Modeling the annual costs of postmenopausal prevention therapy: raloxifene, alendronate, or estrogen-progestin therapy

Mullins C D, Ohsfeldt R L

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
Four strategies for the prevention of osteoporosis were evaluated:

- calcium and vitamin D supplements alone (i.e. no prescribed drugs);
- conjugated equine estrogens plus medroxyprogesterone acetate (CEE+MPA), a specific example of continuous-combined oestrogen-progestin replacement therapy;
- raloxifene hydrochloride, an agent within the class of drugs called selective oestrogen receptor modulators; and
- alendronate, a bisphosphonate.

In all cases, the prescription drug interventions included calcium and vitamin D supplements.

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The base-case study population included women who had not had a hysterectomy and who initiated therapy at age 55 years. They had a normal distribution of age-related baseline risks for the outcomes of interest.

Setting
The setting was primary care. The economic analysis was carried out in Baltimore, USA.

Dates to which data relate
The effectiveness evidence was obtained from studies dating from 1996 to 2002. The resource use data were taken from studies published from 1993 to 2000. The price year was 2000.

Source of effectiveness data
The effectiveness data were derived from a review of completed studies.

Modelling
A decision-analytic model was used to compare the different prevention strategies, both in terms of costs and clinical events. Although not specifically stated, it can be inferred from the original paper (figure 1) that the authors used a
Markov type model to model disease progression. For each intervention (including no drug intervention), in each period, every woman faced some risk of an event. For example, fracture (vertebral or hip), myocardial infarction (MI; fatal or nonfatal), or breast cancer (differentiated by stage at diagnosis). The health events excluded were other osteoporotic fractures, non-MI coronary heart disease, uterine cancer and venous thromboembolic events. The model had a 7-year time horizon. The Markov cycle length appears to have been 1 year.

Outcomes assessed in the review
The clinical outcomes included vertebral and hip fractures, fatal and nonfatal MI, and breast cancer. Rates of persistence (i.e. the percentage of women who have not discontinued therapy) with the different therapies were also considered.

Study designs and other criteria for inclusion in the review
Not all of the study designs were reported. Most of the studies used to populate the model parameters of effectiveness appear to have been randomised controlled trials or pooled placebo-controlled trials, as well as some observational studies. Rates of persistence with therapy were taken from an observational study from a large managed care organisation and another study, the design of which was not reported.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
Not stated.

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

Number of primary studies included
Nineteen studies were included to inform the effectiveness inputs for the model.

Methods of combining primary studies
A narrative method was used to combine the primary studies.

Investigation of differences between primary studies
Not stated.

Results of the review
The relative risk decreases or increases of the different strategies compared with no prescription drug for the different years (Y) were as follows.

With CEE+MPA:

- hip fractures, -18% (Y1) and -35% (>Y1);
- vertebral fractures, -45% (Y1) and -35% (>Y1);
- breast cancer, 0% (Y1-Y4) and +25% (>Y4);
coronary heart disease (CHD), +75% (Y1), +15% (Y2) and 0% (>Y2).

With raloxifene:

- hip fractures, 0%;
- vertebral fractures, -65% (Y1) and -50% (>Y1);
- breast cancer, 0% (Y1) and -55% (>Y1);
- CHD, 0% (Y1-Y2) and -15% (>Y2).

With alendronate:

- hip fractures, -25% (Y1) and -50% (>Y1);
- vertebral fractures, -60% (Y1) and -50% (>Y1);
- breast cancer and CHD, 0%.

The authors reported that all assumptions about risk reductions in efficacy and safety were rounded to the nearest 5%.

The persistence rates were assumed to be equal for all three drugs in the base-case model. It was assumed that 41% of the patients were persistent at the end of the first year and 26% (Y2), 19% (Y3), 17% (Y4), 15% (Y5), 14% (Y6) and 13% (Y7) at the end of subsequent years.

Methods used to derive estimates of effectiveness

The authors made assumptions, based mostly on the literature, to derive estimates.

Estimates of effectiveness and key assumptions

To be conservative, the base-case model scenario assumed no fracture prevention efficacy for raloxifene at the hip, and a 2-year lag for a reduction in the risk of CHD. The base-case model scenario assumed that the persistence rates across all three therapy arms were identical to the rate assumed for CEE+MPA. Other assumptions were that side effects occurred during the first year and ended with drug discontinuation.

Measure of benefits used in the economic analysis

The measure of benefits used was the number of clinical events prevented (vertebral and hip fractures, CHD and breast cancer).

Direct costs

The quantity/cost boundary adopted was that of the health service. The health service costs were the annual drug costs (assumed to require one physician visit), the costs of side effects of therapy, and direct medical savings or costs of related events (hip and vertebral fracture, fatal and nonfatal MI, breast cancer treatment according to stage at diagnosis). The resource use data were derived from the literature, while the costs were obtained from different sources. More specifically, the average wholesale price for drugs, Medicare payment rates for resource use for side effects, and different studies for the direct costs of other events. The total costs were derived using modelling. Discounting was not undertaken, which was inappropriate due to the medium-term time horizon of the study. The unit costs and the resource quantities were not reported separately. The price year was 2000. The costs from the literature were converted to 2000-equivalent dollars using the medical care component of the consumer price index.

Statistical analysis of costs
The costs were treated deterministically.

**Indirect Costs**
The indirect costs were not considered.

**Currency**
US dollars ($).

**Sensitivity analysis**
Sensitivity analyses were conducted to address uncertainty surrounding the assumptions about the effects of therapy, discontinuation rates, and baseline population risk. Alternative model scenarios were evaluated. The method used to select the ranges used was not explicitly described.

**Estimated benefits used in the economic analysis**
Over the first 3 years of raloxifene therapy, the base-case model scenario suggested an expected reduction of about 1.8 events per 1,000 women initiating therapy. This increased to 4.0 events per 1,000 initiating therapy after 7 years. The estimated difference in events after 7 years is about 0.7 per 1,000 for alendronate. In contrast, CEE+MPA use was associated with a cumulative net harm (negative events avoided) in all 7 years. The exact figure was not reported but it was shown to be between 2 and 3 excess events over 7 years (figure 3). No incremental benefits were reported.

**Cost results**
The base-case model scenario suggested that the annual net costs per woman aged 55 initiating raloxifene averaged about $860 during the first year of therapy. This cost declined to about $330 per woman by the second year, and further declined to about $90 per woman by the seventh year.

The annual net costs per woman were expected to average about $682 during the first year, and decline to about $50 by the seventh year.

For alendronate, the annual incremental costs per woman were expected to average about $950 during the first year, and decline to about $110 by the seventh year.

The decline observed in all arms was mostly due to early discontinuation of therapy.

The costs of adverse effects were included in all drug strategies.

**Synthesis of costs and benefits**
Only cost-effectiveness ratios of the different therapies compared to no therapy were included. In the base-case scenario, the cost per event avoided over the first 7 years of therapy with raloxifene was about $455,000, compared with about $2.9 million per event avoided with alendronate. For CEE+MPA, cost-effectiveness is not a relevant issue in the base-case scenario due to its estimated net harm. An incremental analysis was not performed and all strategies were compared with no therapy.

No incremental cost-effectiveness ratios were calculated and, as such, none of the sensitivity analyses informed the relative cost-effectiveness of the interventions.

**Authors’ conclusions**
The annual costs of long-term prevention therapy were highest during the first few years. The results of the model suggested that raloxifene provides greater cost-effectiveness than alendronate for women initiating therapy at age 55 for
the first 7 years of treatment. Conjugated equine estrogens plus medroxyprogesterone acetate (CEE+MPA) should not be considered as a long-term prevention strategy. Raloxifene remains more cost-effective than alendronate as long as it provides clinical benefits beyond fracture prevention.

CRD COMMENTARY - Selection of comparators
The selection of the comparators was not explicitly justified, but the authors chose strategies from the different prescription drugs explored that seemed to represent current practice. For example, oestrogen-progestin therapy, selective oestrogen modulators such as raloxifene, and biphosphonates such as alendronate. Alternative biphosphonates regimes were also explored in the sensitivity analysis. You should decide if the comparators represent current practice in your setting.

Validity of estimate of measure of effectiveness
The authors did not state that a systematic review of the literature was undertaken, and the methodology of the review was not reported. Estimates of effectiveness from primary studies were combined using a narrative method. The method of rounding the effectiveness estimates to the nearest 5% may not be appropriate, as 5% differences may have non-negligible impacts on the results. The authors did not explore this possibility. Although the authors excluded some outcomes such as other fractures, non-MI coronary heart disease events, uterine cancer, Alzheimer's disease and venous thromboembolism, they adequately discussed the potential biases this may have introduced.

Validity of estimate of measure of benefit
The measure of benefit was the number of events avoided. This is a disease-specific measure so any cost-effectiveness ratios derived would not be comparable with those calculated for other diseases.

Validity of estimate of costs
All the categories of costs relevant to the perspective adopted were included in the analysis, although there were insufficient details of the derivation of the costs of side effects. This issue was not explored in the sensitivity analysis, although it was possibly not too influential. The resource use data were derived from the literature. A sensitivity analysis of the quantities was not conducted, which may limit the interpretation of the study findings. The unit costs were taken from published sources and a sensitivity analysis of the prices was not conducted. The price data were adequately reported and reflated to year 2000 when necessary. Although discounting was not used, it was appropriate. The costs and the quantities were not reported separately, which may limit transferability exercises to other settings.

Other issues
The unit price of raloxifene was so much less than the alternatives that it was always likely to have a superior cost-effectiveness ratio. An incremental cost-effectiveness analysis should have been performed, as should a sensitivity analysis varying the price data. An aspect of generalisability to other settings was addressed by incorporating persistence rates more relevant to real practice, rather than those of clinical trials usually used in other models.

Another issue addressed by the authors was that the paper was initially submitted before the availability of Women Health Initiative study results, which showed the inadequacy of considering hormone replacement therapy as a long-term preventive alternative. A further limitation was the exclusion of recent data that may warrant inclusion in future analysis, such as data on stroke and colorectal cancer, which may be influenced by some of the evaluated strategies.

Implications of the study
Beyond the stated conclusions, the authors made no further recommendations for policy or treatment practice, or for further research.

Source of funding
