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

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Authors’ objectives
To compare the effectiveness of pharmacological and non-pharmacological interventions in preventing osteoporotic fractures in patients with osteopaenia, osteoporosis or established osteoporosis.

Searching
A number of databases including MEDLINE, EMBASE and the Cochrane Controlled Trials Register were searched; further details were reported in the review. Full search strategies were also reported to be available from the authors on request. There were no language restrictions. In addition, the references lists of relevant studies were checked and citations searches were carried out using the Science Citation Index. Further attempts to identify studies were made by consulting experts, health technology assessment and guideline producing agencies, and research and trials registers via the Internet. Up-to-date literature was also requested from relevant pharmaceutical companies. Five journals, identified as particularly relevant by the authors, were handsearched from January 1990 onwards.

Study selection

Study designs of evaluations included in the review
Only published, randomised controlled trials (RCTs) were eligible.

Specific interventions included in the review
Studies that evaluated the following interventions were eligible: bisphosphonates, vitamin D, 1-alpha hydroxylated derivatives of vitamin D, calcitonin, pharmacological doses of calcium, oestrogens, oestrogen-like molecules, anabolic steroids, fluoride salts, thiazide diuretics, selection oestrogen receptor modulators (SERMs), and non-pharmacological interventions.

Participants included in the review
Studies that included patients with a diagnosis of established osteoporosis, osteopaenia or osteoporosis were eligible. Patients with primary and secondary disease were included.

Outcomes assessed in the review
Studies that reported vertebral or non-vertebral fractures were included.

How were decisions on the relevance of primary studies made?
A single reviewer assessed the titles and, when available, abstracts of identified studies for relevance. Two subject experts checked a sample of 20 abstracts against the inclusion criteria.

Assessment of study quality
The methodological quality of the included studies was assessed using a tool developed by Gillespie et al. (see Other Publications of Related Interest no.1). Definitions of the various levels of randomisation and concealment of randomisation, as derived from Prendiville et al. (see Other Publications of Related Interest no.2) were also incorporated into the tool. A single reviewer carried out the quality assessment of the included studies. Two experts assessed a sample of 5 studies using the same tool.

Data extraction
A single reviewer extracted data from the included studies using a predefined data extraction form. No further details of the data extraction were reported.

For each study that reported fracture incidence as the number of patients sustaining fractures, the relative risk (RR) of
patients in the intervention group developing a new fracture(s) compared to those in the control group was calculated.

**Methods of synthesis**

**How were the studies combined?**

Data from studies that allowed the RR to be calculated for patients in the intervention group developing a new fracture(s) compared to those in the control group were combined in a fixed-effect model. The authors assessed publication bias for interventions for which at least 5 trials were included in a meta-analysis.

**How were differences between studies investigated?**

Differences between the included studies were discussed within the text of the review. In addition, the authors carried out two sensitivity analyses. The first excluded studies in which fracture was not a primary end point, while the second excluded studies in which it was not specified that the outcome assessors were blinded to the treatment.

**Results of the review**

A total of 83 RCTs met the inclusion criteria for the review.

Vertebral fracture: the data presented suggested that bisphosphonates, calcitonin, fluoride, raloxifene and possibly vitamin K2 reduced the risk of vertebral fracture. The authors also reported that calcium appeared to be effective in patients with low calcium intakes. There was no evidence from the included studies that vitamin D derivatives, oestrogen, oestrogen-like molecules, anabolic steroids, protein supplements or brisk walking reduced the risk of fracture. For treatment with bisphosphonate, fluoride, and SERMS, there was no significant difference in the risk of fracture when patients were stratified according to the presence or absence of prevalent vertebral fractures.

Non-vertebral fracture: the authors stated that bisphosphonates were the only intervention that demonstrated a reduction in the risk of non-vertebral fracture. The bisphosphonate, alendronate, also decreased the incidence of hip fractures. No intervention demonstrated a reduction in the risk of non-vertebral fracture in patients without prior fracture.

**Cost information**

Yes. At age 50 years, hormone replacement therapy (HRT) and calcium plus vitamin D (assuming that the agent would decrease the risk of appendicular fractures at this age) were cost-effective. At age 80 years, the following agents were cost-effective: HRT, calcium with or without vitamin D, alfacalcidol, alendronate and bisphosphonate.

**Authors’ conclusions**

The principal findings of the review showed that there are effective treatments for established osteoporosis in women.

**CRD commentary**

The methodological quality of the review was high, and the search was comprehensive and included contact with experts and handsearching. The study selection, data extraction and validity assessment processes were described. The data were clearly presented and appropriate methods were used to combine the data. This was a thorough review of the area and the authors’ conclusions follow from the data presented.

**Implications of the review for practice and research**

Practice: The authors stated that calcium is the agent of choice at ages of 50 to 70 years and bisphosphonates at age 80 years. However, the authors stated that it would be unwise to recommend a hierarchy of preferred treatments.

Research: The authors stated that a health economics assessment, based on the probability of fracture, is an important area for further research.
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