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Etidronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women (Review)

Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Welch V, Coyle D, Tugwell P

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Etidronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women (Review)

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[Intervention Review]

Etidronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women

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ABSTRACT

Background

Osteoporosis is an abnormal reduction in bone mass and bone deterioration leading to increased fracture risk. Etidronate belongs to the bisphosphonate class of drugs which act to inhibit bone resorption by interfering with the activity of osteoclasts.

Objectives

To assess the efficacy of etidronate in the primary and secondary prevention of osteoporotic fractures in postmenopausal women.

Search methods

We searched CENTRAL, MEDLINE and EMBASE for relevant randomized controlled trials published between 1966 to 2007.

Selection criteria

Women receiving at least one year of etidronate for postmenopausal osteoporosis were compared to those receiving placebo and/or concurrent calcium/vitamin D. The outcome was fracture incidence.

Data collection and analysis

Study selection and data abstraction was done in duplicate. Meta-analysis of fracture outcomes was performed with data presented as relative risks and a relative change greater than 15% was considered clinically important. Study quality was assessed through the reporting of allocation concealment, blinding and withdrawals.

Main results

Eleven studies representing a total of 1248 patients were included in the review.

A significant 41% relative risk reduction (RRR) in vertebral fractures across eight studies (RR 0.59, 95% CI 0.36 to 0.96) was found. The six secondary prevention trials demonstrated a significant RRR of 47% in vertebral fractures (RR 0.53, 95% CI 0.32 to 0.87) and a 5% absolute risk reduction (ARR); compared with the pooled result for the two primary prevention trials (RR 3.03, 95% CI 0.32 to 28.44), which was not

significant. There were no statistically significant risk reductions for non-vertebral (RR 0.98, 95% CI 0.68 to 1.42), hip (RR 1.20, 95% CI 0.37 to 3.88) or wrist fractures (RR 0.87, 95% CI: 0.32 to 2.36).

For adverse events, no statistically significant differences were found in the included studies. However, observational data has led to concerns regarding potential risk for upper gastrointestinal injury.

Authors' conclusions

Etidronate, at 400 mg per day, demonstrated a statistically significant and clinically important benefit in the secondary prevention of vertebral fractures. No statistically significant reductions in vertebral fractures were observed when it was used for primary prevention. In addition, no statistically significant reductions in non-vertebral, hip, or wrist fractures were found, regardless of whether etidronate was used for primary or secondary prevention. The level of evidence for all outcomes is Silver (www.cochranemsk.org.)

PLAIN LANGUAGE SUMMARY

Etidronate for preventing fractures caused by osteoporosis in postmenopausal women

This summary of a Cochrane review presents what we know from research about the effect of etidronate for preventing fractures (broken bones) caused by osteoporosis.

In women who have already been diagnosed with low bone density, putting them at risk of a fracture or have already had a fracture in the bones of their spine, etidronate:

- may prevent fractures in the bones of the spine.
- may lead to no difference in hip or wrist fractures or fractures in the bones other than in the spine.

In women whose bone density is closer to normal or who may not have had a fracture in the bones of their spine yet, etidronate:

- may lead to no difference in fractures in the bones of the spine, or in bones other than those of the spine.
- it is not known whether etidronate prevents hip or wrist fractures since no evidence was found that looked at the effect of etidronate in these women.

We often do not have precise information about side effects and complications. This is particularly true for rare but serious side effects. Possible side effects may include digestive problems such as heartburn, nausea and upset stomach.

What is osteoporosis and what is etidronate?

Bone is a living, growing part of your body. Throughout your lifetime, new bone cells grow and old bone cells break down to make room for the new, stronger bone. When you have osteoporosis, the old bone breaks down faster than the new bone can replace it. As this happens, the bones lose minerals (such as calcium). This makes bones weaker and more likely to break even after a minor injury, like a little bump or fall.

Women who have gone through menopause are more likely to get osteoporosis than other people. Etidronate belongs to the class of drugs called bisphosphonates. It is a type of medication that slows down the cells that break down the old bone.

The best estimate of what happens to women that have already been diagnosed with low bone density or have already had a fracture in the bones of their spine:

Fracture of the spine:

- 11 out of 100 women had a fracture when taking a placebo
- 6 out of 100 women had a fracture when taking etidronate

Fractures in bones other than the spine:

- 13 out of 100 women had a fracture when taking a placebo
- 14 out of 100 women had a fracture when taking etidronate

Fractures in the hip or wrist:

- there was no difference in the number of women who had hip or wrist fractures which may be the result of chance

The best estimate of what happens to women whose bone density is closer to normal or who may not yet have had a fracture in the bones of their spine:

Fracture of the spine

- 0 out of 100 women had a fracture when taking a placebo
- 1 out of 100 women had a fracture when taking etidronate

Fractures in bones other than the spine

- 11 out of 100 women had a fracture when taking a placebo
- 6 out of 100 women had a fracture when taking etidronate

For these women, fractures in the hip or wrist were not measured in the studies.

BACKGROUND

Osteoporosis is in part a natural consequence of aging in postmenopausal women (Hodsman 2002). It is a skeletal disorder characterized by decreased bone mass and deterioration in microarchitecture of bone resulting in an increased risk of fracture (NIH Consensus 2001).

The most common consequences of osteoporosis are fractures of the hip, wrist and vertebrae. (Hodsman 2002). "Bone strength reflects the integration of two main features: bone density and bone quality" (Brown 2002). The clinical indicator of bone quality is a patient's history of a fragility fracture. A fragility fracture is a fracture caused by an injury that would be insufficient to fracture normal bone (for example a fall from a standing height or less) (Brown 2002). The preferred method of evaluating bone density is the measurement of bone mineral density (BMD) of the lumbar spine and hip by dual energy X-ray absorptiometry (DXA), which can be used to assess response to therapy (Hanley 2003).

The interpretation of BMD results is based on comparison of a patient's BMD with the mean value for a young adult population. The 'T-score' is the number of standard deviations (SDs) above or below the mean BMD for normal young adults (Brown 2002). The World Health Organization (WHO) Study Group on Osteoporosis defined osteoporosis as "a hip BMD level of more than 2.5 SDs below the mean BMD for young, white, adult women" (WHO 1994). Using the WHO definition, approximately 30% of postmenopausal women have osteoporosis (Kanis 1994; WHO 1994). It should be noted that there are limitations associated with the WHO definition. The predictive value of BMD measurement for fracture varies depending on the site selected, the database used for comparison and the technology used. Furthermore, T-scores do not provide a good basis to establish comparable diagnostic thresholds between different regions of interest and different bone mass measurement techniques (Black 2000). As a result, between-site and technique variability introduces potential for misclassification and inappropriate treatment of some individuals.

Osteoporosis can be detected by BMD measurement or diagnosed by presence of osteoporosis-related fractures. The presence of pre-existing osteoporotic fractures is an important risk factor for future fractures (Hodsman 2002). It is reported that 25% of women aged 80 years have had at least one vertebral fracture (Melton 1989) and Cauley et al (Cauley 2000) have demonstrated excess mortality in women who have experienced a clinical vertebral fracture. The cumulative lifetime fracture risk for a 50-year old woman with osteoporosis is stated to be as high as 60% (Cummings 1989). As a result, effective fracture prevention would have a major impact on morbidity and a smaller but important impact on mortality in these women.

Osteoporosis-related morbidity is associated with significant medical and social consequences (Brown 2002). The major source of morbidity and mortality from osteoporosis is attributed to hip fractures. Hip fractures are not only associated with an increased mortality risk but also influence long-term function and independence. Fifty per cent of women who sustain a hip fracture do not return to their previous functional state and become dependent on others for their daily activities (Brown 2002). The mortality associated with hip fractures in older women may be as high as 20% in the first year (Cauley 2000). This excess mortality

may not be directly attributable to the hip fracture but to co-morbid conditions (Browner 1996; Cooper 1993).

Prevention and treatment of osteoporosis can be complex, due to the multifactorial etiology of the disorder. Anabolic therapies directed at increasing bone formation, such as teriparatide PTH (1-34) (Shukla 2003), are available, however, most currently available osteoporosis drugs are anti-resorptive agents that act to decrease bone turnover. One class of anti-resorptive drugs includes the bisphosphonates: etidronate, alendronate and risedronate. They are recommended as first-line preventive agents in postmenopausal women with low BMD and as first-line agents for the treatment of postmenopausal women with osteoporosis (Brown 2002).

Bisphosphonates are stable analogues of naturally occurring pyrophosphates. The mechanism of action of these drugs is to inhibit bone resorption through their effects on osteoclast function (Brown 2002). Bisphosphonates are poorly absorbed and avidly taken up by bone on active sites of resorption. Etidronate is a first-generation non-nitrogen containing bisphosphonate that inhibits osteoclastic resorption and decreases bone turnover (Fleisch 1997). It is considered a weaker anti-resorptive agent than the other bisphosphonates. It is given orally on a cyclical schedule, 400 mg for 2 weeks every 90 days, followed by calcium, to minimize any potential to inhibit bone mineralization and result in osteomalacia. Etidronate, relative to control, has been shown to increase bone mineral density after one to three years of treatment, by 4.06% (95% CI 3.12 to 5.0) in the lumbar spine and 2.35% (95% CI 1.66 to 3.04) in the femoral neck (Cranney 2001).

OBJECTIVES

The aim of this systematic review was to assess the clinical efficacy of etidronate in the primary and secondary prevention of osteoporotic fractures in postmenopausal women receiving these agents compared with untreated women over a follow-up period of at least one year.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) with a duration of at least one year were included in this review.

Types of participants

Only postmenopausal women were included and both primary and secondary prevention trials were accepted. A hierarchy was used to define primary versus secondary prevention according to the information available. We selected a definition of primary and secondary prevention that gave more weight to study inclusion criteria than baseline statistics. That is, if the inclusion criteria restricted the population to women whose bone density was at least 2 SD values below the peak bone mass or the inclusion criteria restricted the population to women who had experienced previous vertebral compression fractures, then the trial was considered a secondary prevention study. If such inclusion criteria were not provided then the baseline statistics were considered as follows: (a) we considered the trial as primary prevention if the average T-score (and SD) was such that it included women whose bone

density was within 2 SD of the mean or if the prevalence of vertebral fracture at baseline was less than 20%; and (b) when these data were not available, we considered a trial as secondary prevention if the average age was above 62 years.

Types of interventions

Treatment: intermittent oral etidronate at any dose.

Comparators: no treatment (including placebo or calcium or vitamin D, or both). If the study used calcium and/or vitamin D controls these same treatments would have to be given concurrently in the etidronate group.

Types of outcome measures

Incidence of fractures including vertebral, non-vertebral, hip and wrist fractures.

Search methods for identification of studies

The Cochrane Collaborative approach for identifying randomized controlled trials (RCTs) as described by Dickersin et al ([Dickersin 1994](#)) and modified for the Cochrane Musculoskeletal Group guided our literature search. We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE® (1966 to November 2004), Current Contents® and citations of relevant articles. No language restrictions were applied to the search strategy. The actual literature search was conducted in three stages. The first stage was the basis for our systematic review published in 2001 ([Cranney 2001](#)) and the second stage involved updating the search. For the first search (1966 to 1998) included MEDLINE®, Current Contents® and handsearching of conference abstract books (Osteoporosis International, Journal of Bone and Mineral Research). This was followed by a MEDLINE® search (1998 to November 2004). This MEDLINE search was confirmed by a parallel literature search that was conducted for a companion bisphosphonate economic report ([CADTH 2006](#)). For the final update (2004 to February 2007), we searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE.

Search strategy for MEDLINE using the OVID interface

1. osteoporosis, postmenopausal/
2. osteoporosis/
3. osteoporosis.tw.
4. exp bone density/
5. bone loss\$.tw.
6. (bone adj2 densit\$).tw.
7. or/2-6
8. menopause/
9. post-menopaus\$.tw.
10. postmenopaus\$.tw.
11. or/8-10
12. 7 and 11
13. 1 or 12
14. etidronic acid/
15. etidronate.tw,rn.
16. (xidifon or xidiphon\$).tw.
17. (ehdp or ethanehydroxydiphosphonate).tw.
18. or/14-17
19. 13 and 18
20. meta-analysis.pt,sh.
21. (meta-anal: or metaanal:).tw.
22. (quantitativ: review: or quantitativ: overview:).tw.

23. (methodologic: review: or methodologic: overview:).tw.
24. (systematic: review: or systematic: overview).tw.
25. review.pt. and medline.tw.
26. or/20-25
27. 19 and 26
28. clinical trial.pt.
29. randomized controlled trial.pt.
30. tu.fs.
31. dt.fs.
32. random\$.tw.
33. (double adj blind\$).tw.
34. placebo\$.tw.
35. or/28-34
36. 19 and 35

Data collection and analysis

Selection of studies

Two review authors examined each title generated from the search and identified potentially eligible articles, for which we obtained the abstracts. For abstracts consistent with study eligibility, the full-text article was obtained. Overall, we only considered for inclusion studies for which findings were published, either as a full article or an abstract.

Data abstraction strategy

Two review authors independently abstracted all information and data using standardized data abstraction forms with a third review author verifying the data. Abstraction included information on pertinent methodological aspects of the study design, characteristics of the participants, the specific dose of the study drug used and the outcomes assessed (for example number of vertebral, non-vertebral, hip and wrist fractures). For fracture data, all reported fractures (whether clinical or radiographic) were considered.

For the yearly data, our unit of analysis was number of patients sustaining a fracture. If an article reported yearly data, we used the time points available. For baseline denominators we used the same baseline denominator for each time point. For follow-up denominators we used any yearly follow-up number of patients reported in the article, if available. If these were not available, we assumed a uniform dropout rate for each year and calculated the denominators by determining the proportion of participants that would have remained at the end of the year in question based on the number of withdrawals over the course of the study. If an article reported only end of study outcomes these were used for our analysis, with the exception of outcomes for which the numerator was zero for both treatment groups. In these instances we included the outcome (with any necessary adjustments for follow-up denominators) for the earlier years in the duration of the study. For example, if a trial reported zero hip fractures for both treatment arms at the end of year three, we would also include in our analysis zero hip fractures for that trial at years one and two.

For person year data, the unit of analysis, if available, was number of fractures. When these data were not available (that is in the majority of cases), we used the number of women sustaining a fracture. For denominators, we multiplied the number of women followed by the length of the study. For radiographic vertebral fractures we used the number of women with available

radiographs, if the number was reported in the article. For clinical fractures, we estimated the number of women followed over the duration of the study by taking the mean of the baseline and follow-up denominators.

Strategy for quality assessment

Two review authors assessed each eligible RCT for quality based on allocation concealment. Research has shown that lack of adequate allocation concealment is associated with bias ([Higgins 2005](#)) and studies can be judged on the method of allocation concealment. The method for assigning participants to interventions should be robust against patient and clinician bias and its description should be clear. The review authors were required to indicate whether allocation concealment was adequate (A), unclear (B), or inadequate (C) as per the Cochrane Collaboration criteria, as follows.

Adequate: some approaches that can be used to ensure adequate concealment schemes are centralized or pharmacy-controlled randomization, pre-numbered or coded identical containers which are administered serially to participants, on-site computer system combined with allocations kept in a locked unreadable computer file that can be accessed only after the characteristics of an enrolled participant have been entered or sequentially numbered or sealed, opaque envelopes. Other approaches may include those similar to ones listed previously, along with reassurance that the person who generated the allocation scheme did not administer it.

Inadequate: approaches to allocation concealment that are considered inadequate include alternation, use of case record numbers, dates of birth or day of the week and any procedure that is entirely transparent before allocation, such as an open list of random numbers.

Unclear: when studies do not report any concealment approach adequacy should be considered unclear. Examples include merely stating that a list or table were used, only specifying that sealed envelopes were used and reporting an apparently adequate concealment scheme in combination with other information that leads the review author to be suspicious.

In addition, blinding and loss to follow up were assessed.

Data analysis

For the analysis of fractures (that is vertebral, non-vertebral, hip and wrist), the relative risk (RR) of fracture was calculated using a fixed-effect model. The methods we used for pooling the results are described elsewhere by Fleiss ([Fleiss 1993](#)). The pooled or weighted RRs were calculated using the general inverse variance method for the weights. For the pooled results, site-specific 95% confidence intervals (CIs) were calculated for vertebral, non-vertebral, hip and wrist fractures and we tested for association using a chi-square test procedure taking a P value < 0.05 for presence of statistical association. Statistically significant risk reductions were considered to be clinically important if a 15% or greater relative benefit was shown. We also tested for homogeneity using a chi-square test procedure taking the specific cut off for presence of statistical heterogeneity as $P = 0.10$. In the event of significant heterogeneity, a random-effects model was used.

If the relative risk reduction (RRR) was significant ($P < 0.05$), then the absolute risk reduction (ARR) and number needed to treat (NNT) were calculated. For these calculations, the five-year risk of fracture in the untreated population was based on the FRACTURE Index (FI) of Black et al ([Black 2001](#)) and the lifetime and five-year age-specific risks in the untreated population were based on the model by Doherty et al ([Doherty 2001](#)) for predicting osteoporotic fractures in postmenopausal women ([Figure 1](#); [Figure 2](#); [Figure 3](#); [Figure 4](#)).

Figure 1. FRACTURE Index (based on Black et al 2001)

Question		Point Score
1. What is your current age?	< 65	0
	65-69	1
	70-74	2
	75-79	3
	80-84	4
	≥ 85	5
2. Have you broken any bones after age 50?	Yes	1
	No / Don't know	0
3. Has your mother had a hip fracture after age 50?	Yes	1
	No / Don't know	0
4. Do you weigh 125 pounds or less?	Yes	1
	No	0
5. Are you currently a smoker?	Yes	1
	No	0
6. Do you usually need your arms to assist yourself in standing up from a chair?	Yes	1
	No / Don't know	0
<i>If you have a current bone mineral density (BMD) assessment, then answer next question.</i>		
7. BMD results: Total Hip T-score	≥ -1	0
	-1 to -2	2
	-2 to -2.5	3
	< -2.5	4

Figure 2. Five year risk of fracture by Quintiles of the FRACTURE Index: Assessment with bone mineral density

FRACTURE Index	Risk of Fracture (%)		
	Vertebral	Non-Vertebral	Hip
1-2	1.2	8.6	0.4
3-4	2.5	13.1	0.9
5	5.3	16.5	1.9
6-7	7.1	19.8	3.9
8-13	11.2	27.5	8.7

Figure 3. Five year risk of fracture by Quintiles of the FRACTURE Index: Assessment without bone mineral density

FRACTURE Index	Risk of Fracture (%)		
	Vertebral	Non-Vertebral	Hip
1	1.4	10.5	0.6
2	2.9	12.5	1.4
3	5.1	16.4	2.1
4	7.0	18.7	3.2
5-9	9.9	26.1	8.2

Figure 4. Estimated five year age-specific risks of first and subsequent osteoporotic fractures (from Doherty et al 2001)

Age (years)	Risk of Fracture (%)					
	Spine		Hip		Other*	
	First	Subsequent	First	Subsequent	First	Subsequent
50-54	0.2	0.5	0.0	0.0	1.6	2.6
55-59	0.4	4.0	0.2	0.4	2.1	3.4
60-64	1.0	9.7	0.2	0.2	3.1	6.2
65-69	1.5	14.3	0.8	0.9	4.2	8.4
70-74	1.8	17.2	1.6	2.2	6.5	11.2
75-79	3.3	24.2	3.8	5.2	7.4	12.0
80-84	2.3	19.1	7.1	9.2	10.3	15.9
85-89	2.5	20.9	16.7	20.1	13.5	18.4
90+	4.7	27.9	20.9	22.8	35.2	37.7

* 'Other' non-vertebral includes wrist, forearm, humerus, tibia/fibula, pelvis, ribs, femur; but excludes hip

Trials varied as to the length of treatment (for example one to four years) and the number of patients available for study at the start of treatment (that is the baseline denominator) compared to those available at different time points during the trial (that is follow-up denominators). The base case taken for the review of fractures considered the data available for the longest period of time for the treatment in the trial (that is 'all years') and used the baseline denominators for the number of patients in the trial.

Data was initially pooled broadly across primary and secondary prevention trials. The overall analysis was also considered using person years of observation. In addition, we conducted subgroup analysis for: 1) primary versus secondary prevention, 2) treatment duration and 3) treatment dose. Furthermore, we conducted sensitivity analysis for: 1) baseline denominators versus follow-up denominators, 2) fixed-effect versus random-effects model and 3) baseline vertebral fracture rate. For the last sensitivity analysis, recall that the vertebral fracture criteria for a trial to be considered secondary was a prevalence of vertebral fracture at baseline of greater than 20%. A sensitivity analysis using different vertebral fracture rates (that is 100%, > 80%, > 60%, > 40%, > 20%) without the BMD and age criteria was conducted. Such sensitivity analysis allowed evaluating whether the effect of bisphosphonates on the secondary prevention of osteoporotic fractures varied depending on how strictly secondary prevention was defined.

Grading of evidence

We used the grading system described in the 2004 book Evidence-based Rheumatology (Tugwell 2004) and recommended by the Cochrane Musculoskeletal Group.

Platinum

To achieve the platinum level of evidence, a published systematic review that has at least two randomized controlled trials, each satisfying the following, is required.

- * Sample sizes of at least 50 per group - if these do not find a statistically significant difference, they are adequately powered for a 20% relative difference in the relevant outcome.
- * Blinding of patients and assessors for outcomes.
- * Handling of withdrawals > 80% follow up (imputations based on methods such as last observation carried forward (LOCF) are acceptable).
- * Concealment of treatment allocation.

Gold

The gold level of evidence requires at least one randomized clinical trial meeting all of the following criteria for the major outcome(s), as reported.

- * Sample sizes of at least 50 per group - if these do not find a statistically significant difference, they are adequately powered for a 20% relative difference in the relevant outcome.
- * Blinding of patients and assessors for outcomes.
- * Handling of withdrawals > 80% follow up (imputations based on methods such as LOCF are acceptable).
- * Concealment of treatment allocation.

Silver

The silver level of evidence requires a randomized trial that does not meet the above criteria for gold or platinum ranking or evidence from at least one study of non-randomized cohorts that did and did not receive the therapy, or evidence from at least one high quality case-control study. A randomized trial with a 'head-to-head' comparison of agents would be considered silver-level ranking unless a reference was provided to a comparison of one of the agents to placebo showing at least a 20% relative difference.

Bronze

The bronze level of evidence requires at least one high quality case series without controls (including simple before and after studies in which patients act as their own control) or a conclusion derived from expert opinion based on clinical experience without reference to any of the foregoing (for example argument from physiology, bench research or first principles).

Clinical relevance tables

Clinical relevance tables were compiled under 'Additional tables' to improve the readability of the review. Results were presented

within the context of both the study population and moderate to high risk women from the population at large. The number needed to treat (NNT) was calculated using the relative risk (RR) in combination with either the risk of fracture in the control group or the five year FRACTURE Index ([Black 2001](#)). To do this, the Visual Rx NNT calculator ([Cates 2004](#)) was used. The weighted absolute risk difference was calculated using the risk difference (RD) statistic in RevMan and RR-1 was used to calculate the relative per cent change ([Table 1](#); [Table 2](#)).

In addition, for the outcomes of vertebral and hip fractures we prepared Summary of Findings tables using the GRADE criteria from the GRADE working group ([GRADE 2004](#)), ([Figure 5](#); [Figure 6](#)).

Figure 5. Summary of Findings Primary Prevention

Etidronate 400 mg for 1-3 years - Summary of Findings for Primary Prevention						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Without etidronate	With etidronate				
Vertebral fractures	Low-risk population		RR 3.03 (0.32 to 28.44)	315 (3 studies)	⊕○○○ Very low	
	12 per 1000	36 (4 to 341) Not statistically significant				
	Moderate-risk population					
	53 per 1000	161 (17 to 645) Not statistically significant				
Hip fractures	Moderate risk population		No trials available	No trials available	No trials available	
	4 per 1000	No trials available				
	High risk population					
	19 per 1000	No trials available				
Withdrawals due to side effects	28 per 1000	17 per 1000 (7 to 42) Not statistically significant	RR 0.61 (0.25 to 1.49)	796 (5 studies)	⊕⊕○○ Low	
*The basis for the assumed risk (e.g. the low and moderate risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is calculated based on the assumed risk in the study control groups and the relative effect of the intervention (and its 95% CI).						
CI: Confidence interval; RR: Risk ratio GRADE: GRADE Working Group grades of evidence (see explanations)						

Assumed Risk Without Alendronate

Moderate and High Risk, are 5 year community population risks derived from the following variables in the FRACTURE Index: age, fracture after 50 yrs, maternal hip fracture, weight < 125 lbs, smoking, using arms to assist standing and BMD. Low = FRACTURE Index score 1-2, Moderate = FRACTURE Index score 5 (Black 2001).

Quality assessment- GRADE

RCTs start at "high" quality, then are downgraded based on the following criteria: 1. Study limitations (-1 if serious limitations, -2 if very serious), 2. Consistency of results (-1 if inconsistent), 3. Directness of evidence (-1 if not direct), 4. Imprecision (-1 if imprecise), 5. Reporting bias (-1 if likely based on funnel plot or other data). Grades are as follows: **High** - further research is very unlikely to change our confidence in the estimate of effect; **Moderate** - Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; **Low** - Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; **Very low** - We are very uncertain about the estimate.

Figure 6. Summary of Findings Secondary Prevention

+

ETIDRONATE 400 mg for 1-3 years - Summary of Findings for Secondary Prevention						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	<u>Without risedronate</u>	<u>Without risedronate</u>				
Vertebral fractures	Moderate-risk population		RR 0.53 (0.32 to 0.87)	695 (5 studies)	⊕⊕⊕○ Moderate	
	53 per 1000	13 per 1000 (17 to 46)				
	High-risk population					
	112 per 1000	59 per 1000 (35 to 98)				
Hip fractures	moderate risk population		RR 1.20 (0.37 to 3.88)	589 (4 studies)	⊕⊕○○ Low	
	19 per 1000	23 (7 to 74) Not statistically significant				
	High risk population					
	87 per 1000	104 (32 to 338) Not statistically significant				
Withdrawals due to side effects	28 per 1000	17 per 1000 (7 to 42) Not statistically significant	RR 0.61 (0.25 to 1.49)	796 (5 studies)	⊕⊕○○ Low	
*The basis for the assumed risk (e.g. moderate and high risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is calculated based on the assumed risk in the study control groups and the relative effect of the intervention (and its 95% CI).						
CI: Confidence interval; RR: Risk ratio GRADE: GRADE Working Group grades of evidence (see explanations)						

Assumed Risk Without Alendronate

Moderate and High Risk, are 5 year community population risks derived from the following variables in the FRACTURE Index: age, fracture after 50 yrs, maternal hip fracture after 50 yrs, weight < 125 lbs, smoking, using arms to assist standing and BMD. Moderate = FRACTURE Index score 5, High = FRACTURE Index score 8-13 (Black 2001).

Quality assessment- GRADE

RCTs start at "high" quality, then are downgraded based on the following criteria: 1. Study limitations (-1 if serious limitations, -2 if very serious), 2. Consistency of results (-1 if inconsistent), 3. Directness of evidence (-1 if not direct), 4. Imprecision (-1 if imprecise), 5. Reporting bias (-1 if likely based on funnel plot or other data). Grades are as follows: **High** - further research is very unlikely to change our confidence in the estimate of effect; **Moderate** - Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; **Low** - Further research is very likely to have an important impact on our confidence in

Figure 6. (Continued)

Moderate - Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; **Low** - Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; **Very low** - We are very uncertain about the estimate.

RESULTS

Description of studies

Quantity of research available

The literature search revealed 766 citations. Of these, 43 articles were retrieved for further review. A total of 32 articles were excluded for various reasons including lack of an appropriate control group (14) ([Anderson 1984](#); [Cortet 2001](#); [Guanabens 2000](#); [Harris 1993](#); [Hesch 1988](#); [Hodsman 1989](#); [Iwamoto 2001](#); [Iwamoto 2003 a](#);

[Iwamoto 2003 b](#); [Jowsey 1971](#); [Masud 1998](#); [Miller 1999](#); [Morishige 2003](#); [Steiniche 1991](#)), lack of randomization (9) ([Bolanca 1988](#); [Hyldstrup 2001](#); [Mallette 1989](#); [Miller 1997](#); [Orme 1994](#); [Ott 1994](#); [Ryan 1994](#); [Smith 1989](#); [Storm 1996](#)), study duration less than one year (1) ([Heaney 1976](#)) and no fracture outcome reported (8) ([Adami 2000](#); [Chilibeck 2002](#); [Evans 1993](#); [Gurlek 1997](#); [Heath 2000](#); [Iwamoto 2002](#); [Terranova 1999](#); [Terranova 1999](#)). In the end, 11 trials ([Herd 1997](#); [Ishida 2004](#); [Lyritis 1997](#); [Meunier 1997](#); [Montessori 1997](#); [Pacifci 1988](#); [Pouilles 1997](#); [Shiota 2001](#); [Storm 1990](#); [Watts 1990](#); [Wimalawansa 1998](#)) met all of the selection criteria ([Figure 7](#)).

Figure 7. Summary of Literature Search for Etidronate

Trial characteristics

The characteristics of the 11 selected trials are provided in the Characteristics of included studies table. In total, there were 1248 women enrolled in the trials and of these 624 received placebo. Eight trials included women with established osteoporosis and were classified as secondary prevention trials (Ishida 2004; Lyritis 1997; Montessori 1997; Pacifici 1988; Shiota 2001; Storm 1990; Watts 1990; Wimalawansa 1998) and the remaining three were classified as primary prevention trials (Herd 1997; Meunier 1997; Pouilles 1997). Nine trials (Herd 1997; Lyritis 1997; Meunier 1997; Montessori 1997; Pacifici 1988; Pouilles 1997; Storm 1990; Watts 1990; Wimalawansa 1998) administered etidronate cyclically at the standard dose of 400 mg and two trials (Ishida 2004; Shiota 2001) used a 200 mg dose. Follow up for the 11 studies ranged from two to four years and the mean age of the participants was 53 to 72 years. Two studies (Montessori 1997; Watts 1990) excluded women with a history of gastrointestinal (GI) disease and only one trial (Watts 1990) reported fractures as a stated primary outcome.

We did not include data from the hormone replacement therapy (HRT) treatment arm or combined HRT and etidronate arm of the study by Wimalawansa (Wimalawansa 1998). In one study (Watts 1990) there were four treatment groups included, of which two were placebo groups. As a result, this study was analyzed as two separate studies (Watts A and Watts B). In Watts A, cyclical etidronate was compared with placebo whereas in Watts B cyclical etidronate and phosphate were compared with placebo and phosphate. Due to the separation of the Watts study into two, the analysis of fracture data reported in the following tables is considered to come from a possible total of 12 trials.

Risk of bias in included studies

Allocation concealment was unclear for all 11 trials. Seven trials had a loss to follow up from 5% to 20% (Herd 1997; Ishida 2004; Meunier 1997; Montessori 1997; Pouilles 1997; Watts 1990; Wimalawansa 1998), for three trials it was over 20% (Lyritis 1997; Pacifici 1988; Storm 1990) and one trial did not report the loss to follow up (Shiota 2001). Five trials (Herd 1997; Meunier 1997; Pouilles 1997; Storm 1990; Watts 1990) were double blind.

Effects of interventions

Data analysis and synthesis

Effect on fractures

Considering the data available for the longest treatment duration in the trials and using the baseline denominators for the number of patients in the trial (that is base case), a summary of the overall review of fractures for the standard dose of etidronate (400 mg for two weeks every three months) is given in Figure 8. In general, the pooled estimate of RR of fracture after treatment with etidronate was not significant for non-vertebral, hip and wrist fractures whether it was used for primary or secondary prevention. For vertebral fractures, the pooled estimate of the RR was significant for secondary prevention but not for primary prevention. The Clinical relevance table provides a summary of the absolute and relative results.

Figure 8. Weighted relative risk (RR) of fracture after etidronate (400 mg)

Weighted relative risk (RR) of fracture after etidronate (400 mg)

Fracture Sites	Primary / Secondary Prevention	# of Trials	# Participants (treatment / control)	RR (95% CI)	Association p-value	Heterogeneity p-value
Vertebral	Overall	8	430 / 428	0.59 (0.36; 0.96)	0.03	0.70
	Primary	2	81 / 82	3.03 (0.32; 28.44)	0.3	0.99
	Secondary	6	349 / 346	0.53 (0.32; 0.87)	0.01	0.77
Non-Vertebral	Overall	7	393 / 394	0.98 (0.68; 1.42)	0.9	0.87
	Primary	2	81 / 82	0.56 (0.20; 1.61)	0.3	0.81
	Secondary	5	312 / 312	1.07 (0.72; 1.60)	0.7	0.88
Hip	Overall	4	295 / 294	1.20 (0.37; 3.88)	0.8	0.53
	Primary	0	N/A	N/A	N/A	N/A
	Secondary	4	295 / 294	1.20 (0.37; 3.88)	0.8	0.53
Wrist	Overall	4	295 / 294	0.87 (0.32; 2.36)	0.8	0.51
	Primary	0	N/A	N/A	N/A	N/A
	Secondary	4	295 / 294	0.87 (0.32; 2.36)	0.8	0.51

RR=Relative Risk; CI=Confidence Interval; N/A=Not Applicable

Vertebral fractures

Vertebral fractures were reported in all 11 trials. Among these, two trials (Ishida 2004; Shiota 2001) used a nonstandard dose of 200 mg and were later considered in the section on subgroup analysis. One trial (Storm 1990) reported results in person years only and the Watts trial was considered to consist of two studies, as previously explained. As a result, we considered the eight trials reporting vertebral fractures corresponding to the standard 400 mg dose. One trial reported that no fractures occurred in either treatment group (Herd 1997).

The pooled estimate of the RR of vertebral fractures from the eight trials (Herd 1997; Lyritis 1997; Meunier 1997; Montessori 1997; Pacifici 1988; Pouilles 1997; Watts 1990A; Watts 1990B; Wimalawansa 1998) that could be analyzed resulted in a significant 41% reduction in vertebral fractures (RR 0.59, 95% CI 0.36 to 0.96) as detailed in Figure 8 and as Comparison 01, 01. This demonstrated a fracture risk reduction with etidronate and results were consistent across the eight trials ($P = 0.70$). The significance in the overall RR of vertebral fractures was fundamentally due to the six secondary prevention trials that demonstrated a significant relative risk reduction (RRR) of 47% in vertebral fractures (RR 0.53, 95% CI 0.32 to 0.87); compared to the pooled result for the two primary prevention trials (RR 3.03, 95% CI 0.32 to 28.44), which was not significant.

Corresponding to the significant RRR of 47% for the secondary prevention of vertebral fractures, the measures (ARR, NNT) of the five year risk of vertebral fracture after treatment with etidronate were calculated for different levels of increasing risk as measured by the fracture index (FI). Results are provided in Figure 9 as well as for increasing age in Figure 10. For the illustrative case of the patient with a FI of 6 to 7, the ARR in vertebral fracture was 3.3% (that is a reduction in risk from 7.1% to 3.8%) and the NNT was 30 (that is 30 patients would need to be treated to avoid one vertebral fracture). Across the range of increasing FI risk, the ARR for vertebral fracture ranged from 0.6% to 5.3% and the NNT to avoid one vertebral fracture ranged from 167 to 19. For the illustrative patient in the age group 60 to 64 years, the ARR for the first vertebral fracture was 0.5% (that is a reduction in risk from 1.0% to 0.5%) and the NNT was 213 patients treated to avoid the first fracture. The ARR for a subsequent fracture was 4.6% (that is a reduction in risk from 9.7% to 5.1%) and the NNT was 22 patients treated to avoid one subsequent fracture. For increasing age, the 5-year age-specific ARR for the first vertebral fracture increased from 0.1% for the youngest age group (50 to 54 years) to 2.2% in the highest age group (90+ years). Accordingly, the NNT decreased from 1064 to 45. For the subsequent fracture, ARR increased from 0.2% to 13.1% and the NNT decreased from 426 to 8.

Figure 9. Five year FRACTURE Index specific risk of fracture after etidronate (400mg)

Fracture Site Prevention RR (95%CI)	FRACTURE Index	Risk of Fracture (untreated)	Risk of Fracture (treated)	RRR	ARR	NNT
Vertebral Secondary 0.53(0.32; 0.87)	1-2	1.2%	0.6%	0.47	0.6%	167
	3-4	2.5%	1.3%	0.47	1.2%	83
	5	5.3%	2.8%	0.47	2.5%	40
	6-7	7.1%	3.8%	0.47	3.3%	30
	8-13	11.2%	5.9%	0.47	5.3%	19

RR=Relative Risk; CI=Confidence Interval; RRR=Relative Risk Reduction; ARR=Absolute Risk Reduction; NNT=Number Needed to Treat

Figure 10. Five year age-specific risk of first and subsequent fracture after etidronate (400 mg)

Five year age-specific risk of first and subsequent fracture after etidronate (400 mg)

Fracture site Prevention RR (95 %CI)	Fracture	Risk Measure	Age group (years)								
			50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89	90+
Vertebral Secondary 0.53 (0.32; 0.87)	First	ARR	0.1%	0.2%	0.5%	0.7%	0.8%	1.6%	1.1%	1.2%	2.2%
		NNT	1,064	532	213	142	118	64	93	85	45
	Subsequent	ARR	0.2%	1.9%	4.6%	6.7%	8.1%	11.4%	9.0%	9.8%	13.1%
		NNT	426	53	22	15	12	9	11	10	8

RR=Relative Risk; CI=Confidence Interval; ARR=Absolute Risk Reduction; NNT=Number Needed to Treat

Non-vertebral fractures

Etidronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women (Review)

Non-vertebral fractures were reported in six trials (Lyritis 1997; Meunier 1997; Pouilles 1997; Storm 1990; Watts 1990; Wimalawansa 1998). The lack of effect of etidronate on non-vertebral fractures is depicted in Figure 8 and Comparison 02,01. The 95% CI around the RR estimate for all non-vertebral fractures was wide with a RRR of approximately 32% and a RR increase of 42% (RR 0.98, 95% CI 0.68 to 1.42). Results were consistent across the seven trials ($P = 0.87$).

A similar lack of effect of etidronate on non-vertebral fractures was found for both primary and secondary prevention trials. Pooled results for both primary prevention trials (RR 0.56, 95%CI 0.20 to 1.61) and the five secondary prevention trials (RR 1.07, 95% CI 0.72 to 1.60) were not significant.

Hip fractures

Hip fractures were only reported in three trials (Lyritis 1997; Storm 1990; Watts 1990A; Watts 1990B). Results of the pooled hip fracture data (RR 1.20, 95% CI 0.37 to 3.88) were not significant, as detailed in Figure 8 and Comparison 03, 01.

Wrist fractures

Wrist fractures were reported in the same three secondary prevention trials (Lyritis 1997; Storm 1990; Watts 1990) as were hip fractures. Similarly, results of the pooled wrist fracture data (RR 0.87, 95% CI 0.32 to 2.36) were not significant, as detailed in Figure 8 and Comparison 04, 01.

Additional analyses

Person years

When the approach of person years was used, similar results were found for vertebral, non-vertebral, hip and wrist fractures (Figure 11). Of note, the pooled result for vertebral fractures was not significant for the two primary prevention trials; however, for the six secondary prevention trials a significant 55% reduction in vertebral fractures (RR 0.45, 95% CI 0.31 to 0.64) was found with results consistent across the secondary trials ($P = 0.40$).

Figure 11. Weighted relative risk (RR) of fracture with etidronate (400 mg): Person years

Fracture Sites	Primary / Secondary Prevention	# of Trials	#Participants (treatment / control) Person years	RR (95% CI)	Association p-value	Heterogeneity p-value
Vertebral	Overall	8	972 / 896	0.48 (0.34; 0.68)	< 0.0001	0.37
	Primary	2	151 / 152	3.00 (0.32; 28.50)	0.3	0.99
	Secondary	6	821 / 744	0.45 (0.31; 0.64)	< 0.0001	0.40
Non-Vertebral	Overall	5	821 / 780	0.95 (0.65; 1.40)	0.8	0.61
	Primary	2	151 / 152	0.56 (0.19; 1.63)	0.3	0.83
	Secondary	3	670 / 628	1.04 (0.68; 1.58)	0.9	0.47
Hip	Overall	3	670 / 628	1.14 (0.34; 3.90)	0.8	0.28
	Primary	0	N/A	N/A	N/A	N/A
	Secondary	3	670 / 628	1.14 (0.34; 3.90)	0.8	0.28
Wrist	Overall	3	670 / 628	0.80 (0.27; 2.37)	0.7	0.96
	Primary	0	N/A	N/A	N/A	N/A
	Secondary	3	670 / 628	0.80 (0.27; 2.37)	0.7	0.96

RR=Relative Risk; CI=Confidence Interval; N/A=Not Applicable

Subgroup analysis

Treatment duration

No trends over years of treatment deviated from the overall RR estimates found. For details please refer to Figure 12 and Comparisons 05, 01; 06, 01; 07, 01; 08, 01; 09, 01.

Figure 12. Weighted relative risk of fracture after etidronate (400 mg) by years of treatment

Weighted relative risk of fracture after etidronate (400 mg) by years of treatment

Fracture Site	Primary / Secondary Prevention	Weighted Relative Risk (95% CI) of Fracture			
		Year 1	Year 2	Year 3	Year 4
Vertebral	Overall	0.39 (0.09; 1.62)	0.50 (0.29; 0.85)	0.29 (0.11; 0.79)	0.51 (0.22; 1.18)
	Primary	3.05 (0.13; 73.38)	3.03 (0.32; 28.44)	NA	NA
	Secondary	0.17 (0.02; 1.33)	0.43 (0.24; 0.76)	0.29 (0.11; 0.79)	0.51 (0.22; 1.18)
Non-Vertebral	Overall	NA	1.05 (0.69; 1.60)	0.83 (0.28; 2.46)	0.67 (0.20; 2.28)
	Primary	NA	0.56 (0.20; 1.61)	NA	NA
	Secondary	NA	1.21 (0.76; 1.92)	0.83 (0.28; 2.46)	0.67 (0.20; 2.28)
Hip	Overall	NA	3.98 (0.45; 35.33)	0.50 (0.05; 5.25)	0.50 (0.05; 5.34)
	Primary	NA	NA	NA	NA
	Secondary	NA	3.98 (0.45; 35.33)	0.50 (0.05; 5.25)	0.50 (0.05; 5.34)
Wrist	Overall	NA	1.00 (0.20; 4.91)	0.67 (0.12; 3.73)	1.00 (0.15; 6.82)
	Primary	NA	NA	NA	NA
	Secondary	NA	1.00 (0.20; 4.91)	0.67 (0.12; 3.73)	1.00 (0.15; 6.82)

CI=Confidence Interval; NA=Not Available

Treatment dose

A 200 mg dose of etidronate was used in two secondary prevention trials (Ishida 2004; Shiota 2001). Results were available for two years of treatment. For the base case, a significant reduction (68%) in vertebral fractures (RR 0.32, 95% CI 0.16 to 0.64), a non-significant reduction in hip fractures (RR 0.33, 95% CI 0.01 to 8.04) and a non-significant reduction in wrist fractures (RR 0.50, 95% CI 0.05 to 5.38) were found, as detailed in Comparison 11, 01. Similar results were obtained using person years. Results were consistent with those for the standard 400 mg dose with significance demonstrated only for vertebral fractures.

Sensitivity analysis

Baseline versus follow-up denominators

By using the data available for longest treatment duration, standard dose of etidronate (400 mg) and follow-up denominators for the number of patients in the trials, a summary of the overall review of fractures was prepared (Figure 13). These data are also provided by years of treatment (Figure 14). Pooled estimates of the RR of fracture after etidronate were essentially the same as those obtained using the baseline denominators.

Figure 13. Weighted relative risk of fracture after etidronate (400 mg): Follow-up denominators

Weighted relative risk of fracture after etidronate (400 mg): Follow-up denominators

Fracture Sites	Primary / Secondary Prevention	# of Trials	# Participants (treatment / control)	Relative Risk (95% CI)	Association p-value	Heterogeneity p-value
Vertebral	Overall	8	369 / 349	0.57 (0.35;0.91)	0.02	0.51
	Primary	2	70 / 70	2.97 (0.32;27.85)	0.3	0.98
	Secondary	6	299 / 279	0.51 (0.31;0.83)	0.007	0.52
Non-Vertebral	Overall	7	328 / 317	0.95 (0.66;1.36)	0.8	0.85
	Primary	2	70 / 70	0.55 (0.20;1.57)	0.3	0.84
	Secondary	5	258 / 247	1.03 (0.70;1.53)	0.9	0.85
Hip	Overall	4	244 / 233	1.14 (0.36;3.67)	0.8	0.52
	Primary	0	N/A	N/A	N/A	N/A
	Secondary	4	244 / 233	1.14 (0.36;3.67)	0.8	0.52
Wrist	Overall	4	244 / 233	0.84 (0.31;2.24)	0.7	0.52
	Primary	0	N/A	N/A	N/A	N/A
	Secondary	4	244 / 233	0.84 (0.31;2.24)	0.7	0.52

CI=Confidence Interval; N/A=Not Applicable

Figure 14. Weighted relative risk of fracture after etidronate (400 mg) by years of treatment: Follow-up denominators

Weighted relative risk of fracture after etidronate (400 mg) by years of treatment:
Follow-up denominators

Fracture Site	Primary / Secondary Prevention	Weighted Relative Risk (95% CI) of Fracture			
		Year 1	Year 2	Year 3	Year 4
Vertebral	Overall	0.37 (0.09;1.54)	0.40 (0.29;0.82)	0.25 (0.09;0.67)	0.47 (0.21;1.05)
	Primary	3.06 (0.13;73.35)	2.97 (0.32;27.85)	NA	NA
	Secondary	0.16 (0.02;1.25)	0.42 (0.24;0.73)	0.25 (0.09;0.67)	0.47 (0.21;1.05)
Non-Vertebral	Overall	NA	1.02 (0.68;1.54)	0.83 (0.30;2.29)	0.61 (0.18;2.03)
	Primary	NA	0.55 (0.20;1.57)	NA	NA
	Secondary	NA	1.17 (0.74;1.84)	0.83 (0.30;2.29)	0.61 (0.18;2.03)
Hip	Overall	NA	3.85 (0.43;34.12)	0.50 (0.05;5.06)	0.45 (0.04;4.74)
	Primary	NA	NA	NA	NA
	Secondary	NA	3.85 (0.43;34.12)	0.50 (0.05;5.08)	0.45 (0.04;4.74)
Wrist	Overall	NA	0.96 (0.20;4.72)	0.67 (0.12;3.57)	0.90 (0.13;6.04)
	Primary	NA	NA	NA	NA
	Secondary	NA	0.96 (0.20;4.72)	0.67 (0.12;3.57)	0.90 (0.13;6.04)

CI=Confidence Interval; NA=Not Available

Random-effects versus fixed-effect model

There was no instance where heterogeneity of the trial results necessitated that a random-effects model be used. Results obtained using the random-effects and fixed-effect models were similar.

Using different baseline vertebral fracture rates (that is 100%, > 80%, > 60%, > 40%, > 20%) for defining secondary trials, a summary of the overall review of fractures was prepared (Figure 15). For all fracture sites, the pooled estimates of the RR of fracture after etidronate were essentially the same as those obtained using the definition of secondary trials with the > 20% baseline fracture rate.

Baseline vertebral fracture rate

Figure 15. Weighted relative risk (RR) of fracture after etidronate (400 mg): sensitivity analysis by baseline prevalent vertebral fracture site

Weighted relative risk (RR) of fracture after etidronate (400 mg): sensitivity analysis by baseline prevalent vertebral fracture rate

Fracture Sites	Primary / Secondary Prevention (prevalent vertebral fracture rate)	# of Trials	# Participants (treatment / control)	RR (95 % CI)	Association p-value	Heterogeneity p-value
Vertebral	Secondary (100%)	5	309 / 306	0.56 (0.33;0.95)	0.03	0.79
	Secondary (>80%)	5	309 / 306	0.56 (0.33;0.95)	0.03	0.79
	Secondary (>60%)	5	309 / 306	0.56 (0.33;0.95)	0.03	0.79
	Secondary (>40%)	5	309 / 306	0.56 (0.33;0.95)	0.03	0.79
	Secondary (>20%)	6	349 / 346	0.53 (0.32;0.87)	0.01	0.77
	Secondary	6	349 / 346	0.53 (0.32;0.87)	0.01	0.77
Non-Vertebral	Secondary (100%)	5	312 / 312	1.07 (0.72;1.60)	0.7	0.88
	Secondary (>80%)	5	312 / 312	1.07 (0.72;1.60)	0.7	0.88
	Secondary (>60%)	5	312 / 312	1.07 (0.72;1.60)	0.7	0.88
	Secondary (>40%)	5	312 / 312	1.07 (0.72;1.60)	0.7	0.88
	Secondary (>20%)	5	312 / 312	1.07 (0.72;1.60)	0.7	0.88
	Secondary	5	312 / 312	1.07 (0.72;1.60)	0.7	0.88
Hip	Secondary (100%)	4	295 / 294	1.20 (0.37;3.88)	0.8	0.53
	Secondary (>80%)	4	295 / 294	1.20 (0.37;3.88)	0.8	0.53
	Secondary (>60%)	4	295 / 294	1.20 (0.37;3.88)	0.8	0.53
	Secondary (>40%)	4	295 / 294	1.20 (0.37;3.88)	0.8	0.53
	Secondary (>20%)	4	295 / 294	1.20 (0.37;3.88)	0.8	0.53
	Secondary	4	295 / 294	1.20 (0.37;3.88)	0.8	0.53
Wrist	Secondary (100%)	4	295 / 294	0.87 (0.32;2.36)	0.8	0.51
	Secondary (>80%)	4	295 / 294	0.87 (0.32;2.36)	0.8	0.51
	Secondary (>60%)	4	295 / 294	0.87 (0.32;2.36)	0.8	0.51
	Secondary (>40%)	4	295 / 294	0.87 (0.32;2.36)	0.8	0.51
	Secondary (>20%)	4	295 / 294	0.87 (0.32;2.36)	0.8	0.51
	Secondary	4	295 / 294	0.87 (0.32;2.36)	0.8	0.51

RR=Relative Risk; CI=Confidence Interval

Adverse events

A summary of the adverse drug events reported in the 11 randomized placebo-controlled trials of etidronate is provided in

Figure 16; Figure 17; Figure 18. In general, the reported events were similar between etidronate and placebo.

Figure 16. Summary of adverse drug events reported in randomized placebo-controlled trials of etidronate (part 1)

Summary of adverse drug events reported in randomized placebo-controlled trials of etidronate

Trial (Primary/ Secondary Prevention)*	Number of Patients (Treatment/ Control)	Outcomes and frequencies				Description in Text of Trial Report	All Withdrawals (%)
		Event	Etidronate N (%)	Control N (%)			
Herd 1997 (Primary)	152 (75/77)	<u>Most Common Events:</u> Infection Back Pain Arthritis Flu Syndrome <u>GI events:</u> Nausea Dyspepsia Diarrhea Pts with serious AEs Withdrawals due to AEs	18 (24.3) 12 (16.2) 11 (12.2) 9 (12.2) 10 (13.2) 6 (7.9) 5 (6.6) 7 (9.2) 5 (6.8)	22 (29.0) 14 (18.4) 10 (13.2) 9 (11.8) 3 (4.1) 3 (4.1) 3 (4.1) 8 (10.8) 0 (0.0)		The most frequently reported adverse events were infection and back pain. The majority of infections were colds, throat and chest with the proportion of infections being similar in both groups. Low back pain and back ache comprised the majority of back pain. 5 etidronate and 7 placebo patients had a pre study history of back pain. One patient in the placebo group was diagnosed with endometrial carcinoma but continued in the study.	Etidronate: 11/75 (14.6%) Placebo: 6/77 (7.8%) Total: 17/152 (11.2%)
Iskida 2004 (Secondary)	132 (66/66) (other treatment groups reported in paper but not analyzed - HRT, calcitonin, alfacalcidol, vitamin K.)	NR	NR	NR		1 patient in Etidronate group withdrew due to an adverse event.	Etidronate: 6/66 (9.1%) Control: 4/66 (6.1%) Total: 10/132 (7.6%)
Lyritis 1997 (Secondary)	100 50/50	NR	NR	NR		AEs minimal in both groups. Drop outs mostly due to non attendance and not AEs.	Etidronate: 11/90 (22%) Control: 15/50 (30%) Total: 26/100 (26.0%)

Figure 17. Summary of adverse drug events reported in randomized placebo-controlled trials of etidronate (part 2)

Trial (Primary/ Secondary Prevention)*	Number of Patients (Treatment/ Control)	Outcomes and frequencies			Description in Text of Trial Report	All Withdrawals (%)
		Event	Etidronate N (%)	Control N (%)		
Mosmar 1997 (Primary)	54 (27/27)	No AE reported No. pts with AEs No. pts with serious AEs Asthenia Pain Pharyngoma GI: Nausea Diarrhea Dyspepsia Constipation Abdominal pain Flatulence Gastroenteritis	144 24 (94.2) 2 (7.4) 4 (22.2) 5 (18.5) 5 (18.5) 4 (14.8) 1 (3.7) 3 (11.1) 3 (11.1) 4 (14.8) 1 (3.7) 1 (3.7)	154 24 (94.2) 4 (22.2) 8 (29.6) 5 (18.5) 4 (14.8) 3 (11.1) 4 (14.8) 2 (7.4) 0 (0.0) 1 (3.7) 3 (11.1) 3 (11.1)	Discontinuation due to AEs: 2 in placebo group. All patients with abdominal pain had pre study history of GI problems and experienced intolerance to the calcium supplement	Etidronate: 2/27 (7.4%) Placebo: 3/27 (11.1%) Total: 5/54 (9.3%)
Montessori 1997 (Secondary)	80 (40/40)	NE	NE	NE	Most common AEs: flu, bone and joint pain, bronchitis, back pain, heartburn, constipation, cystitis, abdominal cramps, diarrhea and diarrhea. Symptoms mild and evenly distributed between groups. 1 withdrew almost immediately after enrollment due to diarrhea, and 2 in control group withdrew due to cancer.	Etidronate (2 yrs): 0/40 (0%) Control (2 yrs): 4/40 (10%) Total (3 yrs): 14/80 (20%)
Pacifici 1988 (Secondary)	57 30/27 HEI group (n=34) not included	NE	NE	NE	NE	Etidronate: 14/50 (44.7%) Control: 12/27 (44.4%) Total: 26/57 (45.6%)

Figure 18. Summary of adverse drug events reported in randomized placebo-controlled trials of etidronate (Part 3)

Trial (Primary/ Secondary Prevention)*	Number of Patients (Treatment/ Control)	Outcomes and frequencies			Description in Text of Trial Report	All Withdrawals (%)
		Event	Etidronate N (%)	Control N (%)		
Pouilles 1997 (Primary)	109 54/55	Any AE Serious AE Abdominal pain Other digestive AEs Moderate to severe GI AEs	44 (83.2) 7 (13.0) 7 (13.0) 10 (18.4) 1 (malabsorption of ulcer) (1.9)	44 (83.4) 9 (16.4) 4 (10.9) 19 (34.4) 2 (esophage- gic and gastric) (3.4)	Event not considered to be related to study drug.	Etidronate: 904 (14.7%) Placebo: 905 (16.4%) Total: 1809 (16.5%)
Shiota 2001 (Secondary)	40 20/20	NE	NE	NE	No adverse effects of treatment were noted by any patient in either group.	Withdrawals not reported
Storm 1990 (Secondary)	44 33/63	NE	NE	NE	Etidronate well tolerated. No significant SEs related to drug were observed. 5 deaths in each treatment group occurred and were not related to study drugs or osteoporosis.	Etidronate: 13/33 (39.4%) Placebo: 13/63 (39.4%) Total: 26/96 (39.4%)
Watts 1990 (Primary)	423 212/211	Withdrawals due to AEs	4 (1.9)	3 (1.4)	Nausea: 5-6% in all groups. Diarrhea: 7-9% in all groups. No mineralisation defects detected in any post-treatment biopsy samples.	Etidronate: 27/212 (12.7%) Placebo: 33/211 (15.6%) Total: 60/423 (14.2%)
Wimalawansa 1998 (Secondary)	33 17/16 HEI group (n=37) not included	Withdrawals due to intolerance of medication. Withdrawals due to other medical problems	1 (5.9) 1 (5.9)	1 (5.4) 2 (11.1)	4 patients complained of nausea following etidronate administration which improved over time and did not result in withdrawal. 23 pts across groups (HEI included) complained of minor SEs attributable to Ca but continued supplementation. No other AEs observed.	Etidronate: 3/17 (17.6%) Control: 4/16 (22.2%) Total: 7/33 (20.0%)

Toxicity and withdrawals

The number of discontinuations due to adverse events or dropouts overall were available and analyzed for five (Herd 1997; Ishida 2004; Meunier 1997; Watts 1990; Wimalawansa 1998) and ten (Herd 1997; Ishida 2004; Lyritis 1997; Meunier 1997; Montessori 1997; Pacifici 1988; Pouilles 1997; Storm 1990; Watts 1990; Wimalawansa 1998) of the etidronate trials, respectively. The pooled estimate demonstrated no significant difference between etidronate and placebo for the risk of withdrawal due to adverse events (RR 0.61, 95% CI 0.25 to 1.49) or for dropouts overall (RR 0.91, 95% CI 0.71 to 1.26) (Comparisons 10, 01; 10, 02). Results were consistent across the trials.

DISCUSSION

Overall, using data available for the longest treatment duration and baseline denominators for the number of patients in the included trials, the pooled estimate of RR of fracture after etidronate was not statistically significant for non-vertebral, hip or wrist fractures. This was found whether etidronate was used for primary or secondary prevention (Silver level evidence). For vertebral fractures, the pooled RR estimate was significant for secondary but not for primary prevention. The evidence that in postmenopausal women with osteoporosis etidronate reduces the incidence of vertebral fractures is Silver level.

The pooled analysis suggests that etidronate, when used as part of a 90-day cyclical regimen, reduces the RR of vertebral fractures by 47%. It is cautioned that the 95% CI around this estimate was relatively wide and the upper boundary representing

the smallest effect consistent with the data showed a RRR of only 13%. Nonetheless, a reduction in vertebral fractures is clinically important if associated with reduction in pain and functional disability. Observational studies have suggested such an association between fractures and pain (Ettinger 1992; Ross 1994; Okeksik 1999; Silverman 1999). Furthermore, it has been recently recognized that women who have suffered one incident vertebral fracture are at substantial risk of a subsequent vertebral fracture within the next year (Lindsay 2001). Despite the effect on vertebral fractures, the point estimate of the effect of etidronate on non-vertebral fractures (as well as hip and wrist fractures individually) suggest no impact. Of note, the CIs were wide and for non-vertebral fractures a RRR of up to 32% remains possible. To conclude on etidronate's efficacy, readers are cautioned to the fact that the wide CIs observed indicates that a certain level of uncertainty still prevails around the drug's effect. A relatively small number (total = 624) of participants were recruited in the etidronate trials.

Secondary analyses showed that etidronate at a dose of 200 mg for secondary prevention resulted in a statistically significant reduction in vertebral fractures (RR 0.32, 95%CI 0.16 to 0.64) (Silver level evidence). This resulted from the pooling of two small trials (Ishida 2004; Shiota 2001) representing a total of 172 patients. No trials were available to assess the effectiveness of the 200 mg dose for secondary prevention of non-vertebral fractures or the primary prevention of any endpoint. Fracture reductions for the secondary prevention of hip and wrist fractures were not statistically significant.

There were no substantive differences in the results whether baseline, end of study or person year denominators were used.

Sensitivity analyses indicated that there were no major differences based on the percentage of baseline vertebral fractures. Further, no trends were found for years of treatment.

From a drug tolerance perspective, adverse effects observed in the included trials were similar between etidronate and placebo. Also, the use of etidronate was not associated with statistically significant differences in either the rate of withdrawals due to adverse events (RR 0.61, 95% CI 0.25 to 1.49) or overall withdrawals (RR 0.91, 95% CI 0.71 to 1.26) when compared to placebo. It follows that study participants tolerated their etidronate treatment.

The results from our analysis are consistent with those of a previous meta-analysis by Cardona and Pastor ([Cardona 1997](#)). They reported a reduction in vertebral fractures of 28.3 per 1000 patient-years (95% CI 26.2 to 30.4); however, they did not derive a pooled estimate for non-vertebral fractures. This meta-analysis suggested a beneficial effect of etidronate on reducing vertebral fractures and the data provided no support for reduction of non-vertebral fractures.

Study limitations

The results of this systematic review are believed to be robust as a comprehensive literature search was performed, inclusion and exclusion criteria were specified and a rigorous data analysis was conducted. A potential limitation of our approach may be that the update search (from 2000 to 2004) did not include non-MEDLINE® indexed journals. Recent empirical evidence indicates that this approach may have introduced a slight risk of bias into our meta-analysis. On average, such bias is estimated to result in a 6% variation in the pooled results ([Egger 2003](#); [Sampson 2003](#)). Accordingly, given that the initial literature search (from 1966 to 2000) was very extensive, the impact of only using MEDLINE® for the search update is expected to be minimal, if any. This was confirmed by a parallel literature search update (from 1999 to July 2004) that was conducted for an economic report published by The Canadian Agency for Drugs and Technologies in Health (CADTH) ([CADTH 2006](#)). The search update included etidronate, alendronate and risedronate in addition to teriparatide. A number of databases were searched (*The Cochrane Library*, MEDLINE®, EMBASE®, BIOSIS Previews®, Toxfile, PubMed) and no additional articles meeting the inclusion criteria were identified.

While our methodology was robust, the results of our meta-analysis, however, are only as strong as the primary studies included. In keeping with this, the main limitations with regard to study quality were fracture assessment and classification, the lack of clarity of the concealment of allocation, length of follow up and the small number of participants enrolled in the trials.

A potential source of heterogeneity is the lack of uniform definition of non-vertebral fracture. While some researchers may use a rather liberal definition (any fracture other than vertebral fracture), others may use a more conservative definition which includes only fractures of the hip, clavicle, humerus, wrist, pelvis or leg ([Mayo Clinic 2005](#)). Also, the statistical power to detect heterogeneity was extremely limited for some tests due to the low number of fractures in some categories. Another consideration is the fact that fracture data was not the primary outcome in the majority of the trials.

Another methodological limitation concerns the approach used for concealment of treatment allocation, which was not reported for any of the trials (that is classified as 'unclear').

An additional limitation is the length of follow up in the studies (one to four years). It is difficult to extrapolate beyond the duration of the follow-up trials in the review with respect to the long-term impact on fractures. Ultimately, data from longer-term trials will help establish if the effect on fractures is maintained, increased or diminished.

For more uncommon events such as hip fractures, large sample sizes are required to detect important differences. For etidronate, the small pooled sample sizes for the non-vertebral outcomes (non-vertebral (N = 624), hip (N = 589) and wrist fractures (N = 589)) make this a particular concern.

In regards to our own methodology, we acknowledge that the approach used to evaluate the effect of bisphosphonates over time may result in some estimates that are not robust. In particular, in order to determine the effect on the five-year risk of fracture we based our evaluation on the FRACTURE Index by Black et al ([Black 2001](#)) and for lifetime and five-year age-specific risks we used an existing model from Doherty et al ([Doherty 2001](#)). Although this latter approach allowed us to estimate the variation in risks between younger and older postmenopausal women these estimates may be associated with a certain level of uncertainty. Nonetheless, we believe such information may be useful to decision makers.

Lastly, a limitation of evaluating data on adverse effects from summary meta-analyses is that participants in RCTs tend to be healthier with fewer co-morbid diseases and therefore the results may not be generalizable to clinical practice. Patients with pre-existing GI disorders were excluded in two ([Montessori 1997](#); [Watts 1990](#)) of the 11 trials. An additional trial ([Pouilles 1997](#)) possibly excluded GI patients as it indicated that patients were excluded for "any condition contraindicating study medication". Furthermore, RCTs are underpowered for rare effects and meta-analyses of these trials generally cannot provide conclusive information pertaining to drug toxicity. In addition, the heterogeneity of the adverse drug events (ADEs) reported in the RCTs described in this review, including their nature, low occurrence, and way they were assessed by investigators, made these improper for meta-analysis. Finally, because RCTs are not designed to measure ADEs, particularly rare ones, it is common practice to include sources of information other than RCTs. While some review authors include ADEs reported in observational studies we elected to obtain information from the Canadian Adverse Drug Reaction Monitoring Program (CADRMP), a governmental reporting system ([CADRMP 2005](#)) (see below).

Generalizability of findings

Generalizability of our findings is limited by the controlled design of the trials included in our review. Study participants were carefully selected in these trials and so utilization of the drugs in real life may vary substantially from study conditions. Furthermore, study participants were observed for periods of time varying from one to four years. Consequently, while our results provide support for efficacy (that is can the intervention have an effect on outcome?) they may possibly only provide partial information on the long-term effectiveness (that is does the intervention have an effect on outcome?) of etidronate in preventing osteoporotic fractures.

From a safety perspective, we could not find any statistically significant difference in either the rates of adverse drug events or withdrawal rates due to adverse drug events between patients receiving etidronate or patients receiving a placebo. However, outside controlled trials concerns exist regarding the safe use of bisphosphonate drugs (Kherani 2002). While such adverse events have mainly been identified through case reports and endoscopic studies, similar concerns are also reflected in the proportions of

gastrointestinal adverse drug reactions associated with the use of bisphosphonates as reported to the CADRMP (CADRMP 2005). Indeed, GI adverse drug reactions represented 18% of all reactions for etidronate Figure 19. These proportions should however be interpreted with caution as adverse drug reactions are reported to CADRMP on a volunteer basis by health professionals, which means that several reactions may be unreported (Medeffect 2005). Also, a definite cause-effect relationship has not been established for these adverse drug reactions.

Figure 19. Adverse drug reactions reported to CADRMP for etidronate, alendronate and risedronate

	Etidronate (n=257) %	Alendronate (n=451) %	Risedronate (n=130) %
Auditory / visual	4	6	8
Cardiovascular	12	13	18
Central nervous system	11	13	12
Endocrine	4	3	3
Gastrointestinal	18	38	35
Hematological	4	3	3
Infections	2	1	3
Musculoskeletal	29	24	36
Respiratory	5	6	7
Skin / mucous / membrane	16	19	12
Urological / renal	4	2	2
Other	42	14	12

* These proportions were calculated from the adverse drug reactions reports received at CADRMP. These reflect all adverse drug reactions reported since the initial marketing of the each of the bisphosphonate drug until February 28, 2005.

In total, there were 257 adverse drug reaction reports for etidronate. Subjects reporting adverse events had a mean age of 70 years and 90% were female. Serious reactions constituted 55% of the reports. CADRMP defines a serious adverse reaction as one which requires inpatient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death. Adverse reactions that require significant medical intervention to prevent one of these outcomes are also considered to be serious. The frequency of reporting categorized as 'Other' was high since this included 'Efficacy, lack of' of which there were approximately 70 instances.

In the case of alendronate, there were 451 adverse drug reaction reports. Subjects reporting adverse events had a mean age of 65 years and 92% were female. Serious reactions constituted 27% of the reports. Finally, there were 130 adverse drug reaction reports for risedronate. Subjects reporting adverse events had a mean age of 66 years and 93% were female. Serious reactions constituted 62% of the reports.

AUTHORS' CONCLUSIONS

Implications for practice

Etidronate, used at 400 mg per day, demonstrated a clinically important benefit in the secondary prevention of vertebral fractures. The secondary prevention population was defined as having a bone density of at least 2 SD values below peak bone mass or one or more vertebral compression fractures, or both. There were no statistically significant reductions in vertebral fractures when used for primary prevention. Furthermore, no statistically significant reductions in non-vertebral, hip or wrist fractures were observed regardless of whether etidronate was used for primary or secondary prevention. No increased incidence in adverse effects was found in the included studies but the possibility of upper gastrointestinal symptoms cannot be ruled out from randomized controlled trials.

The prevention of osteoporotic fractures is an important public health intervention. This is particularly true for hip and clinical vertebral fractures (that is fractures of the spine that present for medical attention). The RR of death following such fractures is 6 to 9-fold greater in postmenopausal women aged 55 to 81 years with low BMD, which represents a typical postmenopausal population (Cauley 2000). In most cases the mortality increase reflects poor underlying health status and comorbidity in addition to the fracture itself (Cauley 2000). Osteoporotic fractures are also associated with increases in morbidity as it is reported that 50% of women who sustain a hip fracture do not return to their usual daily activities (Brown 2002) while 33% will require long-term care. Although a significant reduction in hip fractures was not observed for etidronate (possibly due to the paucity of data available), reducing the incidence of such fractures can potentially increase the quality of life of patients with osteoporosis. Such interventions may also potentially decrease mortality.

Implications for research

For etidronate, most trials enrolled a small number of participants and were not necessarily designed to measure fractures, which limits our findings.

With regards to the bisphosphonates as a class, It has been suggested from clinical trials (Black 2000b; Harris 1999; McClung 2001) that their effect in reducing non-vertebral fractures may be greater in those patients with lower BMD who initiate treatment. The existing data have not fully resolved the question of whether important differences in risk reduction across groups of patients with varying degrees of osteoporosis exist. The impact of bisphosphonates on the RR of non-vertebral fractures in populations without osteoporosis also merits further investigation. Additional research is needed to clarify the role of bisphosphonates in the primary prevention of osteoporotic fractures. There is also a need for further post-marketing safety surveillance. Finally, research into combination therapy with higher doses of vitamin D or anabolic agents would be merited as would research concerning adherence to bisphosphonate therapy.

Given the morbidity consequences associated with osteoporotic fractures, preventing their recurrence can potentially lessen the need for community-based health services (for example home care). It may also reduce or delay the demand for long-term care beds. However, very little comparative information is currently available to support this (Hodsman 2002). There is also a lack of studies which evaluated the effect of bisphosphonates on hospital admissions (Hodsman 2002).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Herd 1997

Methods	Randomized controlled trial. Parallel group Primary prevention Study length: 2 years Blinding: double, unspecified Withdrawals: Etidronate: 11/75 (14.6%) Placebo: 6/77 (7.8%) Total:17/152 (11.2%)
Participants	Source: GP referrals and subjects responding to an article on osteoporosis. Country - UK. Inclusion Criteria: White, ambulatory, 1-10 yrs postmenopausal (FSH confirmed). T-score 0 to -2 (DPA spine, hip and total body were measured). Exclusion Criteria: Prevalent fracture unrelated to severe trauma, hyperparathyroidism or bone disease, cancer, drug treatment affecting bone less than 6 months prior to study. Treatment N = 75 Control N = 77 Age: 54.8 (4.9); Years since menopause: 5.5 (2.9) Calcium: not reported BMD: 0.84 g/cm ² T-score: -1.9 Fractures: 0% (excluded)
Interventions	Etidronate 400mg/day vs placebo (76 days) (500mg calcium /day)

Herd 1997 (Continued)

Outcomes Vertebral Fractures: Lateral radiographs of thoracic and lumbar spine at baseline and 24 months).

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Ishida 2004

Methods	Randomized controlled trial. Parallel group Secondary prevention Study length: 2 years Blinding: blinded endpoint committee Withdrawals: Etidronate: 6/66 (9.1%) Control: 4/66 (6.1%) Total: 10/132 (7.6%)
Participants	Source: A single hospital in Japan Inclusion Criteria: Ambulatory women aged 50-75 at least 5 years since natural or surgical menopause. Osteoporosis defined as 1 or more vertebral fractures plus BMD at least 20% below young adult mean (-2.5 distal radius T-score, or BMD at least 30% (-3.5) below young adult mean alone. Exclusion Criteria: Recent cancer, metabolic bone disease, drugs affecting bone metabolism, history of bilateral hip fractures. Treatment N = 66 Control N = 66 Control N = Age: 54.8 (4.9); YSM: 5.5 (2.9) Calcium: not reported BMD: 0.84 g/cm ² T-score: -1.9 Fractures: 0% (excluded)
Interventions	Etidronate 200 mg/day vs no treatment (70 days) (no concurrent therapy reported)
Outcomes	Vertebral Fractures: Lateral thoracic and lumbar spine radiographs at baseline and 3 month intervals. Incident fractures diagnosed quantitatively (a decrease of at least 20% for intact vertebrae at baseline or at least 4 mm for fractured vertebrae at baseline) and semiquantitatively (Vertebrae were scored as 0 no fractures through to 3 for severe fractures. An incident fracture was defined as a grade change of at least 1. Non-vertebral Fractures: Femoral neck - ascertainment not reported. Forearm - ascertainment not reported. (These 2 sites were reported under heading of non-vertebral. It is unclear whether other non vertebral sites were ascertained).

Ishida 2004 (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Lyrithis 1997

Methods	Randomized controlled trial. Parallel group Secondary prevention Study length: 4 years Blinding: open study Withdrawals: Etidronate: 11/50 (22%) Control: 15/50 (30%) Total: 26/100 (26.0%)
Participants	Source: A single osteoporosis clinic in Greece. Inclusion Criteria: Osteoporotic women aged 67-77 with at least one non-traumatic vertebral collapse, BMD > 2SD and normal biochemical bone markers. Exclusion Criteria: Bone acting drugs 1 year prior, secondary osteoporosis. Treatment N = 50 Control N = 50 Age: 72.0 (0.4); YSM: 25.8 (1.7) Calcium: 522mg (48) BMD: 0.57g/cm ² : -4.3 Fractures: 100%
Interventions	Etidronate 400mg/day vs control (65 days) (500mg calcium /day and 2ug calcitriol x 5 days prior to cycle)
Outcomes	Vertebral Fractures: Lateral radiographs of dorsolumbar spine. Use of spinal deformity index (0 (no fracture) 1 (mild - 20-25% reduction in anterior, middle or posterior height accompanied by an area reduction of 10-20%) , 2 (moderate - 25-40% reduction in height, 20-40% reduction in area) and 3 (severe - reduction of 40% in height and area)) is described but it is unclear as to how this index was used in determining an incident fracture. Non-vertebral Fractures, Hip and Wrist: All fractures of appendicular skeleton recorded by 2 independent observers.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Meunier 1997

Methods	Randomized controlled trial. Parallel group Primary prevention Study length: 4 years Blinding: double, identical placebo Withdrawals: Etidronate: 2/27 (7.4%) Placebo: 3/27 (11.1%) Total: 5/54 (9.3%)
Participants	Source: A single centre in France. Recruited from GP and gynaecologists referral. Inclusion Criteria: Caucasian, ambulatory, between 45 and 90 kg within 15% of normal BMI, between 6 and 60 months postmenopause (confirmed by serum estradiol and FSH), normal BMD (Z score within 2 SD for their age). Exclusion Criteria: bilateral oophorectomy or hysterectomy, disease affecting bone metabolism, prolonged treatment with calcitonin, vit D >400 IU/day calcium greater than 500 IU/day in previous 6 months, estrogen, progesterone in past year, any past treatment with BR or fluoride. Treatment N = 27 Control N = 27 Age: 52.7 (4.0); YSM: 2.4 (1.8) Calcium: 876 mg (559) BMD: 0.90 g/cm ² T-score: -1.3 Fractures: not reported
Interventions	Etidronate 400 mg/day vs placebo. (77 days) (500 mg calcium /day)
Outcomes	Vertebral fracture: Lateral and antero/posterior incidence x-rays of thoracic and lumbar spine taken at baseline and 24 mos. However, the only fracture reported was clinical traumatic. Non-vertebral fractures: Ascertainment not described. However, all undesirable clinical experiences occurring during the study were assessed at each patient visit.
Notes	
Risk of bias	
Bias	Authors' judgement Support for judgement
Allocation concealment?	Unclear risk B - Unclear

Montessori 1997

Methods	Randomized controlled trial. Parallel group Study length: 3 years Secondary prevention Blinding: open Withdrawals:
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Montessori 1997 (Continued)

Etidronate (2 yrs): 0/40 (0%)
Control (2 yrs): 6/40 (15%)
Total (3 yrs): 16/80 (20%)

Participants	<p>Source: Most patients recruited from screening program within the practices of 2 GPs in the Netherlands.</p> <p>Inclusion Criteria: Postmenopausal at least 1 year, age 55-74, ambulatory, active, Age matched BMD Z score <-1SD.</p> <p>Exclusion Criteria: estrogen, androgens, vitamin D, calcium supplementation >1g/day or bisphosphonates in previous year. Secondary osteoporosis, metabolic bone disease, active GI or liver disease, renal disease, cancer</p> <p>Treatment N = 40 Control N = 40 Age: 62.5 (6.2); YSM: 14.9 (6.1) Calcium: 874mg BMD: 0.67 g/cm² T-score: -3.4 Fractures: 29%</p>
Interventions	<p>Etidronate 400mg/day vs control (76 days) (500 mg calcium /day)</p>
Outcomes	<p>Vertebral Fractures: Postero-anterior and lateral radiographs of thoracic and lumbar spine performed at entry and every year were evaluated by 2 blinded radiologists. Use of spinal deformity score 0 (normal) to 3 is described but it is unclear as to how this index was used in determining an incident fracture.</p> <p>Non-vertebral Fractures: Ascertainment not described. They may have been assessed as adverse events which were evaluated every 3 months during hospital visits, phone interviews and information from GP. Only femoral fractures are reported and it is unclear as to whether other non vertebral sites were assessed.</p>
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Pacifici 1988

Methods	<p>Randomized controlled trial. Parallel group Study length: 2 years Secondary prevention Blinding: open study, blinded radiologists Withdrawals: Etidronate: 14/30 (46.7%) Control: 12/27 (44.4%) Total: 26/57 (46%)</p>
Participants	<p>Source: Women who came to one USA hospital for osteoporosis screening.</p>

Pacifici 1988 (Continued)

Inclusion Criteria: At least 1 non traumatic vertebral fracture and/or evidence of spinal demineralization by QCT.

Exclusion Criteria: Any condition influencing calcium metabolism or contraindicating study medications.

Treatment N = 30

Control N = 27

Age: 61 (7.8); YSM: 13.8 (9.5)

Calcium: 875 mg/day (406)

QCT: 79.1 mg/cm³ (26.3)

Fractures: 100% had fractures and/or evidence of demineralization on QCT

Interventions	Etidronate 400mg/day with 7.5g K phosphate/cycle vs control (56 days) (1g calcium /day)
Outcomes	Vertebral Fractures: Caliper measurement of vertical height for anterior, central and posterior regions of each vertebra in lateral spine films. Compression fracture was defined by a 15% greater loss of posterior height compared with nearest intact vertebrae. In vertebrae with normal posterior height, wedging and biconcave fractures were defined by a loss of anterior and central height > 20% of posterior height of same vertebrae. Number of new fractures was calculated every 12 months.
Notes	
Risk of bias	
Bias	Authors' judgement Support for judgement
Allocation concealment?	Unclear risk B - Unclear

Pouilles 1997

Methods	Randomized controlled trial. Parallel group Study length: 2 years Primary prevention Blinding: double blind unspecified Withdrawals: Etidronate: 9/54 (16.7%) Placebo: 9/55 (16.4%) Total: 18/109 (16.5%)
Participants	Source: Seven centres in France. Inclusion Criteria: Caucasian, ambulatory, active between 45 and 80 kg within 20% of normal BMI, between 6 and 60 months post menopause (confirmed by serum estradiol and FSH), normal BMD (Z score within 2 SD for their age). Exclusion Criteria: History of alcoholism, physical, radiological or laboratory evidence of bone metabolism disorder, treatment which could interfere with bone metabolism. Treatment N = 54 Control N = 55 Age: 53.8 (3.1); YSM: 2.6 (1.4) Calcium: not reported BMD: 0.96 gm/cm ²

Pouilles 1997 (Continued)

T-score: -0.8
Fractures: not reported

Interventions	Etidronate 400mg/day vs placebo. (77 days) (500mg calcium/day)
Outcomes	Vertebral and Non-vertebral Fractures: Ascertainment not described. However, all undesirable clinical experiences occurring during the study were assessed at each patient visit.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Shiota 2001

Methods	Randomized controlled trial. Parallel group Secondary prevention Study length: 2 years Blinding: not reported Withdrawals: not reported
Participants	Source: Patients who visited the Orthopaedic Surgery outpatient clinic at one centre in Japan complaining of lumbo-dorsal pain. Subjects were randomly selected from those who met inclusion criteria. Inclusion Criteria: Women over age 50 with postmenopausal osteoporosis diagnosed by DEXA BMD of < 0.70g/cm ² . Exclusion Criteria: Patients with fractures between L2 and L4. Treatment N = 20 Control N = 20 Age: 61.7; YSM: 14.6 (7.8) Calcium: not reported BMD: 0.56 (0.08) T-score: -4.3 Fractures: 60% (patients with fractures at L2-4 were excluded)
Interventions	Etidronate 200mg/day vs control (70 days) (2g calcium /day and 0.5ug alfacalcidol/day)
Outcomes	Vertebral Fractures: Compression fracture defined according to criteria of Japanese Society for Bone and Mineral Research which is based on ratios of centre, anterior and posterior heights of each vertebrae in the lateral view of thoracolumbar X-rays. In patients with vertebra plana a fracture was diagnosed if centre, anterior and posterior heights were <80% of the values of adjacent vertebrae. Number of fractures was counted at baseline and final assessment.
Notes	

Risk of bias

Shiota 2001 (Continued)

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Storm 1990

Methods	Randomized controlled trial. Parallel group Secondary prevention Study length: 3 years Blinding: double blind, blinded radiologist Withdrawals: Etidronate: 13/33 (39.4%) Placebo: 13/33 (39.4%) Total: 26/66 (39.4%)
Participants	Source: Appears to be a single centre in Denmark. Inclusion Criteria: Postmenopausal women with osteoporosis defined as 1 to 4 atraumatic vertebral crush fractures and radiographically demineralization of vertebrae. Exclusion Criteria: Secondary causes of osteoporosis. Impairment of renal, cardiac or thyroid function. Treatment with corticosteroids, estrogens, calcitonin, calcium or vitamin D > 3 months in previous 6 months or any in previous 2 months. History of fluoride or diphosphonate therapy. Treatment N = 33 Control N = 33 Age: 68.3 (7.3); YSM: 21.6 (10.2) Calcium: not reported BMD: 25.1g (7.3) Fractures: 100%
Interventions	Etidronate 400mg/day vs placebo. (91 days) (500 mg calcium /day and 400IU Vitamin D daily)
Outcomes	Vertebral Fractures (included only for person years analysis): Radiographs of thoracic and lumbar spine performed at baseline, week 60, 120 and 150. A semiquantitative score was assigned to each vertebrae ranging from 0 to 3 (no fracture to severe. A new fracture was diagnosed if a vertebrae with a 0 score on the previous X-ray, now received a 1 or higher. Non-vertebral Fractures, Hip, Wrist: Both spontaneous and traumatic were included. Ascertainment specific to fractures were not reported however all clinical side effects and deaths occurring during the study were recorded and their causes investigated.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Watts 1990

Methods	Randomized controlled trial. Parallel group Secondary prevention Blinding: double blind, blinded radiologist Study length: 2 years Withdrawals: Etidronate: 27/212 (12.7%) Placebo: 33/211 (15.6%) Total: 60/423 (14.2%)
Participants	<p>Source: Seven centres in the USA. Patients were recruited by media announcements and letters to physicians.</p> <p>Inclusion Criteria: Generally healthy, white and Asian women age 75 or younger who had been post-menopausal for at least 12 months. Weight between 40 kg and 80 kg. All had osteoporosis defined as 1-4 vertebral compression fractures plus radiographic evidence of osteopenia.</p> <p>Exclusion Criteria: Treatment with estrogen, steroids, glucocorticoids, phosphate or calcium > 1.0 g/day or vitamin D > 1000 IU/day in previous 6 mos. Treatment with thiazide in previous 2 months or any treatment with fluoride, calcitonin or bisphosphonate. Any medical conditions - active RA, GI, liver, alcoholism, renal.</p> <p>Treatment N = 212 Control N = 211 Age: 65.1 (13); YSM: 17.9 (16.5) Calcium: 746 mg/day (782) BMD: 0.86 g/cm² T-score: -1.7 Fractures: 100%</p>
Interventions	Comparison (A) Etidronate 400mg/day vs placebo Comparison (B) Etidronate 400mg/day with 3g phosphorous vs placebo with 3g phosphorous. (91 days) (500 mg calcium /day) (500 mg calcium /day)
Outcomes	<p>Vertebral Fractures: Lateral radiographs of thoracic and lumbar spine performed at baseline, 12 and 24 months, were reviewed by a single blinded radiologist. A new fracture was defined as a reduction of 20% or more in anterior, middle, or posterior height with a reduction of 10% or more in area of a previously unfractured vertebra.</p> <p>Non-vertebral Fractures, Hip and Wrist: Ascertainment not specified however patients were questioned about symptoms and intercurrent illnesses at each visit.</p>
Notes	
Risk of bias	
Bias	Authors' judgement Support for judgement
Allocation concealment?	Unclear risk B - Unclear

Watts 1990A

Methods	Please see Watts 1990 for details	
Participants		
Interventions	Etidronate 400mg/day vs placebo (91 days) (500 mg calcium/day)	
Outcomes		
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Watts 1990B

Methods	Please see Watts 1990 for details	
Participants		
Interventions	400mg/day with 3g phosphorous, vs placebo with 3g phosphorous. (91 days) (500 mg calcium)	
Outcomes		
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Wimalawansa 1998

Methods	Randomized controlled trial. Parallel group Secondary prevention Study length: 4 years Blinding: blinded radiologist Withdrawals: Etidronate: 3/17 (17.6%) Control: 4/18 (22.2%) Total: 7/35 (20.0%)	
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Wimalawansa 1998 (Continued)

Participants	<p>Source: Patients attending a hospital's metabolic outpatient clinics. Country - unclear whether USA or UK.</p> <p>Inclusion Criteria: Postmenopausal women with osteoporosis defined as 1-4 radiographically demonstrable atraumatic thoracic vertebral crush fractures and spine DXA BMD 2.0 SD below age 35 normal.</p> <p>Exclusion Criteria: Surgical menopause, secondary osteoporosis, medical conditions affecting skeleton, medications affecting calcium metabolism in previous 3 yrs., any treatment with HRT, steroids, glucocorticoids, calcitonin, fluoride or bisphosphonates since menopause.</p> <p>Treatment N = 17 Control N = 18 (Hormone replacement therapy group N = 37 not included in this review) Age: 64.9 (7.8); YSM: 15.1 (6.8) Calcium: 696 mg (339) BMD: 0.83 g/cm² T-score: -2.0 Fractures: 100%</p>
Interventions	<p>Etidronate 400mg/day vs control (84 days) (1g calcium/day and 400IU Vitamin D daily)</p>
Outcomes	<p>Vertebral Fractures: Lateral radiographs of thoracic (T4 to T12) and lumbar (L1 to L4) spine performed at baseline and 4 years were read by a single radiologist blinded to sequence and therapy. A new fracture was defined as a reduction of 20% or more in anterior, middle, or posterior height with a reduction of 15% or more in area of a previously unfractured vertebra.</p> <p>Non-vertebral: Clinically apparent non-vertebral fractures were assessed.</p>
Notes	
Risk of bias	
Bias	Authors' judgement Support for judgement
Allocation concealment?	Unclear risk B - Unclear

T-score calculated using the lumbar spine BMD [(LS BMD -1.047)/0.110];

YSM = Years Since Menopause; BMD = Bone Mineral Density; Txt = Treatment; HRT = Hormone Replacement Therapy; QCT = Quantitative Computerized Tomography

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Adami 2000	No fracture outcome reported.
Anderson 1984	Lack of an appropriate control group.
Bolanca 1988	Non-randomized.
Chilibeck 2002	No fracture outcome reported.
Cortet 2001	Lack of an appropriate control group.
Evans 1993	No fracture outcome reported.

Study	Reason for exclusion
Guanabens 2000	Lack of an appropriate control group.
Gurlek 1997	No fracture outcome reported.
Harris 1993	Lack of an appropriate control group.
Heaney 1976	Study duration less than one year.
Heath 2000	No fracture outcome reported.
Hesch 1988	Lack of an appropriate control group.
Hodsman 1989	Lack of an appropriate control group.
Hyldstrup 2001	Non-randomized.
Iwamoto 2001	Lack of an appropriate control group.
Iwamoto 2002	No fracture outcome reported.
Iwamoto 2003 a	Lack of an appropriate control group.
Iwamoto 2003 b	Lack of an appropriate control group.
Jowsey 1971	Lack of an appropriate control group.
Mallette 1989	Non-randomized.
Masud 1998	Lack of an appropriate control group.
Miller 1997	Non-randomized.
Miller 1999	Lack of an appropriate control group.
Morishige 2003	Lack of an appropriate control group.
Orme 1994	Non-randomized.
Ott 1994	Non-randomized.
Ryan 1994	Non-randomized.
Smith 1989	Non-randomized.
Steiniche 1991	Lack of an appropriate control group.
Storm 1996	Non-randomized.
Terranova 1999	No fracture outcome reported.
Wimalawansa 1995	No fracture outcome reported.

DATA AND ANALYSES

Comparison 1. Etidronate 400 mg vs Control - all years baseline denominators

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vertebral Fractures	9	1010	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.36, 0.96]
1.1 Vertebral primary prevention	3	315	Risk Ratio (M-H, Fixed, 95% CI)	3.03 [0.32, 28.44]
1.2 Vertebral secondary prevention	6	695	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.32, 0.87]

Analysis 1.1. Comparison 1 Etidronate 400 mg vs Control - all years baseline denominators, Outcome 1 Vertebral Fractures.

Comparison 2. Etidronate 400 mg vs Control - all years baseline denominators

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Non Vertebral Fractures	7	787	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.68, 1.42]
1.1 Non vertebral primary prevention	2	163	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.20, 1.61]
1.2 Non vertebral secondary prevention	5	624	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.72, 1.60]

Analysis 2.1. Comparison 2 Etidronate 400 mg vs Control - all years baseline denominators, Outcome 1 Non Vertebral Fractures.

Comparison 3. Etidronate 400 mg vs Control - all years baseline denominators

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hip Fractures	4	589	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.37, 3.88]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Hip secondary prevention	4	589	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.37, 3.88]

Analysis 3.1. Comparison 3 Etidronate 400 mg vs Control - all years baseline denominators, Outcome 1 Hip Fractures.

Comparison 4. Etidronate 400 mg vs Control - all years baseline denominators

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Wrist Fractures	4	589	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.32, 2.36]
1.1 Wrist secondary prevention	4	589	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.32, 2.36]

Analysis 4.1. Comparison 4 Etidronate 400 mg vs Control - all years baseline denominators, Outcome 1 Wrist Fractures.

Comparison 5. Etidronate 400 mg vs Control - 1 year baseline denominators

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fractures	3	361	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.09, 1.62]
1.1 Vertebral primary prevention	2	261	Risk Ratio (M-H, Fixed, 95% CI)	3.05 [0.13, 73.37]
1.2 Vertebral secondary prevention	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.02, 1.33]

Analysis 5.1. Comparison 5 Etidronate 400 mg vs Control - 1 year baseline denominators, Outcome 1 Fractures.

Comparison 6. Etidronate 400 mg vs Control - 2 years baseline denominators

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fractures	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Vertebral primary	3	315	Risk Ratio (M-H, Fixed, 95% CI)	3.03 [0.32, 28.44]
1.2 Vertebral secondary	5	660	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.24, 0.76]
1.3 Non vertebral primary	2	163	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.20, 1.61]
1.4 Non vertebral secondary	2	423	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.76, 1.92]
1.5 Hip secondary	2	423	Risk Ratio (M-H, Fixed, 95% CI)	3.98 [0.45, 35.33]
1.6 Wrist secondary	2	423	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.20, 4.91]

Analysis 6.1. Comparison 6 Etidronate 400 mg vs Control - 2 years baseline denominators, Outcome 1 Fractures.

Comparison 7. Etidronate 400 mg vs Control - 2 years baseline denominators

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fractures	8		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Vertebral	8	975	Odds Ratio (M-H, Fixed, 95% CI)	0.47 [0.26, 0.84]
1.2 Non vertebral	4	586	Odds Ratio (M-H, Fixed, 95% CI)	1.06 [0.65, 1.72]
1.3 Hip	2	423	Odds Ratio (M-H, Fixed, 95% CI)	4.04 [0.45, 36.42]
1.4 Wrist	2	423	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.20, 4.97]

Analysis 7.1. Comparison 7 Etidronate 400 mg vs Control - 2 years baseline denominators, Outcome 1 Fractures.

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
7.1.1 Vertebral					

Favours treatment 0.1 0.2 0.5 1 2 5 10 Favours control

Comparison 8. Etidronate 400 mg vs Control - 3 years baseline denominators

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fractures	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Vertebral secondary	2	180	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.11, 0.79]
1.2 Non vertebral secondary	1	66	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.28, 2.46]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Wrist secondary	1	66	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.12, 3.73]
1.4 Hip secondary	1	66	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.05, 5.25]

Analysis 8.1. Comparison 8 Etidronate 400 mg vs Control - 3 years baseline denominators, Outcome 1 Fractures.

Comparison 9. Etidronate 400 mg vs Control - 4 years baseline denominators

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fractures	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Vertebral secondary	2	135	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.22, 1.18]
1.2 Non vertebral secondary	2	135	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.20, 2.28]
1.3 Hip secondary	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.05, 5.34]
1.4 Wrist secondary	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.15, 6.82]

Analysis 9.1. Comparison 9 Etidronate 400 mg vs Control - 4 years baseline denominators, Outcome 1 Fractures.

Comparison 10. Etidronate 400 mg vs Control - all years baseline denominators

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Withdrawals due to side effects	5	796	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.25, 1.49]
2 Withdrawals overall	10	1208	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.71, 1.16]

Analysis 10.1. Comparison 10 Etidronate 400 mg vs Control - all years baseline denominators, Outcome 1 Withdrawals due to side effects.

Analysis 10.2. Comparison 10 Etidronate 400 mg vs Control - all years baseline denominators, Outcome 2 Withdrawals overall.

Comparison 11. Etidronate 200 mg vs Control - 2 years baseline denominators

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Sites	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Vertebral secondary	2	172	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.16, 0.64]
1.2 Hip Secondary	1	132	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.04]
1.3 Wrist secondary	1	132	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.05, 5.38]

Analysis 11.1. Comparison 11 Etidronate 200 mg vs Control - 2 years baseline denominators, Outcome 1 Sites.

ADDITIONAL TABLES

Table 1. Clinical Relevance Table for Fracture - Primary Prevention Trials

Outcome	# Patients # Trials	Control Event Rate	Wt Ab- solute RD	Wt Rel % Change	NNT B	Statistical Sig	Quality of Evidence
Vertebral Fractures - (Trial Population) Primary Prevention (400 mg for 2 yrs)	315 (3)	0% 0 out of 100 patients	1% 1 more patient out of 100	203% (W)	Not applica- ble	Not statisti- cally signifi- cant	Silver
95% confidence in- terval			(-1, 4)	(-68, 2,744)			
Vertebral Fractures - (Low Risk Woman) Primary Prevention (400 mg for 2 yrs)	315 (3)	1.2% (1 out of 100)	Not applica- ble	203% (W)	Not applica- ble	Not statisti- cally signifi- cant	Silver
95% confidence in- terval				(-68, 2,744)			
Vertebral Fractures - (Moderate Risk Woman) Primary Prevention (400 mg for 2 yrs)	315 (3)	5.3% (5 out of 100)	Not applica- ble	203% (W)	Not applica- ble	Not statisti- cally signifi- cant	Silver
95% confidence in- terval				(-68, 2,744)			
Non-vertebral Frac- tures - (Trial Popu- lation) Primary Pre- vention (etidronate 400 mg for 2 yrs)	163 (2)	11.0% (11 out of 100)	5% 5 fewer patients out of 100	44% (I)	Not applica- ble	Not statisti- cally signifi- cant	Silver
95% confidence in- terval			(-13, 4)	(-80, 61)			
Non-vertebral Fractures - (Low Risk Woman) Pri- mary Prevention (etidronate 400 mg for 2 yrs)	163 (2)	8.9% (9 out of 100)	Not applica- ble	44% (I)	Not applica- ble	Not statisti- cally signifi- cant	Silver

Table 1. Clinical Relevance Table for Fracture - Primary Prevention Trials (Continued)

95% confidence interval		(-80, 61)					
Non-vertebral Fractures - (Moderate Risk Woman) Primary Prevention (etidronate 400 mg for 2 yrs)	163 (2)	16.5% (17 out of 100)	Not applicable	44% (I)	Not applicable	Not statistically significant	Silver
95% confidence interval		(-80, 61)					
Hip Fractures	No trials available	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Wrist Fractures	No trials available	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Legend	Secondary prevention = bone density of at least 2 SD values below peak bone mass and/or one or more vertebral compression fractures.	For Trial Population rates are based on the event rate in the control group. Low and Moderate Risk, are 5 year community population risks derived from the following variables in the FRACTURE Index: age, fracture after 50 yrs., maternal hip fracture after 50 yrs., weight < 125 lbs, smoking, using arms to assist standing and BMD. Low = FRACTURE Index score 1-2, Moderate = FRACTURE Index score 5 (Black 2001) see Figure 1	Wt = weighted, RD = risk difference	Wt Rel = weighted relative percent change, I = improvement	NNT B = number needed to benefit	Gold level: At least one randomised clinical trial meets all of the following criteria for the major outcome(s) as reported: Sample sizes of at least 50 per group. If a statistically significant difference is not found they must be powered for 20% relative difference in the relevant outcome. Blinding of patients and assessors for outcomes. Handling of withdrawals > 80% follow up (imputations based on methods such as Last Observation Carried Forward (LOCF) acceptable). Concealment of treatment allocation. Silver level: Randomised trial does not meet the above criteria.	

Table 2. Clinical Relevance Table for Fracture - Secondary Prevention Trials

Outcome	# Patients # Trials	Control Event Rate	Wt Absolute RD	Wt Rel % Change	NNT B	Statistical Sig	Quality of Evidence
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Table 2. Clinical Relevance Table for Fracture - Secondary Prevention Trials *(Continued)*

Vertebral Fractures - (Trial Population) Secondary Prevention (400 mg for 2-4 yrs)	695 (6)	11.0% (11 out of 100 patients)	-5% 5 fewer patients out of 100	-47% (I)	20	Statistically significant	Silver
95% confidence interval			(-1, -9)	(-13, -68)	(14, 70)		
Vertebral Fractures - (Moderate Risk Woman) Secondary Prevention (400 mg for 2-4 yrs)	695 (6)	5.3% (5 out of 100)	Not applicable	-47% (I)	41	Statistically significant	Silver
95% confidence interval				(-68, -13)	(28, 146)		
Vertebral Fractures - (High Risk Woman) Secondary Prevention (400 mg for 2-4 yrs)	695 (6)	11.2% (11 out of 100)	Not applicable	-47% (I)	19	Statistically significant	Silver
95% confidence interval				(-68, -13)	(14, 69)		
Non-vertebral Fractures - (Trial Population) Secondary Prevention (etidronate 400 mg for 2-4 yrs)	624 (5)	12.8% (13 out of 100)	1% 1 more patient out of 100	7% (W)	Not applicable	Not statistically significant	Silver
95% confidence interval			(-4, 6)	(-28, 60)			
Non-vertebral Fractures - (Moderate Risk Woman) Secondary Prevention (etidronate 400 mg for 2-4 yrs)	624 (5)	16.5% (17 out of 100)	Not applicable	7% (W)	Not applicable	Not statistically significant	Silver
95% confidence interval				(-28, 60)			
Non-vertebral Fractures - (High Risk Woman) Secondary Prevention (etidronate 400 mg for 2-4 yrs)	624 (5)	27.5% (28 out of 100)	Not applicable	7% (W)	Not applicable	Not statistically significant	Silver
95% confidence interval				(-28, 60)			
Hip Fractures - (Trial Population) Secondary Prevention (etidronate 400mg 2-4 yrs)	589 (4)	1.4% (1 out of 100 patients)	0% 0 fewer patients out of 100	20% (W)	Not applicable	Not statistically significant	Silver

Table 2. Clinical Relevance Table for Fracture - Secondary Prevention Trials (Continued)

95% confidence interval			(-2, 3)	(-63, 288)			
Hip Fractures - (Moderate Risk Woman) Secondary Prevention (etidronate 400mg 2-4 yrs)	589 (4)	1.9% (2 out of 100)	Not applicable	20% (W)	Not applicable	Not statistically significant	Silver
95% confidence interval				(-63, 288)			
Hip Fractures - (High Risk Woman) Secondary Prevention (etidronate 400mg 2-4 yrs)	589 (4)	8.7% (9 out of 100)	Not applicable	20% (W)	Not applicable	Not statistically significant	Silver
95% confidence interval				(-63, 288)			
Wrist Fractures - Secondary Prevention(etidronate 400 mg 2-4 yrs)	589 (4)	2.4% 2 out of 100 patients	0% 0 fewer patients out of 100	-13% (I)	Not applicable	Not statistically significant	Silver
95% confidence interval			(-3, 2)	(-68, 136)			
Wrist Fractures - Secondary Prevention(etidronate 400 mg 2-4 yrs)	589 (4)	Not available	Not applicable	-13% (I)	Not applicable	Not statistically significant	Silver
95% confidence interval				(-68, 136)			
Wrist Fractures - Secondary Prevention(etidronate 400 mg 2-4 yrs)	589 (4)	Not available	Not applicable	-13% (I)	Not applicable	Not statistically significant	Silver
95% confidence interval				(-68, 136)			
Legend	Secondary prevention = bone density of at least 2 SD values below peak bone mass and/or one or more vertebral compression fractures.	For Trial Population rates are based on the event rate in the control group. Moderate and High Risk, are 5 year community population risks derived from the following variables in the FRACTURE Index: age, fracture after 50 yrs., maternal hip fracture after 50 yrs., weight < 125 lbs, smoking, us-	Wt = weighted, RD = risk difference	Wt Rel = weighted relative percent change, I = improvement	NNT B = number needed to benefit	Gold level: At least one randomised clinical trial meets all of the following criteria for the major outcome(s) as reported: Sample sizes of at least 50 per group. If a statistically significant difference is not found they must be powered for 20% relative difference in the relevant outcome. Blinding of pa-	

tients and assessors for outcomes. Handling of withdrawals > 80% follow up (imputations based on methods such as Last Observation Carried Forward (LOCF) acceptable). Concealment of treatment allocation. Silver level: Randomised trial does not meet the above criteria.

Table 2. Clinical Relevance Table for Fracture - Secondary Prevention Trials *(Continued)*

ing arms to assist standing and BMD. Moderate = FRACTURE Index score 5, High = FRACTURE Index score 8-13 (Black 2001) see Figure 1

WHAT'S NEW

Date	Event	Description
13 August 2008	Amended	Absolute event rates included in the Plain language summary.
28 May 2008	Amended	Converted to new review format. CMSG ID C033-R

HISTORY

Review first published: Issue 3, 2001

Date	Event	Description
14 November 2007	New citation required and conclusions have changed	See published notes for details on update.

CONTRIBUTIONS OF AUTHORS

George Wells was involved in the conception, design and implementation of the project and contributed significantly to the writing of the report.

Ann Cranney was involved with the conception of the review, data abstraction, analysis, interpretation and revision of the final report.

Joan Peterson screened the literature, was involved in the data abstraction, quality assessment and analysis of the primary trials and contributed significantly to the writing of the report.

Michel Boucher assisted in the design of the analysis, reporting and interpretation of the findings and was involved in the writing of the report.

Beverley Shea was involved in developing the protocol and conducting the systematic review.

Vivian Robinson was involved in developing the protocol and conducting the systematic review.

Douglas Coyle assisted with the design of the review and reviewed the analysis.

Peter Tugwell provided clinical rheumatology expertise and methodological guidance.

DECLARATIONS OF INTEREST

None at present.

The Cochrane Funding Arbitration Panel recommended withdrawal of the original review from *The Cochrane Library*. The original review was externally supported by Merck and Proctor & Gamble to support research staff.

This current review was updated without the support of any industry sponsor.

SOURCES OF SUPPORT

Internal sources

- Ottawa Hospital Research Institute, Canada.

External sources

- Canadian Agency for Drugs and Technologies in Health, Canada.

NOTES

This review updated a previous review of etidronate conceived, conducted and completed, in part, by the authors of this report (Cranney 2001b). There were four general differences in the manner in which the two reviews were conducted. First, the search was extended to include articles up to February 2007 and the current review included two trials (Ishida 2004; Shiota 2001) published after the previous review was completed. Second, although both published and additional data from study investigators were used in the previous review, only published data were used in this one. Third, in the previous review the random-effects model was always used whereas in the present review the base analysis used the fixed-effect model unless the results were heterogeneous. Fourth, although the previous review considered both bone mineral density (BMD) and fracture data, this review was only concerned with fractures and therefore the definition of primary and secondary prevention put more of an emphasis on the fracture study inclusion criteria.

Specifically, there were three changes in the choice and classification of the included trials. First, in the previous etidronate review (Cranney 2001b) the trial by Watts (Watts 1990) was classified as primary prevention since the average t score was -1.7 and, as a result, women were included that were within 2 SD of the mean peak mass. However, an inclusion criterion restricted the population of women in the trial to those experiencing 1 to 4 previous vertebral compression fractures and, therefore, the trial was classified as secondary prevention in this review. Second, for the trial by Storm (Storm 1990), additional vertebral data were obtained from the authors and this information was not used in the current review. Third, for vertebral fractures, the trials by Meunier and Pouilles (Meunier 1997, Pouilles 1997) were excluded from the analysis of the previous review due to low incidence of vertebral fractures but they were included in this review.

The overall results (that is primary and secondary prevention combined) of the two reviews are essentially identical. For primary prevention, there are some differences: the RR of vertebral fracture is now greater than one but with a much wider CI; and for non-vertebral fractures, the RR of fracture is now smaller than one. However, for both reviews these results were non-significant. For secondary prevention, the RR for vertebral fracture is now smaller and is statistically significant. For non-vertebral fractures, the RR is larger and now above one but is still non-significant.

The differences in the results for primary and secondary prevention are due to reclassifying the Watts (Watts 1990) trial as secondary prevention. If this trial is considered as a primary prevention trial then the primary and secondary results for the two reviews are essentially the same. The sensitivity analysis of including and excluding unpublished data did not substantively change the results. Similarly, including and excluding the results of the trials by Meunier and Pouilles (Meunier 1997, Pouilles 1997) did not change the results.

In summary, the conclusions are similar in that both reviews found no statistically significant reductions in vertebral fractures when etidronate is used for primary prevention; and no statistically significant reductions in non-vertebral fractures were observed, regardless of whether etidronate was used for primary or secondary prevention. However, in the current and previous reviews etidronate demonstrated a significant benefit in the secondary prevention of vertebral fractures.

INDEX TERMS

Medical Subject Headings (MeSH)

Bone Density [drug effects]; Bone Density Conservation Agents [adverse effects] [*therapeutic use]; Etidronic Acid [adverse effects] [*therapeutic use]; Hip Fractures [prevention & control]; Osteoporosis, Postmenopausal [*drug therapy] [prevention & control]; Spinal Fractures [etiology] [*prevention & control]; Wrist Injuries [prevention & control]

MeSH check words

Female; Humans