Treatment of established osteoporosis: a systematic review and cost–utility analysis

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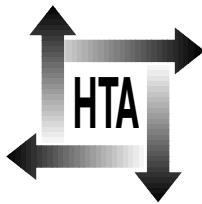
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Executive summary

Health Technology Assessment
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the various committees.

Executive summary

Background and aims

Osteoporosis is a systemic skeletal disease, characterised by low bone mass and micro-architectural deterioration of bone tissue with a subsequent increase in bone fragility and susceptibility to fracture.

The most serious clinical consequence of osteoporosis is hip fracture, which increases in incidence exponentially with age and incurs high morbidity, mortality and healthcare expenditure. Other common fractures occur at the spine, forearm and shoulder.

Osteoporosis is operationally defined by the measurement of bone mineral density (BMD) at the hip, and is diagnosed in women when BMD is 2.5 standard deviations (SDs) or more below the average for young healthy women. Established osteoporosis denotes the disease in the presence of one or more fragility fractures.

A variety of agents are available for the treatment of osteoporosis. The evidence for their efficacy is examined and their cost-effectiveness is modelled in established osteoporosis.

Methods

Therapeutic intervention
A systematic review was undertaken of all random-ised controlled trials (RCTs) in which fracture was measured as an outcome. RCTs that studied fracture benefits in patients in whom osteoporosis or osteopaenia was not identified were excluded, as were epidemiological studies, although account was taken of these lower levels of evidence in the interpretation and subsequent analysis of infor-mation. The interventions reviewed were: bisphos-phonates, vitamin D, 1-alpha hydroxylated deriv-atives of vitamin D, calcitonin, calcium, oestrogens, oestrogen-like agents, anabolic steroids, fluoride salts, thiazide diuretics, raloxifene, vitamin K_2, protein supplements and exercise.

Epidemiology, costs and utilities
The annual risk of osteoporotic fracture was characterised for women from the UK. Fractures of the hip, spine, distal forearm and humerus were designated as being osteoporotic. Collectively, they account for approximately 70% of osteoporotic fractures in postmenopausal women and more than 70% of the morbidity.

The risk of osteoporotic fractures in women at the threshold for osteoporosis was determined from a published meta-analysis of the relationship between BMD and fracture risk. The risk of such a fracture in the presence of a prior osteoporotic fracture was computed from a published meta-analysis of the relationship between the prior occurrence of fracture of each type and the risk of a future fracture of each type.

The consequences of fracture on mortality were assessed for each fracture type. The annual risk of breast cancer, coronary heart disease (CHD) and mortality were reviewed so that extraskeletal risks and benefits of hormone replacement therapy (HRT) and raloxifene could be modelled.

Costs and utilities were determined for osteo-porosis in the UK by systematic review of the literature.

Health economics model
A model was developed comprising an individual patient-based approach that simulated whether or not events occurred in each subsequent year for each patient.

Transition states included fracture states (hip, wrist, vertebral and proximal humerus), death from hip fracture, nursing home admission owing to the hip fracture, fatal and non-fatal CHD, fatal and non-fatal breast cancer, and death from other causes.

The model simulated cohorts at fixed ages (50, 60, 70 and 80 years) with established osteoporosis. The proportions of the population with different fracture types were simulated from the known distribution of these fractures at different ages.

Effectiveness was populated from the systematic review of interventions in osteoporosis. Treatments were given for 5 years using a 5-year offset time, except for calcium and calcitonin for which a ▶

3-year offset time was used (in this context, offset time is the duration for which an effect persists after the treatment stops). The analytic framework was set at 10 years. Because of the many uncertainties, particularly for hip fracture and extra-skeletal risks and benefits, extensive sensitivity analyses were undertaken for each agent.

Results

The results of the systematic review of RCTs indicated that bisphosphonates, calcitonin, calcium, fluoride salts and raloxifene reduced the incidence of vertebral fracture. The bisphosphonate, alendronate, also decreased non-vertebral fracture, including hip fracture.

For several agents, failure to demonstrate efficacy, particularly for hip fracture, was largely due to the lack of appropriate RCTs. Epidemiological evidence suggested that treatment with calcium, calcitonin, HRT, thiazide diuretics, etidronate and anabolic steroids decreased hip fracture risk. There was also RCT evidence that calcium plus vitamin D decreased fracture risk in patients for whom BMD was not known.

The results for each agent at each age are presented as a central estimate of cost per quality-adjusted life-year (QALY) gained compared with no treatment. Costs were discounted at 6% and QALYs at 1.5% in base-case scenarios. The estimate was bounded by a 90% confidence interval representing the range of cost–utility that was incurred by 90% of the combinations of relative risks (RRs) for efficacy.

Cost-effectiveness was graded A–D from the range of cost-effectiveness ratios using a threshold value of £30,000/QALY gained to denote good cost-effectiveness.

Only those agents that RCT data showed to have significant effectiveness for at least one fracture outcome were tested – raloxifene, HRT, calcium (with and without vitamin D), calcitonin, alendronate, other bisphosphonates, fluoride and alfacalcidol.

It was not cost-effective to treat established osteoporosis with raloxifene in the time frame modelled. If cardiovascular benefits were assumed, treatment was only cost-effective compared with no intervention at ages of at least 70 years.

HRT was not cost-effective except below the age of 60 years. However, treatment became cost-

effective from the age of 50 years if the effects on appendicular fractures reported in epidemiological studies were included. Additional benefits from reductions in CHD, with additional risks from an increased incidence of breast cancer, did not markedly change the conclusions on cost-effectiveness.

Treatment with calcium alone was cost-effective compared with no intervention from age 60 years, assuming an effect only on vertebral fracture risk. Treatment was cost-effective at all ages if effects on appendicular fractures were included, as shown by the RCT data for calcium with vitamin D.

Treatment with calcitonin was not cost-effective at any age largely because of its high costs. Treatment with alendronate was only cost-effective from age 70 years onwards.

Since no difference in efficacy between the bisphosphonates could be shown, a pooled analysis was undertaken using the cost of intervention equivalent to etidronate. 'Bisphosphonate' treatment was cost-effective from age 60 years solely because its therapeutic cost was lower than that for alendronate.

Using the meta-analysis of RCTs, treatment with fluoride was not cost-effective, largely because of a high point estimate for hip fracture risk (RR = 1.78). If no adverse effect on hip fracture was assumed, then treatment became cost-effective from age 60 years.

Compared with no treatment, it was not cost-effective to treat established osteoporosis with alfacalcidol except at ages of 70 years or more.

Further sensitivity analyses were undertaken, focussing on those agents with cost-effectiveness grades A or B.

Age and cost of intervention were important determinants of cost-effectiveness. Cost-effectiveness ratios were sensitive to changes in discount rates for benefits and in the assumption relating to offset of effect (offset time). Cost-effectiveness was markedly improved when women with T-scores under –2.5 SD were selected.

The results were not markedly affected by the threshold used for cost-effectiveness, poor compliance, variations in the assumptions about mortality after hip fracture, duration of treatment and duration of analysis. The inclusion of costs for added years of life had little effect in the elderly ▶

but improved cost-effectiveness in women aged up to 60 years. In contrast, the inclusion of all vertebral fractures (in addition to clinically overt fractures) had a marked effect on improving cost-effectiveness.

Conclusions

Cost-effective scenarios for several interventions in the management of established osteoporosis were identified. Cost-effectiveness ratios decrease with age. At age 50 years, only HRT and calcium plus vitamin D were cost-effective (assuming that the agent would decrease the risk of appendicular fractures at this age). At age 80 years, HRT, calcium with or without vitamin D, alfacalcidol, alendronate and bisphosphonate were all cost-effective.

The conclusions derived are conservative, mainly because of the assumptions made in the absence of sufficient data. The conservative assumptions included the following:

(i)   not all osteoporotic fractures are included
(ii) not all vertebral fractures are included
(iii) base-case scenarios are modelled at the threshold for osteoporosis
(iv) risks of re-fracture in the few years after a fracture are likely to be underestimated
(v)   vertebral fracture incurs no reversible mortality
(vi) long-term effects of osteoporotic fractures on utilities are ignored.

Thus conclusions that treatments are cost-effective are reasonably secure. In contrast, scenarios shown to be cost-ineffective are less secure. As information in these areas becomes available, the implications on cost-effectiveness of interventions should be reappraised.

Recommendations for research
Intervention thresholds differ substantially from diagnostic thresholds, and should be based on the absolute fracture probability that depends not only on the T-score but also on other independent risk factors. Health economics assessment based on probability of fracture is an important area for further research.

Other areas for further research arise from gaps in empirical knowledge on utilities and side-effects that are amenable to primary research. Further secondary research should be undertaken to more closely evaluate the impact of vertebral deformities (rather than clinically overt vertebral fractures) on cost-effectiveness.

Publication

NHS R&D HTA Programme

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This has meant that the HTA panels can now focus more explicitly on health technologies ('health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care) rather than settings of care. Therefore the panel structure has been redefined and replaced by three new panels: Pharmaceuticals; Therapeutic Procedures (including devices and operations); and Diagnostic Technologies and Screening.

The HTA Programme continues to commission both primary and secondary research. The HTA Commissioning Board, supported by the National Coordinating Centre for Health Technology Assessment (NCCHTA), will consider and advise the Programme Director on the best research projects to pursue in order to address the research priorities identified by the three HTA panels.

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