searched	Search terms	Citations
1	Embase.com (MEDLINE EMBASE)	<1966 – September 2003	((raloxifene:de and (english):la) or raloxifene or evista) and ('menopause':de or 'postmenopause':de or 'postmenopause osteoporosis':de or 'aged':de or menopause* or postmenopaus* or perimenopaus* or climacter* and (english):la, in english, between 1992 and 2003.	1038
TOTAL	Non duplicate citations (including CDSR and DARE)			966

Abbreviations: CDSR, Cochrane Database of Systematic Reviews; DARE, Database of Abstracts of Reviews of Effectiveness.

In total, 966 non-duplicate citations were identified. One reviewer assessed the eligibility of all abstracts. After applying the inclusion/exclusion criteria, 15 citations were potentially eligible for inclusion in the review. After review of the full paper of potentially eligible articles, 7 studies were available for inclusion in the review. The reasons for exclusion of citations were noted (see Table 8) and a list of excluded citations and the reason for exclusion of each citation is included in Appendix A.

TABLE 8 RALOXIFENE: REASONS FOR EXCLUSION

Reason for exclusion	Description	Number of exclusions	
		Title/abstract	Full paper
<i>Total number of citations</i>		966	15
Not a clinical study	Citation does not describe the results of a systematic review, randomised controlled trial, cohort study or case-control studies. Narrative reviews, case reports, letters, <i>in vitro</i> studies and animal studies were excluded.	794	0
Not raloxifene	Citation did not assess the effect of raloxifene.	22	0
Not for menopause or postmenopausal osteoporosis	Citation was not assessing the benefit of raloxifene in postmenopausal osteoporotic women.	12	0
Wrong outcomes	Citation did not describe a study assessing fracture.	121	0
Not in English	Due to time constraints, only English-language articles were eligible for inclusion in the review.	0	0
Wrong comparator	Randomised controlled trials without a placebo-controlled arm.	0	0
Wrong study type	Non-randomised trial, non-comparative or case series.	0	0
Study too small	For raloxifene the minimum sample size allowed was 50/arm.	1	0
Systematic review	Included in or published prior to the primary existing systematic review.	0	-
Other	Other reasons.	1	8
<i>Total remaining citations</i>		15	7

2.2.4 CAMs

The CAM search was based on the literature search undertaken by Kronenberg and Fugh-Berman (2002) in their systematic review of the use of alternative therapies in menopause. Terms for specific CAMs were combined with text and keywords relating to menopause and RCTs. For systematic reviews more general terms relating to the most commonly used CAMs used in Australia were used. The search strategy used is outlined in Table 9.

TABLE 9 CAM SEARCH STRATEGY

Search no.	Database	Date searched	Search terms	Citations
1	Embase.com (MEDLINE EMBASE)	<1966 – October 2003	((('menopause':de or 'postmenopause':de or 'postmenopause osteoporosis':de or 'aged':de or menopaus* or postmenopaus* or perimenopaus* or climacter* and (english):la) and (('alternative medicine' or 'herbal medicine' or 'traditional medicine' or 'chinese medicine' or 'ayurveda' or 'naturopathy' or 'phytoestrogen' or 'phytoestrogens' or 'isoflavone' or 'isoflavones' or 'soy' or 'black cohosh' or 'remifemin' or 'red clover' or 'evening primrose oil' or 'chaste tree berry' or 'dong quai' or 'ginseng' or 'motherwort' or 'leonurus' or 'licorice and (english): la) or ('alternative medicine':de or 'herbal medicine':de or 'herbaceous agent':de or 'traditional medicine':de or 'chinese medicine':de or 'chinese drug':de or 'chinese herb':de or 'phytoestrogen':de or 'phytohormone':de or 'isoflavone':de or 'isoflavone derivative':de or 'soybean':de or 'soybean protein':de or 'soybean oil':de or 'cimicifuga racemosa extract':de or 'clover':de or 'primrose oil':de or 'vitex':de or 'vitex agnus castus':de or 'vitex agnus castus extract':de or 'angelica sinensis' or 'ginseng':de or 'ginseng extract':de or 'glycyrrhiza' and (english): la)) and (english):la) and ([toc:TOC@@EMTREE TERMS BELOW@comparative_study] or ('comparative study':de or 'randomized controlled trial':de or 'crossover procedure':de or 'double blind procedure':de or 'parallel design':de or 'single blind procedure':de or 'placebo':de and (english):la) or (randomized or randomization or controlled or comparative or 'open label' or 'double blind' or 'single blind' or placebo and (english):la) or ('meta analysis' or 'meta analysis' or metaanalysis and (english):la) or 'meta analysis':de), in english, between 1992 and 2004	1120
TOTAL	Non duplicate citations (including CDSR and DARE)			1120

Abbreviations: CDSR, Cochrane Database of Systematic Reviews; DARE, Database of Abstracts of Reviews of Effectiveness.

In total, 992 non-duplicate citations were identified. One reviewer assessed the eligibility of all abstracts. After applying the inclusion/exclusion criteria, 13 citations were potentially eligible for inclusion in the review. After review of the full paper of potentially eligible articles, 8 studies were available for inclusion in the review. The reasons for exclusion of citations were noted (see Table 10) and a list of excluded citations and the reason for exclusion of each citation is included in Appendix A.

TABLE 10 CAMs: REASONS FOR EXCLUSION

Reason for exclusion	Description	Number of exclusions	
		Title/abstract	Full paper
<i>Total number of citations</i>		992	13
Not a clinical study	Citation does not describe the results of a systematic review, randomised controlled trial, cohort study or case-control studies. Narrative reviews, case reports, letters, <i>in vitro</i> studies and animal studies were excluded.	264	0
Not CAM	Citation did not assess the effect of one of the selected CAMs.	336	0
Not for menopause	Citation was not assessing the benefit of selected CAMs in postmenopausal women.	256	0
Wrong outcomes	Citation did not describe a study assessing menopausal symptoms.	96	0
Not in English	Due to time constraints, only English-language articles were eligible for inclusion in the review.	0	0
Wrong comparator	Randomised controlled trials without a placebo- or HRT-controlled arm.	1	0
Wrong study type	Non-randomised trial, non-comparative or case series.	7	0
Study too small	For raloxifene the minimum sample size allowed was 20/arm.	7	0
Systematic review	Included in or published prior to the primary existing systematic review.	10	-
Other	Other reasons.	3	5
Total remaining citations		13	8

2.3 HIERARCHY OF EVIDENCE

The aim of this review was to find the highest quality evidence to answer each clinical question. The levels of evidence defined by the NHMRC (1999) were used to define the highest available quality of evidence for each outcome. This hierarchy of evidence is summarized in Table 11.

TABLE 11 HIERARCHY OF EVIDENCE^a

Level	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
II	Evidence obtained from at least one properly-designed randomised controlled trials.
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group.
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group.

^a NHMRC (1999)

The highest level of evidence available is a systematic review of randomised controlled trials, which are considered the study type least subject to various biases. However, in some cases it is not possible or feasible to conduct a randomised controlled trial, either due to ethical or financial constraints. In such cases observational studies such as cohort and case-control studies may be more readily available, particularly for rare outcomes or outcomes which develop long after an exposure (eg, cancer, cardiovascular disease). In these cases, whilst a systematic review of randomised controlled trials may not be possible, a systematic review of observational studies may be. While preferable to a single cohort or case-control study, a systematic review of such studies is subject to the same biases as the individual observational studies and as such is considered to provide a lower level of evidence than individual randomised controlled trials.

The highest levels of available evidence will be presented for each outcome. Where available, the most recent, high quality review will form the basis of the data presented for each outcome and will be supplemented by an examination of original studies published since the review. In the case of the menopausal symptom benefits and early side-effects of HRT only randomised controlled trials will be considered. For the longer-term benefits and risks of HRT, RCTs will be preferentially included. However, given the long-term or rare nature of such outcomes, it is most likely that there will be little RCT evidence available and hence cohort and case-control studies will be included also. Due to the significant amount of bias associated with these observational studies, data will not be formally pooled and a qualitative description of the results will be given.

2.4 LITERATURE SYNTHESIS

As the aim of the current review was to identify the highest level of evidence for each outcome, it was necessary to confirm the availability and quality of the existing systematic reviews before sourcing data from the lower levels of evidence. If a high quality review was available, only original studies published subsequent to the review were sourced.

The characteristics and quality of each included systematic review were assessed by extracting data onto a data extraction form. Quality was assessed using criteria defined by the NHMRC (2000) as well as a number of additional criteria defined by the reviewers. The criteria used to assess the existing systematic reviews are shown in Table 12. Systematic reviews were subjectively rated into three quality categories (good, fair and poor), according to the measures used to minimise bias. The results of the quality assessment of systematic reviews are shown in the data extraction tables in Appendix B.

TABLE 12 SYSTEMATIC REVIEWS: QUALITY CRITERIA

Criteria
Was a clinical question clearly defined?
Was an adequate search strategy used?
Were the inclusion criteria appropriate and applied in an unbiased way?
Was a quality assessment of included studies undertaken?
Were the characteristics and results of the individual studies appropriately summarised?
Were the methods for pooling the data appropriate?
Were sources of heterogeneity explored?

Original studies published since the most recent, high quality review were then identified and retrieved. If no systematic review was available for an outcome, all relevant original studies published after 1992 were retrieved and assessed.

In the case of shorter-term outcomes such as relief of symptoms of menopause and therapy-related side effects, only randomised controlled trials were retrieved. In the case of longer-term outcomes such as risks of HRT or other benefits, observational studies were retrieved in addition to RCTs.

The characteristics and quality of each included original study were assessed using a number of quality criteria specifically designed for each study type, as shown in Table 13. As for systematic reviews, studies were rated good, fair or poor quality. Details of the quality of original studies are shown in the data extraction tables in Appendix B. Quality was not assessed for individual studies in the unwanted side effects section.

TABLE 13 ORIGINAL STUDIES: QUALITY CRITERIA

Quality criteria
<p><i>Randomised controlled trials</i></p> <p>Was allocation to treatment groups concealed from those responsible for recruiting subjects?</p> <p>Was the study double-blinded?</p> <p>Were patient characteristics and demographics similar between treatment arms at baseline?</p> <p>Were all randomised participants included in the analysis?</p> <p>Were the statistical methods appropriate?</p> <p>Were any subgroup analyses carried out?</p>
<p><i>Cohort studies</i></p> <p>How were subjects selected for the 'new' intervention?</p> <p>How were subjects selected for the comparison or control group?</p> <p>Does the study adequately control for demographic characteristics, clinical features and other potential confounding variables in the study design or analysis?</p> <p>Was the measurement of outcomes unbiased (ie, blinded to treatment group and comparable across groups)?</p> <p>Was follow-up long enough for outcomes to occur?</p> <p>Was follow-up complete and were there exclusions from analysis?</p>
<p><i>Case-control studies</i></p> <p>How were the cases defined and selected?</p> <p>How were the controls defined and selected?</p> <p>Does the study adequately control for demographic characteristics and important potential confounders in the study design or analysis?</p> <p>Was measurement of exposure to the factor of interest (eg, the new intervention) adequate and kept blinded to case/control status?</p> <p>Were all selected subjects included in the analysis?</p>

2.5 DATA EXTRACTION

Data was extracted onto specifically designed data extraction forms, and included information regarding study characteristics, quality and results. Data was extracted by one reviewer and checked for accuracy. When studies reported data on multiple outcomes, a separate data extraction form was completed for each outcome.

Unless otherwise specified, the data that was most adjusted for confounders and/or multiple comparisons is reported. Furthermore, where subgroup analyses are available, these were reported if they are deemed more relevant to the Australian setting.

Completed data extraction forms containing detailed information regarding study characteristics and quality, together with a brief summary of study results, can be found in Appendix B.

2.6 DATA PRESENTATION AND SYNTHESIS

If available, pooled estimates from systematic reviews and/or meta-analyses are presented. If unavailable a qualitative summary of study results is provided.

Only data from RCTs was considered suitable for statistical pooling. Methods for the pooling of data from RCTs were the meta-analytic techniques used by the Cochrane Collaboration (Clarke and Oxman, 2003). Data was only pooled if the studies to be pooled were considered to be sufficiently similar.

Data from observational studies is subject to considerable heterogeneity and to biases that vary between studies. As such it was not considered appropriate for statistical pooling. In the case of data from cohort and case-control studies, a qualitative summary of study results is provided.

2.7 METHODOLOGICAL LIMITATIONS OF THE REVIEW

All types of study are subject to bias, with systematic reviews being subject to the same biases seen in the original studies they include, as well as biases specifically related to the systematic review process. Reporting biases are a particular problem related to systematic reviews and include publication bias, time-lag bias, multiple publication bias, language bias and outcome reporting bias (Egger *et al.*, 2001). A brief summary of the different types of reporting bias is shown in Table 14. Other biases can result if the methodology to be used in a review is not defined a priori (ie, before the review commences). Detailed knowledge of studies performed in the area of interest may influence the eligibility criteria for inclusion of studies in the review and may therefore result in biased results. For example, studies with more positive results may be preferentially included in a review, thus biasing the results and overestimating treatment effect.

TABLE 14 REPORTING BIASES IN SYSTEMATIC REVIEWS *

Type of bias	Definition and effect on results of review
Publication bias	The publication or non-publication of research findings. Small, negative trials tend not to be published and this may lead to an overestimate of results of a review if only published studies are included.
Time-lag bias	The rapid or delayed publication of research findings. Studies with positive results tend to be published sooner than studies with negative findings and hence results may be overestimated until the negative trials 'catch up'.
Multiple publication bias	The multiple or singular publication of research findings. Studies with significant results tend to be published multiple times which increases the chance of duplication of the same data and may bias the results of a review.
Citation bias	The citation or non-citation of research. Citing of trials in publications is not objective so retrieving studies using this method alone may result in biased results. Unsupported studies tend to be cited often which may also bias results.
Language bias	The publication of research findings in a particular language. Significant results are more likely to be published in English so a search limited to English-language journals may result in an overestimation of effect.
Outcome reporting bias	The selective reporting of some outcomes but not others. Outcomes with favourable findings may be reported more. For example, adverse events have been found to be reported more often in unpublished studies. This may result in more favourable results for published studies.

* Adapted from Table 7.3.3 Egger *et al.* (2001).

Some of these biases are potentially present in this review of HRT. Data published in peer-reviewed journals is included and no attempt was made to include unpublished material. In addition, the search was limited to English-language publications only so language bias is a potential problem also. Outcome reporting bias and inclusion criteria bias are unlikely as the reviewers had no detailed knowledge of the HRT literature, or each of the outcome areas before the review commenced. Furthermore, the methodology used in the review was defined before the review commenced.

Systematic reviews are only as good as the quality of the information contained within the included studies. There are many biases that may impact on the internal validity of individual clinical trials such as selection bias, performance bias, detection bias and attrition bias (Egger *et al.*, 2001). Observational studies are particularly subject to selection bias as well as information bias and may be profoundly affected by confounding.

Two biases particularly related to the use of observational studies in HRT research are healthy-user bias and surveillance bias. Healthy user bias is a type of selection bias that arises because women who are prescribed HRT are more likely to be healthy, have good nutritional habits, be more compliant with therapy or generally have health habits that may benefit their quality of life or survival. Surveillance bias is another factor to be considered as women on HRT are more likely to be well-educated, have better health insurance, visit their doctors regularly and undergo various screening procedures. This may be of particular concern for conditions such as heart disease, osteoporosis or cancer where this increased surveillance may result in these conditions being picked up earlier and hence more successfully managed or treated. As such, the results of case-control and cohort studies should always be viewed with these potential biases in mind and care should be taken to ensure that these potential confounders have been adjusted for in the analyses of such studies.

3 RESULTS

The results section will be organised such that HRT, raloxifene, tibolone and selected CAMs will each be examined separately. The following outcomes will be examined for each treatment:

1. HRT

- a. Benefits for the relief of menopausal symptoms
- b. Early side effects
- c. Other health benefits
- d. Other health risks

2. Raloxifene

- a. Other health benefits (osteoporotic fracture only)
- b. Early side effects
- c. Other health risks (selected)

3. Tibolone

- a. Benefits for the relief of menopausal symptoms
- b. Early side effects

4. Selected CAMs

- a. Benefits for the relief of menopausal symptoms
- b. Early side effects

In all sections, where sufficient evidence is available, the effects of therapy in relation to nature, duration and time since last use of therapy will be examined.

The evidence for the following section will be based primarily on data available from existing systematic reviews, where available. This will then be supplemented by a description of the results of any original studies published since the most recent, high quality systematic review.

3.1 HRT

3.1.1 BENEFITS FOR THE RELIEF OF MENOPAUSAL SYMPTOMS

Summary

The available evidence clearly supports the efficacy of HRT for the treatment of vasomotor symptoms in postmenopausal women. The benefits appear to be present across the Australian-approved dose regimens of both combined oestrogen/progestogen therapy and oestrogen only therapy.

In general, HRT appears to have a beneficial effect upon urogenital symptoms and sexual dysfunction associated with menopause. On the basis of the available evidence, vaginal preparations appear to be as effective as oral HRT in the alleviation of vaginal symptoms.

The use of HRT appears to improve sleep, but it is not possible to determine if this improvement is independent of the alleviation of vasomotor and urogenital symptoms. The impact of HRT upon psychological wellbeing and general quality of life is less clear, but it is important to note that baseline results for these outcomes largely fall within the age-specific normal range.

Vasomotor symptoms are the most common complaint occurring with the menopause. Colloquially known as 'hot flush', this symptom can be described as "recurrent, transient periods of flushing, sweating, and a sensation of heat, often accompanied by palpitations, feelings of anxiety, and sometimes followed by chills" (Kronenberg, 1990). Whilst most women experience only mild discomfort, 15–25% of women experience severe or frequent hot flushes (Utian, 1989). Hot flushes and night sweats often result in disturbed sleep, fatigue, nervousness, depression and irritability, which in turn impact upon quality of life in general.

A second important group of symptoms are secondary to urogenital changes that occur during the menopause. These include urethral atrophy and vaginal atrophy and dryness. These changes may lead to painful sexual intercourse, repeated urinary or vaginal infections and dysuria, with consequent impact upon psychological wellbeing and quality of life.

As a result, an intervention that ameliorates vasomotor and urogenital symptoms is likely to impact upon sleep, psychological wellbeing and quality of life in general. For this reason, this review initially focuses upon the effect of HRT upon the vasomotor and urogenital symptoms, prior to considering the effect of HRT upon sleep, psychological wellbeing, menopausal symptoms as measured by global scales and quality of life.

For the following section, therapies containing oestrogen alone, or oestrogen in combination with progestogen/progesterone will be examined. No original studies of oestrogen in combination with testosterone met the inclusion criteria for this review. However, the results of two excluded cross-over studies will be discussed with respect to the treatment of sexual dysfunction, well-being and side-effects in Addendum A (Section 5).

Vasomotor symptoms

Existing systematic reviews

One recent, high quality systematic review of placebo-controlled RCTs was identified by the literature search performed for this review (MacLennan *et al.*, 2001a,b). This included literature searched to January 2000 resulting in 21 included RCTs, with a total of 2511 patients. Whilst the primary outcomes were vasomotor symptoms (hot flushes/night sweats), the effect of HRT upon other symptoms of menopause and quality of life during menopause were also investigated. The characteristics and quality of this systematic review are presented in Table 15. For further details see Appendix B (Section 9.1.1).

TABLE 15 HRT: VASOMOTOR SYMPTOMS – EXISTING SYSTEMATIC REVIEWS

Study	Study type (number of included studies) Study quality	Population	Intervention	Comparator	Outcomes
Level I evidence					
MacLennan <i>et al.</i> (2001a,b)	Systematic review of RCTs (21) Good	Peri and postmenopausal women 2511 patients	Oral oestrogen, alone or together with progestogen/progesterone for at least 3 months Any dose	Placebo	Hot flushes, Night sweats – frequency and severity (measured on a 0-3 scale or Greene's vasomotor subscale)

See Section 9.1.1

Abbreviations: RCT, randomised controlled trial.

The results indicated that both the frequency and severity of vasomotor symptoms were reduced by HRT. In summary, women on HRT experienced 17 less hot flushes per week when compared to placebo (WMD -17.5, 95% CI -24.7, -10.2) and the severity of hot flushes was reduced (OR 0.13, 95% CI 0.08–0.22). Similar results were obtained whether measured at 3 months or at the end of study period, irrespective of study duration.

Original studies

As there was a recent, good quality systematic review reporting an unambiguous result, no additional studies of vasomotor effects of HRT were reviewed. Furthermore, it is recognised that global menopause indices reported below are typically heavily weighted toward vasomotor symptoms.

Urogenital symptoms/sexual dysfunction

Existing systematic reviews

Five systematic reviews examining the effects of HRT on urogenital symptoms or sexual dysfunction were identified by the literature search. Two reviews examined the effects of HRT on urogenital symptoms. The review by Crandall (2002) consists of level I evidence however it is considered to be of poor quality due to the limited literature search performed, lack of clear inclusion/exclusion criteria, and no quality assessment of included studies. The second review, by Cardozo *et al.* (1998), was considered to be level I/IV evidence as it contains data from RCTs and uncontrolled case series (which will not be considered in this review). This review was considered to be of fair quality as a thorough literature search was performed and clear inclusion criteria for studies were stated. However, they did not assess the methodological quality of the included studies. Two reviews examined the effects of HRT specifically on the urinary system. Cardozo *et al.* (2001) carried out a review of the effect of HRT on urinary tract infection using RCTs and observational studies (level I/III-2). This review was considered to be of fair quality. The effect of HRT on urinary incontinence was examined by Fantl *et al.* (1994) using a combination of data from RCTs and uncontrolled case series (which will not be considered here; level I/IV evidence). While this review considered a number of different surrogate measures of urinary incontinence, only the patient's subjective rating will be considered here. This review was considered to be of poor quality due to a lack of quality assessment of studies and lack of study characteristics reported. One review examined the effect of HRT on sexual dysfunction. This review, by Modelska *et al.* (2003) was considered to be of fair methodological quality. A brief summary of the characteristics of the systematic reviews is shown in Table 16. For further details see Appendix B (Section 9.1.1). It should be noted that due to a lack of reasonable quality reviews for these outcomes, the poor quality reviews will be considered here.

TABLE 16 HRT: UROGENITAL SYMPTOMS/SEXUAL DYSFUNCTION – EXISTING SYSTEMATIC REVIEWS

Study	Study type (number of included studies) Study quality	Population	Intervention	Comparator	Outcomes
Level I evidence					
Modelska & Cummings (2003)	Systematic review of RCTs (3) <i>Fair</i>	Postmenopausal women	HRT Mode of administration not specified Any dose	Placebo	Sexual dysfunction
Crandall (2002)	Systematic review of RCTs (9) <i>Poor</i>	Women using vaginal oestrogens	Oestrogen Vaginal cream, ring or tablets Any dose	Placebo or other HRT	Vaginal and urinary symptoms
Cardozo <i>et al.</i> (2001)	Systematic review of RCTs (5), case-control studies (2) and self-controlled studies (3) <i>Fair</i>	Postmenopausal women	Oestrogen Any mode of administration Any dose	No HRT	UTI
Cardozo <i>et al.</i> (1998)	Systematic review of RCTs (10) <i>Fair</i>	Women with urogenital atrophy	Oestrogen Any mode of administration Any dose	No HRT	Urogenital atrophy
Fantl <i>et al.</i> (1994)	Systematic review of RCTs (6) and uncontrolled trials (17) <i>Fair</i>	Postmenopausal women with urinary incontinence	Oestrogen Any mode of administration Any dose	Unclear	Urinary incontinence

See Section 9.1.1

Abbreviations: RCT, randomised controlled trial; UTI, urinary tract infection.

The results of the existing systematic reviews are summarised in Table 17. In general, the reviews conclude that there is a beneficial effect of HRT upon urogenital/sexual symptoms. HRT appears to reduce vaginal dryness and urogenital atrophy, which in turn result in a reduction in infections and improved sexual function.

TABLE 17 HRT: UROGENITAL SYMPTOMS/SEXUAL DYSFUNCTION – EXISTING SYSTEMATIC REVIEW RESULTS

Study	Number of included studies	Results and conclusion
Crandall (2002)	22 RCTs (results from 8 placebo-controlled studies considered only)	<p>SUBJECTIVE OUTCOMES: vaginal</p> <p>Vaginal dryness Three studies. Vaginal oestradiol tablets and oestradiol rings were superior to placebo/no treatment and dienestrol cream superior to non-hormonal vaginal lubricant.</p> <p>Dyspareunia Four studies. Showed oestradiol rings and vaginal oestradiol tablets superior to placebo/no treatment. Dienestrol cream equivalent to non-hormonal vaginal lubricant.</p> <p>Pruritis Two studies. Oestradiol ring equivalent to no treatment. Dienestrol cream equivalent to non-hormonal vaginal lubricant.</p> <p>Irritation or burning One study. Dienestrol cream equivalent to non-hormonal vaginal lubricant.</p> <p>SUBJECTIVE OUTCOMES: Urinary</p> <p>Dysuria, urinary urgency, urinary frequency One study. No difference in change between oestradiol ring and no treatment.</p> <p>Urge incontinence, stress incontinence One study. Oestradiol ring superior to no-treatment</p> <p>OBJECTIVE OUTCOMES ^a</p> <p>Decreased atrophy Five studies. Oestradiol ring superior for pallor and friability. Vaginal oestradiol tablet superior to placebo. Oestradiol ring superior to no treatment. 2mg/24h oestradiol ring superior to placebo.</p> <p>UTI/cystitis Three studies. (i) cumulative proportion of subjects remaining free of UTI was higher for oestradiol ring vs placebo (45% vs 40%), (ii) decreased recurrent cystitis for vaginal oestradiol pessary vs placebo, (iii) oestradiol superior to placebo.</p> <p>The authors conclude that "all preparations are effective in decreasing signs and symptoms of vaginal atrophy, but they differ slightly in their adverse event profiles".</p>
Cardozo (2001)	10 studies (5 RCTs, 2 case-controls and 3 self-controls)	<p>Prevention of recurrent urinary tract infection Meta-analysis of 5 RCTs showed that the odds ratio for placebo versus oestrogen in preventing recurrent UTI was 2.51 (1.48, 4.25) suggesting oestrogen decreases the risk of UTI. When routes of administration were considered, the vaginal route was superior (OR 4.62; 2.32, 9.25) to the oral route (1.10; 0.49, 2.46). There were no differences when comparing different types of oestrogen.</p>
Cardozo (1998)	64 studies (10 RCTs and 54 uncontrolled case series)	<p>Urogenital atrophy Meta-analysis of the 10 RCTs showed that for patient symptoms (6 studies), dyspareunia (2 studies) and physician assessment (2 studies) oestrogen was shown to be more effective than placebo. The authors conclude that "estrogen is efficacious in the treatment of urogenital atrophy and low-dose vaginal preparations are as effective as systemic estrogen therapy..."</p>
Fantl (1994)	23 studies (6 RCTs and 17 uncontrolled case series)	<p>Urinary incontinence Statistically significant subjective improvement was shown in 5 studies. Not significant in 2 studies. (note: authors state there were only 6 RCTs). Meta-analysis shows a significant improvement in treated versus control women ($p < 0.01$). The authors conclude that "it appears from this analysis that estrogen subjectively improves urinary incontinence in postmenopausal women. However; the studies included non-homogeneous groups, and the diagnostic criteria, therapeutic interventions, and outcome assessments varied considerably."</p>
Modelska (2003)	1 relevant RCT	<p>Sexual function: oestrogen plus testosterone Oestrogen 0.625 mg plus testosterone 300 mg increased frequency of sexual activity and improved the score for problems affecting sexual function compared with placebo ($P = 0.03$ and 0.07 respectively).</p>

Abbreviations: RCT, randomised controlled trial; UTI, urinary tract infection.

^a Only selected patient relevant outcomes included here. Others included improved vaginal mucosal maturation, decreased vaginal pH and increase in proportion of lactobacilli

Original studies

One original study has been published since the existing systematic reviews which report on the efficacy of HRT in relieving the urogenital symptoms of menopause. The main characteristics and quality of this study is summarised in Table 18. For further details see Appendix B (Section 9.1.1). This study was considered to be of fair methodological quality with regards to these outcomes.

One further study measured a urogenital symptom score based on the Kupperman Index (von Holst and Salbach, 2000). This data will not be included here as the total Kupperman Index score is already included in the relevant section.

No original studies were identified which examined the association between HRT and sexual dysfunction.

TABLE 18 HRT: UROGENITAL SYMPTOMS – ORIGINAL STUDIES

Author	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Level II evidence					
Grady et al. (2001)	RCT HERS 4.1 years follow-up Fair	Postmenopausal women aged < 80 years with intact uterus and existing CHD N=1525	Oral conjugated equine oestrogen 0.625 mg plus 2.5 mg medroxyprogesterone acetate N=768	Placebo N=757	Urinary incontinence

See Section 9.1.1

Abbreviations: CHD, coronary heart disease; HERS, Heart and Estrogen/progestin Replacement Study; RCT, randomised controlled trial.

The results of the Grady study are summarised in Table 19. They suggest that rather than improve this symptom, the use of combined HRT makes this symptom significantly worse in postmenopausal women with existing heart disease compared with placebo.

TABLE 19 HRT: UROGENITAL SYMPTOMS – RCT RESULTS

Author	Measurement unit/ Timing of measurement	HRT	no HRT	Statistical significance
EPRT				
Urinary incontinence				
Grady (2001)	% improved compared with baseline (mean all follow-up visits)	20.9%	26.0%	P = 0.001 ^a
	% worsened compared with baseline (mean all follow-up visits)	38.8%	27.0%	

Abbreviations: EPRT, oestrogen + progestogen therapy; nr, not reported.

^a In favour of placebo

Sleep disturbances

Existing systematic reviews

There are currently no systematic reviews available reporting the effect of HRT upon sleep disturbances.

Original studies

Original studies published since 1992 that investigated the impact of HRT upon sleep disturbances were retrieved. Only randomised controlled trials using therapeutically relevant doses that are currently recommended for use in Australia were included. Studies with fewer than 50 patients in each arm were also excluded to reduce the likelihood of type II error. The main characteristics and quality of the studies that examined the association between HRT and sleep are summarised in Table 20. For further details see Appendix B (Section 9.1.1).

TABLE 20 HRT: SLEEP DISTURBANCES – ORIGINAL STUDIES

Author	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Level II evidence					
Hays et al. (2003)	RCT WHI Good	Postmenopausal women with an intact uterus Mean age 63 N=16,608	Oral conjugated equine oestrogen 0.625 mg plus medroxyprogesterone 2.5 mg N=8506	Placebo N=8102	WHI insomnia rating
Barnabei et al. (2002)	RCT HERS Good	Postmenopausal women aged < 80 years with an intact uterus and established CHD N=2608	Oral conjugated equine oestrogen 0.625 mg plus medroxyprogesterone 2.5 mg N=1293	Placebo N=1315	% women with frequent or somewhat frequent trouble sleeping at 1 year
Strickler et al. (2000)	RCT Good	Postmenopausal women Mean age 55 N=189	Oral conjugated equine oestrogen 0.625 mg N=90	Placebo, (raloxifene) N=99	Sleep domain of WHQ
Wiklund et al. (1993)	RCT Fair	Postmenopausal women requiring HRT for climacteric symptoms Mean age 53 N=223	Transdermal oestradiol 50 µg N=112	Placebo N=111	Sleep domain of WHQ

See Section 9.1.1

Abbreviations: CHD, coronary heart disease; RCT, randomised controlled trial; WHI, Women's Health Initiative; WHQ, Women's Health Questionnaire.

Results are summarised in Table 21. The studies indicated an improvement in sleep with HRT, however it should be pointed out that the magnitude of the change was often small relative to the scales upon which it was measured.

TABLE 21 HRT: SLEEP DISTURBANCES – RCT RESULTS

Author	Measurement unit/ Timing of measurement	HRT	no HRT	Statistical significance
Hays (2003)	Mean change 12 months	+0.5	+0.1	p<0.001 see text
Barnabei (2002)	Percentage change from baseline in trouble sleeping at 1 year	-2.4%	2.5%	nr
Strickler (2000)	Mean change ^a 12 months	+0.130	+0.040	ns
Wiklund (1993)	Mean change ^a 12 weeks	-1.2	-0.3	p<0.001

Abbreviations: nr, not reported; ns, not significant.

^a Strickler, 2000 and Wiklund, 1993 used inverted scales for the WHQ domain scores. An increase in score indicates an improvement in Strickler and a decrease in score indicates an improvement in Wiklund.

Global menopause symptom, psychological and quality of life scales

Several global indices of menopausal symptoms are used in clinical practice and research. These indices combine vasomotor symptoms with other effects of menopause such as sleep disturbances, mood change, and urogenital symptoms. The most common of these is the Kupperman Index. The Kupperman Index comprises items relating to hot flushes, paresthesia, insomnia, nervousness, melancholia, vertigo, weakness, arthralgia/myalgia, headache, palpitation and formication. Other global menopause symptom scales considered here were the Women's Health Questionnaire, Greene Index and the Quality of Life Menopause Scale.

In an attempt to measure the effect of HRT upon other symptoms of menopause and quality of life in general, randomised, placebo-controlled studies that utilised selected, well-validated psychological wellbeing instruments (Becks Depression Inventory, Hamilton Rating Scale for Depression, Psychological General Wellbeing index, Burnam Depression screening scale; Hospital Anxiety and Depression Scale), or general quality of life instruments (Nottingham Health Profile, Short Form-36, World Health Organisation Quality of Life scale) were also sought.

It should be noted that only original studies using therapeutically relevant doses that are currently recommended for use in Australia were included. Studies with fewer than 50 patients in each arm were also excluded to reduce the likelihood of type II error.

Global menopause symptom scales

Existing systematic reviews

One systematic review was identified which attempted to review the effect of HRT on global menopause symptom scales and quality of life (MacLennan *et al.*, 2001a,b). However, this review found only one very small study with less than 50 subjects per arm (Bech *et al.*, 1998). Therefore, this review will not be considered here.

Original studies

Original placebo-controlled studies published since 1992 that reported global menopause symptom scales were retrieved. The main characteristics and quality of the included studies are summarised in Table 26. For further details see Appendix B (Section 9.1.1).

TABLE 22 HRT: GLOBAL MENOPAUSE SYMPTOMS – ORIGINAL STUDIES

Author	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Level II evidence					
<i>Oestrogen only</i>					
Haines <i>et al.</i> (2003)	RCT Good	Chinese postmenopausal women who had undergone hysterectomy Mean age unknown N=152	Oral oestradiol 1 mg or 2mg N=52, 50	Placebo N=50	KI
Studd <i>et al.</i> (1999); Panay <i>et al.</i> (2001)	RCT Good	Postmenopausal white women with ≥ 1 hot flush/day or > 5 in the previous week Mean age 52 N=420	Oestradiol nasal spray 100 μ g; 200 μ g; 300 μ g; 400 μ g or oral 1 mg or 2 mg N \approx 55–65 in each arm	Placebo	KI
De Aloysio <i>et al.</i> (2000)	RCT Good	Postmenopausal women with ≥ 5 hot flushes/day 95% with intact uterus Mean age 53 N=156	Low dose oestradiol transdermal patch 25 or 37.5 μ g N=52, 52	Placebo N=52	KI
De Vrijer <i>et al.</i> (2000)	RCT Good	Postmenopausal women with ≥ 7 moderate to severe hot flushes/day 65% with intact uterus Mean age 52 yr N=254	Oestradiol transdermal patch 50 or 100 μ g N=82, 86	Placebo N=86	KI
Rovati <i>et al.</i> (2000)	RCT Good	Women with natural or surgical menopause with ≥ 7 hot flushes/day Mean age 53 N=311	Oestradiol transdermal patch 25, 50 μ g; 50 μ g (twice weekly patch) N= 80, 77, 74	Placebo N= 80	KI
Strickler <i>et al.</i> (2000)	RCT Good	Postmenopausal women Mean age 55 N=201	Oral conjugated oestrogen 0.625 mg N=96	Placebo N=105, raloxifene 60, 150 mg daily	WHQ
Von Holst & Salbach (2000)	RCT Fair	Postmenopausal women who had undergone hysterectomy with ≥ 1 hot flush/day or > 5 in the previous week Mean age 53 N=186	Oestradiol transdermal patch 50 μ g N=93	Placebo N=93	KI
Bacchi-Modena <i>et al.</i> (1997)	RCT Good	Postmenopausal women with ≥ 7 moderate to severe hot flushes/day Mean age 52 N=109	Oestradiol transdermal patch 50 μ g N=53	Placebo N=56	KI
Wiklund <i>et al.</i> (1993)	RCT Fair	Postmenopausal women requiring HRT for climacteric symptoms Mean age 53 N=223	Oestradiol transdermal 50 μ g N=112	Placebo N=111	KI, WHQ
<i>Oestrogen plus progestogen</i>					
Von Holst & Salbach (2002)	RCT Good	Postmenopausal women with an intact uterus and at least 20 hot flushes/week and KI index > 20 Mean age 53 N=179/172	Oestradiol with intermittent levonorgestrel N=84	Placebo N=88	KI
Alexandersen <i>et al.</i> (2000)	RCT Fair	Postmenopausal Danish women Mean age 59 N=100 ^a	Oral oestradiol 2 mg continuously combined with NETA 1 mg N=50	Placebo N=50	KI

See Section 9.1.1.

Abbreviations: KI, Kupperman Index.; WHQ, Women's Health Questionnaire. ^a Number in relevant arms only

The results of studies using global menopause symptom scales are summarised in Table 23. These studies, predominantly undertaken in women with considerable menopausal symptoms indicate that HRT is efficacious for the treatment of these symptoms. Dose-ranging studies tend to indicate a dose-response pattern, with low dose nasal preparations of oestradiol (not typically used in Australia) failing to show a significant benefit.

TABLE 23 HRT: GLOBAL MENOPAUSE SYMPTOM SCALES – RCT RESULTS

Author	Measurement unit/ Timing of measurement	HRT	no HRT	Statistical significance
Kupperman Index				
<i>Oestrogen only</i>				
Haines (2003)	Mean change 12 months	Oestradiol 1 mg: -4.1 (6.8) 2 mg: -4.4 (7.2)	-1.7 (8.3)	ns p < 0.01
Studd (1999); Panay (2001)	Mean change ^a 12 weeks	nasal: 100 µg: -15 200 µg: -17 300 µg: -18 400 µg: -17 oral: 1 mg: -16 2 mg: -18	-9	nr
De Aloysio (2000)	Mean change 12 weeks	25 µg: -15.5 37.5 µg: -15.5	-9.5	both p < 0.001
De Vrijer (2000)	Mean change 12 weeks	50 µg: -17.8 100 µg: -18.0	-8.0	both p > 0.001
Rovati (2000)	Mean change 12 weeks	25 µg: -17.3 50 µg: -20.9 50 µg (2/wk): -21.5	-11.1	p < 0.001 p < 0.001 p < 0.001
Von Holst (2000)	Mean change 12 weeks ^b	-16.4	-11.0	p < 0.001
Bacchi-Modena (1997)	Mean change 12 weeks	-18.0	-9.0	p < 0.001
Wiklund (1993)	Mean change 12 weeks	-18.8	-6.7	p < 0.001
<i>Oestrogen plus progestogen</i>				
Alexandersen (2000)	Mean percent change 12 weeks	-36%	-6%	ns
Von Holst (2002)	Mean change 12 weeks	-16.8	-11.9	p < 0.001
Women's Health Questionnaire				
<i>Oestrogen only</i>				
Strickler (2000)	Mean change ^c 12 months	+0.041	+0.016	ns
Wiklund (1993)	Mean change ^c 12 weeks	-15.8	-4.4	p < 0.001

Abbreviations: ns, not significant.

^a Mean result estimated from publication figure.

^b A considerable proportion of randomised patients were excluded from the analysis (see Appendix B for further detail).

^c Strickler (2000) and Wiklund (1993) used different scales for the calculated WHQ summary scores.

Psychological scales

Existing systematic reviews

The literature search identified one systematic review which examined the effect of HRT on psychological wellbeing and depression, including studies using the Psychological General Wellbeing (PGWB) index, Becks Depression Inventory and the Hamilton Rating Scale for Depression. This review by Zweifel *et al.* (1997) was considered to be of fair methodological quality. The main characteristics and quality of the review are summarised in Table 24. For further details see Appendix B (Section 9.1.1).

TABLE 24 HRT: PSYCHOLOGICAL SCALES – EXISTING SYSTEMATIC REVIEWS

Study	Review type (number of included studies) Review quality	Population	Intervention	Comparator	Outcomes
Level I evidence					
Zweifel & O'Brien (1997)	Systematic review of RCTs (16 placebo- or no HRT-controlled) Fair	Peri- and postmenopausal women 1226 patients	HRT including oestrogen alone or in combination with a progestogen or androgen, progestogen alone or androgen alone	Placebo, no HRT or other HRT regimen	Various psychological wellbeing and depression scales including PGWB, Becks Depression Inventory and Hamilton Rating Scale for Depression

See Section 9.1.1.

Abbreviations: PGWB, Psychological General Wellbeing index; RCT, randomised controlled trial.

Several meta-analyses were conducted in the Zweifel review, including a number that were restricted to placebo-controlled trials (ie. excluding the pre- vs post-treatment comparisons). The results are summarised in Table 25. For further details see Appendix B (Section 9.1.1). Based on these results the authors concluded that the use of HRT appeared to have a moderate to large effect on reducing depressed mood in postmenopausal women.

TABLE 25 HRT: PSYCHOLOGICAL WELL-BEING/DEPRESSION SCALES – EXISTING SYSTEMATIC REVIEW RESULTS (ZWEIFEL AND O'BRIEN, 1997)

Comparison	No. of comparisons/ studies ^a	Mean d ^b	Variance ^c	Fail safe number ^d	p value
ERT vs placebo	12/10	0.694	0.21	70	<0.001
EPRT vs placebo	3/3	0.454	0.00	25	0.001
Any HRT vs placebo	18/12	0.684	0.14	100	<0.001

See Section 9.1.1.

^a Outcomes measured in the studies include those relating specifically to general well-being/depression (eg, Hamilton Depression Scale, Beck Depression Inventory) and other more general scales (Kupperman Index, Daily Menopausal Rating Scale).

^b Measure of effect. Determined as one-tailed tests and corrected for reliability and bias.

^c Corrected for sampling error.

^d The number of comparisons with null results that would be needed to disconfirm the conclusion that a relationship exists.

Original studies

Because the Zweifel review included a literature search up to 1995, only those original placebo-controlled studies reporting psychological wellbeing that were published since 1995 were retrieved. The main characteristics and quality of these included studies are summarised in Table 26. See Appendix B (Section 9.1.1) for further details.

Two studies were large and used the Burnam Depression Scale. One study, performed in Chinese women, used the Hospital Anxiety and Depression Scale (HADS) while another study reported results from the PGWB. No studies reporting the Becks Depression Inventory or the Hamilton Rating Scale for Depression, subsequent to the Zweifel review.

TABLE 26 HRT: PSYCHOLOGICAL SCALES – ORIGINAL STUDIES

Author	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Level II evidence					
<i>Oestrogen only</i>					
Haines <i>et al.</i> (2003)	RCT Good	Chinese postmenopausal women who had undergone hysterectomy Mean age unknown N=152	Oral oestradiol 1 mg or 2mg N=52, 50	Placebo N=50	HADS
Wiklund <i>et al.</i> (1993)	RCT Fair	Postmenopausal women requiring HRT for climacteric symptoms Mean age 53 N=223	Oestradiol transdermal 50 µg N=112	Placebo N=111	PGWB
<i>Oestrogen plus progestogen</i>					
Hays <i>et al.</i> (2003)	RCT WHI Good	Postmenopausal women aged >65 years with an intact uterus Mean age 63 N=16608	Oral conjugated equine oestrogen 0.625 mg and medroxyprogesterone 2.5 mg N=8506	Placebo N=8102	Burnam depression screening scale
Hlatky <i>et al.</i> (2002)	RCT HERS Good	Postmenopausal women < 80 years with established CHD and intact uterus Mean age 67 N=2763	Conjugated equine oestrogen and medroxyprogesterone N=1380	Placebo N=1383	Burnam depression screening scale

See Section 9.1.1.

Abbreviations: CHD, coronary heart disease; HADS, Hospital Anxiety and Depression Scale; HERS, Heart and Estrogen/progestin Replacement Study; PGWB, Psychological General Wellbeing index; RCT, randomised controlled trial; WHI, Women's Health Initiative.

^a Number in relevant arms only

The results of the four included studies are summarised in Table 27. Two studies showed a significant benefit with ERT and EPRT, whilst the others did not. It is important to note that baseline scores were typically well within the normal range and that the magnitude of improvement seen in the Hays study was small.

TABLE 27 HRT: PSYCHOLOGICAL SCALES – RCT RESULTS

Author	Measurement unit/ Timing of measurement	HRT	no HRT	Statistical significance
HADS				
<i>Oestrogen only</i>				
Haines (2003)	Mean change 12 months	1 mg: -0.1 (5.1) 2 mg: -0.4 (4.6)	-0.6 (4.6)	ns ns
Burnam Screening scale				
<i>Oestrogen plus progestogen</i>				
Hays (2003)	Mean change 12 months	-0.1	-0.1	ns
Hlatky (2002)	Mean change 36 months	nr; see text	nr; see text	P=0.005
PGWB				
<i>Oestrogen only</i>				
Wiklund (1993)	Mean change 12 weeks	13.5	6.5	P=0.005

Abbreviations: nr, not reported; ns, not significant.

Quality of life

Existing systematic reviews

One systematic review was identified which attempted to review the effect of HRT on global menopause symptom scales and quality of life (MacLennan *et al.*, 2001a,b). However, this review found only one very small study with less than 50 subjects per arm (Bech *et al.*, 1998). Therefore, this review will not be considered here.

Original studies

There were no original placebo-controlled studies which reported results using the Greene Index or the Menopause Specific Quality of Life instrument (MENQOL), or the Short Form (SF)-36. One study reported on the efficacy of oestradiol therapy with regards to quality of life (as measured by the World Health Organisation Quality of Life scale; WHOQOL) in Chinese women (Haines *et al.*, 2003) and one study used the Nottingham Health Profile (NHP). The main characteristics and quality of these studies are summarised in Table 28. See Appendix B (Section 9.1.1) for further details.

TABLE 28 HRT: QUALITY OF LIFE SCALES – ORIGINAL STUDIES

Author	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Level II evidence					
<i>Oestrogen only</i>					
Haines <i>et al.</i> (2003)	RCT Good	Chinese postmenopausal women who had undergone hysterectomy Mean age unknown N=152	Oral oestradiol 1 mg or 2mg N=52, 50	Placebo N=50	WHOQOL
Wiklund <i>et al.</i> (1993)	RCT Fair	Postmenopausal women requiring HRT for climacteric symptoms Mean age 53 N=223	Oestradiol transdermal 50 µg N=112	Placebo N=111	NHP

See Section 9.1.1. Abbreviations: NHP, Nottingham Health Profile; RCT, randomised controlled trial; WHOQOL, World Health Organisation Quality of Life scale.

The results of these studies are summarised in Table 29. In the Haines study no significant change in quality of life was seen for either dose of oestradiol compared with placebo. These contrast with the results of the Wiklund study.

TABLE 29 HRT: GENERAL QUALITY OF LIFE SCALES – RCT RESULTS

Author	Measurement unit/ Timing of measurement	HRT	no HRT	Statistical significance
WHOQOL				
<i>Oestrogen only</i>				
Haines (2003)	Mean change 12 months	1 mg: 0.50 (20.9) 2 mg: -2.40 (20.2)	0.91 (23.0)	ns ns
NHP				
<i>Oestrogen only</i>				
Wiklund (1993)	Mean change 12 weeks	-58.2	-17.3	p<0.001

Abbreviations: WHOQOL, World Health Organisation Quality of Life scale; SF-36, Short form-36; NHP, Nottingham Health Profile; ns, not significant.

3.1.2 UNWANTED SIDE EFFECTS

Summary

There is level I and II evidence to indicate increased irregular bleeding with oral HRT compared with placebo. This was the case for both oestrogen-only and oestrogen plus progestogen, particularly when the latter was continuous. Increased bleeding also occurs with oestrogen-only transdermal administration, other than with a low dose (25 µg). No transdermal oestrogen plus progestogen studies of bleeding were available at the time of the review.

When considering the level I and II evidence on balance, it is apparent that there is no effect of HRT on weight gain.

HRT results in an increased likelihood of breast tenderness but no increase in fluid retention or migraine/headache.

The following section examines the unwanted side effects most commonly associated with HRT use. These include bleeding, weight gain, breast tenderness, migraine/headache, nausea/vomiting and hair loss. In addition, the effect of HRT on hypertension in already hypertensive women is assessed.

Only RCTs with greater than 20 subjects per arm were eligible for inclusion as original studies. In addition, for inclusion for each adverse outcome, adverse event data from RCTs had to be systematically collected and reported. Due to these strict inclusion criteria, there was no assessment of study quality in this section, nor were the individual study characteristics of each study be presented.

Bleeding

Existing systematic reviews

One systematic review of RCTs was identified by the literature search (Lethaby *et al*, 2000; Level I evidence). This review was considered to be of good methodological quality. The characteristics and quality of the included systematic review are summarised in Table 30. For further details see Appendix B (Section 9.1.2).

TABLE 30 HRT: BLEEDING – EXISTING SYSTEMATIC REVIEWS

Study	Study type (number of included studies) Study quality	Population	Intervention	Comparator	Outcomes
<i>Level I evidence</i>					
(Lethaby <i>et al</i> . 2000)	Systematic review of RCTs (18) Good	Postmenopausal women with an intact uterus	HRT Mode of administration not specified but only oral included Any dose	Placebo or other oestrogen-containing HRT	Incidence

See Section 9.1.2.

Abbreviations: RCT, randomised controlled trial.

The main results of the systematic review of RCTs are summarised in Table 31. Note that the authors of the review evaluated bleeding occurring within six months of starting treatment or occurring at a longer duration of time.

TABLE 31 HRT: BLEEDING – EXISTING SYSTEMATIC REVIEW RESULTS

Comparison	Number of included studies	Number of participants	Peto odds ratio (95% CI)
Oestrogen vs placebo			
<i>Irregular bleeding patterns after 6 months of starting Rx</i>			
Low dose	3	237	0.87 (0.46, 1.64)
Moderate dose	3	216	1.90 (1.05, 3.46)
High dose	1	106	6.01 (2.81, 12.86)
<i>Oestrogen + progestogen (continuous) vs placebo</i>			
Irregular bleeding patterns within 6 months of starting Rx	2	139	6.37 (2.69, 15.08)
Irregular bleeding patterns after 6 months of starting Rx	4	219	6.08 (2.70, 13.68)
<i>Oestrogen + progestogen (sequential) vs placebo</i>			
Irregular bleeding patterns within 6 months of starting Rx	1	96	0.66 (0.11, 3.95)
Irregular bleeding patterns after 6 months of starting Rx	4	287	1.21 (0.51, 2.86)

Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: OR, odds ratio; CI, confidence interval; Rx, treatment.

The authors concluded that there was strong and consistent evidence that unopposed oestrogen therapy, at moderate and high doses, is associated with increased rates of endometrial hyperplasia, irregular bleeding and consequent non-adherence to therapy. Irregular bleeding is less likely under sequential than continuous therapy.

Original studies

The date of the literature search for the Lethaby systematic review is not reported. However the last amendment to the review was made in February 1999. The most recent studies referred to in the review were published in 1997. Table 32 refers to original studies of HRT versus placebo published since then containing bleeding data that were systematically collected during the trial period and with doses relevant to Australian practice. Figure 6 shows the forest plot for the corresponding data.

Bleeding data have been expressed as a proportion of evaluable patients with an intact uterus, unless otherwise stated. For trials of ERT or continuous EPRT, any bleeding was included for analysis, as regular bleeding is not expected in these groups. No trials of sequential EPRT are listed in Table 32. Any relevant details on the intensity of the recorded bleeding have been footnoted. Where no extra details have been footnoted, no further information is available.

A meta-analysis was performed for bleeding as there were sufficient studies using the same dosage to warrant this. Where a trial had more than one HRT arm being compared to a single placebo arm, a 'total' value was calculated by adding the results for the HRT arms together; this was done throughout this section on unwanted side effects for RCTs with several arms. For bleeding, a risk estimate (Peto OR) has been calculated for each trial arm compared to placebo, the calculated 'total' compared to placebo, and, if possible, a pooled result for each regimen broken down by dose (see forest plot). Peto OR was used as the risk estimate in order to provide a comparison with the oral therapies listed in the systematic review by Lethaby *et al.* (2000).

TABLE 32 HRT: BLEEDING – RCT RESULTS

Author	HRT daily dose	RCT duration	HRT n/N (%)	Placebo n/N (%)	Peto OR (95% CI)
ERT					
<i>Oral administration</i>					
Archer <i>et al.</i> (2001) ^a	CE 0.625 mg CE 0.45 mg CE 0.3 mg	1 year	114/173 (65.9) 97/205 (47.3) 79/198 (39.9) total: 290/576 (50.3)	56/173 (32.4)	3.81 (2.50, 5.80) 1.86 (1.23, 2.80) 1.38 (0.91, 2.11) 2.06 (1.46, 2.89)
Cherry <i>et al.</i> (2002) ^b	E2V 2 mg	2 years	208/373 (55.8)	26/399 (6.5)	10.26 (7.55, 13.95)
Goldstein <i>et al.</i> (2000) ^c	CE 0.625 mg	1 year	29/100 (29.0)	6/109 (5.5)	5.35 (2.59, 11.05)
Stevens <i>et al.</i> (2000) ^d	CE 0.3, 0.625 or 1.25 mg	12 weeks	10/72 (13.9)	3/48 (6.3)	2.19 (0.68, 7.06)
<i>Transdermal administration</i>					
De Aloysio <i>et al.</i> (2000 2285 /id) ^e	E2 25 µg E2 37.5 µg	12 weeks	5/48 (10.4) 9/51 (17.6) total: 14/99 (14.1)	7/49 (14.3)	0.70 (0.21, 2.34) 1.28 (0.44, 3.71) 0.99 (0.37, 2.63)
DeVrijer <i>et al.</i> (2000) ^f	E2 100 µg E2 50 µg	12 weeks	4/82 (4.9) 8/86 (9.3) total: 12/168 (7.1)	0/86 (0.0)	8.05 (1.11, 58.24) 8.05 (1.95, 33.13) 4.86 (1.43, 16.50)

Author	HRT daily dose	RCT duration	HRT n/N (%)	Placebo n/N (%)	Peto OR (95% CI)
Rovati <i>et al.</i> (2000) ^g	E2 25 µg, 1 × weekly patch E2 50 µg, 1 × weekly patch E2 50 µg, 2 × weekly patch	12 weeks	18/80 (22.5) 13/77 (16.9) 15/74 (20.3) total: 46/231 (19.9)	9/80 (11.3)	2.22 (0.97, 5.06) 1.59 (0.65, 3.91) 1.98 (0.83, 4.71) 1.81 (0.93, 3.52)
Cohen <i>et al.</i> (1999) ^h	E2 37.5 µg	12 weeks	37/107 (34.6)	20/102 (19.6)	2.12 (1.15, 3.89)
Utian <i>et al.</i> (1999) ⁱ	17-β-E2 25 µg 17-β-E2 50 µg 17-β-E2 100 µg	12 weeks	6/19 (31.6) 14/25 (56.0) 12/21 (57.1) total: 32/65 (49.2)	2/21 (9.5)	3.83 (0.83, 17.74) 7.42 (2.22, 24.76) 8.10 (2.28, 28.78) 5.16 (1.90, 14.04)
Bacchi-Modena <i>et al.</i> (1997) ^j	E2 50 µg	12 weeks	8/53 (15.1)	7/56 (12.5)	1.24 (0.42, 3.68)
Continuous EPRT					
Oral administration					
Barnabei <i>et al.</i> (2002) ^k	CE 0.625 mg; MPA 2.5 mg	1 year	401/1293 (31.0)	27/1315 (2.1)	8.25 (6.71, 10.15)
Alexandersen <i>et al.</i> (2001) ^l	E2 1 mg; NETA 0.5 mg	1 year	12/38 (31.6)	1/40 (2.5)	7.90 (2.42, 25.80)
Archer <i>et al.</i> (2001) ^a	CE 0.625 mg; MPA 2.5 mg CE 0.45 mg; MPA 2.5 mg	1 year	159/204 (77.9) 135/208 (64.9) total: 294/412 (71.4)	56/173 (32.4)	6.39 (4.25, 9.62) 3.66 (2.45, 5.48) 5.05 (3.52, 7.25)
Alexandersen <i>et al.</i> (2000) ^m	17-β-E2 2 mg; NETA 1 mg	2 years	4/48 (8.3)	0/46 (0.0)	7.57 (1.03, 55.50)
Limpaphayom <i>et al.</i> (2000) ⁿ	17-β-E2 2 mg; NETA 1 mg	12 weeks	3/27 (11.1)	0/26 (0.0)	7.70 (0.77, 77.47)
Baerug <i>et al.</i> (1998) ^o	E2 1 mg; NETA 0.5 mg	12 weeks	3/40 (7.5)	2/41 (4.9)	1.56 (0.26, 9.45)

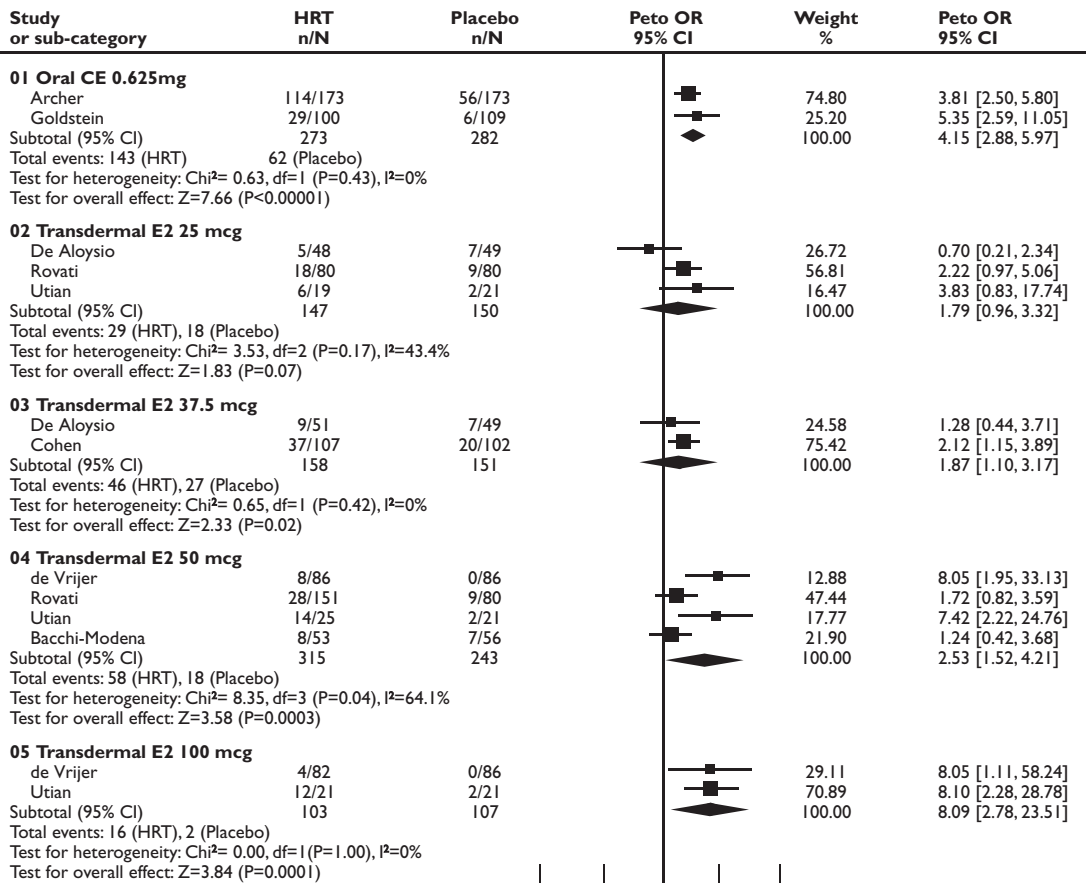
Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: CE, conjugated oestrogens; CI, confidence interval; E2, oestradiol; E2V, oestradiol valerate; MPA, medroxyprogesterone acetate; NETA, norethisterone acetate; OR, odds ratio.

See Section 9.1.2 for footnotes relating to Table 32.

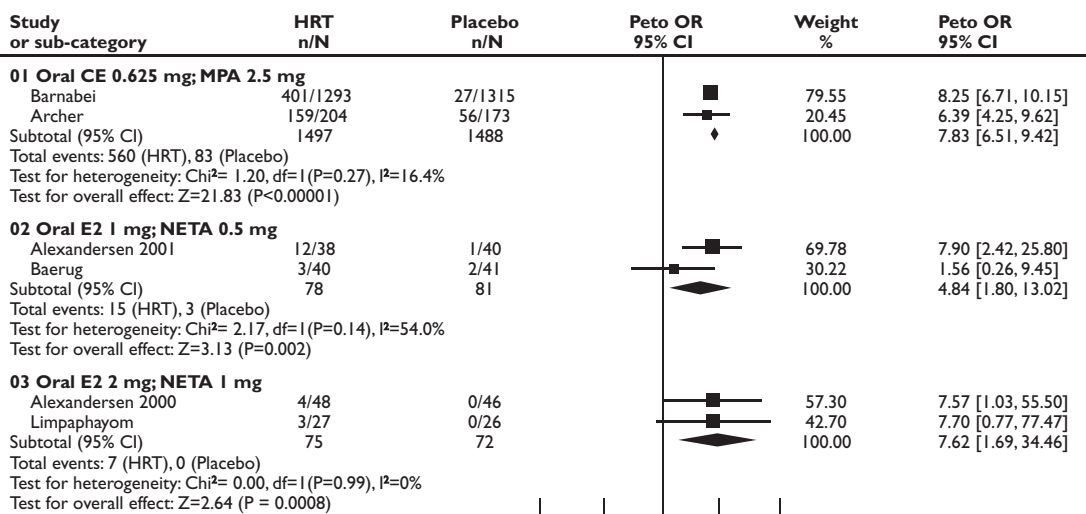
Figure 6 HRT: bleeding – RCT results

Review: HRT
 Comparison: 01 Oestrogen vs placebo
 Outcome: 05 Bleeding



0.01 0.1 1 10 100
 Favours HRT Favours placebo

Review: HRT
 Comparison: 02 Oestrogen + progesterone (continuous) vs placebo
 Outcome: 04 Bleeding



0.01 0.1 1 10 100
 Favours HRT Favours placebo

For ERT vs placebo, the results from the meta-analysis of RCTs involving oral administration of 0.625 mg conjugated oestrogen show that a significantly higher proportion of patients in the HRT arms experienced bleeding than in the placebo arms. Trial arms involving other doses of conjugated oestrogen or estradiol valerate that were not meta-analysed showed the same trend but not always with statistical significance, most notably trials involving lower doses of conjugated oestrogens (0.3 mg). The results from the meta-analysis of RCTs involving transdermal administration also show that moderate and high doses of unopposed oestrogen (37.5, 50 and 100 µg) result in statistically significantly more bleeding for patients taking ERT than placebo. Patients receiving 25 µg unopposed oestrogen showed the same trend but without statistical significance.

For continuous EPRT vs placebo, the results from the meta-analysis of RCTs involving oral administration of 0.625 mg conjugated oestrogen + 2.5 mg medroxyprogesterone acetate show that a significantly higher proportion of patients in the HRT arms experienced bleeding than in the placebo arms. The meta-analyses of RCTs involving oral administration of 1 mg oestradiol + 0.5 mg norethisterone acetate or 2 mg oestradiol + 1 mg norethisterone acetate give the same result.

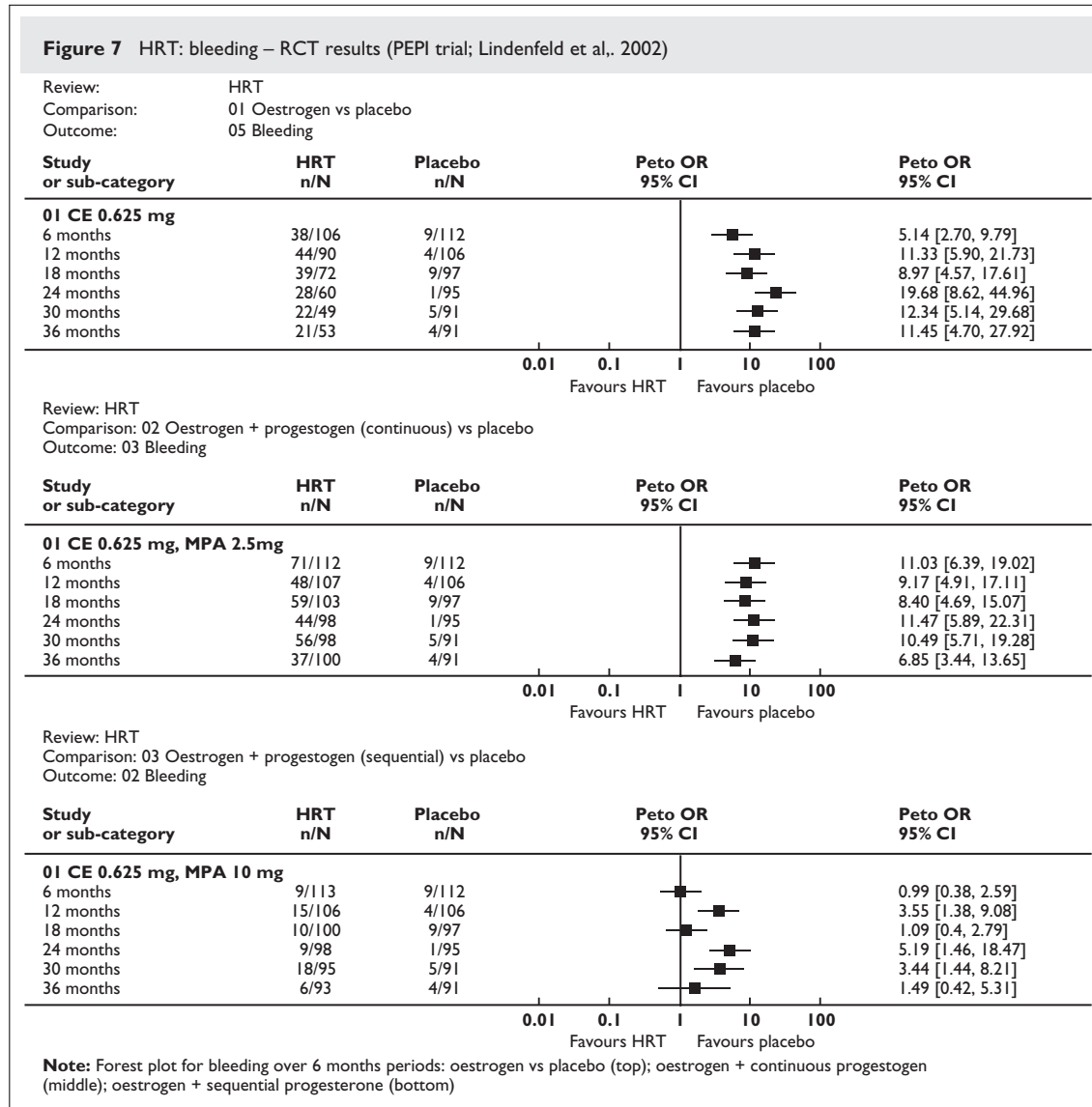
No studies of transdermal continuous EPRT or any administration of sequential EPRT were available for analysis.

Overall, the results from the included RCTs for all types of available regimens (ERT or EPRT) and administration (oral or transdermal) show that a greater proportion of patients experienced bleeding with HRT arms compared to placebo. A statistically significant difference was seen for patients receiving combined continuous therapy or moderate to high doses of unopposed oestrogen. These results are generally in agreement with those published in the systematic review by Lethaby *et al.* (2000).

One further study to be considered in the analysis for bleeding is the Postmenopausal Estrogen and Progestogen Interventions (PEPI) trial (Lindenfeld *et al.*, 2002). This five-arm study, of which the oral dosages in four arms are relevant to Australian practice, is the only trial included for analysis examining sequential EPRT. The relevant regimens administered during the trial were:

- Unopposed oestrogen: conjugated oestrogens 0.625 mg
- Oestrogen + continuous progestogen: conjugated oestrogens 0.625 mg; medroxyprogesterone acetate 2.5 mg
- Oestrogen + sequential progestogen: conjugated oestrogens 0.625 mg; medroxyprogesterone acetate 10 mg for 12 of 28 days
- Placebo

An episode of bleeding or spotting during the sequential regimen was defined as bleeding or spotting for 1 – 10 days, and participants reporting more than 10 days of bleeding or more than six episodes in six months were considered to have excess bleeding. For the unopposed oestrogen or combined continuous regimens, any bleeding or spotting was considered excess bleeding. Lindenfeld *et al.* (2002) contains bleeding data for women with an intact uterus with at least 80% adherence, broken down into six month periods, as shown in the forest plot in Figure 7.



The results from the PEPI study indicate that while statistically significantly more patients who took unopposed oestrogen or combined continuous therapy experienced bleeding compared to placebo over all time periods, the difference is not as pronounced in patients taking combined sequential therapy compared to placebo. Furthermore, the number of excess bleeding episodes among those women who reported excess bleeding was generally two to three times higher for women taking unopposed oestrogen or combined continuous therapy compared to women taking combined sequential therapy or placebo (data not shown). Bleeding patterns did not appear to change substantially for any of the regimens over time.

Overall, this trial suggests that a reduced rate of bleeding may be experienced by patients taking combined sequential therapy rather than combined continuous therapy or moderate dose unopposed oestrogen. Once again, this result is in agreement with the conclusions reached in the systematic review by Lethaby *et al.* (2000).

Weight gain

Existing systematic reviews

One systematic review of RCTs was identified and was considered to be of good methodological quality (Norman *et al.*, 2000; Level I evidence). The characteristics and quality of the included systematic review are summarised in Table 33. For further details see Appendix B (Section 9.1.2).

TABLE 33 HRT: WEIGHT GAIN – EXISTING SYSTEMATIC REVIEWS

Study	Study type (number of included studies) Study quality	Population	Intervention	Comparator	Outcomes
Level I evidence					
Norman <i>et al.</i> (2000)	Systematic review of RCTs (22) Good	Postmenopausal or perimenopausal women of any ethnicity	HRT oral, transdermal patch or percutaneous gel Any dose	Placebo or no treatment	Overall weight, body mass index, fat mass, waist/hip ratio, skinfold thickness

See Section 9.1.2.

Abbreviations: RCT, randomised controlled trials.

The main results of the Norman review and meta-analysis pertaining to weight gain are summarised in Table 34. In general there was no significant change in weight associated with HRT use, with the exception of a 1.6 kg weight loss associated with moderate-dose EPRT and a near significant 2 kg weight gain associated with low-dose ERT.

TABLE 34 HRT: WEIGHT GAIN – EXISTING SYSTEMATIC REVIEW RESULTS

Comparison	Number of studies	Number of participants	Weighted mean difference kg (95% CI)
Oestrogen alone			
Any dose oestrogen	7	1497	0.66 (-0.62, 1.93) ^a
Low dose oestrogen ^b	1	688	2.02 (0.00, 4.04)
Moderate dose oestrogen ^b	6	715	-0.42 (-2.14, 1.31) ^a
High dose oestrogen ^b	1	185	1.10 (-2.05, 4.25)
Oestrogen plus progestogen			
Any dose oestrogen	10	1695	-0.47 (-1.63, 0.69) ^a
Low dose oestrogen ^b	2	718	1.71 (-0.27, 3.70) ^a
Moderate dose oestrogen ^b	8	977	-1.60 (-3.04, -0.17) ^a
High dose oestrogen ^b	2	120	-0.41 (-3.78, 2.95) ^a

Note: Weighted mean differences in italics are considered statistically significant as they do not include zero.

Abbreviation: CI, confidence interval

^a Fixed effect model

^b Dosages were broken down for analysis into low, medium and high dose categories and equivalences as follows: moderate dosages are conjugated oestrogen 0.625 mg – 1.25 mg; 17- μ g-oestradiol 1.0 mg – 2.0 mg; micronised oestradiol 1.0 mg – 2.0 mg; oestradiol valerate 1.0 mg – 2.0 mg; transdermal oestradiol 50 μ g; ethinyl oestradiol 15 μ g – 20 μ g. Anything below the aforementioned units was considered low, and anything above, high dosages.

The authors concluded that there is evidence of no effect of ERT or EPRT on body weight, indicating that these regimens do not cause extra weight in addition to that normally gained at menopause.

Original studies

The date of the literature search in the Norman review was not stated; however the last amendment to the review was made in May 1999. The most recent studies referred to in the review were published in 1998. Table 35 refers to original studies of HRT versus placebo published since 1998 containing weight gain data that were systematically collected during the trial period and with doses relevant to Australian practice. Figure 8 shows the forest plot for the corresponding data. Weight gain data have been expressed as a proportion of evaluable patients, unless stated otherwise. Low, moderate and high doses have been defined as per the systematic review by Norman *et al.* (2000). No summary estimate has been calculated for weight gain as the number of studies was insufficient.

TABLE 35 HRT: WEIGHT GAIN – RCT RESULTS

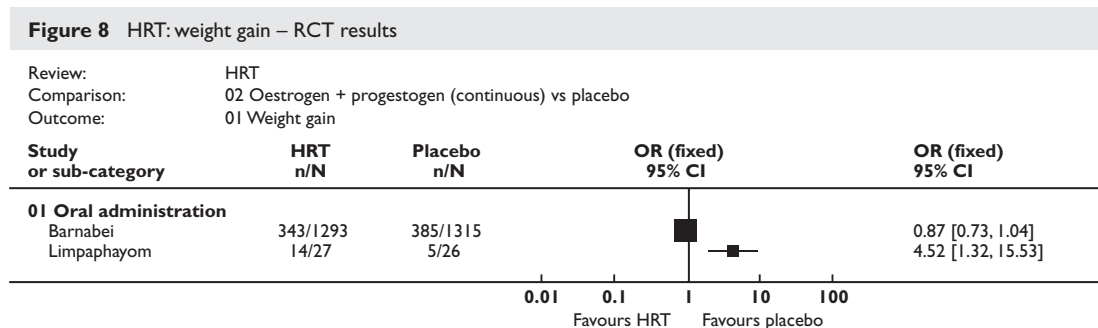
Author	HRT daily dose	RCT duration	HRT n/N (%)	Placebo n/N (%)	Peto OR (95% CI)
Oestrogen plus progestogen (continuous)					
Oral administration					
Barnabei 2002 ^a	CE 0.625 mg; MPA 2.5 mg	1 year	343/1293 (26.5)	385/1315 (29.3)	0.87 (0.73, 1.04)
Limpaphayom 2000 ^b	17-β-E2 2 mg; NETA 1 mg	12 weeks	14/27 (51.9)	5/26 (19.2)	4.52 (1.32, 15.53)

Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: CE, conjugated oestrogens; CI, confidence interval; E2, oestradiol; MPA, medroxyprogesterone acetate; OR, odds ratio.

^a Very frequent and somewhat frequent added together; definition of weight gain not given in publication

^b Definition of weight gain not given in publication. This study was conducted in Thai women



For oral administration of moderate dose oestrogen plus continuous progestogen, Barnabei *et al.* (2002) show no significant difference in the proportion of patients on HRT who gained weight compared to those not on HRT. This supports the findings of the Norman review. In contrast, Limpaphayom and Bunyavejchevin (2000) show that a higher proportion of patients in the HRT arm gained weight than in the placebo arm, with a statistically significant difference. It is important to recognise that this was a small study conducted in Thai women and therefore the extent to which this result can be generalised to the Australian population is unclear.

In summary, there is level I and II evidence of no effect of ERT or EPRT on body weight, indicating that these regimens do not cause extra weight in addition to that normally gained at menopause.

Other unwanted side effects

Tables 36–39 and Figures 9–12 refer to original studies of HRT versus placebo published in 1992 or later, containing adverse event data that were systematically collected during each trial period and with doses relevant to Australian practice. Adverse event data have been expressed as a proportion of evaluable patients, unless otherwise stated. No summary estimate has been calculated for adverse events other than bleeding as there are not a sufficient number of studies with the same dosages to warrant performing a meta-analysis. Where an RCT has more than one arm, the risk estimate applies to the calculated 'total' compared to placebo.

Migraine/headache

Table 36 shows the occurrence of migraine/headache in the HRT and placebo arms of the included trials. Figure 9 shows the forest plot for the corresponding data. Note that in clinical trials, migraine/headache is treated both as a symptom of menopause and an unwanted side effect of HRT and no distinction is made between the two.

TABLE 36 HRT: MIGRAINE/HEADACHE – RCT RESULTS

Author	HRT daily dose	RCT duration	HRT n/N (%)	Placebo n/N (%)	Peto OR (95% CI)
Oestrogen alone					
<i>Oral administration</i>					
Stevens et al. (2000) ^a	CE 0.3, 0.625 or 1.25 mg	12 weeks	49/72 (68.1)	32/48 (66.7)	1.07 (0.49, 2.32)
<i>Transdermal administration</i>					
Rovati et al. (2000) ^b	E2 25 µg, 1 × weekly patch E2 50 µg, 1 × weekly patch E2 50 µg, 2 × weekly patch	12 weeks	1/80 2/77 1/74 total: 4/231 (1.7)	1/80 (1.3)	1.39 (0.15, 12.64)
Cohen et al. (1999) ^c	E2 37.5 µg	12 weeks	2/130 (1.5); 1/130 (0.8)	2/127 (1.6); 2/127 (1.6)	0.98 (0.14, 7.04); 0.48 (0.04, 5.41)
Good et al. (1996)	E2 50 µg E2 100 µg	12 weeks	11/88 20/94 total: 31/182 (17.0)	21/91 (23.1)	0.68 (0.37, 1.27)
Oestrogen plus progestogen (continuous)					
<i>Oral administration</i>					
Barnabei et al. (2002) ^d	CE 0.625 mg; MPA 2.5 mg	1 year	298/1293 (23.0)	299/1315 (22.7)	1.02 (0.85, 1.22)
Alexandersen et al. (2000)	17-β-E2 2 mg; NETA 1 mg	2 years	10/48 (20.8)	4/46 (8.7)	2.76 (0.80, 9.55)
Limpaphayom et al. (2000) ^e	17-β-E2 2 mg; NETA 1 mg	12 weeks	1/27 (3.7)	1/26 (3.8)	0.96 (0.06, 16.22)

Note: Risk estimates in italics are considered statistically significant as they do not include one.

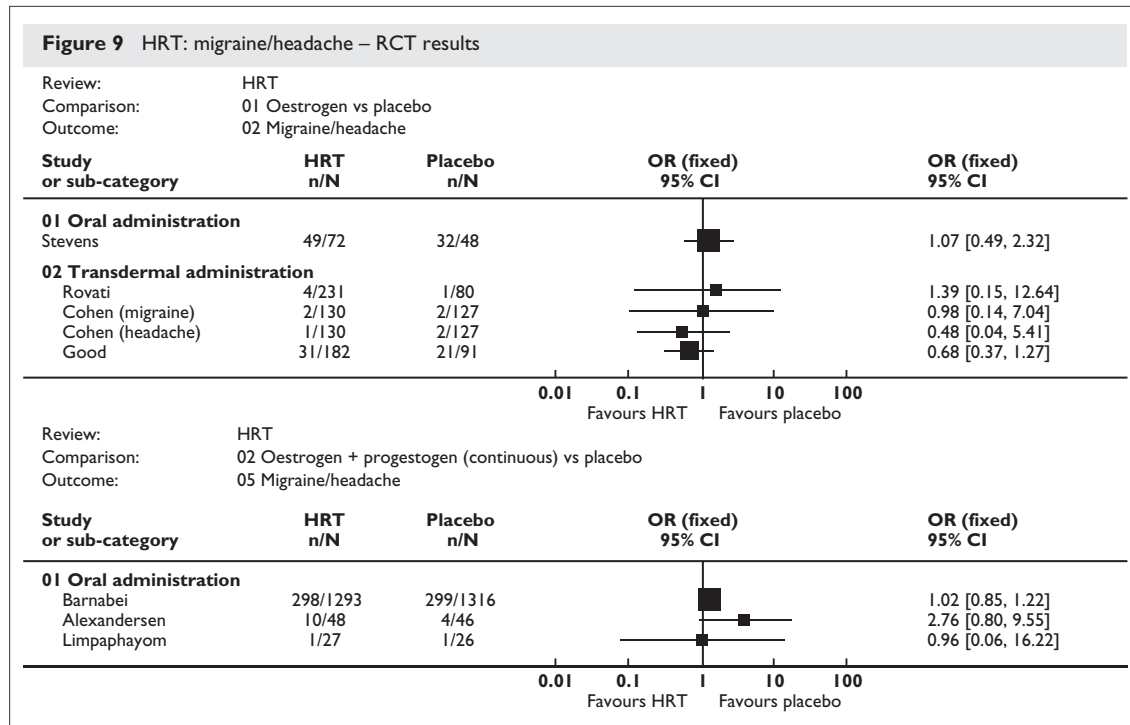
Abbreviations: CE, conjugated oestrogens; CI, confidence interval; E2, oestradiol; MPA, medroxyprogesterone acetate; NETA, norethisterone acetate; OR, odds ratio.

^aThe active arm consisted of patients taking conjugated oestrogens 0.3 mg, 0.625 mg or 1.25 mg/day (distribution unknown); dosage was varied as symptoms or side effects warranted. Thus, a proportion of patients took 1.25 mg/day, which is above the recommended dose. Migraine/headache reported as percentages in publication; proportions have been calculated from randomised patients.

^bHeadache reported as a proportion of treated patients

^cSafety data provided for treated rather than evaluable patients only. Data on migraine/headache provided for migraine (1st value) and headache (2nd value).

^dVery frequent and somewhat frequent added together



**This study was conducted in Thai women*

Overall, the results show that there are no statistically significant increase in migraine/headache associated with oral or transdermal ERT or oral continuous EPRT.

Nausea/vomiting

Table 37 shows the occurrence of nausea/vomiting in the HRT and placebo arms of the included trials. Figure 10 shows the forest plot for the corresponding data. Definitions of nausea/vomiting described in each trial are provided in the footnotes to the table.

TABLE 37 HRT: NAUSEA/VOMITING – RCT RESULTS

Author	HRT daily dose	RCT duration	HRT n/N (%)	Placebo n/N (%)	Peto OR (95% CI)
Oestrogen alone					
Transdermal administration					
Rovati <i>et al.</i> (2000) ^a	E2 25 µg, 1 × weekly patch E2 50 µg, 1 × weekly patch E2 50 µg, 2 × weekly patch	12 weeks	0/80 1/77 1/74 total: 2/231 (0.9)	0/80 (0.0)	1.75 (0.08, 36.92)
Good <i>et al.</i> (1996) ^b	E2 50 µg E2 100 µg	12 weeks	4/88 4/94 total: 8/182 (4.4)	10/91 (11.0)	0.37 (0.14, 0.98)

Author	HRT daily dose	RCT duration	HRT n/N (%)	Placebo n/N (%)	Peto OR (95% CI)
Oestrogen plus progestogen (continuous)					
<i>Oral administration</i>					
Barnabei <i>et al.</i> (2002) ^c	CE 0.625 mg; MPA 2.5 mg	1 year	60/1293 (4.6)	53/1315 (4.0)	1.16 (0.79, 1.69)
Alexandersen <i>et al.</i> (2000) ^b	17-β-E2 2 mg; NETA 1 mg	2 years	3/48 (6.3)	1/46 (2.2)	3.00 (0.30, 29.94)
Limpaphayom <i>et al.</i> (2000) ^d	17-β-E2 2 mg; NETA 1 mg	12 weeks	6/27 (22.2)	0/26 (0.0)	16.02 (0.85, 300.73)

Note: Risk estimates in italics are considered statistically significant as they do not include one.

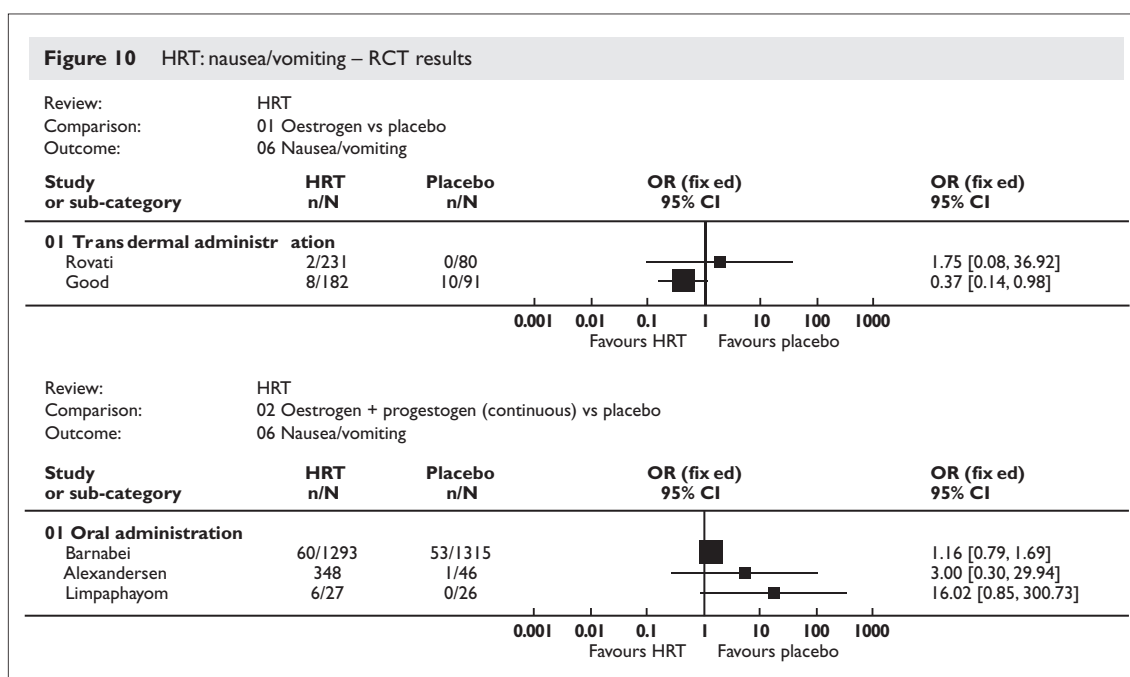
Abbreviations: CE, conjugated oestrogens; CI, confidence interval; E2, oestradiol; MPA, medroxyprogesterone acetate; NETA, norethisterone acetate; OR, odds ratio.

^a Reported nausea or dyspepsia (not defined further) as a proportion of treated patients

^b Reported nausea (not defined further)

^c Reported nausea or vomiting (not defined further). Very frequent and somewhat frequent added together.

^d Reported nausea and vomiting (not defined further). This study was conducted in Thai women



For ERT vs placebo, one study involving transdermal administration showed that a lower proportion of patients in the HRT arm experienced nausea/vomiting than in the placebo arm, with a statistically significant difference. Another study showed that transdermal ERT did not cause nausea/vomiting.

For continuous EPRT vs placebo, of the three included studies only one showed a near significant increase in nausea/vomiting associated with ERT, however this study was very small and was limited to Thai women.

In summary, the results suggest that HRT does not cause significant nausea/vomiting.

Breast tenderness

Table 38 shows the occurrence of breast tenderness in the HRT and placebo arms of the included trials. Figure 11 shows the forest plot for the corresponding data. Note that two studies listed in Table 38 could not be included in the forest plot (Greendale 1998 and Rovati 2000) as dichotomous data from these studies are not available.

TABLE 38 HRT: BREAST TENDERNESS – RCT RESULTS

Author	HRT daily dose	RCT duration	HRT n/N (%)	Placebo n/N (%)	Peto OR (95% CI)
ERT					
<i>Oral administration</i>					
Goldstein et al. (2000)	CE 0.625 mg	1 year	18/100 (18.0)	0/109 (0.0)	49.11 (2.92, 826.79)
Stevens et al. (2000) ^a	CE 0.3, 0.625 or 1.25 mg	12 weeks	21/72 (29.2)	7/48 (14.6)	2.41 (0.93, 6.23)
Greendale et al. (1998) ^b	CE 0.625 mg	3 years	–	–	1.16 (0.70, 1.93)
<i>Transdermal administration</i>					
De Aloysio et al. (2000) ^c	E2 25 µg E2 37.5 µg	12 weeks	22/52 21/52 total: 43/104 (41.3)	5/52 (9.6)	6.63 (2.43, 18.03)
de Vrijer et al. (2000) ^d	E2 100 µg E2 50 µg	12 weeks	52/86 21/82 total: 73/168 (43.5)	9/86 (10.5)	6.57 (3.09, 13.99)
Rovati et al. (2000) ^e	E2 25 µg, 1 × weekly patch E2 50 µg, 1 × weekly patch E2 50 µg, 2 × weekly patch	12 weeks	22% 33% 35% average: 30%	16%	–
Cohen et al. (1999) ^f	E2 37.5 µg	12 weeks	13/130 (10.0)	1/127 (0.8)	14.00 (1.80, 108.69)
Good et al. (1996)	E2 50 µg E2 100 µg	12 weeks	4/88 5/94 total: 9/182 (4.9)	0/91 (0.0)	10.02 (0.58, 174.11)
Continuous EPRT					
<i>Oral administration</i>					
Barnabei et al. (2002) ^g	CE 0.625 mg; MPA 2.5 mg	1 year	518/1293 (40.1)	119/1315 (9.0)	6.72 (5.40, 8.36)
Alexandersen et al. (2000)	17-β-E2 2 mg; NETA 1 mg	2 years	23/48 (47.9)	2/46 (4.3)	20.24 (4.40, 93.10)
Limpaphayom et al. (2000) ^h	17-β-E2 2 mg; NETA 1 mg	12 weeks	24/27 (88.9)	3/26 (11.5)	61.33 (11.21, 335.54)
Greendale et al. (1998) ^b	CE 0.625 mg; MPA 2.5 mg	3 years	–	–	1.92 (1.16, 3.09)
Sequential EPRT					
<i>Oral administration</i>					
Greendale et al. (1998) ^b	CE 0.625 mg; MPA 10 mg ^b	3 years	–	–	2.27 (1.39, 3.56)

Note: Risk estimates in *italics* are considered statistically significant as they do not include one.

Abbreviations: CE, conjugated oestrogens; CI, confidence interval; E2, oestradiol; MPA, medroxyprogesterone acetate; NETA, norethisterone acetate; OR, odds ratio.

^a The active arm consisted of patients taking conjugated oestrogens 0.3 mg, 0.625 mg or 1.25 mg/day (distribution unknown); dosage was varied as symptoms or side effects warranted. Thus, a proportion of patients took 1.25 mg/day, which is above the recommended dose. Breast tenderness reported as percentages in publication; proportions have been calculated from randomised patients.

^b In the Greendale 1998 study, the HRT arms share the same placebo arm. Odds ratios are adjusted for baseline symptom level, clinical site and uterus status. For combined sequential administration, MPA given for 12 of 28 days.

^c Breast tenderness expressed out of all treated patients

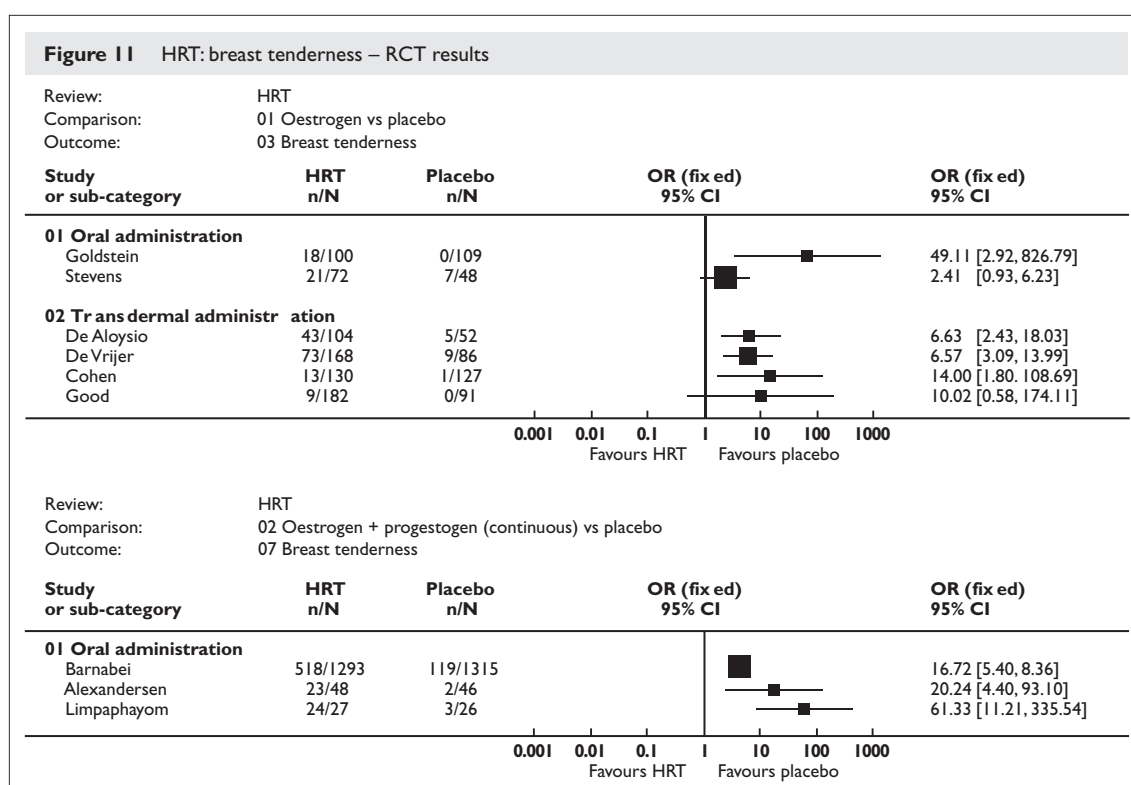
^d Breast tenderness reported as a proportion of treated patients

^e For breast tenderness at 12 weeks, publication states that percentages reported refer to 'per-protocol' incidence: unable to deduce to which population this refers.

^f Safety data provided for treated rather than evaluable patients only

^g Percentages read off graph and converted to patient numbers; values given for years two, three and four also, but reported for each timepoint, ie, not cumulative (not tabulated). Breast symptoms, ie, pain (pain, discomfort, aching, throbbing, soreness, tenderness, heaviness, tingling, burning or sensitivity) or swelling (swelling, enlargement or fullness) tabulated as breast tenderness.

^h This study was conducted in Thai women



In general, the results from the included RCTs show that a greater proportion of patients experienced breast tenderness in the HRT arms (ERT and EPRT) compared to the placebo arms in all the included studies, with a statistically significant difference in eight out of ten studies.

Fluid retention

Table 39 shows the occurrence of fluid retention in the HRT and placebo arms of the included trials. Figure 12 shows the forest plot for the corresponding data.

TABLE 39 HRT: FLUID RETENTION – RCT RESULTS

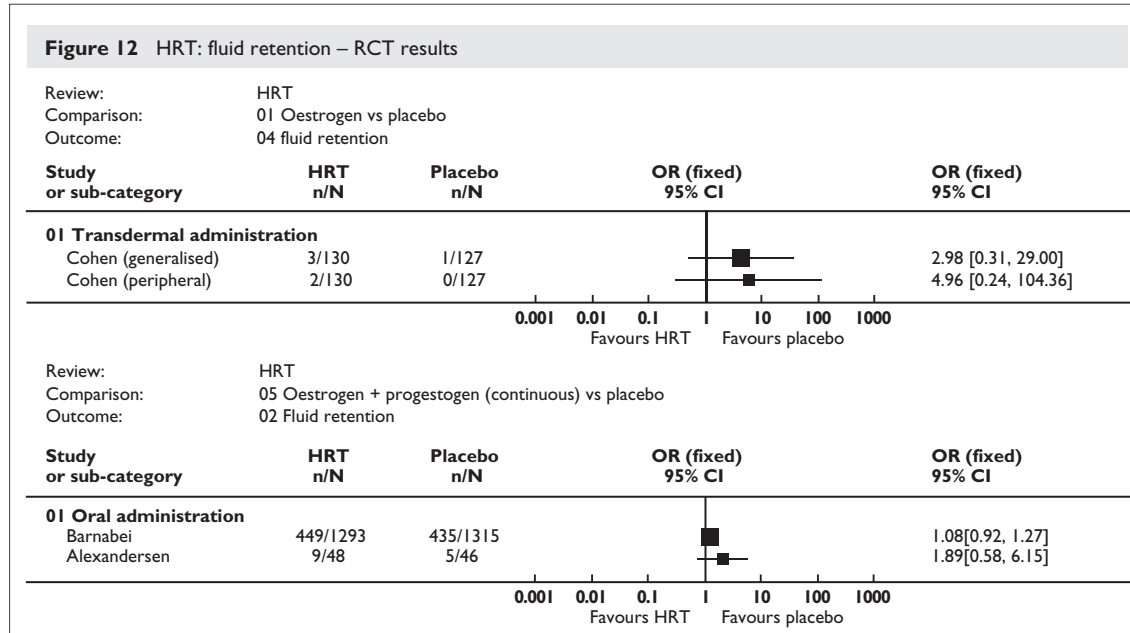
Author	HRT daily dose	RCT duration	HRT n/N (%)	Placebo n/N (%)	Peto OR (95% CI)
Oestrogen only					
<i>Transdermal administration</i>					
Cohen et al. (1999) ^a	E2 37.5 µg	12 weeks	3/130 (2.3); 2/130 (1.5)	1/127 (0.8); 0/127 (0.0)	2.98 (0.31, 29.00); 4.96 (0.24, 104.36)
Oestrogen plus progestogen (continuous)					
<i>Oral administration</i>					
Barnabei et al. (2002) ^b	CE 0.625 mg; MPA 2.5 mg	1 year	449/1293 (34.7)	435/1315 (33.1)	1.08 (0.92, 1.27)
Alexandersen et al. (2000)	17-β-E2 2 mg; NETA 1 mg	2 years	9/48 (18.8)	5/46 (10.9)	1.89 (0.58, 6.15)

Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: CE, conjugated oestrogens; CI, confidence interval; E2, oestradiol; MPA, medroxyprogesterone acetate; NETA, norethisterone acetate; OR, odds ratio.

^a Safety data provided for treated rather than evaluable patients only. Data on fluid retention provided for generalised (1st value) and peripheral (2nd value).

^b Very frequent and somewhat frequent added together.



Overall, the results from the included RCTs showed that there were no statistically significant differences between the HRT and placebo arms with respect to fluid retention.

Hypertension in hypertensive women

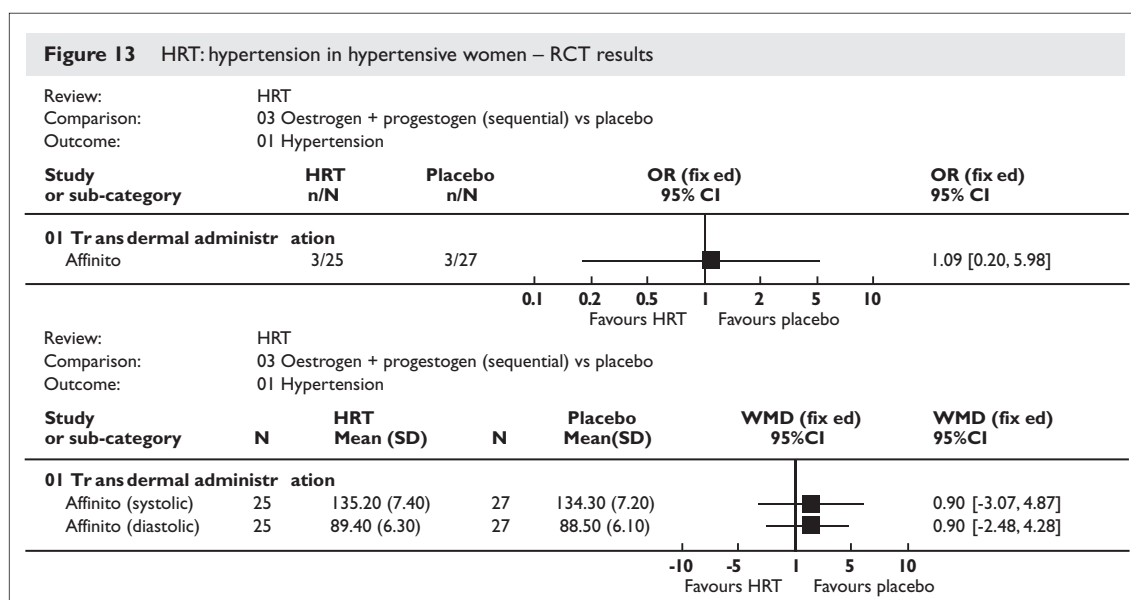
Table 40 shows the occurrence of hypertension in previously hypertensive women in the HRT and placebo arms of the included trials. Figure 13 shows the forest plot for the corresponding data.

TABLE 40 HRT: HYPERTENSION IN PREVIOUSLY HYPERTENSIVE WOMEN – RCT RESULTS

Author	HRT daily dose	RCT duration	HRT n/N (%) or mmHg \pm SD	Placebo n/N (%) or mmHg \pm SD	Risk estimate
Sequential EPRT					
Transdermal administration					
Affinito et al. (2001) ^a					
Blood pressure increase			3/25 (12.0)	3/27 (11.1)	1.09 (0.20, 5.98)
Standard sphygmomanometer					
Systolic			135.2 \pm 7.4	134.3 \pm 7.2	0.90 mmHg (-3.07, 4.87)
Diastolic			89.4 \pm 6.3	88.5 \pm 6.1	0.90 mmHg (-2.48, 4.28)
24-hour ambulatory recording	E2 50 μ g; MPA 10 mg	6 months			
Systolic					
Phase I			134.5	139.2	–
Phase II			133.4	139.4	–
Diastolic					
Phase I			85.1	89.4	–
Phase II			85.3	89.2	–

Abbreviations: E2, oestradiol; MPA, medroxyprogesterone acetate; SD, standard deviation.

^a MPA administered orally for 12 of 28 days; dichotomous data refers to an 'increase in blood pressure', ranging from between two and eight mmHg; values for blood pressure measured over 24 hours read from graph; phase I: day 10 to day 16 (oestrogenic phase), phase II: day 20 to day 27 (oestro-progestogenic phase); for dichotomous data, risk estimate refers to odds ratio (95% confidence interval); for continuous data, risk estimate refers to weighted mean difference (95% confidence interval); weighted mean differences unable to be calculated for 24 hour ambulatory recordings as standard deviations not available; medication for blood pressure was maintained in all patients during the trial period.



Overall, the results from the single included RCT involving transdermal administration of sequential EPRT showed that the differences in blood pressure between the patients taking HRT and patients taking placebo were small and, using two measurement methods, statistically insignificant.

Hair loss/gain

No studies were identified that contained data on hair loss/gain.