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Bisphosphonates for Paget's disease of bone in adults (Review)

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[Intervention Review]

Bisphosphonates for Paget's disease of bone in adults

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ABSTRACT

Background

Bisphosphonates are considered to be the treatment of choice for people with Paget's disease of bone. However, the effects of bisphosphonates on patient-centred outcomes have not been extensively studied. There are insufficient data to determine whether reducing and maintaining biochemical markers of bone turnover to within the normal range improves quality of life and reduces the risk of complications.

Objectives

To assess the benefits and harms of bisphosphonates for adult patients with Paget's disease of bone.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, ISI Web of Knowledge and trials registers up to March 2017. We searched regulatory agency published information for rare adverse events.

Selection criteria

Randomised controlled trials (RCTs) of bisphosphonates as treatment for Paget's disease in adults.

Data collection and analysis

Two review authors independently screened search results, extracted data and assessed studies for risk of bias. We used standard methodological procedures expected by The Cochrane Collaboration.

Main results

We included 20 trials (25 reports, 3168 participants). Of these, 10 trials (801 participants) compared bisphosphonates (etidronate, tiludronate, ibandronate, pamidronate, olpadronate, alendronate, risedronate, zoledronate) versus placebo, seven compared two bisphosphonates (992 participants), one trial compared a bisphosphonates with a bisphosphonate plus calcitonin (44 participants), and two studies, the largest trial (1331 participants) and its interventional extension study (502 participants), compared symptomatic treatment and intensive treatment where the goal was to normalise alkaline phosphatase.

Most studies were assessed at low or unclear risk of bias. Six of 10 studies comparing bisphosphonates versus placebo were assessed at high risk of bias, mainly around incomplete outcome data and selective outcome reporting.



Participant populations were reasonably homogeneous in terms of age (mean age 66 to 74 years) and sex (51% to 74% male). Most studies included participants who had elevated alkaline phosphatase levels whether or not bone pain was present. Mean follow-up was six months.

Bisphosphonates versus placebo

Bisphosphonates tripled the proportion (31% versus 9%) of participants whose bone pain disappeared (RR 3.42, 95% confidence interval (CI) 1.31 to 8.90; 2 studies, 205 participants; NNT 5, 95% CI 1 to 31; moderate-quality evidence). This result is clinically important. Data were consistent when pain change was measured as any reduction (RR 1.97, 95% CI 1.29 to 3.01; 7 studies, 481 participants).

There was uncertainty about differences in incident fractures: 1.4% fractures occurred in the bisphosphonates group and none in the placebo group (RR 0.89, 95% CI 0.18 to 4.31; 4 studies, 356 participants; very low-quality evidence).

None of the studies reported data on orthopaedic surgery, quality of life or hearing thresholds.

Results regarding adverse effects and treatment discontinuation were uncertain. There was a 64% risk of mild gastrointestinal adverse events in intervention group participants and 48% in the control group (RR 1.32, 95% CI 0.91 to 1.92; 6 studies, 376 participants; low-quality evidence). The likelihood of study participants discontinuing due to adverse effects was slightly higher in intervention group participants (4.4%) than the control group (4.1%) (RR 1.01, 95% CI 0.41 to 2.52; 6 studies, 517 participants; low-quality evidence). Zoledronate was associated with an increased risk of transient fever or fatigue (RR 2.57, 95% CI 1.21 to 5.44; 1 study, 176 participants; moderate-quality evidence).

Bisphosphonates versus active comparator

More participants reported pain relief with zoledronate than pamidronate (RR 1.30, 95% CI 1.10 to 1.53; 1 study, 89 participants; NNT 5, 95% CI 3 to 11) or risedronate (RR 1.36, 95% CI 1.06 to 1.74; 1 study, 347 participants; NNT 7, 95% CI 4 to 24; very low quality evidence). This result is clinically important.

There was insufficient evidence to confirm or exclude differences in adverse effects of bisphosphonates (RR 1.05, 95% CI 0.95 to 1.76; 2 studies, 437 participants; low-quality evidence) and treatment discontinuation (2 studies, 437 participants) (RR 2.04, 95% CI 0.43 to 9.59; 2 studies, 437 participants; very low-quality evidence).

Intensive versus symptomatic treatment

There was no consistent evidence of difference to response in bone pain, bodily pain or quality of life in participants who received intensive versus symptomatic treatment.

Inconclusive results were observed regarding fractures and orthopaedic procedures for intensive versus symptomatic treatment (intensive treatment for fracture: RR 1.84, 95% CI 0.76 to 4.44; absolute risk 8.1% versus 5.2%; orthopaedic procedures: RR 1.58, 95% CI 0.80 to 3.11; absolute risk 5.6% versus 3.0%; 1 study, 502 participants; low-quality evidence).

There was insufficient evidence to confirm or exclude an important difference in adverse effects between intensive and symptomatic treatment (RR 1.05, 95% CI 0.79 to 1.41; low-quality evidence).

There was insufficient evidence to confirm or exclude an important difference of risk of rare adverse events (including osteonecrosis of the jaw) from the regulatory agencies databases.

Authors' conclusions

We found moderate-quality evidence that bisphosphonates improved pain in people with Paget's disease of bone when compared with placebo. We are uncertain about the results of head-to-head studies investigating bisphosphonates. We found insufficient evidence of benefit in terms of pain or quality of life from intensive treatment. Information about adverse effects was limited, but serious side effects were rare, and rate of withdrawals due to side effects was low.

PLAIN LANGUAGE SUMMARY

Bisphosphonates for Paget's disease of bone in adults

Review question

We wanted to find out if using bisphosphonate treatment was better or worse than dummy treatment (placebo) to relieve bone pain in people with Paget's disease of bone and determine if treatment could prevent complications. We also wanted to discover which bisphosphonates were better.

What is Paget's disease of bone and what are bisphosphonates?



Paget's disease of bone is a chronic problem which usually affects one or a few bones. Paget's disease causes bone renewal and repair to become abnormal; bones become weak enlarged and misshapen, leading to pain, fractures and arthritis in joints close to affected bones.

Bisphosphonates are medications that slow down the bone remodelling process.

Search date

March 2017.

Study characteristics

We included 20 studies that involved 3168 people. Of these, 10 studies (801 people) compared bisphosphonates with placebo. Studies included elderly people; slightly more participants were men; and nearly all had raised blood serum markers of bone turnover. Fourteen studies recruited participants from hospitals, outpatient and general practitioner clinics. Studies were performed in USA, Canada, UK, Europe; Australia, New Zealand and Argentina.

What are the effects of bisphosphonates in people with Paget's disease of bone?

Bisphosphonates probably help to relieve bone pain. We are uncertain which bisphosphonate is better. Results were similar across studies.

We are uncertain if bisphosphonates can prevent bone fractures.

Effects on quality of life, need for orthopaedic surgery and hearing loss prevention were not reported in studies that compared bisphosphonates with placebo.

What are the side effects of bisphosphonates in people with Paget's disease of bone?

Most studies did not report details about drug-related side effects and complications. Bisphosphonates may make little or no difference in side effects except for temporary fever or tiredness with intravenous treatments and mild gastrointestinal side effects with oral medications. Severe side effects causing treatment discontinuation were rare.

What happens to people with Paget's disease of bone treated with bisphosphonates?

Pain

We found that of 100 adults with Paget's disease of bone, 31 would experience complete pain relief if they took bisphosphonates for six months compared with 9 people not taking bisphosphonates.

Side effects

We found that of 100 adults with Paget's disease of bone, 64 would experience side effects if they took bisphosphonates for six months compared with 48 not taking bisphosphonates.

The number of people who stopped treatment due to side effects was the same for the bisphosphonate and placebo groups (4 out of 100).

Quality of evidence

Pain relief data provided moderate-quality evidence, but data on fractures was assessed as providing very low-quality evidence. Data on side effects provided low-quality evidence; treatment discontinuation data provided moderate-quality evidence. Evidence was downgraded mainly due to limited data and concerns about study design.

Study funding sources

Eleven studies were funded by drug manufacturers. Four studies were funded by government agencies or charities. Data on funding sources were not provided or unclear in five studies.



Summary of findings for the main comparison. Bisphosphonates versus placebo for Paget's disease of bone

Bisphosphonates versus placebo for Paget's disease of bone

Patient or population: Paget's disease of bone

Settings: Inpatients and outpatients in America, Europe, Australasia and Africa

Intervention: Bisphosphonates

Comparison: Placebo

Outcomes	7		Relative effect (95% CI)	№ of partici- pants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with bis- phosphonates		(**************************************	(533.52)	
Number of participants with change in bone pain (disap-	Study population	1	RR 3.42 - (1.31 to 8.90)	205 (2 RCTs)	⊕⊕⊕⊝ MODERATE ²	NNTB 5 (1 to 35)
pearance of pain) ¹ assessed on VAS	91 per 1000	311 per 1000 (119 to 809)	- (1.51 to 6.50)	(2 KC15)	MODERATE	Absolute risk difference: 23% more (12% to 34%)
Follow up: mean 6 months						Relative percent change: 242 % (31% to 790%) (Improvement)
Number of participants who experienced radiologically-con-	Low (study popu	lation)³	RR 0.89 - (0.18 to 4.31)	356 (4 RCTs)	⊕⊝⊝⊝ VERY LOW ^{2 4 5}	Absolute risk difference: 1% more (-2% to 5%)
firmed fractures Follow up: mean 6 months	0 per 1000	0 per 1000 (0 to 0)		, , ,		Relative percentage change: 11% (-82% to 331%) (improvement)
	Moderate ³					Effect is uncertain due to very low
	9 per 1000	8 per 1000 (2 to 39)				quality evidence
	High ³					
	52 per 1000	46 per 1000 (9 to 224)				
Number of participants who	See comments	See comments	Not estimable	0	See comments	Outcome not reported in the included studies
needed orthopaedic surgery (not measured)				(0 RCTs)		studies

Number of participants with change in quality of life measures (not measured)	See comments	See comments	Not estimable	0 (0 RCTs)	See comments	Outcome not reported in the included studies
Number of participants with change in hearing thresholds (not measured)	See comments	See comments	Not estimable	0 (0 RCTs)	See comments	Outcome not reported in the included studies
Number of participants who experienced side effects related to use of bisphosphonates Follow up: mean 6 months	Study population 483 per 1000 638 per 1000 (440 to 928)		RR 1.32 - (0.91 to 1.92)	678 (6 RCTs)	⊕⊕⊝⊝ LOW ^{6 7}	Absolute risk difference: 11% more (0% to 22%) Relative percent change: 32 % (-10% to 92%) (worsening) Gastrointestinal side effects (diarrhoea, dyspepsia, vomiting, nausea, oesophagitis or gastritis) were the most common
Number of participants who withdrew due to adverse events Follow up: mean 6 months	Study population 41 per 1000	41 per 1000 (17 to 102)	RR 1.01 - (0.41 to 2.52)	517 (6 RCTs)	⊕⊕⊙⊝ LOW ^{8 9}	Absolute risk difference: 0% (-4% to 3%) Relative percent change: 1% (-59% to 152%) (worsening)

^{*}The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; NNTB: Number needed to treat for an additional beneficial outcome; OR: odds ratio; RR: risk ratio;

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

When pain was assessed as any pain reduction instead of disappearance of pain, the outcomes were consistent: 227 per 1000 in placebo vs. 446 per 1000 (292 to 682) in bisphosphonates group (RR 1.97, 95% CI 1.29 to 3.01), NNTD 4 (2 to 13), absolute risk difference 33% more (18% to 49%), relative percentage change 97% (29% to 201% improvement), based on results from seven RCTs (481 participants). Visual analogue scale ranging from 0 to 10 was used in four of the seven studies. One study classified pain in three groups; the tool used for pain assessment was not detailed in the other two studies. Moderate quality evidence: downgraded by one level; there was high risk for attrition bias in three studies and high risk for reporting bias in three studies. The outcome did not change in a sensitive analysis excluding high risk of bias studies.

² Downgraded by one level (imprecision). Few events, resulting in wide CI.

³ The 0% calculated assumed risk in the control group (no fractures in placebo group) is misleading. This outcome is likely due to the short follow-up period of the studies. To give a more accurate data we have added two scenarios of moderate and high prevalence using data from a study with a longest follow-up period, the PRISM-EZ trial (Tan 2017). In summary there are three scenarios to calculate the assumed risk in the control group: 1) To calculate low prevalence we used data from the included studies (placebo groups).

- ⁴ Downgraded by two levels (limitation of studies). Most data were from studies assessed at high risk of bias; there was high risk for attrition bias in two studies and high risk for reporting bias in one study.
- ⁵ Downgraded by one level (indirectness). Long-term impact on fractures was not assessed.
- ⁶ Downgraded by one level (limitation of studies). High risk for attrition bias in two studies.
- ⁷ Downgraded by one level (inconsistency). The side effects considered in the studies were heterogeneous. In addition, considerable heterogeneity was found when the six studies were meta-analysed ($l^2 = 75\%$, P = 0.001). However, only one study (McClung 1995) showed more adverse events in the placebo group than the bisphosphonates group. The heterogeneity could not be explained by differences in design of this study since it was similar to other studies. A sensitivity analysis excluding this study found low heterogeneity $I^2 = 6\%$ (RR 1.38, 95% CI 1.08 to 1.78).
- 8 Downgraded by two levels. Half of the included studies were assessed at high risk of bias; there was high risk for attrition bias in three studies and high risk for reporting bias in one study.
- ⁹ Rated down for imprecision. Optimal information size criterion was not met. The 95% CI is too wide.

Summary of findings 2. Zoledronate versus pamidronate or risedronate for Paget's disease of bone

Zoledronate versus pamidronate or risedronate for Paget's disease of bone

Patient or population: Paget's disease of bone

Settings: Inpatients and outpatients in America, Europe, Australasia and Africa

Intervention: Zoledronate

Comparison: Pamidronate or risedronate

Outcomes	i i i i i i i i i i i i i i i i i i i		Relative effect (95% CI)	№ of partici- pants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with pamidronate or risedronate	Risk with zole- dronate		((0.2.2.2.)	
Number of participants	Study population		RR 1.31 (1.15 to 1.51)	436 (2 RCTs)	⊕⊝⊝⊝ VERY LOW ^{2 3}	NNTB: 7 (4 to 14)
assessed on VAS.	405 pci 1000 005 pci 1000	Absolute risk difference: 17% (8% to 26%)				
Follow up: mean 6 months (535 to 702)				Relative percent change: 31% (15% to 51%) (improvement)		
					Not pooled effects:	
					Zoledronate vs. pamidronate (89 participants); RR 1.30 (1.10 to 1.53), NNTB 4 (3 to 13).	

						Zoledronate vs. risedronate (347 participants); RR 1.36 (1.06 to 1.74), NNTB 8 (4 to 45).
Number of participants who experienced fractures (not measured)	See comments	See comments	Not estimable	0 (0 RCTs)	See comments	Outcome not reported in the included studies
Number of participants who needed orthopaedic surgery (not measured)	See comments	See comments	Not estimable	0 (0 RCTs)	See comments	Outcome not reported in the included studies
Number of participants with change in quality of life measures (not measured)	See comments	See comments	Not estimable	0 (0 RCTs)	See comments	Effect is uncertain. Zoledronate showed a marginal improvement at 6 months in QoL when compared with risedronate. The physical component summary score of SF-36 improved with zoledronate compared to risedronate (1.6 vs. 0.3 change from baseline score, on a 0 to 100 scale). This result is unlikely to be of clinical importance
Number of participants with change in hearing thresholds (not measured)	See comments	See comments	Not estimable	0 (0 RCTs)	See comments	Outcome not reported in the included studies
Number of participants who experienced side ef-	Study population	1	RR 1.05 - (0.95 to 1.16)	437 (2 RCTs)	⊕⊕⊝⊝ LOW²	Absolute risk difference: 4% (-4% to 12%)
fects related to use of bis- phosphonates. Follow up: mean 6 months	745 per 1000	782 per 1000 (707 to 864)	- (0.33 to 1.10)	(2 NC13)	LOW	Relative percent change: 5% (-5% to 16%) (worsening)
Number of participants who withdrew due to ad-	Study population	1	RR 2.04 - (0.43 to 9.59)	437 (2 RCTs)	⊕⊝⊝⊝ VERY LOW ^{2 4}	Absolute risk difference: 1% (-2% to 3%)
verse events (withdrawals) follow up: mean 6 months	9 per 1000	18 per 1000 (4 to 83)	- (0.43 to 3.33)	(2 NC13)	VERT LOW	Relative percent change: 104% (-57% to 859%) (worsening)

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; NNTB: Number needed to treat for an additional beneficial outcome; OR: odds ratio; QoL: quality of life; RCT: randomised controlled trial; RR: risk ratio; VAS: visual analogue scale

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

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Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹Unlike Summary of findings for the main comparison (comparing bisphosphonates vs. placebo) when compared zoledronate vs pamidronate or risedronate we used any change of pain instead of disappearance of pain because data were not available. However, readers could find data on disappearance of pain in the original zoledronate vs. pamidronate manuscript (Merlotti 2007) [10/47 vs. 6/60, RR 2.12 95% IC 0.83-5.43]. We did not include these data because we think they are misleading. They come from accumulate zoledronate effects in two different study phases (30 zoledronate patients from phase 1 + 17 patients no responders to pamidronate in phase 1 treated with zoledronate in phase 2) vs. pamidronate in only one study phase (60 patients).

² Downgraded by two levels (limitation of studies). Information is from studies at high risk of bias. High risk for performance bias in 1 study and high risk for reporting bias in 1 study. ³ Downgraded by one level (indirectness). In the risedronate study, the author assessed bodily pain but not bone pain associated directly with Paget's bone lesions (Change in bone pain was defined as "5-point improvement from baseline" in SF-36 bodily pain item). In the pamidronate study change in bone pain was defined as "subjects reported disappearance or decrease in pain".

⁴Downgraded by one level (imprecision). There were few events, resulting in wide CI,



BACKGROUND

Description of the condition

Paget's disease of bone is a common disorder characterised by focal areas of increased and disorganised bone remodeling affecting one or more bones throughout the skeleton. Paget's disease preferentially targets the axial skeleton, most frequently affecting the pelvis (70% of cases), femur (55%), lumbar spine (53%), skull (42%) and tibia (32%) (Ralston 2013). Paget's disease of bone is rare before the age of 55 years, but increases in prevalence thereafter, affecting about 5% of women and 8% of men by the eighth decade of life in the United Kingdom (Van Staa 2002). The incidence and prevalence rates of Paget's disease of bone vary widely, but both have decreased in most regions over recent years. The changes are heterogeneous among and within countries; the largest changes have occurred in areas that previously had high prevalence (Corral-Gudino 2013).

Paget's disease of bone is a cause of substantial morbidity in people who come to medical attention. Up to 50% of these people experience complications such as bone pain, bone deformity, pathologic fracture, deafness and secondary osteoarthritis that adversely affect quality of life (Tan 2014; Van Staa 2002). People with Paget's disease of bone run a significantly increased risk of developing osteoarthritis (Van Staa 2002) and their need for hip replacement is substantially higher than among age-matched controls (Van Staa 2002). Osteosarcoma (malignant bone tumour) is a rare complication; however, virtually all osteosarcomas found in adults aged over 60 years occur in people with Paget's disease of bone (Sandberg 2003). Other uncommon complications of Paget's disease of bone include spinal stenosis (narrowing of the spinal canal), internal hydrocephalus (raised pressure within the brain), basilar impression (compression at the base of the skull affecting the spinal cord and blood flow to the brain) or cranial nerve deficits and other nerve compression syndromes (Selby 2002).

Description of the intervention

Medical therapy is based on drugs that inhibit the increased osteoclastic bone resorption that characterises Paget's disease of bone. Bisphosphonates are considered to be the treatment of choice for people with Paget's disease of bone because they are highly effective in suppressing elevated bone turnover. The principal indication for anti-resorptive therapy is localised bone pain thought to be caused by increased metabolic activity (Selby 2002).

How the intervention might work

Bisphosphonates share a common phosphorous-carbonphosphorous core to which various chemical side chains are attached. These side chains have a profound effect on the antiresorptive potency of bisphosphonates and on the mechanism by which osteoclast inhibition occurs. Non-aminobisphosphonates, such as etidronate, clodronate or tiludronate, are relatively weak anti-resorptive agents; nitrogen-containing bisphosphonates (aminobisphosphonates) are much more powerful.

Bisphosphonates selectively bind to mineral surfaces in bone. During the process of bone resorption, bisphosphonates are internalised by osteoclasts and interfere with osteoclast survival and bone resorptive function. Non-aminobisphosphonates are metabolically incorporated into non-

hydrolysable analogues of adenosine triphosphate, which interfere with adenosine triphosphate-dependent intracellular pathways. These compounds inhibit formation of adenosine triphosphate in the osteoclast, thereby depleting intracellular energy stores and promoting apoptosis (programmed cell death) (Frith 2001). Aminobisphosphonates such as alendronate, neridronate, pamidronate, olpadronate, ibandronate, risedronate, or zoledronate, are much more potent than non-aminobisphosphonates and act by inhibiting the enzyme farnesyl pyrophosphate synthase. Aminobisphosphonatemediated inhibition of this enzyme disrupts signalling pathways in osteoclasts, leading to failure of their resorptive function and cell death.

Aminobisphosphonates have greater inhibitory effects on bone turnover in Paget's disease of bone than non-aminobisphosphonates and offer the prospect of reducing bone turnover to normal levels in a greater proportion of people than is possible with non-aminobisphosphonates (Miller 1999; Siris 1996). Bone biopsy studies have shown that aminobisphosphonates therapy can restore the architecture of newly formed bone to normal (Siris 1996b). This raises the possibility that the more potent bisphosphonates, by giving greater inhibitor of bone turnover, may be able to prevent long-term complications of the disease such as progression of deafness, bone deformity, fractures and progression of osteoarthritis.

Why it is important to do this review

Many experts believe that bisphosphonate therapy should be administered with the aim of normalising bone turnover in the hope this will arrest disease progression and prevent the development of some complications such as facial deformity, deafness when the skull base is affected, and spinal cord dysfunction in people with spinal Paget's disease of bone (Selby 2002). However, there are insufficient data to determine whether maintaining alkaline phosphatase levels within the normal range reduces the risk of complications. There is no evidence that people who are asymptomatic benefit from anti-resorptive therapy (Langston 2010).

This review aimed to gather published evidence to inform us if bisphosphonate therapy improves clinical outcomes or prevents complications, apart from the known effect, over the biochemical markers of bone turnover.

OBJECTIVES

To assess the benefits and harms of bisphosphonates for adult patients with Paget's disease of bone.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised controlled trials (RCTs) or controlled clinical trials (CCTs) comparing bisphosphonate versus placebo or other active treatment for Paget's disease of bone in adults, including those that compared regimens of bisphosphonates aimed to normalise biochemical markers of bone turnover with those that did not.



Types of participants

Participants aged 18 years and over with Paget's disease of bone confirmed by plain radiographs or isotope bone scintigraphy (Selby 2002).

Types of interventions

The experimental intervention was defined as the use of bisphosphonates including non-aminobisphosphonates (etidronate, clodronate or tiludronate) or aminobisphosphonates (alendronate, neridronate, pamidronate, olpadronate, ibandronate, risedronate or zoledronate).

The comparators were defined as placebo or other interventions including calcitonin, comparisons between non-aminobisphosphonates and aminobisphosphonates; comparisons between different aminobisphosphonates, or comparisons among different treatment strategies using bisphosphonates.

We compared:

- · bisphosphonates versus placebo;
- bisphosphonates versus calcitonin;
- bisphosphonates versus bisphosphonates:
 - o non-aminobisphosphonates;
 - o aminobisphosphonates and non-aminobisphosphonates;
 - o different aminobisphosphonates;
- bisphosphonates regimens that aimed to normalise elevated bone turnover with those that did not (intensive versus nonintensive treatment); and
- bisphosphonates versus bisphosphonates plus calcitonin.

We considered calcium, vitamin D supplementation and analgesics as co-interventions if use was equally available to all treatment groups.

The planned analysis according time points (3 or 6 months from the start of treatment; 1, 2, 3, 4 or more years from the start of treatment; and at the end of the trial) were not performed because nearly all included trials had only six months follow-up.

Types of outcome measures

Major outcomes

We included assessment of the following patient-oriented evidence.

- Change in pain:
 - we included studies reporting any of the following tools for measuring pain: visual analogue scales (VAS), nominal scales or pain domains in generic quality of life measures (e.g. 'bodily pain' in the Short-Form Health Survey (SF-36));
 - we included only evaluations of pain rated by the participant and excluded physician-rated evaluations;
 - we measured change in pain as a continuous variable whenever possible. Whenever pain was assessed as the number of participants with improved bone pain from baseline, we considered the following categories:
 - complete reduction of pain (reduction from baseline is 100%);
 - complete/partial reduction of pain (reduction from baseline ≥ 50%, up to and including complete reduction);

- any reduction in pain.
- Number of participants experiencing radiologically-confirmed clinical fractures. Pathological fractures are uncommon (5.7%) and need long follow-up to be assessed adequately (Tan 2014).
 We considered follow-up periods longer than one year to properly assess this outcome.
- Number of participants who underwent orthopaedic surgery.
- Change in quality of life:
 - we included studies reporting use of tools for measuring generic quality of life including the Medical Outcomes Study (MOS), SF-36, EuroQoL five dimensions questionnaire (EQ-5D) and tools for measuring arthritis-specific quality of life including the arthritis-specific version of the SF-36, and Stanford Health Assessment Questionnaire (HAQ) disability
 - we measured change in quality of life as a continuous variable whenever possible. Whenever quality of life was assessed as the number of participants with improved quality of life from baseline, we considered any improvement in quality of life.
- Change in hearing thresholds or degree of deafness:
 - we included studies reporting audiometric assessment and hearing threshold examinations;
 - we measured change in hearing thresholds or degree of deafness measured as a continuous variable whenever possible;
 - we also considered the number of participants who received hearing aids as an assessment of degree of deafness.
- Number of participants experiencing adverse events related to
 use of bisphosphonates. We considered the following as serious
 adverse events: symptomatic hypocalcaemia, oesophagitis,
 oesophageal cancer, osteonecrosis of the jaw, osteonecrosis
 of the external auditory canal, uveitis, arrhythmias, atypical
 fracture and renal failure. We considered influenza-like
 symptoms as a mild adverse events. Influenza-like symptoms
 include myalgia, pyrexia, nausea, diarrhoea, dyspepsia,
 abdominal pain, headache, bone pain and fatigue.
- Number of participants who withdrew due to adverse events.

Minor outcomes

For patient-oriented evidence, we considered numbers of participants who relapsed due to recurrence of bone pain. For disease-oriented evidence, we included:

- 1. mean percentage change from baseline in serum total alkaline phosphatase activity. We also recorded the number of participants who achieved normalised alkaline phosphatase levels; and
- 2. number of participants who relapsed due to recurrence of increased alkaline phosphatase level.

We did not consider data on radiographic changes or microscopic structure changes as outcomes following bisphosphonate therapy.

Search methods for identification of studies

Electronic searches

We searched:

1. MEDLINE (1946 to 3 March 2017) (Appendix 1);



- 2. Embase (1980 to 3 March 2017) (Appendix 2);
- Cochrane Central Register of Controlled Trials (CENTRAL) (all issues to 3 March 2017) (Appendix 3);
- 4. ISI Web of Knowledge (all years to 8 March 2017) (Appendix 4).

We used the 'Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity-maximising version (2008 revision); Ovid format' for identifying randomised trials as proposed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). For Embase, we used a combination of the search filters for identifying randomised trials listed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We set no year, language or country of publication restrictions.

Searching other resources

We screened the reference lists of all included articles to identify additional eligible studies. We focused on systematic reviews and meta-analyses and reference lists from identified RCTs to identify further relevant studies.

We searched the ISRCTN registry on metaRegister of Controlled Trials (mRCT) and ClinicalTrials.gov to identify ongoing trials (Date of last search: 20 February 2017). The mRCT includes the International Clinical Trials Registry Platform (ICTRP) of the World Health Organization (WHO) and the United Kingdom Clinical Trials Gateway (UKCTG).

We also handsearched for abstracts presented from 2010 to 2016 at scientific meetings from the following societies and included those with sufficient information in the body of the abstract:

- American Society for Bone and Mineral Research;
- International Bone and Mineral Society;
- International Osteoporosis Foundation/European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis; and
- European Calcified Tissue Society.

accordance with Cochrane Musculoskeletal recommendations we searched the websites of the regulatory agencies to broaden our search for specific and rare adverse events: USA Food and Drug Administration MedWatch (FDA), European Medicines Agency (EMA), and the UK Medicines and Healthcare products Regulatory Agency pharmacovigilance and drug safety updates (MHRA) using the terms 'Paget's' and 'bisphosphonate' (Date of last search for the regulatory agencies websites: 22 February 2017). We also searched in the Australian Adverse Drug Reactions Bulletin (AADRB) [published from 1995 to 2009 and available at https://www.tga.gov.au/publication/ australian-adverse-drug-reactions-bulletin] and in the Australian Therapeutic Goods Administration website (Date of last search: 22 February 2017).

Data collection and analysis

Selection of studies

Three review authors (AT, LCG, JdPM) independently assessed results from searches of electronic databases to identify potentially-relevant articles based on title or title and abstract. We retrieved the full manuscripts of potentially-relevant articles for further assessment. Review authors (AT and LCG; JdPM and LCG)

screened the selected articles independently against the inclusion criteria. We resolved any differences of opinion during the selection process by discussion and consensus, or by consulting a third review author (SHR) if needed.

Data extraction and management

Two review authors (AT, LCG) extracted relevant data using a predefined data collection form designed according to guidelines from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). One review author (AT) who was involved in data extraction was also an author of a primary study (PRISM-EZ trial Tan 2017). Because authors of primary studies should not extract data from their own studies, we recruited an additional reviewer (JdPM) who extracted trial data from Tan 2017.

We extracted the following data:

- Study identification: author, year of publication, journal.
- Characteristics of the trial: study design, calculation of sample size before the study, use of intention-to-treat analysis, setting or location, number of centres, country, period of study, followup period, outcomes, methods of randomisation, allocation concealment and blinding.
- Study inclusion and exclusion criteria.
- Participants' characteristics: age, gender, presence of monostotic disease, whether treated previously for Paget's disease of bone, symptomatic participants, numbers who were randomised and excluded (post-randomisation), reasons for exclusion, participants assessed, withdrawals and reasons for withdrawals.
- Characteristics of intervention: drug analysed, comparator, dosage, duration of treatment, co-interventions.
- · Risk of bias assessment.
- Outcome data (Types of outcome measures).
- · Source of funding.
- · Conflicts of interest.

We created a specific database to carry out the data extraction process. We resolved any differences of opinion during the data extraction process by discussion and consensus or discussion with a third author (SHR).

When data were neither available from the original manuscript, nor following requests to authors, data were directly extracted from figures in the manuscript using a vector graphics editor.

Assessment of risk of bias in included studies

Two authors (AT, LCG) assessed the risk of bias in included studies independently as recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We assessed the following methodological domains.

- Adequate sequence generation (checking for possible selection bias): were methods used to generate the allocation sequence for each included study reported in sufficient detail to enable assessment of whether groups were comparable.
- Adequate measures to conceal allocation (checking for possible selection bias): were methods used to conceal the allocation sequence for each included study reported in sufficient detail and we could determine whether intervention allocation could



have been foreseen in advance or during recruitment, or changed after assignment.

- Blinding of study participants and study researchers (checking for possible performance bias): were methods used to blind participants and study researchers from knowledge of which intervention a participant received for each included study reported.
- Blinding of outcome assessors (checking for possible detection bias): were methods used to blind outcome assessors from knowledge of which intervention a participant received for each included study reported.
- Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations): the completeness of data including attrition and exclusions from the analysis was assessed. We stated whether attrition and exclusions were reported; the numbers included in the analysis at each stage (compared with the total randomised participants); reasons for attrition or exclusion where reported; and whether missing data were balanced across groups or were related to outcomes. We did not consider that a high attrition rate was a source of bias if an intention-to-treat (ITT) analysis was performed. Where sufficient information was reported or could be supplied by the study authors, we re-included missing data in the analyses which we undertook.
- Selective outcome reporting (checking for possible reporting bias): differences, if any, between the planned protocol analysis data and the reported data for each included study, to look for unreported findings.
- Other potential threats to validity (considering external validity, e.g. relevant use of co-intervention).

Each of these criteria were explicitly judged as 'low risk, 'high risk or 'unclear risk' of bias.

We assessed the likely overall magnitude of the bias for each included study and whether it was likely to impact on the findings. We elaborated a summary assessment of the risk of bias for each outcome. In order to assess the risk of bias within a study, we evaluated adequate sequence generation, allocation sequence concealment and incomplete outcome data as key domains for all the outcomes. We evaluated blinding of study participants and study researchers as key domains for change in pain, reporting of adverse events and change in quality of life. We did not consider blinding as a key domain for assessing the risk of bias for fractures, receiving orthopaedic surgery, change in hearing thresholds and total alkaline phosphate activity. Other potential threats to validity such as the use of analgesics as co-interventions were considered a key domain for changes in pain and quality of life.

For each outcome, we considered low risk of bias to be present across studies when most information was from studies assessed at low risk. We considered high risk of bias across studies when the proportion of information from studies at high risk of bias was sufficient to affect the interpretation of results. Lastly, we considered unclear risk of bias when most information was from studies at low or unclear risk of bias.

We resolved any difference of opinion during the assessment of risk of bias process by discussion and achieving consensus. For disagreements not resolved by consensus, we consulted a third review author (SHR).

Measures of treatment effect

For dichotomous outcomes, we estimated the effect of treatment across trials using the risk ratios (RRs) with the corresponding 95% confidence intervals (Cls). For significant outcomes, we computed the number needed to treat to benefit (NNTB) one participant or the number needed to treat to harm (NNTH) one participant as the inverse of the pooled risk differences (RDs).

Our dichotomous outcomes were numbers of participants who:

- · experienced adverse events;
- experienced radiologically-confirmed clinical fractures;
- received orthopaedic surgery;
- withdrew due to adverse events;
- · relapsed due to recurrence of bone pain; and
- relapsed due to recurrence of increased serum alkaline phosphatase level.

Where continuous scales of measurement were used to assess the effects of treatment, we used the mean difference (MD) with the corresponding 95% CI. If different scales were used to measure an outcome, we calculate the standardised mean difference (SMD).

Our continuous outcomes were:

- · change in pain;
- · change in quality of life;
- change in hearing thresholds; and
- mean percentage change from baseline in serum total alkaline phosphatase activity.

Unit of analysis issues

The unit of analysis was individual people undergoing treatment for Paget's disease of bone. We included only RCTs and CCTs, and we were not expecting studies with non-standard designs such as cross-over trials.

For studies with more than one intervention group, such as different doses of the same bisphosphonate, we combined data from the experimental intervention groups to create a single pairwise comparison versus the control group.

Dealing with missing data

When outcome data were not available from trials, we contacted the primary investigators of the eligible trials. We contacted study authors using email addresses published in the studies. When there was no response from the study author, we analysed the available data only, ignoring missing data, because we assumed that data were missing at random.

We performed a sensitivity analysis according to the missing data to assess the robustness of our assumption that data were missing data at random (Sensitivity analysis). We addressed the potential impact of missing data on findings in the Discussion.

Assessment of heterogeneity

We computed global estimates for each variable effect by metaanalysing study single effect measures (RR for dichotomous variables and MD or SMD for continuous variables) using Review Manager 2014. Before calculating estimates of effect, we assessed



the presence and degree of heterogeneity using the I² statistic to describe the percentage of variability in effect estimates due to heterogeneity rather than chance. We categorised I² values greater than 75% as considerable heterogeneity (Higgins 2011).

We undertook a narrative review of potential heterogeneity according to variability in populations, interventions, outcomes and settings.

Assessment of reporting biases

Because we anticipated inclusion of several studies with small sample sizes, we assessed the likely impact on our findings of small-study effects (tendency for estimates of the intervention effect to be more beneficial in smaller studies) by using inverted funnel plot techniques. We planned to construct funnel plots when there were at least 10 included studies in comparisons. However, none of the comparisons included 10 studies, so funnel plots could not be constructed. We provided a narrative summary of potential small-study effect in the Discussion.

Data synthesis

We used Review Manager 2014 for data synthesis. Quantitative synthesis was planned if more than one eligible study was identified. Where appropriate, we calculated a pooled estimate of treatment effect across similar studies for each pre-specified outcome. We estimated overall effect by meta-analysis using a random-effects model. We did not conduct meta-analysis if there was considerable heterogeneity (I² > 75%) (Higgins 2011). We

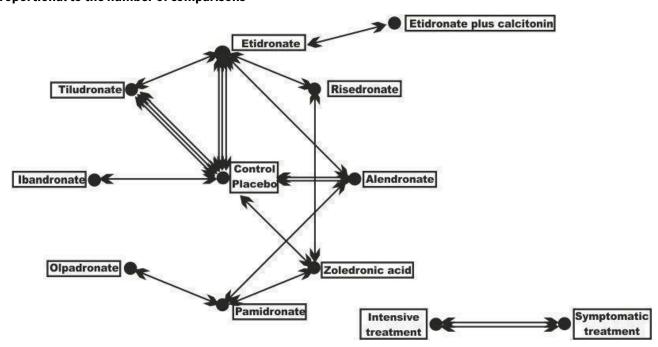
calculated RRs and 95% CIs for dichotomous data. We calculated the number needed to treat to provide an indication for each dichotomous outcome, reflecting the number of participants required to obtain a beneficial outcome with the intervention. For continuous data measured on the same scale, we calculated MDs. When different scales were used, we calculated SMDs. When possible, we analysed data using an intention-to-treat (ITT) model.

We used the mean and standard deviation when available. If only median and interquartile ranges were reported, we followed guidance from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), where the median was used as the mean and the standard deviation was set as 1.35. If no standard deviation was given at the end of the study, we used the baseline standard deviation at the end as well.

We undertook a narrative review of eligible studies where statistical synthesis of data from more than one study was not possible or appropriate.

Although we included different bisphosphonates whose comparisons against placebo which together create a network (Figure 1), we did not perform a network meta-analysis. The reason for this was that tor the major outcome of change in pain, heterogeneity within studies in the definition of 'change in pain' did not allow us to conduct a meaningful network meta-analysis. For the other major outcomes, such as fractures or orthopaedic surgery, there were few comparisons between bisphosphonates.

Figure 1. Geometry of the network of randomised trials of bisphosphonates for Paget's disease of bone. The nodes of the network represent the treatments compared. The links reflect comparisons and the number of links is proportional to the number of comparisons



Subgroup analysis and investigation of heterogeneity

Neither of the planned subgroup analyses: symptomatic bone pain versus those who were asymptomatic; and biochemically active (raised alkaline phosphatase) Paget's disease of bone versus non-biochemically active Paget's disease of bone (normal alkaline phosphatase) were possible.



Sensitivity analysis

We planned to perform the following sensitivity analyses:

- To determine the robustness of pooled effect estimate in terms of risk of bias by including or excluding studies with high or unclear risk of bias from the comparative analysis.
- 2. To determine the robustness of the pooled effect estimate in terms of missing data by including or excluding studies with high levels of missing data, more than 20% of missing data for the overall trial population, or for any of the trial arms from the comparative analysis.
- 3. To determine the robustness of the pooled effect estimate in terms of withdrawals by performing either worst-case scenario sensitivity analysis (all withdrawal data treated as negative events) or the same-as-control scenario sensitivity analysis, where the rate of negative events in the withdrawal data were the same as in the control group.

'Summary of findings' table

We evaluated the quality of the evidence using the GRADE approach and developed 'Summary of findings' tables (Guyatt 2008). These tables have the following three elements:

- the outcomes most relevant to people (critical and important outcomes according to GRADE);
- 2. a summary measure for the quality of the evidence (confidence in estimate of a treatment effect); and
- 3. a summary estimate for the RR and absolute effect for the interventions of interest.

The seven important outcomes that we considered for the 'Summary of findings' tables were numbers of participants:

- 1. with change in bone pain;
- who experienced severe side effects related to use of aminobisphosphonates;
- 3. who experienced fractures;
- 4. who needed orthopaedic surgery;
- 5. with change in quality of life measures including bodily pain;
- 6. with change in hearing thresholds; and
- 7. who withdrew due to adverse events.

We used GRADEpro GDT 2015 to create 'Summary of findings' tables.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

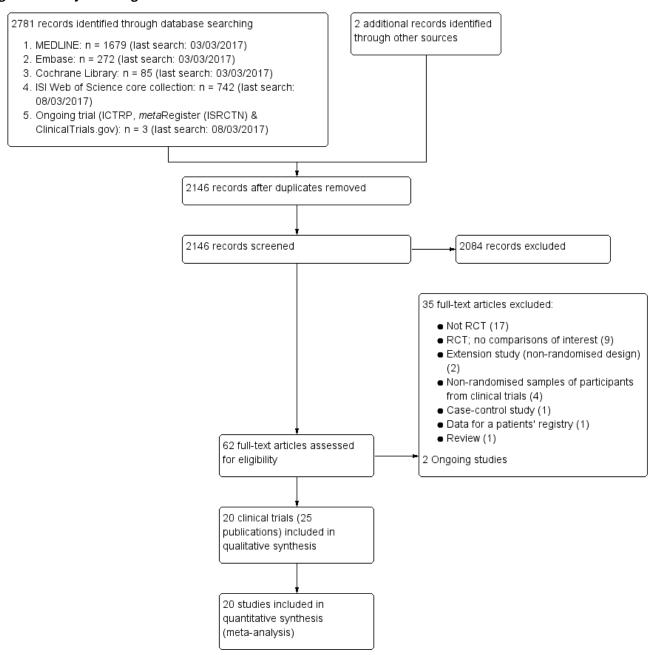
Results of the search

Quantity of research available

The literature search identified 2781 potentially-relevant records (Figure 2). Of these, 63 full text articles were retrieved for further assessment for inclusion.



Figure 2. Study flow diagram



Inconsistent or missing information

We attempted to contact most study authors to request additional information or to clarify inconsistencies. Appendix 5 presents the status of requests to study authors for further information or clarification.

Included studies

We included 20 trials (25 references) that met our selection criteria. Sixteen individual studies with a single reference, (Altman 1973; Canfield 1977; Fraser 1997; Langston 2010; McClung 1995; Merlotti 2007; Miller 1999; O'Doherty 1992; O'Donoghue 1987; Ralston 1987; Reginster 1992; Reid 1996; Roux 1995; Siris 1996; Tan 2017 Walsh 2004) 3 studies with two references (Barreira 2009; Buckler 1999; Reid 2004) and 1 study with 3 references (Reid 2005).

The trials involved a total of 3168 participants. All included studies were published in English language. One trial was published only as an abstract (Barreira 2009).

Characteristics of included studies

See Characteristics of included studies.

We included 10 studies (801 participants) that compared bisphosphonates and placebo (Altman 1973; Buckler 1999; Canfield 1977; Fraser 1997; McClung 1995; O'Doherty 1992; Ralston 1987; Reginster 1992; Reid 1996; Reid 2004). One study (234 participants) compared two non-aminobisphosphonates (Roux 1995). Two studies (212 participants) compared non-aminobisphosphonates and aminobisphosphonates (Miller 1999; Siris 1996). Four studies



(546 participants) compared two aminobisphosphonates (Barreira 2009; Merlotti 2007; Reid 2005; Walsh 2004). One study (44 participants) compared etidronate and etidronate plus calcitonin (O'Donoghue 1987). One study compared intensive treatment (aimed at normalising alkaline phosphatase) and symptomatic treatment (aimed at treating bone pain) (PRISM trial Langston 2010; 1331 participants). An extension of Langston 2010 (PRISM-EZ trial Tan 2017; 502 participants) investigated the effects of these treatment strategies for up to 7.3 years. PRISM-EZ is described separately in Characteristics of included studies because although the study was defined by the authors as an extension study, it was an interventional extension study (rather than an observational extension study) where the researchers continued intensive or symptomatic treatment as in the core study. In this case, zoledronate was used as the treatment of first choice in the extension as compared with risedronate in the PRISM study.

None of the included studies used a run in period.

The different comparisons investigated by the studies are represented in Figure 1. The sample sizes ranged from 15 to 1331 participants; 11 studies included fewer than 100 participants. Only Langston 2010 included more than 1000 participants. Sample size calculations were performed in advance of the study for only five trials (Fraser 1997; Langston 2010; Reid 2005; Roux 1995; Walsh 2004).

The study populations were reasonably homogeneous in terms of participants' age and gender. A summary of the principal characteristics of trial samples is provided in Table 1. Participants' mean age ranged from 66 years to 74 years, the percentage of males ranged from 51% to 74%, and the percentage of symptomatic participants ranged from 63% to 100%. Nearly all participants had raised serum total alkaline phosphatase, but one study (Langston 2010) included participants with normal alkaline phosphatase at baseline (707/1324; 53%). Alkaline phosphatase was normal at baseline in participants who were enrolled into an extension of the Langston 2010 study (Tan 2017) (355/502; 71%). The percentage of symptomatic participants (defined as those with pain due to Pagetic bone lesions) ranged from 66% to 100%; this information was not recorded for about half the included studies.

For all but one study (Langston 2010) and its extension (Tan 2017) the primary outcome was change in serum total alkaline phosphatase activity. Most studies did not include the major outcomes (bone fracture, need for orthopaedic surgery, change in quality of life or hearing thresholds) of primary interest in this review.

Thirteen studies had six months of follow-up; two studies (Buckler 1999; Ralston 1987) had only three months follow-up. Another three

studies (Miller 1999; O'Donoghue 1987; Walsh 2004) had 12 months of follow up. The authors of the Reid 2004 study published long-term follow-up data (nearly 10 years), but analysis of these data was limited due to change in the initial randomisation allocation (see Characteristics of included studies). The PRISM study (intensive versus symptomatic treatment, Langston 2010) was an event-driven trial with an average of three years follow-up (range 2 years to 5 years). In PRISM-EZ, Tan 2017 followed up participants for an additional three years (total of 7.3 years follow-up). An extension to the comparison of zoledronate and risedronate followed up participants for up to 6.5 years but these were a select group who had normalised alkaline phosphatase during the core study (Reid 2005).

Study funding sources

Eleven included studies were funded by drug manufacturers. Of these, four were co-funded by government agencies or charities. Although a further three studies reported funding by government agencies or charities, the study drugs were supplied by drug manufacturers. One article was funded only by government agencies. Funding sources were not mentioned or unclear in five studies.

Excluded studies

We excluded 35 studies: 17 were non-randomised clinical trials (Adami 1994; Altman 1985; Arlot 1981; Atkins 1987; Cundy 2016; Dewis 1985; Filipponi 1994; Gallacher 1991; Grauer 1999; Gutteridge 1996; Hosking 1976; Khairi 1977; Mazeries 1996; O'Doherty 1995; Pepersack 1994; Russell 1974; Stone 1990); nine were RCTs that lacked comparisons of interest for this review (Adami 2002; Buckler 1998; Delmas 1982; Hooper 2009; Khan 1997; Merlotti 2011; Reginster 1988; Reginster 1993; Vega 1994); two were non-randomised extension studies (Khairi 1974; Siris 1980); four were non-randomised samples of participants from clinical trials (Devogelaer 1997; Garnero 1998; Garnero 2001; Goldman 1975); one was a case control study (Donáth 2004); one provided data for a patient registry (Devogelaer 2014); and one was a review (Lombardi 1999).

Ongoing studies

We identified two ongoing studies (NCT02106455; ISRCTN11616770). These studies will be assessed for inclusion in a future update of this review.

Risk of bias in included studies

For details on the risk of bias of included studies see Characteristics of included studies. For an overview of review authors' judgements about each risk of bias item for individual and across all studies see Figure 3 and Figure 4.



Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

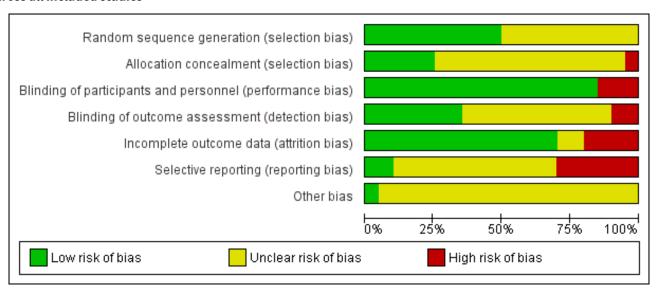
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Altman 1973	?	?	•	?	•	?	?
Barreira 2009	?	?	•	?	?	?	?
Buckler 1999	?	?	•	?	•	?	?
Canfield 1977	?	?	•	?	?	•	?
Fraser 1997	•	?	•	?	•	?	?
Langston 2010	•	•	•	•	•	•	•
McClung 1995	?	?	•	?	•	?	?
Merlotti 2007	•	?	•	•	•	?	?
Miller 1999	•	•	•	?	•	?	?
O'Doherty 1992	?	?	•	?	•	•	?
O'Donoghue 1987	?	?	•	?	•	•	?
Ralston 1987	•	•	•	•	•		?
Reginster 1992	•	?	•	?	•	?	?
Reid 1996	•	?	•	•	•	?	?
Reid 2004	•	?	•	•	•	•	?
Reid 2005	•	•	•	•	•	•	?
Roux 1995	?	?	•	?	•	?	?
Siris 1996	?	?	•	•	•	?	?
Tan 2017	?	•	•	•	•	•	?
Walsh 2004	•	•			•	?	?



Figure 3. (Continued)



Figure 4. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



Allocation

The generation of the random sequence for allocation was considered to be adequate in 10 studies (low risk of bias; Fraser 1997; Langston 2010; Merlotti 2007; Miller 1999; Ralston 1987; Reginster 1992; Reid 1996; Reid 2004; Reid 2005; Walsh 2004). Risk of bias was judged as unclear in the remainder (Altman 1973; Barreira 2009; Buckler 1999; Canfield 1977; McClung 1995; O'Doherty 1992; O'Donoghue 1987; Roux 1995; Siris 1996; Tan 2017). Allocation concealment was considered adequate in only six studies (low risk of bias; Langston 2010; Miller 1999; Ralston 1987; Reid 2005; Tan 2017; Walsh 2004) and judged as unclear in the remainder (Altman 1973; Barreira 2009; Buckler 1999; Canfield 1977; Fraser 1997; McClung 1995; Merlotti 2007; O'Doherty 1992; O'Donoghue 1987; Reginster 1992; Reid 1996; Reid 2004; Roux 1995; Siris 1996). No included studies were considered to be at high risk of bias for this domain.

Blinding

Fifteen studies were double-blinded (Altman 1973; Barreira 2009; Buckler 1999; Canfield 1977; Fraser 1997; McClung 1995; Miller 1999; O'Doherty 1992; Ralston 1987; Reginster 1992; Reid 1996; Reid 2004; Reid 2005; Roux 1995; Siris 1996) and their risk of bias was judged as low. Five studies were open-label (Langston 2010; Merlotti 2007; O'Donoghue 1987; Walsh 2004; Tan 2017). The performance risk of bias was considered as high for subjective outcomes as pain or quality of life for all of them. The performance risk of bias was considered low for two of the open-label studies (Langston 2010; Tan 2017) because the main outcome (radiologically-confirmed clinical fracture) was not likely to be influenced by lack of blinding. The outcome assessment was not blinded in another study (Miller 1999).

Incomplete outcome data

The risk of bias due to incomplete outcome data was considered to be low in fourteen studies (Buckler 1999; Fraser 1997; Langston 2010; McClung 1995; Merlotti 2007; O'Donoghue 1987; Ralston 1987; Reid 1996; Reid 2004; Reid 2005; Roux 1995; Siris 1996; Tan 2017; Walsh 2004). Four studies were judged at high risk of bias because of significant missing data (Reginster 1992), differences between the follow-up of the different control and experimental group (O'Doherty 1992) or data inconsistencies in the manuscript (Altman 1973; Miller 1999). Risk of bias was unclear in two studies (Barreira 2009; Canfield 1977).

Selective reporting

Selective reporting bias was difficult to evaluate because study protocols were available for only four studies (Langston 2010; Reid 2004; Reid 2005; Tan 2017). Five studies were judged at high risk of bias due to selective reporting because data on adverse events were not clearly detailed (Canfield 1977); there were no data on adverse events (O'Doherty 1992; O'Donoghue 1987); or because adverse events were not systematically recorded in the trials (Ralston 1987; Reid 2004). Two studies were judged at high risk of bias due to selective reporting because details of assessment for some outcomes included in the results sections (pain, fractures) were not detailed in methods sections (O'Doherty 1992; O'Donoghue 1987). Conversely in another study, some outcomes mentioned in the methods section (pain, fractures) were not provided in the results section (high risk of bias) (Reid 2005). Risk of bias was judged as unclear for the remainder of the included studies. No studies were assessed as at low risk of bias.



Other potential sources of bias

Langston 2010 and its extension study (Tan 2017) were assessed with potential risk of bias for subjective outcomes due to their open-label designs. In these studies, the attending clinician was able to choose which bisphosphonate should be prescribed, resulting in heterogeneity between groups in numbers and types of bisphosphonate used. However, adherence to the randomised treatment strategy was confirmed by the fact that alkaline phosphatase values were significantly lower in the intensive group as compared with the symptomatic group for both trials.

Effects of interventions

See: Summary of findings for the main comparison Bisphosphonates versus placebo for Paget's disease of bone; Summary of findings 2 Zoledronate versus pamidronate or risedronate for Paget's disease of bone

Summary of findings for the main comparison presents findings for bisphosphonates versus placebo; Summary of findings 2 presents findings for bisphosphonates versus bisphosphonates.

Major outcomes

Effect on bone pain

Bone pain was not considered as a primary outcome by any of the included studies, although 15 reported change in bone pain as secondary outcomes. Eight studies assessed pain on visual analogue scales (VAS; range 0 to 10) (Fraser 1997; McClung 1995; Ralston 1987; Reid 2005; Reginster 1992; Roux 1995; Siris 1996; Walsh 2004).

Studies classified pain using different categories. Merlotti 2007 classified pain as: never in pain, pain disappeared, pain decreased or no change in pain. Altman 1973 applied three categories: mild pain, moderate pain or severe pain. Langston 2010 and Tan 2017 categorised pain according to whether or not participants had bone pain. Three studies measured bone pain using the SF-36 bodily pain domain (Langston 2010; Miller 1999; Tan 2017). Three studies did not report the tool used for pain assessment (Canfield 1977; O'Doherty 1992; O'Donoghue 1987). Analyses were based on any bone pain reduction and disappearance of bone pain to assess changes in bone pain.

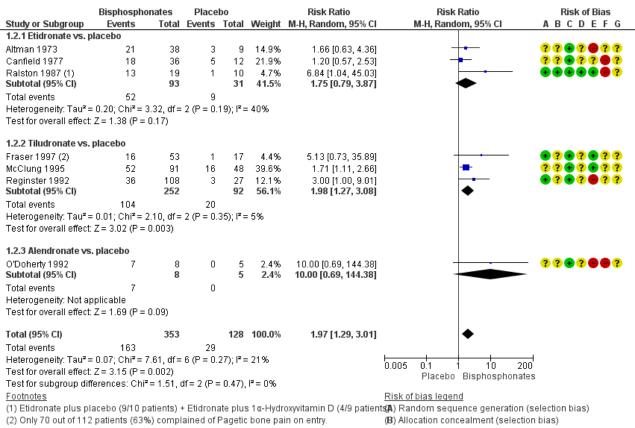
Bisphosphonates versus placebo

Two studies (Fraser 1997; Reginster 1992) compared tiludronate versus placebo. The overall effect on disappearance of pain (defined as complete reduction of pain) favoured bisphosphonates (RR 3.42, 95% CI 1.31 to 8.90; NNTB 5, 95% CI 1 to 35; absolute risk of event 31% versus 9%; Analysis 1.1).

When effect on bone pain was defined as any reduction in pain, the overall effect favoured bisphosphonates (RR 1.97, 95% CI 1.29 to 3.01; RD 0.33, 95% CI 0.18 to 0.49; NNTB 4, 95% CI 2 to 13; absolute risk of event 45% versus 23%). Results were consistent across the trials; all studies included in the meta-analysis showed a favourable effect (RR range from 1.20 to 10.00; Analysis 1.2; Figure 5).



Figure 5. Forest plot of comparison: 1 Bisphosphonates versus placebo, outcome: 1.2 Number of participants with change in bone pain



- (C) Blinding of participants and personnel (performance...
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Results for effect on bone pain (defined as pain disappearance or any reduction in pain) were consistent.

When change in bone pain was assessed as a continuous variable, data were heterogeneous. Ralston 1987 used a linear analogue scale and reported that etidronate was better than placebo. McClung 1995 measured bone pain using the Huskisson pain severity score instrument and reported no detectable difference between bisphosphonates and placebo in average pain scores. Reid 1996 used the Brief Pain Inventory and reported detectable differences favouring placebo when compared with alendronate (placebo -1.4 \pm 0.3 versus alendronate -0.7 \pm 0.5, difference favoured placebo -0.7, 95% CI 0.41 to 0.99).

Bisphosphonates versus active comparator

There was insufficient evidence to confirm or exclude an important difference (MD -2.60, 95% CI -5.03 to -0.17) in pain scores (0 to 100) when etidronate was compared with risedronate (measured on SF-36) (Miller 1999) or alendronate (measured on the Brief Pain Inventory slightly modified for use in Paget's disease of bone) (Siris 1996) (Analysis 2.1). Pain assessment as a dichotomous variable was not made for this comparison.

Zoledronate showed a statistically- and clinically-significantly greater effect on partial or total pain relief (binary outcome) when compared with the aminobisphosphonates pamidronate (RR 1.30, 95% CI 1.10 to 1.53; Merlotti 2007; 89 participants; NNTB 4, 95% CI 3 to 13; absolute risk of event 97% versus 75%) and risedronate (RR 1.36 95% CI 1.06 to 1.74; Reid 2005; 347 participants; NNTB 8, 95% CI 4 to 45, absolute risk of event 50% versus 37%; Analysis 3.1). However, there was no evidence of an effect when bone pain was assessed as a continuous outcome (scores) between zoledronate and risedronate (Reid 2005) (Table 2). Results were inconclusive between treatments for Pagetic bone pain, Pagetic joint pain, or non-Pagetic pain when alendronate was compared with pamidronate (Walsh 2004). Scores for bone pain, joint pain and non-Pagetic pain all fell significantly (P < 0.05) from baseline during the first 12 months of the study in both treatment groups (Walsh 2004). Between-group numerical results were not provided in Walsh 2004.

Adding calcitonin to etidronate (O'Donoghue 1987) reduced the proportion of participants experiencing partial or total pain relief as compared with etidronate alone (RR 0.73, 95% CI 0.43 to 1.25; Table 3).



Intensive versus symptomatic treatment

In Langston 2010 and the extension study Tan 2017, there was insufficient evidence to confirm or exclude a important difference for partial or total pain relief or change in bodily pain measured using the SF-36 between symptomatic and intensive treatment groups (improvement in bone pain RR 0.86, 95% CI 0.67 to 1.10) (Table 4).

Effect on fractures

Radiologically-confirmed clinical fracture was the primary outcome in Langston 2010 and its extension study Tan 2017, and a secondary outcome in six studies (Altman 1973; Canfield 1977; Fraser 1997; Reid 2005; Reginster 1992; Roux 1995). The number of new fractures were extremely low in all studies except Langston 2010 and its extension Tan 2017.

Bisphosphonates versus placebo

We could not determine whether the intervention had an important effect on fractures because the sample size was small and the long-term impact on fractures was not assessed. Etidronate (Altman 1973; Canfield 1977) and tiludronate (Fraser 1997; Reginster 1992) were compared to placebo (pooled RR, 0.89 95% CI 0.18 to 4.31; 0 fractures in the placebo group; Analysis 1.3). The mean follow-up period was six months (Altman 1973; Canfield 1977; Fraser 1997; Reginster 1992).

Bisphosphonates versus active comparator

Tiludronate was compared to etidronate (Roux 1995) and zoledronate to risedronate (Reid 2005) with no evidence of a difference between these bisphosphonates (Table 5; Table 2). The results were inconclusive because long-term impact on fractures was not assessed and samples sizes were small.

Intensive versus symptomatic treatment

The Langston 2010 study of intensive bisphosphonate treatment versus symptomatic treatment showed no evidence of an effect in the number of new fractures between treatment approaches (6.7% versus 7.4%, RR 0.94, 95% CI 0.64 to 1.39; Table 4). Follow-up was long enough duration to assess long-term impact on fractures (3 years mean follow-up). In the extension study by Tan 2017, all fractures and fractures in Pagetic bone were more common in the intensive treatment group (8.1% versus 5.2%, RR 1.58, 95% CI 0.80 to 3.11; 1.9% versus 0.9%, RR 2.15, 95% CI 0.42 to 10.96 respectively). However, the confidence intervals were wide. It should be noted that Tan 2017 reported hazard ratio for fractures in the intensive versus symptomatic group when corrected for baseline differences between groups using propensity scoring. This showed a hazard ratio for fracture in the intensive versus symptomatic group of 1.90 (95% CI 0.91 to 3.98).

Effect on need for orthopaedic surgery

The need for orthopaedic surgery was not considered as a primary outcome by any of the included studies; only Langston 2010 and Tan 2017 included this outcome.

Bisphosphonates versus placebo

No included studies addressed need for orthopaedic surgery for bisphosphonates versus placebo.

Bisphosphonates versus active comparator

No included studies addressed need for orthopaedic surgery for comparison between bisphosphonates.

Intensive versus symptomatic treatment

There was no evidence of a difference between intensive and symptomatic treatment; 7.3% of participants in the intensive treatment group and 8.3% participants in the symptomatic treatment group needed orthopaedic surgery (RR 0.88, 95% CI 0.60 to 1.27; Table 4). In Tan 2017, all orthopaedic procedures were more common in intensive group participants (5.6% versus 3.0%, RR 1.84, 95% CI 0.76 to 4.44) as were procedures in Pagetic bone; 2.6% versus 1.7% (RR 1.50, 95% CI 0.45 to 5.07). However, the confidence intervals were wide. It should be noted that Tan 2017 reported hazard ratio for orthopaedic procedures in the intensive versus symptomatic group when corrected for baseline differences between groups using propensity scoring. This showed a hazard ratio for orthopaedic procedures in the intensive versus symptomatic group of 1.81 (95% CI 0.71 to 4.61).

Effect on quality of life

The impact of bisphosphonates on quality of life was included as a secondary outcome by six studies (Langston 2010; Merlotti 2007; Miller 1999; Reid 2005; Tan 2017; Walsh 2004).

Bisphosphonates versus placebo

No studies addressed effects on quality of life for the comparison of bisphosphonates versus placebo.

Bisphosphonates versus active comparator

There was no evidence of an effect on quality of life when zoledronate was compared with risedronate (Reid 2005), although zoledronate showed a marginal improvement at six months, with a mean difference in change on the physical component summary score of 1.30 (95% CI 1.18 to 1.42: Table 2). Furthermore, in the extension study (Reid 2011), participants who attained normal alkaline phosphatase levels following zoledronate maintained lower levels of total SF-36 score when compared with risedronate for a period of up to 54 months (Table 2). For the pain domain of the SF-36, changes from baseline were significant in the zoledronate group at 24 months (7.5 \pm 2.6) and 36 months (5.6 \pm 2.4); whereas no significant changes were observed for the risedronate group at any time point.

General health score on the SF-36 was higher when alendronate was compared to pamidronate according to Walsh 2004. There was no evidence of a difference between treatments in the other seven domains of the SF-36 or in the mental and physical component summary scores. Numeric data were not provided in the study report (Walsh 2004). Merlotti 2007 did not detect a difference when zoledronate was compared to pamidronate. The authors of both Walsh 2004 and Merlotti 2007 reported there were no differences, but numeric data were not provided.

Intensive versus symptomatic treatment

A comparison of intensive and symptomatic treatment did not detect a difference in quality of life between treatment groups (Langston 2010). Mean changes in bodily pain, physical and mental summaries of SF-36 are shown in Table 4. In the extension study to Langston 2010, Tan 2017 reported small differences



between groups at Year 1 (physical component summary scores and arthritis-specific health index) which favoured the intensive treatment group. However, there was no sustained difference in quality of life at Year 2 or Year 3.

Effect on deafness and hearing thresholds

Deafness and hearing thresholds were not considered as a primary outcome by any of the included studies; only Langston 2010 included data on these outcomes.

Bisphosphonates versus placebo

No included studies addressed effects on deafness and hearing thresholds for the comparison of bisphosphonates versus placebo.

Bisphosphonates versus active comparator

No included studies addressed effects on deafness and hearing thresholds for the comparison of bisphosphonates with an active comparator.

Intensive versus symptomatic treatment

A comparison of intensive and symptomatic treatment did not detect a difference between groups in deafness or hearing thresholds. Changes in hearing thresholds were recorded in 26.7% of participants in the intensive treatment group versus 27.4% of participants in the symptomatic group (RR 0.97, 95% CI 0.79 to

1.19). Changes in hearing loss and hearing classification data are provided in Table 4.

Adverse events

Four trials (Canfield 1977; O'Doherty 1992; O'Donoghue 1987; Ralston 1987) did not report on adverse events related to bisphosphonates. Data from other trials on adverse events were heterogeneous; adverse events reporting was not comprehensive. Furthermore, assessment of adverse events severity varied among studies. Adverse events reported in trials comparing bisphosphonates versus placebo (Altman 1973; Buckler 1999; Fraser 1997; McClung 1995; Reginster 1992; Reid 1996), bisphosphonates versus bisphosphonates (Barreira 2009; Merlotti 2007; Miller 1999; Reid 2005; Roux 1995; Siris 1996; Walsh 2004) or intensive versus symptomatic treatment (Langston 2010) are provided in Table 6, Table 7 and Table 8 respectively.

Bisphosphonates versus placebo

When we considered studies of all bisphosphates versus placebo we did not detect a difference in adverse events although the RR was not equal to one (RR 1.32, 95% CI 0.91 to 1.92; Analysis 1.4; Figure 6). When we considered studies of zoledronate we found that this bisphosphonate had a significantly increased risk of adverse events when compared with placebo (RR 2.57, 95% CI 1.21 to 5.44). Gastrointestinal side effects were common for oral bisphosphonates and fatigue or fever for intravenous bisphosphonates (Table 6).



Figure 6. Forest plot of comparison: 1 Bisphosphonates versus placebo, outcome: 1.4 Number of participants who experienced adverse events related to use of bisphosphonates

	Bisphospho	onates	Place	bo		Risk Difference	Risk Difference	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	ABCDEFG
1.4.1 Etidronate vs.	placebo							
Altman 1973 Subtotal (95% CI)	5	38 38	1	9 9	13.2% 13.2 %	0.02 [-0.21, 0.25] 0.02 [-0.21, 0.25]	•	??•?•??
Total events Heterogeneity: Not a			1					
Test for overall effec	t: Z= 0.17 (P=	0.86)						
1.4.2 Zoledronate v	s. placebo							
Buckler 1999	62	141	6	35	19.5%	0.27 [0.12, 0.42]		??•?•??
Subtotal (95% CI)		141		35	19.5%	0.27 [0.12, 0.42]	-	
Total events Heterogeneity: Not a	62 Species blo		6					
Test for overall effec		0.0004)						
	•	0.0004)						
1.4.3 Tiludronate vs	-							
Fraser 1997	65	86	14	26	14.5%	0.22 [0.01, 0.43]		•?•?•??
McClung 1995	79	91	43	48	23.0%	-0.03 [-0.14, 0.08]	—	??•?•?
Reginster 1992 Subtotal (95% Cl)	71	117 294	17	32 106	15.8% 53.4 %	0.08 [-0.12, 0.27] 0.07 [-0.08, 0.22]		
Total events	215	234	74	100	33.470	0.07 [-0.00, 0.22]		
Heterogeneity: Tau ²		484 df=		09*IP=	: 59%			
Test for overall effec			2 (1 - 0.	.00/, 1 =	- 00 /0			
4.4.4.Blandranatass	n ulaasha							
1.4.4 Alendronate vs Reid 1996	s. piaceno 8	27	5	28	13.8%	0.401.044.0041		. ???
Subtotal (95% CI)	0	27 27	5	28	13.8%	0.12 [-0.11, 0.34] 0.12 [-0.11, 0.34]	-	
Total events	8		5		101070	0112 [0111, 0101]		
Heterogeneity: Not a								
Test for overall effec		0.30)						
Total (95% CI)		500		178	100.0%	0.11 [-0.00, 0.22]	•	
Total events	290	000	86		1001070	0111 [0100, 0122]		
Heterogeneity: Tau ²		12.17. df		0.03); P	= 59%		+ + + + + + + + + + + + + + + + + + +	
Test for overall effec				/			-1 -0.5 0 0.5 Biphosphonates Placebo	1
Test for subgroup di	ifferences: Chi	² = 4.74, (df = 3 (P =	= 0.19),	$I^2 = 36.7^{\circ}$	%	Dipliospholiates Flacebo	
Risk of bias legend								
(A) Random sequer	nce generation	(selectio	n bias)					
(B) Allocation conce								
(C) Blinding of partic		-	•		is)			
(D) Blinding of outco		-		;)				
(E) incomplete outco	ome data (attrit	ion bias)						

- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Bisphosphonates versus active comparator

We did not detect a difference in occurrence of adverse events among bisphosphonates, nor when compared risedronate or alendronate was compared to etidronate (RR 0.98, 95% CI 0.72 to 1.35; Analysis 2.2). There was no evidence of a difference when newer aminobisphosphonates (zoledronate, olpadronate) were compared to older aminobisphosphonates (pamidronate, risedronate) (RR 0.93, 95% CI 0.73 to 1.19; Analysis 3.2). Influenzalike illnesses were common among participants who received intravenous bisphosphonates. Symptomatic hypocalcaemia was uncommon (<1%).

Intensive versus symptomatic treatment

No difference was detected for total number of adverse effects when intensive treatment was compared with symptomatic treatment (RR 1.05, 95% CI 0.79 to 1.41; Table 4). Serious adverse effects were more frequent with intensive treatment; 32.2% versus 28.4%, (RR 1.28, 95% CI 0.96 to 1.72). One case each of osteonecrosis of the jaw and uveitis (both in intensive group participants) and

three delayed unions of fracture (2 in the intensive group, 1 in the symptomatic group) were recorded in the PRISM-EZ trial (Tan 2017).

Rare adverse events

In addition to data from the included trials, we reviewed data on six specific rare events obtained from the websites of three regulatory agencies (FDA, EMA, and MHRA) and the AADRB / Australian TGA.

Osteonecrosis of the jaw

The risk of developing osteonecrosis of the jaw is substantially greater for people receiving intravenous bisphosphonates for cancer indications (metastatic cancer of bone, tumour-associated hypercalcaemia and multiple myeloma) than for those with Paget's disease of bone or osteoporosis. According to the EMA 2009 Committee for Medicinal Products for Human Use (CHMP) assessment report on bisphosphonates and osteonecrosis of the jaw, people receiving oral bisphosphonates for Paget's disease of bone are considered to be at much lower risk for developing osteonecrosis of the jaw. Reported incidence ranged



from 0.0004% to 0.06%. There is no clear evidence regarding the risk of osteonecrosis of the jaw following use of intravenous bisphosphonates for Paget's disease of bone. The evidence further suggests that the cumulative dose is a risk factor for osteonecrosis of the jaw, so the very low number of reports of osteonecrosis of the jaw in people with Paget's disease could be explained by the short courses of bisphosphonates used (EMA, FDA, MHRA, TGA).

Osteonecrosis of the external auditory canal

Oseonecrosis of the external auditory canal has been reported with use of bisphosphonates both for cancer-related bone disease and osteoporosis, but not for Paget's disease of bone (MHRA).

Ocular inflammation

A small number of reports describe inflammatory eye disorders such as uveitis, iritis, scleritis/episcleritis, haemorrhage and optic neuritis. Inflammatory ocular disorders appear to be a rare effect of all bisphosphonates. There is no specific evidence about the risk of ocular inflammation in people with Paget's disease of bone after bisphosphonate use (AADRB).

Atrial fibrillation

Evidence regarding atrial fibrillation suggests an increased risk of atrial fibrillation for zoledronate, pamidronate and possibly for alendronate in people treated for osteoporosis and cancer-related bone disease. There is no specific evidence about the risk of atrial fibrillation in Paget's disease of bone following bisphosphonate treatment (EMA, MHRA).

Atypical femoral fracture

Atypical femoral fracture is considered to be a class effect of bisphosphonates. These fractures have been seldom reported and mainly among those receiving long-term treatment for osteoporosis. Only one post-marketing report of possible atypical femoral fracture with zoledronate in a patient with Paget's disease has been received according EMA (Assessment report for bisphosphonates containing medicinal products 2011). The very low number of reports of atypical fractures in Paget's disease of bone patients could be explained by the short bisphosphonates regimens used for this disease compared osteoporosis (EMA, MHRA).

Oesophageal cancer risk

There was insufficient evidence of a link between the risk of oesophageal cancer and the use of oral bisphosphonates. This suggested association has been proposed for people taking oral bisphosphonate for more than five years, a therapeutic schedule that is not used for people with Paget's disease of bone (EMA, MHRA).

Withdrawals due to adverse events

Discontinuations due to adverse events were reported and analysed for 13 trials.

Bisphosphonates versus placebo

The pooled estimate for the comparison between bisphosphonates and placebo demonstrated no evidence of effect in the risk of discontinuing medication due to adverse events (RR 1.01, 95% CI 0.41 to 2.52; 6 studies, 517 participants; Analysis 1.5). The results

were consistent among trials, with low rates of withdrawals in both treatment groups.

Bisphosphonates versus active comparator

Results were inconclusive for the comparison between two non-aminobisphosphonates (Roux 1995) (RR 2.55, 95% CI 0.57 to 11.35; Table 5). There was no evidence of a difference between aminobisphosphonates and non-aminobisphosphonates (RR 0.69, 95% CI 0.25 to 1.89; 2 studies, 212 participants; Analysis 2.3) or between aminobisphosphonates (RR 0.93, 95% CI 0.37 to 2.35; 3 studies; Analysis 3.3).

Intensive versus symptomatic treatment

No difference was detected in the risk of discontinuing medication due to adverse events between intensive and symptomatic treatment (Langston 2010) (RR 1.05, 95% CI 0.79 to 1.41; Table 4).

Minor outcomes

Relapses due to recurrence of bone pain

Relapses due to recurrence of bone pain were analysed only by Fraser 1997. When compared to placebo, tiludronate achieved a significant reduction in the number of participants who relapsed due to bone pain (RR 0.51, 95% CI 0.32 to 0.80; Table 9).

Effect on serum total alkaline phosphatase activity

Changes in serum bone markers, especially changes in serum total alkaline phosphatase activity, was considered as the primary outcome in all but two included trials (Langston 2010; Tan 2017).

Bisphosphonates versus placebo

Bisphosphonates achieved a significantly greater reduction in serum total alkaline phosphatase activity when compared to placebo (MD 50.1%, 95% CI 32.5 to 67.7; Analysis 1.6). In line with the greater reduction in serum alkaline phosphatase activity, a high proportion of participants normalised their alkaline phosphatase levels (RR 9.96, 95% CI 3.74 to 26.58; Analysis 1.7).

Bisphosphonates versus active comparator

Among non-aminobisphosphonates, tiludronate was more effective than etidronate (Roux 1995) (RR 2.27, 95% CI 1.16 to 4.43; Table 5) for normalisation of alkaline phosphatase levels.

Aminobisphosphonates had greater effect on serum biochemical markers of bone turnover than non-aminobisphosphonates. This was shown in the comparisons between risedronate and etidronate (Miller 1999) or alendronate and etidronate (Siris 1996). The pooled mean difference in the reduction in alkaline phosphatase activity was 41.0% (95% CI 32.8 to 49.1; Analysis 2.4). The pooled RR for normalisation of alkaline phosphatase levels was 4.30 (95% CI 2.72 to 6.79; NNTB 2, 1 to 4; Analysis 2.5).

Zoledronate was the most effective of the aminobisphosphonates. The mean difference in reduction of alkaline phosphatase activity for zoledronate compared to risedronate was 22.7% (95% CI 19.3 to 26.1; Analysis 3.4); RR for normalisation of alkaline phosphatase levels was 1.53 (95% CI 1.33 to 1.76; NNTB 3, 3 to 5). Alendronate was more effective than pamidronate (Walsh 2004) in normalising alkaline phosphatase levels (RR 1.48, 95% CI 1.09 to 2.00; Analysis 3.5).



When etidronate was compared with etidronate plus calcitonin, the combination showed a greater reduction in alkaline phosphatase than etidronate alone: 71% at 6 months versus 56% (CI not reported) (O'Donoghue 1987).

Intensive versus symptomatic treatment

Intensive treatment had a greater effect than symptomatic treatment (Langston 2010) in reducing mean alkaline phosphatase level (22.5%, 95% CI 15.4 to 29.6) and in the percentage of participants whose alkaline phosphatase level was normalised (RR 1.26, 95% CI 1.18 to 1.36; Table 4).

Relapse due to recurrence of increased serum alkaline phosphatase level

Bisphosphonates versus placebo

No included studies evaluated the recurrence of increased serum alkaline phosphatase level following treatment for bisphosphonates versus placebo.

Bisphosphonates versus active comparator

Three trials evaluated relapse due to recurrence of increased serum alkaline phosphatase level following treatment. Miller 1999 compared aminobisphosphonates and non-aminobisphosphonates and reported that risedronate was more effective than etidronate (RR 0.25, 95% CI 0.05 to 1.11; Table 10). Among aminobisphosphonates, zoledronate was more effective than pamidronate (Merlotti 2007) or risedronate (Reid 2005) (RR 0.06, 95% CI 0.01 to 0.42; NNTB 3, 95% CI 3 to 5; Analysis 3.6).

DISCUSSION

Summary of main results

Evidence from two studies (205 participants) indicated that compared with placebo bisphosphonates helped to relieve bone pain (disappearance of pain) (RR 3.42 95% CI 1.31 to 8.90, NNTB 5 95% CI 1 to 35%; moderate-quality evidence). Data on any pain reduction were in accordance with complete disappearance of pain (RR 1.97, 95% CI 1.29 to 3.01; 7 studies, 481 participants; NNTB 5 95% CI 2 to 15; moderate-quality evidence). Zoledronate provided better pain relief than pamidronate (RR 1.30, 95% CI 1.10 to 1.53) or risedronate (RR 1.36, 95% CI 1.06 to 1.74; very low-quality evidence).

There was insufficient evidence to evaluate whether bisphosphonate therapy prevented fractures compared with placebo; few studies were designed to study the effects of treatment on the occurrence of fractures (bisphosphonates versus placebo: RR 0.89, 95% CI 0.18 to 4.3; very low-quality evidence).

There was limited evidence to make firm conclusions about the impact of bisphosphonate on hearing thresholds, deafness, bone deformity, fractures or need for orthopaedic surgery. When zoledronate was compared with risedronate, a marginal improvement in some aspects of quality of life were reported. Differences were also observed in quality of life with long-term follow-up but this was restricted to the subgroup of participants who had normal levels of alkaline phosphatase after the original study comparing zoledronate with risedronate.

Bisphosphonates were highly effective in reducing biochemical markers of bone turnover. Bisphosphonates achieved a

greater reduction in alkaline phosphatase values compared with placebo (50.1%, 95% CI 32.5 to 67.7; moderate-quality evidence). Aminobisphosphonates were more effective than non-aminobisphosphonates in reducing alkaline phosphatase (RR 4.3, 95% CI 2.72 to 6.79, moderate-quality evidence). Among aminobisphosphonates, zoledronate was more effective than pamidronate (RR 2.57, 95% CI 1.79 to 3.70; moderate-quality evidence) and risedronate (RR 1.53, 95% CI 1.33 to 1.76; moderate-quality evidence) in normalising alkaline phosphatase levels.

Adverse events were numerically more common with bisphosphonate treatment than placebo, but differences were not significant, yielding results that were inconclusive (RR 1.32, 95% CI 0.91 to 1.92; risk of event 64% versus 48%; low-quality evidence). Zoledronate had a significantly increased risk of adverse events than placebo (RR 2.57, 95% CI 1.21 to 5.44). Results were inconclusive for other bisphosphonates. Gastrointestinal side effects were common among participants in oral bisphosphonates trials, whereas transitory influenza-like illness or pyrexia (3 days or fewer) were common with intravenous bisphosphonates. Serious adverse events attributable to bisphosphonates were rare. The rate of withdrawals due to serious adverse events was low. There were no clinically significant differences in adverse events when different bisphosphonates were compared.

The PRISM trial, which involved 1331 participants, addressed the issue of a 'treat to target' design using bisphosphonates in participants with Paget's disease of bone with fractures as the primary endpoint (Langston 2010). Langston 2010 compared two strategies; in the symptomatic group, bisphosphonates and other treatments were administered with the aim of treating bone pain. In the intensive group, bisphosphonates were administered with the aim of normalising alkaline phosphatase levels. Langston 2010 reported no differences in fractures between treatment groups, or for secondary outcomes, including pain relief, hearing thresholds, need for orthopaedic surgery or quality of life. An extension study by Tan 2017, which involved 502 participants, reported no benefits from intensive treatment on quality of life. There was a non-significant trend for increased risk of fractures and need for orthopaedic procedures in the intensive treatment group (lowquality evidence).

Overall completeness and applicability of evidence

The review process included an extensive and systematic literature search that included articles published in all languages. We also searched trials registers to identify potentially relevant, but not yet published, studies.

The included trials covered the usual spectrum of older people diagnosed with Paget's disease of bone. Many studies focused on participants with raised serum biochemical markers of bone turnover, but the PRISM (Langston 2010) and PRISM-EZ (Tan 2017) studies also included participants with normal serum biomarkers, some with no bone pain. Therefore, the included trials included covered a wide range of participants with differing degrees of metabolic activity and symptoms.

We found no evidence that bisphosphonates could prevent bone deformity or long-term complications such as bone fractures, need for orthopaedic surgery or progression of deafness in participants with skull involvement. However, few studies were conducted that evaluated effects on these outcomes.



Most studies planned to analyse change in serum bone turnover markers as the primary outcome. While the treatment group always achieved a reduction on serum bone turnover markers compared to control groups, it is noteworthy that the biochemical improvements were not necessarily associated with similar improvements in patient-oriented outcomes. Only pain relief, as a short-term patient-oriented outcome, was addressed in most trials.

Based on available data, there was no clinical benefit from adopting a strategy of administering bisphosphonates with the aim of normalising alkaline phosphatase in people with Paget's disease of bone. A long-term study of intensive bisphosphonate treatment reported no benefit in quality of life compared with symptomatic treatment and a trend toward increased risk of fractures with intensive treatment, although the difference between groups was not significant.

Quality of the evidence

The review includes 20 trials (3168 participants). Of these, ten trials (801 participants) compared bisphosphonates versus placebo. Seven trials compared two bisphosphonates (992 participants). One trial compared a bisphosphonates with a bisphosphonate plus calcitonin (44 participants). One trial (1331 participants) and its interventional extension study (502 participants) compared symptomatic treatment and intensive treatment where the goal was to normalise alkaline phosphatase.

'Summary of findings' tables are presented that compare bisphosphonates and placebo (Summary of findings for the main comparison) and zoledronate and risedronate or pamidronate (Summary of findings 2). Evidence quality for effects on seven patient-relevant outcomes ranged from very low to moderate (4 outcomes); several outcomes could not be assessed because of lack of reporting in the included studies.

Evidence quality was assessed as moderate for bone pain relief (7 studies, 481 participants). Evidence was downgraded by one level due to high risk for attrition bias in three studies and a high risk for reporting bias in another three studies. None of the included studies were assessed at high risk for performance bias for bisphosphonates compared with placebo. The heterogeneity of methods for assessing and defining Pagetic bone pain and lack of a standard way to assess changes in bone pain made comparisons between studies difficult. Differentiation of the cause of pain was also difficult because pain could be related to increased metabolic activity in Pagetic bone, co-existing arthritis, nerve compression syndromes from misshapen bones or other causes.

Despite the heterogeneity of definitions, the conclusion regarding the role of bisphosphonates to improve pain in people with Paget's disease of bone is robust. Results were consistent among trials, sensitivity analyses excluding studies at high risk of bias or including only studies that used total disappearance of pain as response definition did not alter findings.

We found low-quality evidence for effects of bisphosphonates on fractures. Evidence was downgraded by three levels because most data were from studies at risk of bias (2 studies with high risk for attrition bias and 1 study with high risk for reporting bias). The design of most studies was not suitable to study the long-term impact on fractures because the mean follow-up period was six

months, and there were few events, resulting in wide confidence intervals.

We found low-quality evidence for adverse events. Evidence was downgraded by one level because two studies were assessed at high risk of attrition bias and downgraded another level because of inconsistency. A potential source of heterogeneity was lack of uniform definitions of adverse events reported in included studies. Adverse events were not assessed as a primary outcome in any included study, and in many studies, was not assessed at all. Furthermore, reporting of adverse events was frequently incomplete and studies were not sufficiently powered to address rare adverse effects. We tried to avoid outcome reporting bias by contacting study authors for additional data on adverse events. However, since the included studies were carried out many years ago, requests for further information frequently remained unanswered, or study authors confirmed that original study data were no longer available. Another limitation of evaluating data on adverse events from summary meta-analyses is that study participants tend to be healthier, with less comorbid disease. Therefore, the results may not be generalisable to routine clinical practice. Furthermore, five included studies (Fraser 1997; Reid 1996; Reid 2005; Siris 1996; Walsh 2004) excluded participants with preexisting gastrointestinal disease. Considerable heterogeneity was found in the meta-analysis. However, only one study reported more adverse events in placebo than bisphosphonates group participants. A sensitivity analysis excluding this study had no heterogeneity.

The quality of the evidence for withdrawals due to adverse events was assessed as moderate. Evidence was downgraded by one level because four of the studies were assessed at high risk of bias: three for attrition bias (Altman 1973; O'Doherty 1992; Reginster 1992); and one for reporting bias in (O'Doherty 1992). Although there was a wide confidence interval due to few events, this outcome was not downgraded because the relative risk was close to one.

Another methodological limitation concerned concealment of treatment allocation methods which were unclear in 15 of 20 included studies.

Another limitation was the length of follow-up. Most studies were short-term with duration of six months or fewer. It was difficult to extrapolate beyond the duration of follow-up studies in this review with respect to long-term impact on fractures and other complications of Paget's disease of bone.

Only a few included studies provided data for comparisons between bisphosphonates. The quality of evidence for comparisons between two non-aminobisphosphonates was low; only one trial compared tiludronate versus etidronate. The quality of evidence for aminobisphosphonates versus non-aminobisphosphonates was low; only two small trials provided data. Evidence for comparison among aminobisphosphonates was also low because only four studies provided data; of these two were open label, and one was published only in abstract form. The quality of evidence for the comparison between zoledronate and risedronate was drawn from a trial that compared these bisphosphonates (357 participants), with a low risk of bias for most of the endpoints assessed.

Evidence from PRISM trial (Langston 2010), and its extension study which compared two treatment strategies (Tan 2017), was limited



by assessment of high risk of bias for patient-reported outcomes due to its open-label design. However the PRISM and PRISM-EZ studies were the only trials that collected data on fractures and need for orthopaedic procedures.

Potential biases in the review process

The principal limitation of this review was the limited evidence provided by the included studies and low-quality evidence for patient-related outcomes that were the focus of the review, such as fractures, need for orthopaedic procedures, bone deformity and progression of deafness. Many included studies were assessed at high risk of bias or were relatively small and underpowered. Reporting of study design and methods was generally poor, especially among the older trials. We found protocols or trial registration records for four included studies (Langston 2010; Reid 2004; Reid 2005; Tan 2017).

Reporting bias was difficult to evaluate since the planned funnel plots for all analysed outcomes could not be constructed due to there being few included studies for each outcome. We made attempts to reduce reporting bias and to find unpublished studies by gathering information in clinical trial registers, contacting experts in the field and checking for abstracts presented at scientific meetings. It is therefore unlikely that reporting was high for aminobisphosphonates since these drugs' trials were performed from the 1990s to the first decade of the 21st century when nearly all studies should be registered. Nonetheless, it is possible that we have missed some old studies from the 1970s to the 1990s when there were no systematic registers of clinical trials.

We conducted an extensive search of the literature in all relevant databases and identified two ongoing trials. For rare adverse events we searched in the websites of four regulatory agencies (FDA, EMA, AADRB and MHRA). We attempted to obtain missing data by contacting study authors or to extract data from figures in reports. However, few data were obtained from attempts to contact study authors.

Agreements and disagreements with other studies or reviews

We summarised the evidence from randomised controlled trials designed to test bisphosphonates as a treatment for people with Paget's disease of bone. We did not find any other systematic reviews that analysed bisphosphonates in Paget's disease of bone. We found four relevant clinical guidelines: the Bone and Tooth Society of Great Britain and the National Association for the Relief of Paget's Disease guideline (Selby 2002), the Belgian guideline (Devogelaer 2008); the Japanese guideline (Takata 2006) and the Endocrine Society Clinical Practice Guideline (Singer 2015).

Findings from our review agree with the British guideline (Selby 2002) which stated that "...bone pain is the only complication of Paget's disease of bone for which there is firm evidence that specific anti pagetic therapy is associated with clinical benefit". Four of the five studies cited in support of this statement were included in our review (Altman 1973; Ralston 1987; Reginster 1992; Reid 1996); one was excluded (Khairi 1974; Characteristics of excluded studies). Selby 2002 also stated there was no evidence to support the use

of specific treatment to prevent deafness, fractures, osteoarthritis, progression of bone deformity or spinal cord compression.

Other guidelines support pain as the only evidence-based indication for the treatment of Paget's disease of bone.

Ralston 2013 highlighted inclusion of zoledronate versus risedronate trials (Reid 2005) which reported a better profile for zoledronate for normalising alkaline phosphatase and evidence for benefit in some aspects of quality of life.

Our review findings disagreed with certain aspects of the Endocrine Society guideline which suggested that bisphosphonate therapy should be given to normalise biochemical markers of bone turnover with the aim of preventing complications (Singer 2015). We found no evidence of benefit for this strategy in participants with established Paget's disease of bone and there was some evidence that it may even be harmful (Tan 2017).

AUTHORS' CONCLUSIONS

Implications for practice

Based on the included studies, there is moderate-quality evidence that bisphosphonates improve pain in people with Paget's disease of bone. There was insufficient evidence to determine the effects of bisphosphonates for other complications or impact on quality of life. There was limited evidence on the effects of long-term treatment on complications such fractures, deformity, progression of deafness or need for orthopaedic surgery. Among the bisphosphonates, there was low-quality evidence that zoledronate may have a better balance between benefit and harm for the treatment of Paget's disease of bone compared with risedronate or pamidronate. However, there was evidence of increased risk of adverse events with zoledronate.

The body of evidence did not enable conclusions to be drawn about the risk of rare adverse events with bisphosphonates treatment. Lastly, based on our review which included one study of intensive versus symptomatic treatment, we found insufficient evidence to establish the benefits and harms of intensive versus symptomatic treatment strategies.

Implications for research

The currently available data did not resolve the question of whether bisphosphonates could prevent long-term outcomes such as fractures, deafness progression or need for orthopaedic surgery. Appropriately designed clinical trials including long-term evaluations and larger sample sizes are needed. Additional research is needed to clarify the impact of bisphosphonates in quality of life of people with Paget's disease of bone; the current evidence indicates these drugs have limited impact on quality of life (evidence from one study comparing zoledronate versus risedronate). The role of bisphosphonates for people who are asymptomatic with biochemical markers of bone turnover within normal range also merits further investigation.

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References to other published versions of this review

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Langston AL, Campbell MK, Ralston S, Robertson C. Aminobisphosphonates versus other active treatment for Paget's disease of the bone in adults. *Cochrane Database of Systematic Reviews* 2004, Issue 4. [DOI: 10.1002/14651858.CD004956]



* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Methods	RCT. Randomisation ratio: 9 (placebo): 7 (etidronate 1 mg/kg/day): 7 (etidronate 2.5 mg/kg/day): 9 (etidronate 5 mg/kg/day): 8 (etidronate 10 mg/kg/day): 7 (etidronate 20 mg/kg/day).
	Superiority design
Participants	Diagnostic criteria: x-ray evidence of Paget's disease of bone.
	Inclusion criteria: Pain at one or more sites of Paget's bone involvement and elevated serum alkaline phosphatase or urinary hydroxyproline at least twice the upper limit of normal (ULN) range.
	Exclusion criteria: not stated.
	Number screened: not stated.
	Number randomised: 50.
	Number analysed : 47 (65 years, 60% male; percentages monostotic, symptomatic and previously treated for Paget's disease of bone not stated)
Interventions	6 parallel treatment groups; placebo and etidronate in 5 different doses (1 mg, 2.5 mg, 5 mg, 10 mg and 20 mg/kg/day).
	Co-interventions: not stated
Outcomes	Outcomes reported in abstract:
	 change in bone pain (recorded as mild, moderate or severe);
	 adverse events related to use of bisphosphonates;
	withdrawal due to adverse events;
	 radiologically-confirmed clinical fracture; and
	 mean percentage change from baseline in serum total alkaline phosphatase activity (measured using thymolphthalein monophosphate method).
	Time points for measurement: 6 months.
	How were the outcomes measured: prospectively
Setting and date	One hospital bone unit (Miami, FL, USA).
	Period when the study was conducted: Not stated
Follow up period	6 months
Publication details and funding source	Language of publication: English. Publication status: peer-reviewed journal; full article
	Funding source : Supported in part by the General Clinical Research Center and a grant from the National Institute of Health (5MO1-RR-261-08). Etidronate was supplied by the Procter and Gamble Company, Cincinnati, OH, USA
	Declarations of interest among primary researchers: Not stated
Notes	Etidronate groups data were pooled for meta-analysis



Altman 1973 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	There were no data about how participants were selected. The authors did not use the term 'randomization', but the study was double-blinded, so the study design should have had some way of randomising participants to administer treatment. However, the risk of bias should be likely high because no information was provided for the clinical characteristics of groups before starting the study (gender, age) and the data on mean alkaline phosphatase or urinary hydroxyproline are clearly different at the start of the study for all groups
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (perfor- mance bias) All outcomes	Low risk	Quote: "double-blind study". Comment: Probably done.
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "Scans were coded and read blind for qualitative change by at least two observers".
All outcomes		Comment: Outcome assessment was blinded for scans, but there was insufficient information to permit judgement about other outcomes
Incomplete outcome data (attrition bias)	High risk	Data from the original manuscript (Altman 1973) did not agree with data in the extension study (Khairi 1974).
All outcomes		Altman 1973: "Fifty patients entered the study".
		Khairi 1974: "Fifty-four patients started in this study".
		Numbers of participants included in the treatment groups differed for Altman 1973 and Khairi 1974. In Altman 1973 23 participants were randomised to placebo plus 1 mg/kg and 2.5 mg/kg dose groups; this number was 24 in Khairi 1974. Altman 1973 reported randomising 9, 8 and 7 participants respectively to 5 mg/kg, 10 mg/kg and 10 mg/kg groups; in Khairi 1974 8, 10 and 8 participants were reported to have been randomised to these respective treatment arms
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement. Methods and results sections were consistent. We did not have access to a trial register record or study protocol to know if there was a prespecified record of the studies outcomes
Other bias	Unclear risk	There were no data on exposure to co-interventions other than bisphosphonates. No other risks of bias found, but reporting was insufficient to permit judgement.

Barreira 2009

Methods	RCT. Randomisation ratio: 1:2 (pamidronate: olpadronate).
	Superiority design
Participants	Diagnostic criteria: Not stated.
	Inclusion criteria: active Paget's disease of bone despite previous therapies.



Barreira 2009 (Continued)			
	Exclusion criteria: not	t stated.	
	Number screened: no	t stated.	
	Number randomised:	27.	
		(age and sex not stated; percentages monostotic, symptomatic and previously ease of bone were not stated)	
Interventions	Two parallel treatment 12 days.	t groups; pamidronate 400 mg/day for 4 months vs. olpadronate 200 mg/day for	
	Co-interventions: Not	reported	
Outcomes	Outcomes reported in	abstract	
	Primary endpoint: Mety.	an percentage change from baseline in serum total alkaline phosphatase activi-	
	Secondary endpoints phosphonates.	: Number of participants who experienced adverse events related to use of bis-	
	Time points for meas	urement: 6 months.	
	How were the outcom	nes were measured: Insufficient information. Likely prospectively	
Setting and date	Multicentre; Argentina.		
	Period when the stud	y was conducted: Not stated	
Follow up period	6 months		
Publication details and funding source	Language of publication: English. Publication status: conference abstracts only.		
	Funding source: Not stated.		
	Declarations of intere	est among primary researchers: Not stated	
Notes	Data only from abstracts		
Risk of bias			
Bias	Authors' judgement	Support for judgement	
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized in a 1:2 schedule." Randomisation method not reported	
Allocation concealment (selection bias)	Unclear risk	Randomisation method not reported	
Blinding of participants	Low risk	Quote: "Both formulations were double dummy with placebos"	
and personnel (perfor- mance bias) All outcomes		Comment: Probably done.	
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement	



Barreira 2009 (Continued)		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement. Only an abstract of the trials was published. Many data were lacking; there were no data on attrition, exclusions or adverse events
Selective reporting (reporting bias)	Unclear risk	Insufficient reporting to permit judgement. Methods and results sections were poorly described. It was not possible to assess if they were consistent. We did not have access to a trial register record or study protocol to know if there was a prespecified record of the studies outcomes
Other bias	Unclear risk	There were no data on exposure to co-interventions other than bisphosphonates. No other risks of bias found, but reporting was insufficient to permit judgement.

Buckler 1999

Methods	RCT. Randomisation ratio: 1:1:1:1:1 (placebo: zoledronate 50 μ g: 100 μ g; 200 μ g; 400 μ g)
	Superiority design
Participants	Diagnostic criteria: x-ray evidence of Paget's disease of bone
	Inclusion criteria: Paget's disease of bone and serum alkaline phosphatase concentrations at least twice the ULN
	Exclusion criteria: Treatment with bisphosphonates in the previous 6 months or calcitonin or plicamycin in the previous 3 months. Creatinine clearance < 60 mL/min. Abnormal liver function
	Number screened: not stated
	Number randomised: 176
	Number analysed : 172 (71 years, 61% male; percentages monostotic, symptomatic or previously treated for Paget's disease of bone were not stated)
Interventions	5 parallel treatment groups; placebo and zoledronate in 4 doses (50 μg, 100 μg, 200 μg and 400 μg in a single intravenous infusion)
	Co-interventions: Not reported
Outcomes	Outcomes reported in abstract
	Primary endpoint: Mean percentage change from baseline in serum total alkaline phosphatase activity
	Secondary endpoints: Numbers of participants who experienced adverse events related to use of bisphosphonates
	Time points for measurement : Baseline, 5 days, 10 days, 30 days, 45 days, 60 days and 90 days.
	How were the outcomes measured: prospectively
Setting and date	20 sites in USA and UK.
	Period when the study was conducted: Not stated
Follow up period	3 months
Publication details and funding source	Language of publication: English. Publication status: peer-reviewed journal; full article.
	tisasse of hone in adults (Peview)



Buckler 1999 (Continued)

Funding source: Funding source not reported in the manuscript, but one author, P Richardson, indicated "Ciba Pharmaceuticals" (abstract) and "Clinical Research, Novartis Pharmaceuticals, East Hanover, NJ, USA" (primary reference) affiliations

Declarations of interest among primary researchers: Not stated

Notes Zoledronate groups data were pooled for meta-analysis	
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Risk of bias

Bias	Authors' judgement	Support for judgement		
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomized in a double-blind manner". The allocation method was not described		
Allocation concealment (selection bias)	Unclear risk	The allocation method was not described		
Blinding of participants and personnel (perfor- mance bias) All outcomes	Low risk	Quote: "Randomized in a double blind manner". Comment: Probably done.		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement. The risk of bias was likely to be low for serum data because assays for bone-specific alkaline phosphatase, urinary calcium, creatinine, hydroxyproline, pyridinoline and deoxypiridinoline were conducted in a central laboratory (Nichols Institute, San Juan Capistrano, CA, USA)		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All efficacy analyses were based on all randomised patients who had at least one post baseline measurement (intention-to-treat analysis). Four of the 176 patients did not complete all post baseline evaluations". Comment: Attrition data were provided		
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement. Methods and results sections were consistent. We did not have access to a trial register record or study protocol to know if there was a prespecified record of the studies outcomes		
Other bias	Unclear risk	There were no data on exposure to co-interventions other than bisphosphonates. No other risks of bias found, but reporting was insufficient to permit judgement		

Canfield 1977

Canfield 1977	
Methods	RCT. Randomisation ratio: 12 (placebo): 7 (etidronate 2.5 mg/kg/day): 8 (etidronate 5 mg/kg/day): 11 (etidronate 10 mg/kg/day): 10 (etidronate 20 mg/kg/day).
	Superiority design
Participants	Diagnostic criteria: x-ray evidence of Paget's disease of bone.
	Inclusion criteria: symptoms referable to the disorder, elevation of serum alkaline phosphatase and urinary hydroxyproline (with at least twice the normal value of one these indices).
	Exclusion criteria: No co-existing condition that would complicate the interpretation of therapeutic results. No other specific therapy for Paget's disease for at least 6 months before entry into the study.



Canfield 1977 (Continued)				
	Number screened: not stated.			
	Number randomised:	48.		
		(age not stated, 58% male; percentages monostotic, symptomatic or previously ease of bone were not stated)		
Interventions	5 parallel treatment gr day).	oups; placebo, and etidronate in 4 doses (2.5 mg, 5 mg, 10 mg and 20 mg/kg/		
	Co-interventions: Not	reported		
Outcomes	Outcomes reported in	n abstract		
	Primary endpoint: mety.	ean percentage change from baseline in serum total alkaline phosphatase activi-		
	Secondary endpoints firmed clinical fracture	change in bone pain (assessment tool used not reported); radiologically-con-		
	Time points for meas	urement: Baseline, 1 month, 2 months, 3 months, 4.5 months, 6 months.		
	How were the outcom	nes measured: prospectively		
Setting and date	Participants admitted	to 4 New York City Hospitals.		
	Period when the stud	y was conducted: Not stated		
Follow up period	6 months			
Publication details and funding source	Language of publication: English. Publication status: peer-reviewed journal; full article.			
	Funding source : Supported by National Institute of Health grants (MO1.RR00645, 5.MO1-RR-96, AM-09579, TIAM-05397 and TIAM-05531). Etidronate was supplied by the Procter and Gamble Company, Cincinnati, OH, USA.			
	Declarations of intere	est among primary researchers: Not stated		
Notes	Etidronate groups data	were pooled for meta-analysis.		
	Data from 27 additional participants treated with etidronate in a non-blinded, non-randomised basi were included in the manuscript			
Risk of bias				
Bias	Authors' judgement	Support for judgement		
Random sequence generation (selection bias)	Unclear risk	Quote: "each patient was assigned randomly" Comment: Randomisation method was not reported		
Allocation concealment (selection bias)	Unclear risk	Randomisation method was not reported		
Blinding of participants and personnel (perfor- mance bias)	Low risk	Quote: "for all the patients in treatment group A neither the investigator nor the patient knew the identity of the treatment".		
All outcomes		Comment: Probably done.		
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information provided to permit judgement		



Canfie	ld	1977	(Continued)
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Αl	outcome	S

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No losses to follow-up reported. However, it was not clear how many participants were included
Selective reporting (reporting bias)	High risk	We did not have access to a trial register record or study protocol to know if there was a prespecified record of the studies outcomes.
		Likely selective reporting risk is high due to vague data on adverse events. There are no specific number of patients but only sentences as "some patients showed a rise in serum phosphate"
Other bias	Unclear risk	There were no data on exposure to co-interventions other than bisphosphonates. No other risks of bias found, but reporting was insufficient to permit judgement

Fraser 1997

Methods	RCT. Randomisation ratio: 1:1:1:1 (placebo: tiludronate 200 mg, 400 mg, 600 mg).	
	Superiority design	

Participants

Diagnostic criteria: Paget's disease confirmed by scintigraphy or radiography or both

Inclusion criteria: Age ≥ 18 years; serum alkaline phosphate concentration at least twice the ULN

Exclusion criteria:

- prior treatment with bisphosphonates other than etidronate within the past 2 years;
- treatment with etidronate, mithramycin or calcitonin within 6 months;
- prior treatment at any time if the current serum alkaline phosphatase concentration was < 30% above the lowest concentration then achieved;
- recent fracture or confinement to bed;
- current peptic ulceration;
- clinically significant liver, kidney or haematological disorder;
- pre-menopausal women;
- malignant neoplasia within the previous 5 years or breast malignancy within the previous 10 years; or
- recent change in dose of hormone replacement therapy, vitamin D or corticosteroids.

Number screened: not stated.

Number randomised: 112.

Number analysed: 112 (70 years, 54% male, 30% monostotic, 63% symptomatic, percentage previously treated for Paget's disease of bone not stated)

Interventions

4 parallel treatment groups; placebo and tiludronate in 3 doses (200 mg, 400 mg, 600 mg/day) for 12 weeks

Co-interventions: Not reported

Outcomes

Outcomes reported in abstract

Primary endpoint: Mean percentage change from baseline in serum total alkaline phosphatase activity. Treatment success was defined as 50% reduction in serum alkaline phosphatase concentration compared with baseline after 12 weeks' treatment. (Concentration decreased by 25% or less compared with week 0 reading was defined as resistant).



Fraser 1997 (Continued)

Secondary endpoints

- change in bone pain (measured using VAS. Scale ranged from no pain to agonising pain);
- adverse events related to use of bisphosphonates;
- radiologically-confirmed clinical fracture;
- participants who required orthopaedic surgery;
- · withdrawal due to adverse events; and
- relapse due to recurrence of bone pain.

Time points for measurement: Baseline, 2 weeks, 8 weeks, 12 weeks, 24 weeks.

How were the outcomes measured: prospectively

Setting and date	16 hospitals in the UK.	
	Period when the study was conducted: Not stated	
Follow up period	6 months. An additional follow-up to assess the need for re-treatment was carried out 18 months after the last participant had completed the 6 month trial. Follow-up was via a postal questionnaire with participants who had completed at least 11 weeks of treatment	
Publication details and funding source	Language of publication: English. Publication status: peer-reviewed journal; full article.	
	Funding source: Research supported by Sanofi Winthrop Ltd.	
	Declarations of interest among primary researchers : Not stated	
Notes	Tiludronate groups data were pooled for meta-analysis	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were allocated sequential study numbers and randomly assigned to one of the four treatment groups". Comment: Likely there was a central allocation because 16 hospitals recruited participants in the UK
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided to permit judgement
Blinding of participants and personnel (perfor- mance bias) All outcomes	Low risk	Quote: "double-blind randomised study". Comment: Probably done.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information provided to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Data were analysed on an 'intention to treat' basis". Comment: Reasons for missing outcome data (lost to follow-up and withdrawals) are reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement. We did not have access to a trial register record or study protocol to know if there was a prespecified record of the studies outcomes.



Fraser 1997 (Continued)		Quote: "A visual analogue scale was used for patients to assess their Pagetic pain".
		Comment: Although stated that "there were no significant differences between any of the treatment groups" data for pain assessment were only provided for placebo and tiludronate higher dose groups
Other bias	Unclear risk	There were no data on exposure to co-interventions other than bisphosphonates. No other risks of bias found, but reporting was insufficient to permit judgement

Langston 2010

Langston 2010	
Methods	RCT. Randomisation ratio: 1:1 (symptomatic treatment: intensive treatment).
	Superiority design
Participants	Diagnostic criteria: diagnosis confirmed on plain radiograph of at least one skeletal site according standard criteria from UK guidelines (Selby 2002).
	Inclusion criteria: Paget's disease of bone and life expectancy > 1 year.
	Exclusion criteria: No specific exclusion criteria were applied on the basis of treatment history, baseline alkaline phosphatase or co-existing diseases.
	Number assessed: 2110.
	Number randomised: 1331.
	Number analysed: 1159 (74 years, 51% male, 35% monostotic, 69% symptomatic, 90% previously treated with bisphosphonates for Paget's disease, 52% had normal alkaline phosphatase at baseline)

Interventions

Two parallel treatment groups; symptomatic vs. intensive treatment.

Symptomatic treatment: Philosophy; treat bone pain, not alkaline phosphatase.

- No treatment was administered for participants without symptoms referable to Paget's disease of
 - For participants with pain caused by Paget's disease of bone, first-line treatments were analgesics and nonsteroidal anti-inflammatory drugs;
 - If there was an inadequate response, participants could be treated with tiludronate (400 mg daily for 3 months), etidronate (400 mg daily for 3 to 6 months) or calcitonin (subcutaneously administered 50 to 100 units daily for 3 months);
 - Pamidronate (an initial dose of 30 mg and further infusions of 30 mg until a response occurred to a maximum dose of 180 mg), and
 - Risedronate (30 mg daily for 2 months) could be used if there was inadequate response to previous treatment.

Intensive treatment: Philosophy; maintain normal alkaline phosphatase.

- No treatment was administered for participants with normal alkaline phosphatase;
 - For participants with elevated alkaline phosphatase risedronate (30 mg daily for 2 months) was
 chosen as first-line treatment. Also pamidronate (3 intravenous infusions of 60 mg, total dose 180
 mg) could be used. Treatment was administered with the aim of restoring alkaline phosphatase;
 - If there was an inadequate response, participants could be re-treated.

Co-interventions: Analgesics and nonsteroidal anti-inflammatory drugs for symptomatic and intensive treatment group



Langston 2010 (Continued)

Outcomes

Outcomes reported in abstract

Primary endpoint: Radiologically-confirmed clinical fracture.

Secondary endpoints:

- change in bone pain (assessed as participant reporting pain/no pain. Physicians asked to assess if they
 considered if reported bone pain was due to Paget's disease of bone);
- adverse events related to use of bisphosphonates;
- · need for orthopaedic surgery;
- change in quality of life measures (assessed by Stanford Health Assessment Questionnaire Disability Index, EQ-5D, SF-36, arthritis-specific version of SF-36 (ASHI));
- change in hearing thresholds;
- · withdrawals due to adverse events; and
- mean percentage change from baseline in serum total alkaline phosphatase activity (alkaline phosphatase values were normalised to the upper limit of the reference range for each hospital, which was set to a level of 1.0).

Time points for measurement: Visits scheduled at 4 monthly intervals.

How were the outcomes measured: prospectively

Setting and date

39 secondary referral centres in the UK.

Period when the study was conducted: December 2001 to June 2004

Follow up period

Median 3 years (range 2 to 5 years)

Publication details and funding source

Language of publication: English.

Publication status: peer-reviewed journal; full article.

Funding source: Supported by grants from the Arthritis Research Campaign UK (Ref. 13627), National Association for Relief of Paget's Disease, Procter & Gamble Pharmaceuticals and Sanofi-Aventis.

Declarations of interest among primary researchers:

- Stuart H Ralston: consultant for Procter & Gamble, Novartis and Merck.
- William D Fraser: consultant for Procter & Gamble, MSD, Novartis, Sanofi Aventis, Nycomed and Roche.
- Peter L Selby: consultant for Procter & Gamble, Novartis, Nycomed and Roche.
- Anne L Langston: received a travel bursary from Procter & Gamble and Sanofi-Aventis.
- · All other authors stated no conflicts of interest

Notes

The study was described by the authors as a "pragmatic randomised controlled trial designed to compare the effects of two management strategies". The study was not blinded

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were assigned to the treatment groups by an integrated telephone and web-based randomization system"
Allocation concealment (selection bias)	Low risk	Quote: "Treatment allocation employed minimization to ensure that the treatment group were balanced with respect to key prognostic variables"
Blinding of participants Low risk	Low risk	Quote: "The study was not blinded".
and personnel (perfor- mance bias)		Comment:



Langston 2010 (Continued) All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Information provided by authors: The assessments of events were performed by individuals who were unaware of the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Information provided by authors: The study was an event-driven trial, with fracture as the primary endpoint. Data on all fracture events were available even in subjects who had withdrawn from the study. Comment: The risk of attrition bias was low for data at 2 years (minimum du-
		ration of follow-up). The rate of losses to follow-up at this point was 12% and 13% respectively. The risk of attrition bias is high for 36 or 48 months
Selective reporting (reporting bias)	Low risk	Study protocol available. All proposed outcomes were reported
Other bias	Low risk	Comment: The study design allowed the attending clinicians to choose different drugs within a specified treatment strategy. Evidence that the attending clinicians adhered to the allocated strategy came from the observation that alkaline phosphatase levels differed significantly between groups

Methods	RCT. Randomisation ratio: 1:1:1 (placebo: tiludronate 200 mg: tiludronate 400 mg).
	Superiority design
Participants	Diagnostic criteria: Diagnosis confirmed by radiographic and clinical criteria.
	Inclusion criteria: participants aged > 32 years and with serum alkaline phosphatase values at least twice ULN.
	Exclusion criteria:
	 no other metabolic skeletal disorders or medical problems that would interfere with assessments in this study;
	 had not received pamidronate within 2 years or any other bisphosphonates or mithramycin within 6 months, or calcitonin or gallium nitrate within the previous 2 months;
	 had not experienced fracture of a long bone, had not undergone skeletal surgery or received systemic glucocorticoid therapy in the past 6 months.
	Number screened: not stated.
	Number randomised: 139.
	Number analysed: 134 (70 years, 54% male; percentages monostotic, symptomatic or previously treat ed for Paget's disease of bone not stated)
Interventions	Three parallel treatment groups; placebo and tiludronate in two different doses (200 mg, 400 mg) nightly for 12 weeks.
	Co-interventions : Calcium-containing food and supplements were avoided around the time the study medication was taken
Outcomes	Outcomes reported in abstract

Primary endpoint: Mean percentage change from baseline in serum total alkaline phosphatase activi-

ty.



McClung 1995 (Continued)

Secondary endpoints:

- change in bone pain (measured on Huskisson pain severity score (derived from a 10 cm VAS ranging from no pain (0 cm) to maximum pain (10 cm))
- adverse events related to use of bisphosphonates
- · withdrawals due to adverse events.

Time points for measurement: Baseline, 2 weeks, 4 weeks, 8 weeks, 12 weeks, 16 weeks, 20 weeks, 24 weeks.

How were the outcomes measured: prospectively

Setting and date	20 centres in the USA and Canada.		
	Period when the study was conducted: Not stated		
Follow up period	6 months		
Publication details and funding source	Language of publication: English. Publication status: peer-reviewed journal; full article.		
	Funding source: Research supported by Sanofi Winthrop Ltd.		
	Declarations of interest among primary researchers: Not stated		

Data on the tiludronate groups were pooled for meta-analysis

Risk of bias

Notes

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "In a randomized, double-blind, placebo-controlled study were enrolled at 20 centers throughout the USA and Canada"
		Comment: Likely that the risk of bias was low because for a multicentre design, the allocation process should be centralized
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided to permit judgement
Blinding of participants and personnel (perfor- mance bias) All outcomes	Low risk	"Double-blind"
Blinding of outcome as-	Unclear risk	Insufficient information to permit judgement.
sessment (detection bias) All outcomes		The risk is probably low for laboratory data because two laboratories were involved:
		Routine biochemical and haematologic laboratory studies, urinary hydrox- yproline was measured at SciCor (Indianapolis, IN, USA).
		2. Urinary pyridinoline assays were performed at Ostex International (Seattle, WA, USA)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for attrition and exclusion were reported. 2/91 (2%) participants were lost from the interventions group and 3/48 (65) participants from the placebo group



McClung 1995 (Continued)				
Selective reporting (reporting bias)	Unclear risk	Methods and results sections were consistent. Insufficient information to permit judgement. We did not have access to a trial register record or study protocol to know if there was a prespecified record of the studies outcomes.		
		Comment: Data for pain assessment were poorly reported		
Other bias	Unclear risk	No other risks of bias found, but reporting was insufficient to permit judgement.		
Merlotti 2007				
Methods	RCT. Randomisatio	on ratio: 2:1 (pamidronate: zoledronate).		
	Superiority design			
Participants	Diagnostic criteri	a: confirmed by bone scintigraphy and x-ray of areas of increased isotope uptake.		
	Inclusion criteria: Presence of serum total alkaline phosphatase above ULN (298 IU/L) on 2 consecutive measurements and no treatment with bisphosphonates or other drugs affecting bone metabolism for at least 6 months before the study.			
	Exclusion criteria:			
	 major comorbidity; metabolic bone disease other than uncomplicated osteoporosis; recent fracture of Pagetic bone; clinically significant liver disease; and kidney impairment. 			
	Number screened: not stated.			
	Number randomised: 90.			
		l: 89 (70 years, 64% male; percentage monostotic not stated, 99% symptomatic, reated for Paget's disease of bone)		
Interventions	2 parallel treatment groups; 4 mg single infusion of zoledronate or 30 mg infusion of pamidrona consecutive days every 3 months.			
	Co-interventions: 1 g calcium and 800 IU cholecalciferol per day			
Outcomes	Outcomes reported in abstract			
	Primary endpoint: Rate of therapeutic response (defined as normalisation of alkaline phosphatase levels or a reduction of at least 75% in total alkaline phosphatase excess).			
	Secondary endpoints:			
	 change in bone pain (pain was recorded as never pain, disappearance, decrease and no change. It was the participant's and investigator's decision whether or not pain was related to Paget's disease of bone); 			
	 adverse events related to use of bisphosphonates; change in quality of life measures (measured by a validated Italian version of Stanford Health Assessment Questionnaire functional disability index); 			
	 withdrawals due to adverse events; and mean percentage change from baseline in serum total alkaline phosphatase activity. 			
	Thean percentage change from basetine in serum total alkaline phosphatase activity.			

Time points for measurement: Baseline and 6 months.



Merlotti 2007 (Continued)	
	How were the outcomes measured: prospectively
Setting and date	One centre in Siena, Italy.
	Period when the study was conducted: Not stated
Follow up period	6 months
Publication details and funding source	Language of publication: English. Publication status: peer-reviewed journal; full article.
	Funding source: Not stated.
	Declarations of interest among primary researchers: No authors had conflicts of interest
Notes	The study was subdivided:
	 During the first 6 months participants were randomised to pamidronate or zoledronate (This was in- cluded study in the review).
	After 6 months, participants who did not respond to pamidronate were crossed-over to zoledronate or started on neridronate. (This was not included in the review because participants were not ran- domised)
Risk of bias	
	Authoral independs Compant for independs

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomized study randomization was stratified according to base- line alkaline phosphatase levels and previous bisphosphonate treatment (as a binary variable: yes or no)".
		Comment: Random sequencing was probably computer-generated; the randomisation was stratified
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided to permit judgement
Blinding of participants and personnel (perfor- mance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "29 of 30 patients receiving zoledronate and 60 of 60 patients receiving pamidronate completed the follow-up at 6 mo". Comment: Only one participant was lost to follow-up at 6 months
Selective reporting (reporting bias)	Unclear risk	Methods and results sections were consistent. Insufficient information to permit judgement. We did not have access to a trial register record or study protocol to know if there was a prespecified record of the studies outcomes
Other bias	Unclear risk	No other risks of bias found, but reporting insufficient to permit judgement



1iller 1999				
Methods	RCT. Randomisation ratio: 1:1 (risedronate: etidronate). Superiority design			
Participants	Diagnostic criteria: c onfirmed by bone scintigraphy or x-ray.			
	Inclusion criteria: participants aged 18 to 85 years, with serum alkaline phosphatase concentration of at least twice the ULN. Women had to be at least 1 year postmenopause or using contraception.			
	Exclusion criteria:			
	 evidence of organic or psychiatric disease that would prevent the participant completing the study; history of cancer (except skin cancer or cervical carcinoma in situ); history of hyperparathyroidism, hyperthyroidism or osteomalacia within 1 year before enrolment; markedly abnormal laboratory parameters; those who had received: oral or parenteral glucocorticoid or anabolic steroids within 3 months of study commencement; 			
	 calcitonin; vitamin D > 1000 IU/day or calcitriol 1.5 μg/week within 1 month before study commencement; ο any bisphosphonates, fluoride, plicamycin, gallium nitrate or parathyroid hormone within 6 months of study commencement. 			
	Number screened: 179.			
	Number randomised: 123.			
	Number analysed: 103 (66 years, 69% males, 24% monostotic, 91% symptomatic, 72% previously treated for Paget's disease of bone)			
Interventions	Two parallel treatment groups; oral risedronate 30 mg daily for 2 months and oral etidronate 400 mg for 6 months.			
	Co-interventions: Not reported			
Outcomes	Outcomes reported in abstract			
	Primary endpoint: Mean percentage change from baseline in serum total alkaline phosphatase activity.			
	Secondary endpoints:			
	change in bone pain (measured on SF-36);			
	adverse events related to use of bisphosphonates;			
	 change in quality of life measures (measured on SF-36); withdrawal due to adverse events; and 			
	 relapse due to recurrence of increased serum alkaline phosphatase level (relapse was defined as 50% increase in serum alkaline phosphatase concentration from the lowest concentration and reach ing at least twice the ULN. 			
	Time points for measurement : Baseline and 1 through 6, 8, 10, 12, and 18 months for laboratory measures. Baseline, 2, 6 and 12 months for quality of life (including pain).			
	How were the outcomes measured: prospectively			
Setting and date	12 study centres in the USA and Canada.			
	Period when the study was conducted: Not stated			



Miller 1999 (Continued)

Publication details and funding source

Language of publication: English

Publication status: peer-reviewed journal; full article.

Funding source: Supported by Procter & Gamble Pharmaceuticals, Cincinnati, OH, USA.

Declarations of interest among primary researchers: Not stated

Notes None

Bias	Authors' judgement	Support for judgement		
Random sequence generation (selection bias)	Low risk	Quote: "Patients were assigned unique, sequential identification numbers according to the chronological order of entry at each of the 12 centers and were stratified into those who had, and those who had not, received previous etidronate treatment. Within each center, and within each stratum of previous etidronate use, patients were assigned to one of the two treatment groups according to a randomisation schedule generated using SAS Version 6.07 PLAN procedure (SAS Institute, Cary, NC)".		
Allocation concealment (selection bias)	Low risk	Computerised random number generator was used		
Blinding of participants	Low risk	Quote: "Double blind design".		
and personnel (perfor- mance bias) All outcomes		Comment: Probably done.		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information provided to permit judgement		
Incomplete outcome data (attrition bias) All outcomes	High risk	 Comment: Although the authors stated that the study included an intention-to-treat analysis: the study reported a total follow-up period of 12 months for all participants and an optional 6 month extended follow-up (total study period 18 months). However, neither the number of participants who were followed-up for at least 12 months nor reasons for missing outcome data are clearly explained in the text. according to Table 2 (Results) only 3 participants were excluded from the final data (60 vs. 60 participants). However, in the text the authors stated different numbers of participants: "Of the patients for whom data were also available at month 12, 62% (33 of 53) in the risedronate group and 10% (5 of 50) in the etidronate group were still in biochemical remission." (50 vs. 53 participants) 		
Selective reporting (reporting bias)	Unclear risk	Methods and results sections were consistent. Insufficient information to permit judgement. We did not have access to a trial register record or study protocol to know if there was a prespecified record of the studies outcomes		
Other bias	Unclear risk	There were no data on exposure to co-interventions other than bisphosphonates. No other risks of bias found, but reporting insufficient to make judgement		



Methods	RCT. Randomisation ratio: 2:1 (alendronate: placebo).				
	Superiority design				
Participants	Diagnostic criteria: diagnosis established by finding hyperphosphatasia and characteristic radiographic and scintigraphic features.				
	Inclusion criteria: participants diagnosed as active Paget's disease of bone.				
	Exclusion criteria:				
	 treatment for Paget's disease of bone with drugs other than analgesic in 3 months prior to trial enrol ment; 				
	 taking medication or suffering from disorders likely to affect skeletal metabolism. 				
	Number screened: not stated.				
	Number randomised: 15.				
	Number analysed: 15 (67 years, 60% male, % monostotic not stated, 87% symptomatic, 66% previous ly treated for Paget's disease of bone)				
Interventions	Two parallel treatment groups: intravenous alendronate 10 mg/day for 5 days and placebo.				
	Co-interventions: Not reported				
Outcomes	Outcomes reported in abstract:				
	Primary endpoint: Mean percentage change from baseline in serum total alkaline phosphatase activity.				
	Secondary endpoints:				
	 change in bone pain (measurement tool used not reported); adverse events related to use of bisphosphonates; withdrawal due to adverse events. 				
	Time points for measurement : Baseline and 2, 3 and 4 weeks from the start of treatment and monthly thereafter for 6 months.				
	How were the outcomes measured: prospectively				
Setting and date	One centre in Sheffield, UK.				
	Period when the study was conducted: Not stated				
Follow up period	6 months.				
	Comment: The blind was broken 4 weeks after the start of treatment. The 10 participants who received treatment with alendronate were additionally followed for 6 months. The 5 participants who received placebo were allowed to withdraw from the study after the blind was broken				
Publication details and funding source	Language of publication: English Publication status: peer-reviewed journal; full article.				
	Funding source : Supported by a Programme Grant from the Medical Research Council and by Merck, Sharp and Dohme Research Laboratories, Woodbridge, NJ, USA and Harlow, UK.				
	Declarations of interest among primary researchers: Not stated				
Notes	None				



O'Doherty 1992 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "A group of 15 patients with active Paget's disease of bone were randomised prospectively".
		Comment: Insufficient information provided to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided to permit judgement
Blinding of participants and personnel (perfor- mance bias)	Low risk	Quote: "receive 5 days of treatment with either alendronate (10 mg/day) or placebo under double-blind conditions".
All outcomes		Comment: Probably done.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information provided to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "The blind was broken 4 weeks after the start of treatment. The 10 participants who received treatment with alendronate were additionally followed for 6 months. The 5 participants who received placebo were allowed to withdraw from the study after the blind was broken."
		Comment: The follow-up was different for participants in the placebo and experimental groups (e.g. data on urinary hydroxyproline and serum alkaline phosphatase (Figure 1) were registered to different weeks from the start of treatment for alendronate or placebo)
Selective reporting (reporting bias)	High risk	We did not have access to a trial register record or study protocol to know if there was a prespecified record of the studies outcomes.
		Comment: Pain data were reported, but pain was not defined as an outcome. There was no reporting of how pain was assessed. There were no data reported on adverse effects.
Other bias	Unclear risk	There were no data on exposure to co-interventions other than bisphosphonates. No other risks of bias found, but reporting was insufficient to permit judgement

O'Donoghue 1987

O Dollogilue 1987	
Methods	RCT. Randomisation ratio: 1:1 (etidronate: etidronate plus calcitonin).
	Superiority design
Participants	Diagnostic criteria: Iliac crest bony biopsy, skeletal radiography and scintigraphy were performed to confirm the diagnosis of Paget's disease.
	Inclusion criteria: participants with biochemically active Paget's disease whose bone pain was unresponsive to simple analgesia or nonsteroidal anti-inflammatory agents.
	Exclusion criteria: Not stated.
	Number screened: not stated.



O'Donoghue 1987 (Continued)				
	Number randomised:	44.		
		(age and sex not stated; percentage monostotic not stated, 100% symptomatic, I for Paget's disease of bone)		
Interventions		groups: oral etidronate 400 mg and oral etidronate 400 mg in combination with in 100 MRC units thrice weekly for six months.		
	Co-interventions: Par	ticipants were on a constant calcium low gelatin diet.		
Outcomes	Outcomes reported in	ı abstract		
	Primary endpoint: Mety.	an percentage change from baseline in serum total alkaline phosphatase activi-		
	Secondary endpoints	:		
	• change in bone pair	n (assessment tool not reported);		
	radiologically-confirmed clinical fractures; and			
	adverse events related to use of bisphosphonates.			
	Time points for measurement : Baseline, monthly during treatment, and every 2 to 3 months for an additional 6 months period.			
	How were the outcomes measured: prospectively			
Setting and date	One centre in Nottingham, UK.			
	Period when the study was conducted: Not stated			
Follow up period	12 months			
Publication details and funding source	Language of publication: English Publication status: peer-reviewed journal; full article.			
	Funding source: Not stated.			
	Declarations of interest among primary researchers: Not stated			
Notes	The study randomised a group of participants to be treated with etidronate or etidronate plus calcitonin. The authors also compared these two groups with data accumulated from participants who received calcitonin alone prior to the introduction of etidronate in the metabolic unit (28 participants); this group was excluded because participants were not randomised			
Risk of bias				
Bias	Authors' judgement	Support for judgement		
Random sequence generation (selection bias)	Unclear risk	Quote: "Forty-four sequential patients were randomised to treatment".		
		Comment: Insufficient information provided to permit judgement		
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided to permit judgement		
Blinding of participants and personnel (performance bias)	High risk	Quote: "patients were randomised to treatment with either EHDP 400 mg daily alone (21 patients) or in combination with SCT 100 MRC units thrice weekly (23 patients)"		

patients)".

mance bias)

All outcomes



	Superiority design	1
Methods	RCT. Randomisation plus placebo).	on ratio: 1:1:1 (etidronate plus $1lpha$ -hydroxyvitamin D: etidronate plus placebo: placebo
Ralston 1987		
Other bias	Unclear risk	No other risks of bias found, but reporting insufficient to make judgement
		 Authors stated that "patients were seen monthly to monitor clinical and biochemical responses, side-effects and compliance". However, adverse events were not reported in the study results
		 Although fractures were not defined as an outcome, these were reported ("four patients with fissure fractures nontraumatic extension of fissure fractures occurred in two patients, one given combined treatment and the other given EHDP").
		1. To be included, participants had pain due to Paget's disease of bone ("Patients with biochemically active Paget's disease whose bone pain was unresponsive to simple analgesia or nonsteroidal anti-inflammatory agents were studied"). However, the method to assess pain was not described, although pain should be measured during the study ("If the bone pain remained severe and the disease was biochemically active treatment was continued for a further 6 months", "Treatment was continued for a further 6 months in 38 participants (11 SCT + EHDP: 21 SCT: 6 EHDP) who were still symptomatic with a persistently elevated disease activity".
		Comment: There are some contradictions between methods and results sections.
Selective reporting (reporting bias)	High risk	We did not have access to a trial register record or study protocol to know if there was a prespecified record of the studies outcomes.
All outcomes		Comment: Attrition rate was low; only two participants were lost to follow-up. The proportion of missing outcomes compared with observed event risk was insufficient to have a clinically-relevant impact on the intervention effect estimate
Incomplete outcome data (attrition bias)	Low risk	Quote: "Two patients treated with EHDP defaulted from follow-up but the other 70 were reevaluated in the metabolic unit after 6 months".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information provided to permit judgement
'Donoghue 1987 (Continued)		Comment: Because there was no mention of placebo, it is likely that one group was treated with oral drugs alone and the other with a combination of oral and subcutaneous drugs; hence, blinding was not possible

Number screened: not stated.

Number randomised: 32.

ment.



Ralston 1987 (Continued)	Number analysed: 29 ously treated for Paget	(age and sex not reported; 31% monostotic, 100% symptomatic, 37.5% previ- 's disease of bone)		
Interventions		nt groups: oral etidronate 400 mg plus 1α-hydroxyvitamin D 0.5 μg, oral placebo and placebo plus placebo for three months.		
		ticipants received other medications according to routine practice (e.g. anal- ti-inflammatory drugs) (information provided by authors).		
Outcomes	Outcomes reported in	abstract		
	Primary endpoint: Mety	an percentage change from baseline in serum total alkaline phosphatase activi-		
	Secondary endpoints pain) to 30 (very severe	change in bone pain (linear analogue technique with a scale ranging from 0 (no		
	Time points for meas	urement: Baseline, and after 2, 8 and 12 weeks on drug therapy.		
	How were the outcom	nes measured: prospectively		
Setting and date	One centre in Glasgow	, UK.		
	Period when the stud	y was conducted: not stated		
Follow up period	3 months			
Publication details and funding source	Language of publication: English Publication status: peer-reviewed journal; full article.			
	Funding source : Partially supported by a grant to BFB from the Scottish Hospital Endowments Research Trust and a grant to ITB from Brocades (UK) Ltd. The 1α -hydroxyvitamin D and placebo tablets were supplied by Leo Laboratories Ltd.			
	Declarations of intere	est among primary researchers: not stated		
Notes	Data on etidronate plus 1α -hydroxyvitamin D and etidronate plus placebo groups were pooled for meta-analysis.			
	Transiliac bone biopsies were obtained before therapy in all cases and after therapy in 28 participants. Bone histomorphometry data were reported			
Risk of bias				
Bias	Authors' judgement	Support for judgement		
Random sequence genera-	Low risk	Quote: "On entry to the trial patients were randomised".		
tion (selection bias)		Information provided by authors: Allocation by referring to random numbers		
Allocation concealment (selection bias)	Low risk	Information provided by authors: Investigators were blinded to treatment allocation		
Blinding of participants	Low risk	Quote: "double blind"		
and personnel (perfor- mance bias) All outcomes		Information provided by authors: A double dummy was used with place-bo/placebo, etidronate/placebo and etidronate/ 1α -hydroxyvitamin D		
Blinding of outcome assessment (detection bias) All outcomes	Low risk Information provided by authors: Investigators were blinded to treatment when assessing outcome			



Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "There were three withdrawals from the trial after randomisation".
		Comment: The rate of withdrawals (and reasons) were reported
Selective reporting (reporting bias)	High risk	We did not have access to a trial register record or study protocol to know if there was a prespecified record of the studies outcomes.
		The authors reported symptoms and side effects and described only one adverse event ("one patient who developed increasing pain and radiological deterioration at the site of an asymptomatic pseudofracture of the tibia"). However, at the start of the results section the authors described another adverse event which was not included in the "symptoms and side effects" paragraph ("1 patient in Group A stopped medication because of dyspepsia"). Data on hypercalcaemia are on biochemistry ("One patient developed mild hypercalcaemia"). There were no other data on adverse events.
		Information provided by authors: Adverse events were not systematically recorded
Other bias	Unclear risk	No other risks of bias found, but reporting insufficient to make judgement

Reginster 1992

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RCT. Randomisation ratio: 1:1:1:1:1 (placebo: tiludronate 100 mg: tiludronate 200 mg: tiludronate 400 mg: tiludronate 800 mg).

Superiority design

Participants

Diagnostic criteria: Paget's disease of bone with characteristic radiologic lesions and/or with 99mTc bisphosphonates scintigraphic evidence of local increase in bone turnover.

Inclusion criteria: Serum alkaline phosphatase levels were at least twice the ULN.

Exclusion criteria:

- free of kidney, liver, neurologic, haematologic, inflammatory and immune disorders.
- taking no medications known to interfere with bone metabolism. Different minimal washout periods prior to the study were established for bone drugs: 6 months for etidronate, 2 months for calcitonin, 2 years for tiludronate and 2 years for clodronate.

Number screened: not stated.

Number randomised: 149.

Number analysed: 149 (69 years, 54 % male, % monostotic not stated, % symptomatic participants not stated, 82% previously treated for Paget's disease of bone)

Interventions

The study was divided into 2 periods. In the first period there were five parallel treatment groups: placebo (4 x placebo capsules), tiludronate 100 mg (2 x placebo and 2 x 50 mg tiludronate capsules), tiludronate 200 mg (4 x capsules 50 mg tiludronate), tiludronate 400 mg (4 x capsules 100 mg), tiludronate 800 mg (4 x capsules 200 mg tiludronate). All participants took 2 capsules at 10.00 am and 2 capsules at 4.00 pm daily for 3 months.

In the second period all participants received 4 placebo capsules.

The investigators initiated tiludronate therapy during the second period for participants experiencing a lack of efficacy (participants were considered discontinued from the study).

Co-interventions: Not reported



Reginster 1992 (Continued)

Outcomes

Outcomes reported in abstract

Primary endpoint: Mean percentage change from baseline in serum total alkaline phosphatase activity.

Secondary endpoints:

- change in bone pain (Huskisson VAS; range 0 cm (no pain) to 10 cm (maximal pain). A pain index was derived from pain severity and time course scores. Only pain in bones or joints in which Pagetic lesions had been clearly demonstrated by radiography or bone scans were considered. For each painful bone or joint, the participant rated pain severity (mild = 1, moderate = 2, severe = 3) and time course (on motion = 1, intermittent = 2, constant = 3). By multiplying the scores for severity and time course, a pain index was calculated for each site. The scores for all sites were added to yield an overall pain index;
- adverse events related to use of bisphosphonates;
- · withdrawal due to adverse events; and
- achieved normalised alkaline phosphatase level.

Time points for measurement: Baseline and monthly intervals.

How were the outcomes measured: prospectively

Setting and date

29 centres in Belgium, France and USA.

Period when the study was conducted: Not stated

Follow up period

6 months

Publication details and funding source

Language of publication: English

Publication status: peer-reviewed journal; full article.

Funding source: Supported by Sanofi Research, Montpellier, France.

Declarations of interest among primary researchers: Not stated

Notes

Data on tiludronate groups were pooled for meta-analysis

Bias Authors' judgement Support		Support for judgement
Random sequence genera-	Low risk	Quote: "double-blind, randomised, placebo-controlled study".
tion (selection bias)		Comment: Insufficient information provided to permit judgement, but probably low risk because the allocation process should have been centralized because the study involved 29 centres in different countries
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided to permit judgement
Blinding of participants and personnel (perfor- mance bias) All outcomes	Low risk	Quote: "double-blind, randomised, placebo-controlled study".
		Comment: Probably done.
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "All biochemical determinations were performed at a central location throughout the period of study."
All outcomes		Comment: Insufficient information provided, but likely low risk because it is unlikely that the blinding was broken in a central location



Re	gins	ter 1	992	(Continued)
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Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Follow up assessments were available for all 149 patients." Quote: "Thirty-five patients withdrew prematurely from the study. The reason were lack of efficacy in 9, adverse events in 15, at the patient's request in 4, lost to follow-up in 4, and miscellaneous reasons unrelated to treatment in 3. There was no relationship noted between the dosage of tiludronate and the number of study withdrawals."		
		Comment: Although the reasons for missing outcome data were explained and withdrawals balanced between groups, the proportion of missing outcomes (25%) compared with observed event risk is enough to induce clinically-relevant bias in intervention effect estimate		
Selective reporting (reporting bias)	Unclear risk	Methods and results sections were consistent. Insufficient information to permit judgement. We did not have access to a trial register record or study protocol to know if there was a prespecified record of the studies outcomes		
Other bias	Unclear risk	There were no data on exposure to co-interventions other than bisphosphonates. No other risks of bias found, but reporting insufficient to permit judgement		

Reid 1996

Kelu 1996					
Methods	RCT. Randomisation ratio: 1:1 (placebo: alendronate 40 mg).				
	Superiority design				
Participants	Diagnostic criteria: Paget's disease of bone documented by standard clinical, radiological or scintigraphic methods or both.				
	Inclusion criteria:				
	 participants who had not received bisphosphonate therapy previously were required to have a base line serum alkaline phosphatase activity at least twice the ULN. participants who had taken bisphosphonate therapy previously were required to have a baselin serum alkaline phosphatase activity at least four times the ULN and exceeding the previous post-treat ment nadir by an amount ≥ the ULN range. 				
	Exclusion criteria:				
	 Active upper gastrointestinal disease in the previous year or a history of surgery for peptic ulcer disease. 				
	2. Medical conditions or taking medications likely to affect bone metabolism.				
	Number screened: not stated.				
	Number randomised: 55.				
	Number analysed: 53 (70 years, 56 % male, percentage monostotic or symptomatic not stated, 35% previously treated for Paget's disease of bone)				
Interventions	Two parallel treatment groups: placebo and oral alendronate 40 mg daily for 6 months.				
	Co-interventions: Calcium (450 mg to 500 mg) and vitamin D (400 IU to 600 IU)				
Outcomes	Outcomes reported in abstract:				
	Primary endpoint: Mean percentage change from baseline in serum total alkaline phosphatase activity.				



Reid 1996 (Continued)

Secondary endpoints:

- change in bone pain (assessed using the Brief Pain Inventory);
- adverse events related to use of bisphosphonates;
- withdrawal due to adverse events; and
- achieved normalised alkaline phosphatase level.

Time points for measurement: baseline, 3 and 6 months.

How were the outcomes measured: prospectively

Setting and date Three sites in Australia, New Zealand, and UK.

Period when the study was conducted: Not stated

Follow up period 6 months

Publication details and funding source

Language of publication: English.

Publication status: peer-reviewed journal; full article.

Funding source: Supported by Merck Research Laboratories, Rahway, NJ, USA.

Declarations of interest among primary researchers: Not stated

Notes Bone biopsy conducted for 28 participants. Bone histomorphometry data reported

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned".
		Comment: Probably done because the study was multicentre, involving 3 countries
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided to permit judgement
Blinding of participants	Low risk	Quote: "The study was double-blinded".
and personnel (perfor- mance bias) All outcomes		Comment: Insufficient information provided to permit judgement, but probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Radiographs were all evaluated by one skeletal radiologist, who was blinded with respect to film sequence and treatment allocation". "Bone biopsy: Each specimen was coded, so that the reader was unaware of the subjects' drug therapy" Adverse events that were considered by the blinded investigator to be possibly treatment related occurred in"
Incomplete outcome data	Low risk	Quote: "No subjects withdrew from the study because of drug side effects.
(attrition bias) All outcomes		Comment: Attrition rate was low because only two participants did not complete the study in the placebo group but none in the alendronate group.
		The authors did not explain the reasons for not completing the trial for these two participants. However, both participants were from the placebo group and the proportion of missing outcomes compared with observed event risk were insufficient to have a clinically relevant impact on the intervention effect estimate



Reid 1996 (Continued)				
Selective reporting (reporting bias)	Unclear risk	Methods and results sections were consistent. Insufficient information to permit judgement. We did not have access to a trial register record or study protocol to know if there was a prespecified record of the studies outcomes.		
Other bias	Unclear risk	No other risks of bias found, but reporting was insufficient to permit judgement		
Reid 2004				
Methods	RCT: Randomisation ratio: 1:1:1 (placebo: ibandronate 6 mg: ibandronate 12 mg).			
	Superiority design			
Participants	Diagnostic criteri	a: Paget's disease of bone confirmed radiologically.		
	Inclusion criteria: the reference rang	: Serum alkaline phosphatase activities at baseline at least twice the upper limit of e.e.		
	Exclusion criteria: Other medical conditions, or on medications that affect bone or calcium metabolism.			
	Number screened: not stated.			
	Number randomised: 25.			
	Number analysed: 23 (73 years, 74 % male, percentages monostotic and symptomatic not stated, 64% previously treated for Paget's disease of bone)			
Interventions	dronate 6 mg (infu	tment groups: placebo (infusions of normal saline at baseline and at 1 month), ibansions of 6 mg of ibandronate at baseline and normal saline at 1 month), ibandronate f 6 mg of ibandronate at both baseline and 1 month).		
	Co-interventions:	: None (information provided by authors)		
Outcomes	Outcomes report	ed in abstract:		
	Primary endpoint ty.	t: Mean percentage change from baseline in serum total alkaline phosphatase activi-		
	Secondary endpo	ints: Number who achieved normalised alkaline phosphatase level.		
	Time points for measurement : Not reported. At least at baseline, 3, 6 and 12 months.			
	How were the out	tcomes measured: prospectively		
Setting and date	One centre in Auckland, New Zealand.			
	Period when the	study was conducted: Not stated		
Follow up period	6 months (12 months, see notes)			
Publication details and funding source	Language of publ Publication statu	ication: English. s: peer-reviewed journal; full article.		
	Funding source: S Ltd.	Supported by the Health Research Council of New Zealand and Roche Products (NZ)		
	Declarations of in	terest among primary researchers: not stated		
Notes	Ibandronate group	o data were pooled for meta-analysis.		



Reid 2004 (Continued)

Participants were followed for an additional 6 month period after finishing the first 6 months of the study. In this second part of the study, 6 placebo group participants (67%) were given ibandronate in a non-randomised way. Data from this second part of the study were not included in this review.

In 2017 the authors published a manuscript with data from original participants after 10 years follow up

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly allocated to one of three groups using a minimization algorithm to ensure balance between groups for alkaline phosphatase level".
		Quote: "Six subjects who had placebo at both of these time points subsequently were given ibandronate 6 mg at 6 months, so posttreatment data are shown for 20 subjects"
		Quote: "Because the focus of this study was on relative response of markers to ibandronate, the pre- and posttreatment data in the two ibandronate groups and in those patients from the 'placebo' group who went on to have ibandronate have been pooled, so that every subject in the study provides a preand 6 months post-ibandronate value".
		Comment: Although initially participants were randomised, the authors pooled data from participants who were initially randomised to ibandronate with data from placebo participants who received ibandronate in a 6 month study extension.
		Note: Although the study general assessment of risk of bias for random sequence generation is high, we assessed risk as unclear because on we included data from the first part of the study only in the meta-analysis
Allocation concealment (selection bias)	Unclear risk	Comment: As for assessment of random sequence generation, although for the first 6 months the authors probably concealed allocation, when finishing the first part of the study, they treated two thirds of placebo participants with ibandronate so they knew participant allocation at that time.
		Note: Although the study general assessment of risk of bias for allocation concealment is high, we assess the risk as unclear because, on meta-analysis, we introduce only data from the first part of the study.
Blinding of participants and personnel (perfor- mance bias) All outcomes	Low risk	Information provided by authors: Infusions were prepared by staff members who had no contact with the participants, so that study staff and participants were blinded to treatment received
Blinding of outcome as- sessment (detection bias) All outcomes	Low risk	Information provided by authors: Outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "'Placebo' group (nine patients), received infusions of normal saline at baseline and at 1 month, the '6 mg' group (nine patients, eight with follow-up data) received ibandronate 6 mg at baseline and placebo at 1 month, and the '12 mg' group (seven patients, six with follow-up data) received ibandronate 6 mg at both baseline and 1 month".
		Comment: Follow-up data were provided and missing outcome data are likely balanced; however, reasons for missing outcomes were not explained.



Reid 2004 (Continued)		The proportion of missing outcomes compared with observed event risk is not enough to have a clinically-relevant impact on the intervention effect estimate
Selective reporting (reporting bias)	High risk	Information provided by authors: Adverse events were not systematically recorded
Other bias	Unclear risk	No other risks of bias found, but reporting was insufficient to permit judgement

Reid 2005

Methods	RCT. Randomisation ratio: 1:1 (zoledronate acid: risedronate).
	Non inferiority design

Participants

Diagnostic criteria: Paget's disease of bone was confirmed by x-ray, magnetic resonance imaging, computerized tomography, radio-isotope imaging, etc.

Inclusion criteria:

- aged over 30 years;
- serum alkaline phosphatase activities at baseline more than twice the upper limit of the reference range.

Exclusion criteria:

- Serum 25-hydroxyvitamin D level < 15 ng/mL (37 nmol/L);
- Primary hyperparathyroidism;
- evidence of liver or kidney disease;
- history of uveitis or iritis
- upper gastrointestinal disorders that might interfere with adherence to the protocol;
- · diabetic nephropathy or retinopathy;
- use of therapy specifically for Paget's disease in the preceding 180 days;
- allergic reaction to bisphosphonates;
- calculated creatinine clearance < 30 mL/min at baseline; or
- · evidence of vitamin D deficiency.

Number screened: 688 (371 + 317).

Number randomised: 357 (185 + 172).

Number analysed: 349 (70 years, 67.7% male; percentages monostotic or symptomatic not stated; 54% previously treated for Paget's disease of bone).

An extension study of the core trial was published including participants who had therapeutic response defined as normalisation of the alkaline phosphatase level or a reduction of at least 75% in alkaline phosphatase excess (the difference from the midpoint of the reference range) at 6 months of treatment.

Number screened for the extension study: 296 (169 responders from 182 participants from the zoledronate group + 127 responders from 175 participants from the risedronate group).

Number analysed for the extension study: 267 (152 responders from the zoledronate group + 115 responders from the risedronate group) (70 years; sex, monostotic status and symptomatic participants not stated; 100% previously treated for Paget's disease of bone)



Reid 2005 (Continued)

Interventions

Two parallel treatment groups: zoledronate (single 5 mg infusion zoledronate at baseline followed by placebo tablets daily for 60 days), risedronate (saline infusion followed by 30 mg tables of risedronate daily for 60 days).

Co-interventions: All participants received 1 g calcium per day and 400 IU to 1000 IU calciferol per day.

No further interventions were added after treatment in the core trial for the extension study

Outcomes

Outcomes reported in abstract:

Primary endpoint: Proportion of participants who had therapeutic response. Therapeutic response was defined as normalisation of the alkaline phosphatase level or a reduction of at least 75% in the alkaline phosphatase excess (the difference from the midpoint of the reference range) at 6 months.

Secondary endpoints:

- change in bone pain (assessed using SF-36 domain bodily pain (range from 0 (worst) to 100 (best)) and Brief Pain Inventory-Short Form (BPI-SF). This scale values are 0 to 10, a lower score means little to no pain while a higher score means greater pain. Bone pain was not specifically assessed);
- radiologically-confirmed clinical fractures (data not reported);
- adverse events related to use of bisphosphonates;
- change in quality of life measures (assessed on SF-36);
- · withdrawals due to adverse events; and
- relapse due to recurrence of increased serum alkaline phosphatase level.

Time points for measurement: Not reported. Probably at baseline, 10 days, 1, 2, 3 and 6 months according to x-axis graph data.

Quote: "Physical examinations, hematologic tests, and serum chemical tests were performed regularly throughout the six-month study. Serum creatinine and urinary protein were measured 9 to 11 days after intravenous dosing".

How were the outcomes measured: prospectively.

Relapse rate was the primary endpoint for the extension study. Relapse was defined as a return of alkaline phosphatase to within 20% of the pre-treatment baseline value. Partial relapse was defined as an alkaline phosphatase level that was both 50% above its 6 month value and 1.25 times the ULN range. Outcomes were monitored at 6 monthly visits

Setting and date

76 centres in 10 countries (Australia, Belgium, Canada, France, Germany, New Zealand, South Africa, Spain, UK, USA).

Period when the study was conducted: January 2002 to March 2004.

Period when the extension study was conducted: Follow up covers the period from the end of the core trials to 29 January 2009

Follow up period

6 months.

6.5 years observation period in the extension study: median follow-up time from the beginning of the core study was 5.0 years for zoledronate and 3.3 years for risedronate (patient-years of follow-up were 574 years and 340 years respectively)

Publication details and funding source

Language of publication: English.

Publication status: peer-reviewed journal; full article.

Funding source: Supported by a research grant from Novartis Pharma AG, Basel, Switzerland.

Declarations of interest among primary researchers:

• Drs. Luchi, Mesenbrink, Pak, Richardson, Saidi, and Su and Mr. Zelenakas are employees of Novartis and have stock options or other ownership interest in the company.



Reid 2005 (Continued)

- Dr. Richardson is the originator of a patent application for the use of zoledronic acid in the treatment of postmenopausal osteoporosis by a once-yearly intravenous infusion. He receives no royalties from this patent.
- Dr. Brown reports having received consulting and lecture fees from Novartis and Sanofi-Aventis/Procter & Gamble and grant support from Novartis and Sanofi-Aventis.
- Dr. Fraser reports having received consulting fees and lecture fees from Merck Sharpe & Dohme; consulting fees from Novartis, Nycomed, and Roche; lecture fees from Bayer, Boehringer Ingelheim, Boehringer Mannheim/Roche, Procter & Gamble/ Aventis, and Lilly; and grant support from Action Research, the Arthritis Research Campaign, the Biotechnology and Biological Sciences Research Council, Lilly, the Medical Research Council, Merck Sharpe & Dohme, Procter & Gamble, Remedi, Roche, and the Wellcome Trust.
- Dr. Hosking reports having received consulting fees from Merck Sharpe & Dohme, Novartis, Pfizer, and Roche; lecture fees from Lilly, Merck Sharpe & Dohme, and Novartis; and grant support from Lilly, Merck Sharpe & Dohme, Novartis, the ARC Clinical Trials Collaboration, the National Association for the Relief of Paget's Disease, and the Alliance for Better Bone Health.
- Dr. Lyles reports having received consulting and lecture fees from Novartis and Procter & Gamble and grant support from Novartis, Procter & Gamble/Aventis, and the National Institute of Aging. Dr. Lyles is listed as a coinventor, with Novartis Pharmaceuticals, on a use patent for zoledronic acid (U.S. Provisional Patent Application No. 60/411,067, "Methods for preventing or reducing secondary fractures after hip fracture").
- Dr. Miller reports having received consulting and lecture fees from Eli Lilly, Merck, Procter & Gamble, and Roche; consulting fees from Wyeth/Ayerst; lecture fees from Amgen and Novartis Pharmaceuticals; and grant support from Amgen, Eli Lilly, Merck, Novartis Pharmaceuticals, Procter & Gamble, and Roche
- Dr. Reid reports having received consulting fees from Amgen, Merck, Novartis, and Procter & Gamble
 and grant support from Merck, Amgen, Novartis, the Health Research Council of New Zealand, and the
 Lactopharma Consortium.

Notes

The authors reported pooled data from two identical RCTs.

Participants identified as treatment responders were entered to an extended observation period including only those whose alkaline phosphatase was normal at completion of the core study.

Bone biopsies were performed for 22 participants (12 zoledronate acid and 10 risedronate). Bone histomorphometry data were reported

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned in a double-blind fashion through an interactive voice-response system".
		Comment: Probably done; authors describe a telephone system for sequence generation
Allocation concealment (selection bias)	Low risk	Study was conducted using a central allocation system (telephone)
Blinding of participants and personnel (perfor- mance bias) All outcomes	Low risk	Quote: "Patients were randomly assigned in a double-blind fashion".
		Comment: Probably done; placebo treatment is reported.
		The risk of bias was judged as high risk for the extension studies because much of the extended follow-up was conducted with participants and doctors knowing what treatment they received in the core trial (information provided by authors).
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Measurements were made by Covance Central Laboratory Services"



	Information provided by authors: Outcome assessment was blinded	
risk	Quote: "All efficacy variables, except the time to a therapeutic response, were analysed according to the modified intention-to-treat principle, which required patients to have a baseline and at least one post-baseline measurement of alkaline phosphatase."	
	Comment: Participant flow diagram including reasons for losses to follow-up was included. MIssing outcome data were balanced between interventions and the proportion of missing outcomes compared with observed event risk was insufficient to have a clinically relevant impact on the intervention effect estimate.	
	The risk of bias was judged as high risk for the extension studies because only participants who responded to treatment were included in the follow-up. Participants who relapsed or whose physicians provided further treatment for Paget's disease were discontinued from the study during the follow-up.	
risk	Comment: Brief Pain Inventory-Short Form (BPI-SF) was stated as a secondary outcome measure in the study characteristics in the trial registry record, but was not reported in the study publication.	
	Data on fractures were not reported in the study publication but were proposed in the trial registry record	
ear risk	No other risks of bias found, but reporting was insufficient to permit judgement	
Randomisatio	on ratio: 1:1:1 (tiludronate 400 mg 3 months, tiludronate 400 mg 6 months; etidronat	
ng 6 months).		
riority design		
	a: Paget's disease of bone was confirmed by the presence of radiologically evident stic of the disease.	
Inclusion criteria: Serum alkaline phosphatase concentration at least twice the ULN range.		
Exclusion criteria:		
 treated during the previous 6 months with either etidronate or tiludronate, or during the previous 2 years with any other bisphosphonate; 		
 those treated previously (> 6 months earlier) with tiludronate were eligible if their serum alkaline phosphate concentration at entry exceeded twice that obtained at the end of the previous tiludronate treatment; 		
 treated during the previous 2 months with mithramycin or calcitonin; taking any medication or have any disorders likely to affect skeletal and calcium metabolism; and 		
 free of active liver, kidney, or haematologic disorders. 		
Number screened: Not stated.		
Number randomised: 234.		
ee be be	of active liver	

71% previously treated for Paget's disease of bone)



Roux 1995 (Continued)

Interventions

Three parallel treatment groups: tiludronate 400 mg 3 months (2 x 200 mg tiludronate tablets and 2 x etidronate placebo capsules during the first 3 months followed by 2 x tiludronate placebo tablets and 2 x etidronate placebo capsules during the second 3 months), tiludronate 400 mg 6 months (2 x 200 mg tiludronate tablets and 2 x etidronate placebo capsules for 6 months) and etidronate 400 mg 6 months (2 x 200 mg etidronate capsules and 2 tiludronate placebo tablets for 6 months).

Co-interventions: Not reported

Outcomes

Outcomes reported in abstract:

Primary endpoint: Proportion of participants who had a response to treatment. Response to treatment was defined as a reduction of at least 50% in serum alkaline phosphatase concentration after a 3 month treatment period.

Secondary endpoints:

- change in bone pain (measured on the Huskisson VAS (10 cm scale ranging from no pain (0 cm) to maximal pain (10 cm));
- radiologically-confirmed clinical fractures;
- adverse events related to use of bisphosphonates;
- · withdrawal due to adverse events: and
- · normalised alkaline phosphatase level.

Time points for measurement: Baseline, 3 months, 6 months.

How were the outcomes measured: prospectively

Setting and date

85 centres in 6 countries (Belgium, France, Germany, Italy, Netherlands, Spain).

Period when the study was conducted: February 1991 to September 1992

Follow up period

6 months

Publication details and funding source

Language of publication: English.

Publication status: peer-reviewed journal; full article.

Funding source: Supported by Sanofi Recherche, Montpellier, France.

Declarations of interest among primary researchers: Not stated

Notes

Data on tiludronate groups were pooled for meta-analysis

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly allocated into 1 of 3 treatment groups." Comment: Insufficient information provided.
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided to permit judgement
Blinding of participants and personnel (perfor- mance bias) All outcomes	Low risk	Quote: "The study was a double-blind, randomized, multicenter, parallel-group comparison." "According to the randomisation, patients received 4 doses daily: 2 200 mg tiludronate tablets and 2 etidronate placebo capsules during the first 3 months followed by 2 tiludronate placebo tablets and 2 etidronate placebo capsules during the second 3 months, 2 200 mg tiludronate tablets and 2 etidronate placebo capsules for 6 months, or 2 200-mg etidronate capsules and 2 tiludronate placebo tablets for 6 months."



Roux 1995 (Continued)		Comment: Probably done
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "All samples were analysed at a central laboratory (Cerba Laboratories, Cergy-Pontoise, France)."
All outcomes		Comment: Probably done for laboratory assessment. The information provided was insufficient to judge the blinding of outcome for clinical assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Of the 234 patients enrolled, 30 (12.8%) discontinued treatment before completing the 6 months of the study: 14 in the tiludronate 3-month group, 11 in the tiludronate 6-month group, and 5 in the etidronate group." "Intent-to-treat analyses were conducted." "For dichotomous variables, cases with missing data were considered as treatment failures."
		Comment: Proportion of missing data were reported. Although the number of participants who discontinued treatment from both tiludronate groups was twice the number in the etidronate group, the proportion of missing outcomes compared with observed event risk was insufficient to have a relevant impact of the effect estimate
Selective reporting (reporting bias)	Unclear risk	Methods and results sections were consistent. Insufficient information to permit judgement. We did not have access to a trial register record or study protocol to know if there was a prespecified record of the studies outcomes
Other bias	Unclear risk	No other risks of bias found, but reporting was insufficient to permit judgement

Siris 1996

	Superiority design
Participants	Diagnostic criteria: Paget's disease of bone was confirmed by standard clinical, radiological or scinti-

graphic imaging or both methods

Inclusion criteria: Serum alkaline phosphatase at least twice the ULN if the participant had never been treated with bisphosphonates or plicamycin, or at least 4 times the ULN if the participant had received such therapy at any time in the past.

Exclusion criteria:

- treatment with any bisphosphonates or plicamycin within 12 months or calcitonin within 3 months preceding screening;
- osteolytic Pagetic lesion of a weight-bearing bone that may be a contra-indication for etidronate therapy;
- use of medications that might affect bone metabolism;
- associated health problems that could affect participation in the study or interfere with interpretation of the data, including active upper gastrointestinal, genitourinary, cardiovascular, liver, kidney or pulmonary disease.

Number screened: Not stated.

Number randomised: 89.

Number analysed: 88 (69 years, 67% male, percentages of monostotic and symptomatic participants not stated, 25% previously treated for Paget's disease of bone)



Siris 1996 (Continued)

Interventions

Two parallel treatment groups: alendronate 40 mg (1 x etidronate placebo tablet and 1 x 40 mg alendronate tablet for 6 months) and etidronate 400 mg (1 x 400 mg etidronate tablet and 1 x alendronate placebo tablet for 6 months).

Co-interventions: All participants received daily vitamin supplements containing 450 mg calcium carbonate and 400 IU vitamin D. Analgesics were available on demand and use was not balanced ("the regression analysis with adjustment for analgesics use at month 6 between the two treatment groups approached significance")

Outcomes

Outcomes reported in abstract

Primary endpoint: Mean percentage change from baseline in serum total alkaline phosphatase activity.

Secondary endpoints:

- mean percentage change from baseline in pain (measured using Brief Pain Inventory slightly modified for use in Paget's disease of bone);
- · adverse events related to use of bisphosphonates;
- withdrawal due to adverse events;
- participants who normalised alkaline phosphatase level.

Time points for measurement: Baseline, 1 month, 3 months, 6 months.

How were the outcomes measured: prospectively

Setting and date

11 centres in USA.

Period when the study was conducted: Not reported

Follow up period

6 months

Publication details and funding source

Language of publication: English.

Publication status: peer-reviewed journal; full article.

Funding source: Not reported.

Declarations of interest among primary researchers: Not reported

Notes

Transiliac bone biopsy was conducted for 43 participants at month 6. Bone biopsies were obtained from 25 healthy volunteers as control

Bias	Authors' judgement	Support for judgement
Random sequence genera-	Unclear risk	Quote: "the study was randomised".
tion (selection bias)		Comment: insufficient information provided to permit judgement. Allocation was probably centralized because this was a multicentre study
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided to permit judgement
Blinding of participants and personnel (perfor- mance bias)	Low risk	Quote: "The study was randomised and double blind", "The etidronate tablets were purchased as Didronel, crushed, and recompressed into tablets identical to placebo for etidronate".
All outcomes		Comment: Probably done.



Siris 1996 (Continued)		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Baseline and 6 months radiographs of one or more sites were read by one radiologist, who remained blind with respect to both treatment allocation and sequence of films". "Each specimen (bone biopsy) was blinded, so that the reader was unaware of the subjects' drug therapy."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Only one participant was excluded from the analysis (in the alendronate group). Reason for exclusion was reported.
		The proportion of missing outcomes compared with observed event risk was insufficient to have a relevant impact of the effect estimate
Selective reporting (reporting bias)	Unclear risk	Methods and results sections were consistent. Insufficient information to permit judgement. We did not have access to a trial register record or study protocol to know if there was a prespecified record of the studies outcomes
Other bias	Unclear risk	There were differences between groups in co-interventions because analgesics were taken on demand and use was not balanced. However this was thought unlikely to have resulted in bias. No other risks of bias found, but reporting was insufficient to permit judgement

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Interventional extension study including participants who complete a previous RCT (Langston 2010). The bisphosphonate of first choice in the intensive treatment arm was different from the original trial.

Randomisation ratio: 1:1 (symptomatic treatment: intensive treatment).

Superiority design

Participants

Diagnostic criteria: participants with Paget's disease of bone confirmed by plain radiology of at least one skeletal site according standard criteria from UK guidelines (Selby 2002)

Inclusion criteria: Participants who completed the PRISM trial (Langston 2010).

Exclusion criteria: No specific exclusion criteria were applied on the basis of treatment history, baseline alkaline phosphatase or co-existing diseases.

Number invited to participate: 2110

Number enrolled: 502

Number analysed: 404 (76 years, 54% male, 62% symptomatic, 91% previously treated with bisphosphonates for Paget's disease, 70% had normal alkaline phosphatase at baseline)

Interventions

Two parallel treatment groups; symptomatic vs. intensive treatment.

Symptomatic treatment: Philosophy; treat bone pain, not alkaline phosphatase.

- No treatment was administered for participants without symptoms referable to Paget's disease of bone.
 - For participants with pain caused by Paget's disease of bone, the first-line treatment was analgesics and nonsteroidal anti-inflammatory drugs.
 - o If there was an inadequate response, participants could be treated with: tiludronate (400 mg daily for 3 months), etidronate (400 mg daily for 3 to 6 months) or calcitonin (subcutaneously administered 50 to 100 units daily for 3 months).
 - Pamidronate (initial 30 g dose and further infusions of 30 mg until a response occurred to a maximum dose of 180 mg), and
 - Risedronate (30 mg daily for 2 months) could be used if there was inadequate response to previous treatment.



Tan 2017 (Continued)

 Zoledronate (5 mg as a single infusion) could be used if there was inadequate response to previous treatment

Intensive treatment: Philosophy; maintain normal alkaline phosphatase.

- · No treatment was administered for participants with normal alkaline phosphatase.
 - For participants with elevated alkaline phosphatase zoledronate 5 mg intravenously was chosen as
 first-line treatment. Risedronate (30 mg daily for 2 months), pamidronate (3 intravenous infusion of
 60 mg, total dose 180 mg), tiludronate (400 mg daily for 3 months), etidronate (400 mg daily for 3 to
 6 months) or calcitonin (subcutaneously administered 50 to 100 units daily for 3 months) could also
 be used. The aim was to restore and maintain alkaline phosphatase levels within the normal range;
 - o If there was an inadequate response, participants could be re-treated.

Co-interventions: Analgesics and nonsteroidal anti-inflammatory drugs

Outcomes

Primary outcome: radiologically-confirmed clinical fracture.

Secondary outcomes:

- adverse events related to use of bisphosphonates;
- · need for orthopaedic surgery;
- change in quality of life measures (assessed using SF-36) and
- mean percentage change from baseline in serum total alkaline phosphatase activity (alkaline phosphatase values were normalised to the upper limit of the reference range for each centre, which was set to a level of 1.0).

Time points for measurement: Data on fractures, orthopaedic procedures and serious adverse events were collected on a continuous basis. Laboratory data, quality of life, bone pain and adverse events (based on participant diaries) data were measured annually.

How were the outcomes measured: prospectively

Setting and date

30 secondary referral centres in the UK.

Period the study was conducted: January 2007 to January 2012

Follow up period

3 years

Publication details and funding source

Language of publication: English. **Publication status**: Abstract.

Funding source: The study was supported by grants from the Arthritis Research Campaign UK (Ref. 13627) and the National Association for Relief of Paget's Disease.

Declarations of interest among primary researchers:

- SHR reported receiving consulting fees on behalf of his institution from Novartis and Merck and a research grant to his institution from Amgen.
- WDF reported receiving consultancy fees from Siemens, Becton Dickinson and Roche. PLS reported receiving consultancy fees from Internis.
- All other authors stated they had no conflicts of interest.

Notes

The study was described by the authors as a "pragmatic randomised controlled trial designed to compare the effects of two management strategies". The study was not blinded

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "At the end of PRISM, patients were asked if they wanted to continue in the study for a further three years".



Tan 2017 (Continued)		
		Comment: The participants included in this trial had participated in a previous trial (Langston 2010). The risk of bias assessment should be the same as for the previous trial. However, as only participants who voluntarily agreed to continue in the study were included, it is difficult to verify if the balance among the trial groups created in the original trial by randomisation was kept in this extension study. At baseline serum alkaline phosphatase levels were lower in the intensive versus symptomatic group reflecting the fact that these participants already had been subjected to intensive treatment
Allocation concealment (selection bias)	High risk	Comment: The participants included in this trial had participated in a previous trial (Langston 2010). The risk of bias assessment is the same as for the previous trial
Blinding of participants and personnel (perfor- mance bias) All outcomes	Low risk	Comment: The study was not blinded. The main outcome (fractures) was unlikely to be influenced by lack of blinding. The risk of bias was high for quality of life, adverse events or bone pain, but low for other secondary endpoints as orthopaedic procedures or alkaline phosphatase concentrations
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Patient-reported fractures and orthopaedic procedures were validated against medical records and x-ray reports at participating centres by assessors blinded to treatment allocation"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Although a similar proportion of participants were deceased, withdrew from the study, declined to participate or were lost to follow up in each group (41/232 (18%) in the symptomatic versus 57/270 (21%) in the intensive group) at 3 years time, the proportion of missing outcomes compared with observed event risk is enough to induce clinically relevant bias in intervention effect estimate (fracture).
		However, the assessment of attrition bias is not assessed as high but low as, according to authors, the study was an event driven trial, with fracture as the primary endpoint. Data on all fracture events were available even in subjects who had withdrawn from the study
Selective reporting (reporting bias)	Low risk	Study protocol available. There was a prespecified record of the studies outcomes and all of them were included in published manuscript
Other bias	Unclear risk	The study design permitted attending clinicians to choose between different drugs within a specified treatment strategy. Evidence that the attending clinicians adhered to this strategy was confirmed by the observed difference in alkaline phosphatase levels between groups

Walsh 2004

Methods	RCT. Randomisation ratio: 1:1 (alendronate 40 mg: pamidronate 60 mg).
	Superiority design
Participants	Diagnostic criteria: Paget's disease of bone was confirmed by the presence of typical lesions of Paget's disease on isotope bone scanning and radiographs.
	Inclusion criteria: Serum alkaline phosphatase above the upper limit of laboratory reference range.
	Exclusion criteria:

• participants previously treated were excluded if < 3 months had elapsed since calcitonin treatment or < 6 months since bisphosphonate treatment, and if Paget's disease of bone was in biochemical relapse, defined as plasma total alkaline phosphatase > 135 μ /L and at least 50% higher than the nadir



Walsh 2004 (Continued)

value during previous treatment accompanied by radiological relapse of previously demonstrated lytic lesions.

 major comorbidity, untreated vitamin D deficiency, primary hyperparathyroidism, metabolic bone disease other than uncomplicated osteoporosis, recent partial or complete fracture through pagetic bone, clinically significant upper gastrointestinal disease, liver disease, and kidney impairment (plasma creatinine > 150 Amol/L).

Number screened: 139.

Number randomised: 72.

Number analysed: 72 (70 years, 58% male, % monostotic not stated, 94% symptomatic participants, 39% participants previously treated for Paget's disease of bone)

Interventions

Two parallel treatment groups: alendronate 40 mg daily in 3 months blocks and pamidronate four x 60 mg IV infusions a year (once every 3 months). Treatment was continued until biochemical remission was achieved or there were a no significant reduction on two consecutives measurements. Biochemical remission was defined as both, serum total alkaline phosphatase activity and urine deoxypyridinoline/creatinine ratio within the reference range.

Co-interventions: All participants with plasma baseline total alkaline phosphatase > 675 U/L were prescribed ergocalciferol 30,000 U weekly for 3 months and calcium carbonate 600 mg daily for 8 months to minimize bisphosphonate-induced secondary hyperparathyroidism. Other participants were treated with calcium and vitamin D supplements at the treating clinician's discretion

Outcomes

Outcomes reported in abstract:

Primary endpoint: Proportion of participants achieving biochemical remission (see above).

Secondary endpoints: Numbers of participants; with change in bone pain (measured on VAS); with change on quality of life from baseline (assessed using the SF-36 Australian version); who experienced severe side effects related to use of bisphosphonates; who withdrew due to adverse events, mean percentage change from baseline in serum total alkaline phosphatase activity; who normalised alkaline phosphatase level; and who relapsed due to recurrence of increased serum alkaline phosphatase level.

Time points for measurement: Baseline, 3, 6, 9, 12, 18 and 24 months.

How were the outcome measured: Prospectively

Setting and date

Three centres in Western Australia.

Period when the study was conducted: From May 1997 to October 2001

Follow up period

1 year without protocol amendment (2 year with protocol amendment)

Publication details and funding source

Language of publication: English.

Publication status: peer-reviewed journal; full article.

Funding source: Although the authors described the trial as an "investigator-initiated study", the study was supported by research grants from Merck, Sharp & Dohme (Australia), Novartis Pharmaceuticals Australia and the Arthritis Foundation of Western Australia.

Declarations of interest among primary researchers: Not stated

Notes

The initial protocol was amended to cross participants over from pamidronate to alendronate treatment at 12 months. According to the author, it was apparent that some participants randomised to pamidronate were showing little or no biochemical response to treatment and for "ethical" reasons, they amended the protocol so that participants randomised to pamidronate who did not achieve biochemical remission at 12 months were crossed over to alendronate treatment for the second year of the study.

We included data from the first year only in the meta-analysis.



Walsh 2004 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement		
Random sequence generation (selection bias)	Low risk	Quote: "To ensure that the two treatment groups were well matched, randomisation was stratified (using an in-house computer program) by two variables: baseline plasma alkaline phosphatase (in three strata: 136–270, 271–675, > 675 U/L) and previous bisphosphonate treatment (as a binary variable: yes or no)." "In the course of the study, it was apparent that some patients randomised to pamidronate (predominantly in the previously treated subgroup) were showing little or no biochemical response to treatment. For ethical reasons, the protocol was amended so that patients randomised to pamidronate who did not achieve biochemical remission at 12 months were crossed over to alendronate treatment for the second year of the study".		
		Comment: The risk assessment was judged as low risk for first year data. For the second year, allocation was broken, and the risk of bias was assessed as high		
Allocation concealment (selection bias)	Low risk	Authors describe using a computer program to generate the allocation		
Blinding of participants and personnel (perfor- mance bias) All outcomes	High risk	Open label trial		
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open label trial		
Incomplete outcome data (attrition bias)	Low risk	Quote: "Proportions of patients achieving remission for each treatment (on an intention to treat basis) were compared by Fisher's exact test".		
All outcomes		Comment: Data on screened participants, randomised participants and withdrawals (with reasons) are reported in a flow chart (Figure 1)		
Selective reporting (reporting bias)	Unclear risk	Methods and results sections were consistent. Insufficient information to permit judgement. We did not have access to a trial register record or study protocol to know if there was a prespecified record of the studies outcomes		
Other bias	Unclear risk	Likely high at 12 months due to amendment of the initial protocol. No other risks of bias found, but reporting was insufficient to permit judgement		

 $Abbreviations: IV-intravenous; RCT-randomised\ controlled\ trial; ULN-upper\ limit\ of\ normal$

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Adami 1994	Not a randomised clinical study. Study without a comparison of interest. The study compared alendronate (20 mg or 40 mg daily) for 3 to 6 months
Adami 2002	Randomised clinical study. Study without a comparison of interest. The study compared three doses of neridronate (12.5 mg, 25 mg, 50 mg or 100 mg daily for two consecutive days)



Study	Reason for exclusion
Altman 1985	Not a randomised clinical study. Study without a comparison of interest. The study describes the outcomes in a series of participants treated with different regimes of oral Etidronate (5 mg/kg daily for 6 months, 10 mg/kg daily for 3 months, or 20 mg/kg daily for 3 moths).
Arlot 1981	Not a randomised clinical study. Study without an outcome of interest. The study was designed to analyse the effect of different doses of Etidronate (5 mg/kg or 20 mg/kg for 6 months) or clodronate (400 mg/day or 1600 mg/day for 6 months) over the serum acid level.
Atkins 1987	Not a randomised clinical study. Study without a comparison of interest. The study compares three doses of the Neridronate (400 mg oral for one month, 25 mg daily infusion for 5 days and 50 mg daily infusion for 5 days).
Buckler 1998	Randomised clinical study. Study without a comparison of interest. The study compared two regimes of administration of pamidronate (initial 30 mg infusion followed by three infusion of 60 mg and a final placebo infusion at fortnightly intervals or initial placebo infusion followed by three infusion of 60 mg and a final 30 mg infusion at fortnightly intervals), with the same total dose (210 mg).
Cundy 2016	Not a randomised clinical study. Study without a comparison of interest. The study shows data from a cohort of 107 elderly participants (mean age 76 years) treated with intravenous zoledronate followed-up for 10 years.
Delmas 1982	Randomised clinical study. Study without a comparison of interest. The study compared four doses of clodronate (400, 800, 1600 or 2400 mg daily), with (the four doses) or without (only 400 and 1600 mg doses) vitamin D and calcium supplementation (elemental calcium 1g/day and vitamin D2 8000 IU/day).
Devogelaer 1997	Data on a sample of participants diagnosed with Paget's disease of bone from a randomised clinical trial (Roux 1995). The study was designed to analyse radiological changes during treatment with bisphosphonates.
Devogelaer 2014	Not a randomised clinical study. Study without a comparison of interest. Data from the Belgian Paget's Disease Registry of patients diagnosed as Paget's disease of bone and treated with a 5 mg intravenous infusion of zoledronate.
Dewis 1985	Not a randomised clinical study. Study with a comparison of interest. "Open trial" (9 participants were randomised and 8 participants were put directly into one of the two treatment groups) comparing the effectiveness of two bisphosphonates (etidronate 20 mg/kg once daily for 3 months vs. pamidronate 4 to 5 mg/kg twice daily for 3 months).
Donáth 2004	Case-control study. Study without a comparison of interest. Cases were patients diagnosed as Paget's disease of bone with temporal bone involvement. Control were healthy individuals matched for age and sex. The study was designed to analyse the effectiveness of two bisphosphonates (pamidronate 30 mg daily infusion for 6 days or oral tiludronate 400 mg daily for 3 months). The study included audiometric assessment and hearing threshold examination.
Filipponi 1994	Not a randomised clinical study. Study with a comparison of interest. The study compares the effectiveness of two bisphosphonates (Clodronate 300 mg/daily intravenous infusion for 5 consecutive days vs. Alendronate 5 mg/daily intravenous infusion for 5 consecutive days).
Gallacher 1991	Not a randomised clinical study. Study without a comparison of interest. The study compares three regimes of administration of pamidronate, two with a total dose of 180 mg (30 mg weekly infusions for 6 weeks or 45 mg infusions every 3 months for one year) and one with a total dose of 360 mg (30 mg weekly infusions for 6 weeks and 60 mg weekly infusions for three additional weeks). A random subgroup of 6 participants were given placebo infusions of 0.9% saline weekly for three weeks at the start of treatment in a single-blind study in the group of 30 mg weekly doses for 6 weeks (data are not shown on manuscript).



Study	Reason for exclusion				
Garnero 1998	Data on a sample of participants diagnosed as Paget's disease of bone from a randomised clinical trial, and a case-control study. For the case-control study, cases were selected from three of five groups of a clinical trial on Paget's disease of bone (Schaffer 1996). Controls were healthy individuals matched for age and sex. The clinical trial included the cases and was designed to analyse the effect of zoledronate on bone turnover markers.				
Garnero 2001	Data on a sample of participants diagnosed with Paget's disease of bone from a randomised clinical trial and a case-control study (selected from a clinical trial on Paget's disease of bone, Schaffer 1996). Controls were healthy age-matched individuals. The clinical trial included the cases and was designed to analyse the effect of zoledronate on bone turnover markers				
Goldman 1975	Data from a sample of participants diagnosed with Paget's disease of bone from a randomised clinical trial (Altman 1973). The study was designed to assess the changes in radionuclide uptake after bisphosphonate treatment				
Grauer 1999	Not a randomised clinical study. Study without a comparison of interest. The study compared three different doses of ibandronate (2 mg, 4 mg or 6 mg intravenous infusions) for re-treatment of participants previously treated with ibandronate after biochemical <i>relapse</i> (increase of alkaline phosphatase).				
Gutteridge 1996	Not a randomised clinical study. Study without a comparison of interest. The study compared three different doses of pamidronate. Participation allocation had two steps: three groups according to index of bone resorption (urinary hydroxyproline x plasma creatinine/urinary creatinine). The higher the index (< 5 , 5 to 9.99, ≥ 10), the higher the pamidronate dose (120 mg, 180 mg, 240 mg). The three groups were then randomised to two subgroups; total dose in 30 mg infusions or total dose in 60 mg infusions				
Hooper 2009	Randomised clinical study. Study without a comparison of interest. The study compared admini tration of alendronate 280 mg weekly vs. 40 mg daily for 6 months				
Hosking 1976	Not a randomised clinical study. Study without a comparison of interest. The study compared administration of etidronate (7.5 mg/kg or 15 mg/kg daily and etidronate plus calcitonin simultaneously (etidronate 7.5 mg/kg daily together with calcitonin 0.5 mg once daily subcutaneous for 6 months) or sequentially (etidronate 15 mg/kg daily for 6 months followed by calcitonin 0.5 mg twice daily subcutaneous for 6 months)				
Khairi 1974	Extension study (Altman 1973) with a non-randomised crossover design. The groups from the original study (placebo and etidronate doses of 1 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 20 mg/kg) were reassigned to different doses of etidronate for six additional months. Participants from placebo and 1 mg/kg and 2.5 mg/kg groups were reassigned to etidronate on doses of 5 mg/kg, 10 mg/kg or 20 mg/kg. Participants from the 5 mg/kg group were kept on the same dose. Participants from the 10 mg/kg or 20 mg/kg groups were reassigned to placebo or to remain on the same etidronate dose				
Khairi 1977	Not a randomised clinical study. Study without a comparison of interest. Data from a cohort of participants diagnosed with Paget's disease of bone who were treated with etidronate; 60/116 participants took part in a previous study (Khairi 1974)				
Khan 1997	Randomised clinical study. Study without a comparison of interest. The study compared different doses (40 or 80 mg/daily) and regimens (3 or 6 months) of oral alendronate				
Lombardi 1999	Review. Compilation of the results of two RCTs on alendronate for Paget's disease of bone (Reid 1996 and Siris 1996).				
Mazeries 1996	Not a randomised clinical study. Study without a comparison of interest. The study compared two regimens of pamidronate infusion (1 infusion of 60 mg vs. 2 infusions of 60 mg over 24 hours)				



Study	Reason for exclusion
Merlotti 2011	Randomised clinical study. Study without a comparison of interest. The study compared two regimens of neridronate (100 mg intravenous infusion for 2 consecutive days vs. 25 mg intramuscular infusion once a week for 2 months)
O'Doherty 1995	Not a randomised clinical study. Study without a comparison of interest. The study compared three doses of intravenous alendronate (2.5 mg, 5 mg and 10 mg daily) for 5 consecutive days
Pepersack 1994	Not a randomised clinical study. Study without a comparison of interest. The study compared one oral and four intravenous regimens of pamidronate (600 mg daily for 6 months, 40 mg daily for five days, 20 mg daily for 10 days, 10 mg daily for 4 days and a single dose of 10 mg)
Reginster 1988	Randomised clinical study. Study without a comparison of interest. The study compared three regimens of tiludronate (200 mg daily for 6 months, 400 mg daily for 6 months, 200 mg daily for 3 months and 400 mg daily for 3 additional months)
Reginster 1993	Randomised clinical study. Study without a comparison of interest. The study compared three regimens of tiludronate (600 mg, 800 mg and 1200 mg daily) for five days
Russell 1974	Not a randomised clinical study. Study without a comparison of interest. The study compared four doses of etidronate (1 mg, 5 mg, 10 mg and 20 mg) for 6 months and placebo
Siris 1980	Extension study (of Canfield 1977). Only participants from the Columbia Presbyterian Medical Center (1 of the 4 hospitals in the original trial) were included in the study. All participants were treated with etidronate
Stone 1990	Not a randomised clinical study. Study without a comparison of interest. The study compared three regimens of pamidronate (15 mg, 30 mg, or 45 mg infusions) at 6 week intervals
Vega 1994	Randomised clinical study. Study without a comparison of interest. The study compared seven regimens of pamidronate in two formulations (3 dose levels of oral capsules of pamidronate; 300 mg, 600 mg and 900 mg and four dose levels of oral tables of dimethyl pamidronate; 50 mg, 100 mg, 200 mg and 400 mg). Each dose was administered for 15 days

Characteristics of ongoing studies [ordered by study ID]

ISRCTN11616770

Trial name or title	Zoledronate in the Prevention of Paget's: the ZiPP study	
That hame of title	Zolearonate in the Prevention of Paget's: the ZIPP study	
Methods	Multisite double blind placebo controlled randomised trial.	
	Two sub-studies:	
	 Interventional: To determine if targeted intervention with zoledronate can prevent the develop ment of raised bone turnover and/or focal bone lesions in subjects who are genetically predis posed to develop Paget's disease of bone (PDB) because they carry mutations in SQSTM1 that have previously been associated with PDB. 	
	 Observational: To determine if a genetic test cause increased anxiety and depression, even if found not to have the SQSTM1 gene mutation and to determine if there is any difference in the biochemical makers which are predictive of the disease in patients without SQSTM1 gene muta- tion group compared to the group who have the mutation. 	
	Follow up: 5 years.	
Participants	Participant inclusion criteria	



SRCTN11616770 (Continued)				
(continues)	Interventional study: Relatives of patients with SQSTM1 mutations, aged 30 years old or greater, who carry SQSTM1 mutations and who have not already diagnosed with PDB at study entry			
	Observational study:			
	Relatives of patients with SQSTM1 mutations, aged between 30 years old or greater who on screening are found NOT to have SQSTM1 mutations			
	Countries of recruitment: Australia, Belgium, Ireland, Italy, Spain, United Kingdom.			
Interventions	Interventional study: Participants will be randomised to either infusions of zoledronate (Aclasta®) 5 mg by intravenous infusion over 15 minutes or placebo (0.9% saline) at baseline.			
Outcomes	Interventional study:			
	Primary outcome: Total number of subjects who develop new bone lesions between the baseline visit and the final follow up visit.			
	Observational study:			
	Primary outcome: Anxiety/depression, measured using the HADS scale.			
	Both studies:			
	Secondary outcomes:			
	1. Development of elevated bone turnover, as measured by alkaline phosphatase and other biochemical markers of bone turnover.			
	2. Quality of life, and anxiety and depression assessed by the SF-36, BPI and HADS questionnaires.			
Starting date	12/01/2009			
Contact information	Mr Adam Wilson			
	Clinical Trials Manager			
	e-mail: zipptri1@exseed.ed.ac.uk			
Ending date	31/01/2020			
Target number of participants	Intervention study: 188 participants			
	Observational study: 125 participants			
Identifier	ISRCTN11616770 DOI 10.1186/ISRCTN11616770			
Notes	Sponsor information: University of Edinburgh (UK)			
	Funder name: Medical Research Council (MRC) (UK) (ref: G0701625; 85281)			

NCT02106455

Trial name or title	Takeda Study Registration Call Center, post marketing Group Manager		
Methods	Prospective cohort		
Participants	Inclusion criteria: participants diagnosed with Paget's disease of bone treated with sodium risedronate tablets		



NCT02106455 (Continued)	Exclusion criteria: No exclusions by age or gender Countries of recruitment: Japan Sodium risedronate tablets (Benet 17.5 mg) administered orally with a sufficient volume (approximately 180 mL) of water once daily after waking for 8 consecutive weeks.			
Interventions				
Outcomes	Primary outcome:			
	 Frequency of adverse drug reactions (Time Frame: For 48 weeks). Adverse events are defined as any unfavourable and unintended signs, symptoms or diseases temporally associated with ad- ministration of sodium risedronate whether or not it was considered related to treatment. Among these, events that are considered as having a causal relationship with sodium risedronate are de- fined as adverse drug reactions 			
	Secondary outcomes:			
	 Bone metabolism markers (Time Frame: From baseline to week 48) Pain associated with osseous Paget's disease (Time Frame: From baseline to week 48) Serum alkaline phosphatase (Time Frame: From baseline to week 48) Treatment compliance (Time Frame: From baseline to week 48) 			
Starting date	September 2008			
Contact information	Telephone: 1-800-778-2860 (USA & EU), email: medicalinformation@tpna.com			
Ending date	Estimated study completion date: July 2017.			
Target number of participants	2500			
Identifier	ClinicalTrials.gov Identifier: NCT02106455			
Notes	Sponsor information: Takeda			

DATA AND ANALYSES

Comparison 1. Bisphosphonates versus placebo

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Number of participants whose bone pain disappeared completely	2	205	Risk Ratio (M-H, Random, 95% CI)	3.42 [1.31, 8.90]
2 Number of participants with change in bone pain	7	481	Risk Ratio (M-H, Random, 95% CI)	1.97 [1.29, 3.01]
2.1 Etidronate vs. placebo	3	124	Risk Ratio (M-H, Random, 95% CI)	1.75 [0.79, 3.87]
2.2 Tiludronate vs. placebo	3	344	Risk Ratio (M-H, Random, 95% CI)	1.98 [1.27, 3.08]



Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
2.3 Alendronate vs. placebo	1	13	Risk Ratio (M-H, Random, 95% CI)	10.00 [0.69, 144.38]
3 Number of participants experiencing radiologically-confirmed clinical fractures	4	356	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.18, 4.51]
3.1 Etidronate vs. placebo	2	95	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.09, 9.06]
3.2 Tiludronate vs. placebo	2	261	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.09, 8.64]
4 Number of participants who experienced adverse events related to use of bisphosphonates	6	678	Risk Difference (M-H, Random, 95% CI)	0.11 [-0.00, 0.22]
4.1 Etidronate vs. placebo	1	47	Risk Difference (M-H, Random, 95% CI)	0.02 [-0.21, 0.25]
4.2 Zoledronate vs. placebo	1	176	Risk Difference (M-H, Random, 95% CI)	0.27 [0.12, 0.42]
4.3 Tiludronate vs. placebo	3	400	Risk Difference (M-H, Random, 95% CI)	0.07 [-0.08, 0.22]
4.4 Alendronate vs. placebo	1	55	Risk Difference (M-H, Random, 95% CI)	0.12 [-0.11, 0.34]
5 Number of participants who withdrew due to adverse events	6	517	Odds Ratio (M-H, Random, 95% CI)	1.01 [0.38, 2.69]
5.1 Etidronate vs. placebo	1	47	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Tiludronate vs. placebo	3	400	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.34, 2.67]
5.3 Alendronate vs. placebo	2	70	Odds Ratio (M-H, Random, 95% CI)	1.74 [0.06, 50.43]
6 Mean percentage change from baseline in serum total alkaline phosphatase level	8	592	Mean Difference (IV, Random, 95% CI)	-50.09 [-67.72, -32.46]
6.1 Etidronate vs. placebo	3	122	Mean Difference (IV, Random, 95% CI)	-55.85 [-66.50, -45.20]
6.2 Zoledronate vs. placebo	1	176	Mean Difference (IV, Random, 95% CI)	-22.26 [-27.99, -16.53]
6.3 Tiludronate vs. placebo	2	256	Mean Difference (IV, Random, 95% CI)	-58.0 [-64.25, -51.75]



Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
6.4 Alendronate vs. placebo	1	15	Mean Difference (IV, Random, 95% CI)	-39.9 [-51.28, -28.52]
6.5 Ibandronate vs. placebo	1	23	Mean Difference (IV, Random, 95% CI)	-96.1 [-147.01, -45.19]
7 Number of participants who achieved normalised alkaline phosphatase level	8	580	Risk Ratio (M-H, Random, 95% CI)	9.96 [3.74, 26.58]
7.1 Etidronate vs. placebo	3	121	Risk Ratio (M-H, Random, 95% CI)	4.51 [0.90, 22.55]
7.2 Tiludronate vs. placebo	3	381	Risk Ratio (M-H, Random, 95% CI)	13.79 [2.77, 68.61]
7.3 Alendronate vs. placebo	1	55	Risk Ratio (M-H, Random, 95% CI)	27.96 [1.74, 448.28]
7.4 Ibandronate vs. placebo	1	23	Risk Ratio (M-H, Random, 95% CI)	14.00 [0.92, 212.92]

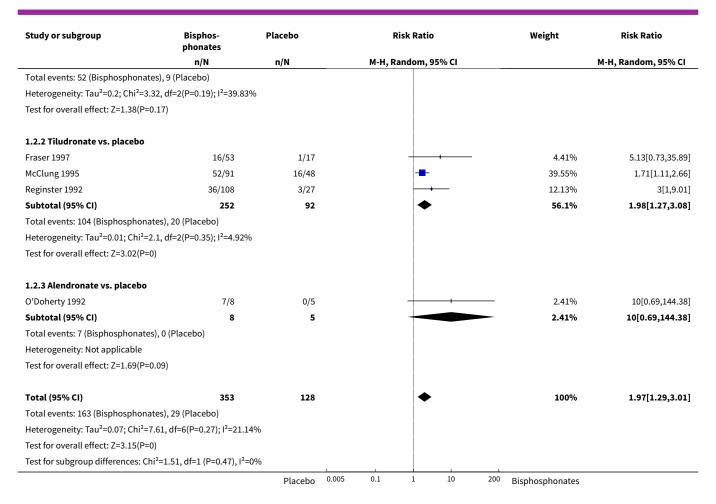
Analysis 1.1. Comparison 1 Bisphosphonates versus placebo, Outcome 1 Number of participants whose bone pain disappeared completely.

Study or subgroup	Bisphos- phonates	Placebo	Risk Ratio					Weight	Risk Ratio	
	n/N	n/N		М-Н	, Random, 95	6% CI			M-H, Random, 95% CI	
Fraser 1997	16/53	1/17			+	-		24.22%	5.13[0.73,35.89]	
Reginster 1992	36/108	3/27						75.78%	3[1,9.01]	
Total (95% CI)	161	44				>		100%	3.42[1.31,8.9]	
Total events: 52 (Bisphosphor	nates), 4 (Placebo)									
Heterogeneity: Tau ² =0; Chi ² =0	.22, df=1(P=0.64); I ² =0%									
Test for overall effect: Z=2.52(P=0.01)		1							
		Placebo	0.02	0.1	1	10	50	Bisphosphonates		

Analysis 1.2. Comparison 1 Bisphosphonates versus placebo, Outcome 2 Number of participants with change in bone pain.

Study or subgroup	Bisphos- Placebo phonates		Risk Ratio					Weight	Risk Ratio	
	n/N	n/N		M-H, Random, 95% CI					M-H, Random, 95% CI	
1.2.1 Etidronate vs. placebo										
Altman 1973	21/38	3/9			+	_		14.92%	1.66[0.63,4.36]	
Canfield 1977	18/36	5/12			-			21.9%	1.2[0.57,2.53]	
Ralston 1987	13/19	1/10			-	+	-	4.68%	6.84[1.04,45.03]	
Subtotal (95% CI)	93	31				-		41.49%	1.75[0.79,3.87]	
		Placebo	0.005	0.1	1	10	200	Bisphosphonates		

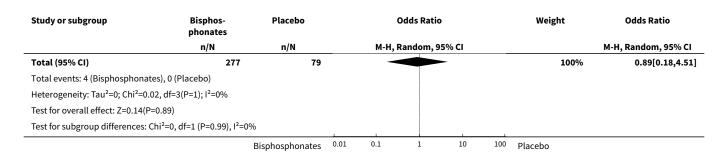




Analysis 1.3. Comparison 1 Bisphosphonates versus placebo, Outcome 3 Number of participants experiencing radiologically-confirmed clinical fractures.

Study or subgroup	Bisphos- phonates	Placebo	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
1.3.1 Etidronate vs. placebo					
Altman 1973	1/38	0/9		24.55%	0.76[0.03,20.17]
Canfield 1977	1/36	0/12		24.76%	1.06[0.04,27.65]
Subtotal (95% CI)	74	21		49.31%	0.9[0.09,9.06]
Total events: 2 (Bisphosphonates)	, 0 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =0.02,	df=1(P=0.89); I ² =0%				
Test for overall effect: Z=0.09(P=0.	93)				
1.3.2 Tiludronate vs. placebo					
Fraser 1997	1/86	0/26		25.3%	0.93[0.04,23.51]
Reginster 1992	1/117	0/32		25.39%	0.84[0.03,21.03]
Subtotal (95% CI)	203	58		50.69%	0.88[0.09,8.64]
Total events: 2 (Bisphosphonates)	, 0 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =0, df=	=1(P=0.96); I ² =0%				
Test for overall effect: Z=0.11(P=0.	91)				
	1	3isphosphonates 0.0	1 0.1 1 10 1	⁰⁰ Placebo	



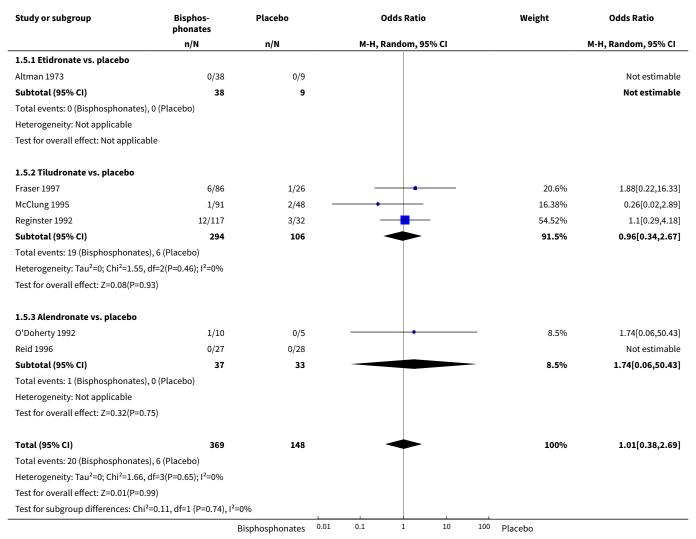


Analysis 1.4. Comparison 1 Bisphosphonates versus placebo, Outcome 4 Number of participants who experienced adverse events related to use of bisphosphonates.

Study or subgroup	Bisphos- phonates	Placebo	Risk Difference	Weight	Risk Difference
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
1.4.1 Etidronate vs. placebo					
Altman 1973	5/38	1/9		13.24%	0.02[-0.21,0.25]
Subtotal (95% CI)	38	9	*	13.24%	0.02[-0.21,0.25]
Total events: 5 (Bisphosphonates), 1	(Placebo)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.17(P=0.86	i)				
1.4.2 Zoledronate vs. placebo					
Buckler 1999	62/141	6/35		19.54%	0.27[0.12,0.42]
Subtotal (95% CI)	141	35	•	19.54%	0.27[0.12,0.42]
Total events: 62 (Bisphosphonates),	6 (Placebo)				
Heterogeneity: Not applicable					
Test for overall effect: Z=3.52(P=0)					
1.4.3 Tiludronate vs. placebo					
Fraser 1997	65/86	14/26		14.55%	0.22[0.01,0.43]
McClung 1995	79/91	43/48	-	23.03%	-0.03[-0.14,0.08]
Reginster 1992	71/117	17/32	- •	15.84%	0.08[-0.12,0.27]
Subtotal (95% CI)	294	106	•	53.42%	0.07[-0.08,0.22]
Total events: 215 (Bisphosphonates), 74 (Placebo)				
Heterogeneity: Tau ² =0.01; Chi ² =4.84	, df=2(P=0.09); I ² =58.7	2%			
Test for overall effect: Z=0.89(P=0.37	·)				
1.4.4 Alendronate vs. placebo					
Reid 1996	8/27	5/28		13.8%	0.12[-0.11,0.34]
Subtotal (95% CI)	27	28		13.8%	0.12[-0.11,0.34]
Total events: 8 (Bisphosphonates), 5	(Placebo)				
Heterogeneity: Not applicable					
Test for overall effect: Z=1.03(P=0.3)					
Total (95% CI)	500	178	•	100%	0.11[-0,0.22]
Total events: 290 (Bisphosphonates), 86 (Placebo)				
Heterogeneity: Tau ² =0.01; Chi ² =12.1	7, df=5(P=0.03); l ² =58.	92%			
Test for overall effect: Z=1.87(P=0.06					
Test for subgroup differences: Chi ² =	4.74, df=1 (P=0.19). I ² =	36.7%			



Analysis 1.5. Comparison 1 Bisphosphonates versus placebo, Outcome 5 Number of participants who withdrew due to adverse events.



Analysis 1.6. Comparison 1 Bisphosphonates versus placebo, Outcome 6 Mean percentage change from baseline in serum total alkaline phosphatase level.

Study or subgroup	Bisph	sphosphonates Pla		lacebo	Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
1.6.1 Etidronate vs. placebo							
Altman 1973	38	-41.4 (0)	9	13 (0)			Not estimable
Canfield 1977	36	-57 (24)	12	5 (27)		16.85%	-62[-79.17,-44.83]
Ralston 1987	18	-53 (24)	9	-1 (12)	-	17.93%	-52[-65.58,-38.42]
Subtotal ***	92		30		•	34.78%	-55.85[-66.5,-45.2]
Heterogeneity: Tau ² =0; Chi ² =0.8	3, df=1(P=0.37); I ² =0%					
Test for overall effect: Z=10.28(F	P<0.0001)						
			Bisp	ohosphonates	-100 -50 0 50 100	Placebo	

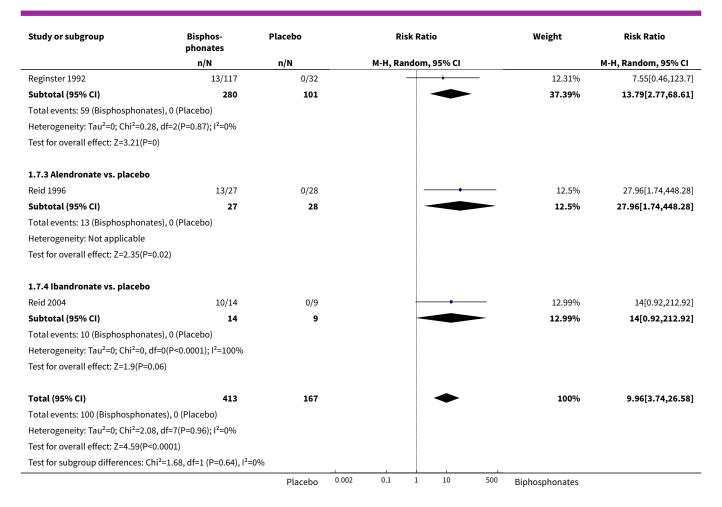


Study or subgroup	Bisph	osphonates	P	lacebo	Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
1.6.2 Zoledronate vs. placebo							
Buckler 1999	141	-28.9 (21.4)	35	-6.6 (13.6)	+	19.64%	-22.26[-27.99,-16.53]
Subtotal ***	141		35		•	19.64%	-22.26[-27.99,-16.53]
Heterogeneity: Not applicable							
Test for overall effect: Z=7.62(P<0.0	0001)						
1.6.3 Tiludronate vs. placebo							
McClung 1995	91	-53 (21)	48	5 (16)	*	19.56%	-58[-64.25,-51.75]
Reginster 1992	85	-45.3 (13.9)	32	8 (0)			Not estimable
Subtotal ***	176		80		♦	19.56%	-58[-64.25,-51.75]
Heterogeneity: Not applicable							
Test for overall effect: Z=18.18(P<0	.0001)						
1.6.4 Alendronate vs. placebo							
O'Doherty 1992	10	-25.7 (10.8)	5	14.2 (10.5)	+	18.51%	-39.9[-51.28,-28.52]
Subtotal ***	10		5		•	18.51%	-39.9[-51.28,-28.52]
Heterogeneity: Not applicable							
Test for overall effect: Z=6.87(P<0.0	0001)						
1.6.5 Ibandronate vs. placebo							
Reid 2004	14	-67.6 (15)	9	28.5 (77)		7.5%	-96.1[-147.01,-45.19]
Subtotal ***	14		9			7.5%	-96.1[-147.01,-45.19]
Heterogeneity: Not applicable							
Test for overall effect: Z=3.7(P=0)							
Total ***	433		159		•	100%	-50.09[-67.72,-32.46]
Heterogeneity: Tau ² =403.38; Chi ² =	32.35, df=5	(P<0.0001); I ² =93	3.93%				
Test for overall effect: Z=5.57(P<0.0	0001)						
Test for subgroup differences: Chi ²	=81.55, df=	=1 (P<0.0001), I ² =	95.09%				

Analysis 1.7. Comparison 1 Bisphosphonates versus placebo, Outcome 7 Number of participants who achieved normalised alkaline phosphatase level.

Study or subgroup	Bisphos- phonates	Placebo	Ri	isk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Ra	ındom, 95% CI		M-H, Random, 95% CI
1.7.1 Etidronate vs. placebo	•					
Altman 1973	7/38	0/9	-	+	12.48%	3.85[0.24,61.82]
Canfield 1977	6/36	0/12	-	+	12.22%	4.57[0.28,75.58]
Ralston 1987	5/18	0/8		+	12.42%	5.21[0.32,84.35]
Subtotal (95% CI)	92	29			37.12%	4.51[0.9,22.55]
Total events: 18 (Bisphosphor	nates), 0 (Placebo)					
Heterogeneity: Tau ² =0; Chi ² =0	0.02, df=2(P=0.99); I ² =0%					
Test for overall effect: Z=1.83((P=0.07)					
1.7.2 Tiludronate vs. placeb	0					
Fraser 1997	27/72	0/21		-	12.67%	16.58[1.05,260.83]
McClung 1995	19/91	0/48			12.4%	20.77[1.28,336.71]
		Placebo	0.002 0.1	1 10 50	⁰ Biphosphonates	





Comparison 2. Aminobisphosphonates versus non-aminobisphosphonates

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Mean change from baseline in pain	1		Mean Difference (IV, Random, 95% CI)	Totals not select- ed
1.1 Risedronate vs. etidronate	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 Number of participants who experienced adverse events related to use of bisphosphonates	2	212	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.72, 1.35]
2.1 Risedronate vs. etidronate	1	123	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.68, 1.43]
2.2 Alendronate vs. etidronate	1	89	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.55, 1.76]
3 Number of participants who with- drew due to adverse events	2	212	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.25, 1.89]

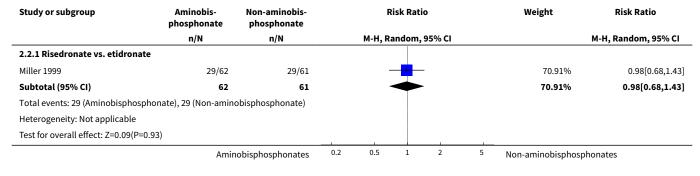


Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
3.1 Risedronate vs. etidronate	1	123	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.22, 2.79]
3.2 Alendronate vs. etidronate	1	89	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.11, 2.90]
4 Mean percentage change from baseline in serum total alkaline phosphatase level	2	212	Mean Difference (IV, Random, 95% CI)	-40.95 [-49.09, -32.81]
4.1 Risedronate vs. etidronate	1	123	Mean Difference (IV, Random, 95% CI)	-43.9 [-48.06, -39.74]
4.2 Alendronate vs. etidronate	1	89	Mean Difference (IV, Random, 95% CI)	-35.1 [-45.85, -24.35]
5 Number of participants who achieved normalised alkaline phosphatase level	2	212	Risk Ratio (M-H, Random, 95% CI)	4.30 [2.72, 6.79]
5.1 Risedronate vs. etidronate	1	123	Risk Ratio (M-H, Random, 95% CI)	4.81 [2.58, 8.98]
5.2 Alendronate vs. etidronate	1	89	Risk Ratio (M-H, Random, 95% CI)	3.78 [1.93, 7.38]

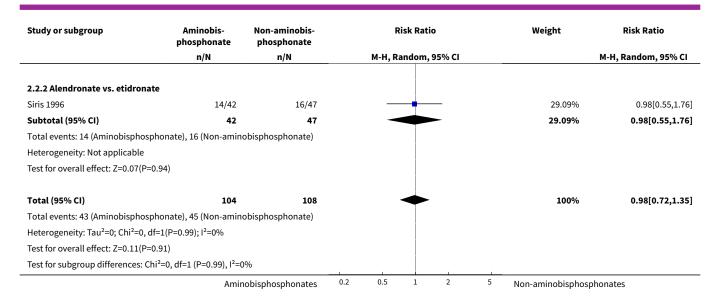
Analysis 2.1. Comparison 2 Aminobisphosphonates versus nonaminobisphosphonates, Outcome 1 Mean change from baseline in pain.

Study or subgroup	Aminobisphosphonate			Non-aminobis- phosphonate		Mean Difference				Mean Difference	
	N	Mean(SD)	N	Mean(SD)		Ran	dom, 95	5% CI		Random, 95% CI	
2.1.1 Risedronate vs. etidronate											
Miller 1999	62	-8.7 (7.3)	61	-6.1 (6.4)		-	-			-2.6[-5.03,-0.17]	
			Amino	obisphosphonates	-5	-2.5	0	2.5	5	Non-aminobisphospho- nates	

Analysis 2.2. Comparison 2 Aminobisphosphonates versus non-aminobisphosphonates, Outcome 2 Number of participants who experienced adverse events related to use of bisphosphonates.







Analysis 2.3. Comparison 2 Aminobisphosphonates versus non-aminobisphosphonates, Outcome 3 Number of participants who withdrew due to adverse events.

Study or subgroup	Aminobis- phosphonate	Non-aminobis- phosphonate	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95%	6 CI	M-H, Random, 95% CI
2.3.1 Risedronate vs. etidronate					
Miller 1999	4/62	5/61		62.8%	0.79[0.22,2.79]
Subtotal (95% CI)	62	61		62.8%	0.79[0.22,2.79]
Total events: 4 (Aminobisphosphona	ite), 5 (Non-aminob	isphosphonate)			
Heterogeneity: Not applicable					
Test for overall effect: Z=0.37(P=0.71))				
2.3.2 Alendronate vs. etidronate					
Siris 1996	2/42	4/47		37.2%	0.56[0.11,2.9]
Subtotal (95% CI)	42	47		37.2%	0.56[0.11,2.9]
Total events: 2 (Aminobisphosphona	ite), 4 (Non-aminob	isphosphonate)			
Heterogeneity: Not applicable					
Test for overall effect: Z=0.69(P=0.49))				
Total (95% CI)	104	108		100%	0.69[0.25,1.89]
Total events: 6 (Aminobisphosphona	ite), 9 (Non-aminob	isphosphonate)			
Heterogeneity: Tau ² =0; Chi ² =0.1, df=	1(P=0.75); I ² =0%				
Test for overall effect: Z=0.72(P=0.47))				
Test for subgroup differences: Chi ² =0	0.1, df=1 (P=0.75), I ²	=0%			
	Amir	obisphosphonates	0.02 0.1 1	10 50 Non-aminobisphos	sphonates



Analysis 2.4. Comparison 2 Aminobisphosphonates versus non-aminobisphosphonates, Outcome 4 Mean percentage change from baseline in serum total alkaline phosphatase level.

Study or subgroup		ninobis- sphonate		-aminobis- sphonate	М	ean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	R	andom, 95% CI		Random, 95% CI
2.4.1 Risedronate vs. etidronate								
Miller 1999	62	-63.9 (7.1)	61	-20 (15)	-		66.51%	-43.9[-48.06,-39.74]
Subtotal ***	62		61		•		66.51%	-43.9[-48.06,-39.74]
Heterogeneity: Not applicable								
Test for overall effect: Z=20.69(P<0	.0001)							
2.4.2 Alendronate vs. etidronate								
Siris 1996	42	-79 (19.4)	47	-43.9 (31.5)			33.49%	-35.1[-45.85,-24.35]
Subtotal ***	42		47		*		33.49%	-35.1[-45.85,-24.35]
Heterogeneity: Not applicable								
Test for overall effect: Z=6.4(P<0.00	001)							
Total ***	104		108		•		100%	-40.95[-49.09,-32.81]
Heterogeneity: Tau ² =21.43; Chi ² =2.	24, df=1(P	=0.13); I ² =55.35%	6					
Test for overall effect: Z=9.86(P<0.0	0001)							
Test for subgroup differences: Chi ²	=2.24, df=1	L (P=0.13), I ² =55.3	35%					
		A	minobis	phosphonates	-50 -25	0 25	50 Non-amino	bisphosphonates

Analysis 2.5. Comparison 2 Aminobisphosphonates versus non-aminobisphosphonates, Outcome 5 Number of participants who achieved normalised alkaline phosphatase level.

Study or subgroup	Aminobis- phosphonate	Non-aminobis- phosphonate	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
2.5.1 Risedronate vs. etidronate					
Miller 1999	44/62	9/61	— 	53.58%	4.81[2.58,8.98]
Subtotal (95% CI)	62	61	•	53.58%	4.81[2.58,8.98]
Total events: 44 (Aminobisphospho	nate), 9 (Non-amino	bisphosphonate)			
Heterogeneity: Not applicable					
Test for overall effect: Z=4.93(P<0.00	001)				
2.5.2 Alendronate vs. etidronate					
Siris 1996	27/42	8/47		46.42%	3.78[1.93,7.38]
Subtotal (95% CI)	42	47	•	46.42%	3.78[1.93,7.38]
Total events: 27 (Aminobisphospho	nate), 8 (Non-amino	bisphosphonate)			
Heterogeneity: Not applicable					
Test for overall effect: Z=3.89(P=0)					
Total (95% CI)	104	108	•	100%	4.3[2.72,6.79]
Total events: 71 (Aminobisphospho	nate), 17 (Non-amin	obisphosphonate)			
Heterogeneity: Tau ² =0; Chi ² =0.27, d	f=1(P=0.6); I ² =0%				
Test for overall effect: Z=6.26(P<0.0	001)				
Test for subgroup differences: Chi ² =	:0.27, df=1 (P=0.6), I ² :	=0%			
	Non-amir	obisphosphonates 0.0	2 0.1 1 10	50 Aminobisphosphon	ates



Comparison 3. Comparison of two aminobisphosphonates

		No. of partici- pants	Statistical method	Effect size	
1 Number of participants with bone pain change	2	436	Risk Ratio (M-H, Random, 95% CI)	1.31 [1.15, 1.51]	
1.1 Zoledronate (1) vs. pamidronate (2)	1	89	Risk Ratio (M-H, Random, 95% CI)	1.30 [1.10, 1.53]	
1.2 Zolendronate (1) vs. risedronate (2)	1	347	Risk Ratio (M-H, Random, 95% CI)	1.36 [1.06, 1.74]	
2 Number of participants who experienced adverse events related to use of bisphosphonates	3		Risk Difference (M-H, Random, 95% CI)	Totals not select- ed	
2.1 Olpadronate (1) vs. pamidronate (2)	1		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]	
2.2 Zoledronate (1) vs. pamidronate (2)	1		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]	
2.3 Zolendronate (1) vs. risedronate (2)	1		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]	
3 Number of participants who withdrew due to adverse events	3		Risk Ratio (M-H, Random, 95% CI)	Totals not select- ed	
3.1 Zoledronate (1) vs. pamidronate (2)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]	
3.2 Zolendronate (1) vs. risedronate (2)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]	
3.3 Alendronate (1) vs. pamidronate (2)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]	
4 Mean percentage change from base- line in serum total alkaline phosphatase level	3		Mean Difference (IV, Fixed, 95% CI)	Totals not select- ed	
4.1 Olpadronate (1) vs. pamidronate (2)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]	
4.2 Zolendronate (1) vs. risedronate (2)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]	
4.3 Alendronate (1) vs. pamidronate (2)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]	
5 Number of participants who achieved normalised alkaline phosphatase level	4		Risk Ratio (M-H, Random, 95% CI)	Totals not select- ed	
5.1 Olpadronate (1) vs. pamidronate (2)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]	



Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
5.2 Zoledronate (1) vs. pamidronate (2)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.3 Zolendronate (1) vs. risedronate (2)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.4 Alendronate (1) vs. pamidronate (2)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Number of participants who experienced biochemical relapse with increased alkaline phosphatase level	2		Risk Ratio (M-H, Random, 95% CI)	Totals not select- ed
6.1 Zoledronate (1) vs. pamidronate (2)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 Zoledronate (1) vs. risedronate (2)	0		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.3 Alendronate (1) vs. pamidronate (2)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 3.1. Comparison 3 Comparison of two aminobisphosphonates, Outcome 1 Number of participants with bone pain change.

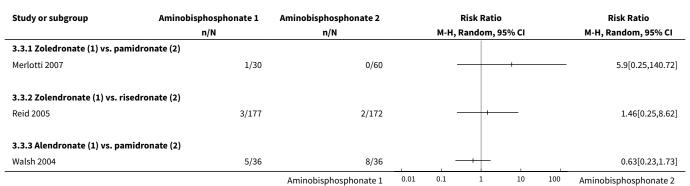
Study or subgroup	Aminobispho- sphonate 2	Aminobispho- sphonate2	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
3.1.1 Zoledronate (1) vs. pamidron	nate (2)				
Merlotti 2007	29/30	44/59		69.39%	1.3[1.1,1.53]
Subtotal (95% CI)	30	59	•	69.39%	1.3[1.1,1.53]
Total events: 29 (Aminobisphosphor	nate 2), 44 (Aminobis	sphosphonate2)			
Heterogeneity: Not applicable					
Test for overall effect: Z=3.12(P=0)					
3.1.2 Zolendronate (1) vs. risedron	nate (2)				
Reid 2005	88/176	63/171		30.61%	1.36[1.06,1.74]
Subtotal (95% CI)	176	171	•	30.61%	1.36[1.06,1.74]
Total events: 88 (Aminobisphosphor	nate 2), 63 (Aminobis	sphosphonate2)			
Heterogeneity: Not applicable					
Test for overall effect: Z=2.44(P=0.01)				
Total (95% CI)	206	230	•	100%	1.31[1.15,1.51]
Total events: 117 (Aminobisphospho	onate 2), 107 (Amino	bisphosphonate2)			
Heterogeneity: Tau ² =0; Chi ² =0.16, df	=1(P=0.69); I ² =0%				
Test for overall effect: Z=3.94(P<0.00	01)				
Test for subgroup differences: Chi ² =0	0.09, df=1 (P=0.76), l	2=0%			
	Amino	obisphosphonate 2 0.3	2 0.5 1 2	5 Aminobisphosphon	ate 1



Analysis 3.2. Comparison 3 Comparison of two aminobisphosphonates, Outcome 2 Number of participants who experienced adverse events related to use of bisphosphonates.

Study or subgroup	Aminobisphosphonate 1	Aminobisphosphonate 2	Risk Difference	Risk Difference	
	n/N		M-H, Random, 95% CI	M-H, Random, 95% CI	
3.2.1 Olpadronate (1) vs. pa	amidronate (2)				
Barreira 2009	9/14	7/7		-0.36[-0.65,-0.06]	
3.2.2 Zoledronate (1) vs. pa	amidronate (2)				
Merlotti 2007	18/30	39/60		-0.05[-0.26,0.16]	
3.2.3 Zolendronate (1) vs. r	risedronate (2)				
Reid 2005	146/176	133/171		0.05[-0.03,0.14]	
		Aminobisphosphonate 1	-1 -0.5 0 0.5	1 Aminobisphosphonate 2	

Analysis 3.3. Comparison 3 Comparison of two aminobisphosphonates, Outcome 3 Number of participants who withdrew due to adverse events.

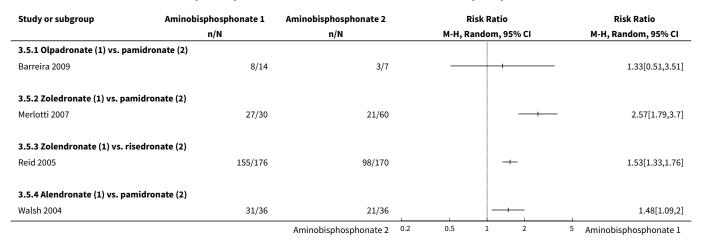


Analysis 3.4. Comparison 3 Comparison of two aminobisphosphonates, Outcome 4 Mean percentage change from baseline in serum total alkaline phosphatase level.

Study or subgroup	Aminobi	isphosphonate 1	Aminobisphosphonate 2		Mean Differe	nce		Mean Difference	
	N	Mean(SD)	N	Mean(SD)		Fixed, 95%	95% CI		Fixed, 95% CI
3.4.1 Olpadronate (1) vs. pamidr	onate (2)								
Barreira 2009	14	-42 (0)	7	-39.4 (0)					Not estimable
3.4.2 Zolendronate (1) vs. risedro	onate (2)								
Reid 2005	158	-49 (13.1)	164	-26.3 (18)		+			-22.7[-26.13,-19.27]
3.4.3 Alendronate (1) vs. pamidro	onate (2)								
Walsh 2004	36	-66.2 (90.3)	36	-51 (63.5)	1				-15.2[-51.26,20.86]
			Amino	bisphosphonate 1	-100	-50 0	50	100	Aminobisphosphonate 2



Analysis 3.5. Comparison 3 Comparison of two aminobisphosphonates, Outcome 5 Number of participants who achieved normalised alkaline phosphatase level.



Analysis 3.6. Comparison 3 Comparison of two aminobisphosphonates, Outcome 6 Number of participants who experienced biochemical relapse with increased alkaline phosphatase level.

Study or subgroup	Aminobisphosphonate 1	Aminobisphosphonate 2	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
3.6.1 Zoledronate (1) vs. par	midronate (2)			
Merlotti 2007	2/30	33/59		0.12[0.03,0.46]
3.6.2 Zoledronate (1) vs. rise	edronate (2)			
3.6.3 Alendronate (1) vs. pa	midronate (2)			
Walsh 2004	1/31	3/21		0.23[0.03,2.03]
		Aminobisphosphonate 1	0.001 0.1 1 10	1000 Aminobisphosphonate 2

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ADDITIONAL TABLES Table 1. Principal study characteristics

Study ID	Intervention	Comparator	Alkaline phos- phatase	Follow-up	N	Age	Male	Sympto- matic	Previous- ly treated
Altman 1973	Etidronate	Placebo	Yes	6 m	50	67 y	60%	NA	NA
Canfield 1977	Etidronate	Placebo	Yes	6 m	48	NA	58%	NA	NA
Ralston 1987	Etidronate	Placebo	No	3 m	32	NA	NA	100%	38%
Fraser 1997	Tiludronate	Placebo	Yes	6 m (18 m)	112	70 y	54%	63%	NA
McClung 1995	Tiludronate	Placebo	Yes	6 m	139	70 y	54%	NA	NA
Reginster 1992	Tiludronate	Placebo	Yes	6 m	149	69 y	54%	NA	82%
O'Doherty 1992	Alendronate	Placebo	Yes	6 m	15	67 y	60%	87%	66%
Reid 1996	Alendronate	Placebo	Yes	6 m	55	70 y	56%	NA	35%
Buckler 1999	Zoledronate	Placebo	Yes	3 m	176	71 y	61%	NA	NA
Reid 2004	Ibandronate	Placebo	Yes	6 m (12 m)	25	73 y	74%	NA	64%
Roux 1995	Tiludronate	Etidronate	Yes	6m	234	69y	59%	74%	71%
Siris 1996	Alendronate	Etidronate	Yes	6m	89	69y	67%	NA	25%
Miller 1999	Risedronate	Etidronate	Yes	12 m (18 m)	123	66 y	69%	91%	72%
Walsh 2004	Alendronate	Pamidronate	Yes	12 m (24 m)	72	70 y	58%	94%	39%
Barreira 2009	Olpadronate	Pamidronate	Yes	6 m	27	NA	NA	NA	NA
Merlotti 2007	Zoledronate	Pamidronate	Yes	6 m	90	70 y	69%	99%	67%
Reid 2005	Zoledronate	Risedronate	Yes	6 m	357	70 y	68%	NA	54%

Table 1. Principal study characteristics (Continued)

16	5	v)	

O'Donoghue 1987	Etidronate + calcitonin	Etidronate	Yes	12 m	44	NA	NA	100%	10%
Langston 2010	Intensive	Symptomatic	No	3 y	1331	74 y	51%	69%	NA
Tan 2017	Intensive	Symptomatic	No	3 y	502	76 y	55%	63%	70%

Alkaline phosphatase: Serum total alkaline phosphatase above the upper limit of normal as an inclusion criterion. Follow-up: Extended follow-up periods are shown in parentheses. N: Number of randomised participants. NA: Not available. SC: Sample size calculated before study.



Table 2. Comparison of two aminobisphosphonates (Reid 2005)

Study ID	Outcome	Zoledronate	•	Risedronate	•	RR (95% IC)
		Events	N	Events	N	
Reid 2005	Radiologically-confirmed clinical fracture	2	177	2	172	0.97 (0.14 to 6.82)
Reid 2011 (ex- tension)	Radiologically-confirmed clinical fracture	3	152	1	115	2.30 (0.24 to 22.36)
Reid 2005	Quality of life change from base- line	48	176	36	171	1.30 (0.89 to 1.89)
Reid 2011 (ex- tension)	Clinical relapse	14	152	29	115	0.30 (0.15 to 0.60)
Study ID	Outcome	Mean (SD)	N	Mean (SD)	N	Mean difference
Reid 2005	Mean change from baseline in pain	-0.5 (1.75)	101	-0.4 (2.13)	92	-0.10 (-0.65 to 0.45)
Reid 2005	Mean change from baseline in quality of life ¹	1.5 (0.5)	176	0.2 (0.6)	171	1.30 (1.18 to 1.42)
Reid 2011 (ex- tension)	Mean change from baseline in to- tal SF-36 score ²	1.3 (3.1)	152	-2.5 (2.6)	115	3.8 (3.12 to 4.49)

¹Physical-component summary (data extracted from Figure 4 in Reid 2005).

Table 3. Bisphosphonates vs. bisphosphonates plus calcitonin (O'Donoghue 1987)

Ouctome	Etidronate plus	calcitonin	Etidronate		RR (95% IC)
	Events	N	Events	N	
Change in bone pain	10	21	15	23	0.73 (0.43 to 1.25)

Table 4. Intensive versus symptomatic treatment

Study ID	Outcome	Intensive	Intensive		atic	RR (95% IC)
		Events	N	Events	N	
Langston 2010	Improvement in bone pain	78	295	96	311	0.86 (0.67 to 1.10)
Langston 2010	Radiologically-confirmed fractures	46	661	49	663	0.94 (0.64 to 1.39)
Tan 2017	Radiologically-confirmed fractures*1	22	270	12	232	1.58 (0.80 to 3.11)

²Total SF-36 scores to 54 months (data extracted from Figure 6 in Reid 2011 extension) (+1.3 ± 3.1 versus -2.5 ± 2.6) [D]



Langston 2010	Radiologically-confirmed fractures (pagetic bone)	8	661	13	663	0.62 (0.25 to 1.49)
Tan 2017	Radiologically-confirmed fractures (pagetic bone) ¹	5	270	2	232	2.15 (0.42 to 10.96)
Langston 2010	Number of orthopaedic surgeries	48	661	55	663	0.88 (0.60 to 1.27)
Tan 2017	Number of orthopaedic surgeries ¹	15	270	7	232	1.84 (0.76 to 4.44)
Langston 2010	Number of orthopaedic procedures	50	661	63	663	0.78 (0.53 to 1.15)
Tan 2017	Number of orthopaedic procedures	16	270	9	232	1.52 (0.69 to 3.39)
Langston 2010	Change in hearing thresholds ²	134	505	133	486	0.97 (0.79 to 1.19)
Langston 2010	Hearing classification worse at study end (left ear) ³	6	50	8	63	0.95 (0.35 to 2.55)
Langston 2010	Hearing classification worse at study end (right ear) ³	4	51	8	60	0.58 (0.19 to 1.84)
Langston 2010	Serious adverse events	345	661	359	663	0.96 (0.87 to 1.07)
Tan 2017	Serious adverse events	87	270	66	232	1.13 (0.87 to 1.48)
Langston 2010	Withdrawal due to adverse events ⁴	83	661	79	663	1.05 (0.79 to 1.41)
Langston 2010	Normalised alkaline phosphatase levels	512	661	406	663	1.26 (1.18 to 1.36)
Study ID	Outcome	Mean (SD)	N	Mean (SD)	N	Mean difference
Langston 2010	Mean change from baseline in quality of life (bodily pain SF-36) ⁵	-0.4 (8.9)	479	0.3 (9.4)	477	-0.7 (-1.8 to 0.5)
Tan 2017	Mean change from baseline in quality of life (bodily pain SF-36) ⁶	0.1 (9.3)	149	-1.0 (9.1)	138	-1.0 (-3.0 to 1.1)
Langston 2010	Mean change from baseline in quality of life (physical summary SF-36)*5	-1.2 (8.1)	408	-1.1 (8.2)	396	-0.1 (-1.3 to 1.0)
Tan 2017	Mean change from baseline in quality of life (physical summary SF-36) ⁶	-1.0 (7.7)	144	-2.7 (7.7)	126	-1.6 (-3.4 to 0.3)
Langston 2010	Mean change from baseline in quality of life (mental summary SF-36)*5	-1.7 (10.2)	408	-2.6 (10.9)	396	0.9 (-0.6 to 2.3)



Table 4. Int	Table 4. Intensive versus symptomatic treatment (Continued)											
Tan 2017	Mean change from baseline in quality of life (mental summary SF-36) ⁶	-1.0 (10.0)	144	-0.4 (9.9)	126	-0.6 (-1.7 to 3.1)						
Langston 2010	Mean hearing loss (left ear) ³	1.8 (14.6)	50	0.0 (12.6)	63	1.8 (-3.4 to 7.0)						
Langston 2010	Mean hearing loss (right ear) ³	2.5 (5.7)	51	2.1 (9.4)	60	0.5 (-2.4 to 3.3)						
Langston 2010	Mean percentage change from base- line in serum total alkaline phos- phatase activity	-40.5 (23.7)	430	-18 (71.2)	424	-22.5 (-29.6 to -15.4)						
Tan 2017	Mean percentage change from base- line in adjusted serum total alkaline phosphatase activity	-0.15 (0.72)	203	-0.05 (0.75)	181	-0.11 (-0.03 to 0.25)						

Data at 24 months for Langston 2010.

Table 5. Comparison of two non-aminobisphosphonates: Roux 1995

Outcome	Tiludronate	Tiludronate			RR (95% IC)
	Events	N	Events	N	
Number of participants with change in bone pain	32	120	10	52	1.39 (0.74 to 2.61)
Number of participants with radiologically-confirmed fractures	1	155	2	79	0.25 (0.02 to 2.77)
Number of participants with severe side effects	75	155	27	79	1.42 (1.00 to 2.00)
Number of participants who withdrew due to adverse events	10	155	2	79	2.55 (0.57 to 11.35)
Number of participants who normalised alkaline phosphatase levels	40	155	9	79	2.27 (1.16 to 4.43)

Table 6. Drug-related adverse events reported in randomised placebo-controlled trials

|--|

¹Data shown for these outcomes are number of events, patient years of follow up, rate ratios and 95% CI calculated using the method described by Cohen 2011.

²Number of participants using hearing aids at the end of the study.

³Patients with baseline and end of the trial measurements.

⁴Serious adverse event: any untoward medical occurrence that: 1) results in death, 2) is life-threatening, 3) requires inpatient hospitalisation or prolongation of existing hospitalisation, 4) results in persistent or significant disability/incapacity, or 5) is a congenital anomaly/birth defect.

⁵Data at 24 months.

⁶Difference between baseline and 36 months.



Altman 1973	Etidronate (38) vs. placebo (9)	Diarrhoea	5 (13%)	1 (11%)	1.18 (0.16 to 8.93)
Buckler 1999	Zoledronate	Fatigue	12 (9%)	0 (0%)	6.34 (0.38 to 104.5) 3.80 (0.50 to
	(141) vs. place- bo (35)	Fever	7 (5%)	0 (0%)	28.88)
		Arthralgia	15 (11%)	3 (9%)	1.24 (0.89 to 1.77)
		Pain, back	14 (10%)	1 (3%)	3.47 (0.53 to 23.02)
		Pain, skeletal	11 (8%)	2 (6%)	1.37 (0.85 to 2.19)
		Hypocalcaemia	3 (2%)	0 (0%)	1.78 (0.74 to 4.24)
Fraser 1997	Tiludronate	Nausea	15 (17%)	2 (8%)	2.27 (0.65 to 7.86)
	(86) vs. placebo (26)	Vomiting	7 (7%)	0 (0%)	4.66 (0.45 to 48.06)
		Dyspepsia	9 (10%)	0 (0%)	5.90 (0.40 to 87.16)
		Diarrhoea	14 (16%)	0 (0%)	9.00 (0.32 to 252.8)
		Arthralgia	8 (9%)	2 (8%)	1.21 (0.91 to 1.61)
		Skeletal pain	5 (6%)	3 (12%)	0.50 (0.13 to 1.97)
		Raised liver enzymes	1 (1%)	0 (0%)	0.93 (0.04 to 22.20)
		Eosinophilia	0 (0%)	1 (4%)	0.10 (0.01 to 2.47)
McClung 1995	Tiludronate (91) vs. placebo (48)	Gastrointestinal	31 (34%)	15 (31%)	1.09 (0.66 to 1.81)
Reginster	Tiludronate	Gastralgia	20 (17.1%)	5 (16.1%)	1.09 (0.45 to 2.69)
1992	(117) vs. place- bo (32)	Nausea	11 (9.4%)	3 (9.6%)	1.00 (0.30 to 3.38)
Reid 1996	Alendronate	Gastrointestinal	2 (7%)	5 (18%)	0.42 (0.09 to 2.00)
	(27) vs. placebo (28)	Gastritis	0 (0%)	1 (4%)	0.35 (0.02 to 8.13)
		Duodenal ulcer	0 (0%)	1 (4%)	0.35 (0.02 to 8.13)

Table 7. Drug-related adverse effects reported in randomised versus non-randomised bisphosphonates trials

1 (4%)

0 (0%)

3.10 (0.13 to 73.10)

Study ID	Comparison	Adverse effect	Bisphospho- nate 1	Bisphospho- nate 2	RR (95% CI)
Roux 1995	Tiludronate (155) vs.	Gastrointestinal	32 (20.8%)	10 (12.7%)	1.63 (0.85 to 3.14)
	etidronate (79)	Abdominal pain	10 (6.5%)	2 (2.5%)	2.55 (0.57 to 11.35)
	(13)	Nausea, vomiting	8 (5.2%)	2 (2.5%)	2.04 (0.44 to 9.37)
		Fracture	1 (1%)	2 (3%)	0.25 (0.02 to 2.77)

Oesophagitis



Miller 1999

Barreira 2009

Merlotti 2007*

Table 7.	Drug-r	elat	ed a	ıdvers	e effec	ts rep	orted i	n randomi	sed vers	us non	-rando	mised b	isphosp	honate	? S
trials (co	ntinued)								2001		240()		0 /0 =0 .	0.00\	

Siris 1996	Alendronate (42) vs.
	etidronate

related advers	e effects reported in ran	domised vers	sus non-random	nised bisphosphonates
Alendronate (42) vs.	Gastrointestinal	11 (26%)	10 (21%)	1.23 (0.58 to 2.60)
etidronate	Abdominal distention	0 (%)	1 (2%)	0.37 (0.02 to 8.90)
(47)	Abdominal pain	3 (7%)	4 (9%)	0.84 (0.2 to 3.54)
	Acid regurgitation	1 (2%)	1 (2%)	1.12 (0.07 to 17.34)
	Dyspepsia	0 (0%)	1 (2%)	0.37 (0.02 to 8.90)
	Melena	1 (2%)	0 (0%)	3.35 (0.14 to 80.05)
	Nausea	2 (5%)	3 (6%)	0.75 (0.13 to 4.25)
	Leg pain	1 (2%)	9 (19%)	0.12 (0.02 to 0.94)
	Laboratory adverse experiences	9 (21%)	6 (13%)	1.68 (0.65 to 4.32)
Risedronate (62) vs.	Upper gastrointestinal	12 (19%)	12 (20%)	0.98 (0.48 to 2.02)
etidronate (61)				
Olpadronate (14) vs.	Digestive	9 (64%)	7 (100%)	0.68 (0.44 to 1.03)
pamidronate (7)				
Zoledronate (47)* vs.	Influenza-like illness	4 (9%)	5 (8%)	1.02 (0.29 to 3.59)
pamidronate	Myalgia	3 (6%)	4 (7%)	0.96 (0.23 to 4.07)
(60)	Pyrexia	3 (6%)	4 (7%)	0.96 (0.23 to 4.07)
	Fatigue	3 (6%)	8 (13%)	0.48 (0.13 to 1.71)
	Headache	4 (9%)	5 (8%)	1.02 (0.29 to 3.59)
	Diarrhoea	1 (2%)	2 (3%)	0.64 (0.06 to 6.83)
	Bone pain	3 (6%)	6 (10%)	0.64 (0.17 to 2.42)

Reid 2005 Zoledronate (177) vs.

risedronate (172)

Study days 1 to 3

Pain in arm or leg

Hypocalcaemia

Dermatitis

Influenza-like illness	17 (9.6%)	7 (4.1%)	2.36 (1 to 5.55)	
Myalgia	13 (7.3%)	6 (3.5%)	2.11 (0.82 to 5.41)	

4 (7%)

1 (2%)

0 (0%)

0.96 (0.23 to 4.07)

3.83 (0.41 to 35.64)

0.42 (0.02 to 10.17)

3 (6%)

3 (6%)

1 (2%)



Table 7. Drug-related adverse effects reported in randomised versus non-randomised bisphosphonates

trials (Continued)		Pyrexia	13 (7.3%)	1 (0.6%)	12.63 (1.67 to 95.53)
		Fatigue	12 (6.8%)	4 (2.3%)	2.92 (0.96 to 8.86)
		Headache	12 (6.8%)	7 (4.1%)	1.67 (0.67 to 4.13)
		Rigor	12 (6.8%)	1 (0.6%)	11.66 (1.53 to 88.72)
		Nausea	11 (6.2%)	3 (1.7%)	3.56 (1.01 to 12.55)
		Bone pain	9 (5.1%)	2 (1.2%)	4.37 (0.96 to 19.95)
		After study day 3			
		Pain in an arm or leg	13 (7.3%)	12 (7%)	1.05 (0.49 to 2.24)
		Arthralgia	9 (5.1%)	19 (11%)	0.46 (0.21 to 0.99)
		Dizziness	9 (5.1%)	5 (2.9%)	1.75 (0.6 to 5.11)
		Nasopharyngitis	9 (5.1%)	14 (8.1%)	0.62 (0.28 to 1.41)
		Diarrhoea	8 (4.5%)	9 (5.2%)	0.86 (0.34 to 2.19)
		Headache	7 (4%)	10 (5.8%)	0.68 (0.26 to 1.75)
		Back pain	4 (2.3%)	12 (7.0%)	0.32 (0.11 to 0.98)
		Symptomatic hypocal- caemia	2 (1.1%)	1 (0.6%)	1.94 (0.18 to 21.24)
Reid 2011 (ex- tension)	Zoledronate (152) vs.	Atrial fibrillation	1 (0.7%)	1 (0.9%)	0.76 (0.05 to 12.20)
terision	risedronate	Atrial flutter	0 (0%)	2 (1.7%)	0.15 (0.01 to 3.13)
	(115)	Osteonecrosis jaw	0 (0%)	0 (0%)	-
Walsh 2004	Alendronate (36) vs.	Gastrointestinal	16 (44%)	4 (11%)	4 (1.48 to 10.80)
	pamidronate	Fatigue	0 (0%)	23 (64%)	0.02 (0.00 to 0.34)
	(36)	General aches/pain	4 (11%)	16 (44%)	0.25 (0.09 to 0.68)
		Deteriorating kidney failure	1 (3%)	0 (0%)	3.00 (0.12 to 71.28)

^{*}Zoledronate group data were extracted from Table 3 in Merlotti 2007. In this table, the authors presented data from 30 participants who took part in the first part of the study (which was included in our systematic review) plus 17 participants from the second part of the study (which was not included in our systematic review).

Table 8. Drug-related adverse events reported in randomised trials comparing regimens aimed to normalise elevated bone turnover (intensive) versus regimens aimed to control bone pain referable to Paget's disease of bone (symptomatic)

udy ID Comparison Side effect Intensive Symptomatic RR (95% CI)



Table 8. Drug-related adverse events reported in randomised trials comparing regimens aimed to normalise elevated bone turnover (intensive) versus regimens aimed to control bone pain referable to Paget's disease of bone (symptomatic) (Continued)

Symptomati	(continued)				
Langston 2010*	Intensive (661)	All adverse events	3429	3471	-
		Serious adverse events	345	359	-
	vs. sympto- matic (663)	Musculoskeletal	691	734	-
		Sensory	203	196	-
		Gastrointestinal	172	157	-
		Cardiovascular	360	327	-
		Arrythmia	13 (1.9%)	7 (1%)	1.86 (0.75 to 4.64)
		Cancer	55	47	-
		Renal	98	78	-
		Other	1850	1932	-
Tan 2017	Intensive	All adverse events	226	196	0.99 (0.91 to 1.07)
	(270) vs.	Serious adverse events	87	66	1.13 (0.87 to 1.48)
	symptomatic (232)	Musculoskeletal	123	104	1.02 (0.84 to 1.23)
		Osteonecrosis of the jaw	1	0	2.58 (0.11 to 63.01)
		Delayed union of fracture	2	1	1.72 (0.16 to 18.83)
		Ophthalmic	34	41	0.71 (0.47 to 1.08)
		Uveitis	1	0	2.58 (0.11 to 63.01)
		Gastrointestinal	54	46	1.01 (0.71 to 1.43)
		Cardiovascular	67	49	1.18 (0.85 to 1.62)
		Arrythmia	14	8	1.50 (0.64 to 3.52)
		Cerebrovascular	4	3	1.14 (0.26 to 5.07)
		Central nervous system	28	28	0.86 (0.52 to 1.41)
		Endocrine	28	21	1.15 (0.68 to 1.96)
		Ear, nose or throat	28	26	0.93 (0.56 to 1.53)
		Genitourinary	41	39	0.90 (0.61 to 1.35)
		Haematological	10	9	0.96 (0.40 to 2.31)
		Respiratory	48	43	0.95 (0.66 to 1.39)
		Skin	41	33	1.07 (0.70 to 1.63)
		Miscellaneous	33	32	0.89 (0.56 to 1.40)

^{*} Data represent total numbers of reported side effects regardless of numbers of participants who experienced them. The authors reported numbers of participants only for arrhythmia.



Table 9. Bisphosphonates versus placebo (Fraser 1997)

Study ID	Outcome	Tiludronate		Placebo		RR (95% IC)
		Events	N	Events	N	
Fraser 1997	Number of participants who relapsed due to bone pain recurrence	23	66	13	19	0.51 (0.32 to 0.80)

Table 10. Aminobisphosphonates versus non-aminobisphosphonates (Miller 1999)

Study ID	Outcome	Risedronate		Tiludrona	te	RR (95% IC)
		Events	N	Events	N	
Miller 1999	Number of participants who relapsed due to recurrence	2	62	8	61	0.25 (0.05 to 1.11)
	of increased serum alkaline phosphatase level					

APPENDICES

Appendix 1. MEDLINE search strategy

- 1. exp bone diseases/
- 2. 1 and paget\$.mp.
- 3. (paget\$ adj10 bone\$).mp.
- 4. exp Osteitis Deformans/
- 5. osteitis deformans.mp.
- 6. ostitis deformans.mp.
- 7. or/2-6
- 8. randomised controlled trial.pt.
- 9. controlled clinical trial.pt.
- 10. randomized.ab.
- 11. placebo.ab.
- 12. drug therapy.fs.
- 13. randomly.ab.
- 14. trial.ab.
- 15. groups.ab.
- 16. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
- 17. exp animals/ not humans.sh.



- 18. 16 not 17
- 19.7 and 18

Appendix 2. Embase search strategy

- 1. exp bone diseases/
- 2. 1 and paget\$.mp.
- 3. (paget\$ adj10 bone\$).mp.
- 4. exp Paget Bone Disease/
- 5. osteitis deformans.mp.
- 6. ostitis deformans.mp.
- 7. or/2-6
- 8. random\$.ti,ab.
- 9. factorial\$.ti,ab.
- 10. (crossover\$ or cross over\$ or cross-over\$).ti,ab.
- 11. placebo\$.ti,ab.
- 12. (doubl\$ adj blind\$).ti,ab.
- 13. (singl\$ adj blind\$).ti,ab.
- 14. assign\$.ti,ab.
- 15. allocat\$.ti,ab.
- 16. volunteer\$.ti,ab.
- 17. crossover procedure.sh.
- 18. double blind procedure.sh.
- 19. randomised controlled trial.sh.
- 20. single blind procedure.sh.
- 21. or/8-20
- 22. exp animal/ or nonhuman/ or exp animal experiment/
- 23. exp human/
- 24. 22 and 23
- 25. 22 not 24
- 26. 21 not 25
- 27.7 and 26

Appendix 3. CENTRAL search strategy

- #1MeSH descriptor Osteitis Deformans explode all trees in MeSH products
- #2 paget near/10 bone in All Fields in all products
- #3 (#1 OR #2)



Appendix 4. Web of Knowlegde/Web of Science search strategy

#1 osteitis deformans

#2 paget bone

#3 #1 OR #2

#4 trial* or random* or placebo* or control* or double or treble or triple or blind* or mask* or allocat* or prospective* or volunteer*or comparative or evaluation or follow-up or followup

#5 #3 AND #4

Appendix 5. Summary of approaches to study authors for further information on trials

Study ID	Study author con- tacted	Study author replied	Additional data provided
Altman 1973	No	-	Not applicable
Barreira 2009	01/12/2014	No	Not applicable
Buckler 1999 (+ Schaffer 1996)	30/06/2016	No	Not applicable
Canfield 1977	No	-	Not applicable
Fraser 1997	30/6/2014	No	Not applicable
Langston 2010 (+ Ralston 1987)	30/6/2014	29/12/2014	Provided more information on co-interventions and blinding (Langston 2010; Ralston 1987), data on pain, QoL, hearing and mean alkaline phosphatase and SD change (Langston 2010)
McClung 1995	30/6/2014	02/07/2014	Original study data no longer accessible
Merlotti 2007	30/6/2014	No	Not applicable
Miller 1999	30/6/2014	No	Not applicable
O'Doherty 1992	30/6/2014	No	Not applicable
O'Donoghue 1987	No	-	Not applicable
Reginster 1992	30/06/2014	30/06/2014	Original study data no longer accessible
Reid 1996; Reid 2004; Reid 2005	30/6/2014	02/09/2014	Provided more information on concealment (Reid 1996; Reid 2004), mean alkaline phosphatase and SD change (Reid 2004), blinding (Reid 2005) and data on adverse events (Reid 2004)
Roux 1995	30/6/2014	08/07/2014	Original study data no longer accessible
Siris 1996	30/06/2014	01/07/2014	Original study data no longer accessible
Tan 2017	28/02/2015	22/06/2015; 10/12/2015	Unpublished data provided. Provided more information on QoL and adverse events



(Continued)

Walsh 2004 30/6/2014 19/08/2014 Provided more information on concealment, mean alkaline phosphatase and SD change, data on pain scores, QoL and ad-

verse events

Abbreviations: QoL - quality of life; SD - standard deviation

WHAT'S NEW

Date	Event	Description
11 December 2017	Amended	The results for the side effects and pain have been edited to remove the absolute risk difference to avoid misinterpretation.

HISTORY

Protocol first published: Issue 4, 2004 Review first published: Issue 11, 2017

Date	Event	Description
5 December 2017	Amended	The plain language summary included a mistake in the number of people experiencing pain relief and the number of people experiencing side effects: the results for the placebo and treatment groups were reversed. The labels on Analysis 1.1 were also inverted. These errors have been corrected in this amendment.
4 September 2008	Amended	converted to new review format.
		CMSG ID: C106-P

CONTRIBUTIONS OF AUTHORS

Draft the protocol: LCG, SHR Study selection: LCG, AT, JdPM

Extract data from studies: LCG, AT, JdPM Enter data into Review Manager 2014: LCG

Carry out the analysis: LCG

Interpret the analysis: LCG, AT, SHR, JdPM Draft the final review: LCG, AT, SHR, JdPM

Disagreement resolution: SHR Update the review: LCG, AT, SHR, JdPM

DECLARATIONS OF INTEREST

Luis Corral-Gudino: none known.

Adrian JH Tan: was co-investigator on the PRISM-EZ study (Tan 2017).

Javier del Pino-Montes: was co-investigator on zoledronate versus risedronate trial (Reid 2005). He has received grants from the research Spanish agencies SACYL and Institute of Health Carlos III and payment for lectures and meeting expenses from Merck Sharp Dohme.

Stuart H Ralston: previously acted as a consultant for Novartis and Merck on behalf of his institution (the University of Edinburgh) and was the principal investigator on three included primary studies (Langston 2010; Ralston 1987; Tan 2017).



SOURCES OF SUPPORT

Internal sources

· No sources of support supplied

External sources

· Arthritis Research, UK.

The review was supported in part by a grant from Arthritis Research UK to SHR (18304)

• Instituto de Salud Carlos III, Spain.

The review was supported in part by a grant from Carlos III

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are nine differences between protocol and review:

- 1. The objective in the original protocol: "To assess the benefits to improve clinical outcomes or prevent complications and the harms of bisphosphonate therapy on patients with Paget's disease of bone in adults", was rewritten as "To assess the benefits and harms of bisphosphonates for adult patients with Paget's disease of bone" according to Cochrane Musculoskeletal Group recommendation.
- 2. Comparison between bisphosphonates was subdivided. In addition, two comparisons were added: comparison of two non-aminobisphosphonates and bisphosphonates versus bisphosphonates plus calcitonin.
- 3. A minor outcome (mean reduction in serum total alkaline phosphatase activity) was renamed: mean percentage change from baseline in serum total alkaline phosphatase activity. A sub outcome: number of participants who achieved normalised alkaline phosphatase level, was added.
- 4. For trials where there were multiple arms with several doses of the same bisphosphonates, we combined the experimental intervention groups to create a single pair-wise comparison versus the control group. Experimental group data were combined as a single group, instead of the planned high dose and low dose groups.
- 5. We estimated overall effect by performing meta-analyses using a random-effect model in all cases. The fixed-effect model was not performed when $I^2 < 40\%$ as planned.
- 6. Some data were extracted directly from figures. (See last paragraph in Data extraction and management).
- 7. We added a specific search for specific rare events found from searches of websites of four regulatory agencies.
- 8. We added a new co-author in March 2017. JdPM was recruited to assess results from the most recent search and analyse the PRISM-EZ trial (Tan 2017).
- 9. We considered one year of follow-up to properly assess the outcome "Number of participants experiencing radiologically-confirmed clinical fractures" that does not have a predefined follow-up period in the protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

Alkaline Phosphatase [blood]; Bone Density Conservation Agents [adverse effects] [*therapeutic use]; Calcitonin [therapeutic use]; Diphosphonates [adverse effects] [*therapeutic use]; Musculoskeletal Pain [drug therapy]; Osteitis Deformans [*drug therapy] [enzymology]; Patient Dropouts [statistics & numerical data]; Randomized Controlled Trials as Topic

MeSH check words

Aged; Female; Humans; Male