A cost-effectiveness evaluation of two continuous-combined hormone therapies for the management of moderate-to-severe vasomotor 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 short-term use of two continuous-combined hormone therapies (CCHT) for the treatment of moderate-to-severe vasomotor symptoms. The therapies studied were 1 mg norethindrone acetate/5 microg ethinyl estradiol (1/5 NA/EE) and 0.625 mg/day of conjugated estrogens/2.5 mg medroxyprogesterone (0.625/2.5 CEE/MPA).

Type of intervention
Secondary prevention.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of women aged 45 to 55 years with intact uterus who were experiencing moderate-to-severe menopausal symptoms and who were considered candidates for CCHT.

Setting
The setting was primary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data were derived from studies published between 2000 and 2003. The quality of life data were derived from studies published between 1993 and 1997. The price year was 2003.

Source of effectiveness data
The effectiveness data were derived from published studies, augmented by the authors' assumptions.

Modelling
A state transition model was used to determine the costs and quality-adjusted survival of the two therapies in comparison with no treatment. The model consisted of five health states. More specifically, well, dead, bleeding, vasomotor symptoms, and vasomotor symptoms plus bleeding. Transitions between states occurred every 3 months (the cycle length). The time horizon of the model was 1 year (3 years in the sensitivity analysis).

Outcomes assessed in the review
The parameters derived from the literature for use as model inputs were:

the incidence of conditions occurring,
prognosis and therapy effectiveness,
breakthrough bleeding or spotting,
amenorrhoea contrasted with bleeding or spotting,
any vasomotor symptoms contrasted with the absence of vasomotor symptoms, and
death.

**Study designs and other criteria for inclusion in the review**
No inclusion criteria were reported.

**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**
Two studies (one for the beneficial effects and one for the adverse effects) produced evidence of the effectiveness of the treatments.

**Methods of combining primary studies**
Not applicable, there being only a single source for each type of evidence.

**Investigation of differences between primary studies**
Not applicable, there being only a single source for each type of evidence.

**Results of the review**
The incidence of amenorrhoea immediately after initiation of therapy was projected to be 63% for 1/5 NA/EE and 47% for 0.625/2.5 CEE/MPA. At 12 months, the incidence was 89% for 1/5 NA/EE and 71% for 0.625/2.5 CEE/MPA.

Thirty-four per cent of patients experienced complete elimination of vasomotor symptoms when receiving 1/5 NA/EE.

The probability of symptom relief in patients receiving no therapy was 10% per 3-month period.

No further details about model efficacy or epidemiological inputs were reported.

**Methods used to derive estimates of effectiveness**
The authors made assumptions to obtain estimates for the effectiveness of 0.625/2.5 CEE/MPA.
Estimates of effectiveness and key assumptions
Owing to a lack of relevant literature, it was assumed that the two CCHTs exhibited the same efficacy (i.e. 0.625/2.5 CEE/MPA was assumed to equal 1/5 NA/EE).

Measure of benefits used in the economic analysis
The measure of benefit was quality-adjusted survival (quality-adjusted life-year, QALY). The utility weights for the well state were derived from the Quality of Well Being Scale, applied to a community sample of adult women. Utility weights, partially adjusted to try to isolate the impact of hormone therapy on quality of life, were derived from two community studies using time trade-off questions. The utility weights for bleeding were based on a single study of women who were asked how many days per year they would trade to avoid bleeding. Benefits were not discounted when the time horizon was 1 year. However, when the time horizon was extended to 3 years in the sensitivity analysis, a discount rate of 3% was applied.

Direct costs
The direct costs comprised direct medical, inpatients and outpatient care costs. Treatment costs for spotting or bleeding and vasomotor symptoms were based on treatment schedules, as assumed by the authors. The unit health care costs were derived from the median charge amounts reported in the Ingenix Medicode National Fee Analyzer (2003) using Common Procedural Terminology (version 4) codes. The drug acquisition costs were based on the average wholesale price published in the 2003 US Redbook. Discounting was not necessary for the baseline case in which the time horizon was restricted to 12 months. When this time horizon was extended in the sensitivity analysis, the costs were discounted at a rate of 3% per annum.

Statistical analysis of costs
The costs were treated stochastically in the probabilistic sensitivity analysis.

Indirect Costs
The indirect costs were not included.

Currency
US dollars ($).

Sensitivity analysis
Sensitivity analyses were used to examine "less conservative" assumptions about the presence of amenorrhoea (by using incidence rather than cumulative incidence in the model), and that all women on CCHT experienced spotting or bleeding (assumption relaxed). They also examined the cost of managing vasomotor symptoms, the utility associated with vasomotor symptoms and the utility associated with bleeding.

One-way sensitivity and threshold analyses were conducted on these variables, with a bivariate sensitivity analysis conducted on some of the combinations of key variables. A probabilistic sensitivity analysis was also undertaken, using a Monte Carlo simulation with 1,000 trials of the model to determine the proportion of runs in which the cost per QALY was less than $50,000 (the estimated probability of treatment being cost-effective).

Estimated benefits used in the economic analysis
Women on 1/5 NA/EE were reported to receive 1.31 more quality-adjusted months than women not receiving CCHT. Women on 0.625/2.5 CEE/MPA were reported to receive 1.25 more quality-adjusted months than women not receiving CCHT. These benefits encapsulated both the quality of life gains from the relief of vasomotor symptoms and the quality of life losses from spotting or bleeding.
The baseline case considered a treatment length of 1 year, while the sensitivity analysis considered the effects of 3 years' treatment. The effects on the long-term health of the women were specifically excluded from the analysis since the aim of the intervention was to provide short-term relief for menopausal symptoms.

Cost results
The model predicted that the cost of treating participants on 0.625/2.5 CEE/MPA was $847.93. The comparable figure for 1/5 NA/EE was $680.64.

The cost of treating people not receiving CCHT was assumed to be $0.00.

The cost of treating vasomotor symptoms was excluded from the baseline case. It was argued that their inclusion would have increased the cost-effectiveness of an intervention that was already highly cost-effective.

The costs were only considered to arise during the 12-month treatment period. The statistical analysis of the costs was incorporated in the probabilistic sensitivity analysis.

Synthesis of costs and benefits
The benefits and costs were expressed as incremental cost-utility ratios. The cost per QALY was $8,200 for 0.625/2.5 CEE/MPA and $6,200 for 1/5 NA/EE.

An incremental analysis of the two treatments was performed. Since 1/5 NA/EE was both cheaper and more effective than CEE/MPA, it was shown to be the dominant option.

Cost-effectiveness was shown to be higher for women with more severe menopausal symptoms, and for women who were less affected by the impact of spotting or bleeding.

The sensitivity analysis showed that 1/5 NA/EE remained the dominant option, irrespective of the values used in the sensitivity analysis. The most critical parameter for 1/5 NA/EE was its effectiveness in alleviating vasomotor symptoms. However, the relative effectiveness of the treatment in comparison with no treatment would need to be very low for the treatment not to be cost-effective.

The baseline case had conservatively assumed that no women would experience bleeding symptoms in the absence of treatment. Relaxing this assumption reduced the incremental cost per QALY to $7,100 for 0.625/2.5 CEE/MPA and to $5,600 for 1/5 NA/EE (compared with no treatment).

Again, conservatively, the baseline case had assumed a zero cost for the treatment of vasomotor symptoms. Relaxing this assumption also reduced the cost per QALY of both treatments. In this case the cost per QALY of 0.625/2.5 CEE/MPA became $4,000, and that of 1/5 NA/EE became $5,800 (both compared with no treatment).

Treatment duration was also subjected to sensitivity analysis. The cost-effectiveness improved if the duration of treatment was extended from 1 year to 3 years.

Over the 1,000 simulations in the probabilistic sensitivity analysis, 1/5 NA/EE resulted in cost-effectiveness estimates of less than $50,000 per QALY.

Authors' conclusions
Continuous-combined hormone therapy (CCHT) was very cost-effective for the short-term (i.e. 1 year and even <= 3 years) treatment of menopausal symptoms. The results of the sensitivity analysis suggested that this finding was robust. This finding ignored the possible long-term effect of hormone replacement therapy on the risk of cancer, cardiovascular disease and osteoporosis. However, it was argued that these are unlikely to be significantly affected by the short-term exposure implied by treatment for menopausal symptoms.
CRD COMMENTARY - Selection of comparators
With concern expressed about the long-term effects of hormone replacement therapy on cancer and cardiovascular disease, the choice of a no treatment option as the comparator was appropriate. You should decide if this represents a valid comparison in your setting.

Validity of estimate of measure of effectiveness
The estimate of the effectiveness of 1/5 NA/EE in relieving vasomotor symptoms was derived from a single study. However, there was no explanation of how the study was identified or of strategies used to search the literature. The authors cited no evidence on the effectiveness of 0.625/2.5 CEE/MPA and assumed its effectiveness to be the same as 1/5 NA/EE. To estimate the probability of side effects (spotting or bleeding), evidence from a single multi-centre study, co-authored by one of the authors of this paper, was used. There was no discussion of how this study was selected, although the evidence used from this study was subjected to rigorous sensitivity analysis. Owing to the lack of reporting around the identification and selection of the studies from which the effectiveness data were derived, it was not possible to assess whether the best available evidence has been used to populate the model.

Validity of estimate of measure of benefit
The measure of benefit was QALYs. These were derived from the model. The quality of life (utility) weightings were obtained from a variety of sources. The weighting for the well state was derived from the Quality of Well Being Scale, which was applied to a sample of adult women who provided a mean score of 0.76. The utility weightings for vasomotor symptoms were calculated as the mean score from two studies using the time trade-off with samples of patients. Figures from one of the studies were re-scaled. The mean figure was itself re-scaled relative to the well state value of 0.76. This procedure would be invalid if the utility weights in the original studies were expressed relative to some notion of full health, which is conventionally assigned a value of 1.0. The effect of the re-scaling would be to underestimate the utility of the symptoms and, hence, enhance the value of treating them.

The utility associated with bleeding was derived from a time trade-off in which the only gain would be the cessation of bleeding (i.e. the patient is not restored to full health). In this case, an adjustment would be appropriate to estimate the utility associated with this state for QALY calculations.

Validity of estimate of costs
All the major costs relevant to the health care purchaser perspective were included in the baseline analysis, with the exception of the costs of treating vasomotor symptoms in the absence of CCHT. However, these costs were subjected to a sensitivity analysis. The price year was reported, which will aid any future reflation exercises. Discounting in the base-case was not appropriate, nor conducted, owing to the short time horizon. The assumptions concerning the use of health care resources were expressed in terms of Current Procedural Terminology codes. The number of such procedures was based on the authors’ opinions and was not subjected to a sensitivity analysis. The prices were derived from standard charges and were subjected to a sensitivity analysis (range: +/- 50%).

Other issues
The authors stated that they were unaware of any other work with which their findings might be compared. The issue of generalisability to other settings was not addressed. The claimed superiority of 1/5 NA/EE over 0.625/2.5 CEE/MPA was not well supported by the evidence presented, as the efficacy of 0.625/2.5 CEE/MPA was based solely on an assumption of equal efficacy with 1/5 NA/EE. Further evidence to back-up this assumption would have given more validity to the results obtained.

Implications of the study
The authors recommended that their work be considered by policy makers to "better understand and formulate the role of this class of agents in the aftermath of the recently released results of the WHI (Women's Health Initiative)".
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Other publications of related interest


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