Comparative Effectiveness Review
Number 53

Effective Health Care Program

Treatment To Prevent Fractures in Men and Women With Low Bone Density or Osteoporosis: Update of a 2007 Report

Executive Summary

Background

Osteoporosis is a systemic skeletal disease characterized by decreasing bone mass and microarchitectural deterioration of bone tissue, with consequent increases in bone fragility and susceptibility to fracture.[1] In addition to fractures, the clinical complications of osteoporosis include disability and chronic pain. Approximately 52 million people in the United States are affected by osteoporosis or low bone density. It is especially common in postmenopausal women,[2] but one in five men will experience an osteoporosis-related fracture at some point in his lifetime.[3]

The economic burden of osteoporosis is large and growing: the most recent estimate of U.S. annual costs due to fractures alone have been nearly $20 billion.[2] A recent projection of the burden and costs of incident osteoporosis-related fractures in the United States from 2005 to 2025 estimates more than 2 million fractures in 2010, with direct medical costs of more than $18 billion (more than 25 percent attributable to men).[4] Although the bulk of these costs are incurred by individuals 65 and older, direct costs and productivity loss among working women under 65 are considerable.[2]

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at **www.effectivehealthcare.ahrq.gov/reports/final.cfm**.

Target audience. This report is intended for health care decisionmakers—patients and clinicians, health system leaders, and policymakers.

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Effective Health Care

Diagnosis and Risk Factors

The clinical diagnosis of osteoporosis may be based on results of bone mineral density (BMD) measurement with dual energy x-ray absorptiometry (DXA).[3,5,6] In postmenopausal women and men over 50 years of age, BMD is classified according to the T-score. The T-score is the number of standard deviations above or below the mean for healthy 20- to 29-year-old adults, as determined by DXA. Osteoporosis is defined as a T-score of -2.5 or less.3,6 A T-score between -2.5 and -1.0 is defined as "low bone density." A T-score of -1 or greater is considered normal. Bone density can also be classified according to the Z-score, the number of standard deviations above or below the expected BMD for the patient's age and sex. A Z-score of -2.0 or lower is defined as either "low BMD for chronological age" or "below the expected range for age," and those above -2.0 are "within the expected range for age." Individuals who have already had minimal trauma fracture are at increased risk of future osteoporotic fracture, independent of BMD.[3] Because the majority of fractures occur in patients with low bone mass rather than osteoporosis,3 risk scores that combine clinical risk factors with BMD testing results, such as FRAX® (World Health Organization Fracture Risk Assessment Tool), have recently been developed to refine the ability to predict fracture risk among people with low bone density.

Risk factors for osteoporotic fracture include (but are not limited to) increasing age, female sex, postmenopause for women, hypogonadism or premature ovarian failure, low body weight, history of parental hip fracture, ethnic background (whites are at higher risk than blacks), previous clinical or morphometric vertebral fracture, previous fracture due to minimal trauma (i.e. previous osteoporotic fracture), rheumatoid arthritis, current smoking, alcohol intake (3 or more drinks/day), low BMD, vitamin D deficiency, low calcium intake, hyperkyphosis, falling, and immobilization, along with chronic use of certain medications, the most commonly implicated being glucocorticoids (GC), anticoagulants, anticonvulsants, aromatase inhibitors, cancer chemotherapeutic drugs, and gonadatropin-releasing hormone agonists.[3]

Several algorithms have been devised and validated for the prediction of osteoporotic fracture risk. Current National Osteoporosis Foundation guidelines as well as others endorse the use of the FRAX to select candidates for treatment.[7-9] The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women.[9,10] FRAX is a set of race- and nationality-specific algorithms that take into account an individual's age, sex, weight, height, previous fracture, parental history of osteoporotic fracture, smoking status, alcohol use, history of use of glucocorticoids, history of rheumatoid arthritis, secondary causes of osteoporosis, and femoral neck BMD to estimate the absolute 10-year risk of major osteoporotic fractures (i.e., clinical vertebral, hip, forearm, or proximal humerus fractures). Risk for osteoporosis may be viewed as a continuum that depends on all of these factors. A question of considerable interest is whether antifracture response to treatment is affected by (or predicted by) FRAX score.[3,11]

Therapy

The most recent National Osteoporosis Foundation Clinician's Guide recommended considering therapy for postmenopausal women and men aged 50 and older presenting with the following: a hip or vertebral (clinical or morphometric) fracture; T-score ≤ -2.5 at the femoral neck or spine after appropriate evaluation to exclude secondary causes; low bone mass (T-score between -1.0 and -2.5 at the femoral neck or spine) and a 10-year probability of a hip fracture ≥ 3 percent or a 10-year probability of a major osteoporosis-related fracture ≥ 20 percent based on the U.S.-adapted World Health Organization (WHO) algorithm.[3]

The increasing prevalence and cost of osteoporosis have heightened interest in the effectiveness and safety of the many interventions currently available to prevent osteoporotic fracture. These interventions include pharmacologic agents, a biological agent, dietary and supplemental vitamin D and calcium, and weight-bearing exercise.

Pharmacologic agents include the bisphosphonate class of drugs, peptide hormones (parathyroid hormone and calcitonin), estrogen (in the form of menopausal hormone therapy) for postmenopausal women, and selective estrogen receptor modulators (raloxifene for postmenopausal women). With the exception of parathyroid hormone, each of these agents acts to prevent bone resorption. Once-daily administration of teriparatide stimulates new bone formation on trabecular and cortical periosteal and/or endosteal bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity. The bisphosphonates are compounds that bind reversibly to mineralized bone surfaces and disrupt resorption by the osteoclasts.

A newer therapeutic agent, denosumab, was approved by the Food and Drug Administration (FDA) in June 2010. Denosumab is a monoclonal antibody that inhibits the Receptor Activator of Nuclear factor Kappa-B Ligand (RANKL), a stimulator of osteoclast differentiation and activation. By inhibiting osteoclast formation, function, and survival, denosumab decreases bone resorption. Although denosumab is classified by the FDA as a biological agent, it will be considered a pharmacological agent for the purposes of this report.

Besides pharmacologic agents, dietary and supplemental calcium and vitamin D, as well as weight bearing exercise, play important roles in preserving bone mass.[3] Lifelong calcium intake is required for the acquisition of peak bone mass and for the subsequent maintenance of bone health. When serum calcium levels are inadequate, bone tissue is resorbed from the skeleton to maintain serum calcium at a constant level. Adequate vitamin D levels play a key role in calcium absorption, bone health, muscle performance, balance, and fall prevention.[3]

The various agents used to prevent and treat osteoporosis have been linked with a range of adverse effects, from the more common, mild effects (such as minor gastrointestinal complaints) to potentially serious issues. Some evidence suggests that these minor complaints, coupled with concerns about more serious effects, may affect the level of compliance with and persistence of treatment. Poor adherence and persistence may, in turn, affect the effectiveness of the treatments. These issues form the scope of this report and its predecessor.

The FDA Approval Process

In 1979, the FDA published its first Guidance Document for the clinical evaluation of the safety and effectiveness of drugs to treat osteoporosis.[12] From the outset, the FDA acknowledged certain difficulties, including quantitative assessment of skeletal bone, the inexact relationship between bone mass and fracture risk, and the study size and duration needed to detect changes in bone density and/or fracture risk. Patient inclusion criteria for FDA clinical trials consisted of objective evidence of disease (i.e., history of an osteoporosis-related fracture) or the less objective criterion of low bone mass, as determined by any one of six methods, all imperfect. In an effort to ease the process of trial implementation, the Guidance Document, rather than requiring evidence of significant decrease in fracture risk, permitted effectiveness to be defined as improvement in bone mass during therapy if the process of new bone formation could be demonstrated to be normal. If new bone formation did not prove normal or if it was not possible to determine normalcy, fracture studies would be required.

The 1984 Guidance Document included several noteworthy changes. It recommended studies that would establish an indication for the prevention of postmenopausal osteoporosis. In addition, it described DXA as providing a valid measure of spinal bone mass, and it recommended that all participants in trials of agents for osteoporosis therapy be supplemented with calcium and vitamin D.

Operating under the initial Guidance Document—which did not require demonstration of fracture risk reduction—calcitonin was approved as an injectable drug for the treatment of osteoporosis in 1984, conditional upon the initiation and eventual completion of a trial to assess fracture risk. Calcitonin is a peptide hormone synthesized in the thyroid. It participates in the physiological regulation of calcium and phosphorus; it had previously been approved for the treatment of Paget's disease (a disease characterized by abnormal bone remodeling). Upon completion of the study, it became apparent that enrollment and retention of patients in this fracture trial was problematic, and the fracture reduction effect of calcitonin remained in doubt. In the early 1990s, the Prevent Reoccurrence of Osteoporotic Fracture (PROOF) trial tested the ability of a nasally administered form of calcitonin (100, 200, and 400 IU) to prevent fracture. Although fracture prevention was seen with 200 IU, none was seen at the higher or lower dose. This lack of dose-related response, combined with a lack of effect on BMD, suggested either that the positive effect of the 200 IU dose was an experimental artifact or that BMD and fracture risk are not well correlated. Nevertheless, the drug is still widely prescribed.

During the 1980s, two additional agents—sodium fluoride (NaF) and the bisphosphonate (see below) etidronate—were evaluated for the treatment of osteoporosis under the initial Guidance Document, which did not require fracture risk reduction. Although both agents increased bone density significantly when tested in large-scale trials of postmenopausal women, evidence suggested that neither agent reduced the risk for vertebral fracture and that at least one (NaF) may have increased fracture risk. Based on this experience, the Osteoporosis Guidance Document was updated again in 1994 to include the

following requirements for approval of a new drug to treat postmenopausal osteoporosis: (1) demonstration that treatment resulted in preservation or improvement in bone density while retaining normal bone quality* in preclinical studies with two laboratory animal species, including an ovariectomized rat model; (2) normal bone quality in a subset of clinical trial participants; (3) significant increase in BMD; and (4) at least a trend toward decreased fracture risk after three years (up from two years) of treatment. The 1994 Guidance Document also affirmed the use of DXA and bone turnover markers for phase I and II trials and provided requirements for approval of agents for prevention of osteoporosis (in individuals at high risk but without history of osteoporotic fracture).[13] It stipulated that only agents that have already been approved for treatment of osteoporosis can be approved for prevention. It suggested further that, for prevention, BMD may serve as an appropriate—and sufficient—outcome measure for efficacy in double-blind randomized controlled trials (RCT) of at least 2 years' duration with multiple dosage arms (to establish a minimum effective dose). The guidance also provided recommendations for the appropriate sample population.

Based on extensive data from observational studies (of estrogen as used to treat menopausal symptoms), estrogen was approved for treatment of postmenopausal osteoporosis. Thus, it was exempted from the requirement that it demonstrate effectiveness for fracture prevention, and was approved for both treatment and prevention based on BMD alone. Subsequently, however, the FDA has required evidence of effectiveness in preventing fracture for approval of selective estrogen receptor modulators (SERMS). In 1997, the first SERM, raloxifene, was approved. The bisphosphonate alendronate was the first nonestrogenic agent to be evaluated and approved for treatment of postmenopausal osteoporosis. In 2004, the FDA began soliciting comments on the 1994 Guidance Document in preparation for its revision. Two issues of particular interest were the continued use of placebo (as opposed to active) controls (an issue with both ethical and technical implications) and the minimum acceptable duration for treatment trials.

Thus, not all drugs currently approved for treatment of osteoporosis were required to demonstrate reduction in fracture risk (e.g., calcitonin). With the exception of estrogen products, all agents approved for prevention of osteoporosis have demonstrated fracture reduction, as they were approved first for osteoporosis treatment. Further, approval of an indication for a different dose, frequency, or route of administration does not require demonstration of reduced fracture risk. (However, approval for a different indication, such as glucocorticoid-induced osteoporosis, does require demonstration of reduction in fracture risk.) These implications of the current guidance have heightened interest in evaluating the effectiveness data for drugs approved to treat and prevent osteoporosis.

In December 2007, the Evidence-based Practice Center (EPC) completed the first Comparative Effectiveness Review (CER) on the efficacy/effectiveness of these interventions in preventing osteoporosis-related fracture, their safety, and compliance with their use.[14]

The review found a high level of evidence suggesting that, compared with placebo, alendronate, etidronate, ibandronate, risedronate, zoledronic acid, estrogen, a fragment of parathyroid hormone (PTH) that contains the first 34 of 84 amino acids (referred to as PTH [1-34] or teriparatide), and raloxifene prevent vertebral fractures; the evidence for calcitonin compared with placebo was fair. The report also found a high level of evidence to suggest that alendronate, risedronate, and estrogen prevent hip fractures, compared with placebo; the evidence for zoledronic acid was fair. No studies were identified that assessed the effect of testosterone on fracture risk. The evidence for an effect of vitamin D on both vertebral and hip fractures varied with dose, analogue, and study population. No antifracture evidence was available for calcium or physical activity.

Further, the evidence was insufficient to ascertain the relative superiority of any agent or to determine whether the agents were more effective in some populations than others.

Regarding adverse events associated with the pharmacologic agents, raloxifene, estrogen, and combined estrogen-progestin increased the risk for thromboembolic events, and etidronate increased the risk for esophageal

* The FDA recognizes that components of bone strength include bone mineral density and bone quality; some aspects of bone quality that might affect fracture risk have been identified but are difficult to measure. Nevertheless, the requirements for approval specify that drugs must not result in accretion of new bone (or preservation of existing bone) with abnormal morphology.

ulcerations and gastrointestinal perforations, ulcerations, and bleeding. The use of menopausal hormone therapy was associated with an increased risk of breast cancer, heart disease, and stroke in the Women's Health Initiative, a 15-year trial sponsored by the National Heart, Lung, and Blood Institute, that enrolled and tracked more than 150,000 women; the trial comprised an observational study of the effects of postmenopausal hormone therapy and a clinical trial of the effects of dietary modification on cardiovascular disease, cancer, bone health, and other clinical conditions. Clinical trials reported mixed findings regarding an association of zoledronic acid with the risk for atrial fibrillation. No data were found from osteoporosis trials to suggest an association between bisphosphonates or any other agents and the development of osteonecrosis: A number of case reports and case series articles reported osteonecrosis of the jaw in cancer patients taking intravenous bisphosphonates.

Although fracture trials that reported data on adherence/compliance tended to find relatively good adherence to medication use, observational studies tended to report poor adherence with osteoporotic medications, as with other chronic conditions. Poor adherence was associated with lower effectiveness.

Scope and Key Questions

Since the release of the original report, several of the bisphosphonates have become available in new, less frequently administered, forms, and a new biological agent, denosumab, is now available. In addition, new data have been released on adverse events associated with bisphosphonates. Thus, in 2008, the EPC was asked to conduct an assessment of the need to update the original report (as well as the other CER reports released up to that time point); this report was submitted in March 2009.[15] For this report, the EPC conducted an abbreviated search and review of the literature addressing the topics of the first review. The abbreviated search consisted of a survey of experts in the field and a Medline® search (using the same search terms as the original report) of 5 of the leading medical journals and 5 leading specialty journals dating from 2006 to mid-2008. The studies identified in this search that addressed the Key Questions of the original report were reviewed and abstracted, and their findings qualitatively assessed using a process devised by the EPC to determine whether they confirmed, contradicted, or augmented the conclusions of the original report.

The update search identified new data on effectiveness and adverse effects. New studies were found for several agents, including denosumab, that were not included in the original report. In addition, studies were found on the effects of calcium and vitamin D and for novel dosing schedules or routes of administration of the bisphosphonates, ibandronate, and zoledronic acid. Based on this evidence, the assessment concluded that at least some of the conclusions of the first report regarding effectiveness may need to be updated (Key Question 1—see below). In addition, the assessment found new evidence on the safety of some agents that might warrant an update. For example, new evidence was found on the risk of atrial fibrillation with the use of some bisphosphonates and the risk of osteosarcoma with the use of teriparatide. Also, the FDA issued a labeling revision in December 2007 regarding the possible association of the use of pamidronate with deterioration of renal function (http://effectivehealthcare.ahrq.gov/ehc/products/125/331/2009_0923UpdatingReports.pdf).

Based on these findings, the Update Assessment suggested an updated review of the adverse effect evidence (Key Question 4).

In July 2009, the EPC was asked by AHRQ to conduct a full update of the original CER. We modified Key Question 1 to include medications that were not approved for the treatment of osteoporosis prior to the release of the original report but have since been approved, including zoledronic acid (IV) (Reclast®; Novartis; once-a-year infusion) and the monoclonal antibody, denosumab (Prolia®; Amgen; every-six-months injection); as well as agents for which no or few data were available for inclusion in the original report, such as injectable ibandronate sodium (Boniva®; Roche Laboratories/Hoffman laRoche; once every three months). We also omitted several agents—etidronate, pamidronate, tamoxifen, and testosterone—based on their not being indicated or used for osteoporosis treatment, and also modified the question to include consideration of the sequential or combined use of different agents. Although new evidence was found for strontium ranelate, this agent is not likely to be considered for FDA approval in the near future, so it was not included.

Key Question 2 originally assessed the evidence for efficacy and effectiveness among particular subpopulations of clinical interest. The subpopulations to be considered in the evidence review update were also augmented to include racial/ethnic differences because of the

evidence for potential group differences in BMD and risk for osteoporosis. The subject matter experts also recommended considering the comparative utility of existing risk assessment algorithms for predicting antifracture effects of osteoporosis pharmacotherapy, i.e., whether differences in antifracture effects would be found among groups with different FRAX (or other) risk assessment cutoffs.

Key Question 3, which addresses compliance and adherence, remains as it was originally.

Key Question 4, which assesses adverse effects of the pharmacologic agents, was modified to exclude uses of the agents for any condition other than osteoporosis/low bone density so as to be congruent with the scope of the report.

The subject matter experts also recommended that an additional question be added. Because the optimal duration for therapy (and the role of monitoring in determining how long to treat) remains unknown, a question was added to address therapy duration and monitoring of effectiveness. Key Question 5 has two parts. The first part aims to assess the evidence that antifracture effect is predicted by DXA monitoring of BMD. The second part (which is really a subquestion to Key Question 1) aims to assess the evidence for comparative effectiveness of long-term therapy (defined by consensus of the technical expert panel as therapy of 5 years or more). Thus the following questions guided the current report. (Figure A shows the report's analytic framework.)

Key Question 1: What are the comparative benefits in fracture risk reduction among the following therapeutic modalities for low bone density:

- Bisphosphonate medications, specifically:
  - Alendronate (Fosamax®, oral)
  - Risedronate (Actonel®; oral once-a-week)
  - Ibandronate (Boniva®)
  - Zoledronic acid (Reclast®IV).
- Denosumab (Prolia®)
- Menopausal estrogen therapy for women (numerous brands and routes of administration)
- Parathyroid hormone (PTH)
  - 1-34 (teriparatide) (Forteo®)
- Selective estrogen receptor modulators (SERMs), specifically
  - Raloxifene (Evista®)
- Calcium
- Vitamin D
- Combinations or sequential use of above
- Exercise in comparison to above agents

Key Question 2: How does fracture risk reduction resulting from treatments vary between individuals with different risks for fracture as determined by the following factors:

- Bone mineral density
- FRAX or other risk assessment score
- Prior fractures (prevention vs. treatment)
- Age
- Sex
- Race/ethnicity
- Glucocorticoid use
- Other factors (e.g., whether the individuals were community dwelling vs. institutionalized, vitamin D deficient vs. not)

Key Question 3: Regarding treatment adherence and persistence†,

- What are the levels of adherence to and persistence with medications for the treatment and prevention of osteoporosis?
- What factors affect adherence and persistence?
- What are the effects of adherence and persistence on the risk of fractures?

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 (e.g., the subpopulations identified in Key Question 2)?

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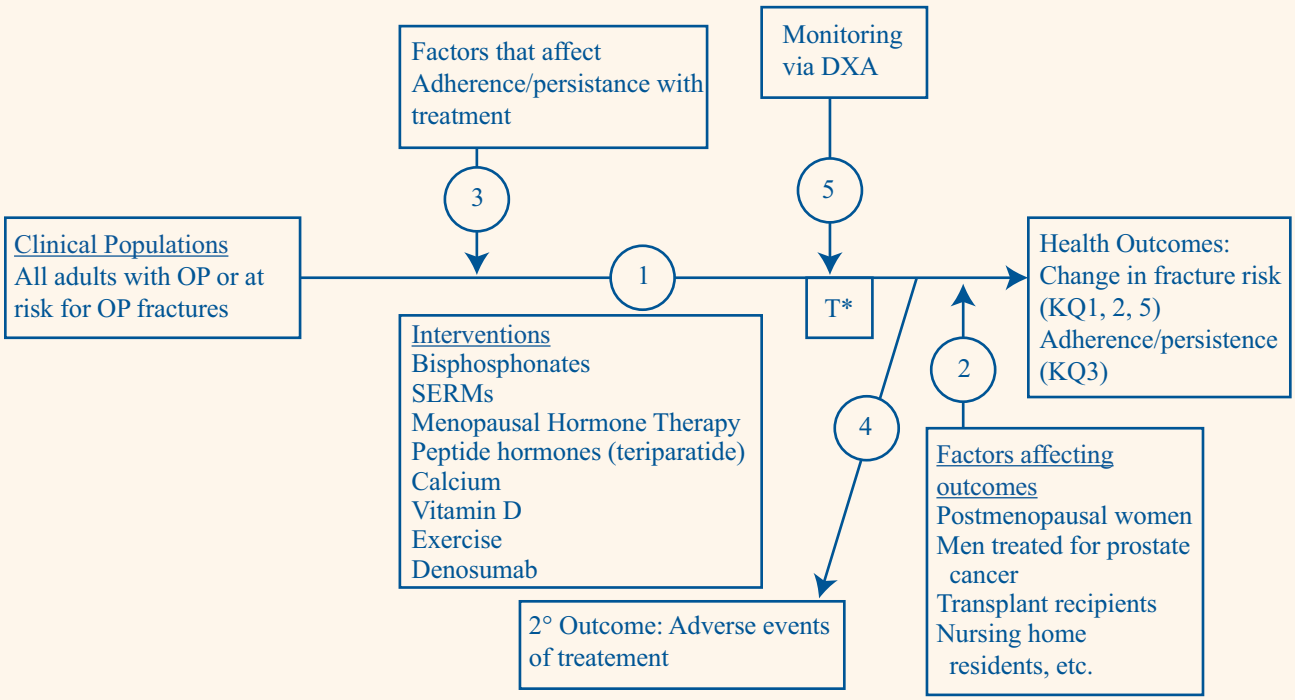
†The terms adherence and persistence are defined based on principles outlined by the International society for Pharmacoeconomics and Outcomes Research (ISPOR). (Cramer, 2008) Adherence (or compliance) is defined as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen." Although not specifically stated in the ISPOR definition, we view adherence to specific dosing instructions (which for bisphosphonates can affect both effectiveness and risk of adverse events) as an important component of adherence. Persistence is defined as "the duration of time from initiation to discontinuation of therapy." (Cramer, 2008)

Key Question 5: With regard to treatment for preventing osteoporotic fracture:

- 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?
- 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?

Figure A. Analytic framework



BMD = bone mineral density; DXA = dual energy x-ray absorptiometry; KQ = Key Question; OP = osteoporosis; SERMs = selective estrogen receptor modulators

*T connotes the timing of outcome measurement for studies that will be included, which will vary by KQ.

Methods

Search Strategy

Our basic search strategy used the National Library of Medicine's Medical Subject Headings (MeSH) keyword nomenclature. Using the same basic search rules used for the original report (with the addition of several new terms for additional drugs), we searched MEDLINE® for the period from January 2005 through March 2011. We also searched Embase, the American College of Physicians (ACP) Journal Club database, the Cochrane controlled trials register, and relevant pharmacological databases.

In searching for efficacy and effectiveness studies, we used terms for osteoporosis, osteopenia, low bone density, and the drugs listed in Key Question 1. In our search for the key adverse events (AE), we used terms for the AE and each of the drugs of interest. In our search for studies of adherence and persistence, we used terms for adherence and persistence and the drugs of interest. In all cases, both generic and trade names were used. In our search for studies on the effects of monitoring, we searched on terms related to monitoring and DXA in combination with the drugs of interest.

For new drugs, we reviewed the list of excluded studies from the original report to retrieve articles that had been rejected on the basis of drugs that were now included within the scope of the update, to find studies prior to 2005. The search was not limited to English-language publications and not limited by study design (e.g., reports of randomized controlled trials (RCT), observational studies, systematic reviews). The texts of the major search strategies are given in Appendix A.

To identify additional systematic reviews not captured in our primary search strategy, we also searched MEDLINE®, the Cochrane Database of Systematic Reviews, the websites of the National Institute for Clinical Excellence, and the NHA Health Technology Assessment Programme. We also manually searched the reference lists of review articles obtained as part of our search ("reference mining").

To augment those searches, the EPC's Scientific Resource Center (SRC) conducted several "grey literature" searches, including a search of relevant trials in the NIH Clinical Trials database, the Web of Science, FDA Medwatch files, and Health Canada files.

Study Eligibility Criteria

To identify studies for this report, we used the following inclusion criteria:

- **Populations:** Studies were limited to those recruiting the following individuals: adults over 18 (not children); healthy adults, those with low bone density, or those with osteoporosis (but not those with Paget's disease, cancer, or any other disease of bone metabolism); those using drugs indicated for the treatment of osteoporosis (but not if the drugs were being used to treat cancer); adults who had low bone density or were at high risk of developing low bone density as a result of chronic use of glucocorticoids (GC) or a condition associated with the chronic use of glucocorticoids (such as asthma, organ transplant, rheumatoid arthritis; adults who had low bone density or were at high risk of developing low bone density as a result of having a condition associated with low bone density (e.g., rheumatoid arthritis, cystic fibrosis, Parkinson's disease).
- **Interventions:** Studies were included if they examined pharmacological interventions for prevention or treatment of osteoporosis approved for use in the United States (or expected to be soon approved for use) or if they assessed the effects of calcium, vitamin D, or physical activity.
- **Comparators:** Studies included for assessing efficacy or effectiveness were those that compared the effectiveness of the intervention in question to that of placebo or another potency or dosing schedule for the same agent or another agent in the same or another class.
- **Outcomes:** For efficacy and effectiveness analysis, only studies that assessed vertebral, hip, and/or total fractures (and did not state that they lacked power to detect a change in risk for fracture) were included. Studies that reported fracture only as an adverse event were excluded from effectiveness analysis; however, studies that reported atypical (low-stress subtrochanteric or femur) fractures as adverse outcomes were included in the adverse event analysis.
- **Duration:** Studies that had a minimum followup time of 6 months were included.

- **Design:** Only RCTs and published systematic reviews of RCTs that met inclusion criteria were included in the assessment of effectiveness;[16] however, for the assessment of effects in subgroups for which no RCTs were available, for the assessment of the effect of adherence on effectiveness, and for the assessment of particular serious adverse events, large observational studies (with more than 1,000 participants) and systematic reviews were included.

Study Selection

Each title list was screened separately by two reviewers with clinical training and experience in systematic review to eliminate obviously irrelevant titles. Abstracts were obtained for all selected titles. Full text articles were then obtained for all selected abstracts. The reviewers then conducted a second round of screening to ascertain which articles met the inclusion criteria and would go on to data abstraction. Selections at this stage were reconciled, and disagreements were settled by consensus (with the project leaders resolving remaining disagreements).

During the second round of screening, we imposed inclusion criteria based on the particular Key Question(s) addressed by the study. For effectiveness/efficacy questions (Key Questions 1, 2, and 5), we accepted any abstracts that indicated the manuscript might include information on the treatment/prevention of osteoporotic fracture (but not bone density alone). Controlled clinical trials and large observational studies (N>1,000) that reported fracture outcomes for one or more of the drugs of interest were accepted for the efficacy analysis and went on to data extraction.

For assessing comparative effectiveness, we included only studies that compared two or more interventions within the same study, rather than attempting to compare treatment effects across studies. The differences in study design and baseline participant characteristics between studies would make interpretation of such comparisons suspect.

For Key Question 2, we identified studies that analyzed treatment efficacy and effectiveness by subgroups by noting, during the initial screening of full-text articles, any articles that reported the results of post hoc analyses of trial efficacy data by a subgroup of interest; by noting whether subgroup analyses were reported while extracting primary effectiveness results from clinical trial reports and large observational studies (over 1,000 participants); and we sought observational studies of any size that assessed effects of the agents of interest in populations not well represented in controlled trials. As with the head-to-head comparisons for Key Question 1, we did not attempt to compare treatment effects across studies because of the vast baseline differences between populations in characteristics considered to be potentially important, such as average age, body mass index, and race/ethnicity.

For Key Question 3 (adherence), articles of any study design that reported rates of adherence/persistence, factors influencing adherence/persistence, or the effects of adherence on effectiveness for any of the drugs of interest were included for further evaluation.

For Key Question 4 (adverse events), any articles were accepted if they suggested that the manuscript included information on the relationship between the adverse event and the drug. Controlled clinical trials and large case control or cohort studies (over 1,000 participants) that reported fracture or BMD or markers of bone turnover for one or more of the drugs of interest and that reported one or more AE, as well as studies of any design that described any of a number of rare adverse events (e.g., osteonecrosis of the jaw, atrial fibrillation, low stress subtrochanteric and femur fracture) in association with any of the drugs of interest, were initially included in adverse event analyses.

For Key Question 5 (effects of monitoring and long-term use), to ensure that we identified all articles that examined the effect of bone density monitoring in predicting treatment effectiveness or efficacy, we searched for these articles in the following ways: During the initial screening of articles, we included any clinical trials that reported fracture results and mentioned monitoring. We also included any trials that reported both BMD and fracture and subsequently assessed whether changes in BMD were compared to fracture outcomes. Where they existed, we also included reports of followups to trials included in the original report to assess the effect of long-term use.

Data Extraction

Study level details, such as population characteristics, comorbidities, inclusion and exclusion criteria, interventions, and outcomes assessed, were extracted and recorded onto specially designed forms.

Data Synthesis

We performed three main analyses: one to evaluate efficacy and effectiveness, one to evaluate adherence, and one to evaluate adverse events. Comparisons of interest for all analyses were single drug versus placebo for each of the drugs of interest, and single drug versus single drug comparisons for drugs within the same class and across classes. In addition, we evaluated comparisons between estrogen combined with progesterone and placebo or single drugs. Studies that included either calcium or vitamin D in both study arms were classified as being comparisons between the other agents in each arm, e.g., alendronate plus calcium versus risedronate plus calcium would be classified as alendronate versus risedronate.

The outcome of interest for assessing effectiveness for this report is fractures, based on FDA requirements. We report data about the following types of fractures (as reported in the studies reviewed): vertebral, nonvertebral, hip, wrist, and humerus. For each of the drug comparisons, we first summarized fracture data from published systematic reviews in tables. Data abstracted from individual controlled clinical trials were grouped by fracture type within each drug comparison of interest. Based on the recommendation of subject matter experts, we did not combine data on different types of fracture; hence we report findings for total fractures only if a study reported data on total fractures (likewise for nonvertebral fractures). The primary outcome for our analysis of effectiveness is the number of people who reported at least one fracture.

To assess adherence, we extracted reported rates of adherence or persistence from trials and observational studies separately, as the rates of adherence and persistence reported for trials are likely to be higher than would be observed in practice. For those studies that provided information on the potential barriers and/or predictors to medication adherence in osteoporosis, we identified those barriers and predictors, using a data abstraction form designed especially for studies of adherence, and determined the number of studies discussing each factor and the characteristics of the study, including population characteristics, specifics on how adherence/persistence are measured, and funding source. For the analysis of adherence/persistence and fracture, we qualitatively reviewed each of these studies and prior systematic reviews addressing this topic.

For adverse events, two main analyses were performed: analyses to assess the relationship between a group of adverse events that were identified a priori as particularly relevant and exploratory analyses of all adverse events that were reported for any of the drugs. For the analyses of adverse events, we examined (where possible given the available data) comparisons of drug versus placebo, and comparisons of drug versus drug, for drugs within the same class and across classes. A list was compiled of all unique adverse events that were reported in any of the studies, and a physician grouped adverse events into clinically sensible categories and subcategories, including a category for each of the adverse events that were identified a priori as being of interest. For groups of events that occurred in three or more trials (including those in the original report), we performed meta-analysis to estimate the pooled OR and its associated 95 percent confidence interval.

Assessments of Quality and Applicability and Rating the Body of Evidence

The methods used for quality assessment were determined by the design of included studies. The quality of RCTs was assessed using the Jadad scale,[17] which was developed for drug trials and which we feel is well suited to the evaluation of quality in this report. The Jadad scale ranges from 0 to 5 based on points given for randomization, blinding, and accounting for withdrawals and dropouts. (Two points are awarded for randomization and two for double blinding.) We also added an assessment of concealment of allocation.

The need to include observational studies was carefully assessed according to the guidelines presented in the Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews. Specifically, we assessed whether clinical trials provided sufficient data to reach conclusions, and where they did not we included observational data. In practice, this meant that we included observational data in two topic areas: adverse events and the assessment of adherence and outcomes. The quality of prospective cohort and case-control studies that addressed adverse events was assessed using the relevant portions of the Newcastle-Ottawa Scales, as follows:[18]

- Are primary outcomes assessed using valid and reliable measures?
- Are outcome measures implemented consistently across all study participants?

- Were the important confounding and modifying variables taken into account in the design and analysis?
- How was the non-exposed cohort selected?
- How was exposure to drugs/exercise ascertained?
- Was it demonstrated that the outcome of interest was not present at the start of the study?

Assessing the quality of observational studies that measure adherence is a challenge, as no such metric currently exists and the items included in other metrics used to rate the quality of observational studies do not apply to most studies that assess adherence. Thus, for each such study, we listed those objective factors that might be related to both quality and generalizability/applicability, such as how adherence was measured and the size and location of the study.

As was done for the original report, we assessed the applicability of each included study based on the similarity of the target populations to those for which this report is intended. This assessment was separate from other quality assessments. The characteristics we used to distinguish efficacy from effectiveness, and therefore to rate applicability, were study setting, study population (stringency of eligibility criteria), duration and attempt to assess treatment compliance, health outcome assessment, adverse event assessment, sample size, and use of intention-to-treat analysis.[19]

The overall strength of evidence for intervention effectiveness using guidance suggested by the U.S. Agency for Healthcare Research and Quality (AHRQ) for its Effective Healthcare Program.[20] This method is based on one developed by the Grade Working Group,[21] and classifies the grade of evidence according to the following criteria:

High = High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence on the estimate of effect.

Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.

Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.

Insufficient = Evidence either is unavailable or does not permit a conclusion.

The evidence grade is based on four primary domains (required) and four optional domains. The required domains are risk of bias, consistency, directness, and precision; the additional domains are dose-response, plausible confounders that would decrease the observed effect, strength of association, and publication bias.

Conclusions

Key Question 1: What are the comparative benefits in fracture risk reduction among and within the included therapeutic modalities?

For this question, we identified 55 RCTs and 10 observational studies in addition to 58 systematic reviews (from both the original and current report) that assessed the effects of interventions compared to placebo: 9 systematic reviews and 10 RCTs for alendronate, 10 systematic reviews and 13 RCTs for risedronate, 3 systematic reviews and 3 RCTs for ibandronate, 4 RCTs for zoledronic acid, 1 systematic review and 2 RCTs for denosumab, 3 systematic reviews and 3 RCTs for raloxifene, 2 systematic reviews and 3 RCTs for teriparatide, 6 RCTs for menopausal estrogen therapy, 4 systematic reviews and 6 RCTs for calcium alone, 15 systematic reviews and 7 RCTs for vitamin D alone, 4 RCTs for vitamin D plus calcium, and 1 systematic review and 1 RCT for physical activity. (Studies that addressed more than one Key Question were counted more than once.) We reached the following conclusions:

- There is a high level of evidence from RCTs that alendronate, risedronate, ibandronate, zoledronic acid, denosumab, teriparatide, and raloxifene reduce the risk of vertebral fractures in postmenopausal women with osteoporosis.
- There is a high level of evidence from RCTs that alendronate, risedronate, zoledronic acid and denosumab reduce the risk of nonvertebral fractures in postmenopausal women with osteoporosis, and moderate evidence that teriparatide reduces the risk of nonvertebral fractures.
- There is a high level of evidence from RCTs that alendronate, risedronate, zoledronic acid, and denosumab reduce the risk of hip fractures in postmenopausal women with osteoporosis.

- The original report found a high level of evidence that estrogen is associated with a reduced incidence of vertebral, nonvertebral, and hip fractures; however, studies identified for this report, which tended to focus on postmenopausal women with established osteoporosis (rather than on postmenopausal women with low bone density only or postmenopausal women in general) did not show significant reductions in fracture risk.
- There is moderate evidence, based on a published systematic review and several RCTs, that there is no difference between calcium alone and placebo in reducing the risk for vertebral and nonvertebral fractures; however, calcium significantly reduced hip fracture risk in one pooled analysis, and overall fracture risk in another pooled analysis.
- A large body of literature showed mixed results for an effect of vitamin D in lowering the risk for fracture, varying with dose, fracture site, analogs (the various molecular and chemical forms of the vitamin, each of which has different biological activity), and population. Evidence is moderate that Vitamin D, 700 to 800 I.U. daily, particularly when given with calcium, reduces the risk of hip and nonvertebral fractures among institutionalized populations (one systematic review) and the overall risk of fractures (a second systematic review).
- There is a high level of evidence, based on six previously published systematic reviews, that there is no difference in vertebral, nonvertebral, or hip fracture risk with administration of vitamin D alone compared to administration of calcium alone.
- The evidence is insufficient to low regarding the effect of physical activity on fracture risk, compared to placebo: One study showed a small effect on fracture prevention. No studies compared the effect of physical activity to that of other interventions.
- The evidence is insufficient from head-to-head trials of bisphosphonates to prove or disprove any agent's superiority for the prevention of fractures.
- The evidence is insufficient, from three head-to-head trials of bisphosphonates compared to calcium, teriparatide, or raloxifene to prove or disprove superiority for the prevention of fractures.
- Evidence is moderate, based on six head-to-head RCTs, that there is no difference in fracture incidence between bisphosphonates and menopausal hormone therapy.
- The evidence is low, based on one head-to-head trial, that the combination of alendronate and calcium significantly decrease the risk for any type of clinical fracture compared with alendronate alone.
- The evidence is low, based on limited head-to-head trial data (two trials), for a difference in fracture incidence between menopausal hormone therapy and raloxifene or vitamin D.
- The evidence is insufficient regarding the use of combinations of osteoporosis therapies or sequential use of osteoporosis therapies in relation to fracture outcomes.

Key Question 2: How does fracture risk reduction resulting from treatments vary between individuals with different risks for fracture as determined by bone mineral density, risk assessment score, prior fractures, age, sex, race/ethnicity, and glucocorticoid use?

Our analysis yielded the following conclusions:

- **Bone mineral density:** Moderate evidence (post hoc analysis of one large RCT) showed that low femoral neck BMD did not predict the effect of alendronate on clinical vertebral or non-vertebral fracture risk. Post hoc analysis of two-year followup data from a large RCT of postmenopausal women with osteopenia and no prevalent vertebral fractures showed that risedronate significantly reduced the risk of fragility fracture in this group, comparable to reductions seen in women with osteoporosis.
- **FRAX risk assessment:** Moderate evidence (post hoc analysis of data from one large RCT) showed no effect of fracture risk as assessed by the WHO's FRAX on the effects of raloxifene in reducing risk for morphometric vertebral fracture among elderly women.
- **Prevalent fractures:**
  - Evidence is insufficient regarding the association between the presence of prevalent fractures (i.e., fractures that predated the start of pharmacological therapy) and the efficacy of alendronate in reducing the risk for fractures. Post hoc analysis of a large

RCT showed that prevalent vertebral fractures do not predict the efficacy of alendronate; however another post hoc analysis of data from the same trial found that alendronate reduced the risk of incident nonvertebral fractures to a greater extent among women without prevalent fractures (but with T-scores ≤-2.5) than among women with prevalent fractures or without prevalent fractures and with T-score -2 to -2.5.

- Evidence is insufficient regarding prevalent fracture and the efficacy of raloxifene. A post hoc analysis of one large RCT showed that raloxifene decreased the risk of major nonvertebral fracture among women with prevalent vertebral fracture, but not among women without prevalent vertebral fracture. However, two other RCTs found no influence of prevalent fracture.
- Evidence is moderate (a post hoc analysis of one RCT) that prevalent fractures increased the relative efficacy of teriparatide in preventing fractures in postmenopausal women.

- **Age**:
  - In general, a high level of evidence suggests that bisphosphonates are at least as effective for older persons as for younger.
  - One RCT found no effect of age on the efficacy of risedronate.
  - One RCT found no influence of age on the effect of zoledronic acid in lowering the risk for vertebral or nonvertebral fractures but found that only women under 75 experienced a benefit in reduced risk for hip fracture. Another RCT found that age influences the effect of zoledronic acid on the risk for vertebral fracture risk but not the risk for nonvertebral or hip fracture. However these studies were not powered to detect differences across age groups.
  - The relative effect of teriparatide on reducing the incidence of new vertebral fractures and nonvertebral fragility fractures was statistically indistinguishable in younger and older patients.
- **Sex**:
  - Evidence is insufficient regarding the effectiveness of therapies to prevent or treat osteoporosis in men. Only one RCT was identified that actually assessed the effect of sex on response to treatment. This study found that calcium plus vitamin D3 reduced the risk of fracture among elderly women but not elderly men.
- **Race/Ethnicity:**
  - A high level of evidence (one post hoc pooled analysis of two RCTs) showed that raloxifene decreases the risk of vertebral fracture but not nonvertebral or hip fracture among Asian women; this finding is similar to that of U.S. and international studies of raloxifene.
- **Glucocorticoid treatment:**
  - Evidence is insufficient regarding the effect of glucocorticoid treatment on response to therapies. One new RCT found that teriparatide treatment was more effective in reducing risk of vertebral fractures than alendronate but equally effective in reducing risk for nonvertebral fractures.
- **Renal function:**
  - Evidence is insufficient from trials assessing the effect of renal function on the efficacy of alendronate, raloxifene, and teriparatide. Two trials report no effect of renal function on the effects of these agents. However, in a third trial, impaired renal function reduced the efficacy of zoledronic acid in preventing vertebral (but not nonvertebral or hip) fractures.

Key Question 3: What are the adherence and persistence with medications for the treatment and prevention of osteoporosis, the factors that affect adherence and persistence, and the effects of adherence and persistence on the risk of fractures?

For this question, we identified two new systematic reviews, 18 RCTs, and 59 observational studies. We reached the following conclusions:

- Definitions of adherence and persistence vary widely across studies and over time.
- Adherence rates are higher in clinical trials than in real life, likely reflecting the select populations and controlled environments in trials; in contrast, adherence rates in observational studies tend to resemble those in real life.

- The rates of adherence and persistence observed in the studies reviewed for this report reflect closely the rates seen and examined in prior systematic reviews on the topic, as well as in the previous report. Adherence and persistence as measured in observational studies is poor. In the U.S. studies overall, about half of patients appeared to show persistence with osteoporosis treatment at 1 year, with adherence ranging widely across studies.
- Many potential barriers to adherence and persistence have been identified. Five of the most commonly assessed in published studies include age, prior history of fracture, dosing frequency, concomitant use of other medications, and adverse effects of the osteoporosis medications. The frequency with which these potential barriers appear in the literature does not necessarily correspond to their importance as barriers/factors related to adherence.
- Age, history of fracture, and number of concurrent medications do not appear to have an important independent association with adherence/persistence.
- Dosing frequency appears to affect adherence/persistence to a point: adherence is improved with weekly compared to daily regimens, but current evidence is lacking to show that monthly regimens improve adherence over that of weekly regimens.
- Adverse effects—and concerns about adverse effects—appear to be important predictors of adherence and persistence. Evidence from a systematic review and 15 out of 17 observational studies suggest that decreased adherence to bisphosphonates is associated with an increased risk of fracture (vertebral, nonvertebral or both).
- The evidence on adherence to raloxifene, teriparatide, and other drugs and its association with fracture risk is insufficient to make conclusions.

Key Question 4: What are the short- and long-term harms (adverse effects) of the included therapies; and do these vary by any specific subpopulations?

For this question, we included 11 systematic reviews, 67 RCTs, 12 large observational studies, and six post hoc analyses. We reached the following conclusions:

- **Acute coronary syndrome, including myocardial infarction (MI):** Evidence is low (a new meta-analysis of 15 placebo-controlled trials of calcium (administered for bone health in all cases but one) for a small but significant increase in the risk for myocardial infarction in pooled results of five trials that contributed patient-level data; however serious concerns have been raised about methodological issues that may have led to bias.
- **Atrial fibrillation:** Evidence is insufficient regarding the risk for this event. The original report identified one study that showed a significant increase in the risk of atrial fibrillation for zoledronic acid relative to placebo but another that did not; the current report identified one additional trial that, when pooled with the two earlier trials of zoledronic acid, showed a significant increase in the risk for atrial fibrillation. A large Bayesian meta-analysis among users of bisphosphonates that did not reach statistical significance and several additional meta-analyses showed mixed results. In March 2010, the FDA issued a followup to its 2007 safety review, noting the inconsistency in the data and requesting that providers and patients report such side effects. Thus, a relationship between zoledronic acid and atrial fibrillation is unproven but still an area of active surveillance.
- **Pulmonary embolism (PE):** The original report identified two large studies that showed higher odds for PE among raloxifene participants than among placebo participants. The current report identified two additional studies that, when pooled with the original two, showed even higher risk for PE. Evidence is high for an increased risk for this event.
- **Venous thromboembolic events:** The original report identified four studies that showed higher risk of thromboembolic events for raloxifene-treated participants than for placebo participants. For the current report, four additional studies were identified that narrowed the confidence interval. Evidence is high for an increased risk for this event.
- **Vasomotor flushing (hot flashes):** A pooled analysis of eight studies, three from the original report and five identified for the current report, that compared raloxifene and placebo found a significant increase in vasomotor flushing among raloxifene users. Evidence is high for an increased risk for this event.
- **Esophageal cancer:** Four large observational studies identified for this report examined the risk of esophageal cancer among users of bisphosphonates. A prospective cohort study using a UK database found no increase in the risk for esophageal cancer, but two

nested case control studies using the same dataset did identify an increased risk. A nested case control study of patients with Barrett's Esophagus who developed esophageal cancer also found no association with use of bisphosphonates. Evidence is insufficient regarding the risk for this event.

- **Mild upper gastrointestinal (GI) events:** We categorized conditions such as acid reflux, esophageal irritation, nausea, vomiting, and heartburn as "mild upper GI events." Pooled analysis of 50 studies of alendronate showed greater odds of all mild upper gastrointestinal (GI) events for alendronate than for placebo. In a head-to-head comparison of alendronate with denosumab, alendronate was also more strongly associated with mild upper GI events than was denosumab. Evidence is high regarding the risk for alendronate and mild upper GI events.
- **Osteonecrosis of the jaw:** The original report identified case series and case reports describing 41 cases of osteonecrosis of the jaw in cancer patients taking intravenous bisphosphonates. One trial, two large observational studies, a post hoc analysis, and a systematic review that reported on the incidence of osteonecrosis of the jaw among individuals taking bisphosphonates to prevent or treat osteoporosis were identified for the current report. Cohort and case control studies range in their estimates of the incidence of osteonecrosis of the jaw associated with the use of bisphosphonates to prevent or treat osteoporosis from fewer than one case to 28 cases per 100,000 person-years of treatment. Thus evidence is high that the prevention and treatment of osteoporosis remains a relatively minor contributor to the development of osteonecrosis of the jaw.
- **Atypical fractures of the femur:** Seven observational studies, a pooled analysis of three trials, and a comprehensive review identified a small increase in the risk for atypical, low-trauma subtrochanteric fragility fractures of the femur with long-term use of bisphosphonates for prevention or treatment of osteoporosis. Based on this American Society of Bone and Mineral Research review, on 13 October 2010, the Food and Drug Administration, which has been conducting its own ongoing review of atypical subtrochanteric femur fracture, updated the risk of atypical fractures to the Warnings and Precautions level, acknowledging that the risk remains low compared with the numbers of osteoporotic fractures prevented by the drugs. Evidence is low for this conclusion.
- **Rashes, injection site reactions, and infection:** Pooled analysis of four trials of denosumab found an increased rate of rash but no increase in the rate of injection site reactions for the biological agent denosumab, compared with placebo. Based on evidence for an increased risk of infection, the FDA has issued a Risk Evaluation and Mitigation Strategy for the drug. A systematic review of four trials confirms the increased risk for infection. Evidence is high for these conclusions.

Key Question 5: How often should patients be monitored (via measurement of BMD) during therapy? How does the antifracture benefit vary with long-term continued use of therapy?

For this question, we identified one systematic review and 4 RCTs. We reached the following conclusions:

- No evidence exists from RCTs regarding how often patients' BMD should be monitored during osteoporosis therapy.
- A high level of evidence exists from RCTs that lumbar spine and femoral neck BMD changes from serial monitoring predict only a small percentage of the change or do not predict the change in fracture risk from treatment with antiresorptives, including alendronate, risedronate, raloxifene, and teriparatide.
- In RCTs, even people who lose BMD during antiresorptive therapy benefit from a substantial reduction in risk of vertebral fracture. Greater increases in BMD did not necessarily predict greater decreases in fracture risk. Thus, improvement in spine bone mineral density during treatment with currently available osteoporosis medications accounts for a predictable but small part of the observed reduction in the risk of vertebral fracture. Vertebral fracture risk is reduced in women who lose femoral neck BMD with teriparatide treatment. Evidence is high for this conclusion.
- Evidence is moderate (one large RCT) that, compared to using alendronate for 5 years followed by discontinuation after 5 years, continuous use of alendronate for 10 years resulted in a lower risk of vertebral fracture.

To aid the readers in identifying "what's new?" we also present these conclusions in Table A, with new conclusions (relative to the original report) identified in bold.

Table A. Summary of evidence	
Strength of Evidence	**Conclusion**
Key Question 1. What are the comparative benefits in fracture risk reduction among the following treatments for low bone density:	
a. Bisphosphonates	
High	Vertebral fractures: alendronate, risedronate, ibandronate, and zoledronic acid reduce the risk of vertebral fractures among postmenopausal women with osteoporosis.
High	Non-vertebral fractures: alendronate, risedronate, and zoledronic acid reduce the risk of nonvertebral fractures among postmenopausal women with osteoporosis.
High	Hip fractures: alendronate, risedronate and zoledronic acid reduce the risk of hip fractures among postmenopausal women with osteoporosis. **The effect of ibandronate is unclear, since hip fracture risk reduction was not a separately reported outcome in trials reporting nonvertebral fractures.**
Low	Wrist fractures: alendronate reduces the risk of wrist fractures among postmenopausal women with osteoporosis. **Risedronate in a pooled analysis of two trials was associated with a lower risk of wrist fractures, but this did not quite reach the conventional level of statistical significance.**
Insufficient	Data are insufficient from head-to-head trials of bisphosphonates to prove or disprove superiority for the prevention of fractures for any agent.
Insufficient	Data are insufficient from head-to-head trials of bisphosphonates compared to calcium, **teriparatide**, or raloxifene to prove or disprove superiority for the prevention of fractures.
Moderate	Based on six RCTs, superiority for the prevention of fractures has not been demonstrated for bisphosphonates in comparison with menopausal hormone therapy.
b. Calcium	
Moderate	The effect of calcium alone on fracture risk is uncertain. Several large, high quality RCTs were unable to demonstrate a reduction in fracture among postmenopausal women. However, a number of studies have demonstrated that compliance with calcium is low, and a subanalysis in one of the RCTs demonstrated a reduction in fracture risk with calcium relative to placebo among compliant subjects.
c. Denosumab	
High	**Denosumab reduces the risk of vertebral, nonvertebral and hip fractures in postmenopausal women with osteoporosis.**
d. Menopausal hormone therapy	
High	Menopausal hormone therapy reduces the risk of vertebral and hip fractures in postmenopausal women.
Moderate	**Menopausal hormone therapy does not reduce fracture risk significantly in postmenopausal women with established osteoporosis.**
e. PTH (teriparatide)	
High	**Teriparatide reduces the risk of vertebral fractures in postmenopausal women with osteoporosis.**
Moderate	**Teriparatide reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis.**

Table A. Summary of evidence (continued)	
Strength of Evidence	**Conclusion**
f. SERMs (raloxifene)	
High	Raloxifene **reduces the risk of** vertebral fractures among postmenopausal women with osteoporosis.
g. Vitamin D	
Low-Moderate	The effect of vitamin D on fracture risk is uncertain. Among a number of meta-analyses, some reported a reduced risk for vitamin D relative to placebo, some did not. There was no reduction in fracture risk for vitamin D relative to placebo in a large, high quality RCT published after the meta-analyses.
h. Exercise in comparison to above agents.	
Insufficient	There are no data from RCTs to inform this question. **One RCT that assessed the effect of a brief exercise program on fracture risk found a small decrease in risk of fractures among exercisers but the study was not powered to detect differences in fracture risk.**
Key Question 2. How does fracture risk reduction resulting from treatments vary between individuals with different risks for fracture as determined by bone mineral density (borderline/low/severe), **risk assessment score**, prior fractures (prevention vs. treatment),†† age, sex, race/ethnicity, and glucocorticoid use?	
High	Alendronate, ibandronate, risedronate, teriparatide, raloxifene, **zoledronic acid,** and **denosumab** reduce the risk of fractures among high risk groups including postmenopausal women with osteoporosis.
Moderate	**Low femoral neck BMD does not predict the effects of alendronate on clinical vertebral or nonvertebral fracture risk.**
Insufficient	**Prevalent fracture predicted the effect of alendronate on fracture risk in one study but not another.**
Low-moderate	**Risedronate reduces the risk of fragility fracture among postmenopausal women with osteopenia who do not have prevalent vertebral fractures.**
Insufficient	**Prevalent fracture predicts the efficacy of raloxifene for fracture prevention in some studies but not others.**
Moderate	**Prevalent fractures increase the relative efficacy of teriparatide in preventing fractures.**
Moderate	Raloxifene prevents fractures in postmenopausal women at low risk for fracture **as assessed by FRAX.**
Insufficient	Teriparatide and risedronate **but not calcium and vitamin D** reduce risk of fracture among *men*.
High	**In general age does not predict the efficacy of bisphosphonates or teriparatide.**
High	**Raloxifene decreases the risk for vertebral fracture but not nonvertebral or hip fracture among postmenopausal Asian women, similar to other postmenopausal women.**
Moderate-High	Among *subjects treated with glucocorticoids*, fracture risk reduction was demonstrated for alendronate, risedronate, and **teriparatide**.
Insufficient	There are limited and inconclusive data on the effect of agents for the prevention and treatment of osteoporosis on *transplant recipients and patients treated with chronic corticosteroids*.
Insufficient	**Evidence is inconclusive on the effects of renal function on the efficacy of alendronate, raloxifene, and teriparatide in preventing fractures.**

†† Prevention vs. treatment: If a person begins pharmacotherapy after having sustained fractures (i.e., the person has prevalent fractures), the therapy is considered treatment because the person, by definition, has osteoporosis and the medication is being administered to treat the condition. When these medications are administered to individuals with no prior fractures, these are individuals who have been identified as being at risk for osteoporosis (due to low bone density), but who don't actually (yet) have osteoporosis. They are being given the medication to prevent the onset of osteoporosis (i.e., further lowering of bone density and/or a first fracture).

Table A. Summary of evidence (continued)	
Strength of Evidence	**Conclusion**
Moderate	Reduction in fracture risk for subjects treated with alendronate, risedronate, or vitamin D has been demonstrated in populations *at increased risk for fracture due to conditions that increase the risk of falling including stroke with hemiplegia, Alzheimer's disease, and Parkinson's*.
Key Question 3. What are the adherence and persistence with medications for the treatment and prevention of osteoporosis, the factors that affect adherence and persistence, and the effects of adherence and persistence on the risk of fractures?	
Moderate	**Eighteen RCTs reported rates of adherence to therapy. Twelve trials with bisphosphonates and two trials with denosumab reported high levels of adherence (majority with over 90% adherence). Two trials with raloxifene had adherence rates 65-70%.**
High	**There is evidence from 58 observational studies, including 24 using U.S. data, that adherence and persistence with therapy with bisphosphonates, calcium, and vitamin D is poor in many patients with osteoporosis. One study described adherence with teriparatide. No studies describe primary nonadherence (i.e. nonfulfillment).**
Moderate	**Based on evidence from 41 observational studies, many factors affect adherence and persistence with medications including, but not limited to, dosing frequency, side effects of medications, co-morbid conditions, knowledge about osteoporosis, and cost. Age, prior history of fracture, and concomitant medication use do not appear to have an independent association with adherence or persistence.**
High	**Based on 20 observational studies, dosing frequency appears to affect adherence/persistence: adherence is improved with weekly compared to daily regimens, but current evidence is lacking to show that monthly regimens improve adherence over that of weekly regimens.**
Moderate	**Evidence from a systematic review and 15 out of 17 observational studies suggest that decreased adherence to bisphosphonates is associated with an increased risk of fracture (vertebral, nonvertebral or both).**
Low	**The evidence on adherence to raloxifene, teriparatide, and other drugs and its association with fracture risk is insufficient to make conclusions.**
Key Question 4. What are the short- and long-term harms (adverse effects) of the above therapies, and do these vary by any specific subpopulations?	
High	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.
High	Estrogen and estrogen-progestin combination participants had higher odds of cerebrovascular accident (CVA) and thromboembolic events than did placebo participants.
High	**A pooled analysis of ten trials found an increased risk with raloxifene for myalgias, cramps, and limb pain.**
High	We categorized conditions such as acid reflux, esophageal irritation, nausea, vomiting, and heartburn as "mild upper GI events." Our pooled analyses **showed alendronate had a slightly increased risk of** mild upper GI events. Alendronate participants also had higher odds of mild upper GI events in head-to-head trials vs. menopausal hormone therapy. **Pooled analysis also showed alendronate users to be at an increased risk for mild GI events compared to denosumab. Denosumab was also associated with an increase in mild GI events**.
Low	**A 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.**
Moderate	**Teriparatide-treated participants showed a significant increase in hypercalcemia.**
Insufficient	The literature is equivocal on the potential association between bisphosphonates and the risk of atrial fibrillation.

Table A. Summary of evidence (continued)	
Strength of Evidence	**Conclusion**
High	One trial, one post hoc analysis of three trials, two 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 one to 28 cases per 100,000 person-years of treatment.
High	Our pooled analysis of eight trials found an increased risk with raloxifene of hot flashes.
Low	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.
Moderate	A pooled analysis of three trials of teriparatide found an increased risk of headaches.
High	A pooled analysis of four trials of denosumab found an increased risk of rash but no increase in the risk for injection-site reactions.
Moderate	A small number of clinical trials have reported an increased risk of hypocalcemia in patients treated with alendronate and zoledronic acid.
Insufficient	Four observational studies that assessed whether the use of an oral bisphosphonate is associated with an increased risk of esophageal cancer had mixed findings.
High	A pooled analysis of four trials of denosumab found an increased risk for infection.
Key Question 5a. How often should patients be monitored (via measurement of bone mineral density) during therapy?	
Insufficient	The role of BMD monitoring during therapy has not been explicitly studied; therefore any conclusions must be based on indirect evidence.
High	Changes in BMD during therapy account for only a small proportion of the decrease in fracture risk; while some studies suggest that greater change in BMD in active therapy groups predicts greater antifracture efficacy, these changes have not been demonstrated to apply to individuals. Even patients who continue to lose BMD during therapy have had statistically significant benefits in fracture reduction. Clinical guidance is lacking on appropriate responses to declines in BMD under active therapy, such as increasing medication dose, or the influence of discontinuing therapy among individuals who experience declines in BMD under active therapy but may nonetheless derive fracture protection.
Key Question 5b. How does the antifracture benefit vary with long-term continued use of pharmacotherapy?	
Moderate	One large RCT showed that after 5 years of initial alendronate therapy, vertebral fracture risk and nonvertebral fracture risk were lower if alendronate was continued for an additional 5 years instead of discontinued.
Low	A post hoc analysis of this same trial reported that there were statistically significant nonvertebral fracture risk reductions for women who at baseline had no vertebral fracture but had a BMD score of –2.5 or less.

What We Know About Whom To Treat and How

For clinicians, this report contributes information that may inform prescribing decisions:

- Evidence for antifracture effects of currently available osteoporosis therapies is greatest among those with established osteoporosis, meaning with existing fracture, or with T-score less than -2.5. Because at least half of osteoporotic fractures occur in individuals with T scores between -1 and -2.5, individuals with T-scores between -1 and -2.5 who are likely to experience fracture need to be identified.
- With the advent of tools such as the WHO's FRAX, selection of treatment candidates will likely be refined. Emerging research is judging the antifracture effects of medications according to level of multivariable risk prediction instruments.
- Older individuals are as likely, or may be even more likely, to benefit from treatment as younger individuals, in terms of reduced fracture risk.
- Bisphosphonates and denosumab are the only agents for which there is a high level of evidence for reduction in hip fracture risk.
- For reduction in vertebral fracture risk, there is a high level of evidence supporting the use of bisphosphonates, raloxifene, teriparatide, and denosumab.
- Raloxifene has been shown to be not effective in reducing the risk of hip or nonvertebral fractures.
- To date, the comparative efficacy of available treatments has not been assessed among men with idiopathic osteoporosis.
- Although not definitive proof of who is likely to benefit from prolonged alendronate therapy, post hoc analyses of open-label extension data support the thesis that certain features predict continued fracture reduction with a 10-year instead of 5-year duration of alendronate therapy: BMD T-score of -1 to -2 (if women have baseline fractures), and BMD T-score <-2 if women do not have baseline fractures. These same factors have not been evaluated with other osteoporosis pharmacotherapies. Studies have not directly compared the antifracture effects of longer durations of therapy among various therapies.
- Clinicians should be aware that, among people taking FDA-approved osteoporosis pharmacotherapy, changes in BMD are not good predictors of antifracture effects. Studies are currently examining whether serial BMD monitoring may be useful for other purposes.

Remaining Issues

Compared with the evidence available at the time of the prior report, additional evidence has emerged to clarify differences in anti-fracture efficacy between pharmacologic agents used to treat osteoporosis (e.g., hip fracture reduction only demonstrated for bisphosphonates and denosumab), and even among bisphosphonates (e.g., hip fracture reduction demonstrated for zoledronic acid, alendronate, and risedronate, but not ibandronate) among postmenopausal women with established osteoporosis. Nonetheless, data are thin regarding the comparative effectiveness or efficacy between different agents, and several concerns remain:

1. Whom should we treat? What is the balance of benefits and harms for postmenopausal women without established osteoporosis? The existing evidence shows that the strength of evidence for a benefit of treatment (in terms of fracture risk reduction) is low to moderate for postmenopausal women with osteopenia and without prevalent fractures and for men compared with postmenopausal women with established osteoporosis for whom the evidence is high. Given the established adverse events associated with treatment, and newly identified risks such as atypical subtrochanteric femur fractures, the question of whom to treat outside of postmenopausal women with established osteoporosis is perhaps less clear now than it was before. One way forward is to move away from BMD-based measures of risk and conduct trials that use a risk assessment-based method of identifying patients, such as the FRAX. Such risk assessment methods can incorporate other variables known to be associated with risk of fracture that go beyond bone mineral density. Re-analysis of existing trials should assess whether application of FRAX estimates post hoc allows for identification of subgroups of subjects at higher or lower risk than the typical subjects.

2. How long should we treat? The evidence base here is especially thin—the existing evidence is really just one trial, and one post hoc analysis of that trial, which suggests that treatment beyond five years with alendronate does not have a benefit in nonvertebral fracture risk

reduction, except possibly in women with low BMD at baseline. Should treatment be for three years, four years, five years, or more? And what patient factors are important (such as the aforementioned low BMD at baseline) in terms of determining length of treatment? "Drug holidays" have been advocated by some clinicians—what are the benefits and harms of such holidays? When should they be timed? For how long should the "holiday" last? Could the efficacy of drug holidays vary according to pharmacologic profiles (e.g., route or frequency of administration) of the various bisphosphonates? And should all therapies be subject to a holiday, a point raised by a recent basic science analysis of denosumab?[22]

3. For people who are good candidates for treatment, how can we improve adherence? There is a moderate to high level of evidence that adherence is commonly poor, and that poor adherence is associated with worse fracture outcomes. This work needs to consider not just the dosing barriers to adherence, but the other factors reported in the evidence (e.g., side effects, knowledge about osteoporosis, and cost.) The role of newer therapies administered once or twice yearly in improving adherence and persistence, and their cost-effectiveness, should be investigated.

4. For patients on treatment, should we monitor changes in BMD, and if so, how often? While no studies have examined explicitly the benefits and harms of BMD monitoring while on therapy, the practice remains popular, although the rationale for it is not clear. Post hoc analyses of trials of treatment show that changes in BMD while on treatment only modestly predict fracture risk reduction, and even patients whose BMD declines while on treatment have statistically significant reductions in fracture risk.

5. What is the comparative effectiveness of sequential treatment (following treatment with one class of agent by treatment with another)? We identified no clinical trials on the use of sequential treatment, although anecdotal evidence suggests that it is done in clinical practice (either intentionally, in the belief that it is superior to continued treatment with a single agent, or because some individuals do not respond to or cannot tolerate a particular agent). Thus studies are needed to assess the effectiveness of sequential regimens.

6. We need to remain vigilant for possible rare side effects. The identification—since our prior 2007 report—of an association between bisphosphonate use and atypical subtrochanteric fractures of the femur demonstrates the importance of the continuing need for surveillance, as this identification was not widely reported until after well more than a decade of widespread use.

References

1. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. JAMA. 2001;285(6):785-95.
2. Sasser ACR, M. D. Birnbaum, H. G. Oster, E. F. Lufkin, E. Mallet, D. Economic burden of osteoporosis, breast cancer, and cardiovascular disease among postmenopausal women in an employed population. Womens Health Issues. 2005;15(3):97-108. PMID: 15894195.
3. National Osteoporosis Foundation. Clinician's Guide to Prevention and Treatment of Osteoporosis. Washington, DC; 2010.
4. Burge R, Dawson-Hughes B, Solomon DH, et al. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. J Bone Miner Res. 2007;22(3):465-75. PMID: 17144789
5. Nelson HD, Haney EM, Dana T, et al. Screening for Osteoporosis: An update for the U.S. Preventive Services Task Force. Annals of Internal Medicine. 2010;153(2):1-11.
6. Kanis JA, Melton LJ III, Christiansen C. Johnston CC, Khaltaev N. The diagnosis of osteoporosis. J Bone Miner Res. 1994;9(8):1137-41. PMID: 7976495.
7. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. WHO Fracture Risk Assessment Tool. www.shef.ac.uk/FRAX/
8. Kanis JA, Johnell O, Oden A, et al. FRAX and the assessment of fracture probability in men and women from the UK. Osteoporos Int. 2008;19(4):385-97. PMID: 18292978.
9. Kanis JA, Oden A, Johnell O, et al. The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. Osteoporos Int. 2007;18(8):1033-46.
10. Lewiecki EM, Binkley N. Evidence-based medicine, clinical practice guidelines, and common sense in the management of osteoporosis. Endocr Pract. 2009;15(6):573-9. PMID: 19491062.
11. Kanis JA, Johansson H, Oden A, et al. Assessment of fracture risk. Eur J Radiol. 2009;71(3):392-7. PMID: 19716672.
12. Colman EG. The Food and Drug Administration's Osteoporosis Guidance Document: past, present, and future. J Bone Miner Res. 2003;18(6):1125-8.
13. Guidelines for Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Postmenopausal Osteoporosis. Rockville, MD: Food and Drug Administration, Division of Metabolic and Endocrine Drug Products; 1994.
14. MacLean CA, Alexander A, Carter J, Chen S, Desai SB, Grossman J, Maglione M, McMahon M, McNamara M, Mojica W, Newberry S, Ranganath V, Suttorp M, Timmer M, Tringale C, Valentine D, Zhou A. Comparative Effectiveness of Treatments To Prevent Fractures in Men and Women With Low Bone Density or Osteoporosis. (Prepared by Southern California/RAND Evidence-based Practice Center under Contract No. 290-02-000.) Rockville, MD. Agency for Healthcare Research and Quality. December 2007. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

15. Shekelle PG, Newberry SJ, Maglione M, et al. Evaluation of the need to update comparative effectiveness reviews. Rockville, MD: Agency for Healthcare Research and Quality; October 2009. www.effectivehealthcare.ahrq.gov/ehc/products/125/331/2009_0923UpdatingReports.pdf.

16. Whitlock EP, Lin JS, Chou R, et al. Using existing systematic reviews in complex systematic reviews. Ann Intern Med. 2008;148(10):776-82. PMID: 18490690.

17. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1-12.

18. Wells GA SB, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. Newcastle- Ottawa Quality Assessment Scale, Cohort Studies. Quality Assessment Scales for Observational Studies. 2004.

19. Gartlehner G, Hansen RA, Nissman D, et al. A simple and valid tool distinguished efficacy from effectiveness studies. J Clin Epidemiol. 2006;59(10):1040-8. PMID: 16980143.

20. Owens DKL, K.N. Atkins, D. Et al. AHRQ series paper 5: Grading the strength of a body of evidence when comparing medical interventions-Agency for Healthcare Research and Quality and the Effective Health Care Program. J Clin Epidemiol. 2010;63(5):513-23.

21. Atkins DB, D. Briss, P. A. Eccles, M. Falck-Ytter, Y. Flottorp, S. Guyatt, G. H. Harbour, R. T. Haugh, M. C. Henry, D. Hill, S. Jaeschke, R. Leng, G. Liberati, A. Magrini, N. Mason, J. Middleton, P. Mrukowicz, J. O'Connell, D. Oxman, A. D. Phillips, B. Schunemann, H. J. Edejer, T. T. Varonen, H. Vist, G. E. Williams, J. W., Jr. Zaza, S. Grading quality of evidence and strength of recommendations. BMJ. 2004;328(7454):1490. PMID: 15205295.

22. Baron R, Ferrari S, Russell RG. Denosumab and bisphosphonates: different mechanisms of action and effects. Bone. 2011;48(4):677-92. PMID: 21145999.

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