A cost-utility analysis of low-dose hormone replacement therapy in postmenopausal women with an intact uterus
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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 study examined the use of low-dose conjugated oestrogens (CE) combined with the progestogen medroxyprogesterone acetate (MPA) (CE/MPA low dose) for the alleviation of menopausal symptoms in postmenopausal women with an intact uterus. CE/MPA low dose consisted of 0.3 mg CE combined with 1.5 mg MPA.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The hypothetical study population comprised cohorts of 100 postmenopausal women with an intact uterus.

Setting
The setting was community care. The economic study was carried out in the UK.

Dates to which data relate
The effectiveness data referred to 1994 - 2003. The resource use and cost data referred to 2003 - 2004. The price year was not reported, but it can be assumed to have been 2003/04.

Source of effectiveness data
The effectiveness data were derived from a review of published studies and expert opinion.

Modelling
A model was used to estimate the costs and quality-adjusted life-years (QALYs) associated with CE/MPA low dose and CE/MPA high dose. The model had a 1-year timeframe.

Outcomes assessed in the review
The outcomes assessed in the review included rates of amenorrhea, bleeding, breast pain, breast symptoms and vaginal candidiasis.

Study designs and other criteria for inclusion in the review
The authors did not specify the study designs or other criteria for inclusion in the review. The majority of the
effectiveness data were obtained from two double-blind randomised controlled trials (RCTs): the Menopause Study Group trial (Archer et al. 1994, see "Other Publications of Related Interest- below for bibliographic details) and the Health, Osteoporosis, Progestin, and Estrogen (HOPE) study (Lobo et al. 2001, see "Other Publications of Related Interest- below for bibliographic details). Since no studies directly compared the clinical effectiveness of CE/MPA low dose with CE/MPA high dose, an intermediate comparator was used (i.e. 0.625 mg CE/2.5 mg MPA). The HOPE study compared 0.625 mg CE/2.5 mg MPA versus CE/MPA low dose, whereas the Menopause Study Group trial compared 0.625 mg CE/2.5 mg MPA versus CE/MPA high dose.

Sources searched to identify primary studies
The authors searched MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews, BIOSIS Previews and the Internet. They also searched the reference lists of all retrieved papers.

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
Two RCTs were included in the review.

Methods of combining primary studies
The HOPE study provided most of the effectiveness evidence for the assumption that the CE/MPA high dose adverse event profile was comparable to that of 0.625 mg CE/2.5 mg MPA. For one outcome, bleeding, data from the included studies were used to calculate an indirect comparison of CE/MPA low dose with CE/MPA high dose. However, the precise method used was not reported.

Investigation of differences between primary studies
The authors stated that the study populations were comparable in terms of their baseline characteristics. They also stated that the studies had similar methods, including end points and inclusion and exclusion criteria. The authors noted that both studies were conducted in American patient populations with patient populations broadly equivalent to those of the UK.

Results of the review
The authors estimated absolute risk reductions (ARRs) for CE/MPA low dose compared with CE/MPA high dose. The ARRs were estimated to be 0.16 for no amenorrhoea in cycles 7 - 13, 0.08 for bleeding, 0.13 (95% confidence interval, CI: 0.07 to 0.17) for breast pain, 0.17 (95% CI: 0.11 to 0.21) for breast symptoms and 0.04 (95% CI: 0.00 to 0.06) for vaginal candidiasis.

Methods used to derive estimates of effectiveness
An expert panel were used to supplement data from the literature review, where necessary, and to determine resource use. The expert panel consisted of clinicians. The methods used to calculate estimates from the expert panel were not reported.

Estimates of effectiveness and key assumptions
The experts estimated that 30% of patients would discontinue treatment following vaginal haemorrhage or heavy bleeding, 10% would discontinue following amenorrhoea, 15% would discontinue due to fear of cancer, and 20% would discontinue following breast pain.

**Measure of benefits used in the economic analysis**
The measure of health benefit was the QALYs. The utility weights were derived from a published study, but the method used was not reported. The utilities for CE/MPA high- and low-dose treatments were assumed to be similar. Separate estimates were obtained for two sub-groups: patients with mild symptoms and patients with severe symptoms.

**Direct costs**
The study included costs to the health service. The unit costs and the resource use quantities were reported separately. The study included the costs of drug acquisition, general practitioner (GP) visits, and outpatient referrals to a gynaecologist. The additional cost of a scan for patients still bleeding after 6 months and the costs of travel to GP surgeries and the acquisition of over-the-counter medicines were not included. The costs were derived from national pricing lists and databases. Discounting was not relevant given the 1 year timeframe of the model. The study reported average and incremental costs. The price data referred to 2003/04.

**Statistical analysis of costs**
Patient-level data were not included. Therefore, a statistical analysis of the costs was not relevant.

**Indirect Costs**
The indirect costs were not included as they were not relevant to the study perspective.

**Currency**
UK pounds sterling (£).

**Sensitivity analysis**
The model was analysed using a probabilistic sensitivity analysis to explore variability and uncertainty in the data. The uncertainty around the model parameters was characterised using normal distributions. This is not appropriate for model parameters that cannot take a value of less than zero, and might have allowed illogical parameter values to be incorporated into the study results. The ranges used in the sensitivity analysis were the lower and upper bounds of CIs where possible and, where not, either expert guidance or a variation of 25.0 to 66.7%. Monte Carlo simulations (1,000) were performed.

**Estimated benefits used in the economic analysis**
Treatment with CE/MPA low dose for one year resulted in an incremental gain of 0.62 QALYs compared with CE/MPA high dose in patients with mild symptoms. This difference was estimated to be 1.49 QALYs in patients with severe symptoms.

**Cost results**
The total cost of treatment with CE/MPA low dose was estimated to be 13,347 over a 1-year timeframe, compared with 14,790 for treatment with CE/MPA high dose, resulting in a cost-saving of £1,443.

The costs of side effects were the main consideration in the economic model.

**Synthesis of costs and benefits**
The costs and benefits were combined to calculate the incremental cost per QALY. CE/MPA low dose was estimated to be more effective and less costly than CE/MPA high dose in both patients with mild symptoms and those with severe symptoms. This resulted in negative incremental cost-utility ratios of -2,329.60 (mild symptoms) and -970.67 (severe symptoms), respectively.

The results of the probabilistic sensitivity analysis were presented graphically using a cost-effectiveness plane. Overall, the sensitivity analysis showed greater health gain at a reduced cost for both mild and severe symptom populations.

Authors’ conclusions
The higher acquisition costs of low-dose conjugated oestrogens (CE) combined with medroxyprogesterone acetate (CE/MPA low dose) are more than offset by cost-savings from reduced adverse events, making it appear less costly and more effective than treatment with CE/MPA high dose.

CRD COMMENTARY - Selection of comparators
The study examined different doses of CE/MPA. The authors stated that CE/MPA low dose is currently recommended for use in Scotland. Other treatment strategies may be available for the alleviation of menopausal symptoms, but these were not included in the analysis. You must consider whether the comparison between CE/MPA low dose and CE/MPA high dose is relevant to your own setting.

Validity of estimate of measure of effectiveness
The effectiveness data were derived from a review of published literature and expert opinion. The effectiveness of the treatments on the alleviation of menopausal symptoms was assumed to be equal. An indirect comparison was used to compare adverse event rates. The authors acknowledged that an intermediate comparator was not ideal, but suggested that the similarity between the two RCTs allowed for an indirect comparison. However, since the precise method used to calculate the indirect comparison was not reported, it was not possible to determine the validity of the estimates. The authors reported that the primary studies were comparable, but did not perform statistical tests. A panel of experts was used to supplement data from published studies. Again, the methods used were not reported in sufficient detail to determine their validity. The estimates were explored in sensitivity analysis using appropriate ranges.

Validity of estimate of measure of benefit
The estimation of health benefits was modelled. The utility estimates did not differentiate between treatments in terms of the adverse events, which were the main health outcome in the economic model. The authors stated that this was because they assumed that hormone replacement therapy would provide a net benefit to patients and the full potential utility gain was applied to patients who continued therapy. This reasoning does not appear to justify the omission of the disutility associated with adverse events. However, this omission is unlikely to have affected the study conclusions. The short timeframe of the model excluded the long-term health outcomes associated with hormone replacement therapy.

Validity of estimate of costs
For the cost perspective adopted, all relevant costs were included. However, the 1-year timeframe excluded the long-term consequences of treatment with hormone replacement therapy. The authors excluded the costs of scans for patients still bleeding after 6 months, and they did not justify this omission. The costs and the quantities were reported separately, which improves the generalisability of the study results. An expert panel provided the resource use estimates and a sensitivity analysis was performed using appropriate ranges. The unit costs were based on national pricing lists for the year 2003/04. Discounting was not necessary and was therefore not performed.

Other issues
The authors did not compare their findings with those from other studies. They assumed that clinical data from America would be generalisable to the UK, and that the study results would be generalisable to a wider patient population than the ones included in the two RCTs used to derive estimates of effectiveness. Their justification for the
assumption that the study results related to a broader patient population was unclear, thus the authors' conclusions may extend beyond the scope of the analysis. The authors do not appear to have presented their results selectively. The use of cost-effectiveness planes for the probabilistic results is less informative than providing the number of simulations in which CE/MPA low dose is cost-effective. However, the probabilistic results may incorporate errors due to the use of normal distributions for variables that cannot take a value less than zero. The author did not report any further limitations.

Implications of the study
The authors did not make any explicit recommendations for changes in policy and practice, or the need for further research.

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