Poor bisphosphonate adherence for treatment of osteoporosis increases fracture risk: systematic review and meta-analysis

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CRD summary

The review found that persistence and compliance were suboptimal for postmenopausal women who underwent bisphosphonate therapy for treatment of osteoporosis. The clinical consequence was an increased fracture risk. The authors' conclusions reflect the evidence presented, but should be considered tentative because of potential biases in the review and wide variation in the studies.

Authors' objectives

To measure the persistence and compliance with bisphosphonates for the treatment of osteoporotic patients and estimate the influence of compliance on fracture risk.

Searching

DARE, HTA Database, Web of Knowledge, The Cochrane Library, EMBASE and MEDLINE were searched for relevant studies from May 2006 to March 2009; search terms were reported. Studies were included from two previously published systematic reviews. Reference lists of retrieved studies were also searched.

Study selection

Observational studies that prospectively analysed administrative databases of pharmacy refills for measures of persistence and compliance in patients who were prescribed either bisphosphonates alone or bisphosphonates as well as other anti-osteoporosis medications were eligible for inclusion. Follow-up periods needed to be one to 2.5 years. Studies were required to define discontinuation as a gap in refills greater than 30 days within one year after initiating osteoporosis treatment. Compliance was to be measured by the medication possession ratio (MPR) (defined as the proportion of doses dispensed in relation to doses prescribed during one year). Where the effect of low compliance on fracture risk was presented, use of Cox proportional regression or conditional logistic regression models in the studies was required for eligibility.

In the included studies, most of the participants were postmenopausal women; one study included participants as young as 18 years. Participants were recruited from a range of administrative databases (reported in the paper). All participants took bisphosphonates; a small proportion also took hormone replacement therapy. Bisphosphonates included alendronate, etidronate, ibandronate and risedronate. Fractures were confirmed clinically in all studies. Studies were undertaken in various locations, including two in UK.

Two reviewers independently selected studies for the review. Disagreements were resolved by consensus.

Assessment of study quality

Studies were appraised for quality using the Newcastle Ottawa Scale for observational studies; nine criteria were used to evaluate cohort and case control studies and six criteria were used to evaluate other study designs.

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Data extraction

Data were extracted on mean persistence days and mean MPR after one year of follow-up and summary effect measures (pooled means) and their 95% confidence intervals (CIs) were calculated. Data were extracted on the risk of fractures according to compliance (good or poor) and summary effect measures (risk ratios (RRs)) and their 95% CIs were calculated. High compliance was categorised ($\geq$80% or $\geq$90%) and compared with low compliance (<80%, <50% or <20%). Where no standard deviations were included, they were imputed or calculated.

The authors did not state how many reviewers performed data extraction.

Methods of synthesis

Studies were pooled in meta-analyses and summary effect measures were calculated for mean persistence (in days) and mean compliance (%) over one year follow-up, together with 95% CIs. Meta-analysis was combined natural logarithms of fracture risks to estimate the association between low compliance and fracture risk, using highly compliant cohorts as reference categories. A DerSimonian Laird random-effects model was used, weighted by the inverse of the variance. Heterogeneity was assessed by the X^2 test. Publication bias was assessed using a funnel plot and Egger's test.

Sensitivity analysis was performed to explore heterogeneity according to age, confirmed osteoporotic diagnostic, compliance level and drug. Subgroup analyses were performed for: fracture risk meta-analysis according to patients treated solely with bisphosphonates and patients treated with bisphosphonates and hormone replacement therapy; studies that used an MPR threshold of 80% to distinguish between poorly and highly compliant patients and those that used other methods to distinguish compliance; studies that included only patients with a previous fracture or a confirmed diagnostic of osteoporosis and the rest; and according to age bands (≥45 years, ≥65 years and ≥78 years). Meta-analysis was performed for all-sites fracture risk, non-vertebral fracture risk, hip fracture risk and vertebral fracture risk.

Results of the review

Fifteen studies (n=704,134) were included in the review: seven cohort studies, one case-control study nested in a well-defined cohort and seven observational longitudinal retrospective studies of large administrative databases with no control group. All studies met at least 77% of the quality criteria and six met all quality criteria.

The pooled persistence mean was 184.1 days (95% CI 163.9 to 204.3; five studies) and the pooled MPR mean was 66.9% (95% CI 63.3 to 70.5; five studies) at one year follow-up.

Low compliance when compared with high compliance was significantly associated with increased overall fracture risk (RR 1.46, 95% CI 1.34 to 1.60; six studies) from one to 2.5 years after starting treatment. Compared to high compliance, low compliance was significantly associated with increased non-vertebral fracture risk (RR 1.16, 95% CI 1.07 to 1.26; three studies) from 1.9 to 2.2 years, increased hip fracture risk (RR 1.28, 95% CI 1.06 to 1.53; four studies) from 1.9 to 2.4 years and increased vertebral fracture risk (RR 1.43, 95% CI 1.26 to 1.63; two studies) from two to 2.2 years follow-up.

Sensitivity analyses found differences in the summary estimates according to drug used. The risk ratio for studies with participants only taking bisphosphonates was 1.59 (95% CI 1.38 to 1.83; four studies) and the risk ratio for participants taking bisphosphonates plus hormone replacement therapy was 1.18 (95% CI 1.16 to 1.20; two studies).

When studies were categorised according to different thresholds of compliance, the fracture risk estimate changed. The risk ratio for studies where compliance was defined as at least 80% versus less than 80% was 1.51 (95% CI 1.36 to 1.68; five studies) and the risk ratio for studies where compliance was defined as at least 90% versus less than 20% to 50% was 1.37 (95% CI 1.28 to 1.48; three studies). Estimates did not markedly change in the sensitivity analyses according to age and confirmed osteoporotic diagnostic.

Statistically significant heterogeneity was identified in all analyses. There was no evidence of publication bias with reference to Egger's test for any of the outcomes. Inspection of the funnel plot for all-sites fracture risk indicated asymmetry, so publication bias could not be ruled out.

Authors' conclusions

Persistence and compliance were suboptimal for postmenopausal women who underwent bisphosphonate therapy for the treatment of osteoporosis. The clinical consequence was increased fracture risk.

CRD commentary

The review addressed a clear research question. Inclusion criteria appeared appropriate. A wide range of relevant

sources were searched. Any language restrictions were not reported, so language bias could not be excluded. Appropriate methods were used to select studies and undertake validity assessment; methods were not reported for data extraction, so reviewer error and bias could not be ruled out. Quality assessment was undertaken with an appropriate tool which indicated that the included studies were of reasonable quality.

The included studies were observational and all used methods to adjust for relevant confounding factors. The number of studies in each analysis was limited as not all studies contributed data to every outcome. Appropriate methods were used to combine studies, assess heterogeneity and publication bias; the latter could not be ruled out. Statistically significant heterogeneity was identified for all analyses and sensitivity analyses were undertaken in an attempt to explain the variation. Studies varied in the combination of drugs used for treatment, categorisation of high and low compliance, age of participants, diagnosis of osteoporosis and site of fracture; variability in the analyses was partially explained by fracture location and drug regimen. The authors acknowledged the deficiency in determining compliance by using the MPR (this value does not actually measure whether patients comply with their treatment).

The authors' conclusions reflect the evidence presented, but should be considered tentative because of potential biases in the review and wide variation in the studies.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that new programs or treatments should be developed to improve adherence to bisphosphonates with regard to preventing new fractures.

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Bibliographic details

PubMedID

DOI

Original Paper URL

Other publications of related interest

Cramer JA, Gold D, Silverman S et al. A systematic review of persistence and compliance with bisphosphonates for osteoporosis. Osteoporosis International 2007; 18:1023-1031.

Kothawala P, Badamgarav E, Ryu S et al. Systematic review and meta-analysis of real-world adherence to drug therapy for osteoporosis. Mayo Clin Proc 2007; 82:1493-1501.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.