Summary of AHRQ’s Comparative Effectiveness Review of Treatment to Prevent Fractures in Men and Women with Low Bone Density or Osteoporosis: Update of the 2007 Report

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Target Audiences
This CME activity is designed to meet the educational needs of physicians, pharmacists, nurses, and case managers.

Learning Objectives
Based on the findings from AHRQ's comparative effectiveness review of research on treatments to prevent fractures in persons with low bone density (osteopenia) or osteoporosis:
1. Compare the benefits and harms of treatments for fracture reduction, and assess the impact of risk factors in subpopulations on efficacy
2. Examine the prevalence rates, barriers to treatment, and consequences on efficacy of nonadherence and nonpersistence
3. Evaluate the effects of monitoring bone mineral density and long-term therapy on patient outcomes
4. Apply the review findings to making effective, patient-centered treatment and management decisions in the prevention of fractures

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DISCLOSURES

Silvina Levis received compensation from PRIME Education, Inc. for work performed in creating this supplement. George Theodore is an employee of PRIME Education, Inc., a medical education company that receives grants and funding for educational programs from various pharmaceutical manufacturers. Theodore analyzed the source document, wrote this summary, and revised this summary with the assistance of Levis.

Richard Mastrole and Donna Chiefari report no financial interest or other relationships with companies with commercial interests in osteoporosis therapy or other potential conflicts of interest related to the subjects in this report. Richard Mastrole, Donna Chiefari, and Kathleen Jarvis were compensated by PRIME to review the manuscript. Brandon Bellows received compensation from PRIME Education, Inc. for writing the commentary and reports no consulting relationships related to the subject of this report. Anne Hume and Nile Barnes report no financial interests or other relationships with companies with commercial interests in the treatment of osteoporosis or other potential conflicts of interest related to the subjects in this report. Diane Schneider is the author of a consumer health book, The Complete Book on Bone Health (2011), and reports consulting relationships with Amgen, Merck, and Warner Chilcott.

DISCLOSURE OF OFF-LABEL USE

The authors report only descriptions of uses approved by the U.S. Food and Drug Administration.

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AHRQ’s Comparative Effectiveness Review of Treatments to Prevent Fractures in Men and Women with Low Bone Density or Osteoporosis: A Summary of the Key Findings

Silvina Levis, MD, and George Theodore, PhD

ABSTRACT

BACKGROUND: In 2007, the Agency for Healthcare Research and Quality (AHRQ) published a systematic review on the comparative effectiveness of treatments for osteoporosis. The review included studies on the benefits and risks of medications and therapies used to prevent fractures in postmenopausal women and men with low bone density (osteopenia) or osteoporosis. Factors that may affect adherence to treatment, and monitoring for the identification of those most likely to benefit from treatment were also included in this review. AHRQ published an updated review in March 2012 that summarized the benefits and risks of osteoporosis medications in treatment and prevention of osteoporosis, including bisphosphonates (alendronate, risedronate, ibandronate, zoledronic acid), parathyroid hormone, teriparatide, calcitonin, estrogens (for prevention in postmenopausal women), selective estrogen receptor modulators (raloxifene), and denosumab (approved by the FDA in 2010). In addition, dietary and supplemental calcium and vitamin D, as well as weight-bearing exercise, for the preservation of bone mass and the decrease of fracture risk in patients with osteoporosis, were evaluated.

OBJECTIVES: To (a) familiarize health care professionals with the methods and findings from AHRQ’s 2012 comparative effectiveness review on treatments to prevent fractures in men and women with low bone density or osteoporosis, (b) encourage consideration and application of the findings of this review in clinical and managed care settings, and (c) identify limitations and gaps in the existing research with respect to the benefits and risks of treatments for osteoporosis.

SUMMARY: Osteoporosis is a prevalent systemic skeletal disease caused by bone deterioration and loss of mass resulting in fractures, chronic pain and physical disability. It is common in postmenopausal women but men are at risk as well for fractures associated with low bone density. The increasing prevalence and cost of treating osteoporosis make the study of safety and effectiveness for currently available osteoporosis therapies pertinent and timely. In 2012, the Agency for Healthcare Research and Quality (AHRQ) published an updated review on the effectiveness and safety of treatments for osteoporosis, including new therapies for the prevention of vertebral and nonvertebral fractures in postmenopausal women and men. The interventions assessed in the review included 1 biological agent, pharmacological agents, dietary and supplemental calcium and vitamin D, and weight-bearing exercise. The updated report included the new agents and indications approved after the 2007 report and new data on effectiveness and adverse events associated with the bisphosphonates; calcitonin was determined by the reviewers to not be appropriate therapy for osteoporosis and was excluded. The updated review examined 5 key questions focused on comparative review of all FDA-approved medicines for osteoporosis in fracture risk reduction, effectiveness in racial/ethnic subpopulations as well as different risk stratification using FRAX (World Health Organization Fracture Risk Assessment Tool) or other cutoffs, compliance and adherence, adverse effects of medications, the prediction of treatment efficacy using bone mineral density (BMD) monitoring by dual energy x-ray absorptiometry (DXA), and comparative effectiveness of long-term therapy.

The AHRQ reviewers found high strength of evidence to support a reduction in risk of vertebral, nonvertebral and hip fractures in postmenopausal women with osteoporosis treated with 1 of 4 agents (alendronate, risedronate, zoledronic acid, or denosumab). A risk reduction for vertebral fractures in postmenopausal women with osteoporosis treated with ibandronate, teriparatide, or raloxifene therapy was supported with high-strength evidence. Evidence was graded high strength for reduction of vertebral and hip fracture with estrogen therapy in postmenopausal women but not in women with established osteoporosis. Evidence was graded moderate for a reduction in nonvertebral fractures with teriparatide or calcium monotherapy. Moderate or low-moderate strength of evidence showed that calcium alone does not reduce the risk of vertebral or nonvertebral fracture, and that vitamin D has mixed results on decreasing overall fracture risk. High-strength evidence supports a reduction in the risk of hip fracture with calcium treatment. Vitamin D treatment significantly reduced vertebral fractures among patients with primary osteoporosis. The combination of calcium plus vitamin C did not reduce vertebral fracture risk, but did reduce nonvertebral fracture risk in certain populations. Calcium plus vitamin D did decrease the risk of fracture in elderly women but not in elderly men. Adherence and persistence to osteoporosis medications varied depending on patient age, prior history of fracture, dosing frequency, concomitant use of other medications, and adverse effects. Adherence to treatment improved with weekly dosing compared with daily regimens, but evidence was lacking to show monthly regimens improved adherence over weekly regimens.

This article recaps the key findings from the AHRQ 2012 review for the purpose of informing health care providers about the efficacy and safety of therapies used to prevent osteoporotic vertebral, nonvertebral, hip, and wrist fractures. Scientific literature on the effects of risk factors, adherence, BMD monitoring, and long-term therapy on patient outcomes is reviewed in order to inform prescribing decisions. In addition, applications of the AHRQ findings to practice are discussed to provide clinicians with information needed to provide evidence-based care for their patients.

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As the population of the United States ages, the increase in chronic diseases is having a profound effect on the health care system. Although osteoporosis is commonly considered a disorder that primarily affects women, men are also affected. Osteoporosis is more common among postmenopausal women, but it is estimated that 1 of 5 men may experience an osteoporosis-related fracture during their lifetime. Osteoporosis or low bone density affects approximately 52 million persons in the United States.1,2 Osteoporosis is characterized by a deterioration of the microarchitectural structure of the bones and a decrease in bone mass.3 These pathological processes lead to increasingly fragile bones. Ultimately, this lack of bone strength results in fractures, which can lead to disability, chronic pain, and even increased mortality.3
About 2 million fractures occurred in the United States in 2010, of which 25% occurred in men. Projections of annual costs related to these fractures exceed $18 billion, mostly in adults over 65 years of age. Fractures can be debilitating and lead to losses in productivity since the patients cannot work. Among the groups where the loss of productivity due to fractures is highest is in working women under the age of 65. Since the disease occurs in many different groups and in both sexes and people with increasing age, efforts have been directed at better identifying risk factors for osteoporosis. The risk factors described thus far in the literature are varied with respect to their temporal impact and intensity (Table 1). Hence, health care providers are gathering information characterizing their patients in order to assess the risk for osteoporotic fractures at different bone sites. Diagnoses can be made clinically as in the case of a fracture, but in order to make assessments in a more standardized fashion, various diagnostic criteria have been established in the absence of a fracture. These criteria were proposed by both national organizations and health care groups. In particular, among women and men of 50 years of age and older, the diagnosis of osteoporosis commonly relies on the measurement of bone mineral density (BMD) using dual energy x-ray absorptiometry (DXA). This method measures BMD in the spine and the hip to establish the diagnosis, assess future risk of fracture, and monitor patients on treatment. The diagnosis of osteoporosis and low bone density is based on the T-score and Z-score. The T-score is applied to postmenopausal women and men over 50 years of age. The T-score is defined as the number of standard deviations above or below the mean BMD for healthy adults 20-29 years of age of the same race and sex. T-scores are classified as normal (T-score –1 and above), low bone density (T-score lower than –1.0 but higher than –2.5), and osteoporosis (T-score –2.5 or below). The Z-score is used for persons younger than 50 years of age, and is defined as the number of standard deviations above or below the expected BMD for each age and sex category. A Z-score below –2.0 is considered low BMD for that particular group. In contrast, Z-scores at or above –2.0 are considered within the expected range for that age group.

An important aspect in the care of patients with osteoporosis is the management and prediction of fracture risk. The risk of fractures is lower in persons with low bone mass than in persons with osteoporosis, but more fractures occur in persons with low bone mass because of the large size of this population. Predicting the risk of fracture is of particular interest among health care providers, and the World Health Organization (WHO) has devised a tool for the assessment of the risk of fracture. The WHO Fracture Risk Assessment Tool, or FRAX, includes algorithms that are specific to nationality while incorporating the individual’s race, sex, age, weight, and height along with several other additional measures of risk. Numerous studies are investigating whether differences in the antifracture effects of osteoporosis pharmacotherapy can be found among groups with different FRAX scores.

New recommendations for initiating therapy for osteoporosis incorporate BMD results with the assessment of risk. The National Osteoporosis Foundation 2010 Clinicians’ Guide recommends pharmacologic therapy for postmenopausal women and men age 50 and older with a previous hip or vertebral fracture, a T-score less than –2.5 or lower (after evaluation that excludes secondary causes), and low bone mass plus a 10-year probability of hip fracture of 3% or higher or a major hip fracture of 20% or higher. Currently, recommended interventions and available treatments include drug therapies, dietary regimens, and weight-bearing exercise (Table 2a).

In December 2007, the Agency for Health Research and Quality (AHRQ) published a comparative effectiveness review (CER) describing the efficacy and safety parameters of interventions for the prevention of osteoporotic fractures in persons with low bone density or osteoporosis. The report also described adherence to treatment, which is considered an important contributor to fracture prevention, and factors affecting adherence. The report included studies that evaluated the impact of monitoring on the identification of patients who would most likely benefit from treatment including long-term treatment for osteoporosis.

Since the 2007 AHRQ original report, several of the bisphosphonates have become available in new forms that are administered less frequently, and a new biological agent, denosumab, was approved in June 2010 by U.S. Food and Drug Administration (FDA). Denosumab is a monoclonal antibody that inhibits the Receptor Activator of Nuclear factor Kappa-B Ligand (RANKL), thereby inhibiting the differentiation and activation of osteoclasts ultimately leading to a decrease in

TABLE 1 Risk Factors for Osteoporosis Evaluated in this Comparative Effectiveness Review

<table>
<thead>
<tr>
<th>Risk Factors for Osteoporosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex and postmenopausal women</td>
</tr>
<tr>
<td>Increase in age</td>
</tr>
<tr>
<td>Low body weight and body mass index</td>
</tr>
<tr>
<td>Previous fractures</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Current smoking</td>
</tr>
<tr>
<td>Alcohol intake (3 or more drinks per day)</td>
</tr>
<tr>
<td>Low calcium intake</td>
</tr>
<tr>
<td>Deficiency in vitamin D</td>
</tr>
<tr>
<td>Hyperkyphosis</td>
</tr>
<tr>
<td>Hypogonadism</td>
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<tr>
<td>Premature ovarian failure</td>
</tr>
</tbody>
</table>

The 2007 AHRQ review included calcitonin, but the 2012 reviewers excluded treatment for osteoporosis. Calcitonin because "most authorities no longer consider calcitonin to be appropriate therapy for osteoporosis." [SERM = selective estrogen receptor modulator.]

A systematic review was conducted by the Evidence-Based Practice Center (EPC) integrated evidence from the 2007 report with current research and data published since the release of the previous review. The 2012 updated Comparative Effectiveness Review (CER) on the efficacy/effectiveness of these interventions for osteoporosis by the EPC is based on recent studies reported in the literature. The investigators for the EPC were directed by 5 key clinical questions, which pertained to persons with low bone density or osteoporosis. The questions are stated as follows:

1. Key Question 1: What are the comparative benefits in fracture reduction among the following therapeutic modalities for low bone density: bisphosphonates, denosumab, menopausal hormone therapy, selective estrogen receptor modulators (raloxifene), parathyroid hormone, calcium, vitamin D, and physical activity?

2. Key Question 2: How does fracture reduction resulting from treatments vary between individuals with different risks for fracture as determined by BMD, FRAX or other risk assessment score, prior fractures, age, sex, race/ethnicity and glucocorticoid use, and other factors (e.g., community dwelling vs. institutionalized, vitamin D deficient vs. not)?

3. Key Question 3: Regarding treatment adherence and persistence:
   a) What are the adherence and persistence to medications for the treatment and prevention of osteoporosis?
   b) What factors affect adherence and persistence?
   c) What are the effects of adherence and persistence on the risk of fractures?

4. Key Question 4: What are the short- and long-term harms (adverse effects) of the above therapies (when used specifically to treat or prevent low bone density/osteoporotic fracture), and do these vary by any specific subpopulations identified in Key Question 2? The update included comparisons of pharmacologic agents such as bisphosphonates, peptide hormones such as parathyroid hormone, estrogen therapy for postmenopausal women, and the selective estrogen receptor modulator raloxifene; calcitonin was excluded because the reviewers found that it should no longer be considered appropriate therapy for osteoporosis. All of the agents included in the review prevent bone resorption with the exception of teriparatide, which stimulates new bone formation. Simplistically, bisphosphonates bind bone surfaces in a reversible fashion and disrupt bone resorption by affecting osteoclast activity. The AHRQ reviewers included calcium and vitamin D because adequate dietary calcium intake reduces bone resorption. Vitamin D is commonly discussed along with calcium because it promotes bone health by aiding in calcium absorption and bone mineralization. Studies were included in the review of treatment for osteoporosis that reported the prevalence of adverse effects as well as the effect of adverse events on medication nonadherence and nonpersistence.

**Systematic Review Methods**

This section summarizes the methods by which the updated comparative effectiveness review was conducted. Complete details about the methods are provided in the full technical report published by AHRQ. The FDA issued a Risk Evaluation and Mitigation Strategy (REMS) for denosumab in June 2010 with an update in September 2011, based on its evaluation of published evidence for an increased risk of infection and other adverse events.

**Summary of FDA-Approved Indications for Osteoporosis Therapies**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Postmenopausal Osteoporosis</th>
<th>Steroid-Induced Osteoporosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Prevention</td>
<td>Treatment</td>
</tr>
<tr>
<td>Alendronate</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Risedronate</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Denosumab☆</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Estrogen</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>✓</td>
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The AHRQ review included calcitonin, but the 2012 reviewers excluded calcitonin because “most authorities no longer consider calcitonin to be appropriate therapy for osteoporosis.” SERM = selective estrogen receptor modulator.
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- Bisphosphonates
- Selective estrogen receptor modulators (SERMS)
- Parathyroid hormone
- Estrogen or estrogen plus progestin
- Denosumab
- Vitamin D and calcium

5. Key Question 5: With regard to treatment for preventing osteoporotic fracture:
   a) How often should patients be monitored (via measurement of bone mineral density) during therapy, how does bone density monitoring predict antifracture benefits during pharmacotherapy, and does the ability of monitoring to predict antifracture effects of a particular pharmacologic agent vary among the pharmacotherapies?
   b) How does the antifracture benefit vary with long-term continued use of pharmacotherapy, and what are the comparative antifracture effects of continued long-term therapy with the various pharmacotherapies?

Literature Search and Study Selection

Studies included in the AHRQ review were identified through comprehensive searches of published biomedical literature using MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, Clinical Trials.gov, the Cochrane Database of Systematic Reviews, the websites of the National Institute for Clinical Excellence, and the NHA Health Technology Assessment Programme. Searches of these databases were conducted by the reviewers and staff at the Evidence Practice Center (EPC) for the period from January 2005 through March 2011. The EPC also searched for relevant trials in the NIH Clinical Trials database, the Web of Science, FDA Medwatch files, and Health Canada files. Two investigators reviewed the studies against predetermined inclusion/exclusion criteria. Existing systematic reviews, randomized controlled trials (RCTs), and large observational studies, where appropriate, were included in the review. The updated review used the National Library of Medicine’s Medical Subject Headings (MeSH) key word nomenclature with the same basic search rules used for the original report. New terms were added for the generic and trade names of the drug therapies covered in the update.

The 2012 comparative effectiveness review added pharmacotherapies that were not included in the original CER. The update included 2 intravenous bisphosphonates (once yearly zoledronic acid, and ibandronate every 3 months) and the monoclonal antibody denosumab (subcutaneous injection every 6 months). The new review also excluded certain agents based on modifications in their use, and modified key questions to include consideration of the sequential or combined use of different agents. In addition to the exclusion of calcitriol, etidronate, pamidronate, tamoxifen, and testosterone were not included in the 2012 updated review.

Studies were limited to those that had recruited adults over 18 and involved pharmacological interventions for prevention or treatment of osteoporosis. These pharmacological interventions had to be FDA-approved in the United States. Studies also included calcium, vitamin D, or physical activity. Studies of interventions with anticipated approval in the near future were also included by the reviewers.

Only studies that were adequately powered for efficacy and assessed vertebral, hip, and/or total fractures were included in analysis of effectiveness. Studies were excluded from the effectiveness analysis when fracture was included only as an adverse event. The main outcome of interest in the effectiveness review was fracture risk. Included studies had to have a minimum follow-up period of 6 months. Data from included studies were analyzed to evaluate efficacy and effectiveness, adherence, and adverse events. These 3 types of analyses were done as comparisons of single drug versus placebo, and head-to-head comparisons for drugs in the same drug class and across different drug classes. Studies reporting low-stress subtrochanteric or femur fractures as adverse events were included in the adverse event analysis. Observational studies were included in the review only if they included more than 1,000 participants.

Based on clinical trials and observational studies, the reviewers extracted the reported rates of adherence and persistence separately for each type of study. The investigators suggested that adherence and persistence rates reported in trials were more likely to be higher than those rates observed in practice. Barriers and predictors of adherence reported in the studies were also noted by the reviewers as was qualitative analysis of adherence/persistence and fracture in studies.

Evaluations of Study Quality and Rating the Strength of the Body of Evidence

EPC investigators independently assessed the quality of each included RCT based on the Jadad criteria, which included rating the studies for appropriateness of randomization scheme, blinding, and description of withdrawals and dropouts, and concealment of allocation was added to the Jadad criteria. Points from 0-5 for each category were used to score the quality of each study, with a score of 3-5 defined as “good” and a score of 0-2 defined as “poor.” Investigators assessed quality of observational studies using items about the study setting, inclusion and exclusion criteria, key characteristics of enrolled subjects, treatment details, outcome details, statistical analyses, and losses to follow-up.

Overall study quality for all studies was assessed as good, fair, or poor based on the risk for bias. Studies rated as good had the least bias and included formal randomized designs and results that were considered valid and devoid of reporting errors. Fair studies were susceptible to some bias and had missing information, while poor studies had high risk of bias with errors in reporting, and design flaws that might have invalidated the results.
The EPC investigators graded the strength evidence for each outcome by comparison of interest using criteria recommended by the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Investigators assessed the strength of evidence by evaluating the number of included studies, strength and quality of study design, consistency of results, directness (i.e., the intervention is linked directly with the most important health or ultimate outcomes), precision, and the magnitude (estimate) of the effect. The evidence was graded as high, moderate, low, or insufficient. For example, high strength evidence indicates high confidence that the evidence reflects the true effect, and further research is unlikely to change confidence in the estimate of the effect. Moderate strength evidence indicates moderate confidence that the evidence reflects the true effect, but further research may change confidence in the estimate of the effect or change the estimate. Low strength of evidence indicates low confidence in the reported effect, and further research is expected to change confidence in the estimate of the effect and is likely to change the estimate. A grade of insufficient indicated that the evidence was not available or did not permit a conclusion.

### Efficacy of Therapies for the Prevention of Osteoporotic Fractures – Key Question 1

The reviewers evaluated several bisphosphonates, drugs commonly prescribed to postmenopausal women with osteoporosis (Tables 2a, 2b). The strength of evidence was high for reduction of vertebral fracture risk for all bisphosphonates, teriparatide, raloxifene, and denosumab in postmenopausal women (Table 3). The strength of evidence was high only for alendronate, risendronate, and zoledronic acid for decreasing the risk of hip and other nonvertebral fractures. In the prevention of hip fractures, the level of evidence was moderate for teriparatide and unclear for ibandronate (Table 3).

High strength of evidence showed that the monoclonal antibody denosumab decreased the risk for vertebral, nonvertebral, and hip fractures. Other forms of treatment such as menopausal estrogen therapy had a high strength of evidence for a decreased risk of both vertebral and hip fractures in postmenopausal women but not in those with osteoporosis. Based on data with only moderate strength of evidence, the reviewers considered that the superiority of bisphosphonates over hormone therapy in the prevention of fractures has not been demonstrated.

Regarding the prevention of wrist fractures (Table 3), the strength of evidence for a decrease in risk with alendronate was low, and data from pooled analyses of trials of risendronate trials were not statistically significant for the prevention of wrist fractures. The EPC investigators found few head-to-head trials, and the available evidence was insufficient to determine superiority in the prevention of fractures for any bisphosphonate, comparisons of bisphosphonates versus calcium, bisphosphonates versus teriparatide, and bisphosphonates versus raloxifene.

Calcium and vitamin D are commonly prescribed in the management of osteoporotic patients and the reviewers included studies of these supplements in their review (Table 2). Compliance with calcium treatment is often low. A moderate level of evidence from several large RCTs suggests calcium does not reduce the risk of vertebral or nonvertebral fracture. However, 2 separate pooled analyses found that calcium significantly reduced hip fracture risk. The value of vitamin D in reducing fracture risk is uncertain despite a large body of literature. A moderate level of evidence suggests that 700 to 800 international units (IU) of vitamin D daily, particularly when given with calcium, reduce the risk of hip and nonvertebral fractures in institutionalized populations (≥ 700 IU) and the overall risk of fractures (≥ 800 IU). A high level of evidence from 6 published systematic reviews shows that there is no difference for vitamin D alone versus calcium alone in the risk of vertebral, nonvertebral, or hip fractures.

There is insufficient evidence, and only 1 systematic review covered limited data from RCTs, for an effect on fracture risk of physical activity compared with placebo. No studies compared physical activity to other interventions. The evidence was rated insufficient regarding the effects on fractures from the use of combinations of osteoporosis therapies or sequential use of osteoporosis therapies.

### Impact of Risk Factors on Therapies for Fracture Risk Reduction – Key Question 2

Treatment outcomes for the prevention of osteoporotic fractures may vary according to the patient characteristics and risk factors (Table 4). The risk factors that were examined to answer Key Question 2 regarding the variation among treatments in
Summary of AHRQ’s Comparative Effectiveness Review of Treatment to Prevent Fractures in Men and Women with Low Bone Density or Osteoporosis: Update of the 2007 Report

<table>
<thead>
<tr>
<th>TABLE 4</th>
<th>Impact of Risk Factors on the Efficacy of Treatment for Fracture Risk Reduction – Key Question 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basis for Risk of Fracture</td>
<td>Strength of Evidence</td>
</tr>
<tr>
<td>Age</td>
<td>High</td>
</tr>
<tr>
<td>BMD</td>
<td>Moderate</td>
</tr>
<tr>
<td>Low to Moderate</td>
<td>Risedronate reduces risk of fragility fracture among postmenopausal women with osteopenia who do not have prevalent vertebral fractures.</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Moderate to High</td>
</tr>
<tr>
<td>Insufficient</td>
<td>Limited and inconclusive data on the effect of agents for prevention and treatment of osteoporosis on transplant recipients and patients treated with chronic corticosteroids.</td>
</tr>
<tr>
<td>FRAX score</td>
<td>Moderate</td>
</tr>
<tr>
<td>High</td>
<td>Alendronate, ibandronate, risedronate, teriparatide, raloxifene, zoledronic acid, and denosumab reduce the risk of fractures among high risk groups including postmenopausal women with osteoporosis.</td>
</tr>
<tr>
<td>Prevalent fractures</td>
<td>Moderate</td>
</tr>
<tr>
<td>Insufficient</td>
<td>Prevalent fractures increase the relative efficacy of teriparatide in preventing fractures.</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td>High</td>
</tr>
<tr>
<td>Insufficient</td>
<td>Inconclusive evidence on the effects of renal function on the efficacy of alendronate, raloxifene, and teriparatide in preventing fractures.</td>
</tr>
<tr>
<td>Sex</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>


BMD = bone mineral density; FRAX = World Health Organization Fracture Risk Assessment Tool; MORE = Multiple Outcomes of Raloxifene Evaluation.

Fracture risk reduction included assessment by BMD, FRAX or other fracture risk score, prior fractures, age, sex, race/ethnicity, glucocorticoid use, and other factors such as vitamin D deficiency and community dwelling versus institutionalization.6 Postmenopausal women are a high-risk group for fractures and the strength of evidence was high for all drugs in the reduction of fracture risk in this group.

Bone mineral density, considered an accurate measure of bone health, was an obvious risk factor addressed in this review. Investigators noted that available evidence for this factor was moderate, with effects appearing to be site specific (e.g., BMD did not predict vertebral and nonvertebral fractures in postmenopausal women with low femoral neck BMD treated with alendronate for 5 years).13 Among women with osteopenia but without prevalent vertebral fractures, low-abdominal exercise showed a significant reduction in risk of fragility fracture for risendronate therapy.14

FRAX test results did not predict the reduced risk of overall clinical fractures or vertebral fractures in elderly women in response to raloxifene treatment.5 Effectiveness did increase among younger women with lower fracture risk. These findings were supported by moderately strong evidence.

The evidence did not support a correlation between prior prevalent fractures and a decrease in fracture risk with alendronate and raloxifene, but there was moderate evidence of greater relative efficacy with teriparatide treatment.13 Fracture reduction among high risk groups treated with the bisphosphonates, teriparatide, raloxifene, as well as denosumab was supported with a high strength of evidence.5,6

For patients treated with corticosteroids, the evidence was graded moderate-to-high that fracture risk is reduced with alendronate, risedronate, or teriparatide. Moderate strength evidence from 2-year follow-up in a large RCT of postmenopausal women with osteopenia and no prevalent fractures showed that risedronate significantly reduced the risk of fragility fracture, comparable to the reduction in fracture risk for women with osteoporosis.13 Furthermore, evidence was insufficient to establish that treatment with glucocorticoids had an effect on the response to osteoporosis therapies.

Many of the studies included in the review addressed the issue of age and sex for osteoporotic fracture risk. Indeed, there was high strength of evidence for similar effects of bisphosphonates and teriparatide in all age groups.15,16 The evidence was graded high strength for lack of a correlation between age and a decreased risk for vertebral or nonvertebral fractures after risendronate or zoledronic acid treatment. Although zoledronic acid decreased the risk of hip fracture among women younger than age 75, these studies were not powered to detect differences by age group.15
The FDA has approved some of the therapies evaluated in the AHRQ review for use by men. However, the reviewers identified only 1 RCT that compared the effect of sex on the response to treatment, and therefore graded as insufficient the evidence from this RCT that calcium and vitamin D3 decreased the risk of fracture in elderly women but not in elderly men.

Differences in response to treatment according to race or ethnicity were also evaluated as is common in analyses of population subgroups. Although they found high strength of evidence for decreased vertebral fractures specifically among Asian women treated with raloxifene, these findings were similar to that of U.S. and other international populations.

The evidence was graded insufficient at the time of this AHRQ review to assess the effect of renal function on the efficacy of therapies except treatment with zoledronic acid, in which impaired renal function reduced the efficacy of zoledronic acid in preventing vertebral (but not hip or other nonvertebral) fractures.

**Treatment Adherence and Persistence in the Prevention of Osteoporosis and Risk of Fractures – Key Question 3**

Adherence and persistence were defined in the CER based on the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) criteria. Adherence (or compliance) is “the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen.” Adding to this definition, the reviewers indicated that adherence to specific dosing instructions is considered an important component of adherence because proper dosing is widely accepted as an important determinant of efficacy. Persistence is defined as “the duration of time from initiation to discontinuation of therapy.” In general, the extent to which a patient’s behavior may correspond to the health care provider’s recommendations is described as adherence. The 2007 AHRQ review concluded that data from observational studies generally show “poor adherence with osteoporotic medications,” and “poor adherence was associated with lower effectiveness.”

To answer Key Question 3 in the 2012 AHRQ update, 18 RCTs, 59 observational studies, and 2 systematic reviews were evaluated. As in the 2007 review, except for the controlled environments of RCTs, adherence and persistence are poor with osteoporotic medications in the real-world situations such as in observational studies where adherence rates vary widely. Analysis showed that less than one-half of the patients achieved a medication possession ratio over 80%, with generally poor adherence found in the studies that included alendronate, etidronate, risendronate, calcitonin, menopausal hormone therapy, raloxifene, and calcium or vitamin D.

Persistence also describes the continuance of a prescribed therapy for the recommended time or duration of treatment. In the 2007 report, persistence varied to a similar extent as adherence with discontinuation rates at 1 year of treatment ranging from 14% to 84%. Many of the studies evaluated were observational, and the authors commented that both adherence and persistence were poor among these studies. In clinical trials conducted in the United States, a wide range of adherence was reported and about one-half of patients were persistent with osteoporosis treatment at 1 year.

A wide range of adherence measurements were reported from studies of different osteoporosis treatments. The difference among observational studies and clinical trials may be due to the trend for higher adherence in clinical trials compared to other settings. Adherence rates in RCTs may not reflect adherence in the real-world where the patients are not monitored as they are in a clinical trial. This point was emphasized in the 2012 report since most prior reviews on adherence and persistence to medications for osteoporosis have excluded randomized trials specifically for that reason. The present review found that overall rates for both adherence and persistence closely reflect the rates reported in the previous CER and prior systematic reviews.

In 6 studies of both adherence and persistence, drug discontinuation was defined by either a gap of 30 days or greater between refills, a gap of 60 days, or of more than 90 days, or was defined as patient self-reported cessation in taking medication for more than 1 month. These methods resulted in different number of days of persistence at 12 months. Fewer than half of the patients were still persistent at 12 months in studies of bisphosphonate use based on pharmacy claims data, and the persistence for teriparatide in particular was 56.9%. A study that combined the 2 measures, both adherence and persistence, found 55% of individuals still on the medication with a proportion of days covered (PDC) over 60% at 1 year. PDC is a measure in which pharmacy fills are used to determine what proportion of all days within a specified time period a patient had enough medication, and the percentage of doses taken as prescribed, which is the percentage of prescribed doses taken as directed by the patient during a specified time.

A study of more than 200,000 health plan members found that 56% of weekly bisphosphonate users and 40% of daily users were persistent at 1 year when persistence was defined as filling at least 1 day of medication each month. Another study based on self-reporting by the patients found a rate of persistence of 66% at 1 year. Another very large study of 166,000 patients relied on data from the Information Management System (IMS) database. In this analysis, mean 1-year persistence was 116 days for weekly alendronate, 113 days for weekly risendronate, and 98 days for monthly ibandronate. About one-half of all individuals in this study persisted with the medication after their first prescription (gap of less than 30 days). Descriptions of potential barriers to adherence appear in the literature with a frequency that may not be representative of...
their importance. The most common barriers assessed in studies included the review were age, prior history of fracture, dosing frequency, concomitant use of other medications, and adverse effects of medications. Age, history of fracture, and number of concurrent medications do not appear to factors that influence persistence or adherence. A high strength of evidence shows that weekly dosing is associated with higher adherence than daily dosing regimens, but there is insufficient evidence that monthly regimens are associated with higher adherence compared with weekly regimens. Adverse effects and concerns about adverse effects are important predictors of adherence and persistence. A systematic review and data from 15 of 17 observational studies provide a moderate strength of evidence that adverse effects from bisphosphonates are associated with decreased adherence and increased risk of fracture (vertebral or nonvertebral or both).

### Variance of Short- and Long-Term Adverse Effects of Therapies on Specific Subpopulations – Key Question 4

Many patients at risk for low bone density or osteoporosis are treated for years to reduce the risk of fractures or progression of the disease. Short and long-term adverse effects for the therapies discussed so far have been variable, but the investigators further assessed potential differences among some specific subpopulations (Table 5).

Regarding cardiovascular adverse effects, the evidence was graded low strength for an increased risk of acute coronary syndrome, including myocardial infarction, in patients taking calcium compared with placebo. The evidence was graded insufficient for an increased risk of atrial fibrillation with bisphosphonates or zoledronic acid, but the FDA maintains surveillance of zoledronic acid following a 2007 safety review, including a request from the FDA in March 2010 for providers

<table>
<thead>
<tr>
<th>Strength of Evidence</th>
<th>Therapy</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alendronate</td>
<td>Pooled analyses showed alendronate had a slightly increased risk of “mild upper GI events” (e.g., acid reflux, esophageal irritation, nausea, vomiting, and heartburn). Alendronate participants also had higher odds of mild upper GI events in head-to-head trials versus menopausal hormone therapy. Pooled analysis also showed alendronate users to be at increased risk for mild GI events compared with denosumab.</td>
</tr>
<tr>
<td></td>
<td>Raloxifene</td>
<td>Participants who took raloxifene showed higher odds for pulmonary embolism than did participants who took a placebo. Raloxifene participants also had greater odds of thromboembolic events. A pooled analysis of 10 trials found increased risk for myalgias, cramps, and limb pain.</td>
</tr>
<tr>
<td></td>
<td>Estrogen and estrogen-progestin</td>
<td>A pooled analysis of 8 trials found increased risk of hot flashes.</td>
</tr>
<tr>
<td></td>
<td>Denosumab</td>
<td>Denosumab was associated with an increase in mild GI events. A pooled analysis of 4 trials of denosumab found an increased risk of rash but no increase in the risk for injection-site reactions. A pooled analysis of 4 trials found an increased risk for infection.</td>
</tr>
<tr>
<td></td>
<td>Bisphosphonates</td>
<td>One trial, 1 post hoc analysis of 3 trials, 2 large observational studies, and a review of 2,408 cases of osteonecrosis of the jaw in patients taking bisphosphonates for osteoporosis prevention or treatment found that the incidence of osteonecrosis of the jaw in this group was small, ranging from less than 1-28 cases per 100,000 person-years of treatment.</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alendronate</td>
<td>A small number of clinical trials reported an increased risk of hypocalcemia in patients treated with alendronate</td>
</tr>
<tr>
<td></td>
<td>Teriparatide</td>
<td>Teriparatide-treated participants showed a significant increase in hypercalcemia. A pooled analysis of 3 trials of teriparatide found an increased risk of headaches.</td>
</tr>
<tr>
<td></td>
<td>Zoledronic acid</td>
<td>A small number of clinical trials reported an increased risk of hypocalcemia in patients treated with zoledronic acid.</td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Calcium</td>
<td>New systematic review of 15 placebo-controlled trials of calcium (administered for bone health in all trials but one) identified a statistically significant increase in the risk of myocardial infarction; however serious concerns have been expressed about possible bias.</td>
</tr>
<tr>
<td></td>
<td>Bisphosphonates</td>
<td>Limited data from clinical trials and observational studies support a possible association between bisphosphonate use and atypical subtrochanteric fractures of the femur. Data are not consistent, nevertheless these data were sufficient for FDA to issue a Warning regarding this possible adverse event.</td>
</tr>
<tr>
<td></td>
<td>Denosumab</td>
<td>A pooled analysis of 4 trials of denosumab found an increased risk of infection.</td>
</tr>
<tr>
<td></td>
<td>Alendronate</td>
<td>A pooled analysis of 4 trials found an increased risk for infection.</td>
</tr>
<tr>
<td></td>
<td>Teriparatide</td>
<td>A pooled analysis of 4 trials of teriparatide found an increased risk of injection-site reactions.</td>
</tr>
<tr>
<td><strong>Insufficient</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Calcium</td>
<td>The literature is equivocal on the potential association between bisphosphonates and the use of oral bisphosphonate is associated with an increased risk of esophageal cancer had mixed findings.</td>
</tr>
</tbody>
</table>


FDA = U.S. Food and Drug Administration; GI = gastrointestinal.
and patients to report treatment side effects in order to gather more data on the potential risk for atrial fibrillation.

There was a high strength of evidence for increased risk of pulmonary embolism and thrombotic events with raloxifene compared with placebo, raising the level of concern about the safety of raloxifene and the need for additional studies to evaluate the consequences of long-term treatment. A pooled analysis of 8 clinical trials produced high strength evidence that raloxifene increases the risk of hot flashes.

Teriparatide therapy includes some warnings from the FDA, so evidence was reviewed for the risk of adverse events during this treatment. The 2007 report contained 2 placebo-controlled trials that reported lower odds of cancer for the teriparatide groups. The incidences for osteosarcomas and other specific cancers were not reported in these studies, and no new trials were reported in the update. Pooled analysis of 3 placebo-controlled trials found a significant increase (OR = 12.9, 95% CI = 10.49-16.00) in hypercalcemia for teriparatide treatment compared with placebo.

In review of the data for gastrointestinal adverse effects, the evidence was graded insufficient to establish increased risk of esophageal cancer with bisphosphonates. A high strength of evidence showed increased risk of “mild” upper gastrointestinal events (acid reflux, esophageal irritation, heartburn, nausea and vomiting) for alendronate compared with placebo and in head-to-head trials compared with menopausal estrogen therapy.

There was high strength of evidence for a small increased risk of osteonecrosis of the jaw with bisphosphonates. A high strength of evidence showed increased risk of “mild” upper gastrointestinal events (acid reflux, esophageal irritation, heartburn, nausea and vomiting) for alendronate compared with placebo and in head-to-head trials compared with menopausal estrogen therapy. There was high strength of evidence for increased risk of atypical fragility fractures of the femur. On October 13, 2010, the FDA updated the risk for atypical fractures on bisphosphonate product labels to the level of “low concern” for women and children at risk for osteoporosis. There was strong evidence that greater increases in BMD did not predict greater reduction in risk of vertebral fracture, there was strong evidence that greater increases in BMD did not predict greater reduction in the risk of osteoporotic fractures. Therefore, improvement in spine BMD during osteoporosis treatment accounted for only a small portion of the decreased risk of vertebral fractures. There was also strong evidence for a decrease in vertebral fracture risk in women who lost femoral neck BMD during teriparatide therapy.

Monitoring of BMD is a common practice in managing osteoporosis since it provides a quantitative measure of changes in the bone mineral content. AHRQ reviewers evaluated the frequency of BMD monitoring during the time that patients were being treated. Since these are long-term therapies, there is interest in the antifracture benefits of serial BMD measurements during pharmacotherapy and the predictive ability of monitoring for antifracture effects of any particular agent. Conclusions regarding the effects of BMD monitoring during the treatment of osteoporosis on outcomes were precluded due to the lack of evidence as there have been no randomized clinical trials evaluating this question. Systematic reviews conducted previously during treatment with antiresorptive drugs or among patients treated with calcium and vitamin D found that numerous additional factors were responsible for any observed risk reductions.

There is no evidence from RCTs to guide how often BMD should be monitored during osteoporosis therapy, and there was a “high level of evidence” from RCTs that serial BMD monitoring of the lumbar spine and femoral neck contributed little or nothing to prediction of the change in fracture risk from treatment with the antiresorptive agents, including alendronate, risedronate, raloxifene, and teriparatide. Although the data from RCTs showed that patients who lost BMD during antiresorptive therapy benefited from substantial reduction in risk of vertebral fracture, there was strong evidence that greater increases in BMD did not predict greater reduction in the risk of osteoporotic fractures. Therefore, improvement in spine BMD during osteoporosis treatment accounted for only a small portion of the decreased risk of vertebral fractures. There was also strong evidence for a decrease in vertebral fracture risk in women who lost femoral neck BMD during teriparatide therapy.

Studies comparing short-term therapy to long-term therapy (defined as 5 years or more) with the same agent were not available. This lack of availability restricted the scope of the review findings. Long-term treatment outcomes demonstrated moderate strength of evidence that continuous alendronate therapy for a period of 10 years decreased risk of vertebral fracture to a greater extent than continuous use for only 5 years.

Limitations and Future Research Directions

Investigators for the EPC mentioned some limitations of the review which may restrict the extent to which results can be applied in the treatment of osteoporosis. Methodological and study design limitations were discussed for all of the key questions included in the review. The reviewers also noted that there were little data concerning the efficacy and comparative effectiveness between different agents.
Conclusions

The 2012 report updated the 2007 systematic review on the effectiveness and safety of treatments to prevent fractures in persons with low bone density or osteoporosis with the objective of including drug therapies introduced after the 2007 report and to assess whether monitoring helps to identify persons most likely to benefit from treatment and the benefits of long-term treatment. As in the previous review, the 2012 update found a high level of evidence that fracture risk reduction is greatest in women who have been diagnosed with osteoporosis and/or have prevalent fractures; diagnosis relied on established osteoporosis, because of an existing fracture or a T-score of less than –2.5. The findings on treatment efficacy showed that alendronate, risendronate, and zoledronic acid reduced the risk of vertebral, nonvertebral, and hip fractures in this population. Ibandronate therapy had similar effects with the exception of lack of efficacy in reducing the risk of hip fractures. There is a low to moderate level of evidence for fracture risk reduction in postmenopausal women with osteopenia and without prevalent fractures. There is a low level of evidence to support treatment in other populations including men. There is little if any evidence to support monitoring BMD, and a low level of evidence for the benefits and risk of long-term therapy.

Among postmenopausal women with osteoporosis, alendronate, risedronate, zoledronic acid, denosumab, and teriparatide reduce the risk of vertebral and nonvertebral fractures; ibandronate and raloxifene reduce the risk of vertebral but not nonvertebral fractures. In postmenopausal women with osteoporosis, the risk of hip fractures is reduced by alendronate, risedronate, zoledronic acid, and denosumab. In men with osteoporosis, risedronate reduces the risk of vertebral and nonvertebral fracture. While the available evidence supports these conclusions regarding fracture risk reduction for these therapies, there are few head-to-head studies and insufficient evidence to support the superiority of one bisphosphonate over another. Moderate evidence from 6 RCTs shows no difference in fracture incidence between bisphosphonates and menopausal hormone (estrogen) therapy.

Conclusions regarding the factors that may affect adherence to treatment were difficult to derive based on the “mixed” evidence. Dosing frequency, side effects, knowledge about osteoporosis, and cost affect adherence, but age, prior history of fracture and use of concomitant medication do not appear to have an independent effect on adherence. Adverse effects, even mild effects such as gastrointestinal complaints, and concerns about adverse effects predict low adherence and persistence. Adherence is improved with weekly compared to daily regimens, but there is insufficient evidence to show that adherence is improved with monthly compared to weekly regimens. Adherence is poor with drug therapy for osteoporosis, about one-half of patients appeared to be persistent at 1 year, but...
rates of adherence and persistence vary widely across studies.

In addition to drug therapy, weight-bearing exercise and dietary and supplemental calcium and vitamin D help preserve bone mass. No evidence was found to guide BMD monitoring during osteoporosis therapy, and changes in BMD explained little or only a small part of the change in fracture risk. The use of various tools such as the WHO FRAX may be of use in the selection of candidates for osteoporosis treatment to enhance efficacy. Evidence is still needed on ways to increase adherence and persistence to osteoporosis medications. There is a high strength of evidence that alendronate,ibandronate, risendronate, teriparatide, raloxifene, zoledronic acid, and denosumab reduce the risk of fractures among high-risk groups including postmenopausal women with osteoporosis.

Commentary: Managed Care Perspective on Comparative Effectiveness Research on Treatments to Prevent Fractures in Low Bone Density or Osteoporosis

Approximately 52 million men and women in the United States have osteoporosis or low bone density (osteopenia) which, unfortunately, leads to an increased risk of fractures. Low bone density and osteoporosis lead to significant increases in health care costs and utilization largely due to associated fractures. In fact, the direct costs of osteoporotic fractures were estimated to be over $18 billion in 2010. Additionally, fractures lead to an increased risk of mortality and are associated with significant decreases in productivity and quality of life. While the majority of fractures and costs are incurred by individuals over the age of 65, postmenopausal working women under 65 are also at an increased risk of osteoporosis. Fortunately, the risk factors for fractures are well-documented and the Fracture Risk Assessment Tool (FRAX) available from the World Health Organization provides an estimate of the 10-year risk of osteoporotic fractures. Managed care can play a significant role in the prevention of fractures by ensuring adequate treatment in at-risk members and promoting medication adherence and persistence. However, there are a number of treatments that have demonstrated efficacy in reducing fractures and thus it is important to know the comparative effectiveness of the available treatments. The Agency for Healthcare Research and Quality has thus released the 2012 update to a previous comparative effectiveness review of treatment and prevention of fractures in patients with low bone density or osteoporosis.

One of the key questions of the review was to compare the fracture reduction among osteoporosis treatments. The review found that alendronate, risendronate, zoledronic acid, and denosumab all had high strength of evidence showing a decreased risk of vertebral, nonvertebral, and hip fractures. However, there was insufficient evidence from head-to-head trials to indicate superiority of one treatment over another. Another key question in the review was to examine the rates of, factors affecting, and impact on fracture rates of medication persistence and adherence. Observational studies included in the review found that adherence and persistence to osteoporosis treatments are poor. While adherence varied widely, overall only about 50% of patients were considered persistent after 1 year of treatment. As expected, the review also identified that patients with decreased adherence to treatments had an increased risk of fracture. Evidence also showed once weekly dosing regimens have improved adherence compared to daily regimens, but not enough evidence was found to determine if monthly regimens have better adherence than weekly regimens. Barriers to adherence also included side effects, knowledge about osteoporosis, comorbidities, and medication cost.

These 2 components of the comparative effectiveness review provide valuable information to managed care organizations that can readily be used in making access and formulary decisions. Consideration should be given to prioritizing treatments with high strength of evidence indicating reduction in vertebral, nonvertebral, and hip fractures when making coverage decisions. Providing improved access to these treatments should ultimately provide the broadest protection to patients while reducing the cost of fractures to the organization. Unfortunately, head-to-head trial data are insufficient to recommend 1 specific treatment over the others. Additional consideration should be given to prioritizing treatments with reduced dosing frequencies, such as once weekly dosing. These dosing frequencies were associated with better adherence than daily dosing schedules and better adherence was associated with a decreased risk of fractures. Improving access to these treatments should also lead to better patient outcomes and reduced fracture costs. Fortunately, many osteoporosis treatments are available with alternative dosing schedules. This information further highlights the need for comprehensive pharmacoeconomic analyses of these 4 osteoporosis treatments (alendronate, risendronate, zoledronic acid, and denosumab) to guide formulary decisions in the United States. Alendronate is currently the only treatment with a high strength of evidence for reducing vertebral, nonvertebral, and hip fractures, with once weekly dosing, and it is available as a generic. Thus, alendronate is well-suited to be a reference treatment for pharmacoeconomic analyses and may be given preference on formularies in the absence of such data. Finally, as persistence and adherence are particularly important with treatment, the review identifies potential barriers to adherence that may be addressed by managed care organizations through patient management and education.

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REFERENCES


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