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Cost-effectiveness of multifaceted evidence implementation programs for the prevention of glucocorticoid-induced osteoporosis

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Abstract

Summary—Using a computer simulation model, we determined that an intervention aimed at improving the management of glucocorticoid-induced osteoporosis is likely to be cost-effective to third-party health insurers only if it focuses on individuals with very high fracture risk and the proportion of prescriptions for generic bisphosphonates increases substantially.

Introduction—The purpose of this study is to determine whether an evidence implementation program (intervention) focused on increasing appropriate management of glucocorticoid-induced osteoporosis (GIOP) might be cost-effective compared with current practice (no intervention) from the perspective of a third-party health insurer.

Methods—We developed a Markov microsimulation model to determine the cost-effectiveness of the intervention. The hypothetical patient cohort was of current chronic glucocorticoid users 50–65 years old and 70% female. Model parameters were derived from published literature, and sensitivity analyses were performed.

Results—The intervention resulted in incremental cost-effectiveness ratios (ICERs) of \$298,000 per quality adjusted life year (QALY) and \$206,000 per hip fracture averted. If the cohort's

baseline risk of fracture was increased by 50% (10-year cumulative incidence of hip fracture of 14%), the ICERs improved significantly: \$105,000 per QALY and \$137,000 per hip fracture averted. The ICERs improved significantly if the proportion of prescriptions for generic bisphosphonates was increased to 75%, with \$113,000 per QALY and \$77,900 per hip fracture averted.

Conclusions—Evidence implementation programs for the management of GIOP are likely to be cost-effective to third-party health insurers only if they are targeted at individuals with a very high risk of fracture and the proportion of prescriptions for less expensive generic bisphosphonates increases substantially.

Keywords

Bisphosphonates; Cost-benefit analysis; Evidence-based practice; Osteoporosis

Introduction

Glucocorticoids are widely prescribed in medical practice [1–3] and are often prescribed chronically for severe inflammatory conditions, such as rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel disease, as well as chronic respiratory conditions, such as chronic obstructive pulmonary disease and asthma [1, 4]. As a result, glucocorticoid-induced osteoporosis (GIOP) is the leading cause of secondary osteoporosis [5] and leads to a significant increased risk of fracture [6, 7]. The prevention of GIOP comprises an assessment of the risk of fracture, often including bone mineral density (BMD) testing, and appropriate treatment with anti-osteoporotic agents, such as bisphosphonates. Despite international recommendations on evidence-based approaches for prevention [8–10], appropriate testing and treatment for GIOP remains low [11].

Determining the most effective methods to translate research into clinical practice comprises an area of type 2 translational research that is gaining interest in national efforts to improve health care quality [12]. The cost-effectiveness of these approaches is of public health and public policy interest to patients, providers, and insurers. Examples of type 2 translational research, including evidence implementation programs for both osteoporosis in general and GIOP in particular [4, 13, 14] have produced variable results. The role of third-party health insurers in the implementation and adoption of best clinical practices in the community has not yet been fully determined. Recent reports suggesting that GIOP prevention is likely to be cost-effective for some patients [5] raise questions about whether evidence implementation programs intended to improve the quality of care in this area might be cost-effective as well.

To further evaluate the potential cost-effectiveness of GIOP evidence implementation programs, we designed and analyzed a decision model with Markov transition states and a 10-year time horizon to compare costs and outcomes in GIOP prevention. We determined under what conditions an evidence implementation program focused on increasing appropriate GIOP testing and treatment might be cost-effective compared with current clinical practice from the perspective of a third-party health insurer who might implement such a program to improve quality of care.

Materials and methods

We developed a Markov decision analysis model to compare the costs and outcomes of an evidence implementation program (intervention) aimed at increasing BMD testing and bisphosphonate prescribing for GIOP with the costs and outcomes of current practice (no intervention). The analysis was conducted from the perspective of a third-party health insurer.

Evidence implementation program intervention

We modeled an idealized multifaceted evidence implementation program based on our previous study utilizing a group randomized trial [4]. This intervention consisted of three components aimed at increasing appropriate BMD testing and osteoporosis medication prescribing: (1) case-based modules relevant to GIOP management; (2) audit and feedback of physicians' GIOP management compared with their peers; and (3) printed physician and patient-targeted GIOP educational materials. Results from the control arm of this randomized study were used to provide model inputs for the no intervention arm of this cost-effectiveness analysis. Notwithstanding, the analyses in this study have general implications for osteoporosis evidence implementation programs overall and do not serve as an evaluation of this specific example program.

Model structure and assumptions

The decision tree model was constructed and analyzed with TreeAge Pro Suite software (TreeAge Software, Inc; Williamstown, MA, USA). Using data from our group randomized control trial to serve as an example of the target population at risk for GIOP in a large managed care plan, we evaluated a hypothetical cohort of current glucocorticoid users that was 70% female with an age range of 50 to 65 years old and 8% of whom had experienced a prior osteoporotic fracture [4]. All expected model outcome values were generated using 1 million first-order Monte Carlo microsimulations (also known as patient-level or discrete-event simulation) in which one individual at a time was sent through the model and the results were averaged [15]. Microsimulation allowed for the inclusion of complex patient histories, such as history of previous fractures and history of previous bisphosphonate treatment and adherence and captured patient-level variability and uncertainty in the model [15].

The Markov model contained four health states: (1) GIOP under active bisphosphonate treatment; (2) GIOP without active bisphosphonate treatment; (3) disability; and (4) death. A simplified version of the decision tree model is shown in Fig. 1. A 1-year cycle length and 10 year total time horizon were used. No individuals entered the model in the disability or death states. Individuals who were not prescribed bisphosphonate in the first year were not considered for treatment again unless they experienced a subsequent fracture. The risk of osteoporotic fracture was determined by an individual's age, sex, history of prior osteoporotic fracture, and bisphosphonate exposure. Fractures were divided into three categories: hip, clinical vertebral, and other. Individuals who experienced osteoporotic fractures had an increased risk of subsequent fracture at all sites. The disability state could only be entered following hip fracture, as this state represented permanent nursing home residents who could only transition to the death state. Individuals in the disability state did not contribute further fractures to the model outcome and did not receive bisphosphonate treatment. The costs of potential subsequent fractures for individuals in the disability state were assumed to be included in the estimate of the annual cost for the disability state [16].

Several assumptions were made regarding treatment with bisphosphonate. A single representative bisphosphonate was considered in the model by combining data available for all bisphosphonates [5]. Individuals prescribed bisphosphonate treatment may have become non-adherent during the first year of treatment or any subsequent year. Individuals who became non-adherent to bisphosphonate treatment remained non-adherent unless they experienced an osteoporotic fracture and were subsequently prescribed treatment. In this case, they again had the same probability of adherence as a first-time user [17]. Individuals who experienced an osteoporotic fracture within the model had a likelihood of being prescribed bisphosphonate treatment that was twice the baseline likelihood of treatment in the first year of the model [18]. The effectiveness of bisphosphonate exposure was extended

for 1 year beyond treatment discontinuation for individuals who received more than 2 years of consecutive treatment (1 year treatment offset) [19, 20]. Bisphosphonate treatment was assumed to have only minimal adverse effects that produced insignificant effects on costs and quality of life [21]. Adverse effects were accounted for in the model via medication discontinuation (non-adherence).

Model probability, cost, and utility parameters

Model parameters were derived from the published literature. Structured Medline searches and the reference sections of identified publications were used to identify relevant publications. The most robust and relevant estimates were aggregated by weighted average methods to determine a parameter's baseline estimate when more than one publication was identified. Preference was given to publications specifically reporting outcomes in GIOP, as opposed to other patient groups. The model probabilities, costs, and utilities of the base case are shown in Table 1.

The rates of BMD testing and bisphosphonate prescribing for the no intervention arm were taken directly from the example randomized controlled trial of the GIOP evidence implementation program intervention [4]. The idealized effect of the evidence implementation intervention was assumed to be a 50% relative increase in BMD testing and bisphosphonate prescribing from the no intervention rates, which corresponds to an 11% absolute increase for both. Patient non-adherence to bisphosphonate treatment was modeled, and initial adherence was a strong predictor of subsequent adherence [17]. Estimates of annual probability of fracture reflect current chronic glucocorticoid exposure [5, 6, 24, 26] and frequent concomitant rheumatic disease [25] among the hypothetical cohort [4]. Only clinical (symptomatic) vertebral fractures were considered in the model.

The annual probability of fracture for men was assumed to be 60% that of women for hip and vertebral fractures and 15% that of women for other fractures [5]. Individuals with a prior osteoporotic fracture had an increased relative risk of subsequent fracture of 2.0 compared with their baseline rate [26, 43, 44]. Bisphosphonate treatment was assumed to decrease an individual's relative risk of fracture as shown in Table 1. Age-dependent annual mortality rates were derived from a standard life table [45]. Following fracture, individuals had an increased relative risk of death compared with the baseline (non-fracture) rate.

The cost of BMD testing reflects the mean 2007 Medicare reimbursement for dual energy X-ray absorptiometry [21]. The cost of bisphosphonates reflects the mean US wholesale price. In sensitivity analyses, the cost of generic bisphosphonates was assumed to be \$360 annually based on the anticipated effects of market competition. Direct costs resulting from fractures were derived directly from Medicare reimbursement expenditure data [46] and were assumed to be similar for private third-party insurance providers. The total cost of the evidence implementation program was assumed to be \$50,000 based on the cost of labor and supplies (web-based computer modules, audit and feedback of physicians' prescribing habits, and printed physician and patient materials) in our example evidence implementation program [4]. This corresponds to approximately \$25 per patient, based on 300 physicians undergoing the intervention and prescribing chronic glucocorticoids to a mean of 6.4 patients each [4]. All costs were adjusted for inflation where necessary and are expressed in 2007 U.S. dollars.

The health outcome of the model was quality adjusted life years (QALYs) in order to capture both the quantity and quality of life experienced by the patients in the cohort [47]. Baseline (non-fracture) utility weights to calculate QALYs reflect patients with chronic illnesses, such as rheumatoid arthritis, that may result in chronic glucocorticoid exposure [39]. Utility weights for ages between 50 and 75 years were interpolated assuming a linear

progression. Individuals who experienced fractures had a one-time decrease in utility according to the fracture type (e.g., a 50-year-old individual with a hip fracture would experience $0.65 \times 0.75 = 0.4875$ QALY for that year). Death was assumed to occur at the mid-point of the cycle. The summary measure of cost per hip fracture averted was also considered in the analysis. All costs and outcomes were discounted at 3% annually.

Sensitivity analysis

Several one-way sensitivity analyses were performed by varying model parameters over a range of plausible extreme values. First, the baseline fracture risk for all patients was increased by 50%. Patient adherence to bisphosphonate treatment in the first year was increased by 50% in the intervention arm, as a possible additional idealized benefit of the evidence implementation program. The cost of bisphosphonates in both intervention and no intervention arms was varied by evaluating different proportions of prescriptions for less expensive generic bisphosphonates. The combined effects of a higher baseline fracture rate and lower bisphosphonate costs were then analyzed. The effect of the cost of the evidence implementation program was evaluated by assuming a no-cost (free) program and one in which the cost per patient was doubled. The effectiveness of bisphosphonates to prevent fractures was varied by 10% on the absolute scale (e.g., relative risk of 0.69 was varied from 0.59 to 0.79). Fracture-related costs including disability were varied from 50% to 150% of their assumed values.

To estimate the joint effect of uncertainty of all of the model parameters simultaneously on the cost-effectiveness of the intervention, second-order Monte Carlo probabilistic sensitivity analysis was performed [48]. Distributions were assigned to each of the model parameters as follows: beta distributions were fitted for probability estimates and utilities, log-normal distributions were fitted for relative risks, and normal distributions were fitted for costs [48]. Constants were used to generate the distributions of utilities and baseline fracture rates in order to maintain their monotonic association with patients' age (e.g., to ensure that utilities could not increase with increasing age within a given sampling of the distribution). The 95% confidence intervals from the chosen distributions for each parameter are shown in Table 1. To perform the probabilistic sensitivity analysis, each of the parameter distributions was independently randomly sampled and the expected outcome of this resultant model was determined using microsimulations. This process of uniquely sampling the parameter distributions and using microsimulation to determine the model outcomes was repeated 1,000 times. The model output results were presented using cost-effectiveness acceptability curves, in which the proportion of second-order trials that are cost-effective is plotted against a range of willingness to pay cost-effectiveness thresholds [48].

Results

The results of the decision analysis model are shown in Table 2. The no intervention strategy resulted in a 10-year cumulative hip fracture incidence of 87 per 1,000 patients and 440 per 1,000 patients for any symptomatic fracture. Although the evidence implementation intervention was assumed to increase BMD testing and bisphosphonate prescribing rates by 50% above baseline, its effectiveness in preventing fractures was very modest, with resultant incremental cost-effectiveness ratios (ICER) of \$206,000 per hip fracture averted and \$298,000 per QALY.

Substantially increasing the baseline risk of fracture in the hypothetical cohort improved the cost-effectiveness of the evidence implementation intervention. When the baseline risk of fracture was increased by 50%, the no intervention strategy resulted in higher 10-year cumulative fracture rates: 140 per 1,000 patients for hip and 680 per 1,000 patients for total

fractures. The resultant ICERs for the intervention were \$137,000 per hip fracture averted and \$105,000 per QALY.

One potential additional benefit of an evidence implementation intervention is an increase in patient adherence to bisphosphonate treatment. Assuming a relative increase of 50% in patient adherence to bisphosphonates during the first year of treatment concurrently with the 50% relative increase in BMD testing and bisphosphonate prescribing, the effects on fracture rates and QALYs were still modest with resultant ICERs of \$215,000 per hip fracture averted and \$228,000 per QALY.

The effects of generic bisphosphonates on the cost-effectiveness of the evidence implementation program are shown in Table 3. As the proportion of all prescriptions for less expensive generic bisphosphonates increases, the ICERs decrease. If 75% of all bisphosphonate prescriptions (with and without the intervention) were for generic formulations, the ICERs for the intervention were significantly lower at \$77,900 per hip fracture averted and \$113,000 per QALY.

Combining the assumptions of the widespread use of generic bisphosphonates and a very high risk of fracture among the hypothetical cohort resulted in a marked improvement of the cost-effectiveness of the evidence implementation program. When 75% of all bisphosphonate prescriptions were generic and the baseline risk of fracture in the cohort was increased by 50%, the resultant ICERs were \$44,700 per QALY and \$58,300 per hip fracture averted.

The cost of implementing the intervention did not have significant effects on the baseline cost-effectiveness results. If the intervention was assumed to have no incremental cost, the resultant ICERs were \$188,000 per hip fracture averted and \$273,000 per QALY. If the intervention was instead assumed to double in cost to \$50 per patient, the resultant ICERs were \$223,000 per hip fracture averted and \$323,000 per QALY.

Varying the risk reduction of fracture due to bisphosphonate therapy by 10% on the absolute scale above and below the baseline assumption produced a wide range of ICER at \$144,000 to \$338,000 per hip fracture averted and \$139,000 to \$322,000 per QALY. The cost-effectiveness of the evidence implementation program appeared to be less sensitive to the fracture-related costs. When the fracture-related costs were varied from 150% to 50% of their assumed values, the following ranges of ICERs were obtained: per hip fracture averted \$186,000 to \$225,000 and per QALY \$270,000 to \$326,000.

The results of probabilistic sensitivity analyses for the baseline model are shown in Fig. 2. For both the QALY and hip fractures averted outcome measures, the evidence implementation intervention dominated (was less expensive and more effective than) current clinical practice in less than 1% of the second-order trials. The intervention did not attain cost-effectiveness in more than 50% of the second-order trials at a willingness to pay threshold of \$250,000 per QALY or per hip fracture averted.

The results of probabilistic sensitivity analyses for the model that assumed a 50% increase in fracture risk and 75% generic bisphosphonate prescriptions are shown in Fig. 3. For both the QALY and hip fractures averted outcome measures, the evidence implementation intervention dominated current clinical practice in approximately 15% of the second-order trials. The intervention attained cost-effectiveness in 50% of the second-order trials at approximately \$75,000 per QALY and \$75,000 per hip fracture averted. Both the QALY and hip fracture averted cost-effectiveness acceptability curves plateaued below a 70% probability of cost-effectiveness at any willingness to pay.

Discussion

Using a decision analysis model, we found that evidence implementation programs in GIOP face considerable challenges to be cost-effective from the perspective of third-party health insurers, unless there is widespread use of generic bisphosphonates. In particular, a multifaceted intervention aimed at increasing the rates of testing and treatment for GIOP among all chronic glucocorticoid users is unlikely to be cost-effective by generally agreed upon standards [49], with projected ICERs of nearly \$300,000 per QALY and over \$200,000 per hip fracture averted, results that were further validated by second-order probabilistic sensitivity analyses. Careful analyses of parameter assumptions, which were based on the existing scientific literature, revealed several potential contributing factors to our results. The evidence implementation program produced a modest decrease in the number of fractures in our model, owing to the modest effectiveness of bisphosphonates, suboptimal patient adherence to therapy, and the limited increase in treatment with bisphosphonates.

One-way sensitivity analyses suggested that the evidence implementation intervention may be considered cost-effective if targeted at patients with a very high risk of osteoporotic fracture (10-year hip fracture risk greater than 14%). This risk profile may possibly be expected in a 65-year-old white woman with rheumatoid arthritis on chronic glucocorticoid therapy and a femoral neck BMD Z-score of -1.75 [50]; however, such high rates of fracture are more commonly seen in elderly females who would be less likely to be beneficiaries of a third-party health insurer. Limiting the scope of the evidence implementation program to only those with the very highest risk of fracture may limit the intervention's significance and impact to a third-party health insurer.

Bisphosphonate therapy has historically been relatively expensive (\$1,080 annually), particularly when compared with the direct costs associated with fractures at sites other than the hip (\$2,930–\$4,210). Sensitivity analyses revealed that the recent introduction of less expensive generic bisphosphonates could dramatically improve the cost-effectiveness of an evidence implementation program. Future bisphosphonate generic prescription fill rates may be expected to be 50% to 75% based on current generic fill rates for medications in other therapeutic classes [51]. If this proportion of generic prescriptions occurs, the ICER of an evidence implementation program for GIOP would likely approach \$100,000 per QALY.

When the assumptions of high baseline risk of fracture and widespread generic bisphosphonate prescribing were combined, the evidence implementation program became much more cost-effective. The mean expected cost per QALY was approximately \$45,000. Second-order probabilistic sensitivity analysis revealed a greater than 50% probability that the intervention would be expected to be cost-effective at a willingness to pay threshold of approximately \$75,000 per QALY, as well as a 15% chance that the intervention would be both cost-saving and more effective than current practice. However, the applicability of these underlying extreme model assumptions regarding fracture risk and treatment cost to actual clinical practice is less clear.

Bisphosphonate therapy appears to result in modest reductions in osteoporotic fractures among patients with GIOP; relative risks of 0.46–0.77 were used in the baseline model. These estimates were derived from studies with limited sample size, particularly for non-vertebral fractures, but are comparable to the effectiveness of bisphosphonates among postmenopausal women [5]. If further studies reveal that bisphosphonates are much more effective in preventing osteoporotic fractures than assumed, then an evidence implementation program aimed at increasing their use would be more cost-effective: an

additional decrease in the relative risk of fracture of 10% on the absolute scale would result in an ICER of \$139,000 per QALY.

Patient adherence to bisphosphonate therapy for osteoporosis is suboptimal, as is common among treatments for chronic asymptomatic conditions. However, even when we hypothesized a relative 50% increase in patient adherence with the evidence implementation intervention, the cost-effectiveness of this approach did not improve significantly. This emphasizes that fracture risk together with treatment cost and effectiveness are the major determinants of the cost-effectiveness of the intervention.

The cost of the intervention was assumed to be \$50,000, corresponding to approximately \$25 per patient, though this estimate may vary based on the particular program being implemented. The principal cost of the example intervention was the audit of physicians' BMD testing and osteoporosis medication prescribing. Therefore, the incremental cost of adding individual physicians to the program is difficult to measure but is likely low. Additionally, the health insurer environment has changed significantly since the example evidence implementation intervention took place in 2004; physician audit and feedback mechanisms are already currently in place and being utilized by many third-party health insurers [52], thus decreasing their cost. Regardless, the cost of the intervention was small compared with the costs of bisphosphonate treatment and the various fracture outcomes. Neither omitting nor doubling the assumed cost of the intervention produced important changes in the cost-effectiveness.

We assumed that the evidence implementation program would result in an idealized 50% relative increase in the rate of BMD testing and bisphosphonate prescribing. This is considerably higher than the rates we and others have observed in randomized studies of multifaceted interventions for GIOP [4, 13, 14] and may have biased the results toward the intervention. One study of GIOP care suggests that an even greater increase in bisphosphonate prescribing may be achieved with the implementation of an organized program of total care including a specialized team of health care providers [53]. Regardless, the ICERs for the intervention in this study remain relatively stable over a very wide range of the number of individuals treated with bisphosphonates due to the small cost of the evidence implementation program compared with the cost of treatment (data not shown). In the baseline case, the cost per patient of the intervention is only approximately 2% the cost of 1 year of bisphosphonate treatment.

The number of patients treated would have had a more significant effect on the ICER if the intervention used a test-and-treat approach to identify those patients with the highest risk of fracture. However, given the considerable risk of fracture for all chronic glucocorticoid users and the increased complexity and cost of implementing a test-and-treat strategy, we chose to model a broad-based, non-prescriptive evidence implementation program for GIOP, such as the one in our example study [4]. Since the ICERs for the intervention were strongly influenced by the baseline risk of fracture in the cohort, further studies of a test-and-treat approach may be warranted and would likely increase the attractiveness of evidence implementation programs for GIOP to a third-party health insurer. Such approaches may benefit from recent efforts to quantify individuals' risk of osteoporotic fracture based on BMD test results and clinical factors [50]. It should be noted, however, that the association between BMD results and fracture risk among patients on glucocorticoids is different from the relationship between fracture risk and BMD in other populations, such as postmenopausal osteoporosis. Supporting the notion of direct toxic effects of glucocorticoids on bone that are independent of BMD, individuals on glucocorticoid therapy may fracture at a lower BMD threshold [54].

The third-party health insurer perspective of our model resulted in important model assumptions. Adults in the United States older than age 65 years generally receive their health benefits from government-sponsored programs (Medicare), as opposed to private third-party health insurers. Accordingly, these older adults were not included in our hypothetical cohort and our model was limited to a 10-year time horizon. Additional sensitivity analyses revealed that more restrictive assumptions regarding subjects' age did not have substantial effects on the cost-effectiveness of the intervention. Starting with the same initial age distribution of 50–65 years and censoring all subjects at age 65 years (when their health care costs are likely to be assumed by Medicare) resulted in ICERs of \$276,000 per QALY and \$283,000 per hip fracture averted in the baseline model and \$131,000 per QALY and \$84,800 in the model that assumed a 50% higher fracture risk and 75% generic bisphosphonate prescriptions. Starting with an initial age distribution of 50–55 years old (such that all subjects would remain 65 years old or younger during the model's 10-year time horizon) resulted in ICERs of \$304,000 per QALY and \$259,000 per hip fracture averted in the baseline model and \$67,500 per QALY and \$83,500 per hip fracture averted in the model that assumed a 50% higher fracture risk and 75% generic bisphosphonate prescriptions. Indirect costs of fracture, which can be considerable for employed adults [21], were not considered in our model. Additionally, morphometric (radiographic) vertebral fractures, which may affect patients' quality of life [55], pulmonary function [56], and the cost-effectiveness of interventions in GIOP [5], were not included in our model. Viewed from a societal perspective that includes older adults and indirect costs, evidence implementation programs in GIOP would likely be much more cost-effective.

Multifaceted evidence implementation interventions have been shown to be successful in increasing the efficiency of medication use in managed care settings [57]. Nevertheless, this approach in the management of GIOP so far appears to be less successful [4, 14]. Cost-effectiveness ratios in the generally acceptable range have been reported for other models of multifaceted interventions, including one regarding post fragility fracture evaluation and treatment for osteoporosis [58]. However, this study did not model GIOP and its assumptions and parameters differed from ours in several key areas: a higher proportion of treated patients versus the non-intervention arm (40% versus 10%); higher adherence to treatment (82% at 1 year); and more effective treatment (0.49 relative risk of fracture) [58].

Consistent with our results, previous cost-effectiveness analyses of treatment strategies for GIOP have reported results that varied substantially based on patient characteristics and risk of fracture. A study of postmenopausal women with rheumatoid arthritis starting glucocorticoid therapy found that screening and treating women with alendronate was cost-effective compared with watchful waiting if the treatment threshold was a BMD T-score was less than -2.5 [16]. Another study reported that using cyclic etidronate to treat women with borderline osteoporosis (BMD T-score less than -1.5) who were initiating glucocorticoids was cost-effective, but this study included indirect costs in the analysis [59]. Analysis of a cost-effectiveness model based on systematic review of the literature predicted that treatment with bisphosphonates for GIOP was cost-effective for all individuals with a prior fragility fracture, as well as for those individuals without a history of fracture who were older than 75 years or had a BMD T-score of less than -2 [5]. Yet, another study concluded that bisphosphonates are cost-effective in GIOP in patients with high fracture risk, such as elderly patients and younger patients with a history of fracture [60]. Therefore, GIOP treatment with bisphosphonates has not been found to be universally cost-effective for all glucocorticoid users. This reinforces our finding that a broad-based, non-prescriptive evidence implementation program for GIOP is not likely to be cost-effective to a third-party health insurer.

The prevention of GIOP is challenging for patients and physicians. Until recently, the lack of inexpensive yet highly effective treatments may have precluded third-party health insurers from sponsoring the dissemination of evidence regarding GIOP testing and treatment given the potential lack of clear cost-effectiveness from their vantage point. Nevertheless, the burden of GIOP-associated fractures leads to significant morbidity.

In summary, evidence implementation programs for the treatment of GIOP are likely to be cost-effective to third-party health insurers only if they are targeted at individuals with a very high risk of fracture and the prescription of less expensive generic bisphosphonates increases. Approaches to successfully minimize the effects of osteoporosis in patients receiving chronic glucocorticoid therapy warrant further investigation to identify more cost-effective solutions.

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References

1. van Staa TP, Leufkens HG, Abenhaim L, Begaud B, Zhang B, Cooper C. Use of oral corticosteroids in the United Kingdom. *QJM*. 2000; 93(2):105–111. [PubMed: 10700481]
2. Walsh LJ, Wong CA, Pringle M, Tattersfield AE. Use of oral corticosteroids in the community and the prevention of secondary osteoporosis: a cross sectional study. *BMJ*. 1996; 313(7053):344–346. [PubMed: 8760745]
3. Mudano A, Allison J, Hill J, Rothermel T, Saag K. Variations in glucocorticoid induced osteoporosis prevention in a managed care cohort. *J Rheumatol*. 2001; 28(6):1298–1305. [PubMed: 11409123]
4. Curtis JR, Westfall AO, Allison J, Becker A, Melton ME, Freeman A, et al. Challenges in improving the quality of osteoporosis care for long-term glucocorticoid users: a prospective randomized trial. *Arch Intern Med*. 2007; 167(6):591–596. [PubMed: 17389291]
5. Kanis JA, Stevenson M, McCloskey EV, Davis S, Lloyd-Jones M. Glucocorticoid-induced osteoporosis: a systematic review and cost-utility analysis. *Health Technol Assess*. 2007; 11(7):iii–iv. ix–xi, 1–231. [PubMed: 17311734]
6. van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Oral corticosteroids and fracture risk: relationship to daily and cumulative doses. *Rheumatol (Oxford)*. 2000; 39(12):1383–1389.
7. Van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Use of oral corticosteroids and risk of fractures. *J Bone Miner Res*. 2000; 15(6):993–1000. [PubMed: 10841167]
8. American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update. *Arthritis Rheum*. 2001; 44(7):1496–1503. [PubMed: 11465699]
9. Adler RA, Hochberg MC. Suggested guidelines for evaluation and treatment of glucocorticoid-induced osteoporosis for the department of veterans affairs. *Arch Intern Med*. 2003; 163 (21):2619–2624. [PubMed: 14638562]
10. Geusens PP, de Nijs RN, Lems WF, Laan RF, Struijs A, van Staa TP, et al. Prevention of glucocorticoid osteoporosis: a consensus document of the Dutch society for rheumatology. *Ann Rheum Dis*. 2004; 63(3):324–325. [PubMed: 14962971]
11. Curtis JR, Westfall AO, Allison JJ, Becker A, Casebeer L, Freeman A, et al. Longitudinal patterns in the prevention of osteoporosis in glucocorticoid-treated patients. *Arthritis Rheum*. 2005; 52 (8): 2485–2494. [PubMed: 16052570]
12. Institute of Medicine. Crossing the quality chasm: a new health system for the 21st century. National Academy Press; Washington D.C: 2001.

13. Naunton M, Peterson GM, Jones G, Griffin GM, Bleasel MD. Multifaceted educational program increases prescribing of preventive medication for corticosteroid induced osteoporosis. *J Rheumatol.* 2004; 31(3):550–556. [PubMed: 14994404]
14. Solomon DH, Katz JN, La Tourette AM, Coblyn JS. Multifaceted intervention to improve rheumatologists' management of glucocorticoid-induced osteoporosis: a randomized controlled trial. *Arthritis Rheum.* 2004; 51(3):383–387. [PubMed: 15188323]
15. Weinstein MC. Recent developments in decision-analytic modelling for economic evaluation. *Pharmacoeconomics.* 2006; 24 (11):1043–1053. [PubMed: 17067190]
16. Solomon DH, Kuntz KM. Should postmenopausal women with rheumatoid arthritis who are starting corticosteroid treatment be screened for osteoporosis? A cost-effectiveness analysis. *Arthritis Rheum.* 2000; 43(9):1967–1975. [PubMed: 11014346]
17. Curtis JR, Westfall AO, Cheng H, Lyles K, Saag KG, Delzell E. Benefit of adherence with bisphosphonates depends on age and fracture type: results from an analysis of 101,038 new bisphosphonate users. *J Bone Miner Res.* 2008; 23(9):1435–1441. [PubMed: 18442318]
18. Hooven F, Gehlbach SH, Pekow P, Bertone E, Benjamin E. Follow-up treatment for osteoporosis after fracture. *Osteoporos Int.* 2005; 16(3):296–301. [PubMed: 15221208]
19. Black DM, Schwartz AV, Ensrud KE, Cauley JA, Levis S, Quandt SA, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. *JAMA.* 2006; 296(24):2927–2938. [PubMed: 17190893]
20. Curtis JR, Westfall AO, Cheng H, Delzell E, Saag KG. Risk of hip fracture after bisphosphonate discontinuation: implications for a drug holiday. *Osteoporos Int.* 2008; 19(11):1613–1620. [PubMed: 18483689]
21. Schousboe JT, Taylor BC, Fink HA, Kane RL, Cummings SR, Orwoll ES, et al. Cost-effectiveness of bone densitometry followed by treatment of osteoporosis in older men. *JAMA.* 2007; 298 (6): 629–637. [PubMed: 17684185]
22. Siris ES, Harris ST, Rosen CJ, Barr CE, Arvesen JN, Abbott TA, et al. Adherence to bisphosphonate therapy and fracture rates in osteoporotic women: relationship to vertebral and nonvertebral fractures from 2 US claims databases. *Mayo Clin Proc.* 2006; 81 (8):1013–1022. [PubMed: 16901023]
23. Singer BR, McLauchlan GJ, Robinson CM, Christie J. Epidemiology of fractures in 15,000 adults: the influence of age and gender. *J Bone Joint Surg Br.* 1998; 80(2):243–248. [PubMed: 9546453]
24. Kanis JA, Johansson H, Oden A, Johnell O, de Laet C, Melton IL, et al. A meta-analysis of prior corticosteroid use and fracture risk. *J Bone Miner Res.* 2004; 19(6):893–899. [PubMed: 15125788]
25. van Staa TP, Geusens P, Bijlsma JW, Leufkens HG, Cooper C. Clinical assessment of the long-term risk of fracture in patients with rheumatoid arthritis. *Arthritis Rheum.* 2006; 54(10):3104–3112. [PubMed: 17009229]
26. van Staa TP, Geusens P, Pols HA, de Laet C, Leufkens HG, Cooper C. A simple score for estimating the long-term risk of fracture in patients using oral glucocorticoids. *QJM.* 2005; 98(3): 191–198. [PubMed: 15728400]
27. Kanis JA, Johnell O, Oden A, Sembo I, Redlund-Johnell I, Dawson A, et al. Long-term risk of osteoporotic fracture in Malmo. *Osteoporos Int.* 2000; 11(8):669–674. [PubMed: 11095169]
28. Zethraeus N, Borgstrom F, Strom O, Kanis JA, Jonsson B. Cost-effectiveness of the treatment and prevention of osteoporosis—a review of the literature and a reference model. *Osteoporos Int.* 2007; 18 (1):9–23. [PubMed: 17093892]
29. Tosteson AN, Gottlieb DJ, Radley DC, Fisher ES, Melton LJ 3rd. Excess mortality following hip fracture: the role of underlying health status. *Osteoporos Int.* 2007; 18(11):1463–1472. [PubMed: 17726622]
30. Forsen L, Sogaard AJ, Meyer HE, Edna T, Kopjar B. Survival after hip fracture: short- and long-term excess mortality according to age and gender. *Osteoporos Int.* 1999; 10(1):73–78. [PubMed: 10501783]
31. Meyer HE, Tverdal A, Falch JA, Pedersen JI. Factors associated with mortality after hip fracture. *Osteoporos Int.* 2000; 11 (3):228–232. [PubMed: 10824238]
32. Johnell O, Kanis JA, Oden A, Sernbo I, Redlund-Johnell I, Pettersson C, et al. Mortality after osteoporotic fractures. *Osteoporos Int.* 2004; 15(1):38–42. [PubMed: 14593451]

33. Jalava T, Sarna S, Pylkkanen L, Mawer B, Kanis JA, Selby P, et al. Association between vertebral fracture and increased mortality in osteoporotic patients. *J Bone Miner Res.* 2003; 18(7):1254–1260. [PubMed: 12854835]
34. Cauley JA, Thompson DE, Ensrud KC, Scott JC, Black D. Risk of mortality following clinical fractures. *Osteoporos Int.* 2000; 11 (7):556–561. [PubMed: 11069188]
35. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: an observational study. *Lancet.* 1999; 353(9156):878–882. [PubMed: 10093980]
36. Cooper C, Atkinson EJ, Jacobsen SJ, O’Fallon WM, Melton LJ 3rd. Population-based study of survival after osteoporotic fractures. *Am J Epidemiol.* 1993; 137(9):1001–1005. [PubMed: 8317445]
37. Red Book. Pharmacy’s fundamental reference (Drug Topics Red Book). Thomson Healthcare Inc; Montvale, NJ: 2007.
38. Kilgore ML, Morrissey MA, Becker DJ, Gary LC, Curtis JR, Saag KG, et al. Health care expenditures associated with skeletal fractures among Medicare beneficiaries, 1999–2005. *J Bone Miner Res.* 2009;10.1359/jbmr.090523
39. Uhlig T, Loge JH, Kristiansen IS, Kvien TK. Quantification of reduced health-related quality of life in patients with rheumatoid arthritis compared to the general population. *J Rheumatol.* 2007; 34 (6):1241–1247. [PubMed: 17516624]
40. Johnell O, Jonsson B, Jonsson L, Black D. Cost effectiveness of alendronate (Fosamax) for the treatment of osteoporosis and prevention of fractures. *Pharmacoeconomics.* 2003; 21(5):305–314. [PubMed: 12627984]
41. Kanis JA, Johnell O, Oden A, Borgstrom F, Zethraeus N, De Laet C, et al. The risk and burden of vertebral fractures in Sweden. *Osteoporos Int.* 2004; 15(1):20–26. [PubMed: 14593450]
42. Merlino LA, Bagchi I, Taylor TN, Utrie P, Chrischilles E, Sumner W 2nd, et al. Preference for fractures and other glucocorticoid-associated adverse effects among rheumatoid arthritis patients. *Med Decis Making.* 2001; 21(2):122–132. [PubMed: 11310945]
43. Klotzbuecher CM, Ross PD, Landsman PB, Abbott TA 3rd, Berger M. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. *J Bone Miner Res.* 2000; 15(4):721–739. [PubMed: 10780864]
44. Kanis JA, Johnell O, De Laet C, Johansson H, Oden A, Delmas P, et al. A meta-analysis of previous fracture and subsequent fracture risk. *Bone.* 2004; 35(2):375–382. [PubMed: 15268886]
45. Arias, E. National vital statistics reports. Vol. 54. National Center for Health Statistics; Hyattsville, MD: 2006. United States life tables, 2003.
46. Kilgore, ML.; Gary, LC.; Curtis, JR.; Saag, KG.; Arora, T.; Morrissey, MA., et al. Incremental costs associated with selected skeletal fractures among Medicare beneficiaries [abstract]. Annual Meeting of the American Society for Bone and Mineral Research; 2008.
47. Gold, MR.; Patrick, DL.; Torrance, GW.; Fryback, DG.; Hadorn, DC.; Kamlet, MS., et al. Identifying and valuing outcomes. In: Gold, MR.; Siegel, JE.; Russell, LB.; Weinstein, MC., editors. Cost-effectiveness in health and medicine. Oxford University Press; New York: 1996. p. 82-123.
48. Claxton K. Exploring uncertainty in cost-effectiveness analysis. *Pharmacoeconomics.* 2008; 26(9): 781–798. [PubMed: 18767898]
49. Neumann PJ, Sandberg EA, Bell CM, Stone PW, Chapman RH. Are pharmaceuticals cost-effective? A review of the evidence. *Health Aff (Millwood).* 2000; 19(2):92–109. [PubMed: 10718025]
50. World Health Organization Collaborating Centre for Metabolic Bone Diseases. FRAX: WHO fracture risk assessment tool. University of Sheffield; UK: <http://www.shef.ac.uk/FRAX/index.htm>
51. Express Scripts 2007 Drug Trend Report. Available from:<http://www.express-scripts.com/industryresearch/industryreports/drug-trendreport/2007/trend.pdf>
52. Landon BE, Rosenthal MB, Normand SL, Frank RG, Epstein AM. Quality monitoring and management in commercial health plans. *Am J Manag Care.* 2008; 14(6):377–386. [PubMed: 18554076]

53. Newman ED, Matzko CK, Olinginski TP, Perruquet JL, Harrington TM, Maloney-Saxon G, et al. Glucocorticoid-Induced Osteoporosis Program (GIOP): a novel, comprehensive, and highly successful care program with improved outcomes at 1 year. *Osteoporos Int.* 2006; 17(9):1428–1434. [PubMed: 16865312]
54. Van Staa TP, Laan RF, Barton IP, Cohen S, Reid DM, Cooper C. Bone density threshold and other predictors of vertebral fracture in patients receiving oral glucocorticoid therapy. *Arthritis Rheum.* 2003; 48(11):3224–3229. [PubMed: 14613287]
55. Cockerill W, Lunt M, Silman AJ, Cooper C, Lips P, Bhalla AK, et al. Health-related quality of life and radiographic vertebral fracture. *Osteoporos Int.* 2004; 15(2):113–119. [PubMed: 14618303]
56. Harrison RA, Siminoski K, Vethanayagam D, Majumdar SR. Osteoporosis-related kyphosis and impairments in pulmonary function: a systematic review. *J Bone Miner Res.* 2007; 22(3):447–457. [PubMed: 17181402]
57. Lu CY, Ross-Degnan D, Soumerai SB, Pearson SA. Interventions designed to improve the quality and efficiency of medication use in managed care: a critical review of the literature—2001–2007. *BMC Health Serv Res.* 2008; 8:75. [PubMed: 18394200]
58. Majumdar SR, Johnson JA, Lier DA, Russell AS, Hanley DA, Blitz S, et al. Persistence, reproducibility, and cost-effectiveness of an intervention to improve the quality of osteoporosis care after a fracture of the wrist: results of a controlled trial. *Osteoporos Int.* 2007; 18(3):261–270. [PubMed: 17086470]
59. Buckley LM, Hillner BE. A cost effectiveness analysis of calcium and vitamin D supplementation, etidronate, and alendronate in the prevention of vertebral fractures in women treated with glucocorticoids. *J Rheumatol.* 2003; 30(1):132–138. [PubMed: 12508402]
60. van Staa TP, Geusens P, Zhang B, Leufkens HG, Boonen A, Cooper C. Individual fracture risk and the cost-effectiveness of bisphosphonates in patients using oral glucocorticoids. *Rheumatol (Oxford).* 2007; 46(3):460–466.

Fig. 1. Simplified structure of the Markov decision model for glucocorticoid-induced osteoporosis evidence implementation intervention. The *square node* represents the decision (intervention) point. The “*M*” *circles* represent the start of the Markov models with the four states shown. The *empty circles* represent chance nodes with probabilities derived from the published literature. The “*L*” *circles* represent logic nodes where an individual’s bisphosphonate treatment history determines the presence of a residual treatment effect. The *triangles* represent terminal nodes and denote the state in which individuals begin the subsequent cycle. Branch points marked by (A) and (B) are identical throughout the model and have been omitted to conserve space

Fig. 2. Cost-effectiveness acceptability curves for baseline model assumptions. The *curves* represent the proportion of second-order trials in which the evidence implementation intervention was cost-effective for the given willingness to pay. **a** Willingness to pay per QALY. **b** Willingness to pay per hip fracture averted

Fig. 3. Cost-effectiveness acceptability curves for model that assumed a 50% increase in baseline fracture risk and 75% generic bisphosphonate prescription rate. The *curves* represent the proportion of second-order trials in which the evidence implementation intervention was cost-effective for the given willingness to pay. **a** Willingness to pay per QALY. **b** Willingness to pay per hip fracture averted

Table 1

Model probabilities, costs, and utilities

Parameter	Value	95% confidence limits	References
Probability of BMD testing			
No intervention	0.21	0.17–0.25	[4]
Intervention	0.32	0.28–0.36	Assumed ^d
Probability of bisphosphonate prescription (active treatment) in 1st year			
No intervention	0.22	0.18–0.26	[4]
Intervention	0.33	0.29–0.37	Assumed ^d
Probability of patient adherence to bisphosphonate treatment			
First year	0.50	0.45–0.55	[17, 22]
Subsequent years	0.80	0.76–0.84	[17, 22]
Annual probability of fracture in women age 50 years ^b			
Hip	0.0033	0.0026–0.0040	[5, 6, 23–26]
Vertebral	0.0053	0.0042–0.0064	[5, 6, 24–27]
Other	0.026	0.021–0.031	[5, 6, 23–26]
Annual probability of fracture in women age 75 years old ^b			
Hip	0.024	0.019–0.029	[5, 6, 23–26]
Vertebral	0.015	0.012–0.018	[5, 6, 24–27]
Other	0.036	0.029–0.043	[5, 6, 23–26]
Relative risk of fracture with bisphosphonate treatment			
Hip	0.69	0.54–0.87	[5]
Vertebral	0.46	0.35–0.59	[5]
Other	0.77	0.67–0.87	[5]
Probability of disability following hip fracture	0.07	0.05–0.09	[28]
Relative risk of death following fracture			
Hip	5.0	3.0–8.1	[29–32]
Vertebral	4.0	1.8–9.1	[32–35]
Other	1.2	1.0–1.6	[32, 35, 36]
Cost of BMD testing	\$80	\$64–\$96	[21]
Cost of bisphosphonate treatment (annual)	\$1080	^c	[37]
Cost of fracture (one-time cost)			
Hip	\$18,370	\$14,700–\$22,040	[38]
Vertebral	\$4,210	\$3,370–\$5,050	[38]
Other	\$2,930	\$2,340–\$3,520	[38]
Cost of disability (annual)	\$50,000	\$37,500–\$62,500	[16]
Utility weights for non-fracture years			
Age 50 years	0.65	0.52–0.78	[39]
Age 75 years	0.60	0.48–0.72	[39]
Disability state (all ages)	0.40	0.32–0.48	[5]
Utility multipliers for fracture years ^d			

Parameter	Value	95% confidence limits	References
Hip	0.75	0.68–0.83	[40–42]
Vertebral	0.63	0.57–0.68	[41, 42]
Other	0.90	0.81–0.99	[40–42]

All costs are in 2007 US dollars

BMD Bone mineral density

^a Assumed 50% relative increase as a result of evidence implementation program

^b Annual probability of fracture for men was assumed to be 60% that of women for hip and vertebral fractures and 15% that of women for other fractures [5]. The probabilities of fracture for ages between 50 and 75 years were determined by interpolation

^c The cost in sensitivity analyses was varied by the proportion of generic bisphosphonates prescribed

^d Utilities for years in which a fracture occurred were the product of the utility multipliers and the age-specific non-fracture utility weights

Table 2

Results of the cost-effectiveness analysis

Model assumptions	Mean cost	Mean QALY	Hip fractures (10year incidence per patient)	Incremental cost	Incremental QALYs	Hip fractures averted	Incremental cost per QALY	Incremental cost per hip fracture averted
Baseline								
No intervention	\$4,140	5.360	0.08734					
Intervention	\$4,438	5.361	0.08589	\$298	0.001	0.00145	\$298,000	\$206,000
Fracture risk increased by 50% in cohort								
No intervention	\$6,169	5.324	0.1366					
Intervention	\$6,484	5.327	0.1343	\$315	0.003	0.0023	\$105,000	\$137,000
Adherence increased by 50% due to intervention								
No intervention	\$4,140	5.360	0.08734					
Intervention	\$4,823	5.363	0.08416	\$683	0.003	0.00318	\$228,000	\$215,000

All costs are in 2007 US dollars

QALY Quality adjusted life year

Table 3

Cost-effectiveness of the evidence implementation program with increasing proportions of generic bisphosphonates prescribed

Proportions of generic bisphosphonates prescribed (Mean annual cost of treatment)	Incremental cost per QALY	Incremental cost per hip fracture averted
0% (\$1,080)	\$298,000	\$206,000
25% (\$900)	\$244,000	\$168,000
50% (\$720)	\$192,000	\$132,000
75% (\$540)	\$113,000	\$77,900
100% (\$360)	\$84,000	\$57,900

All costs are in 2007 US dollars

QALY Quality adjusted life year