Treatment of postmenopausal osteoporosis in women: a systematic review

Tratamento da osteoporose em mulheres na pós-menopausa: uma revisão sistemática

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Abstract

Osteoporosis, a typical disease of the elderly, has become a frequent and relevant public health problem. Several drugs are available for treatment of osteoporosis, some of which are currently dispensed by the Brazilian Unified National Health System. The objective of this study was to present a systematic review of drugs for treatment of osteoporosis, focusing on the adequacy of clinical protocols based on existing evidence in the scientific literature. We conducted a search for randomized clinical trials in PubMed and LILACS that presented results for bone mineral density, incidence of vertebral fractures, and adverse effects. 32 articles met the review's inclusion criteria. Bisphosphonates were reported to have consistently reduced the risk of vertebral fractures. Hormone replacement therapy showed positive outcomes, but its use has been found to increase the risk of cardiovascular disease and breast cancer. Teriparatide and monofluorophosphate also showed efficacy against osteoporosis. Calcium and vitamin D were given to patients as food supplements.

Postmenopausal Osteoporosis; Drugs; Women's Health

Introduction

Osteoporosis is typically a disease of the elderly, and with population aging it has become one of the most frequent and relevant health problems in this age bracket, especially among women [1]. In Brazil, little is known about the prevalence of this illness, although it is the most common disease of bone metabolism. In postmenopausal women, Costa-Paiva et al. [2] found prevalence rates of 14.7% and 38% for vertebral column osteoporosis and osteopenia, respectively, and 3.8% and 32.7% for femoral osteoporosis and osteopenia. A literature review focusing on prevalence in various countries showed point estimates for femoral osteoporosis ranging from 7.9% to 16% in women 50 years or older [3].

The disease is characterized by low bone mineral density (BMD) and degeneration of the bone microarchitecture, which increase the bone brittleness and fracture risk. The disease is identified clinically by the occurrence of non-traumatic fractures, especially in the lumbar spine (vertebral fractures) and forearm, and by the occurrence of femoral fractures after fall from height. The greatest loss of bone mass occurs in women during perimenopause and is associated with estrogen insufficiency, a condition of menopause [4].

Diagnosis of osteoporosis uses data on below-normal BMD for young adults (T score). According to these criteria, bone densitometry with T score ≤ -2.5, associated with fragility fractures,

indicates established osteoporosis; T score ≤ -2.5 alone, osteoporosis; T score from -1 to -2.5, osteopenia; and T score < -1, normal [4].

Various drugs are available for the treatment of osteoporosis and prevention of osteoporotic fractures. In Brazil, the annual costs of such treatment for osteoporosis in the Unified National Health System (SUS) have increased steadily, reaching some U$ 20 million by 2005 (Database of the Unified National Health System; http://www.datasus.gov.br, accessed in December 2006). The drugs included in these expenditures are: alendronate sodium, pamidronate, risedronate, raloxifene, synthetic salmon calcitonin, calcitriol, and alfacalcidol [5].

Information on drug efficacy for treatment of osteoporosis is necessary in the public health sphere to evaluate adequacy and support the updating of clinical protocols, based on the available scientific evidence.

The objective of the current study was to present a systematic review of the available drugs for treatment of osteoporosis, with a focus on evaluating their efficacy.

Methodology

We conducted a search for relevant articles in the PubMed database and in Latin-American Health Sciences Literature (LILACS). The PubMed search used Reference Manager 11 (The Nordic Cochrane Centre; http://www.cc-ims.net/RevMan) and LILACS was searched directly through the BIREME portal in the BVS network (http://www.bireme.br), with the result of the latter search exported to Reference Manager 11.

The following key words were used: {*osteoporosis*} *and* {*postmenopausal*} *or* {*post-menopausal*} *or* {*post menopausal*} *and* {*efficacy*} *and* {*raloxifene*} *or* {*calcitonin*} *or* {*strontium ranelate*} *or* {*bisphosphonates*} *or* {*alendronate*} *or* {*risedronate*} *or* {*ibandronate*} *or* {*pamidronate*} *or* {*parathyroid hormone*} *or* {*zoledronic acid*} *or* {*arzoxifene*} *or* {*lasofoxifene*} *or* {*etidronate*} *or* {*tiludronate*} *or* {*clodronate*} *or* {*zoledronate*} *or* {*neridronate*} *or* {*anti reabsorptive*} *or* {*calcium*} *or* {*vitamin D*} *or* {*estrogen*} *or* {*progesterone*} *or* {*selective estrogen modulator*} *or* {*tamoxifen*} *or* {*alfacalcidol*}.

The search criteria were applied to the titles and abstracts. During the PubMed search, the following limits were set for inclusion of titles and abstracts: language (English, Portuguese, or Spanish), studies on human beings, and articles on treatment efficacy. There was no restriction on the date of publication for articles, and the search was conducted up to October 2007.

In order to identify studies that may not have been detected in the initial strategy, an additional manual search was done in the bibliographic references of the review articles. The references most frequently cited in the articles and that met inclusion criteria were incorporated into the review.

Titles and abstracts of relevant articles were analyzed according to the following eligibility criteria:

- Efficacy study (randomized clinical trial);
- Conducted in a sample of women with postmenopausal osteoporosis;
- Evaluated drugs for treatment of osteoporosis that were previously defined in the search criteria;
- Presented at least one of the following outcomes/results: increase/decrease in lumbar spine BMD; increase/reduction in vertebral fractures; and adverse drug reactions.

The articles meeting the eligibility criteria were selected by two reviewers, and discordant cases were analyzed by a third reviewer. Articles were submitted to detailed reading, and data were grouped in descriptive tables, determining the study author, year, and location, project name (when possible), patient follow-up time, sample size, and intervention, losses, adverse reactions in the treatment group, and score in the evaluation of the study's methodological quality.

Data completion for the number of individuals per intervention was based on those with baseline data and who had taken at least one dose of the drug. Losses were defined as subjects who had not concluded the study's complete follow-up time.

Methodological quality of the selected randomized clinical trials was evaluated using the criteria from the modified Jadad scale [6]. Two independent reviewers conducted this evaluation, and discordant cases were analyzed by the third reviewer. The final inclusion criterion in this review was studies with a score of 5-6, with the best quality and lowest risk of bias.

Results

We found an initial group of 551 titles and abstracts for studies on pharmacological treatment of osteoporosis. According to the eligibility criteria, 156 abstracts were considered eligible by the first reviewer and 220 by the second reviewer, with a kappa coefficient of 0.613 between the two analyses, thus indicating fair-to-good concordance. 98 abstracts were submitted to the third reviewer due to discordance concerning eligibility, of which only four were considered eligible.

The manual search for citations in the publications detected 25 references, but 16 had already been identified during the initial search (Figure 1). Thus, a total of 138 references were selected. Of these, 8 articles could not be retrieved, even after requests for bibliographic exchange (COMUT) or direct communication with the authors themselves. During the data mining, 49 more articles were excluded, since they failed to meet the inclusion criteria, either because they included men in the study or included osteopenic (rather than osteoporotic) women, or because they expressed results that did not allow data comparison, so that 81 articles remained in the final selection.

The methodological quality of 81 studies was evaluated, based on the criteria from the Jadad scale. There was concordance in the classification of 73 articles, with a weighted kappa of 0.942 between the two analyses, indicating high concordance. In cases of discordance between the first two reviewers (8 articles), the score was assigned by the third reviewer.

For the 81 randomized clinical trials, the mean score for the methodological evaluation was 4 points. 40.7% obtained a score of 5-6, considered high quality/low risk of bias. 38.3% obtained a score of 3-4, demonstrating appropriate quality/moderate risk of bias. Only 21% received a score of 0-2, or poor quality/high risk of bias. According to the Jadad criteria, the studies' main limitations were:

- Use of an inappropriate randomization sequence (47 studies);
- Inappropriate masking method (45 studies);
- Lack of intent-to-treat analysis (28 studies);
- Lack of data masking by the data collector or evaluator (25 studies)
- Lack of description of participants that were excluded or dropped out of treatment (18 studies).

According to the proposed methodology, we present and discuss the randomized clinical trials that obtained scores 5 and 6. Of the 32 articles presented in Table 1, 28.1% were published in 2004, and the rest from 1992 to 2007. Most of the studies were multi-center (75%). Iris and Mobile were the most frequent trials covered by articles in this review. Mean follow-up time was 26 months (ranging from 12 to 60). Sample size varied from 75 to 2,929, with a mean of 852 subjects. Losses varied from 0 to 811, with a mean of 87 subjects, while one study lacked this information.

Studies compared alendronate to placebo (n = 3), estrogen (n = 1), raloxifene (n = 2), alfacalcidol (n = 1), at different doses (n = 1), and to teriparatide (n = 1). Risedronate was compared to placebo (n = 4) and at different doses (n = 1). Ibandronate was compared to placebo (n = 4) and at different doses (n = 4). Various articles compared other drugs to placebo: clodronate (n = 1), zoledronic acid (n = 1), estrogen (n = 1), parathyroid hormone (PTH) 1-84 (n = 1), calcitonin (n = 1), strontium ranelate (n = 2), raloxifene (n = 1), and monofluorophosphate (n = 2).

As for outcomes, two studies evaluated vertebral fractures only, 19 evaluated both vertebral fractures and lumbar spine BMD, and 11 studies lumbar spine BMD. Incidence of vertebral fractures ranged from 0 to 56.7%; mean lumbar spine BMD ranged from -2 a 22%, with a mean of 3.8%. In the group treated with some drug, incidence of vertebral fractures varied from 0 to 56.7%, and mean lumbar spine BMD varied from 0 to 22%. In the placebo group, incidence of vertebral fractures ranged from 0 to 54.7%, and mean lumbar spine BMD varied from -2 to 1.7%.

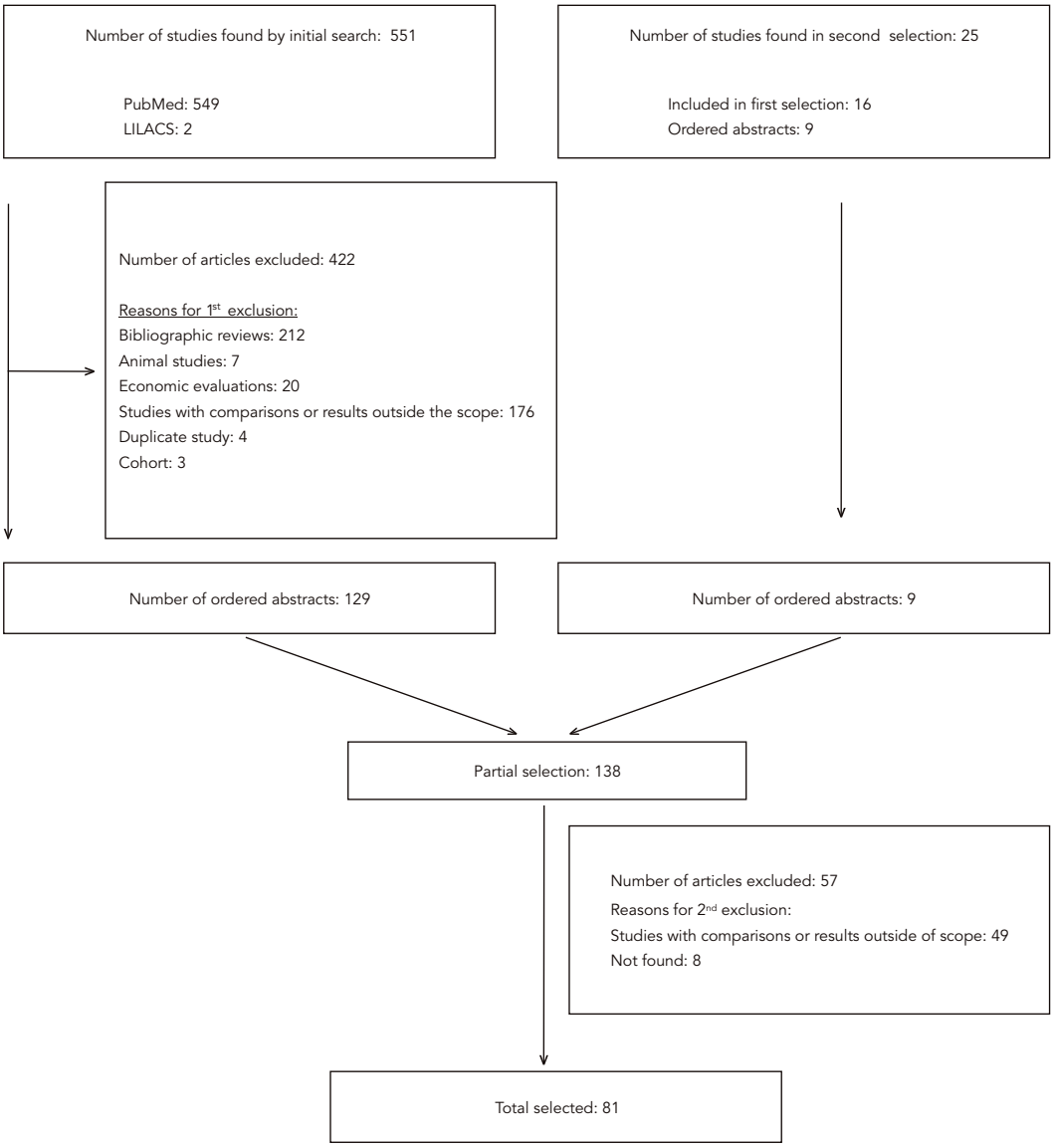
Bisphosphonates

The bisphosphonate class in the selected studies included: alendronate, risedronate, ibandronate, clodronate, and zoledronic acid. Of the studies that evaluated alendronate, five presented vertebral fracture as the outcome and eight presented lumbar spine BMD. In the study that compared alendronate to placebo, the treatment group had significantly fewer vertebral fractures (8%) than the placebo group (15%) [7]. In a study comparing alendronate to alfacalcidol, the incidence of fractures was lower in the group treated with alendronate ($p < 0.05$) [8]. Three studies showed no incidence of fractures in either group (drug versus placebo) [9,10,11].

As for studies on alendronate using lumbar spine BMD as the outcome, one compared alendronate to alfacalcidol, with alendronate showing a higher increase in lumbar spine BMD than alfacalcidol ($p < 0.05$) [8]. When comparing different presentations of alendronate, the drug treatment arms showed better results than placebo ($p < 0.001$), and the best results were at doses of 5 and 10mg [9]. In the study that evaluated different dosages (daily and monthly), there was no statistically significant difference between the two treatments [10]. Comparing alendronate to raloxifene, efficacy was greater in the group treated with alendronate ($p < 0.001$) [11]. Comparing alendronate 10mg to placebo, alendronate was more effective ($p \leq 0.001$) [12]. The study comparing alendronate to estrogen showed synergism in the association of the two drugs, superior to the results when they were taken independently or as compared to placebo ($p < 0.001$) [13]. A study comparing alendronate to raloxifene showed that the mean increase in lumbar spine BMD was greater

Figure 1

Flowchart for selection of articles for systematic review.



in the group treated with alendronate 70mg once a week than in the group treated with raloxifene ($p < 0.001$) [14].

The five studies evaluating the use of risedronate presented the two outcomes (vertebral fractures and lumbar spine BMD) [15,16,17,18,19]. In relation to vertebral fractures, the study comparing different doses (5mg/day and 35 and 50mg/week), showed no statistically significant difference in incidence between the groups [15]. A study comparing risedronate 5mg/day to placebo did not conduct a statistical analysis of the incidence of vertebral fractures, although it was higher in the treatment group (9.1%) as compared to the placebo group (7.1%) [16]. Clemmesen et al. [17] evaluated the continuing effect of treatment with risedronate one year after interrupting use, showing the lack of efficacy of treatment due to the insufficient dose of the drug. There was no statistically significant difference between the

Table 1

Characteristics of studies on osteoporosis in postmenopausal women.

Reference	Country/ Name of study	Time (months)		Sample size and intervention	Losses	Results (%) Vertebral fractures	Results (%) BMD	Adverse reactions	S
Ensrud et al. [7] (1997)	- *	36	1,022	Alendronate 5mg/D 2 years + Alendronate 10mg/D 1 year	-	8.0	-	-	5
			1,005	Placebo		15.0	-		
Kushida et al. [8] (2004)	Japan	36	90	Alendronate 5mg + placebo/D, oral	0	7.8	9.2	Constipation, upset stomach, stomach ache, and gastritis ***	5
			80	Alfacalcidol 1µg + Placebo/D, oral	0	18.8	1.4		
Chesnut III et al. [9] (1995)	USA *	24	32	Alendronate 5mg/D, oral	34 **	0.0	7.3	Nausea, dyspepsia, esophagitis, gastritis, abdominal pain, and skin rash #	5
			30	Alendronate 10mg/D, oral		0.0	7.2		
			32	Alendronate 20mg/D (1 year) + Placebo (1 year), oral		0.0	6.2		
			32	Alendronate 40mg/D (1 year) + Placebo (1 year), oral		0.0	6.2		
			31	Alendronate 40mg/D (3 months) + Alendronate 2.5mg (21 M), oral		0.0	4.5		
			31	Placebo/D, oral		0.0	-1.3		
Luckey et al. [10] (2003)	7 countries *	12	361	Alendronate 5mg/D	63	0.0	3.2	Abdominal pain and distension, acid reflux, dyspepsia, nausea, vomiting, and gastric ulcer #	5
			362	Alendronate 35mg/week	55	0.0	2.9		
Sambrook et al. [11] (2004)	16 countries from Europe, South America, and Asia-Pacific *	12	246	Alendronate 70mg/week + Placebo/D, oral	30	0.0	4.8	Upper GI and vasomotor events were higher in the raloxifene group ##	6
			241	Raloxifeno 60mg/D + Placebo/ week, oral	33	0.0	2.2		
Pols et al. [12] (1999)	34 countries from Europe, Latin America, Australia, Canada, South Africa, and China *	12	959	Alendronate 10mg/D, oral	127	-	5.0	Abdominal pain, nausea, gastritis, acid reflux, dyspepsia, vomiting, esophageal events, ulcer, and dysphagia ***	5
			950	Placebo/D, oral	85	-	0.1		

(continues)

Table 1 (continued)

Reference	Country/ Name of study	Time (months)		Sample size and intervention	Losses	Results (%) Verte-bral fractu-res	BMD	Adverse reactions	S
Bone et al. [13] (2000)	- *	24	50	Placebo Alendronate + Placebo estrogen/D, oral	16	-	-0.6	Upper GI events ***	6
			92	Alendronate 10mg + Placebo estrogen/D, oral	24	-	6.0		
			143	Estrogen 0.625mg + Placebo Alendronate/D, oral	34	-	6.0		
			140	Alendronate 10mg/ + Estrogen 0.625mg/D, oral	30	-	8.3		
Luckey et al. [14] (2004)	USA */ Effect	12	223	Alendronate 70mg/week + placebo/D, oral	44	-	4.4	Nausea, dyspepsia, abdominal pain, heartburn ***	6
			233	Raloxifene 60mg/D + placebo/ week, oral	40	-	1.9		
Brown et al. [15] (2002)	North America *	12	480	Risedronate 5mg/D, oral	77	1.2	4.0	Upper GI events, infection, arthralgia, and constipation ***	6
			485	Risedronate 35mg/week, oral	90	1.0	3.9		
			491	Risedronate 50mg/week, oral	80	0.4	4.2		
Ste-Marie et al. [16] (2004)	-/Vert-Na	60	44	Risedronate 5mg/D, oral	3	9.1	9.2	Upper GI events ***	6
			42	Placebo/D, oral	9	7.1	-0.3		
Clemmen-sen et al. [17] (1997)	Belgium and Denmark *	36	44	Risedronate 2.5mg/D/2 years – in the 3rd year only calcium supplement 1000mg/D, oral	15	29.5	0.8	Back pain, upper GI events #	5
			44	Risedronate 2.5mg/D for 2 weeks Placebo/ 10 week (cycles)/ 2 years- in the 3rd year only calcium supplement 1000mg/D, oral	11	34.1	2.3		
			44	Placebo- in the 3rd year only calcium supplement 1000mg/D, oral	13	45.4	1.7		
Harris et al. [18] (1999)	North America *	36	811	Risedronate 2.5mg/D, oral	811	-	-	Upper GI events ***	6
			813	Risedronate 5.0mg/D, oral	324	11.0	5.4		
			815	Placebo/D, oral	365	16.0	1.1		
Hooper et al. [19] (2005)	Australia *	24	127	Risedronate 2.5mg/D, oral	27	8.7	0.0 ###	Abdominal pain, esophagitis, and esophageal ulcer #	5
			129	Risedronate 5.0mg/D, oral	26	7.7	2.0		
			125	Placebo/D, oral I	32	8.3	-2.0 ###		
Felsen-berg et al. [20] (2005)	Countries of North America and Europe */Bone	36	977	Ibandronate 2.5mg/D, ora	329	5.5	-	Duodenal and gastric ulcer, dyspepsia, eructation, gastritis, gastroenteritis, GI pain, nausea, vomiting ***	6
			975	Placebo/D, oral	347	10.9	-		

(continues)

Table 1 (continued)

Reference	Country/ Name of study	Time (months)		Sample size and intervention	Losses	Results (%) Vertebral fractures	Results (%) BMD	Adverse reactions	S
Chesnut III et al. [21] (2004)	Countries of Europe and North America *	36	977	Ibandronate 2.5mg/D, oral	329	4.7	6.5	Duodenal and gastric ulcer, dyspepsia, eructation, gastritis, gastroenteritis, GI pain, nausea, vomiting ***	6
			977	Ibandronate 20mg (12 consecutive dosesevery3month)+Placebo/D,oral	315	4.9	5.7		
			975	Placebo/D, oral	347	9.6	1.3		
Miller et al. [22] (2005)	USA, Canada, Europe, Australia, South Africa, Mexico, and Brazil */Mobile	12	402	Ibandronate 2.5mg/D, oral	67	-	3.7	Upper GI events, with similar frequency between groups #	6
			404	Ibandronate 50 + 50mg for 2 consecutive days/M, oral	57	-	4.2		
			402	Ibandronate 100mg/M, oral	62	-	3.9		
			401	Ibandronate 150mg/M, oral	57	-	4.8		
Reginster et al. [23] (2006)	USA, Canada, Europe, Australia, South Africa. Mexico, and Brazil */Mobile	24	402	Ibandronate 2.5mg/D, oral	77	-	4.8	Hypertension, dyspepsia, arthralgia, gastric and duodenal ulcer, erosive duodenitis, gastric hemorrhage, hepatic disorder ***	6
			404	Ibandronate 50 + 50mg for 2 consecutive days/M, oral	76	-	5.3		
			402	Ibandronate 100mg/M, oral	86	-	5.3		
			401	Ibandronate 150mg/M, oral	79	-	6.4		
Cooper et al. [24] (2003)	- *	12	121	Ibandronate 2.5mg/D, oral	12	-	3.5	Upper GI, muscular-skeletal, and other events #	6
			114	Ibandronate 20mg/Week, oral	12	-	3.5		
Recker et al. [25] (2004)	-/Íris	36	951	Ibandronate 0.5mg every 3M IV	153	8.7	4.9	Respiratory, muscular-skeletal, and other events #	5
			961	Ibandronate 1.0mg every 3M IV	187	9.2	3.9		
			950	Placebo	163	10.7	1.0 ###		
Adami et al. [26] (2004)	-/Íris	12	131	Ibandronate 1mg every 3M IV	7	-	2.8	Back pain, arthralgia, fever, bronchitis, upper respiratory infection, flu-like syndrome, and headache #	6
			261	Ibandronate 2mg every 3M IV	40	-	5.0		
			128	Placebo every 3M IV	10	-	0.0		
Delmas et al. [27] (2006)	USA, Canada, Mexico, Europe, Australia, and South Africa */ Diva	12	454	Ibandronate 2mg every 2M IV + Placebo/D, oral	72	-	5.1	Dyspepsia, abdominal pain, arthralgia, flu-like symptoms, renal events #	6
			471	Ibandronate 3mg every 3M IV + Placebo/D, oral	77	-	4.8		
			470	Ibandronate 2.5mg/D, oral + Placebo every 2 or 3M IV	61	-	3.8		

(continues)

Table 1 (continued)

Reference	Country/ Name of study	Time (months)		Sample size and intervention	Losses	Results (%) Vertebral fractures	Results (%) BMD	Adverse reactions	S
McClos-key et al. [28] (2004)	UK *	36	236	Clodronate 800mg/D, oral	85	12.7	4.3	-	6
			247	Placebo/D, oral	78	23.3	0.6		
Reid et al. [29] (2002)	10 countries *	12	60	Zoledronic acid 0.25mg IV every 3M	9	0.0	5.1	Muscular-skeletal pain, nausea, fever, and flu-like symptoms ##	5
			58	Zoledronic acid 0.50mg IV every 3M	6	0.0	5.0 ###		
			53	Zoledronic acid 1.0mg IV every 3M	5	0.0	4.3		
			61	Zoledronic acid 2.0mg IV every 6M + Placebo IV	6	0.0	5.0 ###		
			60	Zoledronic acid 4.0mg IV, baseline dose + Placebo IV	7	0.0	5.0 ###		
			59	Placebo IV	2	0.0	0.0 ###		
Lufkin et al. [30] (1992)	USA	12	36	Transdermal Estradiol 0.1mg from 1st to 21st day + oral medroxyprogesterone acetate 10mg/D from 11th to 21st day of 28 day cycle	3	19.4	5.3	Breast pain, endometrial hyperplasia #	5
			39	Transdermal and oral placebo	5	30.8	0.2		
Hodsman et al. [31] (2003)	USA and Canada *	12	50	PTH 1-84 50µg SC/D	6	-	3.0	Injection site reaction, transient hypercalcemia, nausea, fatigue, elevated alkaline phosphatase, hypercalciuria #	5
			52	PTH 1-84 75µg SC/D	4	-	5.1		
			51	PTH 1-84 100µg SC/D	12	-	7.8		
			53	Placebo	9	-	0.9		
Body et al. [32] (2002)	USA, Austria, Belgium, Canada, Israel, and Mexico *	14	73	Teriparatide 40µg/D SC + placebo, oral	22	-	15.0 ###	Leg cramps ## (Teriparatide)	5
			73	Alendronate 10mg/D, oral + placebo SC	16	-	7.0 ###	Back pain * (Alendronate)	
Chesnut et al. [33] (2000)	USA and UK *	60	316	Salmon calcitonin 100UI, nasal spray	192	22.0	1.0 ###	Rhinitis (nasal congestion or alteration or choryza) ##	6
			316	Salmon calcitonin 200UI nasal spray	184	18.0	1.0 ###		
			312	Salmon calcitonin 400UI nasal spray	185	22.0	1.5 ###		
			311	Nasal spray placebo	183	26.0	0.5 ###		
Morii et al. [34] (2003)	Japan	12	92	Raloxifene 60mg/D	13	0.0	3.5	Abdominal distension and fatigue with Raloxifene 120mg ##	5
			95	Raloxifene 120mg/D	14	1.1	2.9		
			97	Placebo	10	2.1	0.0		
Reginster et al. [35] (1998)	Belgium	48	100	Monofluorophosphate 152mg/D (equivalent of 20mg of fluoride)	38	2.4	10.0	Gastrointestinal reactions and pain in lower limbs #	6
			100	Placebo/D	49	10.0	-0.4		

(continues)

Table 1 (continued)

Reference	Country/ Name of study	Time (months)		Sample size and intervention	Losses	Results (%) Vertebral fractures	Results (%) BMD	Adverse reactions	S
Reid t al. [36] (2007)	New Zealand	48	39	Monofluorophosphate (equivalent of 20mg of fluoride/D) + estrogen/ progesterone	15	2.6	22.0	Gastrointestinal reactions, back pain, pain in lower limbs #	5
			41	Placebo + estrogen/progesterone	14	12.2	6.0		
Meunier et al. [37] (2004)	Countries of Europe and Australia */Soti	36	826	Strontium ranelate 2g/D	198	20.9	12.7	Diarrhea ##	5
			814	Placebo	182	32.8	-1.7		
Meunier et al. [38] (2002)	9 European countries */Stratos	24	85	Strontium ranelate 0.5g/D	20	38.8	2.5 ###	Back pain, lumbar pain, abdominal pain. arthralgia, gastrointestinal reactions, and others ***	6
			90	Strontium ranelate 1.0g/D	24	56.7	2.5 ###		
			87	Strontium ranelate 2.0g/D	20	42.0	5.0 ###		
			91	Placebo/D	17	54.7	1.0		

S: score attributed; IV: intravenous; M: month/months; D: day; GI: gastrointestinal; BMD: bone mineral density.

* Multi-center studies;

** Aggregate description of losses;

*** Adverse reactions without statistically significant differences between groups ($p > 0.05$);

No statistical analysis performed;

Adverse reactions with statistically significant differences between groups ($p \leq 0.05$);

Data obtained by interpolation on graph.

results when using the drug or placebo. Two authors compared risedronate 2.5 and 5mg/day to placebo [18,19]. Harris et al. [18] observed better efficacy in the treatment group at 5mg ($p < 0.05$), while at the end of the first year of the trial they detected low efficacy for risedronate at 2.5mg, leading to a change in the initial study design, excluding this group. Meanwhile Hooper et al. [19] did not detect any difference between the three groups in the incidence of vertebral fractures ($p > 0.05$).

In relation to increase in lumbar spine BMD for studies on risedronate, Brown et al. [15] showed no statistically significant difference between groups. Ste-Marie et al. [16] detected BMD better results in the risedronate (9.2%) versus placebo group (-0.3%) ($p < 0.05$). Clemmensen et al. [17] did not observe any statistically significant difference between the results, comparing the drug to placebo. Harris et al. [18] observed a higher increase in lumbar spine BMD in the group treated with the drug at 5mg ($p < 0.05$) as compared to placebo. Hooper et al. [19] detected a difference in lumbar spine BMD ($p < 0.05$), with an increase of 2% using 5mg/day and a reduction of 2% for placebo.

Five studies evaluated oral ibandronate, with two on the incidence of vertebral fractures and four on changes in lumbar spine BMD [20,21,22,23,24]. In relation to incidence of vertebral fractures, in the study comparing ibandronate 2.5mg to placebo, the treatment group showed a better response than the placebo group ($p < 0.0001$) [20]. Another study comparing two different doses to placebo showed better efficacy in the groups treated with the drug (4.7 and 4.9%) as compared to placebo (9.6%), with a statistically significant difference, but the results were similar for the different doses [21].

As for the lumbar spine BMD as the outcome, Chesnut et al. [21] found a statistically significant difference between the treatment and placebo groups, but no difference between the two different dose arms. Three studies evaluated lumbar spine BMD in comparisons between different dose models, but without comparing to placebo [22,23,24]. The different monthly or weekly dose models were not inferior to the daily model. There was only a significant difference when comparing the lowest (2.5mg) to the highest dose (150mg) ($p < 0.001$). Importantly, two of the articles were by Mobile, thus dealing with the same

study, with different follow-up times (12 and 24 months) [22,23]. Three studies evaluated IV ibandronate, with one focusing on vertebral fracture as the outcome and three on lumbar spine BMD [25,26,27]. In relation to the incidence of vertebral fractures, Recker et al. [25], showed no statistically significant difference between the groups. In relation to alteration in lumbar spine BMD, in this same study, treatment was more effective than placebo ($p < 0.0001$) [25]. Adami et al. [26] detected a statistically significant difference between the three groups, with the best efficacy in the group ibandronate 2mg IV every three months. A comparison of oral to IV ibandronate showed better efficacy in the IV group ($p < 0.05$) [27].

Concluding the class of bisphosphonates, two studies compared clodronate and zoledronic acid to placebo [28,29], showing both target outcomes. The study on clodronate showed statistically superior results for lumbar spine BMD and vertebral fracture incidence in the treatment group as compared to placebo ($p < 0.0001$ and $p = 0.001$, respectively). The study on zoledronic acid, evaluating various doses, showed a difference in lumbar spine BMD between the treatment and placebo groups ($p < 0.001$). However, there was no statistically significant difference between the doses investigated. There were no fractures in either the treatment or placebo group [29].

Hormone replacement therapy

Only one article on hormone replacement therapy (HRT) remained in the review, showing better efficacy for estrogen/progesterone as compared to placebo, both for reduction in the incidence of vertebral fractures and increase in lumbar spine BMD, with statistically significant differences [30].

Parathyroid hormone

Two studies on PTH only presented lumbar spine BMD as the outcome [31,32]. In the study on PTH (1-84), the treatment group showed better results (7.8%) ($p < 0.05$) [31]. Meanwhile PTH (1-34), marketed as teriparatide, showed an important increase in lumbar spine BMD as compared to alendronate ($p \leq 0.001$). Both groups showed adverse reactions: leg cramps in the teriparatide group and back pain in the alendronate group [32].

Other studies

Other studies compared calcitonin, raloxifene, monofluorophosphate, and strontium ranelate to placebo [33,34,35,36,37,38]. All of them presented the results for vertebral fractures and lumbar spine BMD. For calcitonin, the increase in lumbar spine BMD was similar in the treatment and placebo groups [33]. As for incidence of vertebral fractures, there was only a difference between the 200 IU dose and placebo ($p < 0.05$) [33].

Raloxifene showed an increase in lumbar spine BMD as compared to placebo ($p < 0.05$), but there was no difference in effect between the two doses ($p = 0.167$). In addition, individuals taking 120mg showed a higher incidence of abdominal distension, and the treatment group had a higher incidence of vertebral fractures than the placebo group. However, according to the author, the study lacked the statistical power to detect a statistical difference in fracture incidence between the groups [34].

Monofluorophosphate showed better results than placebo for lumbar spine BMD and incidence of vertebral fractures ($p < 0.001$ and $p = 0.05$ respectively) [35]. Reid et al. [36] observed efficacy for low-dose monofluorophosphate, both for increased lumbar spine BMD ($p < 0.001$) and reduction in the incidence of vertebral fractures (without presenting the statistical analysis). The authors further reported that low doses of the drug were more effective than high doses. Many studies have used toxic doses, and much lower doses need to be evaluated in order to obtain a safe dose for use of the drug as an anabolic agent.

Comparison of strontium ranelate to placebo showed better efficacy of the drug for both increased lumbar spine BMD and reduction in the incidence of vertebral fractures ($p < 0.01$) [37]. However, the treatment group showed a higher incidence of diarrhea, a decrease in calcium and phosphorus levels, and increased serum creatine [37]. A study on different doses of the same drug showed an increase in lumbar spine BMD that was only statistically significant when comparing the 2.0g dose to placebo ($p < 0.01$) [38]. For the other doses, there was no statistical difference in this outcome. In this same study, considering vertebral fracture as the outcome, the 0.5 and 2.0g doses showed a statistically significant reduction in the risk of fractures. These two studies included an adjustment in the lumbar spine BMD values due to the interference of strontium in the test [37,38].

Adverse reactions

Six studies reported that adverse reactions showed statistically significant differences between groups [11,29,32,33,34,37]. Eleven studies reported that the adverse reactions were similar between groups [8,12,13,14,15,16,18,20,21,22,38]. Meanwhile, the majority (n = 13) did not conduct statistical analysis [9,10,17,19,22,24,25,26,27,30,31,35,36]. Two studies did not evaluate adverse reactions [7,28].

Discussion

In women, osteoporosis and fractures occur mainly as a consequence of postmenopausal estrogen deficiency and an imbalance between bone resorption by osteoclasts and bone formation by osteoblasts, leading to bone loss with each remodeling cycle.

The bisphosphonates are a class of drugs that act on the inhibition of bone resorption. The majority of the clinical trials evaluated alendronate, with well-established efficacy in reducing fractures and increasing lumbar spine BMD. This drug is considered the first choice for treating osteoporosis in postmenopausal women with fracture risk, at the dose of 10mg/day, while there is no clinical evidence for clinical efficacy or tolerability with intermittent doses [39,40].

Risedronate showed efficacy in practically all of the studies, principally at 5mg/day. However, there was no comparison between this drug and alendronate, the first bisphosphonate marketed in Brazil. The literature shows that the reduction in vertebral fracture risk was better in the first year of treatment (64%) than in the third (45%) [41], and the optimum treatment duration was not defined [42]. These data could explain the negative results found in a clinical trial lasting 60 months [16].

Intravenous ibandronate has demonstrated efficacy and is an alternative for bedridden patients or those with gastrointestinal problems [43]. Oral administration (both daily and monthly) has demonstrated efficacy, so it is up to the patient and physician to decide on the best dosing regimen. Pyon [44] reports that patients may prefer monthly administration, since it is more convenient than weekly bisphosphonates.

There was only one study that evaluated clodronate, and one on zoledronic acid. Clodronate is the least potent of the bisphosphonates, and there are conflicting data on its efficacy [45]. In the study on zoledronic acid, the drug's efficacy against fractures was not clear. It is the most potent of the bisphosphonates, but should be used with caution in patients taking nephrotoxic medication, due to the risk of deterioration in renal function [45,46].

HRT showed efficacy in the treatment of postmenopausal osteoporosis and synergic action in increasing lumbar spine BMD when estrogen and alendronate were combined. However, there is controversy concerning the reduction in fracture risk and increase in BMD, and its use has been associated with increased risk of coronary disease, breast cancer, aneurysm, and pulmonary embolism [47,48,49]. A study in the United States with postmenopausal women concluded that the effect of HRT on decrease in fracture risk is valid for short time periods (< 5 years) and that the effect decreased after interrupting its use [50]. Another study on the effects of HRT in the United Kingdom concluded that in the majority of young women (< 45 years), the risks outweigh the benefits, while the opposite was true for older women (> 70 years). The patient and physician should make the choice as to use of HRT, weighing the risks and benefits [51]. Therefore, the tendency is towards a reduction in the use of estrogens, due to the availability of other drugs that have demonstrated good results with less risk to the user's health [52].

PTH (1-84), although showing efficacy against osteoporosis, displayed adverse reactions due to its different biological actions [53]. PTH (1-34), more biologically specific than PTH (1-84), obtained better results for increase in lumbar spine BMD. However, neither of the two clinical trials presented results for reduction in the incidence of vertebral fractures. A review by Hodsman et al. [54] reports that the anti-fracture efficacy of PTH is not superior to the bisphosphonates, and that the treatment costs with teriparatide are significantly higher. In addition, its use is not recommended for more than two years, based partially on the experimental induction of osteosarcoma in rats.

Only one study on calcitonin was evaluated and failed to demonstrate efficacy in increasing lumbar spine BMD and reducing vertebral fractures. However, this drug appears to be useful for treating pain associated with postmenopausal osteoporosis, increasing the levels of β-endorphin, thus acting as a good analgesic agent [55].

Raloxifene, a selective estrogen receptor modulator (SERM), showed efficacy, but adverse reactions can occur with its use. Gennari et al. [56] report that this drug increases the relative risk of venous thromboembolism and fatal stroke. Other molecules from this class are being researched and promise to be more potent and effective for the prevention and treatment of osteoporosis. Raloxifene showed inferior results to alendronate and should only be indicated in cases when the latter is contraindicated.

Low-dose monofluorophosphate showed high efficacy and low toxicity. A meta-analysis demonstrated that low doses of fluoride were associated with a significant reduction in fracture risk, which is not true for higher doses [57].

Strontium ranelate showed efficacy against fractures. A review study reported that although treatment with strontium ranelate is effective, the adverse reactions are dose-dependent and the potential vascular and neurological side effects require further investigation [58].

The principal limitations of the 81 selected studies, according to the methodological evalu-

ation, related to the randomization sequence, often hidden or inappropriate, and the masking method, especially in relation to identification of the placebo.

In relation to study limitations, only clinical vertebral fractures were considered as the outcome. It is known that non-vertebral fractures occur at a much lower frequency than vertebral fractures in osteoporotic women. In addition, only lumbar spine BMD was considered, excluding hip and cervical BMD. There was also a difference in follow-up time between the various clinical trials, which did not allow quantitative comparison between the studies. Another relevant aspect is the fact that the majority of the studies compared drugs to placebo, thus not generating information on the clinical superiority of some drugs over existing treatment.

Conclusion

In postmenopausal women with osteoporosis, BMD can be increased and vertebral fractures effectively prevented with drug treatment. A high correlation is also observed between increase in lumbar spine BMD and reduction in the incidence of vertebral fractures, with BMD serving as the best available predictor for evaluating risk of vertebral fractures [44,59]. The bisphosphonates, principally alendronate 10mg/day and IV ibandronate have proven their clinical efficacy, including in relation to raloxifene. The association of estrogen and alendronate demonstrate synergic action in increasing lumbar spine BMD. However, there is controversy concerning the efficacy of hormone replacement therapy, and its use has been associated with increased risk of various diseases. Teriparatide and monofluorophosphate have also demonstrated efficacy against osteoporosis. Meanwhile, calcitonin and strontium ranelate failed to show relevant increases in lumbar spine BMD or reduction in vertebral fractures. Calcium and vitamin D were given to patients as food supplements in all of the treatment groups in the published clinical trials.

Few studies were found on some drugs, but this observation is not meant to discourage their use. It merely suggests the need for greater caution in their utilization, namely they should only be considered as an alternative in cases when traditional options with proven efficacy have failed to produce satisfactory results, in individuals with specific characteristics.

For public health authorities, it is indispensable to adjust the treatment protocols for osteoporosis with evidence-based medicine. Drug prescribers should also pay greater attention to the information published in different medical communications media, since as observed in this review, the adverse reactions are often neglected in the different studies. In a population with such peculiar characteristics as individuals with osteoporosis, such events can lead to the interruption of the drug's use or even greater harm to the user's health.

Resumo

A osteoporose, doença típica dos idosos, vem se tornando um dos problemas mais freqüentes e relevantes no âmbito da saúde pública. Vários medicamentos estão disponíveis para o seu tratamento, alguns disponibilizados pelo SUS. Este estudo apresenta uma revisão sistemática dos medicamentos destinados ao tratamento da osteoporose, buscando subsidiar as discussões a respeito dos protocolos clínicos, com base em evidências científicas na literatura. Foi realizada busca de ensaios clínicos randomizados na base de dados PubMed e LILACS que apresentavam resultados de densidade mineral óssea, incidência de fraturas vertebrais e reações adversas aos medicamentos. Nos 32 artigos revisados, a classe de medicamentos bifosfonados foi a mais freqüente e a que melhor tem demonstrado sua eficácia clínica, principalmente o alendronato e o ibandronato via endovenosa. A terapia de reposição hormonal demonstrou efeito, mas seu uso tem sido associado ao aumento de risco de doenças cardiovasculares e outras. Teriparatida e monofluorfosfato apresentaram eficácia antiosteoporótica. Cálcio e vitamina D foram dados aos pacientes como suplemento alimentar.

Osteoporose Pós-Menopausa; Medicamentos; Saúde da Mulher

Contributors

C. M. R. Brandão participated in the study's planning and elaboration, selection of the articles, bibliographic review, methodological evaluation, and drafting of the article. F. A. Acúrcio participated in the planning and elaboration of the study and drafting of the article. M. G. Lima participated in the article selection, methodological evaluation, and final drafting of the article. A. L. Silva participated in the article selection, bibliographic review, methodological evaluation, and drafting of the article. G. D. Silva participated in the elaboration of the protocol for the systematic review and final drafting of the article. A. A. Guerra Jr. participated in the elaboration of the protocol for the systematic review and final drafting of the article.

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References

1. Silva LK. Avaliação tecnológica em saúde: densitometria óssea e terapêuticas alternativas na osteoporose pós-menopausa. Cad Saúde Pública 2003; 19:987-1003.
2. Costa-Paiva L, Horovitz AP, Santos AO, Fonsechi-Carvasan GA, Pinto-Neto AM. Prevalência de osteoporose em mulheres na pós-menopausa e associação com fatores clínicos e reprodutivos. Rev Bras Ginecol Obstet 2003; 25:507-12.
3. Frazão P, Naveira M. Prevalência de osteoporose: uma revisão crítica. Rev Bras Epidemiol 2006; 9:206-14.
4. World Health Organization Scientific Group on the Prevention and Management of Osteoporosis. Prevention and management of osteoporosis. Geneva: World Health Organization; 2003. (Technical Report Series, 921).
5. Brasil. Portaria nº. 2.577/GM, de 27 de outubro de 2006. Aprova o componente de medicamentos de dispensação excepcional. Diário Oficial da União 2006; 27 out.
6. Woodroffe R, Yao GL, Meads C, Bayliss S, Ready A, Raftery J, et al. Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: a systematic review and modeling study. Health Technol Assess 2005; 9:1-193.
7. Ensrud KE, Black DM, Palermo L, Bauer DC, Barrett-Connor E, Quandt SA, et al. Treatment with alendronate prevents fractures in women at highest risk: results from the Fracture Intervention Trial. Arch Intern Med 1997; 157:2617-24.
8. Kushida K, Shiraki M, Nakamura T, Kishimoto H, Morii H, Yamamoto K, et al. Alendronate reduced vertebral fracture risk in postmenopausal Japanese women with osteoporosis: a 3-year follow-up study. J Bone Miner Metab 2004; 22:462-8.
9. Chestnut III CH, McClung MR, Ensrud KE. Alendronate treatment of posmenopausal women: effect of multiple dosages on bone mass and bone remodeling. Am J Med 1995; 99:144-52.
10. Luckey MM, Gilchrist N, Bone HG, Davie MW, De Villiers TJ, Wu M, et al. Therapeutic equivalence of alendronate 35 milligrams once weekly and 5 milligrams daily in the prevention of postmenopausal osteoporosis. Obstet Gynecol 2003; 101:711-21.
11. Sambrook PN, Geusens P, Ribot C, Solimano JA, Ferrer-Barriendos J, Gaines K, et al. Alendronate produces greater effects than raloxifene on bone density and bone turnover in postmenopausal women with low bone density: results of EFFECT (Efficacy of FOSAMAX versus EVISTA Comparison Trial) International. J Intern Med 2004; 255:503-11.
12. Pols HAP, Felsenberg D, Hanley DA, Stepan J, Munoz-Torres M, Willkin TJ, et al. Multinational, placebo-controlled, randomized trial of the effects of alendronate on bone density and fracture risk in postmenopausal women with low bone mass: results the FOSIT study. Osteoporos Int 1999; 9: 461-8.
13. Bone HG, Greenspan SL, McKeever C, Bell N, Davidson M, Downs RW, et al. Alendronate and estrogen effects in postmenopausal women with low bone mineral density. J Clin Endocrinol Metab 2000; 85:720-6.

14. Luckey M, Kagan R, Greenspan S, Bone H, Kiel RD, Simon J, et al. Once-weekly alendronate 70mg and raloxifene 60mg daily in the treatment of postmenopausal osteoporosis. Menopause 2004; 11:405-15.
15. Brown JP, Kendler DL, McClung MR, Emkey RD, Adachi JD, Bolognese MA, et al. The efficacy and tolerability of risedronate once a week for the treatment of postmenopausal osteoporosis. Calcif Tissue Int 2002; 71:103-11.
16. Ste-Marie LG, Sod E, Johnson T, Chines A. Five years of treatment with risedronate and its effects on bone safety in women with postmenopausal osteoporosis. Calcif Tissue Int 2004; 75:469-76.
17. Clemmesen B, Ravn P, Zegels B, Taquet AN, Christiansen C, Reginster JY. A 2-year phase II study with 1-year of follow-up of risedronate (NE-58095) in postmenopausal osteoporosis. Osteoporos Int 1997;7:488-95.
18. Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA 1999; 282:1344-52.
19. Hooper MJ, Ebeling PR, Roberts AP, Graham JJ, Nicholson GC, D'Emden M, et al. Risedronate prevents bone loss in early postmenopausal women: a prospective randomized, placebo-controlled trial. Climacteric 2005; 8:251-62.
20. Felsenberg D, Miller P, Armbrecht G, Wilson K, Schimmer RC, Papapoulos SE. Oral ibandronate significantly reduces the risk of vertebral fractures of greater severity after 1, 2, and 3 years in postmenopausal women with osteoporosis. Bone 2005; 37:651-4.
21. Chesnut CH, Ettinger MP, Miller PD, Baylink DJ, Emkey R, Harris ST, et al. Ibandronate produces significant, similar antifracture efficacy in North American and European women: new clinical findings from BONE. Curr Med Res Opin 2004; 21: 391-401.
22. Miller PD, McClung MR, Macovei L, Stakkestad JA, Luckey M, Bonvoisin B, et al. Monthly oral ibandronate therapy in postmenopausal osteoporosis: 1-year results from the MOBILE study. J Bone Miner Res 2005; 20:1315-22.
23. Reginster JY, Adami S, Lakatos P, Greenwald M, Stepan JJ, Silverman SL, et al. Efficacy and tolerability of once-monthly oral ibandronate in postmenopausal osteoporosis: 2 year results from the MOBILE study. Ann Rheum Dis 2006; 65:654-61.
24. Cooper C, Emkey RD, McDonald RH, Hawker G, Bianchi G, Wilson K, et al. Efficacy and safety of oral weekly ibandronate in the treatment of postmenopausal osteoporosis. J Clin Endocrinol Metab 2003; 88:4609-15.
25. Recker R, Stakkestad JA, Chesnut CH, Christiansen C, Skag A, Hoiseth A, et al. Insufficiently dosed intravenous ibandronate injections are associated with suboptimal antifracture efficacy in postmenopausal osteoporosis. Bone 2004; 34:890-9.
26. Adami S, Felsenberg D, Christiansen C, Robinson J, Lorenc RS, Mahoney P, et al. Efficacy and safety of ibandronate given by intravenous injection once every 3 months. Bone 2004; 34:881-9.
27. Delmas PD, Adami S, Strugala C, Stakkestad JA, Reginster JY, Felsenberg D, et al. Intravenous ibandronate injections in postmenopausal women with osteoporosis: one-year results from the dosing intravenous administration study. Arthritis Rheum 2006; 54:1838-46.
28. McCloskey E, Selby P, Davies M, Robinson J, Francis RM, Adams J, et al. Clodronate reduces vertebral fracture risk in women with postmenopausal or secondary osteoporosis: results of a double-blind, placebo-controlled 3-year study. J Bone Miner Res 2004; 19:728-36.
29. Reid IR, Brown JP, Burckhardt P, Horowitz Z, Richardson P, Trechsel U, et al. Intravenous zoledronic acid in postmenopausal women with low bone mineral density. N Engl J Med 2002; 346:653-61.
30. Lufkin EG, Wahner HW, O'Fallon WM, Hodgson SF, Kotowicz MA, Lane AW, et al. Treatment of postmenopausal osteoporosis with transdermal estrogen. Ann Intern Med 1992; 117:1-9.
31. Hodsman AB, Hanley DA, Ettinger MP, Bolognese MA, Fox J, Metcalfe AJ, et al. Efficacy and safety of human parathyroid hormone-(1-84) in increasing bone mineral density in postmenopausal osteoporosis. J Clin Endocrinol Metab 2003; 88:5212-20.
32. Body JJ, Gaich GA, Scheele WH, Kulkarni PM, Miller PD, Peretz A, et al. A randomized double-blind trial to compare the efficacy of teriparatide [recombinant human parathyroid hormone (1-34)] with alendronate in postmenopausal women with osteoporosis. J Clin Endocrinol Metab 2002; 87:4528-35.
33. Chesnut CH, Silverman S, Andriano K, Genant H, Gimona A, Harris S, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Group. Am J Med 2000; 109:267-76.
34. Morii H, Ohashi Y, Taketani Y, Fukunaga M, Nakamura T, Itabashi A, et al. Effect of raloxifene on bone mineral density and biochemical markers of bone turnover in Japanese postmenopausal women with osteoporosis: results from a randomized placebo-controlled trial. Osteoporos Int 2003; 14:793-800.
35. Reginster JY, Meurmans L, Zegels B, Rovati LC, Minne HW, Giacovelli G, et al. The effect of sodium monofluorophosphate plus calcium on vertebral fracture rate in postmenopausal women with moderate osteoporosis. A randomized, controlled trial. Ann Intern Med 1998; 129:1-8.
36. Reid IR, Cundy T, Grey AB, Horne A, Clearwater J, Ames R, et al. Addition of monofluorophosphate to estrogen therapy in postmenopausal osteoporosis: a randomized controlled trial. J Clin Endocrinol Metab 2007; 92:2446-52.

37. Meunier PJ, Roux C, Seeman E, Ortolani S, Badurski JE, Spector TD, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. N Engl J Med 2004; 350:459-68.
38. Meunier PJ, Slosman DO, Delmas PD, Sebert JL, Brandi ML, Albanese C, et al. Strontium ranelate: an increased bone quality leading to vertebral antifracture efficacy at all stages. J Clin Endocrinol Metab 2002; 87:2060-6.
39. Adachi JD. Alendronate for osteoporosis. Safe and efficacious nonhormonal therapy. Can Fam Physician 1998;44:327-32.
40. Tsun EC, Heck AM. Intermittent dosing of alendronato. Ann Pharmacother 2001; 35:1471-5.
41. Adachi JD, Rizzoli R, Boonen S, Li Z, Meredith MP, Chesnut CH. Vertebral fracture risk reduction with risedronate in post-menopausal women with osteoporosis: a meta-analysis of individual patient data. Aging Clin Exp Res 2005; 172:150-6.
42. Crandall C. Risedronate: a clinical review. Arch Intern Med 2001; 161:353-60.
43. Maricic M. New and emerging treatments for osteoporosis. Curr Opin Rheumatol 2007; 19:363-9.
44. Pyon EY. Once-monthly ibandronate for postmenopausal osteoporosis: review of a new dosing regimen. Clin Ther 2006; 28:475-90.
45. Miller PD. Optimizing the management of postmenopausal osteoporosis with biphosphonates: the emerging role of intermittent therapy. Clin Ther 2005; 27:361-76.
46. Epstein S. Update of current therapeutic options for the treatment of postmenopausal osteoporosis. Clin Ther 2006; 28:151-73.
47. Eichner FS, Lloyd KB, Timpe EM. Comparing therapies for postmenopausal osteoporosis prevention and treatment. Ann Pharmacother 2003; 37: 711-24.
48. Writing Group for the Women's Health Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. JAMA 2002; 288:321-33.
49. Rozenfeld S. Terapia hormonal para a menopausa (TH): múltiplos interesses a considerar. Ciênc Saúde Coletiva 2007; 12:437-42.
50. Barret-Connor E, Wehren LE, Siris ES, Miller P, Chen Y, Abbot 3rd TA, et al. Recency and duration of postmenopausal hormone therapy: effects on bone mineral density and fracture risk in the National Ostoporosis Risk Assessment (NORA) study. Menopause 2003; 10:412-9.
51. van Staa TP, Cooper C, Barlow D, Leufkens HGM. Individualizing the risks and benefits of postmenopausal hormone therapy. Menopause 2008; 15:374-81.
52. Fadanelli ME, Bone HG. Combining bisphosphonates with hormone therapy for postmenopausal osteoporosis. Treat Endocrinol 2004; 3:361-9.
53. Cranney A, Papaioannou A, Zytaruk N, Hanley D, Adachi J, Goltzman D. Parathyroid hormone for treatment of osteoporosis: a systematic review. CMAJ 2006; 175:52-9.
54. Hodsman AB, Bauer DC, Dempster DW, Dian L, Hanley DA, Harris ST, et al. Parathyroid hormone and Teriparatide for the treatment of osteoporosis: a review of the evidence and suggested guidelines for its use. Endocr Rev 2005; 26:688-703.
55. Ofluoglu D, Akyuz G, Unay O, Kayhan O. The effect of calcitonin on β-endorphin levels in postmenopausal osteoporotic patients with back pain. Clin Rheumatol 2007; 26:44-9.
56. Gennari L, Merlotti D, Valleggi F, Martini G, Nuti R. Selective estrogen receptor modulators for postmenopausal osteoporosis: current state of development. Drugs Aging 2007; 24:361-79.
57. Vestergaard P, Jorgensen NR, Schwarz P, Mosekilde L. Effects of treatment with fluoride on bone mineral density and fracture risk: a meta-analysis. Osteoporos Int 2008; 19:257-68.
58. O'Donnell S, Cranney A, Wells GA, Adachi JD, Reginster JY. Strontium ranelate for preventing and treating postmenopausal osteoporosis (Cochrane Review). In: The Cochrane Library, Issue 3, 2007. Oxford: Update Software.
59. Wasnisch RD, Miller PD. Antifracture efficacy of antireabsorptive agents are related to changes in bone density. J Clin Endocrinol Metab 2007; 85:231-6.

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