Intravenous zoledronate for postmenopausal women with osteopenia and osteoporosis: a systematic review and metanalysis

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KEYWORDS (MeSH terms):

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ABSTRACT

BACKGROUND: Osteoporosis compromises bone strength and increases the risk of fractures. Zoledronate prevents loss of bone mass and reduces the risk of fractures.

OBJECTIVES: To determine the efficacy and safety of zoledronate in postmenopausal women with osteopenia and osteoporosis.

DESIGN AND SETTINGS: A systematic review and meta-analysis was conducted within the evidence-based health program at the Universidade Federal de São Paulo.

METHODS: An electronic search of the CENTRAL, MEDLINE, Embase, and LILACS databases was performed until February 2022. Randomized controlled trials comparing zoledronate with placebo or other bisphosphonates were included. Standard methodological procedures were performed according to the Cochrane Handbook and the certainty of evidence for the Grading of Recommendations Assessment, Development, and Evaluation Working Group. Two authors assessed the risk of bias and extracted data on fractures, adverse events, bone turnover markers (BTM), and bone mineral density (BMD).

RESULTS: Twelve trials from 6,652 records were included: nine compared zoledronate with placebo, two trials compared zoledronate with alendronate, and one trial compared zoledronate with ibandronate. Zoledronate reduced the incidence of fractures in osteoporotic [three years: morphometric vertebral fractures (relative risk, RR = 0.30 (95% confidence interval, Cl: 0.24–0.38))] and osteopenic women [six years: morphometric vertebral fractures (RR = 0.39 (95%Cl: 0.25–0.61))], increased incidence of post-dose symptoms [RR = 2.56 (95%Cl: 1.80–3.65)], but not serious adverse events [RR = 0.97 (95%Cl: 0.91–1.04)]. Zoledronate reduced BTM and increased BMD in osteoporotic and osteopenic women.

CONCLUSION: This review supports the efficacy and safety of zoledronate in postmenopausal women with osteopenia for six years and osteoporosis for three years.

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INTRODUCTION

Osteoporosis is a silent disease that compromises the density and quality of bones, increasing the risk of fractures. Advanced age and female sex are important risk factors for osteoporosis.¹

Approximately 200 million women worldwide are observed to have osteoporosis,² representing one-fifth of individuals over the age of 50 years.³ Although osteoporosis is responsible for a significant number of fractures, most fractures occur in individuals with osteopenia or with normal bone mineral density (BMD), which can be explained by the high number of people in this T-score range. Therefore, BMD results should be combined with other clinical risk factors for an accurate assessment of fracture risk and to guide treatment decisions.^{4,5} The most common sites where an osteoporotic fracture can occur are the vertebrae, hip, and distal forearm; however, the incidence of occurrence at other sites is also high.^{6,7}

Drugs that increase bone mass do so by affecting bone metabolism. There are three categories: anti-catabolic (bisphosphonates, hormone therapy, selective estrogen-receptor modulators (raloxifene), and calcitonin), anabolic (teriparatide and abaloparatide), and both anabolic and anti-catabolic (romosozumab).⁴ Bisphosphonates are one of the first treatment choices for postmenopausal osteoporosis.^{4,8} They bind to hydroxyapatite in the bone mineral, inhibit the activity of osteoclasts, and prevent bone resorption.⁹

Zoledronic acid (or zoledronate) is an intravenous bisphosphonate that has a high affinity to the mineralized bone.¹⁰ It reduces the blood levels of bone turnover markers (BTM) (produced by osteoclasts) and increases bone mass (observed through densitometry).¹⁰ These findings are observed to correlate with a reduction in the number of new fractures.¹⁰

Prolonged use of bisphosphonates has been associated with complications, such as osteonecrosis of the jaw, excessive suppression of bone remodeling, atypical fractures of the femur, and atrial fibrillation.¹¹

As the incidence of osteoporotic fractures continues to increase, global health demands therapies to reduce the risk of fractures. This systematic review helps to evaluate the evidence on the efficacy and safety of zoledronate in postmenopausal women, presenting an accessible updated synthesis to clinicians, researchers, health policy makers, and consumers, contributing to decision-making for preventing fractures.

OBJECTIVE

To determine the efficacy and safety of zoledronate in postmenopausal women with osteopenia and osteoporosis.

METHODS

The protocol was registered in PROSPERO (number CRD42022309708; https://www.crd.york.ac.uk/prospero/dis-play_record.php?RecordID=309708).

Study selection

All randomized controlled trials (RCTs) of a duration of at least one year comparing zoledronic acid (5 mg) to a placebo or other anti-catabolic agents in postmenopausal women were included. The inclusion criteria for RCTs for osteoporosis were: postmenopausal women with a previous fragility fracture and women with osteoporosis defined by densitometry (BMD T-score \leq -2.5 standard deviation [SD]), with or without previous fragility fractures; and for osteopenia were: postmenopausal women without fragility fractures and with a T-score < -1 SD and > -2.5 SD. Trials that investigated women with secondary osteoporosis (bone loss caused by specific diseases, including malignancy, or medications) were excluded.

Search methods for the identification of studies

On May 13, 2021, and February 15, 2022, electronic databases, such as the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (via PubMed); EMBASE (via Ovid), and LILACS (Latin American and Caribbean Health Science Information database) were searched for all relevant RCTs, regardless of language or publication status. In addition, trial registers for study protocols, ongoing trials, and conference abstracts were searched.

Study outcomes

The primary outcomes were fractures and adverse reactions each year. The fractures were classified as follows: incidence of clinical and morphometric vertebral fractures, non-vertebral fractures, hip fractures, and all fractures. For adverse reactions, the following were considered: non-serious and serious adverse events (SAE), total mortality, atrial fibrillation, post-dose symptoms or influenza-like symptoms, increase in serum creatinine (a rise of more than 0.5 mg per deciliter (or 44 μ mol/L) compared with the baseline level), osteonecrosis of the jaw, atypical femoral fractures, and eye disorders (uveitis, iritis, episcleritis).

The secondary outcomes were percent change in BTM, such as CTX (C-terminal telopeptide of type 1 collagen) and P1NP (Procollagen type 1 N propeptide) after 6 months and after each year, and percent change in BMD of the lumbar spine, femoral neck, and total hip after each year.

Data collection

Data were extracted systematically in a predefined and standardized manner according to the instructions given in the Cochrane Handbook for Systematic Reviews of Interventions.¹² Two review authors independently selected the studies that matched the inclusion criteria, screened titles and abstracts, selected reports to read in full text, and independently extracted all data from the studies. In addition, the risk of bias was assessed using domainbased evaluation criteria and was judged as low, with some concerns, or a high risk of bias. When necessary, a third reviewer was consulted to settle any disagreements.¹²

Data analysis

Risk ratios (RR) were calculated for dichotomous variables with 95% confidence intervals (CI), and the relative percent change was calculated and expressed as a percentage. The number needed to treat for a benefit or the number needed to cause harm was calculated for significant outcomes.^{12,13} The mean difference (MD) in the percent change from baseline with 95% CI was calculated for continuous data.^{12,13} The WebPlotDigitizer program (https://github.com/ankitrohatgi/WebPlotDigitizer, version 3, Pacifica, California, United States) was used to extract values from graphics when the data were not available in the text.¹⁴

Meta-analyses were performed in a random-effects model to avoid 'between-study' variations when the data were clinically and statistically homogeneous, as recommended in the Cochrane Handbook for Systematic Reviews of Interventions.¹³ Heterogeneity was assessed using the chi-square test (with the significance set at a P value of 0.05) and measured through I² (I² > 50% was considered to signify substantial heterogeneity).¹³

The overall certainty of the evidence was independently assessed by two authors using the specific evidence grading system developed by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working.¹⁵ The GRADE approach specifies four levels of certainty of evidence (high, moderate, low, or very low).

A minimum significant reduction value for fractures was established in this review to consider zoledronate effective. The values varied according to the fracture type: 30% for vertebral and hip fractures, 15% for non-vertebral fractures and all clinical fractures.¹⁶ Any increase in serious adverse events or a 10% increase in non-serious adverse events was considered significant.¹⁶ A minimal significant reduction in the BTM levels (CTX and P1NP) of 30%, a minimal significant increase in the BMD values measured by dual-energy X-ray absorptiometry of 5% at the lumbar spine, and a 4% increase at the femoral neck and total hip were considered.¹⁶

RESULTS

Results of the search

A total of 6,652 records were identified. After removing duplicates (1,787 records), 12 RCTs met the eligibility criteria,¹⁷⁻²⁹ and 11 RCTs were included in the meta-analysis (**Figure 1**). One RCT published data in more than one article.^{17,18} Six RCTs compared zoledronate yearly with placebo,¹⁷⁻²³ two RCTs compared zoledronate with alendronate,^{27,28} one RCT compared zoledronate



Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

with ibandronate,²⁹ two RCTs studied a single dose,^{24,25} and one RCT investigated each 18-month period over six years.²⁶ The characteristics of the included studies are summarized in **Table 1**^{17,19-22,27-29} for osteoporosis and **Table 2**²³⁻²⁶ for osteopenia.

Risk of bias in included studies

The risk of bias for each study and outcome is shown in **Figure 2** for osteoporosis and **Figure 3** for osteopenia, respectively.

Primary outcomes

Fractures

The incidence of fracture data was obtained from four RCTs comparing zoledronate with a placebo in women with osteoporosis and one RCT conducted on women with osteopenia. The RCTs comparing zoledronate with alendronate reported fractures as adverse events, whereas the RCT comparing ibandronate did not evaluate fractures.

Postmenopausal osteoporotic women

Upon comparing zoledronate with placebo, high-certainty evidence demonstrating that zoledronate reduces clinical and morphometric vertebral fractures since the first year was obtained (**Figure 4a** and **Figure 4b1**).

For hip fractures (**Figure 4c1**), zoledronate had no effect on reducing or increasing hip fractures after one year; however, moderate-certainty evidence (downgraded for imprecision) indicated that zoledronate probably reduces hip fractures after two years.

There was also moderate-certainty evidence (downgraded for imprecision) that zoledronate probably reduces non-vertebral fractures after two and three years (**Figure 4d1**) and high-certainty evidence that zoledronate reduces all clinical fractures after two and three years (**Figure 4e1**).

Upon comparing zoledronate with alendronate after one year, there was very low-certainty (downgraded by two points for risk of bias and one for imprecision) about the effect of zoledronate on hip fractures and clinical fractures.

Table 1. Summary of characteristics of included studies with osteoporotic women

Study ID	Study duration (years)	Comparator	Number of participants	Ethnicity	Inclusion criteria	Age (years)	Outcomes	Industry funding
Bai et al., ²⁰ 2013	2	0.25 mg activated vitamin D3	242 Zol X 241 Plac	Chinese	low bone mass + fracture or osteoporosis	Zol: 56.5 ± 6.83 Plac: 57.15 ± 6.3	Fractures AEs BMD	No
Black et al., ¹⁷ 2007	3	Placebo	3,875 Zol X 3,861 Plac	More than 15 countries	low bone mass + fracture or osteoporosis	Zol: 73.0 ± 5.2 Plac: 73.1 ± 5.4	Fractures AEs BTM BMD	Yes
Chao et al., ¹⁹ 2013	1	0.25 mg activated vitamin D3	327 Zol X 333 Plac	Chinese	low bone mass + fracture or osteoporosis	Zol: 54.6 ± 7.3 Plac: 55.3 ± 7.5	Fractures AEs	Yes
Liang et al., ²¹ 2017	2	Placebo	175 Zol X 110 Plac	Chinese	only osteoporosis by DXA	Zol: 57.22 ± 2.8 Plac: 57.48 ± 3.2	Fractures BTM BMD	Yes
Yang et al., ²² 2015	1	Placebo	50 Zol X 50 Plac	Chinese	only osteoporosis by DXA	Zol:61.4 \pm 9.5 Plac: 59.7 \pm 8	BTM BMD	No
Hadji et al., ²⁸ 2012	1	Alendronate 70 mg/week	408 Zol X 191 Aln	Germany	only osteoporosis by DXA	Zol: 67.6 ± 8.0 Aln: 68.1 ± 7.9	Fractures (AE) AEs BTM	Yes
Tan et al., ²⁷ 2016	3	Alendronate 70 mg/week	52 Zol X 53 Aln	Chinese	only osteoporosis by DXA	Zol: 68.1 \pm 9.02 Aln: 68.0 \pm 8.55	Fractures (AE) BTM BMD	No
Gonnelli et al., ²⁹ 2014	1	lbandronate 3 mg/3 months	30 Zol X 30 lbn	Italian	low bone mass + fracture or osteoporosis	Zol: 64±6 Ibn: 67.0±8.1	BTM BMD	No

Zol = Zoledronate; Placebo; Aln = Alendronate; lbn = Ibandronate; DXA = dual-energy x-ray absorptiometry (DXA) or bone densitometry; AEs = adverse events; BTM = bone turnover marker; BMD = bone mineral density.

Study ID	Study duration (years)	Comparator	Number of participants	Ethnicity	Inclusion criteria	Age (years)	Outcomes	Industry funding
Grey et al., ²⁴ 2009	2	Placebo	25 Zol X 25 Plac	New Zealand	low bone mass + no fractures	Zol: 62 ± 8 Plac: 65 ± 8	Fractures (AE) AEs BTM BMD	No
Grey et al., ²⁵ 2012	1	Placebo	43 Zol X 43 Plac	New Zealand	low bone mass + no fractures	ZOL: 66 ± 8 Plac: 65 ± 9	Fractures (AE) AEs BTM BMD	No
McClung et al., ²³ 2009	2	Placebo	379 Zol X 202 Plac	25 centers	low bone mass + no fractures	Zol: 59 ± 8 Plac: 60 ± 8	Fractures (AE) AEs BTM BMD	Yes
Reid et al., ²⁶ 2018	6	Placebo	1,000 Zol X 1,000 Plac	New Zealand	low bone mass + no fractures	Zol: 71 ± 5 Plac: 71 ± 5	Fractures AEs BTM BMD	No

Table 2. Summary of the characteristics of included studies with osteopenic women

Zol = Zoledronate; Plac = Placebo; DXA = dual-energy x-ray absorptiometry (DXA) or bone densitometry; AEs = adverse events; BTM = bone turnover marker; BMD = bone mineral density.

Study ID	Experimental	<u>Comparator</u>	<u>Outcome</u>	<u>D1</u>	<u>D2</u>	<u>D3</u>	<u>D4</u>	<u>D5</u>	<u>Overall</u>
Bai et al.20, 2013	Zoledronate	placebo	Fracture	!	+	+	+	+	+
Bai et al.20, 2013	Zoledronate	Placebo	Safety	!	+	+	+	!	!
Bai et al.20, 2013	Zoledronate	Placebo	BMD	!	+	+	+	!	!
Black et al. 17, 2007	Zoledronate	Placebo	Fracture	+	!	+	+	+	!
Black et al. 17, 2007	Zoledronate	placebo	Safety	+	+	+	+	+	+
Black et al. 17, 2007	Zoledronate	placebo	BTM	+	+	+	+	+	+
Black et al. 17, 2007	Zoledronate	placebo	BMD	+	!	+	+	+	!
Chao et al. 19, 2013	zoledronate	placebo	Fracture	+	+	+	+	+	+
Chao et al. 19, 2013	Zoledronate	placebo	Safety	+	+	•	+	!	!
Chao et al. 19, 2013	Zoledronate	placebo	BMD	+	+	+	+	+	+
Liang et al. 21, 2017	Zoledronate	placebo	BMD	+	+	+	+	+	+
Liang et al. 21, 2017	Zoledronate	Placebo	BTM	+	+	+	+	+	+
Yang et al. 22, 2015	Zoledronate	Placebo	BMD	!	+	+	+	!	!
Yang et al. 22, 2015	Zoledronate	Placebo	BTM	!	+	+	+	!	!
Gonelli et al. 29, 2014	Zoledronate	Ibandronate	BMD	•		+	+		•
Gonelli et al. 29, 2014	Zoledronate	Ibandronate	BTM	•	•	+	+	!	•
Hadji et al. 28, 2012	Zoledronate	Alendronate	Safety	•	•	•	•		•
Hadji et al. 28, 2012	Zoledronate	Alendronate	BTM	•		+	+		-
Tan et al. 27, 2016	Zoledronate	Alendronate	BMD	+		+	+		!
Tan et al. 27, 2016	Zoledronate	Alendronate	BTM	+		+	+		
+ Low risk ! Some conce	erns 🕒 High risk								

D1: Randomization process; D2: Deviations from the intended interventions; D3: Missing outcome data: D4: Measurement of the outcome; D5: Selection of reported results.

Figure 2. Risk of bias 2: Risk of bias for each outcome in all randomized controlled trials with osteoporotic women.

	Study ID	Experimental	<u>Comparator</u>	<u>Outcome</u>	D1	D2	D3	D4	D5	Overall
	Grey et al.24, 2009	Zoledronate	Placebo	Safety	+	+	+	+	+	+
	Grey et al.24, 2009	Zoledronate	Placebo	BTM	+	+	+	+	+	+
	Grey et al.24, 2009	Zoledronate	Placebo	BMD	+	+	+	+	+	+
	McClung et al.23, 2009	Zoledronate	placebo	Safety	+	+	+	+	+	+
	McClung et al.23, 2009	Zoledronate	Placebo	BTM	+	+	+	+	+	+
	McClung et al.23, 2009	Zoledronate	Placebo	BMD	+	+	+	+	+	+
	Grey et al. 25, 2012	Zoledronate	Placebo	Safety	+	+	+	+	+	+
	Grey et al. 25, 2012	Zoledronate	Placebo	BTM	+	+	+	+	+	+
	Grey et al. 25, 2012	Zoledronate	Placebo	BMD	+	+	+	+	+	+
	Reid et al.26, 2018	Zoledronate	Placebo	Fracture	+	+	+	+	+	+
	Reid et al.26, 2018	Zoledronate	Placebo	Safety	+	+	+	+	+	+
	Reid et al.26, 2018	Zoledronate	Placebo	BTM	+	+	+	+	+	+
	Reid et al.26, 2018	Zoledronate	Placebo	BMD	+	+	+	+	+	+
Lov D1: Rande reported	<mark>v risk</mark> omization process; D2: Deviat results	cions from the inte	nded intervention	s; D3: Missing out	come data	ı; D4: Me	asureme	nt of the	outcon	ne; D5: Selection of

Figure 3. Risk of bias 2: risk of bias for each outcome in all randomized controlled trials with osteopenic women.

Postmenopausal osteopenic women

D1·

High-certainty evidence indicated that 5 mg of zoledronate every 18 months reduces morphometric vertebral fractures after six years (four doses) (Figure 4b2).

For hip fractures (Figure 4c2), moderate-certainty evidence (downgraded for imprecision) indicated that zoledronate probably results in little to no difference in the reduction of hip fractures after six years (four doses).

For non-vertebral fractures (Figure 4d2), moderate-certainty evidence (downgraded for imprecision) indicated that zoledronate likely results in little to no difference in preventing non-vertebral fractures after one year; however, after three years (2 doses), zoledronate probably reduces and after six years (4 doses), there is a high certainty that it reduces non-vertebral fractures.

For all clinical fractures, moderate-certainty evidence (downgraded for imprecision) indicated that zoledronate probably results in little to no difference in preventing clinical fractures in the first two years (Figure 4e2); however, after three years (2 doses), moderate-certainty evidence (downgraded for imprecision) indicated that zoledronate likely reduces clinical

fractures. Additionally, after six years (4 doses), high-certainty evidence indicated that it reduces clinical fractures.

Adverse reactions

The incidence of adverse events was obtained from seven RCTs comparing zoledronate with placebo and one RCT comparing zoledronate with alendronate. An RCT of ibandronate did not evaluate any adverse events.

A comparison of zoledronate with placebo showed that moderate- to high-certainty evidence indicated that zoledronate increases the post-dose symptoms after one year (Figure 5a). Low-certainty evidence (downgraded for risk of bias and inconsistency) indicated that zoledronate may increase the post-dose symptoms after two years, and high-certainty evidence indicated that zoledronate may increase the post-dose symptoms after three years.

After two years, moderate-certainty evidence indicated that zoledronate may slightly increase non-serious adverse events (Figure 5b), and after three years, high-certainty evidence indicated that zoledronate did not increase non-serious adverse events.

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Study or subaroup	Zoledro	nate	Place	DO		NISKIALIO	Horrado
Study of Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
1.1.1 After 12 months							_
Black et al.,17 2007	6	3689	19	3704	85.0%	0.32 [0.13, 0.79]	
Chao et al.,19 2013	1	327	4	333	15.0%	0.25 [0.03, 2.27]	
Subtotal (95% CI)		4016		4037	100.0%	0.31 [0.13, 0.71]	
Total events	7		23				
Heterogeneity: Tau ² =	0.00; Chi ²	= 0.03,	df = 1 (P	= 0.86)	; I² = 0%		
Test for overall effect: 2	Z = 2.74 (F	P = 0.00	6)				
1.1.2 After 24 months							
Black et al.,17 2007	9	3514	55	3494	60.8%	0.16 [0.08, 0.33]	
Chao et al.,19 2013	4	327	9	333	39.2%	0.45 [0.14, 1.46]	
Liang et al.,21 2017	0	155	0	95		Not estimable	
Subtotal (95% CI)		3996		3922	100.0%	0.24 [0.09, 0.65]	
Total events	13		64				
Heterogeneity: Tau ² =	0.28; Chi ²	= 2.16,	df = 1 (P	= 0.14)	; I ² = 54%		
Test for overall effect: 2	Z = 2.83 (F	P = 0.00	5)				
1.1.3 After 36 months							
Black et al. 17 2007	17	3182	69	3144	100.0%	0.24 [0.14, 0.41]	
Subtotal (95% CI)		3182		3144	100.0%	0.24 [0.14, 0.41]	➡
Total events	17		69				_
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 5.24 (F	< 0.00	001)				
							0.02 0.1 1 10 5

4b1



Figure 4. Incidence of fractures from 12 to 72 months in osteoporotic and osteopenic women [4a: Vertebral fractures (osteoporotic); 4b: Morphometric vertebral fractures (4b1: osteoporotic; 4b2: osteopenic), 4c: Hip fractures (4c1: osteoporotic; 4c2: osteopenic), 4d: Non-vertebral fractures (4d1: osteoporotic; 4d2: osteopenic), and 4e: All clinical fractures (4e1: osteoporotic; 4e2: osteopenic)]. Continue...

4b2

	Zoledro	nate	Place	bo		Risk ratio	Risk ratio	
Study or subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% CI	
3.1.1 After 72 months	s - 4 doses	S						
Reid et al.,26 2018 Subtotal (95% CI)	25	1000 1000	64	1000 1000	100.0% 100.0%	0.39 [0.25, 0.61] 0.39 [0.25, 0.61]		
Total events Heterogeneity: Not ap Test for overall effect: .	25 plicable Z = 4.06 (f	P < 0.00	64)01)					
								100
Test for subgroup diffe	erences: N	Vot app	licable				Favours zoledronate Favours placebo	

4c1

	Zolodro	nato	Diaco	bo		Risk ratio	Risk ratio
Study or subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.3.1 After 12 months							
Black et al.,17 2007 Chao et al.,19 2013 Subtotal (95% Cl)	22 3	3674 327 4001	20 4	3694 333 4027	85.9% 14.1% 100.0%	1.11 [0.60, 2.02] 0.76 [0.17, 3.39] 1.05 [0.60, 1.84]	
Total events Heterogeneity: Tau ² = 0 Test for overall effect: 2	25 0.00; Chi² 1 = 0.17 (F	= 0.20, P = 0.87)	24 df=1 (P)	= 0.65)	; I² = 0%	,	
1.3.2 After 24 months							
Bai et al.,20 2013 Black et al.,17 2007	36 35	242 3494	62 49	241 3499	52.6% 38.7%	0.58 [0.40, 0.84] 0.72 [0.46, 1.10]	- -
Chao et al.,19 2013 Liang et al.,21 2017	7	327 155	13	333 95	8.8%	0.55 [0.22, 1.36] Not estimable	
Subtotal (95% CI)		4218		4168	100.0%	0.62 [0.48, 0.82]	◆
Total events Heterogeneity: Tau² = 0 Test for overall effect: 2	78 0.00; Chi² (= 3.44 (F	= 0.63, ' = 0.00/	124 df = 2 (P 06)	= 0.73)	; I² = 0%		
1.3.3 After 36 months							
Black et al.,17 2007 Subtotal (95% CI)	44	3161 3161	72	3144 3144	100.0% 100.0%	0.61 [0.42, 0.88] 0.61 [0.42, 0.88]	—
Total events Heterogeneity: Not app Test for overall effect: 7	44 Nicable	2 = 0.00 ⁰	72 9)				
1001101 0101011 011001 2	. – 2.02 (i	- 0.00					
							0.1 0.2 0.5 1 2 5 10 Favours zoledronate Favours placebo

4c2



Figure 4. Incidence of fractures from 12 to 72 months in osteoporotic and osteopenic women [4a: Vertebral fractures (osteoporotic); 4b: Morphometric vertebral fractures (4b1: osteoporotic; 4b2: osteopenic), 4c: Hip fractures (4c1: osteoporotic; 4c2: osteopenic), 4d: Non-vertebral fractures (4d1: osteoporotic; 4d2: osteopenic), and 4e: All clinical fractures (4e1: osteoporotic; 4e2: osteopenic)]. Continue...

4d1

	Loieuro	T	Flace				
Study or subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
1.4.1 After 12 months							
Black et al.,17 2007	106	3586	128	3589	63.6%	0.83 [0.64, 1.07]	
Chao et al.,19 2013	4	327	14	333	36.4%	0.29 [0.10, 0.87]	
Subtotal (95% CI)		3913		3922	100.0%	0.57 [0.21, 1.52]	
Total events	110		142				
Heterogeneity: Tau ² =	0.38; Chi ^a	= 3.30,	df = 1 (P	= 0.07)	; I² = 70%	•	
Test for overall effect: 2	Z = 1.13 (F	P = 0.26)				
1.4.2 After 24 months							
Black et al.,17 2007	183	3335	236	3299	81.7%	0.77 [0.64, 0.92]	
Chao et al.,19 2013	28	327	48	333	18.3%	0.59 [0.38, 0.92]	- _
Liang et al.,21 2017	0	155	0	95		Not estimable	
Subtotal (95% CI)		3817		3727	100.0%	0.73 [0.60, 0.89]	◆
Total events	211		284				
Heterogeneity: Tau ² =	0.00; Chi ²	= 1.10,	df = 1 (P	= 0.30)	; I² = 9%		
Test for overall effect: 2	Z = 3.16 (F	P = 0.00	2)				
1.4.3 After 36 months							
Black et al.,17 2007	236	2956	306	2892	100.0%	0.75 [0.64, 0.89]	
Subtotal (95% CI)		2956		2892	100.0%	0.75 [0.64, 0.89]	\bullet
Total events	236		306				
Heterogeneity: Not app	olicable						
Test for overall effect: 2	Z = 3.41 (F	P = 0.00	06)				

4d2



Figure 4. Incidence of fractures from 12 to 72 months in osteoporotic and osteopenic women [4a: Vertebral fractures (osteoporotic); 4b: Morphometric vertebral fractures (4b1: osteoporotic; 4b2: osteopenic), 4c: Hip fractures (4c1: osteoporotic; 4c2: osteopenic), 4d: Non-vertebral fractures (4d1: osteoporotic; 4d2: osteopenic), and 4e: All clinical fractures (4e1: osteoporotic; 4e2: osteopenic)]. Continue...

4e1

Study or subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	
1.5.1 After 12 months								_
Black et al.,17 2007	107	3585	143	3571	89.4%	0.75 [0.58, 0.95]		
Chao et al. 19 2013 Subtotal (95% Cl)	13	327 3912	16	333 3904	10.6% 100.0%	0.83 [0.40, 1.69] 0.75 [0.60, 0.95]		
Total events	120		159					
Heterogeneity: Tau ² =	0.00; Chi ²	= 0.07,	df = 1 (P	= 0.79)	; I² = 0%			
Test for overall effect: 2	Z = 2.38 (F	° = 0.02)					
1.5.2 After 24 months							_	
Black et al.,17 2007	166	3327	261	3257	88.3%	0.62 [0.52, 0.75]		
Chao et al.,19 2013	21	327	35	333	11.7%	0.61 [0.36, 1.03]		
Liang et al.,21 2017	0	175	0	110		Not estimable		
Subtotal (95% CI)		3829		3700	100.0%	0.62 [0.52, 0.74]	◆	
Total events	187		296					
Heterogeneity: Tau ² =	0.00; Chi ^z	= 0.00	df = 1 (P	= 0.95)	; ² = 0%			
Test for overall effect: 2	Z = 5.27 (F	° < 0.00	001)					
1.5.3 After 36 months							_	
Black et al.,17 2007 Subtotal (95% CI)	235	2942 2942	341	2843 2843	100.0% 100.0%	0.67 [0.57, 0.78] 0.67 [0.57, 0.78]		
Total events	235		341					
Heterogeneity: Not app	olicable							
Test for overall effect:	Z = 5.04 (F	° < 0.00	001)					
			,					
								+
							0.2 0.5 1 2 5	5

4e2

	Zoledro	nate	Place	bo		NSK TUD	RISKTALIO
Study or subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
3.4.1 After 12 months -	1 dose						
Grey et al.,25 2012	1	43	0	43	2.1%	3.00 [0.13, 71.65]	
Reid et al.,26 2018 Subtotal (95% Cl)	30	1000 1043	41	1000 1043	97.9% 100.0%	0.73 [0.46, 1.16] 0.75 [0.48, 1.19]	
Total events	31		41				
Heterogeneity: Tau ² = 0.1	00; Chi² = 0).74, df=	= 1 (P = 0).39); l²	= 0%		
Test for overall effect: Z =	= 1.21 (P =	0.23)					
3 A 2 After 24 months	2 doses						
McClung et al. 22 2009	2 00303	100	0	202	100.0%	0 69 10 25 1 991	
Subtotal (95% CI)	0	198	5	202	100.0%	0.68 [0.25, 1.88]	
Total events	6		9				
Heterogeneity: Not appli	cable						
Test for overall effect: Z =	= 0.74 (P =	0.46)					
3.4.3 After 36 months- 2	2 doses						_
Reid et al.,26 2018 Subtotal (95% Cl)	90	1000 1000	122	1000 1000	100.0% 100.0%	0.74 [0.57, 0.95] 0.74 [0.57, 0.95]	
Total events	90		122				
Heterogeneity: Not appli	cable						
Test for overall effect: Z =	= 2.31 (P =	0.02)					
3.4.4 After 72 months	4 doses						_
Reid et al.,26 2018	185	1000	276	1000	100.0%	0.67 [0.57, 0.79]	—
Subtotal (55% Cl)	195	1000	276	1000	100.070	0.07 [0.57, 0.75]	•
Total evente	cable		270				
Total events Heterogeneity: Not appli	cable	0 00001	0				
Total events Heterogeneity: Not appli Test for overall effect: 7 -	- 177 / P <						
Total events Heterogeneity: Not appli Test for overall effect: Z =	= 4.77 (P <	0.00001	,				
Total events Heterogeneity: Not appli Test for overall effect: Z =	= 4.77 (P <	0.0000	·				

Figure 4. Incidence of fractures from 12 to 72 months in osteoporotic and osteopenic women [4a: Vertebral fractures (osteoporotic); 4b: Morphometric vertebral fractures (4b1: osteoporotic; 4b2: osteopenic), 4c: Hip fractures (4c1: osteoporotic; 4c2: osteopenic), 4d: Non-vertebral fractures (4d1: osteoporotic; 4d2: osteopenic), and 4e: All clinical fractures (4e1: osteoporotic; 4e2: osteopenic)].

Moderate-certainty evidence (downgraded for imprecision) indicated that zoledronate probably results in no difference in the SAE or death after two years (**Figure 5c**). After three years, moderate-certainty (downgraded for imprecision) indicated that it

probably does not reduce or increase the SAE or death, and after six years (four doses), moderate-certainty evidence (downgraded for imprecision) indicated that zoledronate probably results in no difference in death.

5a

Study or subaroup	Zoleuro	Tate	Flace				
otady of babgroup	Events	Total	Events	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
2.1.1 After 12 months							
Black et al.,17 2007	1221	3862	237	3852	52.9%	5.14 [4.50, 5.86]	
Grey et al.,25 2012	36	43	16	43	47.1%	2.25 [1.49, 3.39]	
Subtotal (95% CI)		3905		3895	100.0%	3.48 [1.55, 7.81]	
Total events	1257		253				
Heterogeneity: Tau ² =	0.32; Chi ²	= 14.12	, df = 1 (P = 0.0	002); I ² = !	93%	
Test for overall effect:	Z = 3.03 (F	P = 0.00	2)				
2.1.2 After 24 months							
Bai et al.,20 2013	67	242	61	241	49.7%	1.09 [0.81, 1.47]	
Black et al.,17 2007	253	3862	79	3852	50.3%	3.19 [2.49, 4.10]	
Subtotal (95% CI)		4104		4093	100.0%	1.88 [0.66, 5.36]	
Total events	320		140				
Heterogeneity: Tau ² =	0.55; Chi ²	= 29.35	, df = 1 (P < 0.0	0001); I ^z =	97%	
Test for overall effect:	Z = 1.17 (F	P = 0.24)				
2.1.3 After 36 months							
Black et al.,17 2007	108	3862	42	3852	100.0%	2.56 [1.80, 3.65]	_
Subtotal (95% CI)		3862		3852	100.0%	2.56 [1.80, 3.65]	•
Total events	108		42				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 5.22 (F	o < 0.00	001)				
							0.02 0.1 1 10 5

5b

	Zoledro	nate	Place	bo		Riskratio	Risk ratio
Study or subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2.2.1 After 24 months							
Chao et al.,19 2013	275	327	272	333	53.8%	1.03 [0.96, 1.10]	
McClung et al.,23 2009	177	198	160	202	46.2%	1.13 [1.04, 1.23]	│ ── ∎───
Subtotal (95% CI)		525		535	100.0%	1.07 [0.98, 1.17]	
Total events	452		432				
Heterogeneity: Tau ² = 0.0	00; Chi ² = 2	2.68, df :	= 1 (P = 0	.10); i ²	= 63%		
Test for overall effect: Z =	: 1.56 (P = 1	0.12)					
2.2.2 After 36 months							
Black et al.,17 2007	3688	3862	3616	3852	100.0%	1.02 [1.01, 1.03]	
Subtotal (95% CI)		3862		3852	100.0%	1.02 [1.01, 1.03]	•
Total events	3688		3616				
Heterogeneity: Not appli	cable						
Test for overall effect: Z =	: 3.17 (P = 1	0.002)					
						_	
							00600 1 11 12
							0.85 0.9 1 1.1 1.2 Eavours zoledropate Eavours placebo

Figure 5. Incidence of adverse events from 12 to 72 months in osteoporotic and osteopenic women (5a: Any symptom of post-dose acute-phase reactions, 5b: Non-serious adverse events, 5c: Serious adverse event or death, and 5d: Atrial fibrillation). Continue...

5c



5d

	Zoledro	nate	Place	bo		Risk ratio	Riskratio
Study or subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2.4.1 After 36 months	;						
Black et al.,17 2007 Subtotal (95% CI)	94	3862 3862	73	3852 3852	100.0% 100.0%	1.28 [0.95, 1.74] 1.28 [0.95, 1.74]	
Total events	94		73				
Heterogeneity: Not app	plicable						
Test for overall effect:	Z = 1.62 (F	P = 0.10)				
2.4.2 After 72 months	54	1000	55	1000	100.0%	0.09.00.69.1.411	
Subtotal (95% CI)	04	1000	55	1000	100.0%	0.98 [0.68, 1.41]	
Total events Heterogeneity: Not ap Test for overall effect: 2	54 plicable Z = 0.10 (F	P = 0.92	55))				
Taat fan auk warm diffi		1.17 - 4	22 df - 1	(D = 0	07) 12 - 4		0.5 0.7 1 1.5 2 Favours zoledronate Favours placebo
rest for subgroup diffe	erences: C	/nr=1.	23. df = 1	(P = 0)	21), 1* = 1	8.9%	

Figure 5. Incidence of adverse events from 12 to 72 months in osteoporotic and osteopenic women (5a: Any symptom of post-dose acute-phase reactions, 5b: Non-serious adverse events, 5c: Serious adverse event or death, and 5d: Atrial fibrillation).

After three years, moderate-certainty evidence (downgraded for imprecision) indicated that zoledronate may slightly increase the atrial fibrillation; but after six years (four doses), zoledronate probably does not increase atrial fibrillation (**Figure 5d**).

Moderate-certainty evidence (downgraded for imprecision) indicated that zoledronate probably results in little to no difference in eye disorders after one year, and after three years, it probably does not increase jaw osteonecrosis. After three years, high-certainty evidence indicated that the serum creatinine levels has increased.

In a study comparing zoledronate with alendronate, low-certainty evidence (downgraded for risk of bias and imprecision) indicated that zoledronate increases adverse events and influenza-like symptoms, results in little to no difference in serious adverse events or death, and does not increase or reduce atrial fibrillation or eye disorders after one year.

Secondary outcomes

Percent change in bone turnover markers (BTM)

The percent change in BTM was obtained from six RCTs that compared zoledronate with a placebo. Yang et al. also analyzed the BTM; however, the data from this RCT were not used in the review because the baseline values were different when compared to others.²²

Postmenopausal osteoporotic women

After six months, moderate-certainty evidence (downgraded for imprecision) indicated that zoledronate probably reduces P1NP. After one and two years, the certainty was low (downgraded for inconsistency and imprecision), and after three years, high-certainty evidence indicated that zoledronate reduces P1NP (**Figure 6a1**).

After six months and one year, high-certainty evidence indicated that zoledronate reduces the CTX levels. After two and three years, the evidence was moderate (downgraded for imprecision) (Figure 6b1).

Low-certainty evidence (downgraded for the risk of bias and imprecision) indicated that zoledronate results in little to no difference in P1NP and that it probably reduces the CTX compared to alendronate. For zoledronate versus ibandronate, very low-certainty evidence (downgraded by one point for risk of bias and two points for imprecision) indicated that zoledronate has no effect on CTX.

Postmenopausal osteopenic women

After six months, high-certainty evidence indicated zoledronate reduces P1NP, and after one year, low-certainty evidence (down-graded for inconsistency and imprecision). After two years (two doses) and six years (four doses), high-certainty evidence indicated that zoledronate reduces P1NP (**Figure 6a2**).

After six months and one year, moderate-certainty evidence (downgraded for inconsistency) indicated that zoledronate reduces the CTX. High-certainty evidence was observed after two years (two doses) and six years (four doses) (**Figure 6b2**).

6a1



Figure 6. Percent change in bone turnover markers from 6 to 72 months in osteoporotic and osteopenic women [6a- Procollagen type 1 N propeptide (6a1- osteoporotic; 6a2- osteopenic), and 6b- C-terminal telopeptide of type 1 collagen (6b1- osteoporotic; 6b2- osteopenic)].

Continue...

6a2

Study or subaroup	Zo	ledronate			Placebo			Mean difference	Mean difference
2 2 4 After 6 months	Mean	SD	Total	Mean	SD	lotal	weight	IV, Random, 95% CI	IV, Random, 95% Cl
D.z. TAILET 6 MONUS	00.50	40.5000	10	2.27	44 2005	10	10.000	74 00 4 00 4 0 57 4 4	
3rey et al.,25 2012	-08.53	18.5862	43	3.21	44.2885	43	40.3%	-/1.80 [-86.16, -57.44]	
Subtotal (95% CI)	-70	29.703	422	-11.4	87.9350	202	53.7% 100.0%	-64.71 [-77.61, -51.81]	↓ ↓
Heterogeneity: Tau ² = 39.	99; Chi ² :	= 1.85, df =	= 1 (P =	0.17);1	²= 46%				
Fest for overall effect: Z =	9.83 (P <	< 0.00001)							
3.2.2 After 12 months									
Grey et al.,24 2009	-45.4	45.6	25	-7.7	29.6	25	27.3%	-37.70 [-59.01, -16.39]	
Grey et al.,25 2012	-57.24	17.9039	43	5.21	47.6354	43	34.7%	-62.45 [-77.66, -47.24]	-
McClung et al.,23 2009 Subtotal (95% Cl)	-52.7	47.5248	379 447	-14.8	84.3317	202 270	38.1% 100.0%	-37.90 [-50.48, -25.32] -46.36 [-63.24, -29.47]	•
Fest for overall effect: Z =	5.38 (P «	< 0.00001)	- 2 (- 0.04)	1 - 10%				
McClung et al.,23 2009 Subtotal (95% Cl)	-54.9	20.69	198 198	-12	32.73	202 202	100.0% 100.0%	-42.90 [-48.26, -37.54] -42.90 [-48.26, -37.54]	.
Heterogeneity: Not applic	able								
Test for overall effect: Z =	15.70 (P	< 0.00001)						
3.2.4 After 72 months									_
Reid et al.,26 2018 Subtotal (95% Cl)	-43.3	9.6689	1000 1000	-1.7	17.7263	1000 1000	100.0% 100.0%	-41.60 [-42.85, -40.35] -41.60 [-42.85, -40.35]	–
Heterogeneity: Not applic	able								
Test for overall effect: Z =	65.15 (P	< 0.00001)						
									-200 -100 0 100 200

6b1

Chudu an aub anaun	Zole	dronate		P	lacebo			Meandinerence	Medifullerence
Study of Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
3.9.1 After 6 months									
Black et al.,17 2007	-73.61	16.48	237	-11.9	52.13	248	44.1%	-61.71 [-68.53, -54.89]	• · · · · · · · · · · · · · · · · · · ·
Liang et al.,21 2017 Subtotal (95% CI)	-75.375	3.2	155 392	-3.6	1.04	110 358	55.9% 100.0%	-71.78 [-72.31, -71.24] -67.34 [-77.13, -57.55]	•
Heterogeneity: Tau² = Test for overall effect: 2	44.56; Chi Z = 13.48 (i ² = 8.32 (P < 0.00	, df = 1 0001)	(P = 0.0	004); I² =	88%			
3.9.2 After 12 months									
Black et al.,17 2007	-60.28	22.79	201	1	52.09	214	18.5%	-61.28 [-68.94, -53.62]	+
Liang et al.,21 2017 Subtotal (95% CI)	-71.5	20.73	155 356	-6.43	8.1	95 309	81.5% 100.0%	-65.07 [-68.72, -61.42] -64.37 [-67.66, -61.08]	.
Heterogeneity: Tau² = Test for overall effect: 2	0.00; Chi² Z = 38.31 (= 0.77, (P < 0.00	df = 1 (0001)	P = 0.3	3); I² = 0	%			
3.9.3 After 24 months									
Black et al.,17 2007	-54.72	22.77	191	7.77	52.03	196	47.5%	-62.49 [-70.46, -54.52]	•
Liang et al.,21 2017 Subtotal (95% Cl)	-52.32	4.15	155 <mark>346</mark>	-7.79	3.01	95 291	52.5% 100.0%	-44.53 [-45.42, -43.64] -53.06 [-70.63, -35.48]	➡
Heterogeneity: Tau² = Test for overall effect: 2	152.91; C Z = 5.92 (F	hi² = 19. ° < 0.000	28, df: 001)	= 1 (P <	0.0001)	; I² = 95	5%		
3.9.4 After 36 months									_
Black et al.,17 2007	-49.17	58.81	174 174	13.99	51.97	170 170	100.0% 100.0%	-63.16 [-74.88, -51.44] -63.16 [-74.88, -51.44]	↓
Subtotal (95% CI)	licable	(P < 0.00	0001)						
Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2	7 = 10.56								1
Subtotal (95% CI) Heterogeneity: Not apj Test for overall effect: 2	Z = 10.56							-	-100 -50 0 50 100

Figure 6. Percent change in bone turnover markers from 6 to 72 months in osteoporotic and osteopenic women [6a- Procollagen type 1 N propeptide (6a1- osteoporotic; 6a2- osteopenic), and 6b- C-terminal telopeptide of type 1 collagen (6b1- osteoporotic; 6b2- osteopenic)].

Continue...

6b2

	Zo	ledronate			Placebo			Mean difference	Mean difference
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
3.10.1 After 6 months									
Grey et al.,25 2012	-79.71	12.4775	43	8.01	26.4821	43	48.4%	-87.72 [-96.47, -78.97]	- - -
McClung et al.,23 2009	-66.5	14.8515	379	-2.25	20.9748	202	51.6%	-64.25 [-67.51, -60.99]	
Subtotal (95% CI)			422			245	100.0%	-75.62 [-98.61, -52.63]	
Heterogeneity: Tau ² = 26	4.08; Chi	²= 24.28, i	df=1 (F	° < 0.00	1001); I ^z = 9	36%			
Test for overall effect: Z =	: 6.45 (P <	< 0.00001)							
3.10.2 After 12 months									
Grey et al.,24 2009	-63.8	16.4252	25	0.58	49.8571	25	25.2%	-64.38 [-84.96, -43.80]	
Grey et al.,25 2012	-66.2	17.16	43	7.04	26.514	43	35.4%	-73.24 [-82.68, -63.80]	- - -
McClung et al.,23 2009	-54.57	14.1584	379	-3.22	13.839	202	39.4%	-51.35 [-53.73, -48.97]	
Subtotal (95% CI)			447			270	100.0%	-62.38 [-79.43, -45.34]	-
Heterogeneity: Tau ² = 19	0.38; Chi	² = 20.65, (df = 2 (F	P < 0.00	101); I² = 90)%			
l est for overall effect: Z =	: 7.17 (P <	< 0.00001)							
3.10.3 After 24 months									
McClung et al. 23 2009	-56	10 2034	198	4	36 0392	202	100.0%	-60.00 (-65.17 -54.83)	
Subtotal (95% CI)	00	10.2004	198	4	00.0002	202	100.0%	-60.00 [-65.17, -54.83]	→
Heterogeneity: Not applic	cable								-
Test for overall effect: Z =	22.75 (P	< 0.00001)						
			,						
3.10.4 After 72 months									_
Reid et al.,26 2018	-48.1	9.6689	1000	10.2	19.34	1000	100.0%	-58.30 [-59.64, -56.96]	
Subtotal (95% CI)			1000			1000	100.0%	-58.30 [-59.64, -56.96]	•
Heterogeneity: Not applie	cable								
Test for overall effect: Z =	: 85.26 (P	< 0.00001)						
									-100 -50 0 50 10
									Favours zoledronate Favours placebo
Test for subgroup differe	nces: Ch	I* = 2.74, d	f= 3 (P	= 0.43), I* = 0%				

Figure 6. Percent change in bone turnover markers from 6 to 72 months in osteoporotic and osteopenic women [6a- Procollagen type 1 N propeptide (6a1- osteoporotic; 6a2- osteopenic), and 6b- C-terminal telopeptide of type 1 collagen (6b1- osteoporotic; 6b2- osteopenic)].

Percent change in BMD

The MD in BMD was obtained from eight RCTs that compared zoledronate with placebo, one with alendronate, and one with ibandronate.

Postmenopausal osteoporotic women

Moderate-certainty evidence (downgraded for risk of bias) indicated that zoledronate probably does not increase the lumbar spine BMD after one year; however, it was observed to probably increase after two years and increase after three years (**Figure 7a1**).

Moderate-certainty evidence (downgraded for risk of bias) indicated that zoledronate probably does not increase the femoral neck BMD after one year and three years, and low-certainty evidence (downgraded for inconsistency and imprecision) probably results in little increase after two years (**Figure 7b1**).

Moderate-certainty evidence (downgraded for risk of bias) indicated that zoledronate probably does not increase the total hip BMD after one year, may increase after two years, and that it increases after three years (**Figure 7c1**).

For zoledronate versus alendronate, low-certainty evidence (downgraded for risk of bias and imprecision) indicated that zoledronate increases lumbar spine, femoral neck, and total hip BMD. For zoledronate versus ibandronate, very low-certainty evidence (downgraded by one point for risk of bias and two points for imprecision) indicated uncertainty about the presence of an effect on the lumbar spine and total hip BMD.

Postmenopausal osteopenic women

Moderate-certainty evidence (downgraded for inconsistency) indicated that zoledronate probably does not increase the lumbar spine BMD after one year. After two years (two doses), three years (two doses), and six years (four doses), there was high-certainty evidence that zoledronate increases the lumbar spine BMD (**Figure 7a2**).

High-certainty evidence indicated that zoledronate does not increase the femoral neck BMD after one year, and moderate-certainty evidence (downgraded for imprecision) indicated that it results in little to no difference in increasing the femoral neck BMD after two years (**Figure 7b2**).

High-certainty evidence indicated that zoledronate does not increase the total hip BMD after one year, and moderate-certainty (downgraded for imprecision) indicated that it may increase the total hip BMD after two years; however, after three years (two doses) and six years (four doses), high-certainty evidence indicated that it increases total hip BMD (**Figure 7c2**).

7a1

Study or subaroup	Maan	60	Total	Maan	60	Total	Moight	N/ Dandom 05% Cl	W Dandom 05% Cl
	mean	50	Total	mean	50	Total	weight	IV, Random, 95% CI	IV, Kandom, 95% CI
1.12.1 After 12 month	IS								
Black et al.,17 2007	3.894	5.3925	262	0.214	4.8989	258	18.6%	3.68 [2.79, 4.57]	
Liang et al.,21 2017	3.12	0.56	155	-1.25	0.15	95	69.7%	4.37 [4.28, 4.46]	
Yang et al.,22 2015	3.21	2.95	44	-0.62	2.8	46	11.7%	3.83 [2.64, 5.02]	
Subtotal (95% CI)			461			399	100.0%	4.18 [3.73, 4.62]	♦
Heterogeneity: Tau ² =	0.07; Cł	ni² = 3.07,	df = 2	(P = 0.22)	2); I ² = 35	%			
Test for overall effect:	Z = 18.4	4 (P < 0.0	0001)						
1.12.2 After 24 month	IS								
Bai et al.,20 2013	2.2	11.293	242	-1.09	8.984	241	25.1%	3.29 [1.47, 5.11]	│ — ∎ —
Black et al.,17 2007	5.765	6.2537	236	-0.101	6.393	226	33.1%	5.87 [4.71, 7.02]	
Liang et al.,21 2017	5.39	0.854	155	-1.038	0.599	95	41.8%	6.43 [6.25, 6.61]	
Subtotal (95% CI)			633			562	100.0%	5.45 [4.01, 6.89]	•
Heterogeneity: Tau ² =	1.28; Cł	ni² = 12.11	df = 2	2 (P = 0.0	002); I ² =	83%			
Test for overall effect:	Z=7.42	(P < 0.00	001)						
1.12.3 After 36 month	IS								
Black et al.,17 2007	6.94	7.16	228	0.27	7.05	212	100.0%	6.67 [5.34, 8.00]	
Subtotal (95% CI)			228			212	100.0%	6.67 [5.34, 8.00]	▲
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z= 9.84	(P < 0.00	001)						
									-10 -5 0 5 10
		0.00	0.05 44		0.0000	12 0 0 0	70/		Favours pracebo Favours zoledronate

7a2

								Maan difference	Maan difference
Study or subgroup	Zo	ledronat	e	F	Placebo			Mean difference	Mean difference
Study of Subgroup	Mean	SD	Total	Mean	SD.	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
3.7.1 After 12 months - 1	l dose								
Grey et al.,24 2009	4.2	3.6581	25	-0.89	2.5922	25	21.6%	5.09 [3.33, 6.85]	
Grey et al.,25 2012	2.96	1.9496	43	-0.2	3.0869	43	32.8%	3.16 [2.07, 4.25]	
McClung et al.,23 2009	2.33	2.38	379	-0.38	2.39	202	45.6%	2.71 [2.30, 3.12]	-
Subtotal (95% CI)			447			270	100.0%	3.37 [2.28, 4.47]	•
Heterogeneity: Tau ² = 0.6	i4; Chi²∍	= 6.99, df	= 2 (P :	= 0.03);	I ² = 71%				
Test for overall effect: Z =	6.03 (P	< 0.0000	1)						
3.7.2 After 24 months - 2	2 doses								_
McClung et al.,23 2009	5.18	3.83	198	-1.32	3.8	202	100.0%	6.50 [5.75, 7.25]	
Subtotal (95% CI)			198			202	100.0%	6.50 [5.75, 7.25]	•
Heterogeneity: Not applic	able								
Test for overall effect: Z =	17.04 (F	P < 0.000	01)						
3.7.3 After 36 months - 2	2 doses								_
Reid et al.,26 2018	5.58	0.25	1000	-1.09	0.28	1000	100.0%	6.67 [6.65, 6.69]	
Subtotal (95% CI)			1000			1000	100.0%	6.67 [6.65, 6.69]	
Heterogeneity: Not applic	able								
Test for overall effect: Z =	561.91	(P < 0.00	001)						
3.7.4 After 72 months - 4	doses								
Reid et al., 26 2018	7.32	0.34	1000	-1.14	0.39	1000	100.0%	8.46 [8.43, 8.49]	
Subtotal (95% CI)			1000			1000	100.0%	8.46 [8.43, 8.49]	
Heterogeneity: Not applic	able								
Test for overall effect: Z =	517.07	(P < 0.00	001)						
			.,						
									-10 -5 0 5 10
Test for subgroup differe	nces: Cl	hi² = 7894	1.99, df	= 3 (P <	0.00001), I ² = 1	00.0%		Favours pracebo Favours zoredronate

Figure 7. Percent change in bone mineral density from 12 to 72 months in osteoporotic and osteopenic women [7a- lumbar spine (7a1- osteoporotic; 7a2- osteopenic), 7b- femoral neck (7b1- osteoporotic; 7b2- osteopenic), and 7c- total hip (7c1- osteoporotic; 7c2- osteopenic)].

Continue...

7b1

0.1	Zoled	Ironate	F	lacebo			Mean difference	Mean difference
Study or subgroup	Mean	SD Tota	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.13.1 After 12 mont	ıs							
Black et al.,17 2007	2.64	5.45 3522	0.48	4.56	3548	81.9%	2.16 [1.93, 2.39]	
Yang et al.,22 2015 Subtotal (95% Cl)	2.32	2.64 44 356	-0.43	1.89	46 3594	18.1% 100.0%	2.75 [1.80, 3.70] 2.27 [1.82, 2.71]	•
Heterogeneity: Tau² = Test for overall effect:	0.05; Chi² Z = 9.97 (P	= 1.39, df = < 0.00001)	l (P = 0.2	24); I² = 23	3%			
1.13.2 After 24 mont	ıs							
Bai et al.,20 2013	1.56 6	.7126 242	-3.17	4.7284	241	34.3%	4.73 [3.69, 5.77]	
Black et al.,17 2007 Subtotal (95% CI)	3.28 4	.3506 3234 347	-0.54	6.6916	3254 3495	65.7% 100.0%	3.82 [3.55, 4.09] 4.13 [3.29, 4.98]	
Heterogeneity: Tau² = Test for overall effect:	0.26; Chi² Z = 9.56 (P	= 2.77, df= < 0.00001)	I (P = 0.1	0); l² = 6-	4%			
1.13.3 After 36 mont	ıs							
Black et al.,17 2007 Subtotal (95% Cl)	3.95	2.26 3067 306 7	0.96	0.28	3083 3083	100.0% 100.0%	2.99 [2.91, 3.07] 2.99 [2.91, 3.07]	
Heterogeneity: Not ap Test for overall effect:	plicable Z = 72.72 ((P < 0.00001)					
								-4 -2 0 2 4
Test for subgroup diff	erences: C	hi² = 17.00.	df = 2 (P :	= 0.0002), l² = 88	8.2%		Favours placebo Favours zoledronate

7b2



7c1

	Zole	edronate	e	Р	lacebo			Mean difference	Mean difference
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.14.1 After 12 mon	ths								
Black et al.,17 2007	2.83	2.42	3516	-0.02	3.04	3542	46.8%	2.85 [2.72, 2.98]	•
Liang et al.,21 2017	2.06	0.34	155	-0.8	0.54	95	52.5%	2.86 [2.74, 2.98]	
Yang et al.,22 2015	1.8	3.06	44	-0.5	1.92	46	0.7%	2.30 [1.24, 3.36]	
Subtotal (95% CI)			3715			3683	100.0%	2.85 [2.76, 2.94]	
Heterogeneity: Tau ²	= 0.00; Ch	i ² = 1.06	df = 2	(P = 0.59	8); I² = 09	6			
Test for overall effec	t: Z = 63.73	8 (P < 0.0	00001)						
1.14.2 After 24 mon	ths								
Bai et al.,20 2013	1.54	4.7383	242	-3.07	4.7284	241	28.4%	4.61 [3.77, 5.45]	
Black et al., 17 2007	3.71	2.9	3228	-1.02	2.91	3248	35.8%	4.73 [4.59, 4.87]	
Liang et al.,21 2017	1.9	0.262	155	-1.631	0.649	95	35.8%	3.53 [3.39, 3.67]	
Subtotal (95% CI)			3625			3584	100.0%	4.27 [3.29, 5.24]	•
Heterogeneity: Tau ²	= 0.69; Ch	i² = 143.	82, df=	2 (P < 0	.00001);	I ² = 999	6		
Test for overall effec	t: Z = 8.57 ((P < 0.00	0001)						
1.14.3 After 36 mon	ths								
Black et al.,17 2007	4.19	2.82	3061	-1.88	3.4	3077	100.0%	6.07 [5.91, 6.23]	
Subtotal (95% CI)			3061			3077	100.0%	6.07 [5.91, 6.23]	T
Heterogeneity: Not a	pplicable								
Test for overall effec	t: Z = 76.14	↓ (P < 0.0	00001)						
									-10 -5 0 5 10
To at fay and grant di	<i></i>	0.62-4		46 - 0.05		04) 17-	00.00		Favours placebo Favours zoledronate
Test for subaroup di	fferences:	Chi ² = 1	241.19	df = 2 (F	° < 0.000	01), I² =	: 99.8%		

Figure 7. Percent change in bone mineral density from 12 to 72 months in osteoporotic and osteopenic women [7a- lumbar spine (7a1- osteoporotic; 7a2- osteopenic), 7b- femoral neck (7b1- osteoporotic; 7b2- osteopenic), and 7c- total hip (7c1- osteoporotic; 7c2- osteopenic)].

Continue...

7c2

	70	odronate			lacobo			Mean difference	Mean difference
Study or subaroup	Mean	euronate SD	; Total	Moan		Total	Weight	IV Random 95% Cl	Weandom 95% Cl
3.9.1 After 12 months - 1	dose	30	Total	Mean	30	Total	Weight	IV, Random, 35% CI	
Grevetal 24 2009	1 99	2 253	25	-1.36	2 6649	25	11.0%	3 35 [1 98 4 72]	
Grevetal. 25 2012	2.28	0.9748	43	-1.07	1 917	43	34.5%	3 35 [2 71 3 99]	
McClung et al. 23 2009	2.33	2 376	379	-0.38	2.376	202	54.5%	2 71 [2 30 3 12]	-
Subtotal (95% CI)	2.00	2.010	447	0.00	2.010	270	100.0%	3.00 [2.52, 3.48]	•
Heterogeneity: Tau ² = 0.0	7: Chi ² =	: 3.13. df	= 2 (P =	= 0.21):	I² = 36%				
Test for overall effect: Z =	12.16 (F	< 0.000	01)	0.2.7					
			.,						
3.9.2 After 24 months - 2	doses								
McClung et al.,23 2009	2.91	2.9	198	-1.45	2.9	202	100.0%	4.36 [3.79, 4.93]	
Subtotal (95% CI)			198			202	100.0%	4.36 [3.79, 4.93]	•
Heterogeneity: Not applic	able								
Test for overall effect: Z =	15.03 (F	° < 0.000	01)						
3.9.3 After 36 months - 2	doses								_
Reid et al.,26 2018	3.56	0.15	1000	-2.08	0.22	1000	100.0%	5.64 [5.62, 5.66]	· · · · · · · · · · · · · · · · · · ·
Subtotal (95% CI)	-		1000			1000	100.0%	5.04 [5.0 ∠ , 5.00]	
Heterogeneity: Not applic	able ccolool	/D ~ 0.00	0043						
rest for overall effect. ∠ =	009.82	(P < 0.00	001)						
3.9.4 After 72 months - 4	doses								
Reid et al. 26 2018	3 47	0.23	1000	-3.97	0.32	1000	100.0%	7 44 [7 42 7 46]	
Subtotal (95% CI)	0.41	0.20	1000	0.01	0.02	1000	100.0%	7.44 [7.42, 7.46]	
Heterogeneity: Not applic	able								
Test for overall effect: Z =	597.02	(P < 0.00	001)						
			,						
								-	
									-4 -2 U Z 4
Fest for subaroun differe	nces: Ch	ni² = 1453	2.20. d	lf = 3 (P	< 0.0000)1), I ² =	100.0%		Favours placebo Favours zoleuronale

Figure 7. Percent change in bone mineral density from 12 to 72 months in osteoporotic and osteopenic women [7a- lumbar spine (7a1- osteoporotic; 7a2- osteopenic), 7b- femoral neck (7b1- osteoporotic; 7b2- osteopenic), and 7c- total hip (7c1- osteoporotic; 7c2- osteopenic)].

DISCUSSION

In this systematic review, 12 RCTs on the use of zoledronate in postmenopausal women were included: eight RCTs for osteoporosis and four RCTs for osteopenia. To assess whether there is an effective and safe response to zoledronate, thresholds of statistical significance were established according to published data found in the scientific literature.

The main objective for preventing and treating osteoporosis is to reduce the incidence of fractures, although it does not eliminate them. In this review, a minimal significant reduction of 30% was established for vertebral and hip fractures, and a 15% reduction was established for other fractures (non-vertebral and clinical). This decision was based on the thresholds for therapeutic failure published by Diez-Perez et al.¹⁶ They considered a reduced risk of fractures ranging from 30% to 70% for vertebral fractures, 40% to 50% for hip fractures, and 15% to 20% for non-vertebral fractures.¹⁶

The occurrence of fractures in the RCTs was evaluated as both an outcome and an adverse event, which could have influenced the results of the analyses. The evidence for fractures was moderate to high, indicating that zoledronate reduces clinical and morphometric vertebral fractures since the first year of use, increasing its benefits each year during 3 years of treatment for osteoporotic women and for six years (5 mg every 18 months) for osteopenic women. In addition, zoledronate probably reduces the number of hip fractures after two years in osteoporotic women and probably results in little difference after six years (5 mg every 18 months) in osteopenic women. Zoledronate probably reduces non-vertebral fractures after two doses in women with osteoporosis (5 mg each year) and after two doses (5 mg every 18 months) and four doses (six years) in women with osteopenia. It reduces the number of all clinical fractures after two doses in both osteoporotic (after two years) and osteopenic (after three years) women and after six years (four doses) for osteopenic women.

No data were available regarding ibandronate-related fractures. Compared to alendronate, the results were based on fractures reported as adverse events, and the evidence was of very low certainty. Post-dose symptoms were reported mainly after the first infusion but also after the third dose. This was expected because, according to a literature review, acute-phase reactions can occur in up to 30% of patients.³⁰

There were no statistically significant differences with respect to serious adverse events, death, atrial fibrillation, osteonecrosis of the jaw, or eve disorders between the zoledronate and placebo groups. Osteonecrosis of the jaw has been described in cancer patients receiving high doses of intravenous zoledronate; however, its incidence in osteoporotic patients treated with zoledronate is considered very low.³¹ Additionally, concerns have been raised regarding the possible association between bisphosphonate therapy and atrial fibrillation. A meta-analysis of RCTs and observational studies with women and men treated with bisphosphonates for any indication demonstrated an increased risk of atrial fibrillation with bisphosphonates (slightly higher with intravenous bisphosphonates).³² Eye disorders, although rare, were associated with all bisphosphonate treatments.³³ Patel et al. reported an incidence of uveitis and episcleritis of 1.1% (95% CI 0.5-2.1). 34

None of the RCTs included in this review reported atypical femoral fractures. Atypical femoral fractures of the subtrochanteric region are considered rare events; however, bisphosphonate treatment for more than five years increases the risk of such fractures.³⁵

One RCT found a risk of increasing serum creatinine after zoledronate infusion.¹⁷ This effect was noted by the U.S. Food and Drug Administration in 2011, advising no use in patients with creatinine clearance less than 35 mL/min or with acute renal impairment and monitoring of renal function in patients receiving zoledronic acid.³⁶

A position paper endorsed by the International Osteoporosis Foundation published that a significant response to antiresorptive treatments occurs when there is a decline from baseline of at least 25% for CTX and P1NP.¹⁶ Delmas et al. reported that a decrease in the BTM could range from 30 to 50% after starting treatment with bisphosphonates.³⁷ A reduction of at least 30% in BTM was also found in the data presented in this review.

The same study reported that the least significant change in BMD should be approximately 5% in the lumbar spine and 4% in the femoral neck.¹⁶ A meta-regression analysis reported that a 4% increase in BMD of the femoral neck and total hip reduced vertebral fractures by 50% and hip fractures by 30%, and an increase in the lumbar spine BMD of 2% and 8% reduced vertebral fractures by 30% and 60%, and hip fractures by 20% and 40%, respectively.³⁸ Therefore, the present review considered a least significant change of a 5% increase in the lumbar spine and 4% in the femoral neck and total hip. Based on these thresholds and the presented data, the effect of zoledronate on BMD was similar in both osteopenic and osteoporotic women over the years, being statistically significant from the second year for the lumbar spine and from the third year for the femoral neck and total hip. After three years, a dose of 5 mg of zoledronate every 18 months (two doses) in osteopenic women and a dose of 5 mg yearly (three doses) in osteoporotic women increased the BMD similarly; in osteopenic women, a dose of 5 mg of zoledronate every 18 months also increased lumbar spine BMD and total hip BMD after six years (four doses). Evidence comparing zoledronate with alendronate and ibandronate has shown low to very low certainty.

When comparing the present review with others, the findings related to the efficacy were similar to those reported by Sanderson et al., Zhou et al., and He et al.^{39,40,41} The main difference was that the target population included was men, corticosteroid users, and frail women with secondary osteoporosis. Despite these findings, they reported similar results regarding a reduction in fractures and an increase in BMD.

Zoledronate is a well-established option for treating osteoporosis, as recommended in various publications, and the present review highlights its benefits. Although the main evidence for osteopenic women is based on one study, the use of zoledronate (5 mg every 18 months) should be considered in this population.

The AACE recommends alendronate, risedronate, zoledronate, and denosumab as initial therapies for patients at high risk of fracture and teriparatide, abaloparatide, denosumab, romozosumab, or zoledronate for patients at very high risk of fracture and those unable to undergo oral therapy.⁴

The EULAR/EFORT recommends that alendronate and risedronate should be the first-choice agents after fragility fractures in patients older than 50 years and for the prevention of subsequent fractures because of their low cost. It is also recommended that zoledronate or denosumab should be indicated when patients have oral intolerance to bisphosphonates, dementia, malabsorption, and show non-compliance, and anabolic agents are recommended for patients with very severe osteoporosis.⁴²

CONCLUSION

Moderate- to high-certainty evidence supports the use of zoledronate (5 mg) annually for three years in postmenopausal women with osteoporosis and 5 mg every 18 months for six years in postmenopausal women with osteopenia to reduce the risk of fractures.

Zoledronate was considered safe and was associated with transient post-dose symptoms. It significantly reduced the P1NP and CTX levels from the sixth month until the third year in osteoporotic women and the sixth year in osteopenic women. In addition, it increased the BMD in all bone segments analyzed after the second dose in osteopenic and osteoporotic women.

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INTRAVENOUS ZOLEDRONATE FOR POSTMENOPAUSAL WOMEN WITH OSTEOPENIA AND OSTEOPOROSIS: A SYSTEMATIC REVIEW AND METANALYSIS

Peer review information

The São Paulo Medical Journal thanks Cristiano Augusto de Freitas Zerbini and the other anonymous reviewer for their contribution to the peer-review process of this manuscript.

Peer review reports

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