The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women

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CRD summary
This review set out to compare clinical and cost effectiveness of strontium ranelate with bisphosphonate alendronate for prevention of osteoporotic fracture. Limited data from three placebo-controlled trials of strontium ranelate, a lack of direct comparison with bisphosphonates and review weaknesses mean that the authors’ conclusion that strontium ranelate was clinically effective is likely to be of limited reliability and value.

Authors' objectives
To assess the clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fracture in postmenopausal women, at different levels of fracture risk.

Searching
MEDLINE, PREMEDLINE, EMBASE, CINAHL, Cochrane Database of Systematic Reviews, DARE, HEED, NHS EED, NEAT, HTA database, Science Citation Index and TRIP were searched to March 2005 and a search strategy for MEDLINE was reported. No language, date, or study type restrictions were applied. The bibliographies of included studies and industry submissions were searched for additional studies.

Study selection
RCTs that compared strontium ranelate with the bisphosphonate alendronate in postmenopausal women with osteoporosis (with or without previous fracture) were eligible for inclusion. Acceptable outcome measures were survival, incident vertebral fracture, incident non-vertebral fracture, adverse effects, continuance, compliance, cost and health-related quality of life. Studies in which participants were not vitamin D replete and/or had insufficient calcium intake were excluded. All included studies assessed the effectiveness of strontium ranelate at a dose of 2 g/day; one study also assessed doses of 0.5g/day and 1g/day. Two studies used the semi-quantitative method of Genant to define fracture and one used a definition of at least 20% reduction in one of the ratios of vertebral height.

Studies considered relevant from a screening of the titles and abstracts were obtained as full manuscripts and assessed for inclusion; the authors did not report how many reviewers were involved in this process.

Assessment of study quality
The methodological quality of included studies was assessed using a published tool (Gillespie et al) designed for the assessment of trials of interventions to prevent osteoporosis-related fractures. The tool included: adequacy of randomisation and allocation concealment; blinding of outcome assessors; treatment of withdrawals; comparability of groups at baseline; confirmation of diagnosis of hip or other appendicular skeleton fracture; and method of diagnosis of vertebral fracture.

Quality assessment was carried out by one researcher, who was not blinded to the author, institution or journal of publication.

Data extraction
Numbers of participants in each group suffering vertebral fracture, relative risk and 95% confidence interval (95% CI) was extracted for each study and follow-up period; number needed to treat (NNT) was calculated where possible.

Data were extracted by one reviewer using standardised data extraction forms.

Methods of synthesis
Where studies had comparable populations, intervention dosing regimens and outcome measures, and where sufficient data were reported, a pooled estimate of relative risk with 95% CI was calculated using a random-effects model.

**Results of the review**

Three RCTs (STRATOS, SOTI and TROPOS) reported in 24 articles were included in the review. The total number of participants was unclear. The mean age of participants ranged from 66 to 77 years. All included studies compared strontium ranelate with placebo. Participants in STRATOS received calcium and vitamin D supplements in addition to treatment; participants in SOTI and TROPOS received vitamin D supplements in addition to treatment. STRATOS was a two-year randomised multicentre double-blinded phase II dose-ranging study. The other two trials were three-year randomised multicentre double-blinded phase III studies.

Pooled data from SOTI and TROPOS indicated that strontium ranelate was associated with a significant reduction in the risk of vertebral fracture over three years compared with placebo (relative risk 0.60, 95% CI: 0.53 to 0.69, p<0.001) and non-vertebral fracture (relative risk 0.84, 95% CI: 0.73 to 0.97, p<0.01). The studies were not powered to detect significant differences at any specific peripheral site. The pooled number needed to treat for three-year fracture prevention was 11. Subgroup data showed that the risk reduction remained significant for all subgroups.

Strontium ranelate therapy was not generally associated with an increased risk of adverse events. Most adverse events were mild and transient. However, risk of venous thromboembolism was found to be significantly higher for strontium ranelate compared with placebo (relative risk 1.42, 95% CI: 1.02 to 1.98, p = 0.036). Nervous system disorders, including mental impairment, disturbed consciousness, memory loss and seizures were more common in patients randomised to strontium ranelate.

**Cost information**

Results of the algorithm used to assess cost-effectiveness showed that strontium ranelate could be used cost effectively in women at relatively high risk of osteoporotic fracture, but the probabilistic sensitivity analysis indicated that it was not as cost-effective as alendronate.

**Authors' conclusions**

Strontium ranelate was clinically effective in the prevention of osteoporotic fractures. Scenarios had been identified where strontium ranelate can be used cost-effectively, but probabilistic sensitivity analyses indicated that it was less cost effective than the bisphosphonate alendronate.

**CRD commentary**

The review stated a clear research question and defined appropriate inclusion criteria. Despite extensive searches, only a small number of studies were identified and none met all of the inclusion criteria; the comparator in all cases was placebo and not alendronate, as specified. The review process was largely conducted by a single reviewer and was, therefore, potentially susceptible to error and/or bias. An appropriate topic-specific tool was used to assess the methodological quality of included studies, but the results of this assessment were poorly described in the main text (tables were included in appendices to the report). Pooled estimates of three-year relative risk of incident vertebral fracture and non-vertebral fracture were presented, on the basis of which the authors concluded that strontium ranelate was clinically effective. However, these estimates were based on data from only two trials. Given the other limitations of the review (in particular the lack of direct comparison with alternative treatments) they are likely to be of limited value.

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

**Practice:** The authors made no recommendations for practice.

**Research:** Further data was required on the effectiveness of strontium ranelate for the prevention of osteoporotic fracture, particularly in relation to hip fractures. Investigation of the potential relationship between effectiveness and age or absolute risk may be useful. Given that head-to-head comparison trials of strontium ranelate versus bisphosphonates were unlikely to be conducted, indirect comparisons (such as: bisphosphonates with vitamin D and calcium versus vitamin D and calcium; and strontium ranelate with vitamin D and calcium versus vitamin D and calcium) may be useful.
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