Results of indirect and mixed treatment comparison of fracture efficacy for osteoporosis treatments: a meta-analysis
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CRD summary
The authors concluded that there were differences in fracture risk reduction profiles between pharmacologic therapies for postmenopausal osteoporosis and the findings may assist therapy choice. The authors’ conclusions are generally suitably cautious but it remains unclear which of the treatments for osteoporosis most effective.

Authors' objectives
To assess the effectiveness of postmenopausal osteoporosis therapies in reducing fracture risk.

Searching
MEDLINE (from 1950), EMBASE (from 1980), CINAHL and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to November 2009 for publications in English. Search terms were reported in a previous review (published on www.nice.org.uk). Reference lists were screened manually.

Study selection
Eligible studies were randomised placebo controlled trials (RCTs) that compared the efficacy of on-label marketed therapies for osteoporosis on mixed trauma and non-traumatic fracture in postmenopausal women (those at risk of osteoporotic fracture with or without previous fracture, patients with osteoporosis, osteopenia, normal bone mineral density and glucocorticoid-induced osteoporosis). Eligible trials had to include 10 or more patients and report follow-up at 12 months or more. Eligible therapies were denosumab, bazedoxifene, alendronate, risedronate, ibandronate (2.5g/day), zoledronic acid, etidronate, strontium ranelate, teriparatide and raloxifene. Relevant trials that reported fracture as adverse events were eligible for inclusion. Open-label trials and abstracts were excluded from the review.

Included trials were conducted between 1990 and 2010. Where reported, the mean age of women ranged between 51.2 and 83 years. Most trials administered therapies orally at varying doses. Study duration ranged from 52 to 260 weeks.

A team of reviewers screened studies for inclusion.

Assessment of study quality
Trial quality was assessed using the Jadad score of randomisation, blinding and reporting of withdrawals and drop-outs.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Data on new radiologically identified vertebral, clinical vertebral, non-vertebral hip and wrist fractures were extracted to calculate relative risks and their associated 95% confidence intervals.

Two reviewers independently extracted data; discrepancies were resolved through discussion.

Methods of synthesis
Fixed-effect and random-effects models were used to pool relative risks and their 95% confidence intervals to directly compare osteoporosis treatments versus placebo and indirectly compare denosumab versus other active treatments. Where one treatment arm had zero events, 0.5 was added to both arms. Trials with zero events in both treatment arms were excluded from the analyses.

A mixed treatment comparison was conducted using a Bayesian approach to combine data from direct and adjusted indirect comparisons to calculate pooled relative risks and their 95% credible intervals (CrI). Meta-regression methods were used to investigate factors influencing treatment effects.

Statistical heterogeneity was assessed using the Cochran’s Q test and I² statistic. Sensitivity analyses were performed by
including only the trials that reported fractures as adverse events.

**Results of the review**

Thirty-four RCTs (73,464 women) were included in the review. Five RCTs scored 5 on the Jadad scale, nine scored 4, 11 scored 3, four scored 2 and five scored 1.

**Direct comparisons:** All osteoporosis treatments except etidronate showed statistically significant reductions in risk of new vertebral fractures compared to placebo (RR ranged from 0.30 to 0.72). Denosumab, risedronate and zoledronic acid also statistically significantly reduced risk of non-vertebral and hip fractures compared to placebo. Alendronate, strontium ranelate and teriparatide showed statistically significant reductions in risk compared to placebo for non-vertebral fractures. There were no statistically significant differences in risk of wrist fractures for any treatment compared to placebo.

**Mixed treatment comparisons:** The findings for each comparator versus placebo were consistent with direct comparisons for new vertebral fractures. Compared to placebo, risk of non-vertebral fracture was only statistically significantly reduced with teriparatide (RR 0.47, 95% CrI 0.22 to 0.90) and risedronate (RR 0.80, 95% CrI 0.65 to 0.95).

Mixed treatment comparisons showed that denosumab was statistically significantly more effective in preventing new vertebral fractures compared to strontium ranelate, raloxifene, alendronate and risedronate (RR ranged from 0.45 to 0.56). These reflected the adjusted indirect comparison results. No other statistically significant differences between active treatments were identified. Mixed treatment comparisons and indirect comparisons that compared osteoporosis treatments were generally consistent for risk of non-vertebral fracture.

Sensitivity analyses did not significantly alter the findings. Findings from meta-regression were reported in the review.

**Authors’ conclusions**

The evidence indicates there are differences in fracture risk reduction profiles for the available pharmacologic therapies for postmenopausal osteoporosis and provides results that may assist therapy choice.

**CRD commentary**

The review question and supporting inclusion criteria were clearly stated. The search for literature was restricted by language and language bias may have been introduced. Trial quality was assessed using appropriate criteria and the scores showed that trial quality was variable.

A large evidence base was presented but most comparisons were based on a small number of RCTs and some confidence or credible intervals were wide. The authors acknowledged the limitations of mixed treatment comparisons and highlighted the high heterogeneity across trials. The authors went some way to investigate the underlying sources of heterogeneity. The authors acknowledged that some trials were excluded from the analyses due to zero events.

There was potential for bias in the review and some uncertainties regarding the evidence base. The authors’ conclusions were generally cautious. However, it should be borne in mind that comparisons between osteoporosis treatments were based on indirect comparisons and did not compare all the treatments to one another. It therefore remains unclear which treatments are most effective.

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

**Practice:** The authors stated that the review reflects real-life effectiveness provided that the risk of fracture and adherence and persistence to therapy were similar to the original RCTs.

**Research:** The authors stated that future real-world effectiveness can be improved by considering efficacy and side effect profiles in conjunction with patient preference, comorbidities, potential barriers to adherence and cost of therapy when selecting the most appropriate therapy for each patient.

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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.