Economic evaluation of norethisterone acetate/ethinylestradiol (FemHRT) for women with menopausal symptoms

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of a continuous oral preparation of norethisterone (norethindrone) acetate (NA) and ethinylestradiol (EE). The preparation (FemHRT) comprised 1 mg NA and 5 microg EE. For the analysis of NA-EE as a first-line therapy, NA-EE was compared with conjugated equine oestrogen (0.625 mg) plus medroxyprogesterone acetate (2.5 mg) (CEE-MPA) and with no therapy. As a second-line therapy, NA-EE was assumed to be used after a woman was no longer compliant after 6 months of a first-line therapy. NA-EE was compared with no second-line therapy and with CEE-MPA as second-line therapy.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of 50-year-old menopausal women.

Setting
The study setting was primary care. The economic study was conducted in Ottawa, Canada.

Dates to which data relate
The studies from which the effectiveness was derived dated from 1993 to 2001. The price year was 1999.

Source of effectiveness data
The effectiveness data were derived from a review of the literature, supplemented by authors' assumptions.

Modelling
A Markov process with a cycle length of 3 months and a lifetime horizon was used to assess the cost-effectiveness of the interventions. For the base-case analysis, it was assumed that therapy would be for up to 5 years for compliant women. The Markov states related to the presence and absence of vaginal bleeding, menopausal symptoms and hip fracture, which were directly related to compliance with therapy. Thus, the decision analytic model consisted of 5 sub-models (compliance, bleeding, menopausal symptoms, fracture and mortality).

Outcomes assessed in the review
The outcomes assessed in the review were:
the effect of hormone replacement therapy (HRT) and NA-EE on menopausal symptoms;

the effect of HRT and NA-EE on time to amenorrhoea;

the probability of hip fracture for patients in the general population;

the mortality rate immediately post-hip fracture;

the effect of HRT on fracture;

the probability of death from causes other than fracture;

the compliance rate with therapy; and

the utility values for the health states of no problems, hip fracture, severe menopausal symptoms, mild to moderate symptoms, and vaginal bleeding.

**Study designs and other criteria for inclusion in the review**
Transition probabilities relating to control of menopausal symptoms were derived from a placebo-controlled clinical trial of NA-EE and CEE-MPA (0.625 mg-2.5 mg) and a placebo-controlled trial of NA-EE. For purposes of the analysis, the authors considered data pertaining to the 1 mg NA-5 microg EE dosage of FemHRT. The probability of hip fracture for patients in the general population was derived from an analysis of data from the Canadian Institute for Health Information and Statistics Canada. A meta-analysis was only included in the review so that differences in femoral neck bone density could be assessed.

**Sources searched to identify primary studies**
Not reported.

**Criteria used to ensure the validity of primary studies**
Not reported.

**Methods used to judge relevance and validity, and for extracting data**
Not reported.

**Number of primary studies included**
Approximately 11 primary studies were included in the review.

**Methods of combining primary studies**
Not applicable.

**Investigation of differences between primary studies**
Not applicable.

**Results of the review**
The proportion of women experiencing both a 75% reduction in hot flush frequency and elimination of night sweats was 40% for women receiving NA-EE and 9% for women not taking therapy.

The probability that a woman would experience vaginal bleeding on therapy, based on cumulative amenorrhoea rates at
6 months for both NA-EE and CEE-MPA, was 62% (NA-EE) and 34% (CEE-MPA), respectively.

The probability of hip fracture for 50-year-old patients in the general population was 0.1%.

The mortality rate immediately post-hip fracture for Canadian women aged 50 years was 0.7%.

There were no significant differences between women taking NA-EE and those taking CEE-MPA in terms of bone mineral density measured at the lumbar spine, femoral neck and femur.

There was a beneficial effect at 2 years with a weighted mean difference in the percentage change in bone density at the femoral neck of 4.12 (95% confidence interval, CI: 3.44 - 4.80). This translated into an estimated relative risk of hip fracture of 0.79 (95% CI: 0.76 - 0.82). Thus, the rate of fractures would be reduced by 21% within each 3-month cycle whilst on therapy.

The utility associated with the various health events was 0.64 for severe menopausal symptoms, 0.85 for mild to moderate menopausal symptoms, 0.99 for vaginal bleeding, and 0.44 for hip fracture.

Methods used to derive estimates of effectiveness
The authors made assumptions to supplement the effectiveness data derived from the literature. These assumptions were based on guesses supported by the existing literature.

Estimates of effectiveness and key assumptions
The authors assumed that, at the onset of treatment, 53% of patients would have severe menopausal symptoms and 47% of patients would have mild symptoms. For second-line therapies, the authors assumed that all patients had severe menopausal symptoms.

The authors assumed the same transitional probabilities for CEE-MPA as for NA-EE. This was based on evidence that there are no significant differences in the control of menopausal symptoms between different oestrogen regimens.

The authors assumed that bleeding would commence at the onset of treatment and that the proportion experiencing bleeding would decrease at a constant proportional rate for each 3-month cycle.

Within the decision analytic model, the authors assumed the same relative risk reduction in fractures for both NA-EE and CEE-MPA. Thus, differences in fracture rates would occur, not because of differences in efficacy but because of differences in the compliance rate.

A study found the compliance rate with CEE-MPA after 6 months was 26.3%. The authors assumed that all women still experiencing bleeding and/or severe menopausal symptoms after 6 months of therapy would discontinue therapy. Hence, the compliance rate within the model for CEE-MPA was 27.2%. Given that compliance was assumed to be a function of bleeding and menopausal symptoms, the construct of the model assumed greater compliance with NA-EE, with an improvement of approximately 24%.

Measure of benefits used in the economic analysis
The measure of benefit used in the economic analysis was the quality-adjusted life-years (QALYs). The utility weights relating to hip fracture and vaginal bleeding were estimated for health states by direct elicitation, using a sub-sample of patients with osteoporosis from an ongoing study based at Ottawa Hospital. The health states were rated using both visual analogue scale and standard gamble methods. The utilities were calculated using the standard gamble exercise. For menopausal symptoms, the utility values were based on a study in which the utility values were derived using the time trade-off method.

Direct costs
Resource use and the costs were not reported separately. The direct costs included in the analysis were those of the third-
party payer. These comprised:

- the costs of therapy, where the cost of CEE-MPA was derived from the Ontario Drug Benefit Formulary, and the cost for NA-EE was estimated on a proposed list price plus mark up and dispensing fee;
- the costs of vaginal bleeding, assumed to be a one-off cost;
- the costs of menopausal symptoms, which were based on the 3-month cost of clonidine; and
- the cost of hip fractures, which was derived from a study of 504 patients in Hamilton, Canada.

Since the costs were incurred over the lifetime of the patients, discounting was relevant. Hence, future costs were discounted at a rate of 5% per annum. The study reported the average costs. All the costs were adjusted to 1999 prices.

**Statistical analysis of costs**
The costs were treated as point estimates (i.e. the data were deterministic).

**Indirect Costs**
The authors did not include the indirect costs in the analysis because of data constraints. Consequently, the perspective of the third-party payer was considered.

**Currency**
Canadian dollars (Can$).

**Sensitivity analysis**
Sensitivity analyses were performed on several parameters. The parameters investigated were the number of years of therapy (5 years to 1 year), the cost associated with bleeding or severe menopausal symptoms (0), the cost of utility loss associated with bleeding (0), the benefit in terms of fracture reduction for either therapy (0), the discount rate (0 and 3%). Sensitivity analyses were also conducted by considering only patients with severe menopausal symptoms.

**Estimated benefits used in the economic analysis**
The estimated lifetime QALYs for first-line therapy were 15.29 with NA-EE, 15.26 with CEE-MPA, and 14.96 with no therapy.

The estimated lifetime QALYs for second-line therapy were 14.98 with NA-EE, 14.96 with CEE-MPA, and 4.59 with no therapy.

**Cost results**
The lifetime costs of first-line therapy were Can$2,800 with NA-EE, Can$2,200 with CEE-MPA, and Can$2,100 with no therapy.

The lifetime costs of first-line therapy were Can$2,600 with NA-EE, Can$2,200 with CEE-MPA, and Can$2,200 with no therapy.

**Synthesis of costs and benefits**
The costs and benefits were combined in an incremental cost-utility ratio (i.e. the additional cost per QALY gained). For first-line therapy, the incremental cost per QALY gained for NA-EE was Can$2,200 when compared with no therapy and Can$20,300 when compared with CEE-MPA. For second-line therapy, the incremental costs per QALY gained for NA-EE were Can$900 (versus no therapy) and Can$16,400 (versus CEE-MPA), respectively.
The sensitivity analysis identified a threshold value for both the daily costs of NA-EE and the improved compliance with NA-EE, based on a maximum value of a QALY of Can$50,000. The analysis demonstrated that the daily cost of NA-EE could be substantially greater and the cost per QALY gained from NA-EE would remain below Can$50,000. However, the sensitivity analysis also confirmed that NA-EE would have to lead to improved compliance (at least 13% as a first-line therapy and 5% as a second-line therapy) for it to be cost-effective.

Authors' conclusions
A continuous, combined oral preparation of norethisterone acetate (NA) and ethinylestradiol (EE) was a cost-effective therapy for women with menopausal symptoms, both as first- and second-line therapy.

CRD COMMENTARY - Selection of comparators
A justification was given for the comparators used. They represented current practice in the authors' settings. You should decide if these are widely used health technologies in your own setting.

Validity of estimate of measure of effectiveness
To derive measures of effectiveness for the interventions under study, the authors used results from two placebo-controlled trials. It would appear that these trials were randomised, although the authors did not make this explicit. Further data used in the model were supplemented with data derived from the literature and the authors' own assumptions, which were based on data from published studies. The methodology used for the review of the literature was not mentioned. The authors varied their assumptions in the sensitivity analysis.

Validity of estimate of measure of benefit
The estimation of benefits was modelled. The instrument (Markov model) used to derive the measure of health benefit was appropriate. The future health benefits were discounted at a rate of 5% per annum.

Validity of estimate of costs
The authors reported that they could not adopt a societal perspective in the analysis due to data limitations. Consequently, the authors adopted a third-party payer perspective. All the categories of cost and all relevant costs appear to have been included in the analysis. Resource use and the costs were not reported separately, which will limit the generalisability of the authors' results. The costs were derived from published sources and authors' assumptions. Several, cost categories were appropriately varied in the sensitivity analysis. Discounting was relevant since the costs were incurred during the lifetime of the patient. Hence, all future costs were discounted at a rate of 5%. The price year was reported, which will aid any potential inflation exercises.

Other issues
The authors reported that although a number of economic evaluations of HRT had been conducted, there had been no published Canadian study, nor were there any studies explicitly comparing different regimens of HRT. The issue of generalisability to other settings was partly addressed in the limited sensitivity analysis. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis. A number of further limitations to the study were reported. First, the analysis was conducted before the initial results of the Women's Health Initiative Randomised Controlled Trial, which found that HRT increases events such as coronary heart disease and stroke, were reported. The authors reported that the increase in total events found in this trial was small. Second, any modelling study has limitations relating to the availability and reliability of the data used in the model. The authors reported, however, that these limitations were addressed in the sensitivity analyses.

Implications of the study
The authors reported that NA-EE could be an appropriate alternative to CEE-MPA for first-line therapy, assuming improved compliance with therapy.
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