Cost-effectiveness of alendronate therapy for osteopenic postmenopausal women

Schousboe J T, Nyman J A, Kane R L, Ensrud K E

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 5-year treatment with alendronate in postmenopausal women with osteopenia.

Type of intervention
Secondary prevention.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of postmenopausal women with osteopenia, aged 55 to 75 years, and with a bone mineral density (BMD) T-score between -2.4 and -1.5.

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

Dates to which data relate
The clinical data were derived from studies published between 1982 and 2005. The costs and resource use data came from studies published in 2002 and 2004. The price year was 2001.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies and authors' assumptions.

Modelling
A Markov model was constructed to examine the lifetime clinical and economic consequences of 5-year treatment with alendronate, compared with no treatment, among osteopenic postmenopausal women. Eight health states were considered. More specifically, no fracture, post-distal forearm fracture, post-clinical vertebral fracture (i.e. clinically evident at onset), post-radiographic vertebral fracture (i.e. not clinically evident at onset), post-hip fracture, post-other fracture (i.e. fracture of the proximal forearm, humerus, scapula, clavicle, sternum, ribs, pelvis, distal femur, patella, tibia, or proximal fibula), post-hip and vertebral fracture, and death. The cycle length was 6 months and the time horizon was lifetime. Women in the no fracture state could develop a distal forearm, hip, clinical vertebral, radiographic vertebral, or other fracture, at which time transition to that post-fracture state occurred. Different combinations of starting age (55, 65 and 75 years) and femoral neck T-score (-1.5, -2.0 and -2.4) were considered. The model incorporated an increased relative risk for a subsequent fracture after an incident fracture of the same type.

Outcomes assessed in the review
The outcomes estimated from the literature were:

- the probability of fractures,
- the efficacy of alendronate,
- the mortality rates, and
- the quality of life associated with each health state.

**Study designs and other criteria for inclusion in the review**

It was unclear whether a systematic review of the literature had been undertaken to identify the primary estimates. Much of the data were derived from published studies, but limited information on the design and characteristics of the primary studies was provided. Data on the efficacy of alendronate was derived from a clinical trial (the Fracture Interventional Trial). Age-specific first fracture rates were estimated from population-based data of residents in Rochester, Minnesota. Mortality data came from US life statistics. An appendix provided details of the approach used to calculate all transition probabilities and all of the sources used.

**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**

Fourteen primary studies provided clinical evidence.

**Methods of combining primary studies**

A narrative method appears to have been used to combine the primary estimates.

**Investigation of differences between primary studies**

Not stated.

**Results of the review**

The incidence rate of radiographic (but clinically unapparent) vertebral fracture was set at 1.86 times that of clinical vertebral fractures. The rates for other fractures were the sum of incidences of the specific fracture types.

The following relative risks were considered:

- 4.0 for a subsequent vertebral fracture after an incident vertebral fracture,
- 1.7 for a subsequent hip fracture after an incident hip fracture, and
- 2.05 for a subsequent distal forearm fracture after an incident distal forearm fracture.
For women taking alendronate, the relative risk for incident vertebral fractures (over placebo) was 0.54 for those with a femoral neck T-score of -2.0 to -2.4, and 0.82 for those with a T-score of -1.5. The relative risk for non-vertebral fractures was 1.0.

The mortality associated with acute hip fracture was 1.375 times that of the base rate.

Quality of life values were as follows:

- no fracture state, 0.84;
- post-distal forearm fracture, 0.82 in the first year, then 0.839;
- post-other fracture, 0.753 in the first year, then 0.813;
- post-hip fracture, 0.67 in the first year, then 0.68;
- post-clinical vertebral fracture, 0.58 in the first year, then 0.76;
- post-radiographic vertebral fracture, 0.76 in the first 6 years, then 0.84;
- post-hip and clinical vertebral fracture, 0.41 in the first year, then 0.60.

**Methods used to derive estimates of effectiveness**

The authors made some assumptions that were used in the decision model.

**Estimates of effectiveness and key assumptions**

It was assumed that excess mortality was not directly attributable to vertebral fractures or other non-hip fractures. Drug adherence was assumed to have been 100%.

**Measure of benefits used in the economic analysis**

The summary benefit measure used was the quality-adjusted life-years (QALYs). The QALYs were estimated using the decision model. An annual discount rate of 3% was applied. The utility values were derived from the literature.

**Direct costs**

The economic analysis was carried out from a societal perspective. The direct costs included were for alendronate and for the treatment of fractures. The long-term costs of fractures were also considered. The cost of alendronate came from average wholesale prices, while direct costs of fractures (and associated resources) were derived from published studies. The costs associated with follow-up physician visits were obtained from Medicare reimbursement rates. A breakdown of the cost items for fracture costs was not reported and the costs were presented as macro-categories. The unit costs and the quantities of resources used were not reported separately. The price year was 2001. Discounting was relevant, as the costs were incurred during a long timeframe, and an annual rate of 3% was applied.

**Statistical analysis of costs**

The costs were treated deterministically in the base-case.

**Indirect Costs**

The indirect costs (i.e. lost days of work) were included in the analysis. These were derived from age-specific salaries for US women and published workforce participation. Lost days of work after various fractures were estimated from a published study. The workdays lost because of each type of fracture were reported, but the unit costs were not. The price year was 2001. An annual discount rate of 3% was applied.
Currency
US dollars ($).

Sensitivity analysis
A sensitivity analysis was carried out to examine the robustness of the cost-utility ratios to variations in the model inputs and assumptions. A univariate sensitivity analysis was performed, assuming preventable excess mortality for the first year after a clinical vertebral fracture. Drug costs, discount rates, fracture rates, fracture costs, and the disutility from fractures were varied in this analysis. A two-way sensitivity analysis was also carried out in which the relative risks for vertebral and nonvertebral fractures during alendronate therapy were varied from 0.8 to 0.4 and from 1.0 to 0.6, respectively. Sensitivity analyses were also used to model the possible effects of nonadherence to therapy, with alendronate used appropriately for only 2 years (with a 6-month offset of benefit) or used inappropriately for 2 years such that fracture reduction benefit was reduced by one third. A probabilistic sensitivity analysis was carried out using 2-stage Monte Carlo simulations. Ranges of values, which were either based on the literature or were set by the authors, were reported in an appendix.

Estimated benefits used in the economic analysis
In the group of women with a femoral neck T-score of -1.5, the QALYs associated with alendronate and placebo were, respectively, 14.864 and 14.847 for a woman aged 55 years, 11.400 and 11.385 for a woman aged 65 years, and 7.838 and 7.826 for a woman aged 75 years.

In the group of women with a femoral neck T-score of -2.0, the QALYs associated with alendronate and placebo were, respectively, 14.744 and 14.700 for a woman aged 55 years, 11.293 and 11.249 for a woman aged 65 years, and 7.846 and 7.811 for a woman aged 75 years.

In the group of women with a femoral neck T-score of -2.4, the QALYs associated with alendronate and placebo were, respectively, 14.686 and 14.591 for a woman aged 55 years, 11.168 and 11.112 for a woman aged 65 years, and 7.716 and 7.673 for a woman aged 75 years.

Cost results
In the group of women with a femoral neck T-score of -1.5, the costs associated with alendronate and placebo were, respectively, $15,877 and $11,528 for a woman aged 55 years, $13,401 and $9,142 for a woman aged 65 years, and $10,489 and $6,502 for a woman aged 75 years.

In the group of women with a femoral neck T-score of -2.0, the costs associated with alendronate and placebo were, respectively, $20,863 and $16,710 for a woman aged 55 years, $17,568 and $13,502 for a woman aged 65 years, and $13,838 and $10,033 for a woman aged 75 years.

In the group of women with a femoral neck T-score of -2.4, the costs associated with alendronate and placebo were, respectively, $26,820 and $22,739 for a woman aged 55 years, $22,222 and $18,261 for a woman aged 65 years, and $17,298 and $13,580 for a woman aged 75 years.

Synthesis of costs and benefits
An incremental cost-utility ratio was calculated to combine the costs and QALYs of alendronate therapy over placebo.

In the group of women with a femoral neck T-score of -1.5, the incremental cost per QALY gained with alendronate therapy over placebo was $255,823 for a woman aged 55 years, $283,933 for a woman aged 65 years, and $332,250 for a woman aged 75 years.

In the group of women with a femoral neck T-score of -2.0, the incremental cost per QALY gained with alendronate therapy over placebo was $94,386 for a woman aged 55 years, $92,409 for a woman aged 65 years, and $108,714 for a
woman aged 75 years.

In the group of women with a femoral neck T-score of -2.4, the incremental cost per QALY gained with alendronate therapy over placebo was $74,200 for a woman aged 55 years, $70,732 for a woman aged 65 years, and $86,465 for a woman aged 75 years.

The sensitivity analysis showed that base-case results were robust to variations in model inputs and assumptions, and that the resultant incremental cost-effectiveness ratios were higher than $50,000 per QALY in almost all cases.

The cost per QALY gained with alendronate was only less than $50,000 with additional fracture risk factors that, together, conferred a BMD-adjusted relative fracture risk of 2.0 or higher. For a 65-year-old woman with a T-score of -2.0 and no additional BMD-independent fracture risk factors, if alendronate reduced the incidence of vertebral fractures by 50%, then the cost per QALY gained was less than $50,000 only if the relative risk for non-vertebral fractures during alendronate therapy was 0.7 or less.

The probabilistic sensitivity analysis showed that the probability that alendronate had a cost per QALY lower than $50,000 was 1% for a 65-year-old woman with a T-score of -2.0 and no additional BMD-independent fracture risk factors. However, if the cost of alendronate was half that of the 2001 average US wholesale price, the cost per QALY gained was $48,750.

**Authors’ conclusions**

Five-year alendronate therapy in postmenopausal women with osteopenia was not cost-effective in the USA. The authors stated that their results were probably generalisable to risedronate and raloxifene, agents that are of similar cost and efficacy to alendronate. However, their results were not generalisable to oestrogen replacement therapy.

**CRD COMMENTARY - Selection of comparators**

The authors justified the selection of the interventions compared in the study. Alendronate was chosen because it was one of the most commonly prescribed antiresorptive agents. No treatment (i.e. placebo) was selected because it represented the actual management strategies for osteopenic women. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**

The effectiveness evidence came from published studies. However, it was not explicitly stated whether a systematic review of the literature was undertaken to identify the primary estimates, which appear to have been identified selectively. Details of the design of the primary studies and patient sample were not reported clearly. Thus, it was difficult to assess the validity of the primary sources of clinical evidence. However, extensive information on the method used to calculate the transition probabilities was given in the appendix. The primary estimates were combined in the model using a narrative approach and each source provided single estimates. Differences between the primary studies were not investigated. Some assumptions were also made. The issue of uncertainty around the clinical estimates was extensively addressed in the sensitivity analyses (both deterministic and probabilistic).

**Validity of estimate of measure of benefit**

QALYs were used as the summary benefit measure. This was appropriate as they capture the impact of survival and quality of life in a single measure. Discounting was applied, as recommended by US guidelines. Utility adjustments were derived from the literature, but limited information on the source of the data was reported. QALYs are comparable with the benefits of other health care interventions.

**Validity of estimate of costs**

The adoption of a societal perspective was appropriate as all costs were included in the analysis, irrespective of the payer. The costs and resource use data were derived from published studies, thus few details on the approaches used to
estimate the economic data were reported in the current study. The unit costs and the quantities of resources used were not presented, which limits the possibility of replicating the cost analysis in other settings. Alternative sources of values were used in the sensitivity analysis. The price year was reported, which aids reflation exercises in other time periods. Discounting was relevant and was appropriately carried out.

**Other issues**
The authors stated that limited studies had been carried out on the cost-effectiveness of pharmacologic therapy to prevent osteoporotic fractures in osteopenic women. However, it was noted that their findings were consistent with a study carried out by the National Osteoporosis Foundation. The authors stressed that their findings were generalisable only to the postmenopausal white female population in the USA. Extensive sensitivity analyses were performed, which enhance the external validity of the study.

The authors noted some limitations of their study. For example, the model did not include the indirect costs from the loss of ability to do housework or care for other family members, and assumed zero long-term care costs attributable to non-hip fractures. In addition, risk factors that are not measured routinely in clinical practice, such as prevalent radiographic vertebral fracture or elevated markers of bone resorption, or other risk factors such as falls, were not considered. Several strengths of the analysis were also noted. For example, all fractures that may be linked to osteoporosis were included, and the inclusion of indirect costs.

**Implications of the study**
The study results suggested that alendronate therapy is not cost-effective for postmenopausal women who have not had a fracture and who do not have additional risks strongly predictive of fracture independent of BMD. However, the authors pointed out that their conclusion should be reconsidered in the following cases:

- if the cost of drug therapy was significantly lowered;
- if drug therapy reduced the risk for non-vertebral fractures in this population;
- if fracture reduction benefit persisted longer than 10 years after a 5-year treatment course.

**Source of funding**
Funded through grants from Hologic Inc., Eli Lily & Co, Pfizer and NPB Pharmaceuticals.

**Bibliographic details**

**PubMedID**
15867405

**Other publications of related interest**


**Indexing Status**

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NHS Economic Evaluation Database (NHS EED)
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**MeSH**

Aged; Alendronate /economics /therapeutic use; Bone Density; Bone Diseases, Metabolic /complications /diagnosis /drug therapy; Cost-Benefit Analysis; Female; Fractures, Bone /prevention & control; Humans; Longitudinal Studies; Markov Chains; Middle Aged; Postmenopause; Quality-Adjusted Life Years; Risk Factors; Sensitivity and Specificity

**AccessionNumber**

22005008186

**Date bibliographic record published**

31/12/2005

**Date abstract record published**

31/12/2005