Lack of evidence for fracture prevention in early breast cancer bisphosphonate trials: a meta-analysis
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CRD summary
This review concluded that bisphosphonates in the adjuvant setting among women with breast cancer did not decrease the number of fractures compared with placebo or no treatment. The authors' conclusions should be interpreted with caution as they were based on studies of uncertain quality.

Authors' objectives
To investigate the efficacy of adjuvant bisphosphonates in preventing fractures among patients with early breast cancer.

Searching
Published trials in any language were identified through a search of MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Knowledge to January 2009. Search terms were reported. Abstracts from three major scientific meetings were searched electronically. Reference lists of retrieved articles were searched.

Study selection
Randomised controlled trials of adjuvant bisphosphonates compared with no treatment or placebo in patients with early breast cancer were eligible for inclusion. Trials that compared immediate with delayed bisphosphonate were eligible for inclusion. The primary outcome was fracture rate. Intervention bisphosphonates included zoledronic acid, risedronate, ibandronate, clodronate or pamidronate. Comparison groups received no treatment, placebo or delayed zoledronic acid. Duration of treatment ranged from one to five years.

The authors did not state how the studies were selected for the review.

Assessment of study quality
The authors did not systematically assess study quality; they extracted data on randomisation, allocation concealment, withdrawals and blinding for some studies.

Data extraction
Two independent reviewers used data on numbers of events in each group to derive odds ratios (OR) for each trial; disagreements were resolved by consensus.

Studies with zero events in both groups were excluded from analyses. Authors of included studies were contacted if outcomes were missing or omitted from included trials.

Methods of synthesis
Pooled odds ratios and corresponding 95% CIs were calculated by Mantel-Haenszel fixed-effect meta-analysis or DerSimonian-Laird random-effects model. Intention-to-treat analyses were conducted. Statistical heterogeneity was assessed using the Q statistic. Prespecified subgroup analysis investigated the effect of treatment in groups of patients with accelerated bone loss and increased fracture risk, postmenopausal women and patients who received aromatase inhibitors.

Results of the review
Fourteen trials (n=7,461) were included in the review. Sample sizes ranged from 50 to 1,803 participants. Five of the nine trials evaluated for study quality were double blinded. Four trials provided details of randomisation, three gave details of allocation concealment, all described withdrawals and eight trials used an intention-to-treat analysis.

Bisphosphonates did not significantly reduce the fracture rate compared to no treatment (OR 0.84, 95% CI 0.65 to...
1.09; 14 trials). Subgroup analyses showed that bisphosphonates did not reduce the fracture rate in postmenopausal women (OR 0.82, 95% CI 0.55 to 1.20; seven trials) or in women receiving aromatase inhibitors (OR 0.79, 95% CI 0.53 to 1.17; six trials).

No heterogeneity was observed for any outcome. Sensitivity analysis that excluded two studies that did not perform intention-to-treat analyses did not influence the results.

Authors' conclusions
Bisphosphonates in the adjuvant setting among women with breast cancer did not decrease the number of fractures compared with placebo or no treatment.

CRD commentary
This review addressed a clear question supported by appropriate inclusion criteria. A limited number of relevant databases were searched. There were reasonable attempts to identify unpublished data. Publication bias was not considered in the report. Suitable methods to minimise risk of reviewer error and bias were reported for data extraction, but not for study selection. It was unclear whether the authors formally assessed the validity of included trials; it appeared that nine trials were quality assessed, but it was unclear why the remaining five were not. Results were pooled using meta-analysis. Heterogeneity was assessed. The authors noted that none of the trials were powered to detect differences in fracture rates and did not present results on the actual number of fractures that occurred.

There were some methodological difficulties with the review, specifically the lack of quality assessment for all studies; the authors’ conclusions should be interpreted with caution as they were based on studies of uncertain quality.

Implications of the review for practice and research
Practice: The authors stated that bisphosphonates should not be routinely used in the adjuvant treatment of early breast cancer.

Research: The authors stated that trials of prophylactic bisphosphonates in breast cancer patients at high risk for osteoporotic fractures should be carried out.

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