Systematic review of role of bisphosphonates on skeletal morbidity in metastatic cancer

CRD summary
This review assessed the effect of bisphosphonates on skeletal morbidity in people with bone metastases. The authors concluded that, when given for at least 6 months, bisphosphonates decreased skeletal morbidity in metastatic bone disease but did not affect spinal cord compression or survival. The authors did not report full details of the assessment processes and the included studies were diverse.

Authors’ objectives
To assess the effectiveness of bisphosphonates for reducing skeletal morbidity in people with bone metastases.

Searching
MEDLINE (1966 to June 2001), EMBASE (1980 to June 2001), Cancerlit (1975 to June 2001), the Science Citation Index Expanded (1981 to June 2001), the Cochrane Library, and the reference lists of articles were searched; the search terms were reported. The authors also handsearched relevant journals and meeting abstracts, and contacted experts in the field and drug companies for unpublished data. There were no language restrictions.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included.

Specific interventions included in the review
Studies were eligible for inclusion if they compared oral or intravenous bisphosphonate versus another bisphosphonate, placebo or usual care. The intravenous bisphosphonates included pamidronate and zoledronic acid, while the oral bisphosphonates included clodronate and etidronate.

Participants included in the review
Eligible studies included people with confirmed malignant cancer and bone metastases. Haematological malignancies, apart from multiple myeloma, were excluded. The participants were people with breast cancer, multiple myeloma, prostate cancer and various mixed cancer diagnoses.

Outcomes assessed in the review
Eligible studies included at least one skeletal morbidity outcome. The primary outcome measures of the review were time to first skeletal-related event and the reduction in skeletal morbidity assessed by pathological fractures, radiotherapy to bone metastases, spinal cord compression, hypercalcaemia and orthopaedic surgery. The secondary outcomes of interest included the efficacy of bisphosphonates over time, the efficacy of one type over another, the relative effects in different disease groups, the comparison of administration routes, survival and tolerability. Pain relief was not included as an end point because another review has been published on this topic (see Other Publications of Related Interest).

How were decisions on the relevance of primary studies made?
Two independent reviewers determined the relevance of studies for inclusion in the review. It was unclear how any disagreements were resolved.

Assessment of study quality
Trials were assessed for allocation concealment (on a scale of A to D) and blinding according to Cochrane guidelines.

The authors did not state how many reviewers performed the validity assessment. All relevant papers were included at
the initial stage, regardless of whether they satisfied the validity criteria.

**Data extraction**
Two independent reviewers extracted the outcome data as proportions.

**Methods of synthesis**
How were the studies combined?
For studies of at least 6 months’ duration, the authors conducted a meta-analysis with a random-effects model. The odds ratio (OR) was used as a summary measure for each outcome. The inverse variance method was used to weight the included studies.

How were differences between studies investigated?
The authors used chi-squared tests to compare groups.

**Results of the review**
Thirty RCTs fulfilled the inclusion criteria, 18 of which were included in the meta-analyses. These included data from 3 unpublished trials. The number of participants included in each meta-analysis varied (range: 2,543 to 3,894), and the total number of participants overall was not reported.

A meta-analysis of studies (n=18) lasting at least 6 months found that, compared with placebo, bisphosphonates statistically significantly reduced the risk of vertebral fractures (OR 0.69, 95% confidence interval, CI: 0.57, 0.84, P<0.0001), non-vertebral fractures (OR 0.65, 95% CI: 0.54, 0.79, P<0.0001), combined fractures (OR 0.65, 95% CI: 0.55, 0.78, P<0.0001), radiotherapy (OR 0.67, 95% CI: 0.57, 0.79, P<0.0001) and hypercalcaemia (OR 0.54, 95% CI: 0.36, 0.81, P<0.003). There was no effect on spinal cord compression or orthopaedic surgery, although there was a reduction in orthopaedic surgery in studies lasting more than 1 year (OR 0.59, 95% CI: 0.39, 0.88, P<0.009).

Eight studies indicated that bisphosphonates statistically significantly increased time to first skeletal-related event and had no effect on survival. A subgroup analysis found that there was most evidence to support intravenous aminobisphosphonates.

The results of other secondary end points were also reported.

**Authors’ conclusions**
When given for at least 6 months, bisphosphonates statistically significantly decreased skeletal morbidity in people with metastatic bone disease. There appeared to be no effect on survival.

**CRD commentary**
The authors clearly defined the review question, inclusion criteria and search strategy, and steps were taken to minimise bias in the review process. It appeared that all studies were initially included in the review, regardless of whether they met the validity criteria. The quality of the studies included in the meta-analysis was unclear. Although a random-effects model was used to accommodate sources of variation in the subsequent synthesis of studies, the apparent high level of heterogeneity was not fully explored or reported in the paper. The authors’ conclusions reflect the evidence presented, but given the limitations highlighted, their reliability is unclear.

**Implications of the review for practice and research**
Practice: The authors stated that treatment with bisphosphonates should begin at the time of diagnosis and continue until no longer clinically relevant.

Research: The authors stated that further research on the optimum bisphosphonate regimen for people with bone
metastases, and the effects of bisphosphonates in other disease groups, is needed.

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**Other publications of related interest**

This additional published commentary may also be of interest. Munro AJ. Review: bisphosphonates reduce fractures, radiotherapy, and hypercalcaemia and increase time to a first skeletal related event. Evid Based Med 2004;9:83.

**Indexing Status**
Subject indexing assigned by NLM

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**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.