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Transdermal Hormone Replacement Therapy Patches for Women with Postmenopausal Symptoms: Economic Analysis of Short-Term Use

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Transdermal Hormone Replacement Therapy Patches for Women with Postmenopausal Symptoms: Economic Analysis of Short-Term Use

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Authorship

Allan Brown is a health economist at CCOHTA. He was responsible for coordination of the project and the response to reviewers. He wrote the executive summary, issues, objectives, and conclusions; and sections of the introduction, methodology, and discussion.

Doug Coyle is an associate professor at the University of Ottawa and a senior scientist at the Ottawa Health Research Institute. He developed the economic model, wrote significant portions of the economic analysis section, and participated in the selection of studies and data extraction of inputs for the model.

Stella Chen is a research officer at CCOHTA. She had primary responsibility for writing the clinical sections, and participated in the selection of studies and data extraction of inputs for the model.

David Cumming is a professor in the Departments of Obstetrics and Gynaecology and Medicine (Division of Endocrinology) at the University of Alberta. He provided clinical expertise; and reviewed, revised, and approved manuscript drafts.

Shaila Mensinkai is an information specialist at CCOHTA. She was responsible for the design and execution of the literature search strategies; writing the methods section and the associated appendix on literature searching; and verifying and formatting bibliographic references.

All authors contributed revisions to the report in response to reviewers' comments.

Conflicts of Interest

David Cumming has received honoraria from Schering and Boeringer Ingelheim for presentations related to women's health in the postmenopausal period. He has also been involved in research funded by Eli Lilly.

Christine Derzko has received speaker support from Wyeth and Procter & Gamble; and research support from Wyeth, Proctor & Gamble, Lilly, Organon, Pfizer, and Berlex.

All other authors and reviewers reported no conflicts.

REPORT *IN BRIEF*

January 2006

CCOHTA

Transdermal Hormone Replacement Therapy Patches for Women with Postmenopausal Symptoms: Economic Analysis of Short-Term Use

Technology

Transdermal hormone replacement therapy (HRT) patches allow estradiol to be absorbed through the skin and released into the blood stream in metered doses. The patch needs to be changed once or twice a week. The most commonly used HRT patches in Canada are Climara®, Vivelle® and Estraderm MX50.

Issue

Postmenopausal symptoms can be treated with oral or transdermal HRT. Does the use of transdermal HRT patches, which are more expensive than oral HRT, offer advantages that offset the apparent economic disadvantage?

Methods and Results

Inputs for the economic model were obtained from relevant randomized controlled trials (RCTs). Eligible studies compared the efficacy of transdermal HRT patches with oral HRT or with placebo patches. A decision analytic Markov model was developed to assess the costs and quality adjusted life-years (QALYs) for postmenopausal women associated with the short-term (two to three years) use of HRT. Separate analyses were performed according to symptom severity. The cost-effectiveness was assessed for transdermal HRT patches relative to oral HRT or to no treatment. The perspective was that of a third-party payer.

Eight studies reporting nine unique RCTs met the inclusion criteria. For women with moderate or severe symptoms, transdermal HRT patches were as effective as oral HRT, but were more costly. Relative to no treatment, transdermal patches had an incremental cost per QALY of $32,300 and $8,300 for patient groups with moderate and severe symptoms respectively. These results fall in the range of what is generally considered to be cost-effective.

Implications for Decision Making

- **There are no demonstrated clinical advantages to using transdermal HRT.** RCTs show that oral HRT and transdermal HRT patches are comparable in alleviating moderate or severe postmenopausal symptoms.
- **Transdermal HRT patches are not cost-effective, relative to oral HRT, for women with moderate or severe postmenopausal symptoms.** The use of transdermal HRT patches is more costly than using oral HRT despite similar effectiveness.
- **Relative to no treatment, transdermal HRT patches may be cost-effective for women with moderate or severe symptoms.** Transdermal HRT patches may be an appropriate treatment option for patients who do not tolerate oral HRT.

This summary is based on a comprehensive health technology assessment available from CCOHTA's web site (www.ccohta.ca): Brown A, Coyle D, Chen S, Cumming D, Mensinkai S. *Transdermal hormone replacement therapy patches for women with postmenopausal symptoms: economic analysis of short-term use.*

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EXECUTIVE SUMMARY

The Issue

Postmenopausal symptoms include hot flashes, fatigue, night sweats, mood changes, insomnia, myalgias, arthralgias, anxiety, and sexual dysfunction. These symptoms can be treated with hormone replacement therapy (HRT). HRT involves the provision of one or more estrogenic substances, with or without progesterone or progesterone-like drugs, to enhance the circulating hormones, which fall to low levels after the cessation of ovarian hormone production at menopause. While HRT can be delivered orally, transdermal means of application are also available, with the most common being skin patches. The evidence suggests that oral HRT and transdermal HRT are effective in treating postmenopausal vasomotor symptoms. In certain circumstances, clinicians may prefer to prescribe transdermal HRT patches and patients may prefer the convenience of this treatment. Transdermal patches are more expensive than oral HRT. A need was identified for an economic evaluation comparing transdermal patches to oral HRT and to no HRT treatment.

Objectives

The objective of this report is to present an economic analysis of transdermal patches for the short-term treatment of postmenopausal symptoms in women.

Methods

A literature search was performed to select relevant clinical studies as inputs for the economic model. The search covered the years 1990 through to May 2004. The studies considered were randomized controlled trials (RCTs) that compared the efficacy of transdermal HRT patches with oral HRT, or that of transdermal HRT patches with placebo patches. A decision analytic Markov model was developed to assess the costs and quality adjusted life-years (QALYs) of women who were using HRT for postmenopausal symptoms in the short term (two to three years). Separate analyses were performed for women with severe symptoms and women with moderate symptoms. The cost-effectiveness was assessed in terms of transdermal HRT patches relative to oral HRT, and transdermal HRT patches relative to no treatment. The perspective taken was that of a third-party payer.

Results

Eight studies reporting nine unique RCTs met the inclusion criteria of the clinical search and the data were used as inputs to the economic model. For women with moderate symptoms and for women with severe symptoms, transdermal HRT patches were as effective as oral HRT, but at a higher cost. Relative to no treatment, transdermal patches had an incremental cost per QALY of approximately $32,300 for the patients with moderate symptoms. For women with severe symptoms, relative to no treatment, the cost per QALY gained was approximately $8,300.

Conclusions

The economic analysis found that transdermal HRT patches are not cost-effective relative to oral HRT for either the moderate or severe post-menopausal symptom groups. Relative to no treatment, transdermal HRT patches may be cost-effective for women with moderate or severe symptoms. This suggests that transdermal patches may be an appropriate treatment option for patients who do not tolerate oral HRT, especially if they are experiencing severe postmenopausal symptoms.

ABBREVIATIONS

CEE	conjugated equine estrogen
CI	credible interval
GERD	gastroesophageal reflux disease
HDL	high density lipoproteins
HERS	heart and estrogen or progestin replacement study
HRT	hormone replacement therapy
HUI	health utilities index
MPA	medroxyprogesterone acetate
QALY	quality adjusted life-year
RCT	randomized controlled trial
SD	standard deviation
SE	standard error
WHI study	Women's Health Initiative study

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1 INTRODUCTION

1.1 Hormone Replacement Therapy

Hormone replacement therapy (HRT) involves the provision of one or more estrogenic substances, with or without progesterone or progesterone-like drugs, to replace the circulating hormones that fall to low levels after the cessation of ovarian hormone production at menopause. HRT has been used for two indications: menopause-related symptoms, and the prevention of conditions such as osteoporosis and cardiovascular disease, which are associated with the long-term lowering of estrogenic levels. The first indication is the focus of this report.

Women may experience a variety of symptoms associated with estrogen deficiency around the time of menopause.[1] Evidence suggests that the short-term use of HRT is effective at relieving many postmenopausal symptoms.[1] These symptoms include hot flashes, fatigue, night sweats, mood changes, insomnia, myalgias or arthralgias, anxiety, sexual dysfunction, and other symptoms that can significantly affect daily life. In 2004, an estimated 21% of Canadian women were between 45 and 59 years old,[2] an age at which they would most likely experience these symptoms.

Studies such as the Heart and Estrogen/progestin Replacement Study (HERS) and the Women's Health Initiative (WHI) trial suggest that with the long-term use of HRT for the prevention of cardiovascular and other conditions, there may be an increased risk of cardiovascular disease, stroke, venous thromboembolic events, and breast cancer.[3-7] These studies are not without controversy,[8-10] but current recommendations are that HRT use should be restricted to symptomatic women.[3,11-13]

The main forms of estrogen used in HRT include the natural oral estrogens [conjugated equine estrogen (CEE), estrone, and estradiol] and transdermal estrogens (patches and gel containing estradiol). Synthetic estrogens (ethinyl estradiol and mestranol) are infrequently used for HRT.

The first demonstration of the effectiveness of CEE occurred 60 years ago.[14] The widespread use of estrogens did not occur until Dr. Robert A. Wilson's "Feminine Forever" was published in 1966.[15] A range of transdermal estrogen patches and gels have appeared during the last 20 years. Several journal articles about patches were written in 1983 and 1985. The Estraderm patch appeared shortly afterward.[16-19]

1.2 Transdermal Patches and Other Hormone Replacement Therapy for Short-Term Treatment of Postmenopausal Symptoms

Short-term hormone replacement therapy can be defined as the use of estrogen or an estrogen-progestin combination to treat menopausal symptoms for the shortest time possible.[20] Typically, short-term use lasts two to three years, up to a maximum of five years. Long-term use typically lasts more than five years and is associated with the prevention of the clinical consequences of an estrogen-deficient state, such as osteoporosis and cardiovascular disease.[12,21]

HRT can be administered orally in pill form; or transdermally through skin patches, gels and creams for the short-term treatment of postmenopausal symptoms.[22] Oral HRT is commonly used for vasomotor and other symptoms occurring in early menopause. The evidence suggests that it is clinically effective.[1,23-26] With the oral mode of delivery, estrogen is absorbed through the intestines and transported to the liver, through the portal vein. With oral formulations, the action of estrogen on the intestines and liver may cause adverse effects. Estrogen can irritate the intestines, causing nausea and vomiting; and it modifies liver function, resulting in elevated hepatic enzymes, which affect lipid metabolism. Much of the estradiol, the active ingredient in HRT, is lost when metabolized by the liver. This reduces the bioavailability of the hormone and increases the effective dose needed to restore hormonal levels.[27]

Premarin is the most commonly prescribed oral estrogen preparation. The most commonly used doses of Premarin range from 0.625 mg to 1.5 mg. Premarin consists of predominantly estrone with lesser amounts of other estrogenic compounds including equine estrogens.[28,29]

Transdermal delivery of estrogen by skin patches and gels is also used to alleviate postmenopausal symptoms. The method was developed to bypass first-pass hepatic effects by taking advantage of the skin's ability to absorb steroids and pass them directly into the systemic circulation.[30] In transdermal patches, the estradiol is dissolved in a drug reservoir or matrix system that is affixed to the skin by an adhesive layer.[18,31,32] Estradiol is absorbed through the skin and released into the blood stream in metered doses through a rate-controlling membrane. This results in a stable concentration of serum estradiol and avoids first-pass metabolism.[33,34] The system administers estradiol at a controlled rate of 0.025 mg daily, 0.05 mg daily, or 0.1 mg daily. Women are required to change the patches once or twice a week.

The transdermal patch system is unique in that it delivers estradiol into the circulation at a constant rate and delivers sufficient hormone to raise estradiol concentrations to levels that are similar to those of women in the early to mid-follicular phases of their menstrual cycles. It uses a dermal patch that can be applied and removed without difficulty; and the dosage can be easily adjusted.[31] In addition, the transdermal patch contains less hormone than an oral preparation.

A study that investigated the biological effects of transdermal estradiol indicated that the effects of 0.625 mg and 1.25 mg of oral estrogens were similar to those of 0.05 mg and 0.1 mg of transdermal estradiol per day respectively.[31] Transdermal estradiol did not result in a measurable change in either the hepatic protein level or lipid metabolism, while the oral estrogens exerted significant effects on several variables, such as renin substrate, sex hormone-binding globulin, cortisol-binding globulin, and thyroxine-binding globulin.[31]

The most commonly used transdermal patches in Canada are Climara®, Vivelle®, and Estraderm MX50. Table 1 summarizes the Canadian HRT agents analyzed in this report. There are no substantive differences in prices among provinces.

Table 1: HRT agents analyzed*

Drug and Generic Names	Drug Identification Number	Strength and Dosage Form	Cost per Unit (C$)	Dose Used†
Oral Treatment				
Premarin Conjugated estrogens	02043408	0.625 mg per tablet	0.12	One tablet daily
Transdermal Patch Treatments				
Estraderm Estradiol 17-B	00756857	50 µg per patch	2.44	One patch, twice weekly
Vivelle Estradiol 17-B	02204428	50 µg per patch	1.71	One patch, twice weekly
Climara Estradiol 17-B	02231509	50 µg per patch	4.88	One patch, once weekly

*Data source is Ontario Drug Benefit Formulary/Comparative Drug Index (2005). Cost information refers to "Drug Benefit Price."[35] Price for Vivelle was $2.44 per unit in 2003.[36] †Treatment can be continuous, or some patients may be instructed by a physician to not use the drug for five to seven days.

1.3 Hormone Replacement Therapy Use in Canada

Data indicate that the number of prescriptions for oral HRT is higher than for transdermal, both for estrogen plus progesterone and for estrogen-alone formulations. The number of HRT prescriptions has dropped since 2002. This may have been influenced by the results of the Women's Health Initiative (WHI) study,[7] which were released in 2002. Data on the number of prescriptions for 2000 to 2004 were provided by IMS Health (Dorothy Rhodes, IMS Health, Kirkland, QC: personal communication, 2005 Mar 23). Total HRT prescriptions for 2004 were more than five million.

In 2004, about 900,000 Canadian women used HRT, based on an estimate of 5.9 prescriptions annually per woman.[37] Given that there were 3.4 million women between the ages of 45 and 59 in Canada in 2004,[2] a significant proportion of postmenopausal women do not receive HRT therapy.

Table 2: HRT prescriptions and estimated number of users in Canada, 2000 to 2004*

	2000	2001	2002	2003	2004
Total Estrogen	8,641,606	8,620,987	7,952,472	6,054,294	4,951,064
Estrogen tablets	7,157,108	7,084,179	6,445,310	4,712,432	3,733,638
Estrogen patches	875,897	838,008	781,651	638,272	530,928
Other forms of estrogen therapy†	608,601	698,800	725,511	703,590	686,498
Total Estrogen plus Progesterone	170,000	407,032	629,521	493,903	369,599
Estrogen plus progesterone tablets	8,450	214,846	425,487	337,213	250,945
Estrogen plus progesterone patches	161,550	192,186	204,034	156,690	118,654
Total HRT Prescriptions	8,811,606	9,028,019	8,581,993	6,548,197	5,320,663
Estimated Number of HRT Users‡	1,493,493	1,530,173	1,454,575	1,109,864	901,807

*Data on number of HRT prescriptions from Compuscript, IMS Health. †Other forms of estrogen therapy include vaginal cream, skin gel, and injectable estrogen. ‡Data on number of women who received HRT annually in Canada estimated, based on 5.9 prescriptions annually per woman (5.9 estimate based on data from Table 1 of a US study by Hersh *et al.* 2003).[37]

Figure 1: HRT prescriptions in Canadian retail pharmacies – estrogen and estrogen plus progesterone

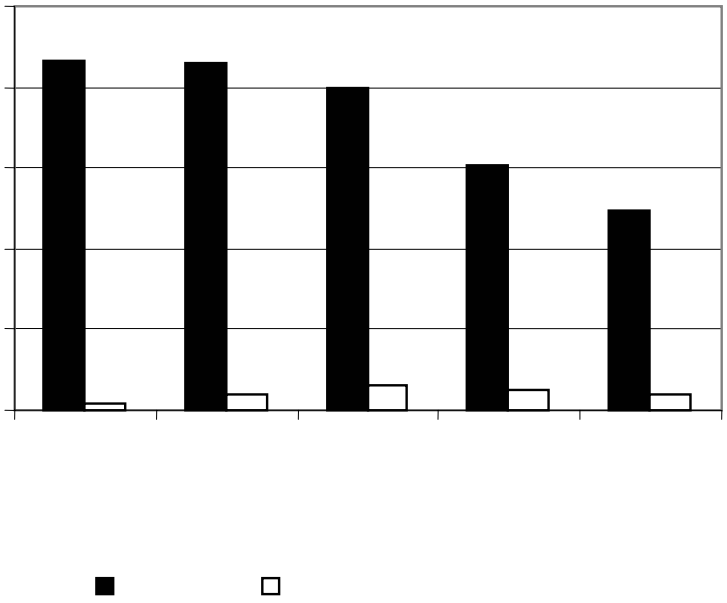
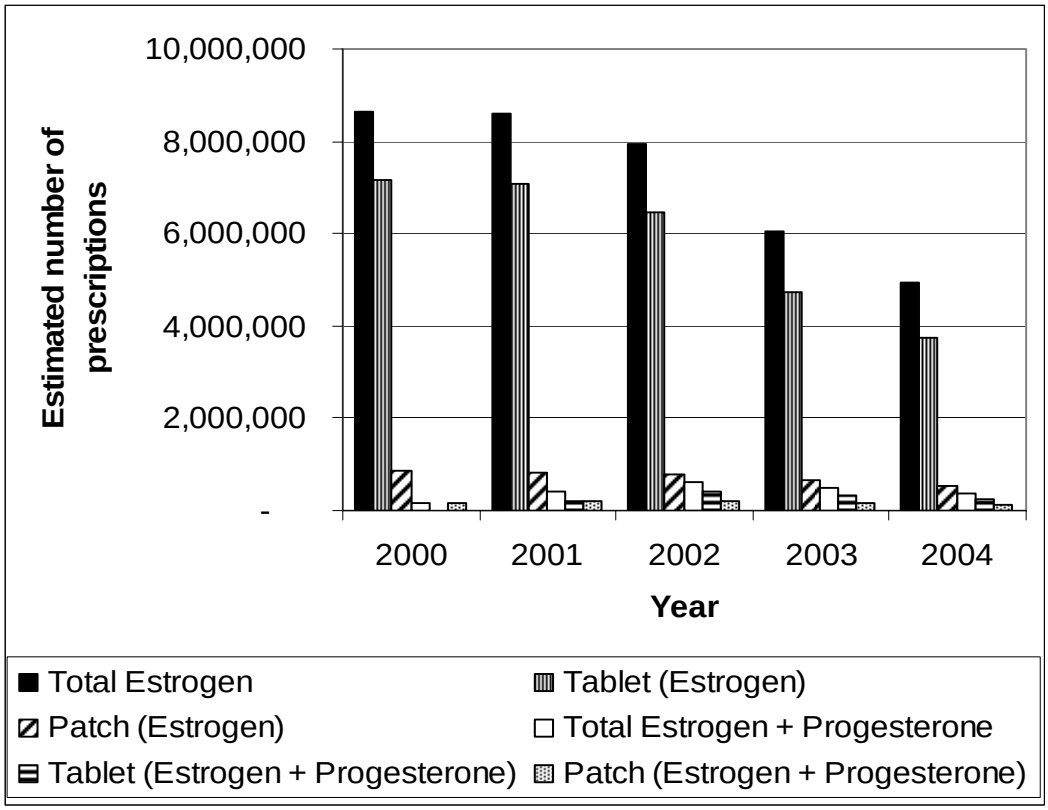


Figure 2: HRT Prescriptions in Canadian retail pharmacies – formulation type



2 THE ISSUE

Postmenopausal symptoms include hot flashes, fatigue, night sweats, mood changes, insomnia, myalgias, arthralgias, anxiety, and sexual dysfunction. These symptoms can be treated with hormone replacement therapy (HRT). HRT involves the provision of one or more estrogenic substances, with or without progesterone or progesterone-like drugs, to enhance the circulating hormones, which fall to low levels after the cessation of ovarian hormone production at menopause. While HRT can be delivered orally, transdermal means of application are also available, with the most common being skin patches. The evidence suggests that oral HRT and transdermal HRT are effective in treating postmenopausal vasomotor symptoms. In certain circumstances, clinicians may prefer to prescribe transdermal HRT patches and patients may prefer the convenience of this treatment. Transdermal patches are more expensive than oral HRT. A need was identified for an economic evaluation comparing transdermal patches to oral HRT and to no HRT treatment.

3 OBJECTIVES

The objective of this report is to present an economic analysis of transdermal patches for the short-term treatment of postmenopausal symptoms in women. The report is intended to help decision makers who are involved in the provision of treatment for symptoms that typically occur after menopause.

The objective is addressed by answering the following questions:

- what is the cost-effectiveness of transdermal patches as a generic class versus oral HRT?
- what is the cost-effectiveness of transdermal patches as a generic class versus no treatment?

4 CLINICAL REVIEW

4.1 Methods

4.1.1 Literature search strategy

A literature search for clinical evidence was performed to select relevant studies to obtain clinical inputs for the economic model. In March 2004, published literature from 1990 onward was identified by searching MEDLINE®, EMBASE®, BIOSIS Previews®, and PASCAL databases using the DIALOG OneSearch® feature. Appropriate keywords, descriptors, subject headings, registry numbers, and generic and trade names were used for commonly prescribed HRTs. No language limits were used. Keywords, descriptors, and subject headings were used to restrict retrieval to those references that compared oral and transdermal HRT therapies. A clinical filter was used to further restrict retrieval to relevant controlled clinical trials (Appendix

1). To obtain additional data for the economic model, an economic filter was combined with the drug and routes of administration search sets, and a sub-set of references was retrieved (Appendix 2). Parallel searches were performed and updated on PubMed, HEED (Health Economics Evaluations database) and the web version of the Cochrane Library, 2004.

Grey literature was retrieved by searching health technology assessment and related web sites and databases. References published only as abstracts were excluded because they provided insufficient data for the economic model. In May 2004, a search update was conducted in all the databases. A Reference Manager database was created to remove duplicates and control these references. Search results were exported into an Excel spreadsheet to facilitate screening (Appendix 1 and Appendix 2).

4.1.2 Selection criteria and method

The following criteria were met before a study was considered for review:

- the study had to be a RCT that compared the efficacy of transdermal HRT patches with that of oral HRT, or the efficacy of transdermal HRT patches with that of placebo patches
- the study included women seeking treatment for postmenopausal symptoms
- in the study, an estradiol-estrone dosage of 0.05 mg daily was used for patches, 0.625 mg daily for oral HRT, and progesterone may or may not have been part of the formulation
- the clinical outcome measures included postmenopausal symptom reduction, bleeding patterns, or both
- the outcomes were followed-up three or six months after therapy commencement.

Two reviewers (SC, DAC) independently screened potentially relevant papers to select those that met the inclusion criteria.

4.1.3 Data extraction strategy

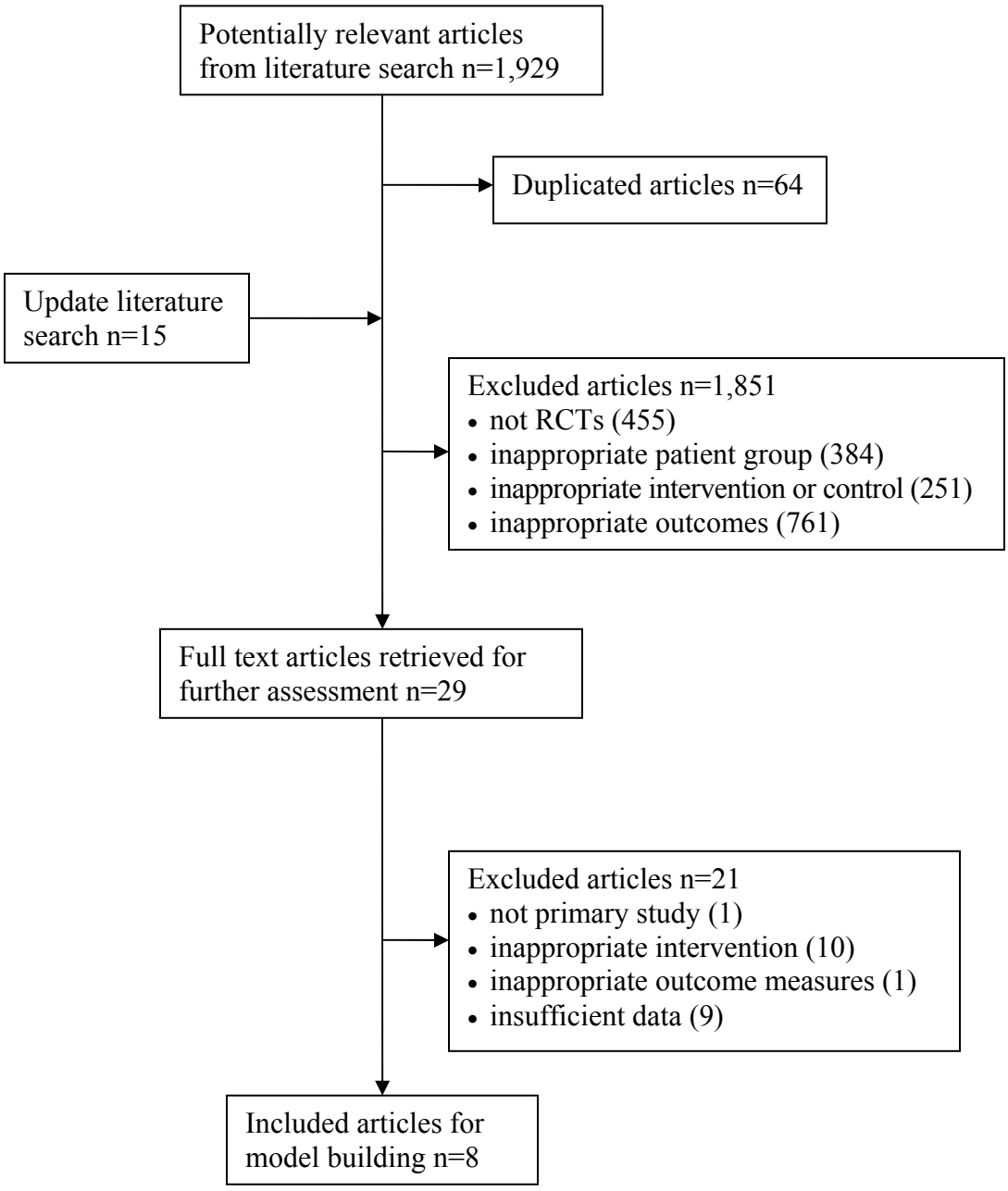
Two reviewers (SC, DAC) independently extracted the relevant data. Disagreements regarding inclusion criteria were resolved by consensus.

4.2 Results

4.2.1 Quantity of research available

A total of eight studies[38-45] reporting nine unique RCTs met the inclusion criteria. Their data were used for the economic model building. (The Gordon *et al.*[39] paper reported on two RCTs: one with placebo as the comparator and the other with oral HRT as the comparator. The Sendag *et al.*[45] study was used for input to the model on bleeding patterns). The document selection procedure is shown in Figure 3.

Figure 3: Potentially relevant clinical studies



4.2.2 Summary of clinical inputs to economic model

Tables 3 and 4 summarize the clinical data that were used in the economic model. A description of included studies can be found in Appendix 3 and Appendix 4. The data in Tables 3 and 4 are on a treatment received basis, as they are inputs to the economic model. Compliance in clinical trials is typically higher than that in daily use. For this economic model, modelling actual compliance is more appropriate than modelling compliance from clinical trials. The data in Appendix 3 and Appendix 4 are on an intention to treat basis.

Table 3: Clinical evidence of transdermal HRT patches versus placebo in postmenopausal women

Study		**Mean Number of Hot Flashes per Day (SE)**	
		Transdermal HRT Patches	**Placebo**
Gordon *et al.*[39]	Baseline	6.6 (0.9)	7.4 (0.6) NS
	12 weeks	2.2 (0.6)	6.6 (0.4) SS
	n	53	50
		SS	NS
Rovati *et al.*[41]	Baseline	9.1 (0.4)	9.1 (0.4) NS
	12 weeks	0.6 (0.4)	4.1 (0.4) SS
	n	77	80
		SS	SS
von Holst *et al.*[42]	Baseline	7.1 (0.7)	5.7 (0.3) SS
	12 weeks	1.5 (0.2)	3.1 (0.3) SS
	n	74	78
		SS	SS
Bacchi-Modena *et al.*[43]	Baseline	10.7 (0.7)	11.1 (0.9) NS
	12 weeks	2.5 (0.6)	7.1 (0.6) SS
	n	56	53
		SS	SS
Notelovitz *et al.*[44]	Baseline	11.5 (0.8)	11.6 (0.6) NS
	12 weeks	2.4 (0.6)	6.3 (0.6) SS
	n	53	59
		SS	SS

n=number of patients in treatment arm; SE=standard error; SS=statistically significant at 95% level; NS=non-significant at 95% level. NS and SS differences are indicated for transdermal HRT relative to placebo patches on the right hand side, and for baseline relative to 12 weeks in the corresponding row.

Results of the comparisons between the transdermal HRT and placebo patches show that the patch significantly relieves the number and intensity of hot flashes when compared with placebo at three months after the start of therapy. Higher doses of estradiol in the patches result in better outcomes. In one study, patients in the patch group report a higher incidence of spotting (Table 3).[43]

The results of comparisons between patches and oral HRT did not show a significant difference in the reduction of postmenopausal symptoms and bleeding patterns at three months or six months after the start of therapy (Table 4).

For inputs to the economic model on bleeding patterns refer to Appendix 4 and the data from the Sendag *et al.*[45] study. Excluded studies and the reasons for their exclusion are listed in Appendix 5.

Table 4: Clinical evidence of oral HRT versus transdermal HRT patches in postmenopausal women

Study		Mean Number of Hot Flashes per Day (SE)	
		Oral HRT	**Transdermal HRT Patches**
Studd *et al.*[38]	Baseline	6.7 (0.3)	7.1 (0.5) NS
	12 weeks	0.5 (0.2)	0.9 (0.2) NS
	n	90	90
		SS	SS
Gordon *et al.*[39]	Baseline	7.6 (0.5)	7.6 (0.5) NS
	12 weeks	2.4 (0.4)	3.0 (0.4) NS
	n	120	114
		SS	SS
Sajtos *et al.*[40]	Baseline	6.0 (0.4)	6.0 (0.4) NS
	12 weeks	1.0 (0.2)	1.0 (0.2) NS
	n	83	83
		SS	SS

n=number of patients in treatment arm; SE=standard error; SS=statistically significant at 95% level; NS=non-significant at 95% level. NS and SS differences are indicated for oral HRT relative to transdermal patches on the right, and for baseline relative to 12 weeks in the corresponding row.

5 ECONOMIC ANALYSIS

5.1 Methods

5.1.1 Analytical approach

a) Decision model

The decision analytic model allows for the assessment of costs and quality adjusted life-years (QALYs) for a 50-year-old woman under alternative courses of management for postmenopausal symptoms. The analysis is stratified by the severity of baseline postmenopausal symptoms. Separate analyses are conducted for women with severe symptoms and for women with moderate symptoms.

The decision analysis adopts a framework assessing the cost-effectiveness of HRT,[46] with more detailed modelling of the impact of vaginal bleeding and postmenopausal symptoms. The framework is that of a Markov process, with a Markov cycle length of three months. The model assumes a maximum time horizon of five years with the sensitivity analysis of two years.

The Markov states in the model are related to the presence or absence of vaginal bleeding and postmenopausal symptoms, which are directly related to compliance with therapy. The effect of therapy on hip fracture is not analyzed, as previous work suggests that it has a negligible impact on the cost-effectiveness of HRT treatment for postmenopausal symptoms.[46]

The decision analytic model consists of four submodels: compliance, bleeding, postmenopausal symptoms, and mortality (Figure 4). The whole population, including non-compliant patients, is followed for five years. For the economic analysis, a cost and utility value (which values the clinical outcome in terms of QALYs) is assigned to each node on the decision tree.

For vaginal bleeding, there are two potential states – no bleeding or bleeding. Given that the modelling of bleeding is based on anticipated time to amenorrhea, transition probabilities are such that women can progress from the presence of bleeding to either bleeding or no bleeding. Transition probabilities are a function of treatment.

For postmenopausal symptoms, three potential states have been defined based on severity: severe postmenopausal symptoms, moderate postmenopausal symptoms, and mild or no symptoms. In the model, women progress to symptom states at the end of each cycle, and transition probabilities are a function of treatment.

b) Monte Carlo simulation

The expected outcomes of interest values are derived through Monte Carlo simulation using the Crystal Ball™ software. In a Monte Carlo simulation, different estimates of outcomes such as costs and life expectancies can be obtained by re-running a decision model using different values for each data input.[47] Values for each data input are randomly selected from specified probability distributions. Based on several such replications, a set of outcomes is obtained. No rule is used to determine the appropriate number of replications, as this is a function of the level of uncertainty around the outcomes of interest. The greater the number of replications conducted, the more precise the estimate of the outcomes. For this analysis, we conducted a simulation of 5,000 replications.

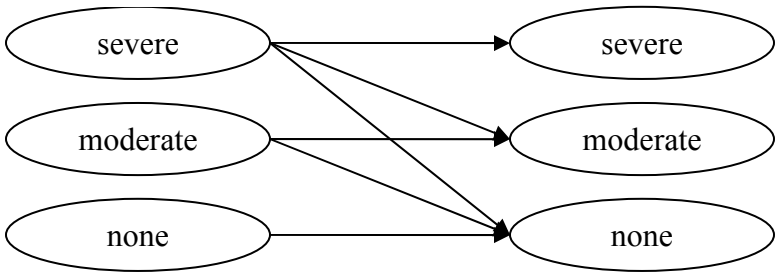
The analysis presents the expected values and 95% credible intervals (CIs) of costs and QALYs for all relevant comparisons. CIs, which are similar to confidence intervals, present the lower and upper limits of a 95% interval for outcomes in an economic model. In addition, the probability of the HRT patch being cost-effective is depicted through cost-effectiveness acceptability curves.[48]

c) Sensitivity analysis

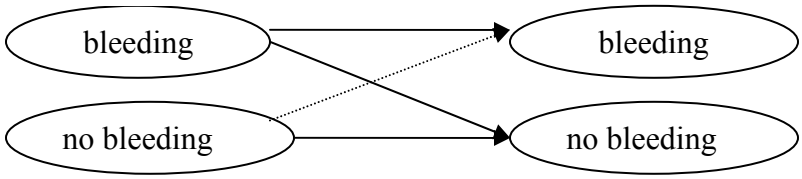
Probabilistic analysis through Monte Carlo simulation provides the most complete and theoretically sound method for determining the impact of uncertainty for input parameters on outcomes. Additional simple sensitivity analyses are conducted to assess the impact of specific assumptions on outcomes.

Figure 4: Design of Markov model by submodel

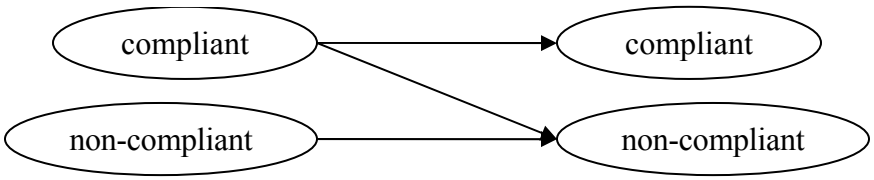
Menopausal Symptoms



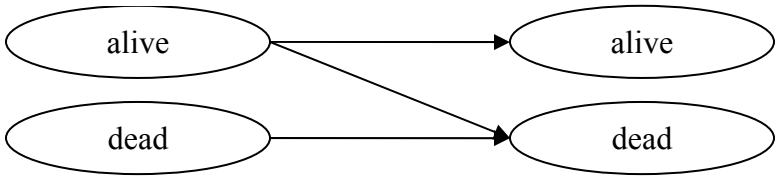
Vaginal Bleeding



Compliance



Mortality



Specific sensitivity analyses were conducted related to:

- discount rate (0% and 3%, rather than 5%)
- choice of functional form for distribution of postmenopausal symptoms (Poisson or gamma)
- shorter compliance (two years rather than five years)
- an extreme assumption of full compliance with transdermal HRT patches for the whole period.

d) Comparators

Oral HRT products and transdermal HRT patch products from different manufacturers are compared as a group instead of being compared individually. It is necessary to compare oral HRT and patches as two groups, because there are insufficient data for individual comparisons of the products available on the Canadian market. Also, the oral products are homogeneous in that they contain the same daily dosage of estradiol. This is also true for the transdermal patch products. Similarly, oral preparations (whether predominantly estrone or estradiol) are mostly absorbed as estrone.

The economic analysis assesses the cost-effectiveness of the use of transdermal hormone replacement (e.g., Climara® released estradiol 50 μg or 100 μg daily, Menorest® released estradiol 50 μg daily) as a first-line therapy compared with oral HRT (Premarin released estradiol 0.625 mg daily) and as a second line therapy (e.g., Estraderm MX 50 released estradiol 50 μg daily, Vivelle released estradiol 50 μg daily, Dermestril® released estradiol 25 or 50 μg daily; and Fem®7 Combi) compared with no additional therapy. The transdermal HRT patch products in the included studies are all estrogen-only patches, except Fem®7 Combi, which consists of a seven-day estradiol patch (released estradiol 50 μg daily) and a seven-day estradiol or levonorgestrel patch (released estradiol or levonorgestrel 50 μg or 10 μg daily).

e) Discounting

For the base case analysis, costs and benefits are discounted at 5% annually. The sensitivity analysis is conducted with discounting at 0% and 3%.

f) Study perspective

Ideally, studies should be conducted from the perspective of society, with secondary considerations detailing analysis from a variety of perspectives. Because of data constraints, the primary perspective of this study is that from a third-party payer.

5.1.2 Data sources

a) Transition probabilities

Transition probabilities relating to the control of postmenopausal symptoms and vaginal bleeding are derived from placebo controlled trials of the HRT patch and controlled trials comparing the patch with oral HRT. Transition probabilities relating to compliance with therapy are derived probabilities (Table 5).

Uncertainty about transition probabilities are characterized by beta or Dirichlet distributions. Beta distributions can be derived from sample data and are appropriate when a patient can transition to one of two states.[49] In such an instance, the probability of transitioning to state A can be represented by a beta distribution characterized by two parameters: alpha (the number of cases in a sample who moved to state A) and beta (the number of cases in the sample who did not move to state A).

Dirichlet distributions are appropriate when a patient can transition to more than two states and can be similarly derived from sample data.[49] A Dirichlet distribution is the multinomial equivalent of the beta distribution. A Dirichlet distribution is characterized by a number of parameters (α_i) equivalent to the number of potential states. When there are three potential states

(A, B, and C) for transition, the Dirichlet distribution will be depicted as Dirichlet ($\alpha_A, \alpha_B, \alpha_C$). Each parameter represents the number of individuals in the sample data who progress to a particular state. The probability of transitioning to state A is the number of individuals in the sample who move to state A (α_A) divided by the total number of samples ($\alpha_A+\alpha_B+\alpha_C$).

Moderate symptoms are assumed to be characterized by three to 9 hot flashes daily. Severe symptoms are characterized as $\geq$10 hot flashes daily. The analysis includes all studies for which it is possible to derive the mean and variance of the number of daily hot flashes at study baseline, and as close to three cycles (12 weeks or three months) as possible.

Uncertainty about postmenopausal symptoms is assumed to form a gamma distribution and it is assumed that all participants in the RCTs had at least moderate symptoms at the onset of the study. For the sensitivity analysis, distributions are assumed to take the form of a Poisson distribution. From this, it is possible to derive the number of women in each grade of symptom severity at baseline and 12 weeks, and to subsequently derive the appropriate transition probabilities between grades.

The probability that a woman will experience vaginal bleeding on therapy is based on cumulative amenorrhea rates at three months for the one comparative study that reported such data.[45] Given that the rates are almost identical for both therapies, it is assumed that there are no differences between therapies for vaginal bleeding. Patients not taking therapy have no bleeding.

The age-specific probability of death from all causes is derived from the most recent Canadian source.[50] Probabilities of death by age group are assumed to be fixed for a given age, because they are derived from population data, although the probability of death increases with age.

Compliance is defined as the proportion of patients who are taking medication after six months. For this study, a compliance rate at one year of 60.8%[51] is adopted and converted into a constant rate for each three-month cycle (88.3%). Uncertainty about this value is characterized by a beta distribution [beta (124, 80)]. Maximum compliance with therapy is assumed to be five years with the sensitivity analysis assuming two years. At three years, the rate of compliance, based on these assumptions, is 26%.

b) Health outcomes

The health outcomes used in the economic model are identified in the clinical search (Tables 3 and 4, Appendix 4, Sendaz *et al.,* bleeding patterns).

c) Costs

The design of the study requires that cost estimates be provided for therapy, vaginal bleeding, and postmenopausal symptoms (Tables 5, 6, 7; Appendix 4). In this report, all costs have been adjusted to Canadian funds (C$) in 2004. For the probabilistic analysis, the costs of therapies are assumed to be fixed. Uncertainties about other costs are assumed to be characterized by normal distributions with a standard error of the mean equivalent to 50% of the expected value. Although there are problems with assuming a normal distribution for both costs and utilities, the choice of distribution has no impact on the estimates of expected values and other distributions have their problems.

Therapy
The cost of oral HRT is based on the sum of the cost of conjugated equine estrogen (CEE) and medroxyprogesterone acetate (MPA). It is derived using the drug benefit price from the Ontario Drug Benefit Plan.[36] Costs for the three-month cycle are $46.05 ($0.38 daily, plus mark up and dispensing fee).

Costs for the three-month cycle of a transdermal HRT patch regimen are estimated to be $83.95, based on $2.44 per patch twice a week, plus $0.07 progestin daily mark up and dispensing fee. Costs are obtained from the same source as that for oral HRT.

For oral and patch HRT, dosage and costs are the same, regardless of the severity of symptoms. Prescription renewals are assumed to be identical.

Vaginal bleeding
There is little information on the costs associated with the treatment of continued bleeding due to HRT. Based on a previous analysis, we assume that treatment for bleeding would involve a one-time cost at six months of $149, which would be for a pelvic examination and a vaginal ultrasound. We assume that 10% of women who continued bleeding at six months would require this treatment.[46] A proportion of women may also undergo an endometrial biopsy, but costs for this procedure are not examined.

Postmenopausal symptoms
There is little information on the additional costs (other than HRT) associated with the treatment of women with severe postmenopausal symptoms. For this analysis, we assume a three-month cost of $25 based on the cost of clonidine. Other more costly alternatives are available for the relief of symptoms, but for this analysis, a conservative assumption is made. There are no additional costs assumed to be associated with the treatment of moderate postmenopausal symptoms.

d) Utilities
Given the design of the decision tree, utility values are required for the following health states: mild or no postmenopausal symptoms, severe postmenopausal symptoms, moderate postmenopausal symptoms, and vaginal bleeding (Table 5). Utility values are estimated, with patients' utilities changing as they move from state to state. For combination states, the base case analysis adopts a multiplicative model similar to that adopted in the estimation of utility values for the Health Utilities Index (HUI).[52]

Vaginal bleeding
Utility weights relating to vaginal bleeding are estimated for health states by direct elicitation from a subsample of osteoporotic patients participating in an ongoing study at the Ottawa Hospital.[53] Each respondent rated descriptive health states that correspond to a selection of the health states detailed here. Health states are rated through the use of the visual analogue scale and of the standard gambles. Utilities are calculated based on the standard gamble exercise.

Postmenopausal symptoms
For postmenopausal symptoms, utility values are based on the detailed study by Daly *et al*.[54] The utility values chosen for this analysis were those of the whole study sample (n=63), derived through the use of the time trade-off.

Table 5: Input parameters

Parameter		Expected Value	Probability Distribution*
Costs	Transdermal HRT patch	83.95	Fixed
	Oral HRT	46.05	Fixed
	Bleeding	14.9	Normal (14, 90, 7.45)
	Additional treatment of severe postmenopausal symptoms	25	Normal (25, 12.5)
Utilities	Severe postmenopausal symptoms	0.64	Normal (0.64, 0.04)
	Mild postmenopausal symptoms	0.85	Normal (0.85, 0.03)
	Bleeding	0.99	Normal (0.99, 0.02)
	Nothing	1	Fixed
Transition probabilities for postmenopausal symptoms: transdermal patches versus oral HRT			
	Severe-severe (patch)	0.179	Dirichlet (10, 34, 12)
	Severe-moderate (patch)	0.607	
	Severe-none (patch)	0.214	
	Moderate-moderate (patch)	0.059	Beta (14, 223)
	Severe-severe (oral)	0.189	Dirichlet (10, 32, 11)
	Severe-moderate (oral)	0.604	
	Severe-none (oral)	0.208	
	Moderate-moderate (oral)	0.008	Beta (2, 245)
Transition probabilities for postmenopausal symptoms: transdermal HRT patch versus no treatment			
	Severe-severe (patch)	0.118	Dirichlet (12, 41, 49)
	Severe-moderate (patch)	0.402	
	Severe-none (patch)	0.480	
	Moderate-moderate (patch)	0.019	Beta (4, 212)
	Severe-severe (no treatment)	0.339	Dirichlet (37, 65, 1)
	Severe-moderate (no treatment)	0.631	
	Severe-none (no treatment)	0.010	
	Moderate-moderate (no treatment)	0.407	Beta (74, 108)
Probability of no vaginal bleeding at 6 months		0.62	Beta (75, 46)
Probability of compliance at 1 year		0.608	Beta (124, 80)
Probability of death (age specific all cause)		0.0007 to 0.0011	Fixed

*Normal distributions are characterized by means and standard errors of the mean. Beta distributors are characterized by number of events and number of non-events. Gamma distributors are characterized by their shape and scale. Dirichlet distributions are characterized by the number of each type of event.

5.1.3 Subgroup analysis

Separate analyses were conducted for women with severe symptoms and for women with moderate symptoms.

5.1.4 Key assumptions

- Placebo treatment in the RCTs is used as a proxy for the "no treatment" option in the economic model.
- Moderate symptoms are characterized by three to 9 hot flashes daily. Severe symptoms are characterized by ≥10 hot flashes daily.
- All participants in the RCTs had at least moderate symptoms at the onset of the study.
- Vaginal bleeding rates for oral and patch HRT are the same, and patients not taking therapy have no bleeding.
- There has been a trend towards the increased use of pharmaceutical alternatives for estrogens and progestogens.[29,55] Women may use treatments other than HRT for postmenopausal symptoms, for example, antidepressants and antiseizure or migraine treatments, or alternative medicine for example, Remifemin (black cohosh), and soy or isoflavones. We assume the equivalent use of these co-interventions for the three comparator groups (oral HRT, transdermal HRT patches, and no HRT treatment).

5.2 Results

5.2.1 Transdermal HRT patch versus oral HRT

The comparison of the transdermal patch versus oral HRT found little difference in the estimated QALYs between treatments for women with moderate or severe postmenopausal symptoms (Table 6). For women with severe symptoms, the expected value for QALYs is 4.41 for both therapies, 95% CI (4.39; 4.44). For moderate symptoms, the expected value for QALYs is 4.49 for both therapies, with the same 95% CI (4.47; 4.51).

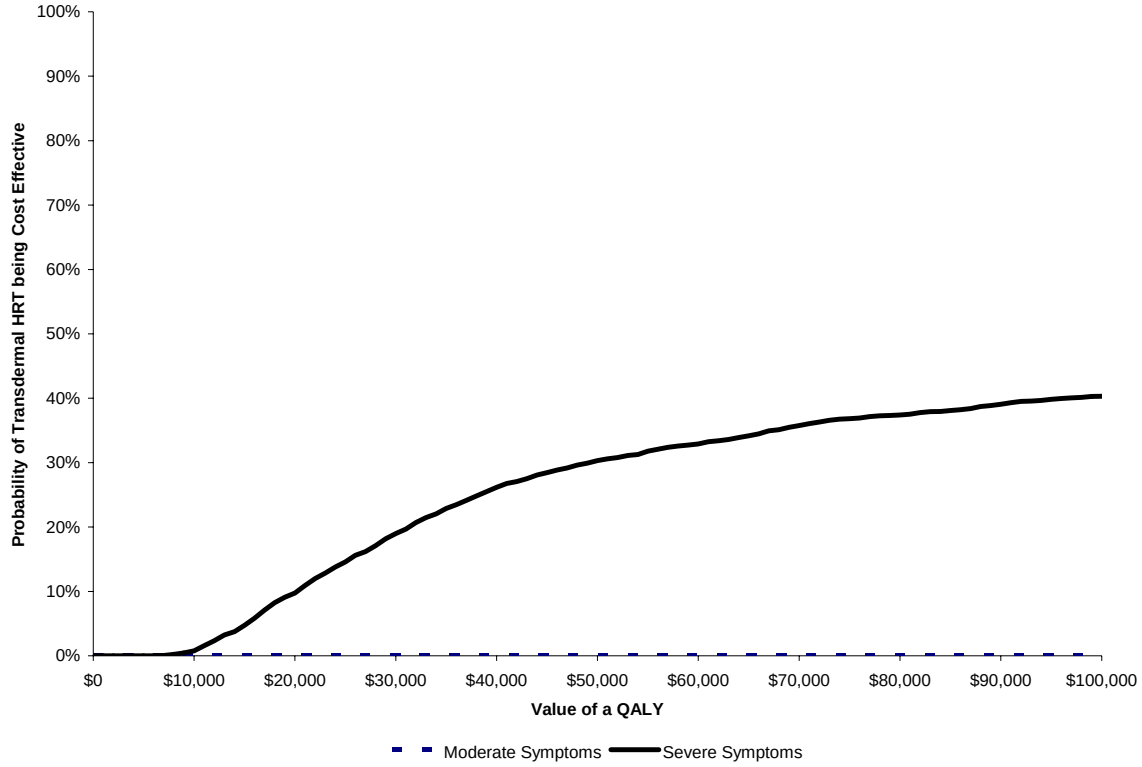
Table 6: Cost-effectiveness results

Transdermal HRT Patch versus Oral HRT			
	Patch HRT (CI)	**Oral HRT (CI)**	**Difference (CI)**
Moderate Symptoms			
Costs	$665 (578; 758)	$369 (319; 418)	$296 (259; 340)
QALYs	4.49 (4.47; 4.51)	4.49 (4.47; 4.51)	0.00 (0.00; 0.00)
Incremental cost per QALY			Dominated*
Severe Symptoms			
Costs	$682 (594; 777)	$385 (334; 441)	$297 (257; 339)
QALYs	4.41 (4.39; 4.44)	4.41 (4.39; 4.44)	0.00 (-0.02; 0.02)
Incremental cost per QALY			Dominated*

*The effectiveness of oral and patch HRT was equal up to four decimal places, but patch HRT has a higher cost. Because of the inherent Monte Carlo error in the analysis, results are presented to two decimal places.

For women with moderate symptoms and women with severe symptoms, the transdermal HRT patch is as effective as oral HRT, but at a higher cost. The cost-effectiveness acceptability curve in Figures 5 and 6 report the probability that treatment is cost-effective as a function of willingness to pay, given the available data.[48] At a QALY of $50,000, the probability that the HRT patch is cost-effective is 30% for women with severe symptoms and 0% for women with moderate symptoms (Figure 5).

Figure 5: Cost-effectiveness acceptability curve for comparison of transdermal HRT patch with oral HRT



5.2.2 Transdermal HRT patch versus no treatment

The comparison of transdermal HRT patches versus no treatment found an increase in QALYs with therapy, and an increase in costs for the treatment of women with moderate or severe postmenopausal symptoms (Table 7).

The QALYs gained from transdermal HRT patches are 0.08 (95% CI: 0.05; 0.11) for women with severe symptoms and 0.02 (95% CI: 0.00; 0.04) for women with moderate symptoms. The incremental costs are $654 (95% CI: 556; 749) for women with severe symptoms and $665 (95% CI: 578; 758) for women with moderate symptoms.

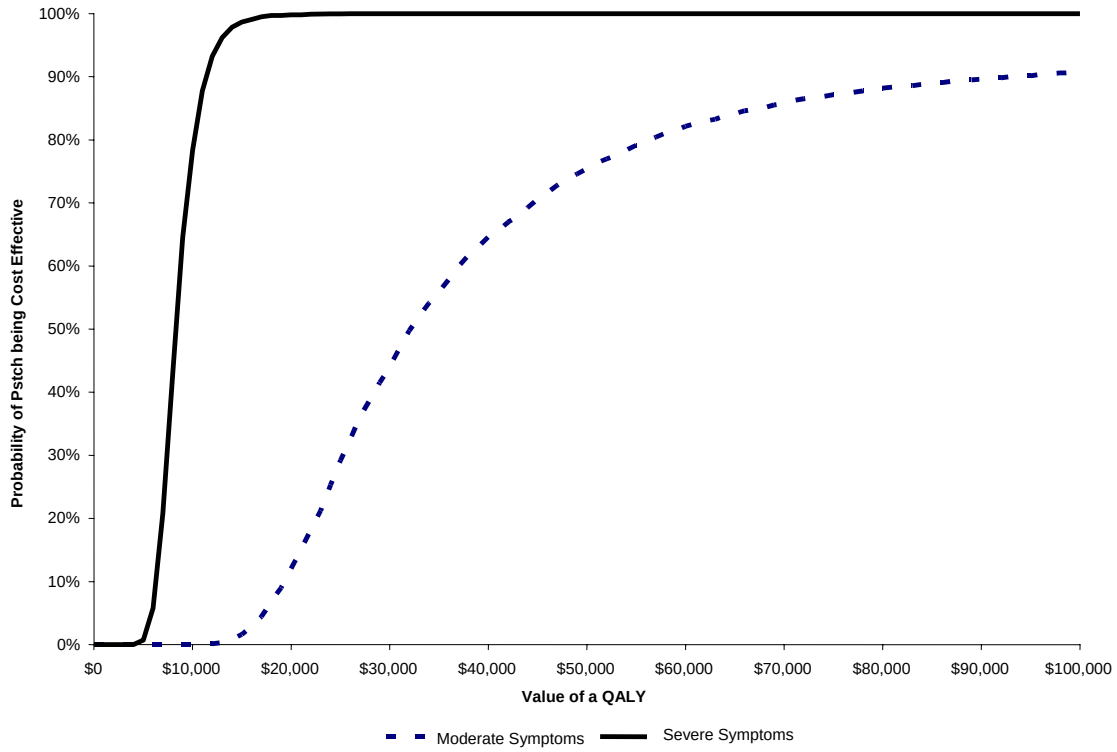
The incremental cost per QALY associated with transdermal HRT patches compared with no treatment is $8,300 for women with severe symptoms and $32,300 for women with moderate symptoms.

Table 7: Cost-effectiveness results

Transdermal HRT Patch versus No Treatment			
	Patch HRT (CI)	**No Treatment (CI)**	**Difference (CI)**
Moderate Symptoms			
Costs	$665 (578; 758)	$0 (0; 0)	$665 (578; 758)
QALYs	4.49 (4.47; 4.51)	4.47 (4.45; 4.48)	0.02 (0.00; 0.04)
Incremental cost per QALY			$32,300
Severe Symptoms			
Costs	$680 (593; 774)	$26 (0; 54)	$654 (556; 749)
QALYs	4.43 (4.41; 4.45)	4.35 (4.32; 4.39)	0.08 (0.05; 0.11)
Incremental cost per QALY			$8,300

At a QALY of $50,000, the probability that the HRT patch is cost-effective is 100% for women with severe symptoms and 75% for women with moderate symptoms (Figure 6).

Figure 6: Cost-effectiveness acceptability curves for comparison of transdermal HRT patch with no treatment



5.2.3 Sensitivity analysis

A simple sensitivity analysis failed to identify scenarios under which the base results altered significantly (Table 8). Assuming full compliance with transdermal HRT patches leads to higher incremental ratios than in the base case, when compared with no treatment, as it is assumed that a large number of women are continuing therapy after the benefit is obtained, leading to a higher cost with minimal improvements in benefits. Full compliance is not assumed to be optimal. Some fall-off is expected if treatment is ineffective for particular patients.

Smaller discount rates lead to higher incremental cost-effectiveness ratios as the gains from HRT are realized more in the short term, relative to the costs for compliant patients, which are incurred more in the longer term if treatment continues.

The sensitivity analysis on alternative distributional forms for the number of postmenopausal symptoms lead to lower ratios, but the impact is minimal, suggesting that the choice of form has little impact.

Table 8: Results of sensitivity analysis

	Moderate Symptoms		**Severe Symptoms**	
	Patch HRT versus Oral HRT*	**Patch HRT versus No Treatment**	**Patch HRT versus Oral HRT***	**Patch HRT versus No Treatment**
Base case	Dominated	$32,300	Dominated	$8,300
Discount rate 3%	Dominated	$33,000	Dominated	$8,500
Discount rate 0%	Dominated	$34,000	Dominated	$8,700
Treatment for 2 years	Dominated	$32,300	Dominated	$8,300
Poisson distribution	Dominated	$32,300	Dominated	$11,500
Full compliance with transdermal patch	Dominated	$76,500	Dominated	$19,300

*Under all scenarios, transdermal patch and oral HRT are equally effective up to two decimal places.

6 DISCUSSION

In this report, the cost-effectiveness of transdermal HRT patches is compared with that of oral HRT and that of no treatment. The report focuses on an economic evaluation. Although the clinical literature was reviewed to obtain input for the economic model, a formal systematic review of the clinical evidence was not done for this project. The clinical review found similar outcomes and adverse events for oral HRT and transdermal HRT patches. These results are supported by a review of clinical evidence by Nelson,[13] which compares oral conjugated equine estrogen with transdermal 17B-estradiol. The Nelson study concludes that the oral and transdermal formulations have consistent and comparable effects on menopausal hot flashes and may have similar short-term adverse effects.[13]

Another systematic review examines the effects of oral estrogen replacement therapy on hot flashes and night sweats.[24] This study by MacLennan *et al.* examines double-blind, randomized, placebo-controlled trials of oral HRT for ≥3 months and reports vasomotor outcomes. It concludes that oral HRT is effective in alleviating hot flashes and night sweats.

In our economic evaluation, separate analyses were performed for women with moderate symptoms (three to nine hot flashes daily) and with severe symptoms (≥10 hot flashes daily). We found that transdermal HRT patches are cost-effective relative to no treatment for patients with severe symptoms. For patients with moderate symptoms, the results also fall in the range of what is generally considered to be cost-effective.[56] Relative to oral HRT, the transdermal patch was not found to be cost-effective, as the outcomes are similar, but the cost is higher.

Significant ethical, legal, and psychosocial issues related to the use of transdermal hormone replacement therapy for postmenopausal symptoms were not found in the preparation of this report.

However, the clinical use of estrogens and progestogens in women through and beyond menopause has been a source of ongoing debate and confusion since the publication of studies such as the Women's Health Initiative (WHI) trial.[7] The use of HRT for the treatment of specific menopause-related symptoms should be distinguished from their use in the prevention of conditions like osteoporosis and cardiovascular disease. There is a difference between perimenopausal initiation for symptom relief and initiation of HRT several years beyond menopause for non-symptom-related reasons.[29] As a result, the objectives, the average age of patients, and the duration of treatment in the WHI study differ from those examined in our report.

In 2002, the initial results of the WHI's RCT were released.[7] The purpose of the trial was to determine whether HRT was effective for the prevention of cardiovascular diseases. In the WHI study, HRT used by postmenopausal women is associated with increases in coronary heart disease, stroke and pulmonary embolism, and breast cancer, in an average treatment period of 5.2 years. Our report looks at the short-term use of HRT (typically two to three years) for the treatment of symptoms appearing at the time of the menopausal transition. Patients are older (by about 10 years) in the WHI study than the patients considered in this report. The WHI study has been the subject of critique and controversy.[8-10] Recommendations for postmenopausal hormone therapy have changed since the WHI study suggested that estrogen may be harmful when used in long-term disease prevention of conditions such as cardiovascular disease and osteoporosis. For the short-term treatment of postmenopausal symptoms (e.g., hot flashes), HRT remains an approved indication for use. Current recommendations restrict the use of HRT to symptomatic women.[3,11-13] There also seems to be a trend towards using lower HRT doses for the shortest duration possible.[13,28,29,57-59]

An economic model must make simplifying assumptions to manage data and limitations. Postmenopausal symptoms cause discomfort for many women. This model cannot address all factors and issues that must go into decision making. Rather, it is one input into the decision making process. The results of our economic analysis should be interpreted in this context.

In our analysis, hot flashes are used as a proxy measure for the presence and severity of postmenopausal symptoms. Including other considerations in the economic model can affect the results. Research in this area often uses hot flashes as a proxy measure for overall symptom severity, and this symptom is the one most commonly reported in the included studies. Bleeding is also analyzed in this report. Other symptoms, such as fatigue, night sweats, mood changes, insomnia, myalgias or arthralgias; and sexual dysfunction, were not evaluated in the model because of the lack of available data. These and other considerations may influence clinicians in choosing to prescribe either transdermal patches or oral HRT in a particular case. For example:

- smoking: nicotine may decrease the effective circulating estrogen levels derived from oral therapy[60]
- lipid profile: oral estrogens may increase HDL but also increase triglycerides and C reactive protein; transdermal estrogens do not appear to have these effects[61,62]
- oral estrogens may increase insulin resistance, transdermals do not appear to do so[63,64]
- blood pressure: occasionally, there is an idiosyncratic elevation of blood pressure with oral HRT, notably with conjugated equine estrogen (CEE) or ethinyl estradiol; if this occurs, use of a transdermal estrogen may be indicated[65]
- coagulation: transdermal HRT may be preferred in patients who are at increased risk for thromboses, as it may be less likely to cause deep vein thrombosis, pulmonary embolism, and clots; by bypassing the liver, it does not stimulate the production of clotting factors in the liver[66]
- sexuality: in patients who are on oral HRT and who are complaining of decreased libido, it may be useful to switch from an oral to a transdermal patch preparation[31,67-70]
- gastrointestinal problems: patients who have nausea or gut problems associated with oral HRT may more easily tolerate transdermal HRT patches.[71]

An extensive sensitivity analysis was carried out for this report. In general, the base results are not altered significantly by the simple or the probabilistic sensitivity analyses. As with all modeling studies, there are limitations associated with the analysis.

- A detailed sensitivity analysis was conducted relating to input parameter values. Results may also be sensitive to the assumptions relating to model structure (e.g., choice of health states, cycle length).
- For this report, studies were systematically screened based on pre-defined inclusion criteria and clinical data were extracted for use in the economic model. As the focus of this report is to evaluate the cost-effectiveness of transdermal HRT patches relative to no treatment and to oral treatments, timeliness was a consideration in not conducting a new formal systematic review of clinical evidence. The fact that clinical reviews in this area have been conducted was also considered.
- It would have been ideal to look at the cost-effectiveness of transdermal HRT patches used by patients who are suffering adverse effects due to oral HRT, but there is insufficient detail in the included studies to do this analysis.
- Oral HRT needs to be taken daily, while transdermal patches can be replaced once or twice a week. Some women find transdermal patches to be more convenient and may prefer them to oral HRT. Additional benefit from patches due to increased convenience is not considered in the model.

- There is no reason to assume that the cost of physician visits would be different between oral HRT and transdermal patches in the clinical trials. For daily medical treatment, HRT users would probably have a higher cost than the non-users, as HRT is not routinely prescribed without a doctor visit. No known data address this point and it was excluded in the possible cost difference of the model.
- A reviewer noted that nausea and vomiting from the adverse effects of estrogen treatment on the intestines and liver may be lower for transdermal patches than for oral HRT. Nausea and vomiting are not analyzed in the economic model, possibly favouring the oral HRT comparator relative to patches.
- Hot flashes are commonly used as the proxy for symptom severity in studies examining the effectiveness of HRT for postmenopausal symptoms. In our model, hot flashes and bleeds have been used as a proxy for total symptom severity. Useful data for other postmenopausal symptoms, such as fatigue, night sweats, mood changes, insomnia, myalgias or arthralgias, anxiety, and sexual dysfunction could not be identified for inclusion in the model.
- A proportion of women may undergo an endometrial biopsy, but this is not considered in this report.
- Co-interventions are assumed to be the same for the three comparator groups.
- There may be a trend to lower HRT doses to a greater degree than the values represented in our model.

7 CONCLUSIONS

Eight studies reporting nine RCTs meet the inclusion criteria for the clinical search, and their data are used as inputs to the economic model. The review of clinical evidence (the included studies and other reviews) suggests that oral HRT for postmenopausal symptoms is effective relative to no HRT treatment, and that oral HRT and transdermal patches are similar in effectiveness and short-term adverse effects.

For women with moderate or severe symptoms, transdermal HRT patches are as effective, but more costly, relative to oral HRT for the short-term treatment of postmenopausal symptoms. Relative to no treatment, transdermal HRT patches have an incremental cost per QALY of $32,300 for patients with moderate symptoms. Relative to no treatment, the cost per QALY gained for transdermal HRT patches is $8,300 for the severe symptom group.

In the economic analysis it was found that transdermal HRT patches are not cost-effective relative to oral HRT for the groups with moderate and severe symptoms. Sensitivity analysis failed to identify any scenarios under which the base results altered significantly. These results are derived from a model that uses hot flashes and bleeding as proxy measures for symptom severity. The results may favour oral HRT, in that factors potentially supportive of HRT patches are not considered in the model (e.g., convenience, smoking, lipid profile, insulin resistance, and blood pressure).

Relative to no treatment, transdermal HRT patches are cost-effective for severe and moderate symptoms. This suggests that HRT patches may be an appropriate treatment option for patients who do not tolerate oral HRT well, especially for those patients with severe postmenopausal symptoms.

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APPENDIX 1: Clinical Search Strategies

Guide to Search Syntax (DIALOG®, Cochrane Library)

! Explode the search term. Retrieve the search concept plus all narrower terms.
? Truncation symbol, single character. Retrieve plural and variant ending of search terms.
* Truncation symbol, any number of characters.
" " Search phrases.
(w) Proximity operator. Words must be adjacent.
() Proximity operator. Words must be adjacent.
(n) Proximity operator. Words must be near each other in any order.
ab Search in article abstract.
de Descriptor i.e., subject heading (a controlled, thesaurus term)
ME Medical subject heading
RN Registry number (i.e., CAS)
ti Search in titles
tw Text word
id Identifier
AD Drug administration (EMBASE); administration & dosage (MEDLINE)
EC Economics
PO Oral drug administration
TP Topical drug administration
TD Transdermal drug administration
L Link to sub-heading
TN Drug brand name

DATABASES	**LIMITS**	**SUBJECT HEADINGS/KEYWORDS**
DIALOG OneSearch® MEDLINE® EMBASE® BIOSIS Previews® PASCAL	Human	MEDLINE®: Hormone replacement therapy! (L)methods/de OR Estradiol (L) AD/de OR EMBASE®: hormone substitution! (L)AD/de OR Estradiol (L)PO AND Estradiol (L)TP, TD, AD OR (Conjugated estrogen/de OR conjugated estrogen plus medroxyprogesterone acetate/de) (L) AD OR BIOSIS®: ((hormonal replacement therapy OR hormone replacement therapy OR estrogen replacement

DATABASES	LIMITS	SUBJECT HEADINGS/KEYWORDS
		therapy OR hormone therapy)/de AND (drug delivery method/de OR drug delivery system/de OR drug administration/de)) OR (Estradiol/de AND (drug delivery method/de OR drug delivery system OR drug adminstration/de)) OR MEDLINE®, BIOSIS®, EMBASE®: RN=50-28-2 OR ALL DATABASES: (climara OR estradot OR oesclim OR oestradiol(1n)patch? OR estrogel OR estraderm OR vivelle)/ti,ab,id,tn OR (estracomb OR estracombi OR estalis OR estalis-sequi OR estragest OR estradiol(1n)levonorgestrel OR estradiol(1n)17(1n)beta OR oestradiol(1n)17(1n)beta OR premarin OR provera OR premarine)/ ti,ab,id,tn OR ((estrogen OR oestrogen OR hormone?) (1n) (therap? OR treatment? OR replacement?))/ ti,ab ***AND*** MEDLINE®: Administration, oral/de OR

DATABASES	LIMITS	SUBJECT HEADINGS/KEYWORDS
		EMBASE®: Oral Drug Administration/de OR ALL DATABASES: (drug?(1n)administration OR drug?(1n)deliver? OR method? OR oral OR cyclical OR pill OR pills OR tablet OR tablets OR capsule OR capsules OR placebo)/ti,ab AND MEDLINE®: (Administration, cutaneous OR administration, topical OR ointments OR gels)/de OR EMBASE®: (Transdermal drug administration OR topical drug administration OR drug comparison)/de OR ALL DATABASES: (gel OR gels OR ointments OR topical? OR salves OR cutaneous? OR transderm? OR trans-derm? OR patch OR patches OR percutaneous? OR transcutaneous?)/ ti,ab ***AND*** (comparison OR versus OR comparative OR alternat?)/ ti,ab OR (major clinical study OR multicenter study OR controlled study! OR randomized controlled trial OR evidence based medicine! OR drug comparison!)/de

DATABASES	LIMITS	SUBJECT HEADINGS/KEYWORDS
		OR MEDLINE®, BIOSIS®, EMBASE® comparative study/de OR ALL DATABASES: (random? OR sham? OR placebo? OR rct?)/ ti,ab OR ((single? OR doubl? OR tripl? OR trebl?) (1n) (blind? OR dumm? OR mask?))/ ti,ab OR ((control? () (study OR studies OR trial?))/ ti,ab OR ((multicent? OR multi()cent? OR multi-cent?) () (study OR studies OR trial?))/ti,ab OR (meta()analy? OR metaanaly? OR meta-analy? OR metanaly?)/ti,ab OR ((meta OR mega) (1n) regression?)/TI,AB OR (metaregression? OR megaregression?)/ ti,ab OR ((systematic? OR methodologic OR quantitative OR integrative OR collaborative) (1N) (review? OR overview? OR synthes?))/ ti,ab OR

DATABASES	LIMITS	SUBJECT HEADINGS/KEYWORDS
		((pool?()analy? OR data()synthes? OR data()extraction? OR data()abstraction)/ ti,ab OR ((handsearch? OR hand()search? OR mantel()haenszel OR peto OR der()simonian OR dersimonian OR fixed()effect? OR latin()square?))/ ti,ab OR ((drug OR drugs (3n) comparison?)/ ti,ab OR head()to()head/ ti,ab OR ((crossover OR cross-over OR cross()over) () (design? OR study OR studies OR trial?))/ ti,ab ***AND*** Human? OR people? OR person? *Search performed on 03 March 2004* *Clinical hits = 1691 records* *Search update was performed on 12 May 2004* *clinical hits = 11 records*
The Cochrane Collaboration & Update Software Ltd. The Cochrane Library, 2004 Issues 1 & 2	Human	HORMONE REPLACEMENT THERAPY exp tree1 (MeSH) OR ESTRADIOL single term (MeSH) OR (climara OR estradot OR oesclim OR (oestradiol next patch*) OR estrogel OR estraderm OR vivelle OR estracomb OR estracombi OR estalis OR estalis-sequi OR estragest OR oestradiol*) ***AND***

DATABASES	LIMITS	SUBJECT HEADINGS/KEYWORDS
		ADMINISTRATION, ORAL single term (MeSH) OR ((drug next administration) OR (drug next deliver*) OR oral OR cyclical pill OR pills OR tablet OR tablets OR capsule OR capsules OR placebo) ***AND*** ADMINISTRATION TOPICAL single term (MeSH) OR ADMINISTRATION CUTANEOUS single term (MeSH) OR OINTMENTS single term (MeSH) OR GELS single term (MeSH) OR (ointments OR gel OR ointment OR gels OR topical* OR salves OR cutaneous* OR transderm* OR trans-derm* OR patch OR patches OR percutaneous* OR transcutaneous*) *Performed 04 March 2004;Update performed on 12 May 2004* *The Cochrane Database of Systematic Reviews =18 complete reviews; 1 protocol; Database of Reviews of Effectiveness=4 references; The Cochrane Controlled Trials Register =609 references; 1abstract by INAHTA and other healthcare agencies* *Update = 1 reference from CENTRAL*
The National Library of Medicine PubMed Updates		MeSH headings and keywords to mirror DIALOG® MEDLINE search.
Websites of Health Technology Assessment (HTA) and related agencies; clinical trial registries; other databases		NICE; National Research Register; University of York NHS Centre for Reviews and Dissemination – CRD Databases; FDA, Health Canada

APPENDIX 2: Economic Search Strategies

Guide to Search Syntax (DIALOG®, Cochrane Library)

!	Explode the search term. Retrieve the search concept plus all narrower terms.
?	Truncation symbol, single character. Retrieve plural and variant ending of search terms.
*	Truncation symbol, any number of characters.
" "	Search phrases.
(w)	Proximity operator. Words must be adjacent.
()	Proximity operator. Words must be adjacent.
(n)	Proximity operator. Words must be near each other in any order.
ab	Search in article abstract.
de	Descriptor i.e., subject heading (a controlled, thesaurus term)
ME	Medical subject heading
RN	Registry number (i.e., CAS)
ti	Search in titles
tw	Text word
id	Identifier
AD	Drug administration (EMBASE); administration & dosage (MEDLINE)
EC	Economics
PO	Oral drug administration
TP	Topical drug administration
TD	Transdermal drug administration
L	Link to sub-heading
TN	Drug brand name

DATABASES	**LIMITS**	**SUBJECT HEADINGS/KEYWORDS**
DIALOG OneSearch® MEDLINE® EMBASE® BIOSIS Previews® PASCAL	Human	MEDLINE®: Hormone replacement therapy! (L)methods/de OR Estradiol (L) AD/de OR EMBASE®: hormone substitution! (L)AD/de OR Estradiol (L)PO AND Estradiol (L)TP, TD, AD OR (Conjugated estrogen OR conjugated estrogen plus medroxyprogesterone acetate)/de (L) AD OR BIOSIS®: ((hormonal replacement therapy OR hormone replacement therapy OR estrogen replacement

DATABASES	LIMITS	SUBJECT HEADINGS/KEYWORDS
		therapy OR hormone therapy)/de AND (drug delivery method OR drug delivery system OR drug administration))/de OR (Estradiol/de AND (drug delivery method/de OR drug delivery system OR drug adminstration/de)) OR MEDLINE®, BIOSIS®, EMBASE®: RN=50-28-2 ALL DATABASES: ((climara OR estradot OR oesclim OR oestradiol)(1n)(patch? OR estrogel OR estraderm OR vivelle))/ti,ab,id,tn OR (estracomb OR estracombi OR estalis OR estalis-sequi OR estragest OR (estradiol(1n)levonorgestrel) OR (estradiol(1n)17(1n)beta) OR (oestradiol(1n)17(1n)beta) OR premarin OR provera OR premarine)/ ti,ab,id,tn OR ((estrogen OR oestrogen OR hormone?) (1n) (therap? OR treatment? OR replacement?))/ ti,ab ***AND*** MEDLINE®: Administration, oral/de OR EMBASE®: Oral Drug Administration/de OR

DATABASES	LIMITS	SUBJECT HEADINGS/KEYWORDS
		ALL DATABASES: (drug?(1n)administration OR drug?(1n)deliver? OR method? OR oral OR cyclical OR pill OR pills OR tablet OR tablets OR capsule OR capsules OR placebo)/ti,ab AND MEDLINE®: (Administration, cutaneous OR administration, topical OR ointments OR gels)/de OR EMBASE®: (Transdermal drug administration OR topical drug administration OR drug comparison)/de OR ALL DATABASES: (gel OR gels OR ointments OR topical? OR salves OR cutaneous? OR transderm? OR trans-derm? OR patch OR patches OR percutaneous? OR transcutaneous?)/ ti,ab OR (comparison OR versus OR comparative OR alternat?)/ ti,ab OR ***AND*** MEDLINE®: (economics OR 'costs and cost analysis'! OR value of life OR economics, medical OR economics, nursing OR economics, pharmaceutical OR models, economic! OR markov chains OR monte carlo method OR decision trees OR quality of life OR patient satisfaction OR quality-adjusted life years OR EC)/de

DATABASES	LIMITS	SUBJECT HEADINGS/KEYWORDS
		OR EMBASE®: (Health economics! OR Pharmacoeconomics! OR economic aspect! OR quality adjusted life year OR quality of life! OR PE)/de OR BIOSIS®: (economic impact OR economic value OR pharmacoeconomics OR health care cost OR economic factors OR cost analysis OR cost OR cost-effectiveness OR costs OR quality of life OR health care cost OR cost savings OR cost-benefit analysis OR hospital costs OR medical costs OR quality-of-life)/de OR ALL DATABASES: (econom? OR cost OR costly OR costing OR costed OR price OR prices OR pricing Or priced OR discount OR discounts OR discounted OR discounting OR expenditure OR expenditures OR budget? OR afford? OR pharmacoeconomic? OR pharmaco(1n)economic? OR markov OR markow OR monte()carlo)/ ti,ab OR ((cost?(1n)(util? OR effective? OR efficac? OR benefit? OR consequence? OR analy? OR minimi? OR saving? OR breakdown OR lowering OR estimate? OR variable? OR unit OR units OR allocation OR control? OR illness OR sharing OR drug? OR hospital OR health(1n)care OR medical life OR lives OR cost? OR affordabl? OR instrument? OR technolog? OR day ? OR fee OR fees OR charge OR charges))/ ti,ab ***AND*** Human? OR people? OR person?

DATABASES	LIMITS	SUBJECT HEADINGS/KEYWORDS
		Search performed on 03 March 2004 *Total hits = 255 records* *Search update was performed on 12 May 2004* *Total hits = 9 records*
The Cochrane Collaboration & Update Software Ltd. The Cochrane Library 2004, Issues 1, 2	Human	HORMONE REPLACEMENT THERAPY exp tree1 (MeSH) OR ESTRADIOL single term (MeSH) OR (climara OR estradot OR oesclim OR (oestradiol next patch*) OR estrogel OR estraderm OR vivelle OR estracomb OR estracombi OR estalis OR estalis-sequi OR estragest OR oestradiol*) ***AND*** ADMINISTRATION, ORAL single term (MeSH) OR ((drug next administration) OR (drug next deliver*) OR oral OR cyclical pill OR pills OR tablet OR tablets OR capsule OR capsules OR placebo) ***AND*** ADMINISTRATION TOPICAL single term (MeSH) OR ADMINISTRATION CUTANEOUS single term (MeSH) OR OINTMENTS single term (MeSH) OR GELS single term (MeSH) OR (ointments OR gel OR ointment OR gels OR topical* OR salves OR cutaneous* OR transderm* OR trans-derm* OR patch OR patches OR percutaneous* OR transcutaneous*) ***AND*** ECONOMICS single term (MeSH) OR COSTS AND COST ANALYSIS explode tree 1 (MeSH OR VALUE OF LIFE single term (MeSH) OR ECONOMICS MEDICAL single term (MeSH) OR ECONOMICS HOSPITAL single term (MeSH) OR ECONOMICS NURSING single term (MeSH) OR

DATABASES	LIMITS	SUBJECT HEADINGS/KEYWORDS
		ECONOMICS PHARMACEUTICAL single term (MeSH) OR FEES AND CHARGES explode tree 1 (MeSH) OR BUDGETS single term (MeSH) OR MODELS ECONOMIC explode tree 1 (MeSH) OR MARKOV CHAINS single term (MeSH) OR MONTE CARLO METHOD single term (MeSH) OR DECISION TREES single term (MeSH) OR QUALITY OF LIFE single term (MeSH) OR PATIENT SATISFACTION single term (MeSH) OR QUALITY-ADJUSTED LIFE YEARS single term (MeSH) OR (econom* OR cost OR costs OR costing OR costed OR price OR prices OR pricing OR priced OR discount OR discounts OR discounted OR discounting OR expenditure OR expenditures OR budget* OR afford* OR pharmacoeconomic* OR (pharmaco near economic*)) OR ((unit near cost) OR (unit* near costs) OR (drug next cost) OR (drug next costs) OR (hospital next costs) OR (health next care next costs) OR (healthcare next costs) OR (health-care next costs) OR (medical next costs) OR markov OR (monte next carlo) OR monte-carlo OR (decision next tree*) OR decision-tree* OR qol OR qoly OR hrqol OR qaly OR qalys OR (quality near life) OR (willingness near pay) OR (quality near adjusted near life near year*)) *Performed 04 March 2004* *The Cochrane Database of Systematic Reviews = 18 complete reviews; 1 protocol; Database of Reviews of Effectiveness=4 references; The Cochrane Controlled Trials Register =154 references; 1 abstract by INAHTA and other healthcare agencies.*

DATABASES	LIMITS	SUBJECT HEADINGS/KEYWORDS
HEED: Health Economics Evaluations Database		Same keywords as the original search and appropriate index and syntax used.
The National Library of Medicine PubMed Updates		MeSH headings and keywords to mirror DIALOG® MEDLINE® search.
Websites of Health Technology Assessment (HTA) and related agencies; clinical trial registries; other databases		NICE; National Research Register; University of York NHS Centre for Reviews and Dissemination – CRD Databases; FDA, Health Canada

APPENDIX 3: Clinical Evidence of Transdermal Patches versus Placebo in Postmenopausal Women

Author	Study Subjects and Follow-up Time	Interventions and Patient Numbers	Results
Bacchi-Modena[43]	Postmenopausal women with moderate to severe* post-menopausal symptoms (≥7 hot flashes daily); 4, 8, 12 weeks	Patch (Estraderm MX 50): 53 Placebo: 56 (no progestin was given)	Hot flashes reduced per day at 4 weeks: patch, from 10.7 to 3.8 (-64.5%); placebo, from 11.1 to 7.2 (-35.1%). Hot flashes reduced per day at 8 weeks: patch, from 10.7 to 2.4 (-77.6%); placebo, from 11.1 to 6.5 (-41.4%). Hot flashes reduced per day at 12 weeks: patch, from 10.7 to 2.5 (-76.6%); placebo, from 11.1 to 7.1 (-36.0%). Reduction in hot flashes at 12 weeks: patch versus placebo, -4.2 (95% CI: -4.5, -1.6). Spotting or bleeding: patch, 15.1%; placebo, 12.5%.
Gordon *et al.*[39]	Postmenopausal women who experienced ≥5 moderate to severe hot flashes weekly; 11 weeks	Patch-1 (Climara®, released estradiol 50 µg daily): 72 Patch-2 (Climara®, released estradiol 100 µg daily): 70 Placebo: 72 (no progestin was given)	Hot flashes reduced per week from baseline at cycle 3 (data were estimated from graph): patch 1, -31 (-67.4%); patch 2, -40 (-76.9%); placebo, -7 (-13.2%). Hot flashes decreased across 3 cycles: patch 1, from 46±6.5 to 20±3.0 (-56.5%); patch 2, from52±4.4 to 16±2.4 (-69.2%); placebo, from 53±4.5 to 46±6.5 (-13.2%). (dispersion of reduction in number of hot flashes were reported graphically)
Notelovitz *et al.*[44]	Postmenopausal women with ≥8 moderate to severe hot flashes and sweating episodes daily; 12 weeks	Patch-1 (Vivelle +NA[44] 140 µg): 54 Patch-2 (Vivelle +NA 250 µg): 59 Patch-3 (Vivelle +NA 400 µg): 53 Placebo: 53 (progestin was	Hot flashes reduced per day from baseline to 12 weeks: patch 1, from 11.48±0.81 to 2.38±0.56 (-81.4%); patch 2, from 10.66±0.40 to 1.42±0.26 (-89.2%); patch 3, from 10.40±0.48 to 1.13±0.28 (-92.9%); placebo, from 11.58±0.63 to 6.28±0.57 (-47.8%). Change in intensity of hot flashes† at 12 weeks: patch 1, from 5.50±0.21 to 0.82±0.22 (-79.5%); patch 2, from 5.51±0.17 to 0.97±0.18 (-82.0%); patch 3, from 5.23±0.20 to 0.56±0.15 (-86.6%);

Author	Study Subjects and Follow-up Time	Interventions and Patient Numbers	Results
		given)	placebo, from 5.36±0.19 to 3.18±0.32 (-38.8%).
Rovati *et al.*[41]	Postmenopausal women with ≥7 moderate to severe hot flashes and sweating episodes daily; 12 weeks	Patch-1 (Dermestril®-Septem 25): 80 Patch-2 (Dermestril®-Septem 50): 77 Patch-3 (Dermestril®): 74 Placebo: 80 (no progestin was given)	Hot flashes reduced per day from baseline to 12 weeks: patch 1, -78%; patch 2, -93%; patch 3, -97%; placebo, -41% (estimated from figure). Disappearance of symptoms at 12 weeks: patch 1, 24%; patch 2, 40%; patch 3, 40%; placebo,10%. Change of severity of hot flashes (measured by VAS scale[41]) from baseline to 12 weeks: patch 1, from 69 (95% CI: 65-72) to 19 (95% CI: 14-25) (-72.5%); patch 2, from 71 (95% CI: 68-74) to 10 (95% CI: 6.1-13) (-85.9%); patch 3, from 71 (95% CI: 68 to 74) to 6.3 (95% CI: 3.4-9.1) (-91.1%); placebo, from 70 (95% CI: 67-74) to 38 (95% CI: 31-45) (-45.7%).
Von Holst[42]	Postmenopausal women with intact uterus and postmenopausal complaints (≥15 to 20 hot flashes per week); 3 months	Patch (Fem7® Combi: estradiol mono patch × 2 weeks, then estradiol or levonorgestrel combination patch × 2 weeks): 84 Placebo: 88 (progestin was given)	Hot flashes reduced per week from baseline to 3 months: patch, -81.2%; placebo, -57.3%. Kupperman Index reduction: patch, from 26.3 to 9.5 (-63.9%); placebo, from 27.1 to 15.9 (-41.3%). (some data were estimated from graphs)

*Moderate to severe hot flashes: a minimum mean number of seven moderate to severe hot flashes per 24 hours. Moderate=warm sensation with sweating, able to continue activity; severe=hot sensation with sweating, must stop activity.
†Intensity of hot flashes: 0=none, 1 to 3=mild, 4 to 6=moderate, 7 to 9=severe.

APPENDIX 4: Clinical Evidence of Transdermal Patches versus Oral HRT in Postmenopausal Women

Author	Study Subjects and Follow-up Time	Interventions and Patient Numbers	Results
Gordon *et al.*[39]	Postmenopausal women experienced ≥5 moderate to severe hot flashes per week; 11 weeks	Patch 1 (Climara®, released estradiol 50 µg daily): 130 Patch 2 (Climara®, released estradiol 100 µg daily): 124 Pill (Premarin 0.625 mg per day): 136 (no progestin was given)	Hot flashes reduced per week from baseline at cycle 3: patch 1, -32 (-71.7%); patch 2, -40 (-89.3%); pill, -36 (-78.1%). Hot flashes decreased across 3 cycles: patch 1, from 53±3.5 to 25±2.6 (-52.8%); patch 2, from 51±3.2 to 16±2.2 (-68.6%); pill, from 53±3.5 to 22±2.6 (-58.5%). (dispersion of reduction in number of hot flashes were reported graphically)
Sajtos *et al.*[40]	Postmenopausal women with moderate to severe post-menopausal symptoms (≥3 hot flashes daily); 12 weeks	Patch (Menorest®): 83 Pill (Presomen®): 83 (progestin was given)	Hot flashes reduced per day at 12 weeks: patch, from 6±4 to 1±1 (-83.3%); pill, from 6±4 to 1±2 (-83.3%). Remission of hot flashes and improvement rate: patch, remission 49 of 83 (59.0%); improved 29 of 83 (34.9%); no change 4 of 83 (4.8%); pill, remission 39 of 83 (47.0%); improved 31 of 83 (37.3%); no change 8 of 83 (9.6%).
Sendag *et al.*[45]	Postmenopausal women; 24 weeks	Patch: 35 Pill: 37 (progestin was given)	Cyclic bleeding at 3 months: patch, 91.4%; pill, 94.6%. Cyclic bleeding at 5 months: patch, 88.6%; pill, 89.2%. Day of onset at 3 months: patch, 14.6; pill, 14.8. Day of onset at 5 months: patch, 14.9; pill, 14.8. Duration of bleeding at 3 months, 3.8 days; pill, 3.8 days. Duration of bleeding at 5 months: patch, 3.7 days; pill, 3.6 days. Spotting at 3 months: patch, 11.4%; pill, 16.2%. Spotting at 5 months: patch, 25.7%; pill, 32.4%. Normal bleeding at 3 months: patch, 85.7%; pill, 83.8%. Normal bleeding at 5 months: patch, 71.4%; pill, 64.9%. Heavy bleeding at 3 months: patch, 2.9%; pill, 0. Heavy bleeding at 5 months: patch, 2.9%; pill, 2.7%.

Author	Study Subjects and Follow-up Time	Interventions and Patient Numbers	Results
			Intermittent bleeding at 3 months: patch, 8.6%; pill, 5.4%. Intermittent bleeding at 5 months: patch, 11.4%; pill, 10.8%.
Studd *et al.*[38]	Postmenopausal women with moderate to severe post-menopausal symptoms (≥21 hot flashes per week); 12 weeks	Patch (Menorest® 50): 100 Pill: 104 (progestin was given)	Hot flashes reduced from baseline to 12 weeks: patch, from 7.14±0.47 to 0.92±0.20 (-87.1%); pill, from 6.66±0.33 to 0.54±0.15 (-91.9%).

APPENDIX 5: RCTs Excluded and Reasons for Exclusion

Blanc *et al.*, 1998:[72] dosage differed from that specified in literature search criteria.
Cohen *et al.*, 1999:[32] dosage differed from that specified in literature search criteria.
De Aloysio *et al.*, 2000:[73] dosage differed from that specified in literature search criteria.
Iversen *et al.*, 1991:[74] dosage differed from that specified in literature search criteria.
Mattsson *et al.*, 1999:[75] dosage differed from that specified in literature search criteria.
Parsey *et al.*, 2000: [76] dosage differed from that specified in literature search criteria.
Pattison *et al.*, 1989:[33] dosage differed from that specified in literature search criteria.
Place *et al.*, 1985:[18] dosage differed from that specified in literature search criteria.
Cortellaro *et al.*, 1991:[77] Kuppermann Index used to report improvement in symptoms; specific values for effect and SD not reported.
De Vrijer *et al.*, 2000:[78] inufficient data for model building; only standard deviation of difference between groups provided.
Good *et al.*, 1996:[79] no dispersion of reduction in frequency of hot flashes reported.
Good *et al.*, 1999:[30] number of hot flashes reported graphically, no actual data provided.
Haas *et al.*, 1988:[80] insufficient data; data reported graphically.
Leodolter *et al.*, 1992:[81] insufficient outcome data; data reported graphically.
Polvani *et al.*, 1991:[82] only Kupperman Index used to assess severity of symptoms; specific values for effect not reported.
Von Holst *et al.*, 2000:[83] only reported difference between comparators; actual effect from baseline not reported.
Utian *et al.*, 1999:[84] number of hot flashes reported graphically; actual numbers not reported.
Pornel *et al.*, 1996:[85] not a primary study; author reporting on Studd's study results.
Speroff *et al.*, 1996:[86] not a primary study and standard deviations not reported.
Hilditch *et al.*, 1996:[87] inappropriate outcome (quality of life, rather than postmenopausal symptoms).
Rozenberg *et al.*, 1997:[88] inappropriate comparators; assessing different doses of progestin in estrogen patches.