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REVIEW

Long-Term Drug Therapy and Drug Discontinuations and Holidays for Osteoporosis Fracture Prevention

A Systematic Review

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Background: Optimal long-term osteoporosis drug treatment (ODT) is uncertain.

Purpose: To summarize the effects of long-term ODT and ODT discontinuation and holidays.

Data Sources: Electronic bibliographic databases (January 1995 to October 2018) and systematic review bibliographies.

Study Selection: 48 studies that enrolled men or postmenopausal women aged 50 years or older who were being investigated or treated for fracture prevention, compared long-term ODT (>3 years) versus control or ODT continuation versus discontinuation, reported incident fractures (for trials) or harms (for trials and observational studies), and had low or medium risk of bias (ROB).

Data Extraction: Two reviewers independently rated ROB and strength of evidence (SOE). One extracted data; another verified accuracy.

Data Synthesis: Thirty-five trials (9 unique studies) and 13 observational studies (11 unique studies) had low or medium ROB. In women with osteoporosis, 4 years of alendronate reduced clinical fractures (hazard ratio [HR], 0.64 [95% CI, 0.50 to 0.82]) and radiographic vertebral fractures (both moderate SOE), whereas 4 years of raloxifene reduced vertebral but not nonvertebral fractures. In women with osteopenia or osteoporosis, 6 years of zoledronic acid reduced clinical fractures (HR, 0.73 [CI, 0.60 to 0.90]), including nonvertebral fractures (high SOE) and clinical vertebral fractures (moderate SOE). Long-term bisphosphonates increased risk for 2 rare harms: atypical femoral fractures (low SOE) and osteonecrosis of the jaw (mostly low SOE). In women with unspecified osteoporosis status, 5 to 7 years of hormone therapy reduced clinical fractures (high SOE), including hip fractures (moderate SOE), but increased serious harms. After 3 to 5 years of treatment, bisphosphonate continuation versus discontinuation reduced radiographic vertebral fractures (zoledronic acid; low SOE) and clinical vertebral fractures (alendronate; moderate SOE) but not nonvertebral fractures (low SOE).

Limitation: No trials studied men, clinical fracture data were sparse, methods for estimating harms were heterogeneous, and no trials compared sequential treatments or different durations of drug holidays.

Conclusion: Long-term alendronate and zoledronic acid therapies reduce fracture risk in women with osteoporosis. Long-term bisphosphonate treatment may increase risk for rare adverse events, and continuing treatment beyond 3 to 5 years may reduce risk for vertebral fractures. Long-term hormone therapy reduces hip fracture risks but has serious harms.

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Osteoporosis is a skeletal disorder of low bone mass and microarchitectural deterioration of bone that leads to bone fragility and increased risk for fracture (1). About 10 million U.S. adults aged 50 years or older have osteoporosis (2), and about 2 million U.S. adults experience an osteoporotic or other low-trauma fracture each year (3). Such fractures often cause pain, disability, and impaired quality of life (4, 5), and hip fractures and clinical vertebral fractures are associated with increased mortality (5, 6). Most fracture risks increase sharply with age; therefore, fracture burden is projected to increase in coming decades as the population ages.

Several osteoporosis drug treatments (ODT) reduce fractures in short-term randomized controlled trials of up to 3 years. Bisphosphonates, denosumab, teriparatide, and abaloparatide reduce nonvertebral fractures and clinical and radiographic vertebral fractures (7, 8). Bisphosphonates and denosumab also lower risk for hip fractures (8). Less is understood about the benefits and harms of initiating long-term ODT or, in patients who have already completed short-term treatment, of continuing versus discontinuing ODT. A recent American College of Physicians guideline recommended ODT with a bisphosphonate or denosumab for 5 years to reduce hip and vertebral fractures in osteoporotic women but suggested that high-risk patients may benefit from longer treatment (8).

Concerns that long-term bisphosphonate use might increase fracture risk by inhibiting normal repair of bone microdamage (9, 10) have led to suggestions

See also:

Related article 51
Editorial comment 62

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to stop bisphosphonate treatment and to restart it or another ODT later (called an ODT "drug holiday") (9). Several groups advocate bisphosphonate drug holidays to minimize harms while preserving as much antifracture benefit as possible. However, consensus is lacking around which patients should have bisphosphonate holidays, when, and for how long, as well as criteria for restarting treatment (9, 11, 12). In contrast, drug holidays are not recommended for denosumab users because bone loss increases rapidly after discontinuation, which may increase risk for vertebral fractures (13).

To focus on these uncertainties, this systematic review addressed 4 questions. First, what are the effects of long-term (>3 years) ODT versus control on risks for incident fractures and harms? Second, do the effects of long-term ODT vary as a function of patient, bone, or drug characteristics? Third, among patients receiving ODT to prevent fracture, what are the effects of continuing versus at least temporarily stopping treatment on risks for incident fractures and harms? Fourth, do outcomes of ODT continuation versus discontinuation vary as a function of patient, bone, or drug characteristics?

METHODS

We developed and followed a standard protocol, which is registered in PROSPERO (CRD42018087006) and available at https://effectivehealthcare.ahrq.gov/topics/osteoporosis-fracture-prevention/research-protocol. The full technical report contains search strategies, flow diagrams, evidence tables, study quality assessment tables, and detailed results (https://effectivehealthcare.ahrq.gov/topics/osteoporosis-fracture-prevention/research).

Data Sources and Searches

We searched MEDLINE, Embase, and the Cochrane Library for studies published from January 1995 through October 2018. We searched bibliographies of relevant systematic reviews published since 2012 and articles suggested by experts. We searched Clinical Trials.gov for additional studies.

Study Selection

We included English-language studies that enrolled postmenopausal women or men aged 50 years or older who were being investigated or treated for fracture prevention. Studies had to evaluate ODTs approved by the U.S. Food and Drug Administration and compare long-term ODT (>3 years) versus control or ODT continuation versus discontinuation (cessation for ≥1 year after ≥1 year of use). Trials reporting incident fractures must have reported results for participants with osteoporosis or osteopenia, whereas controlled observational studies reporting rare harms (such as atypical femoral fracture [AFF]) were not restricted by osteoporosis or osteopenia status. Populations with known secondary causes of osteoporosis were excluded. Two reviewers independently examined articles for eligibility and resolved discrepancies by consensus.

Data Extraction and Quality Assessment

For each eligible study, 2 reviewers independently rated risk of bias (ROB) for outcomes of interest as low, medium, or high on the basis of criteria from the Agency for Healthcare Research and Quality. For articles with low or medium ROB, 1 reviewer extracted details on study design, inclusion criteria, participant characteristics, interventions, treatment duration, and incident fractures and harms, and a second reviewer verified accuracy. Two reviewers graded strength of evidence (SOE) as high, moderate, low, or insufficient on the basis of study limitations, directness, consistency, and precision. We confirmed ROB and SOE assessments by consensus.

Data Synthesis and Analysis

We synthesized data qualitatively because studies had heterogeneous patient populations, intervention (exposure) and control groups, and definitions of incident fractures and harms. We considered studies that compared long-term ODT versus continuous (inactive) control separately from those comparing long-term ODT versus shorter-term ODT followed by discontinuation.

Role of the Funding Source

This review was funded by the National Institutes of Health (NIH) Office of Disease Prevention through an interagency agreement with the Agency for Healthcare Research and Quality. Agency staff, an NIH Office of Disease Prevention working group, an NIH content area expert group, and a technical expert panel helped refine the project scope. The draft report was presented at an NIH Office of Disease Prevention Pathways to Prevention workshop.

RESULTS

We identified 8356 unique publications through October 2018, of which 61 met eligibility criteria and were included in this review. Of the 48 eligible publications with low or medium ROB, 35 were trials (9 unique studies, including 7 of long-term ODT vs. placebo and 2 of ODT continuation vs. discontinuation without resumption) and 13 were controlled observational studies (11 unique studies, including 10 of long-term ODT vs. control and 1 of ODT continuation vs. discontinuation without resumption). Only 1 study included a treatment group of ODT followed by discontinuation and resumption (holiday), but results for its ODT holiday group were pooled with those of its continuous treatment and discontinuation groups.

All trials enrolled only postmenopausal women, most with osteoporosis defined by bone mineral density (BMD) or vertebral fracture history and some with osteopenia defined by BMD. Observational studies included 84% to 100% women. No observational studies reported BMD, but many enrolled participants with past fractures or ODT. Mean participant age was 72 years.

Long-Term ODT

Efficacy

In women with osteopenia or osteoporosis defined by BMD without existing vertebral fracture, 4 years of alendronate compared with placebo reduced radiographic vertebral fractures (hazard ratio [HR], 0.56 [95% CI, 0.39 to 0.80]) (high SOE) but did not significantly reduce nonvertebral fractures (HR, 0.88 [CI, 0.74 to 1.04]) (low SOE) or hip fractures (HR, 0.79 [CI, 0.43 to 1.44]) (low SOE) (14). In women with osteoporosis defined by BMD or past vertebral fracture, 4 years of raloxifene compared with placebo reduced radiographic vertebral fractures (relative risk, 0.64 [CI, 0.53 to 0.76]) and clinical vertebral fractures (relative risk, 0.58 [CI, 0.43 to 0.79]) (both high SOE) (15) but not nonvertebral or hip fractures (high or moderate SOE, respectively). In older women with osteopenia or osteoporosis, 6 years of zoledronic acid compared with placebo reduced clinical fractures (HR, 0.73 [CI, 0.60 to 0.90]) (moderate SOE), including nonvertebral fractures (HR, 0.66 [CI, 0.51 to 0.85]) (high SOE) and clinical vertebral fractures (HR, 0.41 [CI, 0.22 to 0.75]) (moderate SOE) (16). In women with unspecified osteoporosis or osteopenia status, compared with placebo, both estrogen–progestin for 5.6 years (17) and unopposed estrogen for 7 years (18) reduced risk for clinical fractures (high SOE), including hip fractures (moderate SOE) (Table 1) (4, 14–32).

Evidence was insufficient to compare fracture risk between women receiving long-term denosumab therapy and those receiving placebo (19), and we identified no eligible studies addressing the long-term antifracture efficacy of sequential ODTs (for example, anabolic followed by antiresorptive therapy or denosumab followed by bisphosphonate).

Variation in Efficacy by Patient, Bone, or Drug Characteristics

Antifracture efficacy of long-term alendronate therapy varied as a function of baseline BMD (14). In 1 randomized controlled trial, 4 years of alendronate reduced clinical fractures (HR, 0.64 [CI, 0.50 to 0.82]) and radiographic vertebral fractures (HR, 0.50 [CI, 0.31 to 0.82]) in women with osteoporosis defined by BMD only, but not in women with osteopenia (*P* for interaction = 0.01 for clinical fracture; not reported for radiographic vertebral fracture). In a post hoc analysis, 4 years of alendronate also reduced hip fractures in women with osteoporosis defined by BMD only but not in women with osteopenia (14). In additional post hoc analyses—some in osteopenic subgroups (33, 34)—past nonvertebral fracture (34), 10-year probability of major osteoporotic fracture (35), and pretreatment levels of bone turnover markers (36) did not modify the long-term effect of alendronate compared with placebo on risk for any incident fracture.

Whether the antifracture efficacy of zoledronic acid varies as a function of baseline BMD is unclear. In secondary analyses from a 6-year trial in older women with osteopenia or osteoporosis, reduction in nonvertebral fractures with zoledronic acid versus placebo in the subset of women with osteopenia seemed similar to that in women overall (16).

Age (20), baseline BMD (20), and baseline radiographic vertebral fracture (4, 15, 20, 21) did not modify the effect of long-term raloxifene versus placebo on fracture risk. Antifracture efficacy of long-term oral hormone therapy versus placebo did not consistently vary as a function of fracture history, baseline fracture risk score, or BMD category (17, 18).

Harms

Because few events were seen, randomized controlled trials provided insufficient evidence about whether long-term alendronate or zoledronic acid increases risk for radiologically confirmed AFF, subtrochanteric or femoral shaft fractures without radiologically confirmed AFF features (ST/FSF), or osteonecrosis of the jaw (ONJ).

Data from 8 controlled observational studies collectively indicated that long-term use of alendronate (37, 38) and of bisphosphonates as a class (39–44) increased risk for AFF (41, 43, 44) and ST/FSF (37–40, 42) (both low SOE). Relative risk estimates ranged from 1 to more than 100, and the 1 study from which it was possible to estimate absolute risk for AFF or ST/FSF versus neither outcome reported an absolute risk increase for ST/FSF of 0.20% (CI, 0.15% to 0.25%) over a mean duration of about 4 years (38). Although 2 studies suggested that long-term use of alendronate increased risk for radiologically and pathologically confirmed ONJ compared with raloxifene (low SOE) (45) and of diagnostic codes for "inflammatory jaw events" compared with no ODT (low SOE) (46), evidence from a third study was insufficient to draw conclusions about ONJ risk between long-term use of alendronate and that of nonbisphosphonate osteoporosis drugs (47). One study reported that long-term alendronate therapy did not differ from no osteoporosis drug use in risk for atrial fibrillation or flutter (48). We found no eligible observational studies that evaluated risk for these harms with long-term use of zoledronic acid.

Several analyses from 1 trial reported that compared with placebo, long-term raloxifene therapy was associated with a 3-fold increased risk for deep venous thrombosis (15, 22, 23) and a 3- to 4-fold increased risk for pulmonary embolism (15, 21–24), although not all results were statistically significant. In 2 long-term trials, both estrogen and estrogen–progestin compared with placebo increased risk for cardiovascular disease and cognitive impairment among women with unspecified osteoporosis or osteopenia status (49–52). Estrogen–progestin also increased risk for invasive breast cancer. Risk for harms with long-term use of denosumab were indeterminable because the 1 eligible trial combined the continuous, long-term denosumab results with those from all other active control groups (19) (Table 2) (4, 15, 16, 19, 20–31, 37–47, 53).

Table 1. Efficacy of Long-Term Osteoporosis Drug Treatment (>3 Years)

Study Comparison, Participants, and Incident Fracture Outcome	Relative and Absolute Risk Differences (95% CI)	Strength of Evidence (Justification)*
1 RCT (14) comparing alendronate vs. placebo for 4 y		
4432 PM women with osteopenia or osteoporosis (T-score ≤−1.6) and no RVF		
Clinical fracture	No difference: HR, 0.86 (95% CI, 0.73 to 1.01); ARD, −2% (95% CI, −4% to 0%)	Low (IM)
Nonvertebral fracture	No difference: HR, 0.88 (95% CI, 0.74 to 1.04); ARD, −1% (95% CI, −3% to 0%)	Low (IM)
Hip fracture	No difference: HR, 0.79 (95% CI, 0.43 to 1.44); ARD, −0.2% (95% CI, −0.8% to 0.4%)	Low (h-IM)
RVF	Lower risk: HR, 0.56 (95% CI, 0.39 to 0.80); ARD, −2% (95% CI, −3% to −1%)	High
1631 PM women with osteoporosis by BMD (T-score ≤−2.5) and no RVF		
Clinical fracture	Lower risk: HR, 0.64 (95% CI, 0.50 to 0.82); ARD, −7% (95% CI, −10% to −3%)	Moderate (RB)
RVF	Lower risk: HR, 0.50 (95% CI, 0.31 to 0.82); ARD, −3% (95% CI, −5% to −1%)	Moderate (RB)
1 RCT (16) comparing zoledronic acid vs. placebo for 6 y		
2000 PM women aged ≥65 y with osteoporosis or osteopenia		
Clinical fracture	Lower risk: HR, 0.73 (95% CI, 0.60 to 0.90); ARD, −5% (95% CI, −9% to −2%)	Moderate (IM)
Nonvertebral fracture	Lower risk: HR, 0.66 (95% CI, 0.51 to 0.85); ARD, −5% (95% CI, −8% to −2%)	High
Hip fracture	No difference: HR, 0.66 (95% CI, 0.27 to 1.16); ARD, −0.4% (95% CI, −1% to 0.5%)	Low (h-IM)
Clinical vertebral fracture	Lower risk: HR, 0.41 (95% CI, 0.22 to 0.75); ARD, −2% (95% CI, −3% to −1%)	Moderate (IM)
1 RCT (19) comparing denosumab vs. placebo for 4 y†		
365 PM women with osteopenia or osteoporosis by BMD		
Clinical fracture	RR, 0.97 (95% CI, 0.40 to 2.35); ARD, −0.4% (95% CI, −10% to 9%)	Insufficient (RB, IN, h-IM)
1 RCT with 1 CCT extension (4, 15, 20-31) comparing raloxifene vs. placebo for 4 to 8 y		
6828 PM women with osteoporosis by BMD or RVF		
Nonvertebral fracture	No difference: 4 y: RR, 0.93 (95% CI, 0.81 to 1.06)‡; ARD NA 8 y: HR, 1.00 (95% CI, 0.82 to 1.21)§; ARD NA	4 y: High 8 y: Moderate (RB)
Hip fracture	No difference: 4 y: RR, 0.97 (95% CI, 0.62 to 1.52)‡; ARD, 0% (95% CI, −0.6% to 0.5%)	Moderate (IM)
Clinical vertebral fracture	Lower risk: 4 y: RR, 0.58 (95% CI, 0.43 to 0.79)§; ARD, −2% (95% CI, −3% to −1%)	High
RVF	Lower risk: 4 y: RR, 0.64 (95% CI, 0.53 to 0.76)§; ARD, −5% (95% CI, −6% to −3%)	High
1 RCT (18) comparing estrogen vs. placebo for a mean of 7.1 y		
10 739 PM women with hysterectomy		
Clinical fracture	Lower risk: HR, 0.71 (95% CI, 0.64 to 0.80); ARD, −4% (95% CI, −5% to −3%)	High
Hip fracture	Lower risk: HR, 0.65 (95% CI, 0.45 to 0.94); ARD, −0.5% (95% CI, −0.9% to −0.08%)	Moderate (IM)
3816 PM women with hysterectomy and past clinical fracture		
Clinical fracture	Lower risk: HR, 0.73 (95% CI, 0.62 to 0.86); ARD, −5% (95% CI, −7% to −2%)	Low (RB, IM)
Hip fracture	Lower risk: HR, 0.55 (95% CI, 0.32 to 0.94); ARD, −1% (95% CI, −2% to 0%)	Low (RB, IM)
53 PM women with hysterectomy and osteoporosis by BMD		
Clinical fracture	HR, 0.83 (95% CI, 0.17 to 3.91); ARD NA	Insufficient (RB, h-IM)
363 PM women with hysterectomy and osteopenia by BMD		
Clinical fracture	HR, 0.83 (95% CI, 0.49 to 1.40); ARD NA	Insufficient (RB, h-IM)

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Table 1–Continued

Study Comparison, Participants, and Incident Fracture Outcome	Relative and Absolute Risk Differences (95% CI)	Strength of Evidence (Justification)*
1 RCT (17) comparing estrogen–progestin vs. placebo for a mean of 5.6 y		
16 608 PM women with intact uterus		
Clinical fracture	Lower risk: HR, 0.76 (95% CI, 0.69 to 0.83); ARD, −2.4% (95% CI, −3.3% to −1.5%)	High
Hip fracture	Lower risk: HR, 0.67 (95% CI, 0.47 to 0.96); ARD, −0.3% (95% CI, −0.6% to −0.03%)	Moderate (IM)
5897 PM women with intact uterus and past clinical fracture		
Clinical fracture	Lower risk: HR, 0.78 (95% CI, 0.68 to 0.91); ARD, −3% (95% CI, −5% to −1%)	Low (RB, IM)
Hip fracture	No difference: HR, 0.77 (95% CI, 0.48 to 1.22); ARD, −0.3% (95% CI, −0.9% to 0.2%)	Low (RB, IM)
PM women with intact uterus and osteoporosis by BMD (number not reported)		
Clinical fracture	HR, 0.53 (95% CI, 0.25 to 1.10); ARD NA	Insufficient (RB, h-IM)
1 RCT (32) comparing estrogen–progestin vs. nonplacebo control for 4 y		
36 PM women with osteoporosis by BMD (T-score ≤−2) and RVF		
Nonvertebral fracture	RR, 0.93 (95% CI, 0.06 to 13.5); ARD, −0.5% (95% CI, −19% to 18%)	Insufficient (RB, h-IM)
RVF	RR, 0.37 (95% CI, 0.09 to 1.62); ARD, −22% (95% CI, −53% to 8%)	Insufficient (RB, h-IM)

ARD = absolute risk difference; BMD = bone mineral density; CCT = controlled clinical trial; h-IM = highly imprecise; HR = hazard ratio; IM = imprecise; IN = indirect; NA = not available (data not reported); PM = postmenopausal; RB = medium risk of bias; RCT = randomized controlled trial; RR = risk ratio; RVF = radiographic vertebral fracture.
* Definitions of terms for strength-of-evidence grades and domain ratings are detailed in the section of the main report titled Strength of Evidence for Major Comparisons and Outcomes (https://effectivehealthcare.ahrq.gov/topics/osteoporosis-fracture-prevention/research).
† Analyses pooled all participants initially assigned to denosumab, which included both those who received long-term and those who received short-term denosumab treatment.
‡ Results were reported for both raloxifene dosage groups pooled together: 60 mg/d and 120 mg/d.
§ Results were reported for the group that received raloxifene, 60 mg/d.

Variation in Harms by Patient, Bone, or Drug Characteristics

In 3 observational studies, relative to a nonbisphosphonate control, the increased risk for AFF (43) or ST/FSF (40, 42) seemed greater with more than 5 years of bisphosphonate use than with 3 to 5 years of bisphosphonate use, although none of the studies reported testing for an interaction by treatment duration. Variation in relative risk estimates with bisphosphonates for AFF, ST/FSF, and ONJ also may have been associated with differences in study designs. Relative risks for radiologically confirmed AFF compared with control (41, 43, 44) seemed higher than risks for ST/FSF defined only by diagnostic codes (37–40, 42). However, in 2 of 3 studies, AFF risk estimates were calculated using patients with ST/FSF without features of AFF as control participants (43, 44), reflecting not the relative risk for sustaining an AFF but the probability that an ST/FSF will have AFF features (54). Studies also differed in comparing current bisphosphonate use with no use, limited past use, or nonbisphosphonate ODT use and in how they addressed potential confounding. No studies directly tested whether risks differed as a function of any of these study design factors.

In post hoc analyses, risk for deep venous thrombosis and pulmonary embolism in persons receiving long-term raloxifene therapy versus placebo did not vary by baseline cardiovascular risk (25), and stroke risk was lower with raloxifene than with placebo in women at increased cardiovascular risk (26). Trials of long-term oral hormone therapy evaluated whether risk for harms varied by a host of patient characteristics (49–52); results suggested that risk for breast cancer with estrogen–progestin (compared with placebo) may be greater with increased duration of prior use of postmenopausal hormones.

ODT Discontinuation and Holidays

Effects on Fractures

In postmenopausal women who previously received 5 years of alendronate, neither of 2 trials found a reduction in nonvertebral fractures with alendronate continuation for 5 more years versus discontinuation (36, 55–57); however, results for vertebral fractures were mixed. One of these trials studied women with osteoporosis and reported no difference in risk for clinical vertebral fractures (55, 56). The second, larger trial enrolled women with osteopenia or osteoporosis and showed that alendronate continuation halved risk for clinical vertebral fractures (relative risk, 0.45 [CI, 0.24 to 0.85]) but did not reduce radiographic vertebral fractures (57).

In 1 trial in postmenopausal women who previously received 3 years of zoledronic acid therapy for osteoporosis, continuation for 3 more years versus discontinuation did not lower risk for nonvertebral fractures or clinical vertebral fractures, but it halved risk for radiographic vertebral fractures (odds ratio, 0.51 [CI, 0.26 to 0.95]) (58). In another trial, we could not draw conclusions about differences in fracture risk between deno-

Table 2. Harms of Long-Term Osteoporosis Drug Treatment (>3 Years)

Study Comparison, Participants, and Harms	Relative and Absolute Risk Differences (95% CI)	Strength of Evidence (Justification)*
1 RCT (53) comparing alendronate vs. placebo for 3 to 4.5 y		
6459 PM women with osteopenia or osteoporosis (T-score ≤−1.6) with or without RVF		
ST or FS fracture diagnosis with rare radiographic review for confirmation of AFF features (*n* = 2 cases)	HR, 1.03 (95% CI, 0.06 to 16.46); ARD, 0% (95% CI, −0.09% to 0.09%)	Insufficient (h-IM)
2 retrospective cohort observational studies (37, 38, 46) comparing alendronate vs. no osteoporosis drug treatment for 3.8 y (mean) and ≥6 y		
534 adults aged ≥60 y with nonhip fracture (90% women)		
ST or FS fracture diagnosis codes without radiographic confirmation of AFF features (*n* = 5 cases)	≥6 y: HR, 1.37 (95% CI, 0.22 to 8.62); ARD NA	Insufficient (RB, h-IM)
220 360 adults (85% women) exposed to alendronate or no osteoporosis drug; general population control participants from national database		
ST or FS fracture diagnosis codes without radiographic confirmation of AFF features (*n* = 309 cases)	Higher risk: 3.8 y: ST: 0.17% vs. 0.06%; HR, 2.41 (95% CI, 1.78 to 3.27); ARD, 0.11% (95% CI, 0.08% to 0.15%) 3.8 y: FS: 0.12% vs. 0.03%; HR, 2.90 (95% CI, 1.97 to 4.26); ARD, 0.09% (95% CI, 0.06% to 0.12%) 3.8 y: ST/FS: 0.29% vs. 0.09%; ARD, 0.20% (95% CI, 0.15% to 0.25%)	Low (RB, LE)
ONJ diagnosis codes without radiographic or pathology review (*n* = 28 cases)	Higher risk: 3.8 y: HR, 3.15 (95% CI, 1.44 to 6.87); ARD NA	Low (RB, IM, LE)
1 retrospective cohort observational study (45) comparing alendronate vs. raloxifene for a mean of about 4 y		
8354 women aged ≥50 y from database of 1 hospital		
ONJ diagnosis codes with radiographic and pathology features (*n* = 40 cases)	Higher risk with alendronate: HR, 7.42 (95% CI, 1.02 to 54.09); ARD NA	Low (RB, IM, LE)
1 retrospective cohort observational study (47) comparing alendronate vs. raloxifene or calcitonin for ≤6 y		
43 645 adults aged ≥50 y (84% women) with recent hip or vertebral fracture now receiving osteoporosis drug treatment; from national database		
ONJ diagnosis codes without radiographic or pathology review (*n* = 46 cases)	HR, 0.86 (95% CI, 0.44 to 1.69)†; ARD NA	Insufficient (RB, h-IM)
1 RCT (16) comparing zoledronic acid vs. placebo for 6 y		
2000 PM women aged ≥65 y with osteoporosis or osteopenia		
Serious adverse event	No difference: OR, 0.84 (95% CI, 0.70 to 1.00); ARD, −4% (95% CI, −9% to 0%)	Low (IM)
3 observational studies (39, 43, 44) comparing bisphosphonate‡ vs. no bisphosphonate for ≥3 y		
About 2.8 million (retrospective cohort) and 1124 (case-control) adults aged ≥55 y from national database (87% women case patients and 52% women control participants in cohort analysis; 86% women in case-control analysis)		
AFF with radiologic features (*n* = 172 cases)	Higher risk: Cohort ≥4 y: RR, 126 (95% CI, 55 to 288); ARD NA Case-control 3 to 4 y: OR, 40 (95% CI, 17 to 91); ARD NA 4 to 5 y: OR, 116 (95% CI, 58 to 234); ARD NA >5 y: OR, 93 (95% CI, 66 to 132); ARD NA	Low (RB, CO, LE)
264 women aged ≥65 y from national primary practice database (case-control)		
ST or FS fracture diagnosis codes without radiographic confirmation of AFF features (*n* = 44 cases)	Higher risk: >3 y: OR, 9.46 (95% CI, 2.17 to 41.3); ARD NA	Low (RB, LE)
6644 women aged ≥50 y with hip or femoral fracture from 8 hospital medical record databases (nested case-control)		
AFF with radiologic features (*n* = 196 cases)	Higher risk: Mean use, 5.2 y: OR, 25.65 (95% CI, 10.74 to 61.28); ARD NA	Low (RB, LE)

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Table 2–Continued

Study Comparison, Participants, and Harms	Relative and Absolute Risk Differences (95% CI)	Strength of Evidence (Justification)*
2 case–control observational studies (41, 42) comparing current vs. past use of bisphosphonates‡ for ≥3 y		
172 PM women with ≥1 y bisphosphonate use from 1 hospital database		
AFF with radiologic features (*n* = 43 cases)	Higher risk with current bisphosphonate use: HR, 3.36 (95% CI, 1.77 to 11.91) to 5.17 (95% CI, 2.0 to 13.36); ARD NA	Low (RB, LE)
1855 women aged ≥68 y from a provincial database		
ST or FS fracture diagnosis codes without radiograph review (*n* = 325 cases)	Higher risk with current bisphosphonate use: 3 to 5 y: OR, 1.59 (95% CI, 0.80 to 3.15); ARD NA >5 y: OR, 2.74 (95% CI, 1.25 to 6.02); ARD NA	Low (RB, IM)
1 retrospective cohort observational study (40) comparing bisphosphonates‡ vs. pooled raloxifene or calcitonin for ≥3 y		
4097 Medicare beneficiaries (97% women)		
ST or FS fracture diagnosis codes without radiographic confirmation of AFF features (*n* = 34 cases)	3 to 5 y: HR, 1.20 (95% CI, 0.55 to 2.61); ARD, 0.1% (95% CI, −0.3% to 0.5%) >5 y: HR, 2.02 (95% CI, 0.41 to 10.0); ARD, 0.1% (95% CI, −0.1% to 0.4%)	Insufficient (RB, h-IM)
1 RCT (19) comparing denosumab§ vs. placebo for 4 y		
365 PM women with osteopenia or osteoporosis by BMD		
Serious adverse event	RR, 1.64 (95% CI, 0.69 to 3.88); ARD, 7% (95% CI, −3% to 17%)	Insufficient (RB, IN, h-IM)
1 RCT with 1 CCT extension (4, 15, 20-31) comparing raloxifene vs. placebo for 4 to 8 y		
6828 PM women with osteoporosis by BMD or RVF		
Serious adverse event	No difference: 8 y: RR, 0.93 (95% CI, 0.86 to 1.00)‖; ARD, −3% (95% CI, −6% to 0%)	Low (RB, IM)
1 retrospective cohort observational study (38, 46) comparing raloxifene vs. no treatment for a mean of 3.8 y		
19 324 adults (85% women) exposed to raloxifene or no osteoporosis drug; general population control participants from national database		
ST or FS fracture diagnosis codes without radiographic confirmation of AFF features (*n* = 25 cases)	ST: HR, 1.06 (95% CI, 0.34 to 3.32); ARD, 0.04% (95% CI, −0.06% to 0.14%) FS: HR, 0.82 (95% CI, 0.21 to 3.20); ARD, 0.01% (95% CI, −0.07% to 0.09%)	Insufficient (RB, h-IM)
ONJ diagnosis codes without radiographic or pathology review (*n* = 2 cases)	2 cases, only in control group	Insufficient (RB, h-IM)

AFF = atypical femoral fracture; ARD = absolute risk difference; BMD = bone mineral density; CCT = controlled clinical trial; CO = consistent; FS = femoral shaft; h-IM = highly imprecise; HR = hazard ratio; IM = imprecise; IN = indirect; LE = large effect; NA = not available (data not reported); ONJ = osteonecrosis of the jaw; OR = odds ratio; PM = postmenopausal; RB = medium risk of bias; RCT = randomized controlled trial; RR = risk ratio; RVF = radiographic vertebral fracture; ST = subtrochanteric.

* Definitions of terms for strength-of-evidence grades and domain ratings are detailed in the section of the main report titled Strength of Evidence for Major Comparisons and Outcomes (https://effectivehealthcare.ahrq.gov/topics/osteoporosis-fracture-prevention/research).

† Because the higher adjusted incidence rates in the alendronate group (0.15%) than the raloxifene–calcitonin group (0.08%) suggested a possibly increased risk, we manually recalculated the estimate of effect and found an RR of 1.20 (95% CI, 0.59 to 2.56). Authors were contacted for clarification but did not reply.

‡ Included bisphosphonates varied by study. All studies included alendronate, risedronate, and ≥1 of ibandronate, etidronate, and zoledronic acid.

§ Analyses pooled all participants initially assigned to denosumab, which included both those who received long-term and those who received short-term denosumab.

‖ Results were reported for the group that received raloxifene, 60 mg/d.

sumab continuation and discontinuation because fracture results for these treatment groups were combined (19) (Table 3) (19, 55–60).

Variation in Fracture Effects by Patient, Bone, or Drug Characteristics

In trial post hoc analyses, neither baseline BMD nor baseline radiographic vertebral fracture modified the effect of continuation versus discontinuation of alendronate therapy on risk for nonvertebral fracture or clinical vertebral fracture (57, 61). A post hoc subgroup analysis reported that among women without a radiographic vertebral fracture at baseline, continuation versus discontinuation of alendronate therapy reduced risk for nonvertebral fractures in women with osteoporosis defined by BMD but not in those with osteopenia (61). Results were not adjusted for multiple testing, and this single statistically significant outcome may have been due to chance. No study reported whether the effect of continuation versus discontinuation of any

Table 3. Effects of Osteoporosis Drug Continuation Versus Discontinuation on Incident Fractures*

Study Comparison, Participants, and Incident Fracture Outcome	Relative and Absolute Risk Differences (95% CI)	Strength of Evidence (Justification)†
1 RCT (57) comparing AL continuation vs. discontinuation (AL × 10 y vs. AL × 5 y followed by PBO × 5 y) in 1099 PM women who previously received AL for 5 y for osteopenia or osteoporosis (T-score ≤−1.6)		
Clinical fracture	No difference: RR, 0.93 (95% CI, 0.71 to 1.21); ARD, −1% (95% CI, −6% to 4%)	Moderate (IM)
Nonvertebral fracture	No difference: RR, 1.00 (95% CI, 0.76 to 1.32); ARD, −0.1% (95% CI, −5% to 5%)	Moderate (IM)
Hip fracture	RR, 1.02 (95% CI, 0.51 to 2.10); ARD, 0% (95% CI, −2% to 2%)	Insufficient (h-IM)
Clinical vertebral fracture	Lower risk with continuation: RR, 0.45 (95% CI, 0.24 to 0.85); ARD, −3% (95% CI, −5% to −0.5%)	Moderate (IM)
RVF	No difference: RR, 0.86 (95% CI, 0.60 to 1.22); ARD, −1% (95% CI, −5% to 2%)	Moderate (IM)
1 RCT (55, 56) comparing AL continuation vs. discontinuation (AL × 7 y vs. AL × 5 y followed by PBO × 2 y [n = 350]; AL × 10 y vs. AL × 7 y followed by PBO × 3 y [n = 247]) in 350 PM women who previously received AL for 5 y for osteoporosis (T-score ≤−2.5)		
Nonvertebral fracture	AL × 7 y vs. AL × 5 y followed by PBO × 2 y: RR, 0.87 (95% CI, 0.40 to 1.91); ARD, −1% (95% CI, −7% to 5%) AL × 10 y vs. AL × 7 y followed by PBO × 3 y: RR, 0.81 (95% CI, 0.38 to 1.71); ARD, −2% (95% CI, −11% to 6%)	AL × 7 y vs. AL × 5 y followed by PBO × 2 y: insufficient (h-IM) AL × 10 y vs. AL × 7 y followed by PBO × 3 y: insufficient (RB, h-IM)
Clinical vertebral fracture	AL × 7 y vs. AL × 5 y followed by PBO × 2 y: RR, 0.92 (95% CI, 0.40 to 2.10); ARD, −1% (95% CI, −6% to 5%)	Insufficient (h-IM)
RVF	AL × 10 y vs. AL × 5 y followed by PBO × 5 y: RR, 1.40 (95% CI, 0.52 to 3.74); ARD, 2.6% (95% CI, −4.6% to 9.9%)	Insufficient (RB, h-IM)
1 RCT (60) comparing Z continuation vs. discontinuation (Z × 2 y vs. Z × 1 y followed by PBO × 1 y) in 379 PM women with osteopenia		
Clinical fracture	RR, 1.37 (95% CI, 0.39 to 4.78); ARD, 1% (95% CI, −2% to 4%)	Insufficient (h-IM)
1 RCT (58) comparing Z continuation vs. discontinuation (Z × 6 y vs. Z × 3 y followed by PBO × 3 y) in 1233 PM women who previously received Z for 3 y for osteoporosis by BMD or RVF		
Clinical fracture	No difference: HR, 1.04 (95% CI, 0.71 to 1.54); ARD NA	Moderate (IM)
Nonvertebral fracture	No difference: HR, 0.99 (95% CI, 0.7 to 1.5); ARD, −0.3% (95% CI, −3% to 3%)	Moderate (IM)
Hip fracture	HR, 0.90 (95% CI, 0.33 to 2.49); ARD, −0.2% (95% CI, −1% to 1%)	Insufficient (h-IM)
Clinical vertebral fracture	HR, 1.81 (95% CI, 0.53 to 6.2); ARD NA	Insufficient (h-IM)
RVF	Lower risk with continuation: OR, 0.51 (95% CI, 0.26 to 0.95); ARD, −3% (95% CI, −6% to −1%)	Low (h-IM)
1 RCT (59) comparing Z continuation vs. discontinuation (Z × 9 y vs. Z × 6 y followed by PBO × 3 y) in 190 PM women who previously received Z for 6 y for osteoporosis by BMD or RVF		
Clinical fracture	HR, 1.11 (95% CI, 0.45 to 2.73); ARD, 1% (95% CI, −7% to 10%)	Insufficient (h-IM)
RVF	OR, 0.58 (95% CI, 0.13 to 2.55); ARD, −2% (95% CI, −8% to 4%)	Insufficient (h-IM)
1 RCT (19) comparing D continuation vs. discontinuation (D × 4 y vs. D × 2 y followed by PBO × 2 y) in 314 PM women with osteopenia or osteoporosis by BMD		
Clinical fracture	No numerical data	Insufficient (no data)

AL = alendronate; ARD = absolute risk difference; BMD = bone mineral density; D = denosumab; h-IM = highly imprecise; HR = hazard ratio; IM = imprecise; NA = not available (data not reported); OR = odds ratio; PBO = placebo; PM = postmenopausal; RB = medium risk of bias; RCT = randomized controlled trial; RR = risk ratio; RVF = radiographic vertebral fracture; Z = zoledronic acid.
* Discontinuation ≥1 y after prior treatment lasting ≥1 y.
† Definitions of terms for strength-of-evidence grades and domain ratings are detailed in the section of the main report titled Strength of Evidence for Major Comparisons and Outcomes (https://effectivehealthcare.ahrq.gov/topics/osteoporosis-fracture-prevention/research).

other ODT on fracture outcomes varied by patient, bone, or drug characteristics.

Harms

Trials of alendronate and zoledronic acid reported no difference in risk for serious adverse events between continuation and discontinuation (55, 57–61). However, they included too few cases of AFF, ST/FSF, and ONJ to draw definitive conclusions about between-group differences in risk for these outcomes (53, 58). One retrospective cohort study reported higher incidence of ST/FSF with continued versus discontinued bisphosphonate use (0.15% vs. 0.03%; odds ratio, 6.03 [CI, 1.87 to 19.42]; absolute risk increase, 0.13% [CI, 0.08% to 0.19%]) (62). However, analyses did not account for potential confounding variables. Although atrial fibrillation may have been more frequent with continuation versus discontinuation of zoledronic acid treatment, few events were seen, and differences were not statistically significant (58, 59). We could not draw conclusions about differences in harms between continuation and discontinuation of denosumab therapy because the 1 applicable trial pooled results for these groups (19) (Table 4) (19, 55–60, 62).

Variation in Harms by Patient, Bone, or Drug Characteristics

We found no evidence on whether patient, bone, or drug characteristics modify risk for harms of ODT continuation versus discontinuation.

DISCUSSION

In long-term, placebo-controlled trials, among women who were predominately ODT-naive alendronate for 4 years reduced vertebral and nonvertebral fractures in those with osteoporosis, and zoledronic acid for 6 years reduced these fractures in patients with osteopenia or osteoporosis. Observational studies suggested that long-term bisphosphonate treatment may increase risk for AFF, ST/FSF, and ONJ and that risks for AFF and ST/FSF may increase with longer use, but these adverse events were rare. In women with osteoporosis, raloxifene for 4 years compared with placebo reduced vertebral fractures, but not nonvertebral fractures, and increased risk for deep venous thrombosis and pulmonary embolism. In women with unknown osteoporosis or osteopenia status, oral hormone therapy for 5 to 7 years reduced clinical fractures and hip fractures compared with placebo but increased risk for cardiovascular disease and cognitive impairment; estrogen–progestin increased risk for invasive breast cancer. Evidence was insufficient or absent about the benefits and harms of long-term treatment with other ODTs that are approved by the Food and Drug Administration. Trials in women with 3 to 5 years of prior zoledronic acid or alendronate treatment showed that compared with discontinuation, treatment for another 3 to 5 years reduced some vertebral fracture outcomes but not others and did not reduce nonvertebral fractures. Controlled observational studies suggested that bisphosphonate continuation may increase risk for ST/FSF.

Evidence was limited on factors that may modify the effects of long-term ODT and ODT holidays. Long-term treatment with alendronate reduced clinical fractures compared with placebo in women with osteoporosis but not in women with osteopenia. Otherwise, fracture risk with this treatment versus placebo did not vary by history of prior fracture, Fracture Risk Assessment Tool (FRAX) score, or pretreatment levels of bone turnover markers. Difference in fracture risk between long-term raloxifene therapy and placebo did not vary by age, baseline BMD, or history of fracture. Reduction in clinical fractures with oral estrogen and estrogen–progestin compared with placebo did not vary consistently by any of several fracture risk factors examined. We found no information about possible modifiers of fracture risk with long-term zoledronic acid treatment.

Our findings have several clinical implications. In women with osteoporosis, indications for long-term raloxifene therapy may be limited because it reduced only vertebral fractures, whereas both long-term use of zoledronic acid and that of alendronate also reduced nonvertebral fractures. Although the latter reductions seemed similar in older women with osteoporosis, only long-term zoledronic acid reduced nonvertebral fractures in women with osteopenia. We do not know whether these possibly discrepant findings are explained in part by differences in the study populations (for example, the population receiving zoledronic acid was older), and no long-term trials directly compared these treatments in women with osteopenia. Long-term oral hormone therapies decreased clinical and hip fractures in women with unknown osteopenia or osteoporosis status, and results seemed generally similar in those at higher fracture risk. However, the antifracture benefits were offset by risk for serious harms; therefore, these agents are unlikely to be options for long-term ODT. We do not know whether a lower dose or nonoral formulation of hormone therapy would more favorably balance antifracture benefits to harms.

Estimating the balance between the potential antifracture benefits and harms of long-term use of bisphosphonates is challenging. On the basis of studies included in this review, for every 1000 women with osteoporosis treated with alendronate versus placebo for 4 years or with osteopenia or osteoporosis treated with zoledronic acid versus placebo for 6 years, approximately 50 to 70 more women will avoid a clinical fracture and an additional 2 will have an ST/FSF. Because most ST/FSFs do not meet AFF criteria (54), the absolute number of additional AFFs should be smaller. Also, for every 1000 women previously treated for osteopenia or osteoporosis with 3 to 5 years of alendronate or zoledronic acid who continue bisphosphonate treatment for another 3 to 5 years, compared with discontinuation, no additional women will avoid a nonvertebral fracture, approximately 30 more will avoid a vertebral fracture, and 1 additional woman will have an ST/FSF. However, radiographic and clinical vertebral fracture re-

Table 4. Harms of Osteoporosis Drug Continuation Versus Discontinuation*

Study Comparison, Participants, and Harms	Relative and Absolute Risk Differences (95% CI)	Strength of Evidence (Justification)†
1 RCT (57) comparing AL continuation vs. discontinuation (AL × 10 y vs. AL × 5 y followed by PBO × 5 y) in 1099 PM women who previously received AL for 5 y for osteopenia or osteoporosis (T-score ≤−1.6)		
Serious adverse event	Stated no difference, but no data provided	Insufficient (no data)
Subtrochanteric or femoral shaft fracture diagnosis with rare radiographic review (*n* = 3 cases)	HR, 1.33 (95% CI, 0.12 to 14.67); ARD, −0.1% (95% CI, −0.5% to 0.7%)	Insufficient (h-IM)
ONJ not defined (*n* = 0 cases)	No cases in either group	Insufficient (h-IM)
1 RCT (55, 56) comparing AL continuation vs. discontinuation (AL × 7 y vs. AL × 5 y followed by PBO × 2 y; AL × 10 y vs. AL × 7 y followed by PBO × 3 y) in 350 PM women who previously received AL for 5 y for osteoporosis (T-score ≤−2.5)		
Serious adverse event	AL × 7 y vs. AL × 5 y followed by PBO × 2 y: RR, 1.05 (95% CI, 0.57 to 1.96); ARD, 1% (95% CI, −7% to 8%) AL × 10 y vs. AL × 7 y followed by PBO × 3 y: RR, 1.21 (95% CI, 0.75 to 1.96); ARD, 5% (95% CI, −7% to 16%)	AL × 7 y vs. AL × 5 y followed by PBO × 2 y: insufficient (h-IM) AL × 10 y vs. AL × 7 y followed by PBO × 3 y: insufficient (RB, IM)
1 retrospective cohort observational study (62) comparing bisphosphonate continuation vs. discontinuation (continued bisphosphonate for a mean of 3.5 y [persistent group] or 4.1 y [nonpersistent group] vs. bisphosphonate holiday for a mean of 3.1 y) in 39 502 women aged ≥45 y with ≥3 y of prior ≥50% adherent bisphosphonate use (99% AL)		
"AFF" (not defined) (*n* = 47 cases)	Higher risk with bisphosphonate (AL) continuation: pooled continuation groups, 0.15% (44/28 005) vs. discontinuation, 0.03% (3/11 497); OR, 6.03 (95% CI, 1.87 to 19.42); ARD, 0.13% (95% CI, 0.08% to 0.19%)	Low (RB, IM, LE)
1 RCT (60) comparing Z continuation vs. discontinuation (Z × 2 y vs. Z × 1 y followed by PBO × 1 y) in 379 PM women with osteopenia		
Serious adverse event	No difference: RR, 0.91 (95% CI, 0.50 to 1.67); ARD, −1% (95% CI, −7% to 5%)	Low (h-IM)
1 RCT (58) comparing Z continuation vs. discontinuation (Z × 6 y vs. Z × 3 y followed by PBO × 3 y) in 1233 PM women who previously received Z for 3 y for osteoporosis by BMD or RVF		
Serious adverse event	No difference: RR, 1.14 (95% CI, 0.96 to 1.36); ARD, 4% (95% CI, −1% to 9%)	Low (IM)
AFF not defined (*n* = 0 cases)	No cases occurred	Insufficient (h-IM)
ONJ (exposed jaw bone >6 wk) (*n* = 1 case)	1 case occurred (in continuation group)	Insufficient (h-IM)
1 RCT (59) comparing Z continuation vs. discontinuation (Z × 9 y vs. Z × 6 y followed by PBO × 3 y) in 190 PM women who previously received Z for 6 y for osteoporosis by BMD or RVF		
Serious adverse event	No difference: RR, 0.86 (95% CI, 0.54 to 1.36); ARD, −3% (95% CI, −16% to 9%)	Low (IM)
AFF with radiologic features (*n* = 0 cases)	No cases occurred	Insufficient (h-IM)
ONJ (exposed jaw bone >6 wk) (*n* = 0 cases)	No cases occurred	Insufficient (h-IM)
1 RCT (19) comparing D continuation vs. discontinuation (D × 4 y vs. D × 2 y followed by PBO × 2 y) in 314 PM women with osteopenia or osteoporosis by BMD		
Serious adverse event	No numerical data	Insufficient (no data)

AFF = atypical femoral fracture; AL = alendronate; ARD = absolute risk difference; BMD = bone mineral density; D = denosumab; h-IM = highly imprecise; HR = hazard ratio; IM = imprecise; LE = large effects; ONJ = osteonecrosis of the jaw; OR = odds ratio; PBO = placebo; PM = postmenopausal; RB = medium risk of bias; RCT = randomized controlled trial; RR = risk ratio; RVF = radiographic vertebral fracture; Z = zoledronic acid.

* Discontinuation ≥1 y after prior treatment lasting ≥1 y.

† Definitions of terms for strength-of-evidence grades and domain ratings are detailed in the section of the main report titled Strength of Evidence for Major Comparisons and Outcomes (https://effectivehealthcare.ahrq.gov/topics/osteoporosis-fracture-prevention/research).

sults were inconsistent within and between the bisphosphonate continuation–discontinuation trials, and relatively few ST/FSFs meet AFF criteria. These facts suggest that the ratio of vertebral fracture benefits to AFF harms for bisphosphonate continuation versus discontinuation could be considerably larger or smaller.

Available data limited this review in several ways. Few unique trials examined long-term ODT or ODT discontinuation or holidays. Many treatment comparisons had only 1 trial, and there were no eligible long-term trials for sequential treatments or for several ODTs that are approved by the U.S. Food and Drug Administration and have proven short-term efficacy against fractures (that is, risedronate, ibandronate, teriparatide, and abaloparatide). Many studies had low statistical power for clinical fracture outcomes. Restriction of all trials to essentially healthy postmenopausal women limited generalizability. Reporting on harms was sparse and inconsistent. Analyses of factors that may modify effects of ODT and ODT discontinuation and holidays were also sparsely reported, were almost entirely post hoc, and were prone to type I errors. Observational studies estimating AFF and ONJ risks had marked differences in methodology and case selection that likely affected risk estimates. Further, fracture data from a small, long-term trial of denosumab—the only trial that included different durations of ODT discontinuation and ODT resumption—could not be interpreted because results for treatment groups were pooled. One limitation specific to the systematic review methodology was that because data were available only at the study level and not at the individual level, we could not determine whether any differences between trial outcomes were due to differences in population characteristics.

Despite these limitations, review findings may inform decisions about long-term ODT and ODT holidays. For patients without prior ODT use, long-term alendronate and zoledronic acid treatments both reduced nonvertebral fractures far more than long-term use of bisphosphonates seems to increase absolute risks for AFF and ONJ. On the basis of these data, both agents may be long-term options in women with osteoporosis, and zoledronic acid may also be a long-term option in older women with osteopenia. However, this evidence is limited to 4 years for alendronate and 6 years for zoledronic acid compared with placebo. In women with prior bisphosphonate treatment, who should have lower risk for subsequent fracture than those without prior treatment, the balance of benefits to harms for continued treatment versus discontinuation is less clear. It seems less favorable than the balance supporting initial treatment in ODT-naive patients because evidence suggests that continuation does not reduce nonvertebral fractures and only inconsistently reduces vertebral fractures. In addition, uncertainty is greater about the magnitude of excess risk for AFF with continued treatment than with discontinuation. The balance of antifracture benefits and harms with continued bisphosphonate treatment may vary between patients, and clinicians already make treatment decisions based on this assumption. However, we did not identify evidence from included studies showing that any patient or bone characteristics modify the likelihood of fracture benefits and harms with continued treatment or could be used to guide monitoring during a drug holiday.

To guide future decisions about osteoporosis treatment, considerable new research is warranted. Trials of long-term ODT should compare sequential treatments (such as anabolic followed by antiresorptive therapy or denosumab followed by bisphosphonate) with continuous long-term antiresorptive treatment. Future trials should compare ODT holidays of different lengths with and without restarting ODT and should include repeating cycles of ODT alternating with drug holidays. To increase clinical relevance and generalizability, trials should be sufficiently powered for clinical fractures and should include men, older women (for example, aged ≥80 years), and adults with multiple comorbid conditions. Because of the rarity of AFF and ONJ, controlled observational studies are necessary to evaluate risks for these outcomes with long-term ODT and ODT holidays. These studies should use consensus case definitions (63, 64), standard controls, cohort designs to estimate incidence rates, and adequate adjustment for possible confounding by indication and selection bias. Future trials and observational studies should examine how benefits and risks for long-term ODT and ODT holidays vary as a function of patient, bone, and ODT characteristics (such as age, sex, comorbid conditions, duration of prior ODT, and BMD and bone turnover marker levels before and during long-term ODT and ODT holidays) (65, 66). Future modeling studies that account for fracture- and harms-related morbidity and quality of life could help patients better weigh tradeoffs in ODT and ODT holiday decisions. Finally, pooled patient-level data from ODT trials on the associations of early treatment changes in BMD and bone turnover markers with risk for incident fractures may improve understanding of the potential use and limitations of these measures as surrogates for incident fracture (67–69).

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