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[Intervention Review]

Strontium ranelate for preventing and treating postmenopausal osteoporosis

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ABSTRACT

Background

Strontium ranelate is a new treatment for osteoporosis therefore, its benefits and harms need to be known.

Objectives

To determine the efficacy and safety of strontium ranelate for the treatment and prevention of postmenopausal osteoporosis.

Search methods

We searched MEDLINE (1996-March 2005), EMBASE (1996-week 9 2005), the Cochrane Library (1996-Issue 1 2005), reference lists of relevant articles and conference proceedings from the last two years. Additional data was sought from authors.

Selection criteria

We included randomized controlled trials (RCTs) of at least one year duration comparing strontium ranelate to placebo and reporting fracture incidence, bone mineral density (BMD) or adverse events in postmenopausal women. Treatment population was defined as women with prevalent vertebral fractures and/or lumbar spine BMD T-score < -2.5 SD.

Data collection and analysis

Two reviewers independently determined study eligibility, assessed study validity, graded the evidence and extracted relevant data. Disagreements were resolved by consensus. RCTs were grouped by dose and treatment duration. Where possible, meta-analysis was conducted using the random effects model.

Main results

Four trials met the inclusion criteria. Three had losses to follow-up > 20% and only one provided an adequate description of allocation concealment. Three included a treatment population (0.5 to 2 g/day of strontium ranelate) and one a prevention population (0.125, 0.5 and 1 g/day). A 37% reduction in vertebral fractures (RR 0.63, 95% CI 0.56, 0.71), and a 14% reduction in non-vertebral fractures with the upper boundary of the confidence interval approaching one (RR 0.86, 95% CI 0.75, 0.98), were demonstrated over three years with 2 g of strontium ranelate daily in a treatment population. An increase in BMD was shown at all sites after two to three years of treatment in both populations. Lower doses of strontium ranelate were superior to placebo and the highest dose demonstrated the greatest reduction in vertebral fractures and increase in BMD. An increased risk of diarrhea with 2 g of strontium ranelate daily was found; however, adverse events did not affect the risk of discontinuing treatment nor did it increase the risk of serious side effects, gastritis or death. Additional

data suggests that the risk of vascular and nervous system side-effects is increased with taking 2 g of strontium ranelate daily over three to four years.

Authors' conclusions

There is silver level evidence (www.cochranemsk.org) to support the efficacy of strontium ranelate for the reduction of fractures (vertebral and to a lesser extent, non-vertebral) in postmenopausal osteoporotic women and an increase in BMD in postmenopausal women with/without osteoporosis. Diarrhea may occur, however, adverse events leading to study withdrawal were not significantly increased. Potential vascular and neurological side-effects need to be further explored.

PLAIN LANGUAGE SUMMARY

Strontium ranelate for osteoporosis in women after menopause

This summary of a Cochrane review presents what we know from research about the effect of strontium ranelate for osteoporosis in women after menopause. The review shows that:
There is silver level evidence (www.cochranemsk.org) that for treatment of osteoporosis in women after menopause, 2 g of strontium ranelate daily over 3 years decreases fractures in the spine and slightly decreases fractures not in the spine. Most women do not have side effects that would cause them to stop taking strontium ranelate. However, other research shows that harms could include a chance of blood clots and seizures, memory loss and consciousness.

What is osteoporosis and how can strontium ranelate help?

Osteoporosis is a condition in which bone loss occurs. Bone loss leads to weak brittle bones that can break easily, even during everyday activities. Breaks (fractures) of the spine or non-spine (e.g. wrist and hip) are the most common type. There are many drugs and minerals that work to treat osteoporosis. Strontium ranelate is a drug that decreases the chance of fractures by slowing the loss of bone and possibly by building new bone. It is a new drug and therefore its benefits and harms need to be known.

What are the results of this review?

Women in the studies took 2 g of strontium ranelate or a placebo (fake tablets or powder). After 2 to 3 years, the number of fractures that occurred and bone mineral density was measured. Bone mineral density is a lab test to measure how dense or strong bones are in the hip, spine or neck. The higher the bone density the better.

Benefits of strontium ranelate

In women after menopause who have osteoporosis:

- strontium ranelate decreases spine fractures:

13 out of 100 women had spine fractures taking strontium ranelate

21 out of 100 women had spine fractures taking a placebo

- strontium ranelate may decrease fractures that are not in the spine:

10 out of 100 women had non-spine fractures taking strontium ranelate

12 out of 100 women had non-spine fractures taking a placebo

- strontium ranelate increases bone mineral density

1 in 3 women had an increase in spine and hip bone mineral density taking strontium ranelate

Harms of strontium ranelate

In women after menopause who have osteoporosis:

- strontium ranelate did not cause side effects that would make them stop taking it

- strontium ranelate did not lead to serious side effects, stomach infections, back pain or death

- strontium ranelate increased diarrhea

6 out of 100 women had diarrhea taking strontium ranelate

4 out of 100 women had diarrhea taking a placebo

Other research shows that harms could include a chance of blood clots, and seizures, memory loss and consciousness. The cause of these vascular and neurological side effects are not known.

This review has several limitations which include difficulty interpreting the change in bone mineral density due to the unique aspects of strontium in bone as well, incomplete follow-up of some patients within the individual trials.

BACKGROUND

Osteoporosis is a skeletal disorder characterized by low bone mass and micro-architectural deterioration of bone resulting in an increase in bone fragility and risk of fracture (1993 Consensus; NIH 2001). It most often affects postmenopausal women as reductions in circulating levels of estrogen lead to accelerated bone turnover and resorption. The most common sites of osteoporotic fracture are the wrist, hip and spine however, osteoporotic fractures do occur at other sites (Seeley 1991). Osteoporotic fractures are a major burden for the individual, their families and society (Johnell 2004; Kanis 2003; Cauley 2000). Individuals who suffer osteoporotic fractures, particularly spine or hip, must deal with the complications which include reductions in health-related quality-adjusted life years, increased morbidity and mortality (Cauley 2000; Johnell 2004; Tosteson 2001). Furthermore, the direct and indirect expenditures associated with the care of these individuals, particularly hip fracture patients, is costly (US Dept Health 2004; Ray 1997). In Europe, the number of osteoporotic fractures was estimated to be 3.79 million in 2000 and the associated total direct costs were 31.7 billion Euros (Kanis 2004). In the United States, approximately 1.5 million osteoporotic fractures occur each year (US Dept Health 2004) and the cost of fractures was estimated to be 20 billion US dollars in 1995 (Ray 1997). With the aging of the population, and the age-specific increases in osteoporotic fracture rates, it has been suggested that these costs will more than double in the coming decades (Burge 2003).

The bone fragility which characterizes this disease is a result of an imbalance in bone remodeling (bone resorption exceeds bone formation) and an increase in the rate of remodeling at the tissue level (Seeman 2002). Risk factors associated with fragility fracture include advancing age, prior fragility fracture, family history of osteoporosis/fracture and low bone mineral density (BMD) (Brown 2002). A working group of the World Health Organization in 1994 proposed that an individual with a BMD more than 2.5 standard deviations (SD) below the young adult mean has osteoporosis (WHO 1994). Furthermore, it has been estimated that for every one SD reduction of BMD, there is an increase in relative risk of fracture of approximately 1.5 to 2.6 (Marshall 1996).

Effective therapies are available and have been demonstrated to reduce the relative risk of fracture by 40 to 60% (Cranney 2002). Pharmacotherapy for prevention and treatment of osteoporosis includes two primary types of drugs, anti resorptive and anabolic agents. Anti resorptive agents increase bone strength by decreasing the number of bone multicellular units. This reduces resorption and prevents further structural damage of trabecular bone and by reducing cortical porosity. In contrast, anabolic agents increase bone strength by increasing bone mass due to an increase in the number of bone multicellular units. As result the magnitude of the formation phase is greater than the resorption phase (Riggs 2005).

The majority of the agents currently available for the treatment of osteoporosis are anti resorptive (e.g. bisphosphonates, estrogen, selective estrogen modulators and calcitonin) and there are a few anabolic agents (e.g. intermittent recombinant human parathyroid hormone and fluoride) (Sorbera 2003). A novel oral agent, strontium ranelate, has been suggested to simultaneously decrease bone resorption and stimulate bone formation although there is some controversy surrounding its mechanism of action.

Strontium ranelate consists of two divalent cation atoms of stable strontium (natural element) and an organic moiety (ranelic acid) which dissociates at the gastro-intestinal level. Strontium is a cation (i.e. positively charged ion) and physically closely related to calcium, an active component of the skeleton. Ranelic acid is an organic, highly polar molecule without pharmacological activity (EMEA 2004). In vitro, strontium ranelate has been suggested to have a dual effect on bone; however, in vivo long term dosing of strontium ranelate in OVX rats and monkeys resulted in increased bone formation but non-significant trends of bone resorption. In human studies (phase III trials), there is some evidence of increases in bone formation markers (serum bone-specific alkaline phosphatase and C-terminal propeptide of type I procollagen) and decreases in markers of bone resorption (serum C-telopeptide and urinary N-telopeptide cross links) from the third month of treatment (2 g of strontium ranelate daily) up to three years. Potential mechanisms of action include activation of calcium-sensing receptor or induction of cellular differentiation. The proposed indication is for treatment of postmenopausal osteoporosis in order to reduce the risk of fracture (EMEA 2004).

Different doses of strontium ranelate have been tested. In a two year randomized controlled trial doses from 0.5 g to 2 g per day were tested in 353 women with postmenopausal osteoporosis (Meunier 2002) and in another two year randomized controlled trial, doses from 0.125 g to 1 g per day were evaluated in 160 early postmenopausal women (Reginster 2002-1). In both trials, the primary efficacy endpoint was BMD and results showed a clear dose response. All tested doses were superior to placebo with the highest dose of strontium ranelate (2 g per day) demonstrating the greatest increase in BMD after adjusting for bone strontium content over two years (Reginster 2003-1). As a result, 2 g of strontium ranelate per day is considered the recommended daily dose and was the only dose evaluated in the two phase III trials (Meunier 2004-1; Reginster 2005).

Given the potential advantages of strontium ranelate in the prevention and treatment of osteoporosis, and that it is a new therapeutic agent, it is important that the benefits and harms of this therapy are fully explored through a systematic review of the literature.

OBJECTIVES

To assess the clinical efficacy and safety of strontium ranelate in the prevention and treatment of osteoporosis compared to placebo or active comparator in postmenopausal women through a systematic review of the literature. The following major endpoints were used for this purpose: 1) Fractures (vertebral and non-vertebral); 2) BMD; 3) Health related quality of life and; 4) Safety. A treatment (versus prevention) population was defined as postmenopausal women with prevalent vertebral fractures and/or lumbar spine BMD T score < -2.5 SD.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized placebo or active comparator-controlled trials of at least one year duration were included in this review. Studies were excluded if they were not truly randomized (e.g. patients

randomized using date of birth) but not on the basis of language of publication.

Types of participants

Postmenopausal women, in which menopause was either surgically or naturally induced, were included.

Types of interventions

Trials that investigated the effect of strontium ranelate versus placebo or an active comparator were included however, trials that investigated multiple interventions where the effect of strontium ranelate could not be separated out were not included.

Types of outcome measures

Efficacy measures:

1. The primary efficacy outcome was the number of women with incident vertebral and non-vertebral fractures (a feasible outcome for a treatment population). Asymptomatic vertebral fractures were included if they were either quantitatively or semi-quantitatively ascertained via a radiographic examination as well, symptomatic (or clinical) vertebral fractures as defined by acute back pain and radiographic findings were also included. Non-vertebral fractures included all appendicular type fractures except fractures of the coccyx, skull, jaw, face, ankle, fingers or toes as they are not considered to be osteoporotic related (Meunier 2004-1; Reginster 2005).

2. The secondary efficacy outcome to fractures (or surrogate outcome) was the mean percent change in BMD of the lumbar spine, femoral neck and total hip measured by Dual Energy X-Ray Absorptiometry (DXA) at baseline and yearly intervals (a relevant outcome for both prevention and treatment populations). Strontium ranelate has a higher atomic number than calcium. When present in bone as it attenuates x-rays to a greater extent than calcium resulting in an overestimation of BMD as measured by DXA (Blake 2005). As a result, BMD measurements should be adjusted for strontium content in order to avoid such an artifactual increase in BMD. The correction used to adjust for the strontium content in bone in the lumbar spine BMD measurements has been described as an indirect method and based on: 1) the correlation between the strontium content measured in the iliac crest on bone biopsy and the area under the curve of the integrated strontium plasma curve; and 2) the correlation between the bone strontium content measured in lumbar vertebrae and the iliac crest in monkeys. However, given that no correlation has been established between femoral neck and iliac crest bone strontium content is not adjusted for at the other BMD sites (Meunier 2002).

3. Health Related Quality of Life (a relevant outcome for a treatment population).

4. Safety measures include the following (relevant for both prevention and treatment populations):
i) Total withdrawals (the total number of withdrawals after enrolment in the study).
ii) Withdrawals due to adverse events (withdrawals as a result of an adverse event)
iii) Number of emergent adverse events (adverse events that developed during the study).
iv) Serious adverse events (adverse events that were immediately life-threatening, or resulted in hospitalization, disability, malignant disease or death) (Reginster 2002-1).
v) Number of adverse events affecting the gastrointestinal system (e.g. diarrhea or gastritis)
vi) Deaths

Search methods for identification of studies

Electronic searches

Strontium ranelate is a relatively new drug and it was anticipated that most of the trials would have been published in the past five years therefore, our search focused on this time period only. Our search aimed to identify all trials of strontium ranelate for either the prevention or treatment of postmenopausal osteoporosis and we employed the following approaches (based on Cochrane search strategy outlined by Robinson and Dickersin) (Robinson 2002):

- An electronic search of MEDLINE (1996 to March 2005), EMBASE (1996 to week 9 2005) and the Cochrane Library (1996 to Issue 1 2005). Our search strategy included MeSH terms such as osteoporosis, postmenopausal and strontium ranelate in addition, complementary free text words. We limited the search to randomized controlled trials and supplemented it to include previously completed systematic reviews. Appendix 1 shows the search strategies.

Searching other resources

We also searched:

- A review of reference lists of relevant articles for additional published trials.
- A hand search of abstracts from Osteoporosis International, Journal of Bone and Mineral Research, Calcified Tissue International and FDA proceedings from the last two years.
- Lastly, additional information was sought from authors and industry sponsors.

Data collection and analysis

Selection of studies

The bibliographic record (i.e. title, authors, keywords and abstract) retrieved from the search were assessed by two independent reviewers (SO'D, AC) for potential eligibility based on the review's a priori eligibility criteria. Those records deemed potentially eligible, or those in which there was not enough information, underwent a full text review to confirm their inclusion.

Data extraction and management

Data were independently extracted by both reviewers (SO'D, AC) using a data extraction form designed specifically for this review. Details of the study population, duration of intervention, baseline demographic data, and the outcomes were collected. Differences with respect to article eligibility, quality assessment and data extraction were resolved by referring to the original publication and establishing consensus (Alderson 2003).

Assessment of risk of bias in included studies

Methodological quality was assessed by two independent reviewers (SO'D, AC) using a validated instrument by Jadad (Jadad 1996). This checklist includes three items pertaining to descriptions

of randomization, blinding, and the inclusion of data for dropouts and withdrawals, with a total score of five. Studies with a score less than or equal to two were considered low quality studies. Allocation concealment was also evaluated by two independent reviewers (SO'D, AC) using the allocation component of a validated instrument (Schulz 1995). As outlined in the Cochrane Reviewer's Handbook, the allocation concealment was determined to be: A) adequate i.e. central randomization; numbered or coded bottles or containers; drugs prepared by the pharmacy; serially numbered, opaque, sealed envelopes; or other description that contained elements convincing of concealment, B) unclear i.e. authors either did not report an allocation concealment approach at all or reported an approach that was neither adequate nor inadequate, C) inadequate i.e. alternation or reference to case record numbers or to dates of birth, and D) not used.

Measures of treatment effect

Where possible, the analyses were based on intention-to-treat data from the individual clinical trials. For fractures and safety outcomes, a weighted relative risk was determined for the number of women with either incident fractures or adverse events using Review Manager 4.2.7 (Fleiss 1993). For BMD, a weighted mean difference (WMD) of the percent change between treatment and control groups for different BMD sites including lumbar spine, femoral neck and total hip was calculated. Analyses of the four trials were conducted using an available data set as it was not possible to carry out an intention to treat analysis with the published data.

In addition to relative measures, the absolute risk reduction (ARR) was calculated and for those outcomes that were statistically significant, the number needed to treat (NNT) was determined. The NNT was calculated by taking the inverse of the ARR (NNT = 1/ARR) where ARR is the control event rate minus the treatment event rate.

Unit of analysis issues

There were no unit of analysis issues identified.

Dealing with missing data

We did not contact authors for missing data.

Assessment of heterogeneity

Heterogeneity of the treatment effect was calculated using a chi-square test with n -1 degrees of freedom; where n is the number of studies and the I^2 statistic (Fleiss 1993; Higgins 2003).

Assessment of reporting biases

This was not undertaken.

Data synthesis

Meta-analysis was conducted according to random effects model.

Subgroup analysis and investigation of heterogeneity

Prior to the pooling, we developed hypotheses that might account for heterogeneity of study results and compared groups according to: 1) treatment duration, 2) dose and, 3) prevention versus treatment populations.

Sensitivity analysis

We idid not undertake any sensitivity analyses.

Summary of findings and assessment of the certainty of the evidence

Grading the strength of the evidence per outcome:
We used the ribbon grading system as described in the 2004 Evidence-based Rheumatology *BMJ* book (Tugwell 2004) to grade the strength of the evidence per outcome. The ribbon grading system uses four categories to rank the evidence from research studies: Platinum, Gold, Silver and Bronze. The ranking is given according to different criteria, including sample size, blinding, handling of withdrawals and concealment allocation (Tugwell 2004). The ranking of the efficacy outcomes (i.e. fractures and BMD) is included in the synopsis, abstract, methodological quality of included studies and the clinical relevance tables (see Additional Tables - 01 and 02) of this review.

These results are summarized in the clinical relevance tables of this review (see Additional Tables - 01 and 02).

Summary of findings and assessment of the certainty of the evidence

Grading the strength of the evidence per outcome:
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These results are summarized in the clinical relevance tables of this review (see Additional Tables - 01 and 02).

RESULTS

Description of studies

Results of the search

A total of 80 potentially relevant studies were identified from the electronic and hand search strategy outlined above and screened for retrieval. Of these, 62 were excluded as they did not meet the review's eligibility criteria and 18 underwent a full text review (Meunier 2003; Meunier 2004-3; Meunier 2002; Meunier 2004-1; Reginster 2002-1; Reginster 2005; Boivin 2003; Meunier 2004-2; Naveau 2004; Pors 2004; Reginster 2002-2; Reginster 2003-1; Reginster 2003-2; Reginster 2004; Reginster 2004-1; Sorbera 2003; Uebelhart 2003; Marquis 2005). Of these 18 records, a total of 13 were excluded as a result of being either a review publication (Meunier 2004-2; Reginster 2003-1; Meunier 2004-3; Boivin 2003; Naveau 2004; Pors 2004; Reginster 2002-2; Reginster 2003-2; Reginster 2004; Reginster 2004-1; Sorbera 2003; Uebelhart 2003) or a description of the study protocol (Meunier 2003). The remaining five studies met our eligibility criteria, four of which were primary studies (Meunier 2002; Meunier 2004-1; Reginster 2002-1; Reginster 2005) and one, an abstract, that was a companion paper to the included study by Meuneir et al., 2004 (Marquis 2005). There was no previous systematic review on this topic.

Included studies

All four included primary studies were randomized placebo controlled trials (Meunier 2002; Meunier 2004-1; Reginster 2002-1; Reginster 2005). Three investigated the efficacy of strontium ranelate in a treatment population (Meunier 2002; Meunier 2004-1; Reginster 2005) and one included a prevention population (Reginster 2002-1). The mean age of the postmenopausal women studied ranged from 54.2 (Reginster 2002-1) to 76.7 years (Reginster 2005). None of the women had a previous vertebral fracture in one study (Reginster 2002-1), approximately half had a prior vertebral fracture in one (Reginster 2005) and all of the women had a prior vertebral fracture in two (Meunier 2002; Meunier 2004-1). The women's mean BMD T score was < - 2.5 SD in three (Meunier 2002; Meunier 2004-1; Reginster 2005) and > - 2.5 SD in one (Reginster 2002-1). With respect to dosages of strontium ranelate received, the three treatment studies included the recommended daily dose of strontium ranelate (2g) (Meunier 2002; Meunier 2004-1; Reginster 2005) whereas in the prevention trial; the highest daily dose was 1 g (Reginster 2002-1). The compliance rate ranged from 80% (Reginster 2005) to 93% (Meunier 2002). All four studies included a calcium supplement in both treatment and control groups which ranged in dose from 500 mg (Meunier 2002; Reginster 2002-1) to 1000 mg (Meunier 2004-1; Reginster 2005) daily. In three trials, women in the treatment and control groups also received vitamin D supplements which ranged from 400 to 800 IU daily based on serum concentrations of 25-hydroxyvitamin D (Reginster 2005; Meunier 2004-1) or 800 IU daily (Meunier 2002). No other osteoporotic treatments were administered. Three studies assessed vertebral fractures (Meunier 2002; Meunier 2004-1; Reginster 2005) and two included non-vertebral fractures (Meunier 2004-2; Reginster 2005). All four studies measured BMD, three of which assessed BMD of the lumbar spine (Meunier 2002; Reginster 2002-1; Meunier 2004-1), three at the total hip (Reginster 2002-1; Meunier 2004-1; Reginster 2005) and four at the femoral neck (Meunier 2002; Reginster 2002-1; Meunier 2004-1; Reginster 2005). Quality of life was assessed in two trials (Meunier 2004-1; Reginster 2005). Total withdrawals, withdrawals due to adverse events, emergent adverse events, serious adverse events and deaths were reported in all four studies (Meunier 2004-1; Reginster 2002-1; Reginster 2005; Meunier 2002) whereas the number of individuals that developed diarrhea or gastritis was reported in three (Meunier 2002; Meunier 2004-1; Reginster 2005). Additional details regarding the characteristics of the included studies are presented in the Characteristics of Included Studies Table of this review.

Excluded studies

At the full text stage, a total of 13 were excluded as a result of being either a review publication (Meunier 2004-2; Reginster 2003-1; Meunier 2004-3; Boivin 2003; Naveau 2004; Pors 2004; Reginster 2002-2; Reginster 2003-2; Reginster 2004; Reginster 2004-1; Sorbera 2003; Uebelhart 2003) or a description of the study protocol (Meunier 2003).

Risk of bias in included studies

The quality of the included studies was assessed using the Jadad instrument (Jadad 1996). Quality scores, percent lost to follow-up and allocation concealment grades are summarized in the Characteristics of Included Studies Table of this review. All four studies were adequately reported as randomized and described adequate methods regarding the sequence of randomization. All reported that the trial was double blind. Of these, two indicated that the recipients of care were unaware of their assigned intervention (Reginster 2002-1; Reginster 2005). One reported that the persons responsible for assessing outcomes were unaware of the assigned intervention (Meunier 2004-1). And one reported that the recipients, those providing the care and persons responsible for assessing outcomes were all unaware of the assigned intervention (Meunier 2002). A description of withdrawals was adequately provided in all four studies. All trials had a methodological quality score of greater than three out five on the Jadad checklist (mean 4.25, range 4-5). However, despite their adequate overall quality scores, three of the included studies had losses to follow-up greater than 20% (Meunier 2002; Meunier 2004-1; Reginster 2005) and only one provided an adequate description of allocation concealment (Meunier 2002). Lastly, the analyses of the four trials were conducted using an available analysis set, which is not preferred but close to the intention to treat' principle (Alderson 2003). For the efficacy outcomes of this review (fractures and BMD), a "silver" level of evidence has been assigned as none of the randomized trials met all of the criteria required for a gold level ranking i.e. sample size of at least 50 in each group, blinding of patients and assessors for outcomes, loss to follow-up < 20% and adequate allocation concealment (Tugwell 2004).

Effects of interventions

FRACTURES:

See Table 1

Vertebral Fractures:
Vertebral fractures were determined by the quantitative morphometric assessment method by Genant (Meunier 2002; Meunier 2004-1) and semi-quantative visual assessments (Meunier 2004-1; Reginster 2005). Patients were not obligated to undergo a vertebral x-ray in one of the phase III trials however, x-rays were obtained for the largest number of patients as possible (total of 3640 patients or 71%) (Reginster 2005).

In osteoporotic women, 2 g of strontium ranelate per day demonstrated a 41% relative reduction in radiographic vertebral fractures over a one year period (three trials, n=5254, RR 0.59, 95% CI 0.46 to 0.74) with a number needed to treat of 32 (Meunier 2002; Meunier 2004-1; Reginster 2005) and a 37% relative reduction over a three year period (two trials, n = 5082, RR 0.63, 95% CI 0.56 to 0.71) with a number needed to treat of 13 (Meunier 2004-1; Reginster 2005) compared to placebo. The chi-square test for heterogeneity of treatment effect was not significant in either of these analyses (i.e. p > 0.1).

There was only one trial (n=1442) that investigated the effects of 2 g of strontium ranelate versus placebo per day on symptomatic or clinical vertebral fractures in osteoporotic women (Meunier 2004-1). The results from this trial demonstrated a 52% relative reduction in risk of a symptomatic fracture (RR 0.48, 95% CI 0.29 to 0.80) over a one year period and a 38% relative reduction (RR 0.62, 95% CI 0.47 to 0.83) over three years.

With respect to the lower doses of strontium ranelate, one trial demonstrated a 31% relative reduction in radiographic vertebral fractures in osteoporotic women using 0.5 g of strontium ranelate versus placebo per day over a two year period however, this was not statistically significant (RR 0.69, 95% CI 0.47 to 1.01)

(Meunier 2004-1). The same study showed a 6% relative reduction in radiographic vertebral fractures using 1.0 g of strontium ranelate daily over the same time frame again, this was not statistically significant (RR 0.94, 95% CI 0.68 to 1.30) (Meunier 2004-1).

Non-vertebral Fractures:
Non-vertebral fractures were reported by study investigators based on radiographic evaluation or written documentation provided e.g. radiological report, copy of the hospitalization/emergency department report (Meunier 2004-1, Reginster 2005).

In osteoporotic women, 2 g of strontium ranelate per day demonstrated a 14% relative reduction in 'all non-vertebral fractures' (including hip but excluding fractures of the coccyx, skull, jaw, face, ankle, fingers and toes) over a three year period (two trials, n = 6572, RR 0.86, 95% CI 0.75 to 0.98) with a number needed to treat of 58 compared to placebo (Meunier 2004-1; Reginster 2005). However, the upper boundary of the confidence interval approximates one. The chi-square test for heterogeneity of treatment effect was not significant.

One study (n = 4932) reported on 'major osteoporotic non-vertebral fractures' defined as fractures of the wrist, pelvis and sacrum, ribs-sternum, clavicle, humerus or hip only in women with osteoporosis and found a 19% relative reduction taking 2 g strontium ranelate daily compared to placebo although the upper boundary of the confidence interval approached one (RR 0.81, 95% CI 0.66 to 0.98) (Reginster 2005).

There were no studies that evaluated the effects of lower doses of strontium ranelate on the incidence of non-vertebral fractures.

Hip:
There was only one trial that assessed the efficacy of 2 g of strontium ranelate per day versus placebo on the relative reduction of hip fractures in women with osteoporosis (Reginster 2005) therefore, we were unable to estimate a pooled relative risk. Hip fractures, similar to other non-vertebral fractures, were determined by a radiological evaluation or by a report from a hospitalization. After three years, the relative risk reduction of hip fractures was 15% (RR 0.85, 95% CI 0.61 to 1.19) in the total group of women (n=4932) versus 36% for a subgroup at high risk of hip fracture (n=1977) defined by age $\geq$ 74 years and a femoral neck BMD T-score $\leq$ - 3 (Looker 1991) (RR 0.64, 95% CI 0.412 to 0.997). The treatment effect was only borderline statistically significant for the subgroup of women at high risk of hip fracture however, this study was not powered for this efficacy outcome.

BMD:

See Table 2

Lumbar Spine BMD:
Using 2 g of strontium ranelate daily versus placebo, an increase in lumbar spine BMD was demonstrated in osteoporotic women over a two year period (two trials, n = 1614, WMD adjusted for strontium content 5.44, 95% CI 3.41 to 7.46 and WMD, not adjusted for strontium content 11.29, 95% CI 10.22 to 12.37) (Meunier 2002; Meunier 2004-1). However, the chi-square test for heterogeneity of treatment effect was significant for the analysis involving the results adjusted for strontium content (p=0.04) and I^2 = 76.6%. We investigated sources of clinical heterogeneity and a possible explanation relates to the difference in timing and methods of the strontium content calculation from bone-biopsy samples between the two trials (Meunier 2004-1; Meunier 2002). Based on pooled estimates, the number needed to treat was 3 for lumbar spine BMD adjusted for strontium content at 2 years. This means that 3 women would have to be treated with strontium ranelate for one of them to have a minimal clinically important improvement in lumbar spine BMD after 2 years. There was only one trial (n=1442) that investigated the effects of 2 g of strontium ranelate daily versus placebo in osteoporotic women on lumbar spine BMD over a three year period and the WMD demonstrated an increase in lumbar spine BMD relative to placebo (WMD adjusted for strontium content 8.09, 95% CI 7.22 to 8.96 and WMD not adjusted for strontium content 14.39, 95% CI 13.40 to 15.38) (Meunier 2004-1).

In terms of the lower doses of strontium ranelate, one study (n=63) investigated the effects of 0.125 g of strontium ranelate daily versus placebo on women without osteoporosis and found a non-significant increase in lumbar spine BMD over a two year period (WMD not adjusted for strontium content 0.37, 95% CI -1.57 to 2.31) (Reginster 2002-1). Women, with and without osteoporosis, taking 0.5 g of strontium ranelate daily compared to placebo showed a non-significant increase in lumbar spine BMD over a two year period when BMD was adjusted for strontium content (two trials, n = 232, WMD 1.01, 95% CI -0.63 to 2.66). However, when BMD was not adjusted for strontium content, the increase was significant (WMD 3.59, 95% CI 1.66 to 5.51) (Meunier 2002; Reginster 2002-1). The chi square test for heterogeneity of treatment effect for the analyses where BMD was not adjusted for strontium content approached significance (p=0.16) and I2 = 49.5%. The inclusion of a treatment (Meunier 2002) versus prevention (Reginster 2002-1) population may explain this finding. Lastly, women with and without osteoporosis, taking 1 g of strontium ranelate daily compared to placebo demonstrated an increase in lumbar spine BMD over a two year period (Meunier 2002; Reginster 2002-1) (two trials, n = 232, WMD adjusted for strontium content 2.14, 95% CI 0.70 to 3.58 and WMD, not adjusted for strontium content 6.68, 5.16 to 8.20). The chi square test for heterogeneity of treatment effect was not significant.

Femoral Neck BMD:
The effects of taking 2 g of strontium ranelate daily versus placebo in osteoporotic women demonstrated an increase in femoral neck BMD over two year (two trials, n=1614, WMD 5.73, 95% CI 5.15 to 6.32) (Meunier 2002; Meunier 2004-1) and three year period (two trials, n=4230, WMD 8.25%, 95% CI 7.84 to 8.66) (Meunier 2004-1; Reginster 2005). The chi-square test for heterogeneity of the treatment effect was not significant for both of these analyses. Based on pooled estimates, the number needed to treat was 3 for femoral neck BMD at 3 years.

With respect to the lower doses of strontium ranelate, one trial (n = 63) explored the effects of 0.125 g/day in women without osteoporosis and found a non significant increase in femoral neck BMD in favour of those receiving the placebo over a two year period (WMD -1.47, 95% CI -3.68 to 0.74) (Reginster 2002-1). The effects of 0.5 g of strontium ranelate daily versus placebo demonstrated a non-significant increase in femoral neck BMD (two trials, n = 232, WMD 1.00, 95% CI -0.52 to 2.52) whereas 1 g of strontium ranelate daily versus placebo showed a significant increase (two trials, n = 233, WMD 2.52, 95% CI 0.96 to 4.09) over a two year period (Meunier 2002; Reginster 2002-1). The chi square test for heterogeneity of treatment effect was not significant for either of these analyses.

Total Hip BMD:
One study (n=1442) demonstrated an increase in total hip BMD in osteoporotic women on 2 g of strontium ranelate daily compared to placebo over a two year period (WMD 1.16, 95% CI 1.05-1.27) (Meunier 2004-1) and two trials (n=4230) demonstrated an increase in total hip BMD over a three year period (WMD 9.83, 95% CI 9.39 to 10.26). The chi-square test for heterogeneity of treatment effect for the latter analyses was not significant. Based on pooled estimates, the number needed to treat was 3 for total hip BMD at 3 years.

Only one trial investigated the effects of lower doses of strontium ranelate on total hip BMD and found a non-significant increase with 0.125 g of strontium ranelate daily (n= 63, WMD 0.67, 95% CI -1.18 to 2.52) and significant increases with 0.5 g/day (n=65, WMD 2.02, 95% CI 0.47 to 3.57) and 1 g/day (n=60, WMD 4.09, 95% CI 2.09 to 6.09) over a two year period (Reginster 2002-1).

Health Related Quality of Life:
Quality of life was assessed using the SF-36 questionnaire in two trials (Meunier 2004-1; Reginster 2005) as well as the Quality of Life questionnaire in Osteoporosis (QUALIOST) in one (Meunier 2004-1). The QUALIOST is a 23 item, disease specific (vertebral osteoporosis) questionnaire, with a global score and two sub-scores: physical and emotional. In both trials, women completed the quality of life assessments at baseline and every six months throughout the duration of the trial (Meunier 2003). The results are not within the published literature however, unpublished data demonstrated that 2 g of strontium ranelate daily compared to placebo has a beneficial effect on quality of life as defined by the QUALIOST in a subset of osteoporotic women (n=1240) after three years of treatment (global score p = 0.016, emotional and physical scores p = 0.019 and 0.032 respectively) (Marquis 2005). Furthermore, results from a back pain assessment included in the QUALIOST questionnaire conducted every six months, revealed that the occurrence of back pain was significantly reduced by 29% in the strontium ranelate group as compared to the placebo group over three years with a significant effect in the first year (p = 0.006) (Marquis 2005).

ADVERSE EVENTS:

All adverse event data was reported by dose regardless of study duration i.e. two years (Meunier 2002; Reginster 2002-1) and three years (Meunier 2004-1; Reginster 2005).

Total withdrawals:
A total of three trials (n = 6847) using the recommended dose of 2 g strontium ranelate versus placebo daily did not find a significant difference in the risk of withdrawals (RR 0.98, 95% CI 0.91 to 1.05) (Meunier 2002; Meunier 2004-1; Reginster 2005). The chi-square test for heterogeneity of the treatment effect was not significant. Similarly, two trials (n=256) using 0.5 g of strontium ranelate versus placebo daily did not demonstrate a significant difference in the risk of withdrawal (RR 0.87, 95% CI 0.36 to 2.11) (Meunier 2002; Reginster 2002-1). The chi square test approached significance (p=0.11) and I^2 = 60.7%, which may be explained by the inclusion of a treatment (Meunier 2002) versus prevention (Reginster 2002-1) population.

Withdrawals due to adverse events:
A total of three trials (n = 6847) reported the safety of using the recommended daily dose of 2 g strontium ranelate versus placebo through withdrawals due to adverse events (Meunier 2002; Meunier 2004-1; Reginster 2005). The pooled estimate of the relative risk was 1.20 (95% CI 0.96 to 1.50) with 22% of the strontium ranelate treated patients versus 19.1% of the controls having withdrawn due to an adverse event however, this finding was not significant (p=0.12). The chi-square test for heterogeneity of the treatment effect was borderline significant (p=0.10) and I^2 =57.0%. This may be attributed to differences in the baseline characteristics including age and frailty (i.e. fracture prevalence). Similarly, for those women taking 0.5 g/day, there was no significant difference in the risk of withdrawals due to adverse events (two trials, n=256, RR 1.10, 95% CI 0.56 to 1.80) (Meunier 2002; Reginster 2002-1). The chi square test for heterogeneity was not significant.

Number of emergent adverse events:
A total of three trials (n = 6847) using the recommended daily dose of 2 g of strontium ranelate versus placebo daily did not find a significant difference in the number of emergent adverse events (RR 0.99, 95% CI 0.98 to 1.01). (Meunier 2004-1; Meunier 2004-1; Reginster 2005). Similarly, two trials (n=256) using 0.5 g of strontium ranelate versus placebo daily did not find a significant difference in the risk of developing an adverse event (RR 0.93, 95% CI 0.86 to 1.00) (Meunier 2002; Reginster 2002-1). The chi-square test for heterogeneity of the treatment effect was not significant for either of these analyses.

Serious adverse events:
A total of three trials (n = 6847) reported the number of participants that developed a serious adverse event using 2 g of strontium ranelate daily versus placebo (Meunier 2002; Meunier 2004-1; Reginster 2005). Serious adverse events occurred in 24.09% of the strontium ranelate treated patients versus 23.97% of the controls. The pooled estimate of the relative risk was 1.01 (95% CI 0.92 to 1.09) demonstrating a non significant difference between the two groups. Similarly, two trials (n=256) reported the number of serious adverse events using 0.5 g of strontium ranelate versus placebo daily and found no significant difference in the relative risk of developing a serious adverse event (RR 0.81, 95% CI 0.44 to 1.48) (Meunier 2002; Reginster 2002-1). The chi-square test for heterogeneity of the treatment effect was not significant for either of these analyses.

Diarrhea:
A total of three trials (n = 6847) reported the number of participants that developed diarrhea using the recommended dose of strontium ranelate versus placebo daily (Meunier 2004-1; Meunier 2002; Reginster 2005). Diarrhea occurred in 6.5% of the strontium ranelate treated patients versus 4.7% in the controls. The pooled estimate of the relative risk was 1.38 (95% CI 1.02 to 1.87) with a number needed to harm of 56. The chi-square test for heterogeneity of the treatment effect was not significant.

Gastritis:
A total of three trials (n = 6847) reported the number of participants that developed gastritis using 2 g of strontium ranelate versus placebo daily (Meunier 2002; Meunier 2004-1; Reginster 2005). Gastritis occurred in 2.7% of the strontium ranelate treated patients and 3.4% of the controls. The pooled estimate of the relative risk was 0.81 (95% CI 0.56 to 1.17). The chi-square test for heterogeneity of the treatment effect was not significant.

Deaths:

A total of three trials (n = 6847) reported the total number of deaths using 2 g of strontium ranelate versus placebo daily (Meunier 2002; Meunier 2004-1; Reginster 2005). A total of 4.97% of the strontium ranelate treated patients versus 5.37% of the controls died during the follow-up period. The pooled estimate of the relative risk was 0.99 (95% CI 0.64 to 1.53). The chi-square test for heterogeneity of the treatment effect was borderline significant with p= 0.17 and I^2 = 42.8%. This may be attributed to differences in the mean age of the study population in addition to their frailty.

Other adverse events from additional sources (EMEA 2004* and Servier**) are summarized in Table 3.

DISCUSSION

Summary of main results

A total of four trials met our inclusion criteria, three of which investigated the effects of strontium ranelate compared to placebo in a treatment population (doses ranged from 0.5 to 2 g daily) and one, in a prevention population (doses 0.125, 0.5 and 1 g daily). The included studies were presumably conducted in calcium and vitamin D replete postmenopausal women.

There is silver level evidence to support the use of 2 g of strontium ranelate daily in osteoporotic postmenopausal women to reduce the risk of vertebral and to a lesser extent, non-vertebral fractures. The pooled estimate of the relative risk for vertebral and non-vertebral fractures over a three year follow-up period were consistent with a reduction of 37% for vertebral fractures and 14% for non-vertebral fractures however, the upper boundary of the confidence interval for the effect on non-vertebral fractures was close to one. Both estimates were statistically significant and there was little heterogeneity of treatment effect however, the upper boundary of the confidence interval of the non-vertebral fractures approached one indicating that the data may be consistent with a null effect. Furthermore, the impact that 2 g of strontium ranelate daily has on reducing the risk of a hip fracture remains unclear as the only included study with data was not powered for this outcome. Although data from direct comparisons with other anti-osteoporotic treatments are lacking, the reduction in the relative risk of vertebral fracture seems similar to the other available therapies which have been shown to reduce the relative risk of recurrent fracture by 40 to 60% (Cranney 2002). The greater reduction in risk of vertebral fractures compared to non-vertebral fractures may be explained by the greater effect that strontium ranelate has on the vertebral versus non-vertebral bone mineral density.

In the TROPOS trial, the primary end point (i.e. all non-vertebral fractures) was recorded in 233 patients on strontium ranelate and 276 on placebo over a three-year period (EMEA 2004). As stated in the EMEA, the incidence of patients experiencing non-vertebral fracture(s) over a three year period using the Kaplan-Meier method and an unadjusted Cox model for inference demonstrated that strontium ranelate was not associated with a RR reduction as the upper boundary of the 95% confidence interval was 1.01 (RR 0.85, 95% CI 0.71 to 1.01) (EMEA 2004). Whereas in the primary paper for the TROPOS trial, the incidence of patients experiencing non-vertebral fracture(s) estimated via the Kaplan-Meier method and a Cox model adjusting for age, femoral neck BMD, body mass index and country demonstrated that strontium ranelate was associated with a RR reduction of 16% (RR 0.84, 95% CI 0.702 to 0.995) however, the upper boundary of the confidence interval was close to one (Reginster 2005). Given that the significant effect on non-vertebral fractures was found upon adjusting for the specified covariates was only marginal, it would appear that adjusting for these potentially relevant covariates did not have a significant impact on the direction of the effect and not likely clinically relevant.

The results of this review support the use of 2 g of strontium ranelate daily in osteoporotic postmenopausal women for increasing BMD at all sites over a two to three year period. In a prevention population, 1 g of strontium ranelate daily was demonstrated to increase BMD at all sites compared to placebo over a two year period. In both the treatment and prevention populations, lower doses of strontium ranelate were superior to placebo with the highest dose of strontium ranelate demonstrating the greatest increase in BMD over a two year period. While the increase in BMD in patients taking 2 g of strontium ranelate daily is impressive, caution is necessary when in interpreting these results. As previously mentioned, the combined effect of strontium distribution in bone and increased x-ray absorption of strontium compared to calcium leads to an amplification of BMD measurement by DXA (Ortolani 2006).

Although limited, there is evidence from one phase III trial to suggest that 2 g of strontium ranelate daily compared to placebo has a beneficial effect on health related quality of life in a subset of postmenopausal women (n=1240) after three years of treatment. In keeping with this, results from a back pain assessment included in the quality of life questionnaire revealed that the occurrence of back pain was significantly reduced by 29% in the strontium ranelate group as compared to the placebo group over three years with a significant effect in the first year (p = 0.006) (Marquis 2005). These findings are presumably due to a reduction in the consequences related to osteoporosis such as vertebral fractures.

Overall incidence rates for adverse events with strontium ranelate did not differ from placebo regardless of dose. There was a statistically significant increase in the risk for diarrhea in patients treated with 2 g of strontium ranelate daily relative to placebo. However; there was no significant difference in the number of withdrawals due to side effects, number of emergent events, serious adverse events, gastritis or deaths regardless of the dose analyzed. Additional data obtained from the scientific report by the European Agency for the Evaluation of Medicinal Products (EMEA 2004), in addition to the industry sponsor (Servier), has illustrated an increased risk in vascular and neurological disorders as well as abnormal laboratory findings. This information is based on results from the two phase III trials which focused on the recommended dose of 2 g of strontium ranelate daily (Meunier 2004-1; Reginster 2005) and has been summarized below and within the appended table entitled "Other adverse events from additional sources" (see Additional Tables -03). Disorders of the vascular system were present in 26.3% of the patients in the strontium ranelate group versus 24.4% in the placebo; Estimated difference = 1.9% (95% CI -0.2 to 4.0) with an increased reporting rate of adverse events of venous thromboembolism (2.2% versus 1.5%, OR 1.5, 95% CI 1.1 to 2.1) and pulmonary embolism (0.8% versus 4.5%, OR 1.7, 95% CI 1.0 to 3.1) over a three year period. Furthermore, the absolute number of patients that suffered a pulmonary embolism resulting

in discontinuation of treatment or death was increased in the strontium ranelate group compared to controls (i.e. 0.2% versus 0.1%). The cause of this increased risk of vascular disorders is not understood. Nervous system disorders were found in 20.9% of the patients in the strontium ranelate group versus 18.9% in the placebo; Estimated difference = 2.0 % (95% CI 0.1 to 3.9) with an increased reporting of seizures (0.3% versus 0.1%), memory loss (2.4% versus 1.9%) and disturbances in consciousness (2.5% versus 2.0%) over a four year period. Again, the etiology of the increased risk in neurological disorders is not clear. Lastly, mean baseline serum creatine kinase levels increased in both groups however, this increase was significantly greater in the strontium ranelate group (31.3 $\pm$ 80.8 IU/L) compared to the controls (13.1 $\pm$ 46.6 IU/L); Estimated difference = 18.2 IU/L (95% CI 14.8 to 21.6). The serum creatine kinase levels was greater than the upper limit of normal on at least one occasion in 29.4% (789/2680) of the women in the strontium ranelate group versus 17.6% (475/2705) of the controls (RR 1.68, 95% CI 1.52 to 1.85) providing evidence of strontium ranelate impacting skeletal muscle cell integrity however, the clinical relevance of these results is not known. In light of these findings targeted surveillance will be needed (EMEA 2004).

Since the main route of elimination of strontium is the kidney (Eisenberg 1973), the risk for side effects due to an increased accumulation of strontium in the bone needs to be considered in individuals whose renal function is compromised. Strontium has been shown to have a causal role (dose-dependent) in the development of osteomalacia in rats with chronic renal failure (Schrooten 1998; Schrooten 2003; Oste 2005). Furthermore, D'Haese et al found an association between increased bone strontium levels and the presence of osteomalacia from 100 biopsies of hemodialysis patients from various geographic areas however, further studies are required to establish if strontium plays a contributory role (D'Haese 2000). In the Summary of Product Characteristics, no dose adjustment is recommended for patients with mild to moderate renal impairment based on the fact that the mean creatine clearance in the Phase III trials was approximately. 50 ml/min. However, due to the absence of bone safety data in patients with severe renal impairment, it is recommended that strontium ranelate not be used in this particular patient population (EMEA 2004).

Overall completeness and applicability of evidence

While the included trials described and performed a correction to adjust for the strontium content in bone for the lumbar spine BMD measurements, there is considerable uncertainty about the accuracy of the results which arises from the small number of participants in whom iliac crest bone biopsy was performed and the reliance on animal data for the correction factor for inferring bone strontium content in the spine (Blake 2005).

Quality of the evidence

Our systematic review has several limitations. Firstly, while the methodological quality of the included studies was high based on the Jadad instrument, three of the four studies had losses to follow-up greater than 20% (Meunier 2002; Meunier 2004-1; Reginster 2005) and three had unclear descriptions of allocation concealment (Meunier 2004-1; Meunier 2004-1; Reginster 2005). Losses to follow-up can threaten the validity of the trial since the event rate may be very different in those lost to follow-up versus those who completed the trial and failure to conceal the participants' treatment allocation could also bias the treatment effect in either direction. Secondly, access to aggregate data only within the published studies resulting in pooling of proportions and limiting our ability to adjust for differences in patient populations. Thirdly, the fact that the included trials within our review were conducted predominately in Europe has implications on the applicability of the results in North American.

Potential biases in the review process

This review will be updated every two years (or earlier) depending on the emergence of new evidence. Review updates will entail repeating, at periodic intervals, the steps involved in the original review. If new evidence addresses important variables that were not included in the original review we will consider including them. In such instances, we will recheck whether any of their earlier identified studies had such information that was overlooked. Furthermore, should we decide to include a new analysis strategy in our updated review we understand that any new analysis strategies represents a substantive change to the review requiring editorial critique through the Cochrane Collaboration's established editorial process.

Agreements and disagreements with other studies or reviews

There was no previous systematic review on this topic.

AUTHORS' CONCLUSIONS

Implications for practice

There is silver level evidence to support the usefulness of strontium ranelate in reducing fractures in postmenopausal osteoporotic women and increasing BMD in women with/without osteoporosis. Pooled estimates using 2 g of strontium ranelate daily compared to placebo in osteoporotic women over a three year period are consistent with a reduction in vertebral fractures (37%); however, there is less of a reduction in non-vertebral fractures (14%) and the effect on hip fractures remains unclear. Strontium ranelate increased BMD at all sites in both treatment and prevention populations and while lower doses of strontium ranelate were superior to placebo, the highest dose demonstrated the greatest increase. There is some evidence to suggest that 2 g of strontium ranelate daily compared to placebo may have a beneficial effect on health related quality of life in postmenopausal women after three years of treatment. Diarrhea may occur, however, adverse events leading to study withdrawal were not significantly increased in the strontium ranelate group. Potential risks to the vascular and neurological system associated with taking 2 g of strontium ranelate daily need to be further explored and quantified.

Implications for research

Further monitoring of the quality, effectiveness and safety of strontium ranelate is essential especially in the prevention of osteoporosis. Additional research is required to confirm its mechanism of action. Long term fracture data are needed to confirm the effect that strontium ranelate has on bone health in both prevention and treatment populations. Long term safety data is required with particular attention to be paid to continued fracture efficacy, neurological and vascular system disorders, specifically venous and pulmonary thromboembolism, bone mineralization and skeletal muscle integrity. Future trials to evaluate the impact

of strontium ranelate treatment on BMD, including the effect on the elimination of bone strontium in patients switching to other anti-resorptive treatments, are needed. In addition, comparative trials evaluating the efficacy of strontium ranelate relative to other osteoporosis therapies such as bisphosphonates and intermittent recombinant human parathyroid hormone are required.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Meunier 2002

Study characteristics	
Methods	Randomized placebo controlled trial Duration = 2 years N = 353
Participants	Postmenopausal women (mean age 66.2, mean (SD) Lumbar spine (LS) T-score by group: -3.80 (0.94) to -.3.97 (0.95), previous vertebral fracture 100%) Treatment Primary outcome: LS bone mineral density (BMD)
Interventions	Strontium ranelate 0.5 g OR 1 g OR 2 g VERSUS placebo daily (calcium supplement 500 mg daily and vitamin D 800 IU daily)
Outcomes	BMD: Lumbar spine and femoral neck Fractures: vertebral (deformities)
Notes	Lost to follow-up: 81/353 (22.9%) Quality Score: 5/5

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Meunier 2004-1

Study characteristics	
Methods	Randomized placebo controlled trial Duration = 3 years N = 1649
Participants	Postmenopausal women (mean age 69.3, mean (SD) LS T-score by group: -3.5 (1.3) to -3.6 (1.2), previous vertebral fracture 100%) Treatment Primary outcome: Vertebral fractures
Interventions	Strontium ranelate 2g VERSUS placebo daily (calcium supplement up to 1000 mg daily based upon dietary intake and vitamin D 400-800 IU daily based on serum concentration of 25-hydroxyvitamin D)
Outcomes	BMD: Lumbar spine, femoral neck and total hip Fracture: Vertebral and non-vertebral

Meunier 2004-1 *(Continued)*

Notes	Lost to follow-up: 389/1649 (23.6%) Quality score: 4/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Reginster 2002-1

Study characteristics

Methods	Randomized placebo controlled trial Duration = 2 years N = 160
Participants	Postmenopausal women (mean age 54.2, mean LS T-score by group: -1.3 to -1.5, previous vertebral fracture 0%) Prevention Primary outcome: LS BMD
Interventions	Strontium ranelate 125 mg OR 500 mg OR 1 g VERSUS placebo daily (calcium supplement 500 mg daily as calcium carbonate)
Outcomes	BMD: Lumbar spine, femoral neck and total hip
Notes	Lost to follow-up: 17/160 (10.6%) Quality score: 4/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Reginster 2005

Study characteristics

Methods	Randomized placebo controlled trial Duration = 5 years (main statistical analysis over 3 years) N = 5091
Participants	Postmenopausal women (mean age 76.7, mean (SD) LS T-score -2.83 (1.63) to -3.24 (1.53), previous vertebral and non-vertebral fracture 55.4 VERSUS 54.2%) Treatment Primary outcome: Non-vertebral fractures
Interventions	Strontium ranelate 2 g VERSUS placebo daily

Reginster 2005 *(Continued)*

	(calcium supplement up to 1000 mg daily based upon dietary intake and vitamin D 400-800 IU daily based on serum concentration of 25-hydroxyvitamin D)
Outcomes	BMD: Femoral neck and total hip Fracture: Vertebral, non-vertebral, major non-vertebral (hip, wrist, pelvis and sacrum, ribs and sternum, clavicle, humerus) and hip
Notes	Lost to follow-up: 1771/5091 (34.8%) Quality Score: 4/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Boivin 2003	Review publication
Meunier 2003	Review of study design
Meunier 2004-2	Review publication
Meunier 2004-3	Review publication
Naveau 2004	Review publication
Pors 2004	Review publication
Reginster 2002-2	Review publication
Reginster 2003-1	Review publication
Reginster 2003-2	Review publication
Reginster 2004	Review publication
Reginster 2004-1	Review publication
Sorbera 2003	Review publication
Uebelhart 2003	Review publication

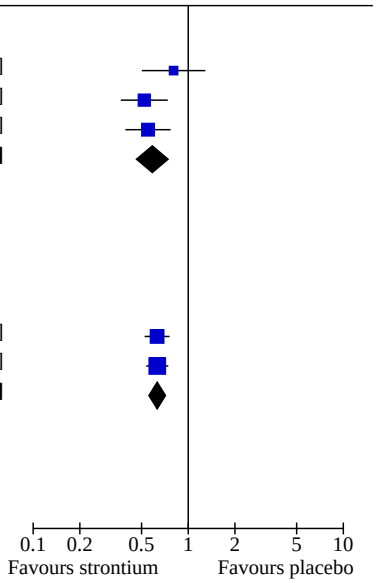
DATA AND ANALYSES

Comparison 1. Fractures

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Verterbral fractures	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1.1 2 g/day - 1 Year	3	5254	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.46, 0.74]
1.1.2 2 g/day - 3 Years	2	5082	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.56, 0.71]
1.2 Non-vertebral fractures	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.2.1 2 g/day - 3 Years	2	6572	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.75, 0.98]

Analysis 1.1. Comparison 1: Fractures, Outcome 1: Verterbral fractures

Study or Subgroup	Strontium Events	Strontium Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 2 g/day - 1 Year						
Meunier 2002	22	85	28	87	22.2%	0.80 [0.50 , 1.29]
Meunier 2004-1	44	719	85	723	37.6%	0.52 [0.37 , 0.74]
Reginster 2005	51	1817	93	1823	40.2%	0.55 [0.39 , 0.77]
Subtotal (95% CI)		**2621**		**2633**	**100.0%**	**0.59 [0.46 , 0.74]**
Total events:	117		206			
Heterogeneity: Tau² = 0.01; Chi² = 2.34, df = 2 (P = 0.31); I² = 14%						
Test for overall effect: Z = 4.47 (P < 0.00001)						
1.1.2 2 g/day - 3 Years						
Meunier 2004-1	139	719	222	723	43.8%	0.63 [0.52 , 0.76]
Reginster 2005	202	1817	321	1823	56.2%	0.63 [0.54 , 0.74]
Subtotal (95% CI)		**2536**		**2546**	**100.0%**	**0.63 [0.56 , 0.71]**
Total events:	341		543			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%						
Test for overall effect: Z = 7.37 (P < 0.00001)						

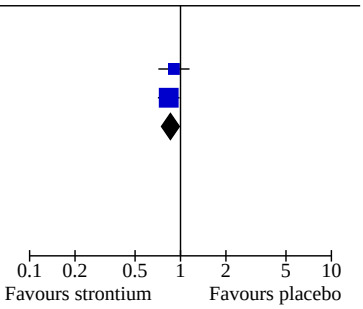


Analysis 1.2. Comparison 1: Fractures, Outcome 2: Non-vertebral fractures

Study or Subgroup	Strontium ranelate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 2 g/day - 3 Years						
Meunier 2004-1	112	826	122	814	32.6%	0.90 [0.71 , 1.15]
Reginster 2005	233	2479	276	2453	67.4%	0.84 [0.71 , 0.99]
Subtotal (95% CI)		**3305**		**3267**	**100.0%**	**0.86 [0.75 , 0.98]**
Total events:	345		398			

Heterogeneity: Tau² = 0.00; Chi² = 0.29, df = 1 (P = 0.59); I² = 0%

Test for overall effect: Z = 2.22 (P = 0.03)

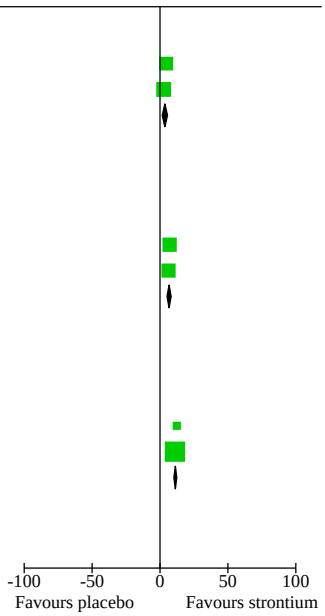


Comparison 2. BMD

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Lumbar spine BMD not adjusted for strontium content	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1.1 0.5 g/day - 2 Years	2	232	Mean Difference (IV, Random, 95% CI)	3.59 [1.66, 5.51]
2.1.2 1 g/d - 2 Years	2	232	Mean Difference (IV, Random, 95% CI)	6.68 [5.16, 8.20]
2.1.3 2 g/day - 2 Years	2	1614	Mean Difference (IV, Random, 95% CI)	11.29 [10.22, 12.37]
2.2 Lumbar spine adjusted for strontium content	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.2.1 0.5 g/day - 2 Years	2	232	Mean Difference (IV, Random, 95% CI)	1.01 [-0.63, 2.66]
2.2.2 1 g/day - 2 Years	2	232	Mean Difference (IV, Random, 95% CI)	2.14 [0.70, 3.58]
2.2.3 2 g/day - 2 Years	2	1614	Mean Difference (IV, Random, 95% CI)	5.44 [3.41, 7.46]
2.3 Femoral neck	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.3.1 0.5 g/day - 2 Years	2	232	Mean Difference (IV, Random, 95% CI)	1.00 [-0.52, 2.52]
2.3.2 1 g/day - 2 Years	2	233	Mean Difference (IV, Random, 95% CI)	2.52 [0.96, 4.09]
2.3.3 2 g/day - 2 Years	2	1614	Mean Difference (IV, Random, 95% CI)	5.73 [5.15, 6.32]
2.3.4 2 g/day - 3 Years	2	4230	Mean Difference (IV, Random, 95% CI)	8.25 [7.84, 8.66]
2.4 Total hip	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.4.1 2 g/day - 3 Years	2	4230	Mean Difference (IV, Random, 95% CI)	9.83 [9.39, 10.26]

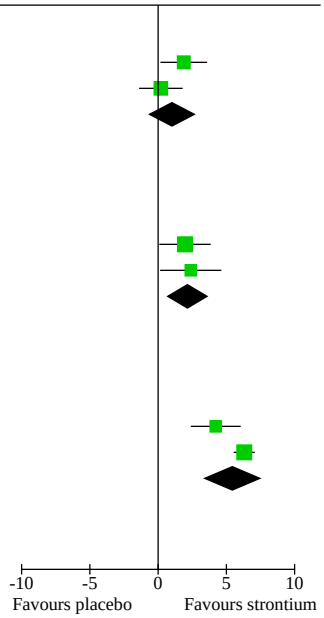
Analysis 2.1. Comparison 2: BMD, Outcome 1: Lumbar spine BMD not adjusted for strontium content

Study or Subgroup	Strontium Ranelate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.1.1 0.5 g/day - 2 Years								
Meunier 2002	5.87	6.59	80	1.25	5.3	87	47.5%	4.62 [2.80 , 6.44]
Reginster 2002-1	1.9	3.59	35	-0.75	3.02	30	52.5%	2.65 [1.04 , 4.26]
Subtotal (95% CI)			**115**			**117**	**100.0%**	**3.59 [1.66 , 5.51]**
Heterogeneity: Tau² = 1.17; Chi² = 2.52, df = 1 (P = 0.11); I² = 60%								
Test for overall effect: Z = 3.65 (P = 0.0003)								
2.1.2 1 g/d - 2 Years								
Meunier 2002	8.33	8.65	86	1.25	5.3	87	50.3%	7.08 [4.94 , 9.22]
Reginster 2002-1	5.53	5.12	29	-0.75	3.02	30	49.7%	6.28 [4.13 , 8.43]
Subtotal (95% CI)			**115**			**117**	**100.0%**	**6.68 [5.16 , 8.20]**
Heterogeneity: Tau² = 0.00; Chi² = 0.27, df = 1 (P = 0.61); I² = 0%								
Test for overall effect: Z = 8.63 (P < 0.00001)								
2.1.3 2 g/day - 2 Years								
Meunier 2002	13.61	8.87	85	1.25	5.3	87	20.8%	12.36 [10.17 , 14.55]
Meunier 2004-1	9.99	9.83	719	-1.02	6.1	723	79.2%	11.01 [10.17 , 11.85]
Subtotal (95% CI)			**804**			**810**	**100.0%**	**11.29 [10.22 , 12.37]**
Heterogeneity: Tau² = 0.19; Chi² = 1.27, df = 1 (P = 0.26); I² = 21%								
Test for overall effect: Z = 20.59 (P < 0.00001)								



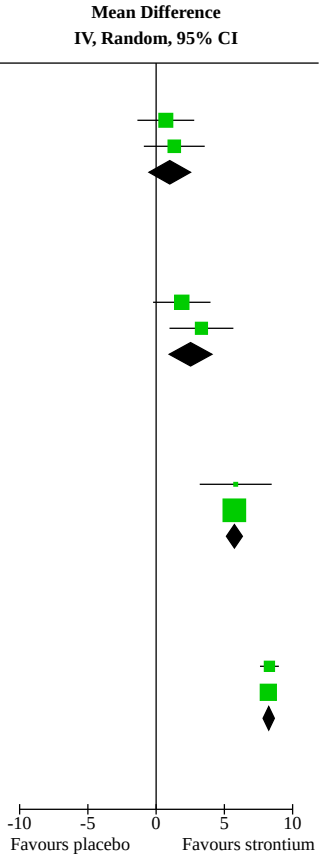
Analysis 2.2. Comparison 2: BMD, Outcome 2: Lumbar spine adjusted for strontium content

Study or Subgroup	Strontium Ranelate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.2.1 0.5 g/day - 2 Years								
Meunier 2002	3.11	5.92	80	1.23	5.31	87	48.2%	1.88 [0.17 , 3.59]
Reginster 2002-1	-0.78	3.42	35	-0.98	3.14	30	51.8%	0.20 [-1.40 , 1.80]
Subtotal (95% CI)			**115**			**117**	**100.0%**	**1.01 [-0.63 , 2.66]**
Heterogeneity: Tau² = 0.70; Chi² = 1.98, df = 1 (P = 0.16); I² = 50%								
Test for overall effect: Z = 1.20 (P = 0.23)								
2.2.2 1 g/day - 2 Years								
Meunier 2002	3.2	7.16	86	1.23	5.31	87	58.7%	1.97 [0.09 , 3.85]
Reginster 2002-1	1.41	5.33	29	-0.98	3.14	30	41.3%	2.39 [0.15 , 4.63]
Subtotal (95% CI)			**115**			**117**	**100.0%**	**2.14 [0.70 , 3.58]**
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%								
Test for overall effect: Z = 2.92 (P = 0.004)								
2.2.3 2 g/day - 2 Years								
Meunier 2002	5.45	6.8	85	1.23	5.31	87	41.9%	4.22 [2.39 , 6.05]
Meunier 2004-1	5.13	8.56	719	-1.18	6.26	723	58.1%	6.31 [5.54 , 7.08]
Subtotal (95% CI)			**804**			**810**	**100.0%**	**5.44 [3.41 , 7.46]**
Heterogeneity: Tau² = 1.67; Chi² = 4.26, df = 1 (P = 0.04); I² = 77%								
Test for overall effect: Z = 5.27 (P < 0.00001)								



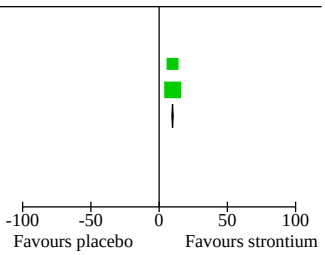
Analysis 2.3. Comparison 2: BMD, Outcome 3: Femoral neck

Study or Subgroup	Strontium Ranelate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.3.1 0.5 g/day - 2 Years								
Meunier 2002	0.24	3.01	80	-0.47	9.39	87	53.5%	0.71 [-1.37 , 2.79]
Reginster 2002-1	0.46	4.7	35	-0.87	4.46	30	46.5%	1.33 [-0.90 , 3.56]
Subtotal (95% CI)			**115**			**117**	**100.0%**	**1.00 [-0.52 , 2.52]**
Heterogeneity: Tau² = 0.00; Chi² = 0.16, df = 1 (P = 0.69); I² = 0%								
Test for overall effect: Z = 1.29 (P = 0.20)								
2.3.2 1 g/day - 2 Years								
Meunier 2002	1.41	3.45	86	-0.47	9.39	87	55.3%	1.88 [-0.22 , 3.98]
Reginster 2002-1	2.45	4.78	30	-0.87	4.46	30	44.7%	3.32 [0.98 , 5.66]
Subtotal (95% CI)			**116**			**117**	**100.0%**	**2.52 [0.96 , 4.09]**
Heterogeneity: Tau² = 0.00; Chi² = 0.80, df = 1 (P = 0.37); I² = 0%								
Test for overall effect: Z = 3.16 (P = 0.002)								
2.3.3 2 g/day - 2 Years								
Meunier 2002	5.36	8.22	85	-0.47	9.39	87	4.9%	5.83 [3.19 , 8.47]
Meunier 2004-1	3.55	6.47	719	-2.18	5.06	723	95.1%	5.73 [5.13 , 6.33]
Subtotal (95% CI)			**804**			**810**	**100.0%**	**5.73 [5.15 , 6.32]**
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.94); I² = 0%								
Test for overall effect: Z = 19.22 (P < 0.00001)								
2.3.4 2 g/day - 3 Years								
Meunier 2004-1	5.51	7.58	719	-2.79	5.67	723	35.7%	8.30 [7.61 , 8.99]
Reginster 2005	5.65	7.9	1393	-2.57	5.8	1395	64.3%	8.22 [7.71 , 8.73]
Subtotal (95% CI)			**2112**			**2118**	**100.0%**	**8.25 [7.84 , 8.66]**
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%								
Test for overall effect: Z = 39.17 (P < 0.00001)								



Analysis 2.4. Comparison 2: BMD, Outcome 4: Total hip

Study or Subgroup	Strontium ranelate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.4.1 2 g/day - 3 Years								
Meunier 2004-1	7.33	7.67	719	-2.49	5.84	723	38.8%	9.82 [9.12 , 10.52]
Reginster 2005	7.09	8.71	1393	-2.74	6.19	1395	61.2%	9.83 [9.27 , 10.39]
Subtotal (95% CI)			**2112**			**2118**	**100.0%**	**9.83 [9.39 , 10.26]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%								
Test for overall effect: Z = 43.90 (P < 0.00001)								



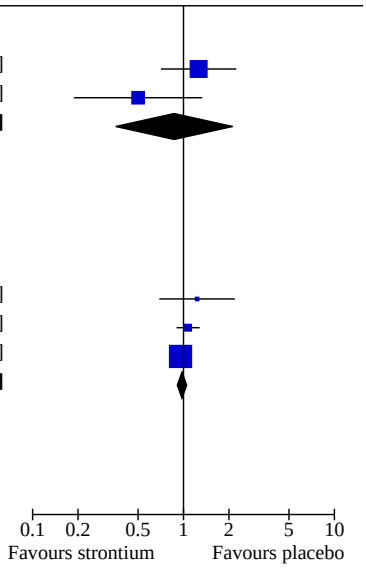
Comparison 3. Adverse Events

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
3.1 Total withdrawls	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1.1 0.5 g/d	2	256	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.36, 2.11]
3.1.2 2 g/d	3	6847	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.91, 1.05]

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
3.2 Withdrawals due to adverse events	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.2.1 0.5 g/d	2	256	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.56, 1.80]
3.2.2 2 g/d	3	6847	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.96, 1.50]
3.3 Number of emer-gent adverse events	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.3.1 0.5 g/d	2	256	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.86, 1.00]
3.3.2 2 g/d	3	6847	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.98, 1.01]
3.4 Serious adverse events	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.4.1 0.5 g/d	2	247	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.44, 1.48]
3.4.2 2 g/d	3	6841	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.92, 1.09]
3.5 Diarrhea	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.5.1 2 g/d	3	6847	Risk Ratio (M-H, Random, 95% CI)	1.38 [1.02, 1.87]
3.6 Gastritis	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.6.1 2 g/d	3	6847	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.56, 1.17]
3.7 Deaths	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.7.1 0.5 g/d	2	256	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.33, 6.19]
3.7.2 2 g/d	3	6847	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.64, 1.53]

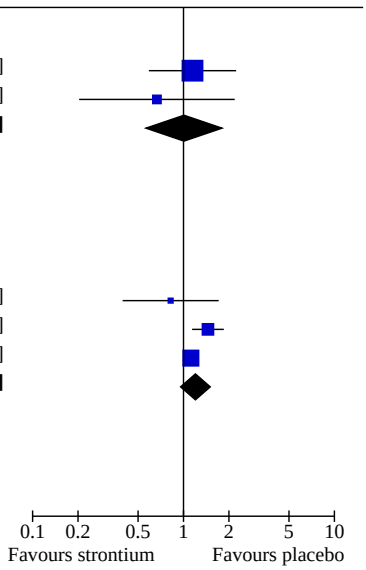
Analysis 3.1. Comparison 3: Adverse Events, Outcome 1: Total withdrawls

Study or Subgroup	Strontium ranelate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 0.5 g/d						
Meunier 2002	20	85	17	91	59.6%	1.26 [0.71 , 2.24]
Reginster 2002-1	5	40	10	40	40.4%	0.50 [0.19 , 1.33]
Subtotal (95% CI)		**125**		**131**	**100.0%**	**0.87 [0.36 , 2.11]**
Total events:	25		27			
Heterogeneity: Tau² = 0.26; Chi² = 2.55, df = 1 (P = 0.11); I² = 61%						
Test for overall effect: Z = 0.31 (P = 0.75)						
3.1.2 2 g/d						
Meunier 2002	20	87	17	91	1.5%	1.23 [0.69 , 2.19]
Meunier 2004-1	198	826	182	814	16.0%	1.07 [0.90 , 1.28]
Reginster 2005	839	2526	870	2503	82.5%	0.96 [0.88 , 1.03]
Subtotal (95% CI)		**3439**		**3408**	**100.0%**	**0.98 [0.91 , 1.05]**
Total events:	1057		1069			
Heterogeneity: Tau² = 0.00; Chi² = 2.01, df = 2 (P = 0.37); I² = 0%						
Test for overall effect: Z = 0.65 (P = 0.52)						



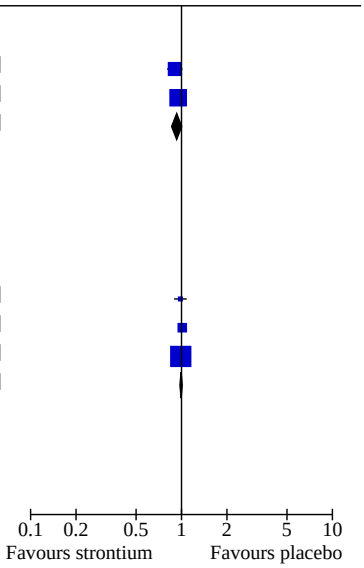
Analysis 3.2. Comparison 3: Adverse Events, Outcome 2: Withdrawals due to adverse events

Study or Subgroup	Strontium ranelate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 0.5 g/d						
Meunier 2002	15	85	14	91	76.1%	1.15 [0.59 , 2.23]
Reginster 2002-1	4	40	6	40	23.9%	0.67 [0.20 , 2.18]
Subtotal (95% CI)		**125**		**131**	**100.0%**	**1.01 [0.56 , 1.80]**
Total events:	19		20			
Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 1 (P = 0.43); I² = 0%						
Test for overall effect: Z = 0.02 (P = 0.98)						
3.2.2 2 g/d						
Meunier 2002	11	87	14	91	8.3%	0.82 [0.39 , 1.71]
Meunier 2004-1	140	826	95	814	36.4%	1.45 [1.14 , 1.85]
Reginster 2005	611	2526	541	2503	55.4%	1.12 [1.01 , 1.24]
Subtotal (95% CI)		**3439**		**3408**	**100.0%**	**1.20 [0.96 , 1.50]**
Total events:	762		650			
Heterogeneity: Tau² = 0.02; Chi² = 4.65, df = 2 (P = 0.10); I² = 57%						
Test for overall effect: Z = 1.58 (P = 0.12)						



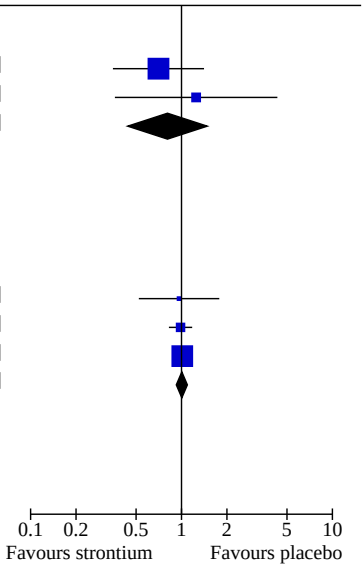
Analysis 3.3. Comparison 3: Adverse Events, Outcome 3: Number of emergent adverse events

Study or Subgroup	Strontium ranelate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.3.1 0.5 g/d						
Meunier 2002	70	85	83	91	42.7%	0.90 [0.80 , 1.02]
Reginster 2002-1	37	40	39	40	57.3%	0.95 [0.86 , 1.05]
Subtotal (95% CI)		**125**		**131**	**100.0%**	**0.93 [0.86 , 1.00]**
Total events:	107		122			
Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 1 (P = 0.49); I² = 0%						
Test for overall effect: Z = 1.89 (P = 0.06)						
3.3.2 2 g/d						
Meunier 2002	78	87	83	91	3.2%	0.98 [0.89 , 1.08]
Meunier 2004-1	730	826	711	814	22.9%	1.01 [0.98 , 1.05]
Reginster 2005	2220	2526	2225	2503	73.9%	0.99 [0.97 , 1.01]
Subtotal (95% CI)		**3439**		**3408**	**100.0%**	**0.99 [0.98 , 1.01]**
Total events:	3028		3019			
Heterogeneity: Tau² = 0.00; Chi² = 1.26, df = 2 (P = 0.53); I² = 0%						
Test for overall effect: Z = 0.72 (P = 0.47)						



Analysis 3.4. Comparison 3: Adverse Events, Outcome 4: Serious adverse events

Study or Subgroup	Strontium ranelate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.4.1 0.5 g/d						
Meunier 2002	11	80	17	87	76.1%	0.70 [0.35 , 1.41]
Reginster 2002-1	5	40	4	40	23.9%	1.25 [0.36 , 4.32]
Subtotal (95% CI)		**120**		**127**	**100.0%**	**0.81 [0.44 , 1.48]**
Total events:	16		21			
Heterogeneity: Tau² = 0.00; Chi² = 0.63, df = 1 (P = 0.43); I² = 0%						
Test for overall effect: Z = 0.69 (P = 0.49)						
3.4.2 2 g/d						
Meunier 2002	16	85	17	87	1.9%	0.96 [0.52 , 1.78]
Meunier 2004-1	188	826	188	814	22.5%	0.99 [0.83 , 1.18]
Reginster 2005	624	2526	611	2503	75.6%	1.01 [0.92 , 1.11]
Subtotal (95% CI)		**3437**		**3404**	**100.0%**	**1.01 [0.92 , 1.09]**
Total events:	828		816			
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 2 (P = 0.96); I² = 0%						
Test for overall effect: Z = 0.12 (P = 0.91)						

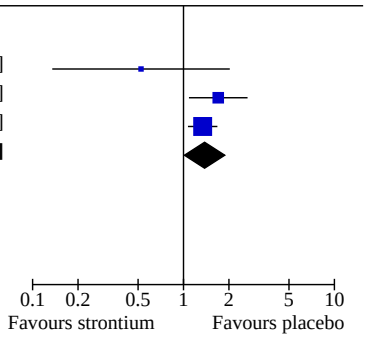


Analysis 3.5. Comparison 3: Adverse Events, Outcome 5: Diarrhea

Study or Subgroup	Strontium ranelate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.5.1 2 g/d						
Meunier 2002	3	87	6	91	4.9%	0.52 [0.13 , 2.03]
Meunier 2004-1	50	826	29	814	31.6%	1.70 [1.09 , 2.66]
Reginster 2005	169	2526	125	2503	63.5%	1.34 [1.07 , 1.68]
Subtotal (95% CI)		**3439**		**3408**	**100.0%**	**1.38 [1.02 , 1.87]**
Total events:	222		160			

Heterogeneity: Tau² = 0.03; Chi² = 2.87, df = 2 (P = 0.24); I² = 30%

Test for overall effect: Z = 2.06 (P = 0.04)

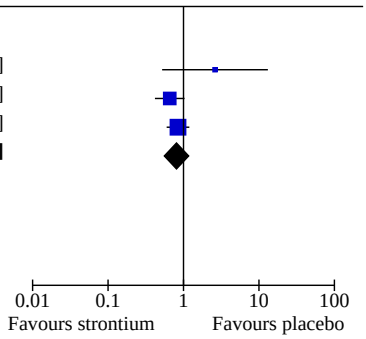


Analysis 3.6. Comparison 3: Adverse Events, Outcome 6: Gastritis

Study or Subgroup	Strontium ranelate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.6.1 2 g/d						
Meunier 2002	5	87	2	91	5.0%	2.61 [0.52 , 13.12]
Meunier 2004-1	30	826	45	814	40.7%	0.66 [0.42 , 1.03]
Reginster 2005	58	2526	68	2503	54.3%	0.85 [0.60 , 1.19]
Subtotal (95% CI)		**3439**		**3408**	**100.0%**	**0.81 [0.56 , 1.17]**
Total events:	93		115			

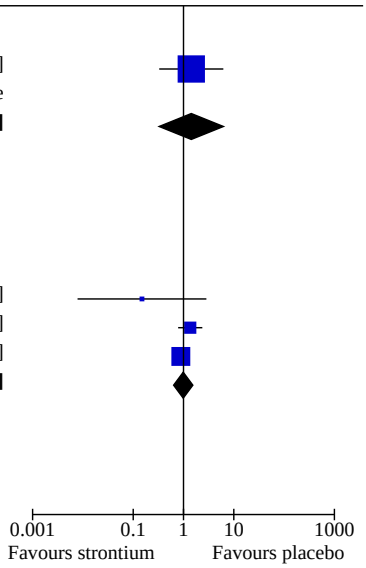
Heterogeneity: Tau² = 0.03; Chi² = 2.90, df = 2 (P = 0.23); I² = 31%

Test for overall effect: Z = 1.13 (P = 0.26)



Analysis 3.7. Comparison 3: Adverse Events, Outcome 7: Deaths

Study or Subgroup	Strontium ranelate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.7.1 0.5 g/d						
Meunier 2002	4	85	3	91	100.0%	1.43 [0.33 , 6.19]
Reginster 2002-1	0	40	0	40		Not estimable
Subtotal (95% CI)		**125**		**131**	**100.0%**	**1.43 [0.33 , 6.19]**
Total events:	4		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.48 (P = 0.63)						
3.7.2 2 g/d						
Meunier 2002	0	87	3	91	2.2%	0.15 [0.01 , 2.85]
Meunier 2004-1	29	826	21	814	34.3%	1.36 [0.78 , 2.37]
Reginster 2005	142	2526	159	2503	63.5%	0.88 [0.71 , 1.10]
Subtotal (95% CI)		**3439**		**3408**	**100.0%**	**0.99 [0.64 , 1.53]**
Total events:	171		183			
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 3.50$, df = 2 (P = 0.17); $I^2 = 43\%$						
Test for overall effect: Z = 0.06 (P = 0.95)						



ADDITIONAL TABLES

Table 1. Clinical relevance table strontium ranelate 2 g per day: Fractures & safety data

Outcome	ER in Sr grp (%)	ER in Ctrl grp (%)	RR (95% CI)	ARD (95% CI)	NNT/NNH (95% CI)	Sr grp: # of women	Ctrl grp: # of women	Rel % change	Quality of evidence
Vertebral fracture (1 year)	117/2621 (4.5%)	206/2633 (7.8%)	0.59 (0.46, 0.74)	-4% (-7, -1)	32 (24 to 50)	5/100	8/100	41% (I)	Silver
Vertebral fracture (3 years)	341/2536 (13.4%)	543/2546 (21.3%)	0.63 (0.56, 0.71)	-9% (-13, -4)	13 (11 to 17)	13/100	21/100	37% (I)	Silver
Non-vertebral fracture (3 years)	345/3305 (10.4%)	398/3267 (12.5%)	0.86 (0.75, 0.98)	-2% (-3, 0)	58 (32 to 401)	10/100	12/100	14% (I)	Silver
Withdrawals due to adverse events	762/3439 (22.1%)	650/3408 (19.1%)	1.20 (0.96, 1.50)	3% (1, 6)	-	-	-	-	Silver
Serious adverse events	828/3437 (24.1%)	816/3404 (24.0%)	1.01 (0.92, 1.09)	0% (-2, 2)	-	-	-	-	Silver
Emergent adverse events	3028/3439 (88.0%)	3019/3408 (88.6%)	0.99 (0.98, 1.01)	-1% (-2, 1)	-	-	-	-	Silver
Gastritis	93/3439 (2.7%)	115/3408 (3.4%)	0.81 (0.56, 1.17)	-1% (-2, 1)	-	-	-	-	Silver
Diarrhea	222/3439 (6.5%)	160/3408 (4.7%)	1.38 (1.02, 1.87)	2% (0, 3)	56 (25 to 1064)	6/100	4/100	38% (W)	Silver
Legend:	ER = Event rate	Ctrl = Controls	RR = Relative risk	ARD = Absolute risk difference	NNT = Number needed to treat	# = Number		Rel = Relative	
	Sr = Strontium ranelate		CI = Confidence interval		NNH = Number needed to harm			I = Improvement	
								W = Worsening	

Table 2. Clinical relevance table strontium ranelate 2 g per day: BMD data

Outcome (scale)	# in Sr: Ctrl group	Mean (SD) Ctrl	WMD (95% CI)	Abs change	Rel % change	NNT	Quality of Evidence
Lumbar spine BMD - not adjusted (2 years)	804:810	-1.02 (6.10)*	11.29 (10.22, 12.37)	11.29	-11.1%	2	Silver
Lumbar spine BMD - adjusted (2 years)	804:810	-1.18 (6.26)*	5.44 (3.41, 7.46)	5.44	-4.6%	3	Silver
Femoral neck BMD (2 years)	804:810	-2.18 (5.06)*	5.73 (5.15, 6.32)	5.73	-2.6%	5	Silver
Femoral neck BMD (3 years)	2112:2118	-2.57 (5.80)**	8.25 (7.84, 8.66)	8.25	-3.2%	3	Silver
Total hip BMD (3 years)	2112:2118	-2.74 (5.80)**	9.83 (9.39, 10.26)	9.83	-3.6%	3	Silver
most representative study:	# = Number	SD = Standard deviation	WMD = Weighted mean difference	Abs = Absolute	Rel = Relative	NNT=number needed to treat	
Meunier, 2004-1*; Reginster, 2005**	Sr = Strontium ranelate	Ctrl = Controls					

Table 3. Other adverse events from additional sources (EMEA 2004* and Servier)**

Adverse event (AE)	Sr (n = 3352)	Control (n= 3317)	ED (95% CI)	OR (95% CI)
VASCULAR SYSTEM DISORDERS	880 (26.3%)*	809 (24.4%)*	1.9% (-0.2, 4.0)*	-
Thrombosis	111 (3.3%)*	72 (2.2%)*	1.1% (0.4, 1.9)*	-
Venous thromboembolism at 3 years	75 (2.2%)**	50 (1.5%)**	-	1.5 (1.1, 2.1)*
Venous thromboembolism at 4 years	87 (2.6%)**	61 (1.8%)**	-	-
Pulmonary embolism (PE)	25 (0.8%)**	15 (0.4%)**	-	1.7 (1.0, 3.1)*
Fatal PE	6 (0.2%)*	3 (0.1%)*	-	-
PE leading to treatment discontinuation	7 (0.2%)*	3 (0.1%)*	-	-
NERVOUS SYSTEM DISORDERS	699 (20.9%)*	627 (18.9%)*	2.0% (0.1, 3.0)*	-
Headaches	131 (3.9%)*	97 (2.9%)*	1.0% (0.1, 1.9)*	-
Seizures at 4 years	9 (0.3%)**	3 (0.1%)**	-	-
Memory loss at 4 years	79 (2.4%)**	63 (1.9%)**	-	-
Disturbance in consciousness at 4 years	83 (2.5%)**	66 (2.0%)**	-	-
LABORATORY RESULTS				
Serum creatine kinase	31.3 (80.8) IU/L*	13.1 (46.6) IU/L*	18.2 (14.8; 21.6) IU/L*	-
Data obtained from the EMEA* and Servier**	Sr = Strontium ranelate		ED= Estimated difference	OR = Odds ratio
			CI = Confidence interval	

APPENDICES

Appendix 1. Search strategies

MEDLINE Search Strategy
1 *Osteoporosis/
2 osteoporos#s.tw.
3 bone loss$.tw.
4 Bone Density/
5 (bone adj2 (density or fragil$)).tw.

6 bone mass.tw.
7 bmd.tw.
8 exp Fractures, Bone/
9 fracture$.tw.
10 or/1-9
11 Postmenopause/
12 (post menopaus$ or postmenopaus$ or post-menopaus$).tw.
13 11 or 12
14 10 and 13
15 clinical trial.pt.
16 randomized controlled trial.pt.
17 tu.fs.
18 dt.fs.
19 random$.tw.
20 (double adj blind$).tw.
21 placebo$.tw.
22 or/15-21
23 22 and 14
24 Strontium/
25 strontium.tw.
26 ranelate.tw.
27 prevos.tw.
28 or/24-27
29 28 and 23
30 limit 29 to yr="1996 - 2005"

Embase Search Strategy
1 exp osteoporosis/
2 bone loss$.tw.
3 osteoporos#s.tw.
4 bone density/
5 (bone adj2 (density or fragil$)).tw.
6 bone mass.tw.
7 bmd.tw.
8 exp Fracture/
9 fracture$.tw.
10 or/1-9
11 postmenopause/
12 (post menopaus$ or postmenopaus$ or post-menopaus$).tw.
13 11 or 12
14 10 and 13
15 random$.tw.
16 factorial$.tw.
17 crossover$.tw.
18 placebo$.tw.
19 (singl$ adj blind$).tw.
20 (doubl$ adj blind$).tw.
21 assign$.tw.
22 allocat$.tw.
23 volunteer$.tw.
24 randomized controlled trials/
25 double-blind method/
26 single-blind method/
27 or/15-26
28 27 and 14
29 STRONTIUM/
30 strontium.tw.
31 ranelate.tw.
32 prevos.tw.
33 or/29-32
34 27 and 33
35 limit 34 to yr="1996 - 2005"

FEEDBACK

Feedback from J Halbekath,

Summary

Date of Submission: 18-Sep-2007
Name: Jutta Halbekath
Email Address: redaktion@arznei-telegramm.de
Personal Description: Occupation physician, editorial staff

Feedback: September, 17 2007

Dear Sir/Madam

A key principle of the Cochrane Collaboration is minimising bias through a variety of approaches such as scientific rigour and avoiding conflicts of interest. Existing conflicts of interest must be disclosed (1). The review on strontium ranelate for preventing and treating postmenopausal osteoporosis (2) appears to violate these standards.

One of the trials included in the review, the TROPOS trial, was a pivotal trial submitted to the European Medicines Agency (EMEA) within the application for marketing authorisation, which was granted in September 2004. According to the European Public Assessment Report (EPAR), this trial was negative for the primary endpoint, the incidence of osteoporosis-related peripheral fractures after three years. As stated in the EPAR, the primary efficacy analysis used the Kaplan Meier method and an unadjusted Cox model, yielding a relative risk of 0,85, with the upper boundary of the 95% CI at 1,01 (3).

In 2005, the TROPOS trial was published in the Journal of Clinical Endocrinology & Metabolism. In contrast to the approach described in the EPAR, the authors state, that they carried out simultaneous adjustments for covariates such as age or body mass index. By this means, they achieved a relative risk of 0,84 and an upper boundary of the 95% CI marginally below 1 (0,995) for the primary endpoint. The fact, that the primary efficacy analysis of the TROPOS trial used an unadjusted Cox model and displayed no significant benefit of strontium ranelate, and that, hence, adjustments for age, BMI etc., were at best part of secondary analyses of the primary endpoint, are not mentioned in the journal article (4). Moreover, the review withholds information about the negative result of the primary efficacy analysis of the TROPOS trial as well (2).

Of course, the difference between the result provided in the EPAR and that given in the journal article is marginal and may be clinically meaningless. However, it may be highly relevant for the manufacturer of strontium ranelate, whom the word "significance" may help marketing his product.

Furthermore, the evidence supporting the potential benefits of strontium ranelate is based on poor-quality trials: concealment of allocation is not adequately described in three of four trials, losses to follow-up are greater than 20% in three of four trials. How to interprete the TROPOS trial, in which the final outcome is not known in more than one third of patients (1.771), in view of a difference in the fracture rate between groups of only 1,9% or 43 women? A slight imbalance in fractures in those lost to follow up favouring the placebo group would render the results inconclusive. Thus, the TROPOS trial does not provide reliable evidence of a clinical benefit of strontium ranelate. We are not able to relate to the positive assessments of the review, which appear to be unaffected by the significant shortcomings of the trials. Especially in the abstract, readers are simply told about "silver level evidence" to support the efficacy of strontium ranelate. Will anyone expect the flawed data hidden behind this precious metal label?

On the other hand, potentially life threatening adverse effects of strontium ranelate are played down in the review. The absolute increase of disorders of the vascular system including venous thromboembolism is 1,9%. Thus it is as large as the potential decrease of peripheral fractures in patients treated with strontium ranelate in the TROPOS trial. Notwithstanding the increased risk in vascular and neurological disorders (including seizures) is described as "slight" (2). The potential risk of osteomalacia, seen in animals (3) and associated with strontium overload in hemodialysis patients (5), is perhaps implied in the list of requirements for research ("particular attention to be paid on bone mineralization"), but not openly discussed.

No conflicts of interests are disclosed, even though J.Y. Reginster has received consulting fees of a variety of pharmaceutical companies, among them Servier, the manufacturer of strontium ranelate (6,7).

Yours sincerely

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1 The Cochrane Collaboration: The Cochrane Manual, Issue 4, Aug. 2007;
http://www.cochrane.org/admin/manual.htm
2 O'DONNELL, S., CRANNEY, A., WELLS, G.A., ADACHI, J.D., REGINSTER, J.Y.:
"Strontium ranelate for preventing and treating postmenopausal osteoporosis.
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3 EMEA: European Public Assessment Report (EPAR) PROTELOS, March 2007;
http://www.emea.europa.eu/humandocs/Humans/EPAR/protelos/protelos.htm
4 REGINSTER, J.Y. et al.: J. Clin. Endocrinol. Metab. 2005; 90: 2816-22
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6 MEUNIER, P.J. et al.: N. Engl. J. Med. 2004; 350: 459-68
7 REGINSTER, J.-Y.: Lancet 2007; 370: 632-34

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Reply

Feedback Comment:
A key principle of the Cochrane Collaboration is minimising bias through a variety of approaches such as scientific rigour and avoiding conflicts of interest. Existing conflicts of interest must be disclosed (1). The review on strontium ranelate for preventing and treating postmenopausal osteoporosis (2) appears to violate these standards.

Response:
We agree that all potential conflicts of interest should be disclosed to minimize bias. This missing information in the original review was an oversight on our part. Therefore, we have updated our systematic review to include the following information:
All four included trials were supported by Servier, the manufacturer of strontium ranelate.
Also, J Y Reginster is an author on the four included trials within this review; in addition Dr. Reginster's disclosure of interest is as follows:
Consulting fees or paid advisory boards: Servier, Novartis, Negma, Lilly, Wyeth, Amgen, GlaxoSmithKline, Roche, Merckle, Nycomed, NPS, Theramex, UCB.

Lecture fees when speaking at the invitation of a commercial sponsor: Merck Sharp and Dohme, Lilly, Rottapharm, IBSA, Genevrier, Novartis, Servier, Roche, GlaxoSmithKline, Teijin, Teva, Ebewee Pharma, Zodiac, Analis, Theramex, Nycomed, Novo-Nordisk.

Grant Support from Industry: Bristol Myers Squibb, Merck Sharp & Dohme, Rottapharm, Teva, Lilly, Novartis, Roche, GlaxoSmithKline, Amgen, Servier.

Lastly, J Adachi has also received speaker fees from Servier.

Feedback Comment:
One of the trials included in the review, the TROPOS trial, was a pivotal trial submitted to the European Medicines Agency (EMEA) within the application for marketing authorisation, which was granted in September 2004. According to the European Public Assessment Report (EPAR), this trial was negative for the primary endpoint, the incidence of osteoporosis-related peripheral fractures after three years. As stated in the EPAR, the primary efficacy analysis used the Kaplan Meier method and an unadjusted Cox model, yielding a relative risk of 0,85, with the upper boundary of the 95% CI at 1,01 (3).

In 2005, the TROPOS trial was published in the Journal of Clinical Endocrinology & Metabolism. In contrast to the approach described in the EPAR, the authors state, that they carried out simultaneous adjustments for covariates such as age or body mass index. By this means, they achieved a relative risk of 0,84 and an upper boundary of the 95% CI marginally below 1 (0,995) for the primary endpoint. The fact, that the primary efficacy analysis of the TROPOS trial used an unadjusted Cox model and displayed no significant benefit of strontium ranelate, and that, hence, adjustments for age, BMI etc., were at best part of secondary analyses of the primary endpoint, are not mentioned in the journal article (4).. Moreover, the review withholds information about the negative result of the primary efficacy analysis of the TROPOS trial as well (2).

Of course, the difference between the result provided in the EPAR and that given in the journal article is marginal and may be clinically meaningless. However, it may be highly relevant for the manufacturer of strontium ranelate, whom the word "significance" may help marketing his product.

Response:
In TROPOS, the primary efficacy outcome was the incidence over time of patients with a non-vertebral fracture which was estimated using the Kaplan-Meier method and a Cox model to estimate the RR (95% CI) of non-vertebral fractures with strontium ranelate versus the placebo group (4). However, as the reviewer has pointed out, the adjusted results, which showed a marginally beneficial effect of strontium ranelate (RR 0.84, 0.702 to 0.995) were published in the primary study (4), whereas the unadjusted results included in the EMEA

demonstrated no significant benefit (RR 0.85, 0.71 to 1.01) (3) were not. Therefore, to ensure the reader is aware of the difference between the unadjusted and adjusted non-vertebral fracture results from the TROPOS trial, we have included both sets of results, in addition to the potential impact from a clinical perspective, within the discussion section of our review.

Having access to aggregate data only, the weighted relative risk for non-vertebral fractures was determined using the number of individuals with at least one incident non-vertebral fracture from the individual clinical trials (RR 0.84, 95% CI 0.702 to 0.995) (4;6). We did not have access to individual patient data.

Feedback Comment:
Furthermore, the evidence supporting the potential benefits of strontium ranelate is based on poor-quality trials: concealment of allocation is not adequately described in three of four trials, losses to follow-up are greater than 20% in three of four trials. How to interprete the TROPOS trial, in which the final outcome is not known in more than one third of patients (1.771), in view of a difference in the fracture rate between groups of only 1,9% or 43 women? A slight imbalance in fractures in those lost to follow up favouring the placebo group would render the results inconclusive. Thus, the TROPOS trial does not provide reliable evidence of a clinical benefit of strontium ranelate. We are not able to relate to the positive assessments of the review, which appear to be unaffected by the significant shortcomings of the trials. Especially in the abstract, readers are simply told about "silver level evidence" to support the efficacy of strontium ranelate. Will anyone expect the flawed data hidden behind this precious metal label?

Response:
As recommended by the Cochrane Musculoskeletal Group, we assessed study validity using the Jadad instrument and graded the evidence for each outcome with the ribbon grading system. Both the Jadad instrument and ribbon grading system are described and referenced within the body of our review to ensure that the related results have context. Furthermore, the results related to these assessments are clearly detailed in the results section. The implications of the limitations (including losses to follow-up) are openly summarized within the discussion section. We also revised the abstract to ensure the reader takes into account the specific limitations related to the quality of the included studies, when interpreting the results of our review.

Feedback Comment:
On the other hand, potentially life threatening adverse effects of strontium ranelate are played down in the review. The absolute increase of disorders of the vascular system including venous thromboembolism is 1,9%. Thus it is as large as the potential decrease of peripheral fractures in patients treated with strontium ranelate in the TROPOS trial. Notwithstanding the increased risk in vascular and neurological disorders (including seizures) is described as "slight" (2). The potential risk of osteomalacia, seen in animals (3) and associated with strontium overload in hemodialysis patients (5), is perhaps implied in the list of requirements for research ("particular attention to be paid on bone mineralization"), but not openly discussed.

Response:
We removed the descriptor "slightly" from sentences within the abstract and the discussion section that reported on the increased risk in vascular and neurological side-effects with taking 2 g of strontium ranelate daily over a 3 to 4 year period. The actual risk data is stated within the discussion section and Table 3 "Other adverse events from additional sources (EMEA 2004* and Servier**)".

The discussion section has been revised to include the potential risk of strontium induced osteomalacia observed in animal studies and associated with increased strontium bone concentrations in dialysis patients (see paragraph seven of the discussion).

It is worth mentioning that since the publication of our review, an updated safety assessment based on the final year study reports from the two five-year clinical trials (SOTI and TROPOS) was submitted. Results showed that the profile of the adverse drug reactions were consistent with the information initially presented in the Summary of Product Characteristics, although the frequencies of the specified adverse events required updating. In addition, following the assessment of the 3rd Periodic Safety Update Report from September 2005 to March 2006, the following effects (<1/10,000 patients) were added to the product information: vomiting, abdominal pain, oral mucosal irritation including stomatitis and/or mouth ulceration, hypersensitivity reactions including rash, angioedema (3). An analysis of transiliac bone biopsies with histomorphometry taken from women receiving strontium ranelate for treatment of postmenopausal osteoporosis after 1-5 years of 2 g/day provided evidence of bone safety with preservation of primary mineralization (8).

Feedback comment:
No conflicts of interests are disclosed, even though J.Y. Reginster has received consulting fees of a variety of pharmaceutical companies, among them Servier, the manufacturer of strontium ranelate (6,7).

Response:
This concern has been addressed (please see response to the reviewer's first comment).

References:
1 The Cochrane Collaboration: The Cochrane Manual, Issue 4, Aug. 2007; http://www.cochrane.org/admin/manual.htm
2 O'DONNELL, S., CRANNEY, A., WELLS, G.A., ADACHI, J.D., REGINSTER,
J.Y.:"Strontium ranelate for preventing and treating postmenopausal osteoporosis. Cochrane Database of Systematic Reviews 2006, Issue 4
3 EMEA: European Public Assessment Report (EPAR) PROTELOS, March 2007;
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7 REGINSTER, J.Y.: Lancet 2007; 370: 632-34
8 ARLOT, M.E. et al.: J Bone Miner Res. 2008; 23(2):215-222.

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Feedback from A. Herxheimer,

Summary

Date of Submission: 18-Sep-2007
Name: Andrew Herxheimer
Email Address: a.herxheimer@ntlworld.com Personal Description: Occupation clinical pharmacologist

Feedback: One of the authors of the review is JY Reginster, who is also an author of each of the four trials included in the review. It is not stated whether these trials were funded by Servier, the manufacturer of strontium ranelate, but that seems likely. Has JY Reginster worked closely with Servier? Has he had any contractual arrangement with Servier? If a review author is an author of one or more trials in a review, that also must be acknowledged as a potential conflict of interest. Yet under 'Conflicts of interest' it is stated "None known".
These points need explicit consideration and open discussion by the editors of the MSG. It seems that for the present the review should be treated with some reserve.

Submitter agrees with default conflict of interest statement:
I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

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One of the authors of the review is JY Reginster, who is also an author of each of the four trials included in the review. It is not stated whether these trials were funded by Servier, the manufacturer of strontium ranelate, but that seems likely. Has JY Reginster worked closely with Servier? Has he had any contractual arrangement with Servier? If a review author is an author of one or more trials in a review, that also must be acknowledged as a potential conflict of interest. Yet under 'Conflicts of interest' it is stated "None known".

Response:
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Consulting fees or paid advisory boards: Servier, Novartis, Negma, Lilly, Wyeth, Amgen, GlaxoSmithKline, Roche, Merckle, Nycomed, NPS, Theramex, UCB.

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Lastly, J Adachi has also received speaker fees from Servier.

Feedback Comment:
These points need explicit consideration and open discussion by the editors of the MSG. It seems that for the present the review should be treated with some reserve.

Response from Musculoskeletal Group:
Thank you for this feedback. This has been discussed by the Coordinating Editors of the CMSG with the authors of the systematic review.

Contributors

Andrew Herxheimer

WHAT'S NEW

Date	Event	Description
23 April 2021	Review declared as stable	Added published note indicating that review will not be updated as the intervention is no longer in use
23 April 2021	Amended	Added published note to explain the review is no longer being updated.

HISTORY

Protocol first published: Issue 2, 2005
Review first published: Issue 3, 2006

Date	Event	Description
28 May 2008	Amended	Converted to new review format. C078-R
14 November 2007	Feedback has been incorporated	Feedback incorporated in response to feedback received 9/18/07

CONTRIBUTIONS OF AUTHORS

Siobhan O'Donnell prepared the protocol and review for submission.

Ann Cranney conceptualized the idea and supervised all stages of the review.

George Wells provided statistical support.

Jonathan Adachi provided feedback on drafts.

Jean-Yves Reginster facilitated the attainment of unpublished data and provided feedback on drafts.

All co-reviewers reviewed and approved the final review.

DECLARATIONS OF INTEREST

All four included trials were supported by Servier, the manufacturer of strontium ranelate.
Also, J Y Reginster is an author on the four included trials within this review; in addition Dr. Reginster's disclosure of interest is as follows: Consulting fees or paid advisory boards: Servier, Novartis, Negma, Lilly, Wyeth, Amgen, GlaxoSmithKline, Roche, Merckle, Nycomed, NPS, Theramex, UCB.

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SOURCES OF SUPPORT

Internal sources

- Ottawa Health Research Institute, Canada

External sources

- Canadian Institutes for Health Research, Canada

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

All protocol methods were followed.

NOTES

This review will not be updated because the intervention is no longer in use. The manufacturer, Les Laboratoires Servier, ceased the worldwide distribution of strontium ranelate in August 2017 due to its restricted indication/limited use and the continuous decrease of patients treated with the drug.

INDEX TERMS

Medical Subject Headings (MeSH)

Bone Density [drug effects]; Bone Density Conservation Agents [adverse effects] [*therapeutic use]; Fractures, Bone [*prevention & control]; Organometallic Compounds [adverse effects] [*therapeutic use]; Osteoporosis, Postmenopausal [*prevention & control]; Randomized Controlled Trials as Topic; Spinal Fractures; Thiophenes [adverse effects] [*therapeutic use]

MeSH check words

Female; Humans