Comparative Effectiveness of Pharmacologic Treatments to Prevent Fractures
An Updated Systematic Review
Carolyn J. Crandall, MD, MS; Sydne J. Newberry, PhD; Allison Diamant, MD, MSHS; Yee-Wei Lim, MD, PhD; Walid F. Gellad, MD, MPH; Marika J. Booth, MS; Aneesa Motala, BA; and Paul G. Shekelle, MD, PhD

Background: Osteoporosis is a major contributor to the propensity to fracture among older adults, and various pharmaceuticals are available to treat it.

Purpose: To update a review about the benefits and harms of pharmacologic treatments used to prevent fractures in adults at risk.

Data Sources: Multiple computerized databases were searched between 2 January 2005 and 4 March 2014 for English-language studies.

Study Selection: Trials, observational studies, and systematic reviews.

Data Extraction: Duplicate extraction and assessment of data about study characteristics, outcomes, and quality.

Data Synthesis: From more than 52,000 titles screened, 315 articles were included in this update. There is high-strength evidence that bisphosphonates, denosumab, and teriparatide reduce fractures compared with placebo, with relative risk reductions from 0.40 to 0.60 for vertebral fractures and 0.60 to 0.80 for nonvertebral fractures. Raloxifene has been shown in placebo-controlled trials to reduce only vertebral fractures. Since 2007, there is a newly recognized adverse event of bisphosphonate use: atypical subtrochanteric femur fracture. Gastrointestinal side effects, hot flashes, thromboembolic events, and infections vary among drugs.

Limitations: Few studies have directly compared drugs used to treat osteoporosis. Data in men are very sparse. Costs were not assessed.

Conclusion: Good-quality evidence supports that several medications for bone density in osteoporotic range and/or preexisting hip or vertebral fracture reduce fracture risk. Side effects vary among drugs, and the comparative effectiveness of the drugs is unclear.

Primary Funding Source: Agency for Healthcare Research and Quality and RAND Corporation.

METHODS

This article is a condensed and further updated version of an evidence review conducted for the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers program (5). This article focuses on the comparative benefits and risks of short- and long-term pharmacologic treatments for low bone density. In addition, we address issues regarding monitoring and duration of therapy. For this updated review, we followed the same methods as our 2007 review, with a few exceptions. A protocol for this review was developed and posted on the Effective Health Care Program Web site (6).

Data Sources and Searches

We searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, the ACP Journal Club database, the National Institute for Clinical Excellence, the
Food and Drug Administration’s (FDA) MedWatch database, and relevant pharmacologic databases from 2 January 2005 to 3 June 2011. The search strategy followed that of the original report, with the addition of terms for new FDA-approved drugs (such as denosumab) and newly reported adverse events. The full search strategies are in our evidence report (5). We later updated this search to 21 January 2013 and used a machine learning method that a previous study showed had high sensitivity for detecting relevant evidence for updating a search of the literature on osteoporosis treatments (7) and then updated the searches to 4 March 2014 using the full search strategy.

**Study Selection**

Eligible studies were systematic reviews and randomized, controlled trials (RCTs) that studied FDA-approved pharmacotherapy (excluding calcitonin and etidronate) for women or men with osteoporosis that was not due to a secondary cause (such as glucocorticoid therapy and androgen-deprivation therapy) and also measured fractures as an outcome at a minimum follow-up of 6 months. In addition, we included observational studies with more than 1000 participants for adverse events and case reports for rare events. As in our original review, only English-language studies were included.

**Data Extraction and Quality Assessment**

Reviews were done in duplicate by pairs of reviewers. Study characteristics were extracted in duplicate, and outcomes data (both benefits and harms) were extracted by the study statistician. Study quality was assessed as it was in the 2007 report using the Jadad scale for clinical trials (with several questions added to assess allocation concealment and other factors) and the Newcastle–Ottawa Scale for observational studies (8, 9). Systematic reviews were assessed using a modified version of the 11 AMSTAR (A Measurement Tool to Assess Systematic Reviews) criteria (the modifications included eliminating the requirements to list all of the excluded studies and assess the conflicts of interest for all of the included studies) (10). The assessments of efficacy and effectiveness used reduction in fracture (all, vertebral, nonvertebral, spine, hip, wrist, or other) as the outcome (studies reporting changes in BMD but not fracture were excluded).

**Data Synthesis and Analysis**

Evidence on efficacy and effectiveness was synthesized narratively. For adverse events, we pooled data as in the 2007 report: We compared agent versus placebo and agent versus agent for agents within the same class and across classes. For groups of events that occurred in 3 or more trials, we estimated the pooled odds ratio (OR) and its associated 95% CI. Because many events were rare, we used exact conditional inference to perform the pooling rather than applying the usual asymptotic methods that assume normality. StatXact PROCs software was used for the analysis (11, 12). Large cohort and case–control studies were included to assess adverse events. Strength of evidence was assessed using the criteria of the Agency for Healthcare Research and Quality Evidence-based Practice Centers program, which are similar to those proposed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group (13).

**Role of the Funding Source**

The update that included studies identified in the 3 June 2011 search was funded by AHRQ. Subsequent updating received no external funding. Although AHRQ formulated the initial study questions for the original report, it did not participate in the literature search, determination of study eligibility criteria, data analysis, or interpretation of the data. Staff from AHRQ reviewed and provided comments on the report.

**RESULTS**

The first search yielded 26 366 titles, 2440 of which were considered potentially relevant (Figure). Of these, 661 full-text articles were reviewed, resulting in 255 articles that were included in the update report. Of these, 174 articles were relevant to this article. The second update search plus hand searching initially yielded 16 589 titles, and machine learning and full-text review identified 107 as relevant. The third update yielded 12 131 titles. After title, abstract, and full-text screening, 34 were relevant. Thus, 55 086 titles were screened and 315 articles met eligibility criteria for inclusion. Not every eligible study is cited in this article. A complete list of studies that met eligibility criteria is available at www.rand.org/health/centers/epc.

**Fracture Prevention**

Our previous review (3) identified 76 randomized trials and 24 meta-analyses and concluded that there was good-quality evidence that alendronate, etidronate, ibandronate, risedronate, zoledronic acid, estrogen, parathyroid hormone, and raloxifene prevented osteoporotic fractures, although not all of these agents prevented hip fractures. The principal new efficacy findings since that time are additional data about zoledronic acid and data about a new agent, denosumab (Tables 1 and 2). The data for zoledronic acid came from 6 placebo-controlled studies of various doses in postmenopausal women (14–19), the 2 largest of which enrolled 7230 women (15) and 2127 women (14). Both studies showed statistically significant reductions in nearly all types of fractures assessed, with relative risk reductions ranging from 0.23 to 0.73 at time points from 24 to 36 months after initiation of treatment. The data for denosumab came from 2 placebo-controlled trials in postmenopausal women, one small (332 enrolled women) (20) and one much larger that followed 7521 women for 36 months (21). This latter study found statistically significant reductions in each anatomical fracture type measured (hip, nonvertebral, vertebral, and new clinical vertebral), with hazard ratios of 0.31 to 0.80. Many
secondary analyses and open-label extension results of this trial report the effectiveness of denosumab in various sub-populations and other circumstances (22–28).

Despite some difficulties in comparing results across trials because of differences in the outcomes reported, high-strength evidence shows that bisphosphonates (alendronate, ibandronate, risedronate, and zoledronic acid), denosumab, and teriparatide (the 1,34 amino acid fragment of the parathyroid hormone) reduce fractures compared with placebo in postmenopausal women with osteoporosis, with relative risks for fractures generally in the range of 0.40 to 0.60 for vertebral fractures and 0.60 to 0.80 for nonvertebral fractures. This range translates into a number needed to treat of 60 to 89 to prevent 1 vertebral fracture and 50 to 67 to prevent 1 hip fracture over 1 to 3 years of treatment, using a pooled average of the incidence of these fractures in the placebo groups from included studies. The effect of ibandronate on hip fracture risk reduction is unclear because hip fracture was not a separately reported outcome in placebo-controlled trials of this agent. The selective estrogen receptor modulator raloxifene has been shown in placebo-controlled trials to reduce only vertebral fractures; reduction in the risk for hip or nonvertebral fractures was not statistically significant.

There is only one randomized, controlled trial of men with osteoporosis that was designed with a primary fracture reduction outcome. Nearly 1200 men with osteoporosis were randomly assigned to placebo or zoledronic acid intravenously once per year for 2 years. At follow-up, 1.6% of treated men had new radiologically detected vertebral fractures, compared with 4.9% of men treated with placebo, with a relative risk of 0.33 (95% CI, 0.16 to 0.70).
Approximately 1.0% of actively treated men, compared with 1.8% of men treated with placebo, had a clinical vertebral or nonvertebral fracture (hazard ratio, 0.6 [CI, 0.2 to 1.5]) (29).

### Comparative Effectiveness

Head-to-head comparative effectiveness studies assessing fracture outcomes are rare, have either not reported statistical testing or fracture outcomes between groups (30), have found significant differences (3), or have analyzed the comparisons on a per-protocol rather than an intention-to-treat basis (31, 32). Thus, there have been several attempts to estimate comparative effectiveness using network meta-analysis and indirect or mixed treatment comparisons. A recent network meta-analysis of 116 placebo-controlled or head-to-head trials assessing alendronate, risedronate, ibandronate, zoledronic acid, raloxifene, denosumab, teriparatide, and calcium concluded that any of the drugs were likely more effective than placebo in preventing vertebral fractures (33).

A second network meta-analysis (AMSTAR score, 6 of 11) included 30 RCTs and found no significant differences in nonvertebral fracture risk in the indirect comparisons among alendronate, risedronate, etidronate, ibandronate, zoledronic acid, raloxifene, denosumab, teriparatide, or strontium, although the authors noted that etidronate, ibandronate, and raloxifene lack direct evidence of superiority to placebo (AMSTAR score, 7 of 11) (34).

A third network meta-analysis, both sponsored by and including coauthors from the manufacturer of one drug, included 21 studies and likewise found no statistically significant difference in indirect or mixed treatment comparisons in nonvertebral fracture risk reduction among alendronate, risedronate, etidronate, ibandronate, zoledronic acid, raloxifene, denosumab, teriparatide, or strontium. These authors also noted that etidronate, raloxifene, and ibandronate did not have direct evidence of a reduction in nonvertebral fractures relative to placebo (AMSTAR score, 3 of 11) (35).

A fourth network meta-analysis (AMSTAR score, 3 of 11), this time assessing alendronate, risedronate, ibandronate, zoledronic acid, and denosumab and restricting inclusion to studies that reported clinical and morphometric vertebral fractures and had a treatment period of at least 3 years, concluded that any of the drugs were likely more effective than placebo in preventing vertebral fractures (36).
years, included 9 RCTs and reported no statistically significant differences among drugs in the mixed treatment comparison (36).

A fifth network meta-analysis, sponsored by and including authors from the manufacturer of one drug, included 8 RCTs to assess the relative effectiveness of alendronate, ibandronate, risedronate, etidronate, and zoledronic acid on many fracture outcomes (AMSTAR score, 6 of 11). Other than the sponsor’s drug and the outcome of morphometric vertebral fractures, this analysis did not find any consistent significant differences among drugs for the various fracture outcomes (37).

All of these network meta-analyses are limited by the dearth of head-to-head studies; nevertheless, their conclusions are consistent with our narrative synthesis of the evidence. Raloxifene does not prevent nonvertebral fractures, and there is less evidence supporting nonvertebral fracture reduction efficacy for ibandronate than for the other bisphosphonates, denosumab, or teriparatide. Other differences in comparative effectiveness among drugs are likely to be small.

Adverse Events
Atypical Subtrochanteric Fractures

An important new potential adverse event is the increased risk for atypical subtrochanteric fractures seen in patients treated with bisphosphonates (Table 3). At present, these associations come entirely from observational studies, and results are not completely consistent (38–71). An increased risk has not been seen in clinical trials, although even an analysis of data aggregated from 3 large trials (a total of 14 195 women) was underpowered to detect an effect (pooled relative risk, 1.33 [CI, 0.12 to 14.7]) (61). A systematic review of case and case series studies (AMSTAR score, 7 of 9) (66) identified 141 women with this fracture, and the FDA issued a warning about the possible link between bisphosphonate use and this adverse event (72).

Since then, a recent meta-analysis of 5 case–control studies and 6 cohort studies (AMSTAR score, 10 of 11) found an overall pooled risk ratio of 1.70 (CI, 1.22 to 2.37) (73). A 2013 analysis of the data from the FDA Adverse Event Reporting System and other international drug safety databases reported a proportional reporting ratio of 4.51 (CI, 3.44 to 5.92) (74) for nonhealing femoral fractures. A 2014 update of the American Society for Bone and Mineral Research task force concluded that evidence for a relationship has become more compelling since its 2010 report, particularly with longer bisphosphonate use (75). Despite the limitation created by the variation in the definition of atypical fracture across studies, data are sufficient to conclude that bisphosphonate use, especially long-term, increases risk for atypical femoral fractures, although the strength of evidence is low. It is important to note that the absolute risk for atypical fractures is 30- to 100-fold less than the risk for hip fracture among untreated persons at risk. In one study from Kaiser Permanente Southern California of 1 835 116 women aged 45 years or older over 5 years, there were 7430 typical hip fractures and 142 atypical femur fractures. The finding that the incidence rate of atypical fractures increased from 1.78 per 100 000 for women receiving bisphosphonates for less than 2 years to more than 100 per 100 000 for women receiving bisphosphonates for 8 years or more supports the idea that treatment duration may be a factor (52). Use of denosumab has also been linked with atypical femoral fractures (26).

Cancer

We found low-strength signals of potential associations with various types of cancer, but additional data are needed. Four large observational studies have assessed a possible association between the use of bisphosphonates and esophageal cancer, 2 of which reported an increased risk (76, 77) and 2 of which did not (78, 79). Several large observational studies found that bisphosphonate use was associated with either no increased risk or, in some cases, a statistically significant decrease in the risk for all types of cancer in general (80–83) and certain types of cancer, specifically breast (81), colon, and other gastrointestinal cancer (80, 84). A meta-analysis of 4 studies (AMSTAR score, 8 of 11) concluded that there were statistically significantly increased odds (1.74) for esophageal cancer in patients

<table>
<thead>
<tr>
<th>Table 2. Principal Conclusions About Monitoring and Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conclusion</strong></td>
</tr>
<tr>
<td>Monitoring is likely not needed in most women</td>
</tr>
<tr>
<td>How long to treat is unknown, but high-risk patients may benefit from treatment longer than 5 y</td>
</tr>
</tbody>
</table>

BMD = bone mineral density.
treated with bisphosphonates (85), but another meta-analysis (AMSTAR score, 7 of 11) that included the same 4 studies and 3 additional ones found no association of risk for esophageal cancer with bisphosphonate use (86). The FDA has not concluded that patients receiving oral bisphosphonate drugs have an increased risk for esophageal cancer. An evaluation of osteosarcoma and teriparatide showed no relationship at 7-year follow-up (87).

**Cardiac Risks**

An adverse event prominently discussed in 2007 was the potential for bisphosphonate use to cause atrial fibrillation. In 2008, the FDA concluded that “there was no clear association” between bisphosphonate use and atrial fibrillation. Since that time, most (88–92) but not all (93) original studies and meta-analyses have concluded that there is no increased risk, and concern about atrial fibrillation has faded. A retrospective cohort study using Danish registry data reported on the risk for a diagnosis of heart failure after bisphosphonate prescription. Risk increased with risedronate use and decreased with alendronate use, rendering interpretation of a causal relationship difficult (94).

**Gastrointestinal Side Effects**

In our previous review, we did a meta-analysis of adverse events that included 417 randomized trials. In this paper, we identified 31 new articles reporting adverse events, 17 of which contributed to updated pooled analyses (18, 32, 80, 95–108). These updated analyses showed increased risk for mild upper gastrointestinal side effects with use of alendronate (OR, 1.07 [CI, 1.01–1.14]), teriparatide (OR, 3.26 [CI, 2.82 to 3.78]), and denosumab (OR, 1.74 [CI, 1.29 to 2.38]). A network meta-analysis attempted to assess the comparative gastrointestinal safety of bisphosphonates and included 50 RCTs (49 of which were also included in our pooled analyses). For the outcome “treatment discontinuation due to adverse events,” this
network meta-analysis did not find any statistically significant differences among any of the bisphosphonates included in our key questions (109). Consistent with our 2007 meta-analysis, a case–control study (804 case and 12 787 control participants) found no statistically significant association between oral alendronate or risedronate use and the risk for subsequent hospitalization for serious upper gastrointestinal diagnoses (perforations, ulcers, and bleeding) (110).

Infection
A pooled analysis of 4 trials of denosumab found an increased risk for infection (risk ratio [RR], 1.28 [CI, 1.02 to 1.60]) (111), and the FDA has issued a Risk Evaluation and Mitigation Strategy for the drug. In the largest denosumab trial, there were imbalances between patients treated with denosumab and those receiving placebo for cellulitis, erysipelas, serious ear infections, infective arthritis, and endocarditis. A causal relationship has not been established.

Osteonecrosis of the Jaw
At the time of our previous review, 41 cases of osteonecrosis of the jaw had been identified, nearly all associated with the use of intravenous bisphosphonates. Since that time, 23 publications have assessed this association (112–134) (not counting individual case reports), including a case series of 2408 cases of osteonecrosis of the jaw that found that 88% were associated with intravenous bisphosphonates and 89% of patients were being treated for a malignant condition (135), a survey of practitioners that estimated an incidence of 28 cases per 100,000 person-years of exposure (129), and 4 systematic reviews (127, 132–134). The most recent of these systematic reviews identified 9 and 12 articles (133, 134), respectively, of studies about osteonecrosis of the jaw in noncancer patients. The first review (133) (AMSTAR score, 6 of 9) reported that limitations in case definition and the identification of the denominator led to wide variation in the reported incidence, from 0.028% to 4.3%, and these authors refrained from statistical pooling. The second review (134) (AMSTAR score, 6 of 11) pooled 12 studies with high heterogeneity and found an OR of 2.32 (CI, 1.30 to 3.91; I² = 41%). This association was of similar magnitude in multiple sensitivity analyses. Osteonecrosis of the jaw has also been reported with denosumab use (26).

Other
Our pooled analyses showed teriparatide to be associated with an increased risk for hypercalcemia (OR, 12.90 [CI, 10.49 to 16.00]) and zoledronic acid (OR, 7.22 [CI, 1.81 to 42.70]) to be associated with an increased risk for hypocalcemia (however, 85% of patients did not require supplemental calcium). Hot flashes (OR, 1.58 [CI, 1.35 to 1.84]), thromboembolic events (OR, 1.63 [CI, 1.36 to 1.98]), pulmonary embolism (OR, 1.82 [CI, 1.16 to 2.92]), and fatal strokes (OR, 1.56 [CI, 1.04 to 2.39]) have been associated with raloxifene use. Headaches (OR, 1.46 [CI, 1.27 to 1.69]) and renal-related adverse events have been associated with teriparatide use. Zoledronic acid infusion is associated with a constellation of symptoms that have been described as myalgia, arthralgia, pyrexia, chills, and influenza-like symptoms. A composite of these symptoms has a pooled OR of 6.39 (CI, 5.76 to 7.09). Table 1 displays the results of our pooled analyses of RCTs for all adverse events (adverse events were included if at least 3 trials discussed that event or if the RCTs regarding the event had sample sizes of at least 1000 patients in both the treatment and placebo groups).

A study using a national registry in Denmark reported that the risk for inflammatory eye reactions in certain patients treated with bisphosphonates is low (136).

Treatment Duration
Only 2 large RCTs have compared shorter with longer durations of therapy. In the Fracture Intervention Trial Long-Term Extension (FLEX) study (the original RCT compared alendronate and placebo for 5 years among postmenopausal women), several subsequent analyses have addressed longer (10-year) versus shorter (5-year) therapy with alendronate. At 10-year follow-up, the cumulative risk for nonvertebral fractures was not significantly different between those continuing (19%) and discontinuing (19%) alendronate (137). However, among women who continued alendronate, there was a significantly lower risk for clinically recognized vertebral fractures (5.3% for placebo vs. 2.4% for alendronate; RR, 0.45 [CI, 0.24 to 0.85]) but no significant reduction in morphometric vertebral fractures.

In a recent post hoc analysis of the FLEX data, investigators assessed whether baseline BMD or preexisting fracture could influence the effects of longer duration of therapy (10 vs. 5 years). Among women without vertebral fracture at FLEX baseline, alendronate continuation reduced nonvertebral fracture among women with FLEX baseline femoral neck T-scores of −2.5 or less (RR, 0.50 [CI, 0.26 to 0.96]) but not among women with T-scores between −2.5 and −2.0 (RR, 0.79 [CI, 0.37 to 1.66]) or those with T-scores of greater than −2.0 (RR, 1.41 [CI, 0.75 to 2.66]; P for interaction, 0.019). Among women with a prevalent vertebral fracture at baseline and a BMD T-score at 5 years of −2.5 or less, continued use of alendronate for 5 years decreased the incidence of new clinical vertebral fractures from 11.1% to 5.3%, compared with placebo. The investigators concluded that continuing with alendronate for 10 years instead of stopping after 5 years reduced nonvertebral fracture risk in women without prevalent vertebral fracture whose femoral neck T-scores, achieved after 5 years of alendronate, were −2.5 or less but did not reduce risk for nonvertebral fracture risk among women without prevalent vertebral fractures whose T-scores were greater than −2.0 (138).
In the Health Outcomes and Reduced Incidence With Zoledronic Acid Once Yearly Pivotal Fracture Trial, approximately 1200 women who had received zoledronic acid for 3 years were randomly assigned to continue for another 3 years or be switched to placebo. Incidence of radiographically detected vertebral fracture was lower in the patients continuing zoledronic acid (3.0% vs. 6.2% in patients receiving placebo; OR, 0.51 [CI, 0.26 to 0.95]), but there were no differences between groups in clinical vertebral fractures, hip fractures, nonvertebral fractures, or all clinical fractures (139).

In a recent FDA review on this subject (which involved the FDA’s own analysis and pooling of data from these 3 trials with an older and much smaller study of risedronate [140]), the FDA found that the rate of vertebral and nonvertebral fractures in patients who received bisphosphonates for more than 6 years was 9.3% to 10.6% compared with 8.0% to 8.8% for patients who switched to placebo. The FDA concluded that “these data raise the question of whether continued bisphosphonate therapy imparts additional fracture-prevention benefit, relative to cessation of therapy after 5 years” (141). In an accompanying commentary, leading osteoporosis experts cautioned that these data came primarily from 2 large studies of alendronate and zoledronic acid, which were subsets of the original randomized cohorts, that they should not be extended to other bisphosphonates, and that FLEX patients with a BMD T-score of −2.5 or less received added benefits from continuing alendronate therapy beyond 5 years (142).

**Dual-Energy X-Ray Absorptiometry Monitoring**

Little direct research has been done on the frequency of monitoring for osteoporosis or how often patients should be monitored once they begin antiresorptive therapy. Two population studies of persons not taking osteoporosis treatment showed that frequent monitoring for the development of osteoporosis may not be necessary, except in women with a T-score of −2.0 to −2.49 (143, 144). For patients receiving antiresorptive therapy for whom serial BMD measurements have not shown an increase, or have even shown decrease in BMD, statistically significant benefits are still obtained in terms of fracture reduction (145–150). Despite a lack of evidence supporting frequent monitoring, one study found that among 549 women being followed at an academic medical center, patients received an average of 3.0 dual-energy x-ray absorptiometry scans over a mean of 2.4 years (for example, an average of >1 per year). A chart review of a random sample of 92 patients found that, for these women, the primary rationale listed for 177 of 196 scans (90%) was that they were “due”; no treatment change was made after 84% of the scans (151). This single-site study cannot support strong conclusions, but does highlight the need for more studies about the appropriate use of dual energy x-ray absorptiometry scans.

**DISCUSSION**

The principal conclusions of this update are presented in Tables 1 and 2. Compared with the evidence available at the time of the previous report, additional evidence has emerged about differences in antifracture efficacy among pharmacologic agents used to treat osteoporosis. Nonetheless, data about the comparative effectiveness or efficacy among agents are thin, and it is likely that differences among the bisphosphonates, denosumab, and teriparatide are modest. The side effect profiles vary among drugs, but many are associated with gastrointestinal effects. Bisphosphonate and possibly denosumab use carry the risk for very rare side effects, such as atypical subtrochanteric fracture or osteonecrosis of the jaw. There is evidence that women with an initial T-score of −1.49 or greater do not benefit from repeated BMD reassessment in less than 15 years. Among persons receiving FDA-approved osteoporosis pharmacotherapy, changes in BMD are not good predictors of antifracture effects. Likewise, the optimal duration of therapy remains murky, although evidence suggests that, at least for alendronate, some groups of patients can have the drug safely discontinued after 5 years of treatment.

There are many limitations to our review. The most important of these is the dearth of head-to-head comparisons of the benefits and harms of the agents. This has led several investigators to estimate comparative effectiveness using indirect methods. Although no consistent differences in efficacy have been found, this does not constitute proof that they do not exist. The lack of data in men leaves clinicians and policymakers to try to extrapolate from data in women, which may not be valid. Additional limitations common to all systematic reviews are the possibility of publication bias and heterogeneity in the definition of outcomes and adverse events. Limitations of this review include our reliance on English-language publications and no assessment of costs.

Osteoporosis treatment is an area of very active research. In addition to published studies of new drugs and combinations of drugs being tested for efficacy (152–155), studies are ongoing about the comparative effectiveness of some agents (156), the treatment of men (157), and the optimal duration of treatment (158).

From David Geffen School of Medicine at the University of California, Los Angeles, and Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles, California; RAND Corporation, Santa Monica, California; Saw Swee Hock School of Public Health, National University of Singapore, Singapore; and RAND Corporation, Pittsburgh Veterans Affairs Medical Center, and the Center for Health Equity Research and Promotion, Pittsburgh, Pennsylvania.

**Acknowledgment:** The authors acknowledge Roberta Shanker, MLS, for conducting the update searches and Kanaka Shetty, MD, and Michael Scarpatici, PhD, for the use of machine learning for the 2013 update searches. In addition, they acknowledge the guidance provided by the technical expert panel members, Roberta Biegel, MA; Bruce Ettinger,
Comparative Effectiveness of Pharmacologic Treatments to Prevent Fractures

MD; Theodore Hahn, MD; Marc Hochberg, MD, MPH; Hau Liu, MD; Catherine MacLean, MD, PhD; Paul Miller, MD; Eric Orwoll, MD; Marcel E. Salive, MD, MPH; and Daniel Solomon, MD, MPH.

Grant Support: By the Agency for Healthcare Research and Quality (AHRQ) (HHS)A290200710062I). No statement in this article should be construed as an official position of AHRQ or the U.S. Department of Health and Human Services.

Disclosures: All authors received grant support from AHRQ during the conduct of the study. Dr. Gellad reports grant support from Express Scripts outside the submitted work. Dr. Shellek reports royalties from UpToDate outside the submitted work and was an author of an American College of Physicians guideline on this topic. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M14-0317.

Requests for Single Reprints: Carolyn J. Crandall, MD, MS, Professor of Medicine, David Geffen School of Medicine, Division of General Internal Medicine & Health Services Research, University of California, Los Angeles, 911 Broxton Avenue, 1st Floor, Los Angeles, CA 90024; e-mail, ccrandall@mednet.ucla.edu.

Current author addresses and author contributions are available at www.annals.org.

References


Current Author Addresses: Drs. Crandall and Diamant: David Geffen School of Medicine, Division of General Internal Medicine & Health Services Research, University of California, Los Angeles, 911 Broxton Avenue, 1st Floor, Los Angeles, CA 90024.
Dr. Newberry, Ms. Booth, and Ms. Motala: RAND Corporation, 1776 Main Street, Santa Monica, CA 90401.
Dr. Lim: Saw Swee Hock School of Public Health, National University of Singapore, Singapore MD3, 16 Medical Drive, Singapore 117597.
Dr. Gellad: Pittsburgh Veterans Affairs Medical Center and the Center for Health Equity Research and Promotion, University Drive, Pittsburgh, PA 15240.
Dr. Shekelle: Veterans Affairs Los Angeles Healthcare System, 11301 Wilshire Boulevard, Los Angeles, CA 90073.

Statistical expertise: M.J. Booth.
Obtaining of funding: P.G. Shekelle.
Administrative, technical, or logistic support: A. Motala, P.G. Shekelle.