Pharmacoeconomic analysis of strategies to treat postmenopausal osteoporosis: a systematic review

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ABSTRACT

Osteoporosis, especially in postmenopausal women, has a high socioeconomic impact on the individual and on the society. There are several drugs for its prevention and treatment; however, their effectiveness and costs vary considerably. Several economic assessments have been conducted in order to evaluate the most effective strategies. This study aimed at conducting a systematic review of complete economic assessments focusing on the treatment of postmenopausal osteoporosis performed in Brazil and worldwide. Articles about economic assessment of drugs for the treatment of postmenopausal osteoporosis were searched in the PubMed and LILACS databases. In general, bisphosphonates were the most frequently assessed strategies and had the best incremental cost-effectiveness ratios. Hormone therapy, vitamin D and calcium, strontium ranelate, raloxifene, teriparatide, and denosumab were assessed and showed variable results depending on the perspective of the country and the assumptions made for each study. None of the results could be extrapolated to the Brazilian population, which limits their use by decision makers.

Keywords: osteoporosis, postmenopausal, review, health economics.

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INTRODUCTION

Osteoporosis implies an increased risk of fractures, which have individual and social consequences.[1] Women, especially over 50 years old, are more vulnerable to fractures because of the postmenopausal hormonal changes responsible for bone mass reduction. The increased life expectancy in many parts of the world means that not only women live more than one third of their lives after menopause, but also the number of postmenopausal women is increasing. In Brazil, in 1990, the number of women over 50 years old was 10,345,440; 20 years after, that figure almost doubled, being the number of women 18.0% higher than that of men.[2] That is also a trend in other countries of America and Europe.[1] Considering the population ageing, the increase in life expectancy, and the feminization of more advanced ages, the great socioeconomic impact of osteoporosis is evident.

According to the population-based Latin American Vertebral Osteoporosis Study (LAVOS), the prevalence of radiographic vertebral fractures in Latin American women is 11.18% (CI: 9.23−13.4).[3] The study conducted in Brazil, Brazilian Osteoporosis Study (BRAZOS), has reported a 6.0% prevalence of osteoporosis and a 15.1% prevalence of fracture in women.[4] Lopes et al.[5] have reported a greater prevalence of osteoporotic fractures in women than in men. According to that study, the major affected sites were as follows: forearm (6.0%); humerus (2.3%); femur (1.3%); and vertebrae (1.1%). The prevalence increases with age. After the age of 40 years, the prevalence of osteoporosis was 33%, and that of osteoporotic fractures, 11.5%.[4]

The anatomical sites most commonly affected by osteoporosis were vertebrae, hips, and wrists.[1] A large number of vertebral fractures is asymptomatic and has low impact on the use of health resources; only 25% of those fractures are

Received on 10/13/2011. Approved on 09/05/2012. The authors declare no conflict of interest. Financial Support: CMRB had a PhD scholarship of Fapemig; FAA has a productivity scholarship in Research, level II, from CNPq and Programa de Pesquisador Mineiro of Fapemig.
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clinically diagnosed.[6] The incidence of hip fractures, usually in the proximal femur, increases with age, being those fractures associated with a significant reduction in quality of life and with high mortality.[7]

Social costs can be considered as direct and indirect, being associated with both osteoporosis prevention and treatment and fracture rehabilitation. A study conducted in the tertiary sector has assessed, under the societal perspective, the annual costs of osteoporosis in postmenopausal women and has found an annual cost per patient of US$775 (1998).[8] The cost of the therapy depends on the intervention strategy chosen and the perspective analyzed. In the Brazilian state of Minas Gerais, the average monthly *per capita* expenditures with medications for the treatment of osteoporosis, under the Brazilian Unified Health Care System (SUS) perspective, were as follows: R$27.64 for patients on alendronate; R$52.85 for those on calcitriol; R$56.73 for those on alfacalcidol; R$94.92 for those on raloxifene; and R$132.75 for those on synthetic salmon calcitonin.[9]

The mean hospital costs for the treatment of acute femur fracture due to osteoporosis in two SUS-affiliated hospitals from the city of São Paulo (Hospital Universitário and Santa Casa de Misericórdia) were estimated as R$8,266.25 and R$1,949.65, respectively. However, the authors have considered that those costs might be underestimated because of the sources and methodologies used for cost assessment.[10] In the private health care system, the estimated cost for the treatment of each fracture was R$24,000.00.[11]

The drug treatment is aimed at reducing the incidence of new vertebral and non-vertebral fractures (mainly of the hip), responsible for the disease-associated morbidity. The assessment of efficacy has not been sufficient to justify the use of such drugs in the public health system, considering budget limitations. Economic analyses allow the joint assessment of effectiveness and distinct cost-related components. Different methodological approaches can be adopted, considering mainly the measurement of results. The types of studies commonly used in Pharmacoeconomics are as follows: cost-minimization analysis; cost-effectiveness analysis; cost-utility analysis; and cost-benefit analysis. According to the type of analysis performed, the benefit to health can be expressed as years of life saved or life expectancy, to estimate cost-effectiveness ratios. If the clinical outcome unit or effectiveness used is the patient's preference or quality of life, then the study assesses cost-utility ratios. If the study converts the clinical outcome into dollars or monetary unit, the calculated ratio is expressed as cost-benefit.[12]

According to the definition of the population studied, different perspectives of economic assessment can be adopted, influencing the types of costs measured. The most commonly used perspectives in those studies are those considering the viewpoints of the patients and their families, the hospitals, the public sector, the health insurance companies, or of the society as a whole.[13]

The results of the economic assessments are commonly expressed as mean ratio and incremental ratio of cost-effectiveness. The cost-effectiveness ratio (CER) is calculated by dividing the cost of the pharmacological strategy by the health benefit obtained with that strategy. The incremental cost-effectiveness ratio (ICER) compares the additional costs of one strategy with those of another, considering the additional proportion of effects, benefits or uses provided. While CER focus on a specific strategy, ICER assesses the difference between the two pharmacological strategies, being, thus, more applicable to decision-making, its use being recommended in cost-effectiveness and cost-utility analyses.[14] According to the World Health Organization (WHO), therapeutic strategies whose ICER does not exceed the threshold of willingness to pay of three times the gross domestic product *per capita* of a certain country are considered cost-effective.[15]

The result measures used in the cost-effectiveness and cost-utility economic assessments of drugs for the treatment of osteoporosis are usually presented as fractures prevented, gained life-years (GLY), or quality-adjusted life-years (QALY). The QALY incorporate not only the life years gained (amount), but also the corresponding quality of life. This effectiveness measure is important when there is an increase in survival under non-ideal health conditions or when therapies do not change survival, but only the quality of life.[14] It has proved to be very useful to estimate chronic diseases, such as osteoporosis.[16]

Economic analyses have been conducted to support decision makers regarding the cost of available therapeutic alternatives, aiming at providing efficient resource allocation to achieve maximum benefit in health care. Such assessments comprise both differences in drug efficacy and the variation in costs with the treatment for osteoporosis.

Data on drug efficacy can be transferred from one location to another. However, the generalization of results of economic assessments in health is difficult due to numerous reasons. Aspects related to external validity, such as differences in the estimates of effectiveness and costs between populations, should be considered before using the results of the economic assessments obtained in different countries. Even studies conducted within the same location might generate results that should not be compared when the perspectives of assessment

differ.[13] Nevertheless, considering those studies might be useful in directing the analyses, providing a comprehensive view of the aspects that are important to the conduction of cost-effectiveness and cost-utility studies. This study aimed at conducting a systematic review of complete economic assessments focusing on the treatment of postmenopausal osteoporosis performed in Brazil and worldwide.

MATERIALS AND METHODS

Search criteria

Articles about economic assessment of drugs for the treatment of postmenopausal osteoporosis were searched in the PubMed database by use of the program JabRef, version 2.6. The following keywords were used: {osteoporosis} and ({postmenopausal} or {post-menopausal}) and ({cost effectiveness} or {cost benefit} or {cost utility} or {economic evaluation}). The search criteria were applied to titles and abstracts.

In addition, studies conducted in Brazil were searched in the LILACS database with the following keywords: {osteoporosis or osteoporosis} and ({postmenopausal} or {post-menopausal} or {pós-menopausa} or {pós menopausa}).

A manual search was also performed in Brazilian non-indexed periodicals. There was no restriction regarding the publication date of the articles; the search was conducted until April 2012.

Inclusion and exclusion criteria

The criteria for selecting the articles were as follows: a) to be a complete economic assessment (cost-effectiveness, cost-utility or cost-benefit); b) the study should have been conducted on a population with postmenopausal osteoporosis; c) the study assessed drugs for the treatment of osteoporosis.

The exclusion criteria were as follows: a) treatment of osteoporosis after breast cancer; b) female population with osteopenia; c) partial economic assessment; and d) comparison of clinical screening strategies.

Selection of the studies

The titles and abstracts were analyzed according to the eligibility criteria by two independent reviewers. Discordant cases were analyzed by a third reviewer.

Presentation of the results

After applying the eligibility criteria, the articles were carefully read and the data were grouped into two descriptive tables. To facilitate the comparison of the studies, the following data were determined: authors and year of the study; place where the study was conducted; perspective of the study; currency in which the result was reported; discount rate used; target population; intervention analyzed; time horizon; authors' affiliations; outcome; ICER; and disclosure of conflict of interest with the pharmaceutical industry. The results were presented according to the chronological order of publication of the studies.

RESULTS

The search yielded 170 titles and abstracts of studies in the PubMed database, 69 articles in the LILACS database, and one article from the manual search. Based on the eligibility criteria, 210 titles and abstracts were excluded, because of the following reasons: the studies were not economic assessments (n = 143); the studies assessed screening strategies (n = 23); and others (n = 44). The pharmacoeconomic review comprised 30 studies.

The 30 articles selected were published as follows: one article per year, in 1998, 1999, and 2005; two articles per year, in 2002 and 2007; three articles per year, in 2003, 2004, and 2011; four articles per year, in 2010; and five articles per year, in 2006 and 2008. Cost-effectiveness and cost-utility studies were found. All results were presented as ICER, except for that by Borgström et al.,[17] whose results were presented as only costs/QALY. To standardize the results, in one of the studies included, the ICER value had to be calculated from the cost and effectiveness data informed in tables.[18] All relevant data regarding the studies selected are shown in Table 1 and Table 2.

Some terms commonly used in Pharmacoeconomics were used in this study and need to be defined for better understanding of the text. "Dominant strategy" refers to a compared therapeutic strategy that is more effective and less expensive than the standard strategy of comparison. Consequently, the dominated strategy should be ruled out. "Cost-saving strategies" produce resource savings; in the case of osteoporosis, the costs of the drug treatment are lower than those resulting from the fractures prevented; thus, its use is highly recommended.

The use of bisphosphonates is the most assessed therapeutic strategy. Most studies have reported efficacy in the treatment with those drugs and ICER within the thresholds of willingness to pay of each country.[19–31] The exceptions were the following three studies: Escolar et al.,[32] who have concluded that alendronate was not cost-effective as compared with placebo to prevent hip fractures; Silva et al.,[33] who have questioned the use of bisphosphonates considering the scarcity of resources in public health; and Kanis et al.,[34] who have reported that the costs exceeded the cost-effectiveness threshold of the country.

Table 1
Methodological characteristics of the economic assessment studies of drugs to treat postmenopausal osteoporosis

Study	Country	Perspective	Currency	Discount rate	Target population	Intervention	Time horizon	Conflicts of interest
Rosner et al., 1998[20]	Canada	Societal	Canadian dollar (1996)	5% C and R	Osteoporosis with fractures in women with and without hysterectomy	Strategy 1 ($Ca^+ \rightarrow$ No drug treatment) Strategy 2 (HT$\rightarrow$ $Ca^+ \rightarrow$ No drug treatment) Strategy 3 (HT $\rightarrow$ Etidronate $\rightarrow$ $Ca^+ \rightarrow$ No drug treatment) Strategy 4 (HT$\rightarrow$ Alendronate $\rightarrow Ca^+ \rightarrow$ No drug treatment)	3 years	Yes
Escolar et al., 1999[32]	Spain	Service provider	Pesetas (1998)	2% C and 0% R	Osteoporosis with fractures	Alendronate Placebo	3 years	No
Iglesias et al., 2002[21]	United Kingdom	Not specified	Euro (1999)	6% C and 1.5% R	Osteoporosis with fractures at age 75 years	No drug treatment Risedronate	Up to 100 years or until death	Yes
Willis et al., 2002[43]	Sweden	National Health System	Krona (2000)	3% C and R	Osteoporosis with fractures at age 70 years	No drug treatment Ca^+ and vit. D3	Up to 90 years or until death	Yes
Silva, 2003[33]	Brazil	Unified Health Care System	Real (2001)	–	Women with and without osteoporosis at ages 50 and 65 years	No drug treatment BMD + alendronate BMD + HT HT Ca^+ + vit. D	1 year	No
Johnell et al., 2003[22]	Sweden	Health care provider	Krona (2000)	3% C and R	Osteoporosis with fractures and 71 years	No drug treatment Alendronate	Up to 100 years or until death	Yes
Brecht et al., 2003[23]	Germany	German Social Insurance	(1999)	5% C and R	Osteoporosis with fractures at age 70 years	Standard treatment Risedronate	3 years of treatment and 10 years of follow-up	Yes
Kanis et al., 2004[34]	United Kingdom	Health care provider	Euro 2000/2001	6% C and 1.5% R	Osteoporosis with fractures at age 70 years	No drug treatment Risedronate	5 years	No
Borgström et al., 2004[38]	Sweden	Health care provider	Euro (2001)	3% C and R	Osteoporosis without fractures at ages 60, 70 and 80 years	No drug treatment Raloxifene	Up to 100 years or until death	Yes
Brecht et al., 2004[39]	Germany	German Social Insurance		5% C and R	Osteoporosis with fractures at age 70 years	No drug treatment Alendronate Risedronate Raloxifene	3 years of treatment and 10 years of follow-up	Yes
Stevenson et al., 2005[19]	United Kingdom	British Health System	Euro (2001/02)	1.5% C and 6% R	Osteoporosis with fractures at ages 50, 60, 70 and 80 years and over, and without fractures at ages 70 and 80 years and over	Alendronate Risedronate Etidronate Raloxifene Teriparatide Estrogens	10 years	No
Borgström et al., 2006[24]	Sweden, Finland, Spain, Belgium	Societal	Euro (2003)	Sweden 3% C/R, Finland 5% C/R, Spain 6% C/R, Belgium 3% C	Osteoporosis with and without fractures at age 70 years	No drug treatment Risedronate	Up to 100 years or until death	No

Table 1
Methodological characteristics of the economic assessment studies of drugs to treat postmenopausal osteoporosis

Study	Country	Perspective	Currency	Discount rate	Target population	Intervention	Time horizon	Conflicts of interest
Liu et al., 2006[26]	United States of America	Societal	US dollar (2003)	3% C and R	Osteoporosis with fractures at age 70 years	Ca^{+} or vit. D Alendronate (5 years) Teriparatide (2 years) Teriparatide (2 years) + alendronate (5 years)	Lifelong	Yes
Lundkvist et al., 2006[18]	Sweden	Societal	Euro (2003)	3% C and R	Osteoporosis* with fractures at age 69 years, stratified according to the presence of recent or old fractures	No drug treatment Teriparatide	Up to 100 years or until death	Yes
Borgström et al., 2006[40]	Sweden	Societal	Krona (2004)	3% C and R	Osteoporosis with fractures at age 69 years, and without fractures at age 77 years	No drug treatment Strontium ranelate	Up to 100 years or until death	No
Goeree et al., 2006[25]	Canada	Provincial government	Canadian dollar (2005)	5% C and R	Osteoporosis without fractures at age 65 years	No drug treatment Etidronate Alendronate Raloxifene Risedronate	Up to 95 years or until death	Yes
Ström et al., 2007[27]	Belgium, Denmark, France, Germany, Italy, Norway, Spain, Sweden, and United Kingdom	Societal	Euro (2004)	3% C and R	Osteoporosis with fractures	No drug treatment Alendronate	Up to 100 years or until death	Yes
Earnshaw et al., 2007[28]	United States of America	Third payer (Health insurance)	US dollar (2006)	3% C and R	Osteoporosis with fractures at age 50 years and over	Bisphosphonates	5 years	Yes
Grima et al., 2008[35]	Canada	Health Ministry	Canadian dollar (2006)	5% C and R	Osteoporosis with and without fractures at age 65 years or over	Risedronate Alendronate	5 years	Yes
Lekander et al., 2008[37]	Sweden, United Kingdom, and United States of America	Societal	US dollar (2006)	3% C and R	Osteoporosis at age 50 years	No drug treatment HT	Up to 100 years or until death	Yes
Araújo et al., 2008[36]	Brazil	Supplementary Health System	Real (2007)	3% C and R	Osteoporosis with fractures	Zoledronic acid Risedronate	5 years	Yes
Tosteson et al., 2008[29]	United States of America	North American Health System	US dollar (2005)	3% C and R	Osteoporosis with and without fractures at ages 65 and 75 years	No drug treatment Risedronate Alendronate Ibandronate Teriparatide	10 years	Yes
Wasserfallen et al., 2008[30]	Switzerland	Health System	Euro (2005)	3% C and R	Osteoporosis with fractures at age 70 years	No drug treatment Risedronate	5 years	Yes
Hiligsmann et al., 2008[41]	Belgium	Payer*	Euro (2006)	3% C 1.5% effectiveness	Osteoporosis without fractures, or with fractures at ages 70, 75 and 80 years	No drug treatment Strontium ranelate	Lifelong	Yes
Hiligsmann et al., 2010[42]	Belgium	Payer*	Euro (2006)	3% C and 1.5% R	Osteoporosis with and without fractures at ages 75 and 80 years	No drug treatment Strontium ranelate Risedronate Strontium ranelate	Lifelong	Yes

Table 1
Methodological characteristics of the economic assessment studies of drugs to treat postmenopausal osteoporosis

Study	Country	Perspective	Currency	Discount rate	Target population	Intervention	Time horizon	Conflicts of interest
Hiligsmann & Reginster, 2010[44]	Belgium	Payer*	Euro (2009)	3% C and 1.5% R	Osteoporosis with and without fractures at ages 70, 75 and 80 years	No drug treatment Denosumab	Up to 105 years or until death	Yes
Berto et al., 2010[31]	Italy	Italian National Health System	Euro	3% C and R	Osteoporosis with fractures at ages 65 years or over	Risedronate Alendronate	6 years	Yes
Borgström et al., 2010[17]	Sweden	Societal	Euro (2007)	3% C and R	Osteoporosis with fractures at age 70 years	No drug treatment Teriparatide PHT (1–84)	6 months	Yes
Jönsson et al., 2011[45]	Sweden	Societal	Euro (2008)	3% C and R	Osteoporosis with fractures at age 71 years	No drug treatment Alendronate Risedronate Strontium ranelate Denosumab	Up to 100 years or until death	Yes
Hiligsman & Reginster, 2011[46]	Belgium	Payer*	Euro (2009)	3% C and 1.5% R	Osteoporosis with and without fractures at age 70 years	Alendronate Risedronate Denosumab	Up to 105 years or until death	Yes

Ca^{+}: calcium; BMD: bone mineral density; HTA: Health Technology Assessment; C: cost; PTH (1–84): parathormone (1–84); R: results; HT: hormone therapy; vit. D: vitamin D.
*Costs paid by the health insurance and patient.

Table 2
Results of the economic assessment studies of drugs to treat postmenopausal osteoporosis

Study	Outcome	Incremental cost-effectiveness ratio	
Rosner et al., 1998[20]	Vertebral fractures	**ICER regarding strategy 1 (more important results)**	
		Intact uterus Strategy 2 = 1,376 Strategy 3 = 2,174 Strategy 4 = 39,488	**Hysterectomized** Strategy 2 = 166 Strategy 3 = 2,331 Strategy 4 = 40,965
Escolar et al., 1999[32]	Hip fractures	RCE Alendronate = 297,879/success RCE placebo = 23,301/ success	ICER Alendronate/placebo = 25,621,491/ success
Iglesias et al., 2002[21]	Vertebral and non-vertebral fractures	**ICER/QALY** Risedronate/ No drug treatment = dominant	
Willis et al., 2002[43]	Hip fractures	**ICER/GLY** 27% efficacy = *cost saving* 20% efficacy = *cost saving* 15% efficacy = 177,600	**ICER/QALY** 27% efficacy = *cost saving* 20% efficacy = *cost saving* 15% efficacy = 74,000
Silva, 2003[33]	Femoral fractures	**ICER/prevented fracture – vit. D/No drug treatment** 50 years No treatment = base BMD + alendronate = 136,217.00 BMD + HT = 37,322.00 HT = 1,479,504.00 Calcium + vit. D = 12,673.00	65 years No drug treatment = base BMD + alendronate = 101,181.00 BMD + HT = 27,179.00 HT = 1,389,939.00 Calcium + vit. D = 12,408.00
Johnell et al., 2003[22]	Vertebral, wrist and hip fractures	ICER/QALY for Alendronate/ No drug treatment = 76,384	
Brecht et al., 2003[23]	Vertebral, wrist and hip fractures	**ICER/QALY** Risedronate/Standard treatment = *cost saving*	
Kanis et al., 2004[34]	Vertebral, wrist and hip fractures	**ICER/ QALY** Risedronate/No drug treatment = dominated	

Table 2
Results of the economic assessment studies of drugs to treat postmenopausal osteoporosis

Study	Outcome	Incremental cost-effectiveness ratio	
Borgström et al., 2004[38]	Vertebral, wrist and hip fractures	**ICER/GLY Raloxifene/ No drug treatment** 60 years = 45,426 70 years = 35,419 80 years = 6,070	**ICER/QALY** 60 years = 40,213 70 years = 32,776 80 years = 28,477
Brecht et al., 2004[39]	Hip fractures	**ICER/prevented hip fracture** No drug treatment = — Risedronate = 37,348 Alendronate = 48,349 Raloxifene = no effect	**ICER/QALY** No drug treatment = — Risedronate = 32,092 Alendronate = 41,302 Raloxifene = 1,247,119
Stevenson et al., 2005[19]	Vertebral, wrist, hip and proximal humerus (shoulder) fractures	**ICER/QALY osteoporosis without fracture** 70 years Alendronate = 40,460 Risedronate = 98,855 Etidronate = 45,071 Raloxifene = 18,664 Teriparatide = 247,660 Estrogens = dominated 80 + Alendronate = 12,181 Risedronate = 17,240 Etidronate = 72,007 Raloxifene = 27,483 Teriparatide = 218,020 Estrogens = dominated	**ICER/QALY established osteoporosis** 50 years Alendronate = 33,621 Risedronate = 42,268 Etidronate = 78,960 Raloxifene = 31,189 Teriparatide = 227,976 Estrogens = dominated 60 years Alendronate = 39,733 Risedronate = 46,596 Etidronate = 89,079 Raloxifene = 20,696 Teriparatide = 268,104 Estrogens = dominated 70 years Alendronate = 16,934 Risedronate = 22,001 Etidronate = 29,742 Raloxifene = 29,993 Teriparatide = 234,728 Estrogens = 69,585 80 + Alendronate = 697 Risedronate = 5,022 Etidronate = 48,521 Raloxifene = 21,183 Teriparatide = 123,205 Estrogens = dominated
Borgström et al., 2006[24]	Vertebral, wrist and hip fractures	**ICER/QALY with previous fracture** Risedronate/ No drug treatment Sweden = 1,176 Finland = 28,377 Spain = 55,026 Belgium = 18,020	**ICER/QALY without previous fracture** Risedronate/ No drug treatment Sweden = 30,062 Finland = 82,000 Spain = 141,353 Belgium = 66,857
Liu et al., 2006[26]	Vertebral, wrist and hip fractures	**ICER/QALY** Ca^{+} or vit. D = base Alendronate (5 years) = 11,600 Teriparatide (2 years) = 172,300 Teriparatide (2 years) + alendronate (5 years) = 156,500	
Lundkkvist et al., 2006[18]	Vertebral, wrist and hip fractures	**History of fracture** ICER/QALY = 64,432 ICER/GLY = 82,972	**History of recent fracture** ICER/QALY = 20,300 ICER/GLY = 25,624
Borgström et al., 2006[40]	Vertebral, wrist and hip fractures	**69-year-old women** ICER/GLY = 678,259 ICER/QALY = 472,586	**77-year-old women** ICER/GLY = 503,507 ICER/QALY = 259,643
Goeree et al., 2006[25]	Vertebral and hip fractures	**ICER /GLY** No drug treatment = standard Etidronate = 143,247 Alendronate = 72,883 Raloxifene = 140,782 Risedronate = 346,872	**ICER /QALY** No drug treatment = standard Etidronate = 32,571 Alendronate = 32,760 Raloxifene = 49,279 Risedronate = 78,275

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Results of the economic assessment studies of drugs to treat postmenopausal osteoporosis

Study	Outcome	Incremental cost-effectiveness ratio	
Ström et al., 2007[27]	Vertebral, wrist and hip fractures	**ICER /QALY Alendronate/ No drug treatment** With previous fracture Belgium = 6,461 Denmark = *cost saving* France = 4,670 Germany = 7,658 Italy = 15,489 Norway = *cost saving* Spain = 13,193 Sweden = *cost saving* United Kingdom= 1,356 Without previous fracture Belgium = 23,684 Denmark = 6,201 France = 27,419 Germany = 27,821 Italy = 39,712 Norway = *cost saving* Spain = 32,943 Sweden = *cost saving* United Kingdom= 11,849	**ICER /GLY Alendronate/ No drug treatment** With previous fracture Belgium = 10,090 Denmark = *cost saving* France = 7,858 Germany = 12,505 Italy = 25,263 Norway = *cost saving* Spain = 21,048 Sweden = *cost saving* United Kingdom= 1,963 Without previous fracture Belgium = 36,975 Denmark = 7,543 France = 45,625 Germany = 45,319 Italy = 64,537 Norway = *cost saving* Spain = 52,783 Sweden = *cost saving* United Kingdom= 17,145
Earnashaw et al., 2007[28]	Vertebral, wrist and hip fractures	ICER/QALY Monthly/No drug treatment = 13,749 Weekly/No drug treatment = 16,657 Monthly/weekly = 9,476	
Grima et al., 2008[35]	Hip fractures	ICER/prevented fracture (Risedronate/alendronate) = 1,867	ICER/QALY gained (Risedronate/alendronate) = 3,877
Lekander et al., 2008[37]	Infarction, venous thromboembolic events, breast cancer, colorectal cancer, hip fracture, vertebral fracture, wrist fracture, and coronary heart disease	**ICER/QALY HT/No drug treatment without previous fractures** Intact uterus Sweden = HT dominated UK = HT dominated US = HT dominated Hysterectomized Sweden = 26,644 UK = 19,265 US = 16,059	**ICER/QALY HT/No drug treatment with previous fractures** Intact uterus Sweden = 16,660 UK = 29,132 US = 49,532 Hysterectomized Sweden = 14,163 UK = 2,054 US = 3,326
Araújo et al., 2008[36]	Femoral fracture	ICER/prevented fracture - zoledronic acid/Risedronate = dominant	
Tosteson et al., 2008[29]	Vertebral and hip fractures	**ICER per QALY**	
		65 years with fractures No therapy = base Risedronate = 22,068 Alendronate = 362,845 Ibandronate = dominated Teriparatide = dominated **65 years without fractures** No therapy = base Risedronate = 66,722 Alendronate = dominated Ibandronate = dominated Teriparatide = dominated	**75 years with fractures** No therapy = base Risedronate = dominated Alendronate = dominated Ibandronate = dominated Teriparatide = dominated **75 years without fractures** No therapy = base Risedronate = 991 Alendronate = dominated Ibandronate = dominated Teriparatide = dominated
Wasserfallen et al., 2008[30]	Vertebral, wrist and hip fractures	**ICER per QALY** Risedronate/ No drug treatment = *cost saving*	
Hiligsmann et al., 2010[41]	Vertebral, wrist and hip fractures or others	**ICER/QALY strontium ranelate / No drug treatment**	
		Without previous fractures 70 years = 15,096 75 years = 6,913 80 years = *cost saving*	**With previous fractures** 70 years = 23,426 75 years = 9,698 80 years = *cost saving*

Table 2
Results of the economic assessment studies of drugs to treat postmenopausal osteoporosis

Study	Outcome	Incremental cost-effectiveness ratio	
Hiligsmann et al., 2010[42]	Vertebral, wrist and hip fractures or others	**ICER/QALY**	
		Ranelato de strontium *vs.* No drug treatment	**Ranelato de strontium *vs.* Risedronate**
		Without previous fractures 75 years = 15,588 80 years = 7,708 With previous fractures 75 years = 16,518 80 years = 6,015	Without previous fractures 75 years = strontium dominant 80 years = strontium dominant With previous fractures 75 years = 11,435 80 years = strontium dominant
Hiligsmann & Reginster, 2010[44]	Clinical vertebral, wrist and hip fractures or others	**ICER/QALY denosumab/ No drug treatment**	
		Price settings of the drug Setting 1 (352.20): ICER/QALY = 22,616	Setting 2 (414.30): ICER/QALY = 28,441 Setting 3 (476.40): ICER/QALY = 34,265
Berto et al., 2010[31]		**ICER/QALY Risedronate/Alendronate**	
		65–69 years = 36,099 70–74 years = 9,737 75–79 years = dominated 80–84 years = dominated	85–89 years = dominated 90–94 years = dominated 95–99 years = dominated
Borgström et al., 2010[17]	Vertebral, wrist and hip fractures or others	**Cost/QALY** Teriparatide/No drug treatment = 43,473 PHT (1-84)/No drug treatment = 104,396	
Jönsson et al., 2011[45]		**ICER/GLY**	
		Denosumab/ No drug treatment = 25,980 Denosumab/ Alendronate = 48,226 Denosumab/ Risedronate = 20,592 Denosumab/ Strontium ranelate = 9,161	Denosumab/ No drug treatment = 14,458 Denosumab/Alendronate = 27,060 Denosumab/ Risedronate = 11,545 Denosumab/ Strontium ranelate = 5,015
Hiligsman & Reginster, 2011[46]	Clinical vertebral, wrist and hip fractures or others	**ICER/QALY**	
		Osteoporosis Alendronate (brand)/ denosumab = 14,120 Alendronate (generic)/ denosumab = 22,220 Risedronate/ denosumab = –209	**Osteoporosis with previous fractures** Alendronate (brand)/ denosumab = 14,166 Alendronate (generic)/ denosumab = 19,718 Risedronate/ denosumab = 4,456

QALY: quality-adjusted life-years; GLY: gained life-years; Ca^{+}: calcium; ICER: incremental cost-effectiveness ratio; C: cost; PTH (1-84): parathormone (1-84); R: results; HT: hormone therapy; vit. D: vitamin D.

Comparing different bisphosphonates, Grima et al.[35] have found that risedronate had a better ICER than alendronate. Araújo et al.[36] have reported that zoledronic acid is dominant relative to risedronate for preventing femur fractures. Tosteson et al.[29] have found that risedronate and alendronate were cost-effective for the treatment of osteoporosis, but ibandronate was dominated (had a higher cost and lower effectiveness than the other alternatives). Berto et al.[31] have reported that risedronate was cost-effective at the 65–74 year age group and was dominated relative to alendronate over the age of 75 years, that is, had a higher cost and lower effectiveness than alendronate.

Discrepancy was observed in the study by Kanis et al.,[34] in which the authors have concluded that, for women with postmenopausal osteoporosis established at the age of 70 years, the treatment was cost-effective, considering the cost-effectiveness threshold of 30,000 per QALY gained. However, the results showed that the drug treatment strategy was dominated relative to no drug treatment, that is, higher cost (10,674 *vs*. 10,471) and lower effectiveness (8,598 *vs*. 8,699 QALY) was observed with treatment.

A study conducted by the Health Technology Assessment, a British initiative with multidisciplinary activity that systematically assesses technologies, has not recommended drug treatment at the age of 50 years. At the age of 60 years, either raloxifene or no treatment is recommended, in this order of ICER. At the age of 70 years, no treatment, alendronate and risedronate, etidronate, raloxifene and estrogen are recommended. At the age of 80 years, alendronate, risedronate, etidronate, raloxifene, estrogen or no treatment are recommended. For women with established osteoporosis, no prior fracture and aged 70 years, the cost-effective interventions were either raloxifene or no treatment. At the age of 80 years, alendronate, risedronate, raloxifene, etidronato and no treatment are recommended.[19]

Earnashaw et al.[28] have performed a study comparing the monthly and weekly frequencies of bisphosphonate

administration to estimate the effect of adherence to treatment on CER. The monthly administration was the most cost-effective intervention, because it had the highest adherence to treatment.

Five studies have assessed the use of teriparatide, which was not considered cost-effective at any age group analyzed[19,29] for populations with and without fractures.[29] Liu et al.[26] have reported that the use of teriparatide for two years was not a rational choice. With the use of teriparatide for two years, followed by alendronate for five years, the costs were lower and there was a higher increment in QALY.[26] Alendronate alone showed an even better ICER.[26] Only Lundkvist et al.,[18] comparing teriparatide and no treatment, have found that the drug is cost-effective in populations with previous fractures, aged 69 years, with a bone mineral density (BMD) T-score of −3. Another study comparing teriparatide with parathormone 1–84 (PTH 1–84) has reported that the former was more cost-effective than the latter; teriparatide was also more cost-effective than no treatment.[17]

Three studies assessing the use of hormone therapy (HT) have reported a good CER, but called attention to the increased risk of breast cancer.[20,33,37] Lekander et al.,[37] considering results of the Women's Health Initiative (WHI), have concluded that HT is cost-effective for hysterectomized patients, regardless of the presence of previous fractures. For women with preserved uterus and no previous fractures, no drug treatment was the preferred option. However, bisphosphonates have shown a similar reduction in the risk of fractures when compared with HT, without increasing the risk for adverse events, even for hysterectomized patients.[37]

Four economic assessments included raloxifene. Two have considered it cost-effective: Borgström et al.,[38] studying patients aged at least 60 years and with no previous fractures; and Stevenson et al.,[19] studying patients aged at least 60 years and with previous fractures and patients aged at least 70 with no previous fractures. Brecht et al.[39] and Goeree et al.,[25] comparing bisphosphonates and raloxifene, have reported that bisphosphonates were more cost-effective.

Four studies have assessed strontium ranelate. In a study conducted in different countries, the authors have concluded that strontium ranelate was cost-effective in 70-year-old women with previous fractures, but not in those with no fractures, because it exceeded the threshold of willingness to pay in some countries (more than 40,000 per QALY gained).[40] Hiligsmann et al.[41,42] have found that the drug was cost-effective, when compared with placebo and risedronate at the ages of 70, 75, and 80 years.

Regarding supplementation with calcium and vitamin D, Rosner et al.[16] have included in their assessment an arm with patients using calcium for a while, compared to other therapeutic strategies. It has not proven to be cost-effective because of the high incidence of vertebral fractures in that group. Willis et al.,[43] comparing the strategy of associating calcium and vitamin D in 70-year-old patients, have reported that the drug is cost saving relative to no drug treatment. According to Silva,[33] that alternative has the best ICER of those analyzed.

Hiligsmann and Reginster[44] have carried out a cost-effectiveness assessment comparing denosumab with no drug treatment. Because the drug was not available for commercialization at the time of the study, the prices were based on the commercial value for risedronate and two settings (−15% and +15%). Denosumab was cost-effective in all settings, considering the threshold of willingness to pay of 35,000 per QALY gained. Jönsson et al.[45] have reported that, although the treatment with denosumab had the highest cost among the alternatives analyzed, it resulted in better ICER due to the greater number of fractures prevented. The authors have considered that the injectable administration of denosumab is a cost-effective alternative to oral osteoporosis treatment, because adherence to treatment is one of the great problems of effectiveness in patients at high risk of fractures. Denosumab proved to be cost-effective as compared to bisphosphonates (alendronate – generic and brand – and risedronate) at the age of 70 years.[46]

Of the studies assessed, 80% have declared conflicts of interests with the pharmaceutical industry, and only six had no representatives of that industry among their authors.

Discounting is a method used to adjust future costs and benefits to their present market values. The discount rate is the rate in which future costs and benefits are adjusted to reflect their present value. Different discount rates are used worldwide. The discount rates used for costs ranged from 1.5% to 6.0%, and, in the results, from 0.0% to 6.0%. The most used discount rates were 3.0% for both costs and effects.

DISCUSSION

The studies about the economic assessment of postmenopausal osteoporosis have shown great methodological variability. That resulted from the following: factors related to the economic model itself, in which different assumptions were considered in an attempt to portray the different realities; and the characteristics of the countries, such as demographic and

epidemiological data, factors related to their health systems and services (perspective of the study), prices, and how their population valued their health status (utility). All studies used the WHO diagnostic criteria. Most studies considered cohorts of osteoporotic women with and without previous fractures. Lundkvist et al.,[18] comparing teriparatide with the no drug treatment option, have considered only individuals with T-score of −3. The results were considered valid only for that population.

Most studies comparing therapeutic strategies with the no drug treatment option have found a reasonable ICER, according to the threshold of willingness to pay of each country. The therapeutic interventions became more cost-effective as age advanced, the BMD decreased, and previous fractures were present. The combination of clinical risk factors with the femoral BMD measure, as recommended by the Fracture Risk Assessment (FRAXTM), is an important strategy to identify candidates for treatment.[47] Recently, the *São Paulo Osteoporosis Risk Index* (SAPORI), an instrument to predict fractures based on risk factors, was created and validated in Brazil. Its use might optimize the beginning of the drug treatment, in addition to reducing costs with the diagnosis, because the physician will establish criteria for requesting densitometry tests when considering quantitatively clinical risk factors.[48]

A study conducted by a Spanish entity has questioned the efficiency of using drugs to prevent the occurrence of fractures. Because fractures tend to occur at more advanced ages, initiating a therapy at the age of 50 years to prevent events that will occur only at the seventh or eighth decades of life has been considered controversial.[49]

Bisphosphonates are the most used drugs to treat osteoporosis and have been the most assessed therapeutic strategies. However, although they are widely used and economic assessments have proved that those drugs represent a cost-effective strategy, severe adverse effects associated with their use have been reported. This has led the Food and Drug Administration (FDA) to review the safety of those drugs. Although rare, osteonecrosis of the jaw continues to be a regularly cited complication.[50,51] In addition, ophthalmic and dermatologic complications have been reported. The FDA has alerted to severe bone pain, atrial fibrillation, and fracture induced by bisphosphonates (subtrochanteric or atypical fracture).[52] Some studies have assessed the costs resulting from the most frequently found adverse reactions in the economic model, which are the gastrointestinal reactions due to bisphosphonates. Considering the importance of the new adverse effects cited, further studies should be conducted to assess the safety of those drugs. If clinical importance and significant increase in costs occur due to the management of reactions, new cost-effectiveness studies should be conducted to assess whether changes in the direction of the results will occur.

The two studies comparing the use of teriparatide and bisphosphonates have reported that bisphosphonates were more cost-effective.[19,29] Teriparatide has proved to be more cost-effective when compared to PTH (1–84)[17] and the no drug treatment option.[18]

Regarding HT, its benefit for the prevention and treatment of postmenopausal bone loss and for the relief of the vasomotor symptoms associated with that period has been well established.[53] Thus, HT is an attractive option to treat postmenopausal symptoms and has a good CER.[20,33,37] However, due to its ability to modulate physiology and the risk of diseases in other tissues, its safety should always be carefully considered before it is prescribed.[54]

Although raloxifene has shown no effect on the reduction of hip and other non-vertebral fractures, its use has proved to be cost-effective when compared to no drug treatment in patients with no previous fracture and at least 60 years old.[38] It has also been cost-effective in patients with previous fractures aged at least 60 years and in patients without previous fractures aged at least 70 years.[19] That drug has not been considered cost-effective when compared with bisphosphonates.[23,25] The favorable results of raloxifene are partially due to the reduction in the breast cancer risk profile shown by that drug and the comparators used (patients with no treatment).

Strontium ranelate has proved to be cost-effective only for some age groups: women aged at least 70 years and with previous fractures.[40–42] Further assessments about that drug are required to analyze the vascular and neurological effects, in addition to diarrhea, associated with its use.[55]

The use of vitamin D alone was not cost-effective.[20] However, Silva[33] has reported that vitamin D is the most cost-effective option when resources are scarce. Willis et al.[43] have reported that its use is more cost-effective than no drug treatment.

Denosumab is a new drug, and the studies assessing it have reported a good CER.[44–46] However, although some studies have demonstrated its efficacy to treat osteoporosis, they have reported the occurrence of adverse reactions, including cutaneous reactions, which should be better studied to assess that drug's safety.[56–58]

Considering the specificities of the Brazilian population ageing, whose life expectancy is around 76.7 years,[59] lower than that of developed countries (usually over 80 years), the results of economic assessments conducted in developed

countries should be carefully appreciated in the Brazilian context. In addition, other factors, such as the presence of conflicts of interest, might influence the results, leading to studies whose designs or interpretation of results are biased.

In Brazil, only two studies have been performed. Silva[33] has conducted a preliminary study of cost-effectiveness aiming at discussing the availability of therapeutic strategies for the treatment of osteoporosis in that country. However, for diseases whose sequence of events after the intervention is constant over time, the Markov model should be used to simulate the results, rather than the decision tree used by the author. Araújo et al.[36] have conducted a study from the perspective of the supplementary health system, considering zoledronic acid for the prevention of proximal femoral fracture for a specific age group (65 years). In that setting, that drug was more cost-effective; however, the results cannot be extrapolated to another health systems (public or from the societal perspective) and that same relation might not be valid for hip, vertebral or non-vertebral fractures.

In Brazil, Pharmacoeconomics is a very recent area, essential to aid in decision-making, especially regarding public health policies. Cost-effectiveness studies approaching the SUS perspective might be useful to define at which age it would be more cost-effective to initiate the treatment and which therapeutic strategies have higher ICER. In an attempt to standardize the conduction of economic assessment studies in Brazil and allow their comparison, the Brazilian Health Ministry has elaborated methodological guidelines for economic assessments, which should be followed. In addition, the costs of therapeutic strategies should be established, and a system of hospitalization costs due to osteoporotic fractures should be adopted, including not only costs with drugs and medical-hospital materials, but also the payments of the health care and administration teams, equipment depreciation, cleaning, and electrical energy. Difficulties in determining costs have been recognized, and so has the importance of those studies for decision-making in the Brazilian context. Studies conducted in other countries cannot be extrapolated to the Brazilian reality, because of the peculiarities of each health system, the extent of the discount rates used and the epidemiological and demographic data of each country.

CONCLUSION

Economic assessment studies, especially cost-effectiveness ones, have been increasingly used to support decision-making regarding health policies, incorporation of new technologies, implementation of preventive programs, and development of guidelines in health care, such as those for the management of osteoporosis.

In general, bisphosphonates have been the most frequently assessed strategy, the one that resulted in the best ICER. Hormone therapy, vitamin D supplementation, strontium ranelate, raloxifene, teriparatide, and denosumab have been analyzed, and their results have varied depending on the perspective, the country, and of the assumptions of each study. None of the results could be extrapolated to the Brazilian population in the SUS context, which limits their use by decision makers.

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