A systematic review assessing the effectiveness of interventions to improve persistence with anti-resorptive therapy in women at high risk of clinical fracture

White HJ, Bettiol SS, Perera R, Roberts NW, Javaid MK, Farmer AJ

CRD summary
The authors concluded that available evidence suggested potential for improving persistence with anti-resorptive medication, improving treatment outcomes and reducing fracture risk in women at high risk of clinical fracture. The authors' cautious conclusions reflect the evidence presented, but the small number of included trials of poor quality and differences between trial interventions and outcomes should be borne in mind.

Authors' objectives
To assess the effectiveness of interventions to improve persistence with anti-resorptive therapy in women at high risk of clinical fracture.

Searching
MEDLINE, EMBASE, CINAHL and the Cochrane Library were searched to May 2009 for articles in any language. Search terms were reported. The Current Controlled Trials website was searched, as were reference lists of retrieved full-text papers.

Study selection
Randomised controlled trials (RCTs) that compared interventions aimed at improving persistence with or adherence to anti-resorptive therapy versus interventions with standard care for women with a high risk of clinical fracture were eligible for inclusion. Trials of educational or motivational interventions, where patients did not adhere with treatment were excluded.

The primary outcome was duration of persistence with medication. Secondary outcomes were different measures of adherence such as rate of fragility fracture, bone mass density and measurement of bone turnover markers.

Interventions in the included trials included biomarker monitoring with feedback to patients or other motivational interventions including educational leaflets, nurse-led education, decision aids and telephone reminders. Only postmenopausal women were included in the trials, but risk factors varied, as did measurement or assessment of risk factors. Participants were prescribed risedronate, alendronate with ibandronate, or raloxifene. Included trials were conducted in Australia, North and South America, Europe and Africa.

Two reviewers independently selected studies for inclusion.

Assessment of study quality
Trial quality was assessed using the Jadad scale; criteria included randomisation, blinding, and losses to follow-up (maximum score was 5 points).

The authors did not state how many reviewers assessed validity.

Data extraction
Data were extracted and used to calculate relative risks (RRs) and corresponding 95% confidence intervals (CIs) for relevant outcomes.

One reviewer extracted data which was verified by a second reviewer.

Methods of synthesis
Data were pooled and summary relative risks and corresponding 95% confidence intervals were calculated using a
Mantel-Haenszel random-effects model. Heterogeneity was assessed using the $I^2$ statistic. Where trials included comparison of two interventions groups with one control group, the control group was divided into two (events and total sample size) to provide separate control groups. Number needed to treat (NNT) was calculated based on the pooled relative risk reduction and the event rate in the control group of the largest trial.

Post-hoc subgroup analysis was conducted according to the type of intervention (biomarker or motivational).

Publication bias was examined by visual inspection of funnel plots.

**Results of the review**

Six RCTs (n=4,648 women, range 33 to 2,382) were included in the review. Two RCTs scored 2 points for randomisation and two RCTs scored 1 point. No RCTs reported blinding. Three RCTs adequately reported losses to follow-up. Duration of follow-up ranged from four months to one year.

Combined results of biomarker feedback and motivational interventions led to a reduction in the proportion of women not persisting with anti-resorptive medication compared with control groups (RR 0.78, 95% CI 0.65 to 0.95, 4 RCTs). There was no evidence of significant heterogeneity ($I^2=47\%$). When stratified by intervention type, the results were no longer significant for: biomarker feedback compared with control (RR 0.86, 95% CI 0.74 to 1.01; $I^2=0$; two RCTs) or for motivational feedback (RR 0.76, 95% CI 0.50 to 1.15; $I^2=38\%$; three RCTs).

One RCT reported that the percentage change in bone turnover markers were significantly correlated with adherence to therapy (data not reported), while four RCTs reported no significant differences between groups. Results of within-trial subgroup analyses were also reported.

**Authors’ conclusions**

Available trials suggested potential for improving persistence with anti-resorptive medication, improving treatment outcomes and reducing fracture risk.

**CRD commentary**

The review question was clear with broad but appropriate inclusion criteria. Several relevant sources were searched with no restriction on language. Appropriate methods to reduce reviewer error and bias were used for the selection of studies and extraction of data, but it was unclear whether similar methods were used to assess study quality.

Trial quality was assessed and results of the assessment were reported. The included trials were clinically heterogeneous, with differences in interventions and outcome measurements as well as participants, so the pooled estimates should be interpreted with some caution. The authors also noted that two large trials accounted for 90% of weighting of overall analysis, while individual trials did not demonstrate consistent effects.

The authors’ cautious conclusions reflect the evidence presented, but the small number of included trials of poor quality and the differences between trial interventions and outcomes should be borne in mind.

**Implications of the review for practice and research**

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

**Research:** The authors stated that further RCTs are needed to clarify which interventions could have the greatest effect on patient adherence and how these could be best implemented. The authors listed a range of recommendations for future research.

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