Skeletal consequences of hormone therapy discontinuance: a systematic review


CRD summary
This review primarily examined the effectiveness of treatments to prevent bone loss after the discontinuation of hormone therapy in postmenopausal women. The authors found only two randomised controlled trials that addressed this question, both of which suggested that alendronate may be beneficial. However, given the differences between the studies and the limited amount of data available, the review findings are cautious.

Authors' objectives
To determine whether data from randomised controlled trials (RCTs) support the observation that bone mineral density (BMD) loss after hormone therapy (HT) cessation is greater than losses either with placebo or after the discontinuation of other therapies. The authors stated that a secondary focus was to provide information on bone loss and any useful countermeasures after the discontinuation of other therapies, relative to placebo and HT.

Searching
MEDLINE, EMBASE and Biotech Abstracts were searched from inception to April 2003; the search terms were reported. The authors also contacted pharmaceutical companies for additional unpublished studies. Other published and unpublished data known to the authors were also included.

Study selection
Study designs of evaluations included in the review
RCTs were eligible for inclusion. The follow-up after treatment discontinuation ranged from 1 to 4 years.

Specific interventions included in the review
HTs for postmenopausal women were eligible for inclusion. The authors did not state any pre-defined comparators. The included studies assessed several cyclic and continuous regimens of oestrogens (conjugated equine oestrogen, estradiol, mestranol) and progestins (medroxyprogesterone acetate, norethindrone acetate, micronised progesterone). The duration of active treatment varied from 1 to 5 years. Most trials included HT, placebo and active comparator arms. All active comparators were antiresorptive agents, except for one trial that included an androgenic anabolic steroid, nandrolone decanoate, in combination with HT. Data for countermeasures to BMD loss after stopping HT were available for two bisphosphonates (alendronate, clodronate), four selective oestrogen receptor modulators (SERMs: raloxifene, levormeloxifene, toremifene and tamoxifen) and the vitamin D analogue calcitriol.

Participants included in the review
Postmenopausal women who had undergone HT but had now stopped were included. The mean age of the included women ranged from 47 to 72 years. Some of the included women had had hysterectomies, oophorectomies, spinal fractures, low BMD and breast cancer. The baseline BMDs varied from low to normal or were not stated in many cases.

Outcomes assessed in the review
The primary outcome was longitudinal assessments of BMD. BMD was generally measured at multiple skeletal sites. Spinal BMD was measured in most cases and was generally representative of observations at other skeletal sites. In two early studies, spinal BMD was not measured and so forearm and metacarpal bone mineral content results were presented instead. Biochemical markers of bone turnover were reported in five studies, four of which used urinary N-telopeptides of type I collagen (NTx); the fifth used urinary hydroxyproline.

How were decisions on the relevance of primary studies made?
Two authors and an acknowledgee independently assessed the relevance of abstracts and full publications. Together they agreed on which studies should be included.
Assessment of study quality
The authors did not state that they carried out a formal assessment of validity. However, some methodological problems were discussed in the text.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. An annualised rate (percentage change per year) was estimated by dividing the total mean percentage change in BMD by the number of follow-up years. The authors tabulated other data: characteristics of the study population at the start of the discontinuation phase; treatment duration in years; BMD change from baseline to end of active treatment (percentage change plus or minus the standard error, +/- SE); BMD change from baseline to end of study (percentage change +/- SE or 95% confidence interval, CI); and change in NTx from baseline to end of study (percentage change +/- SE or 95% CI).

Methods of synthesis
How were the studies combined?
Heterogeneity between the studies meant that the studies were combined in a narrative.

How were differences between studies investigated?
Differences between the studies were described in the tables and discussed in the text. The studies were grouped into three categories depending on the length of time over which BMD changes were reported: changes 1 year after discontinuation; changes over multiple years; and those reporting effects on BMD when another osteoporosis therapy was initiated after stopping HT.

Results of the review
Eleven (n=2,218) RCTs were included.

BMD changes during and after HT discontinuation (9 studies).
All treatment groups except placebo and raloxifene experienced statistically significant gains in spinal BMD relative to baseline during treatment. One year after stopping HT, the mean spinal bone loss ranged from -3.2% to -6.2%. Mean age, enrolment for prevention or treatment of osteoporosis (different BMD levels) and duration of prior treatment (ranging from 1 to 5 years) had no obvious effect on the magnitude of bone loss observed after stopping HT. In general, women in the placebo groups who had not received HT experienced changes in BMD, ranging from -1.9% to 0.1% per year in the 'discontinuation' phase and from -0.6% to -1.8% during the 'active' (randomised to placebo) treatment phase. At completion of follow-up after stopping HT, the mean BMD was not significantly higher than baseline in most studies. In no study did stopping HT or a comparator lead to a final mean BMD that was significantly lower than the untreated placebo group.

Bone resorption markers after treatment discontinuation (4 studies).
During active treatment, the magnitude of NTx decline was similar in the HT and alendronate groups and different from placebo in two studies. In the other two studies (one calcitiol and one nandrolone), the markers rebounded above pre-treatment levels once HT was stopped.

Therapy to prevent bone loss (2 studies).
One study demonstrated that alendronate produced significant increases relative to placebo in spine, hip and total body BMD in women with low bone density who had discontinued HT within the past 3 months, preventing the rapid bone lose seen after the discontinuation of HT. The other study showed that during three years of treatment with SERM/placebo, participants sustained significant bone loss at the spine; there was no change in participants receiving SERM/clodronate.
Authors' conclusions
There are limited data addressing treatment after the cessation of HT: only two studies specifically evaluated therapy to protect bones after hormone discontinuation. Taken together, these two studies demonstrated that alendronate produced significant increases relative to placebo in spine, hip and total body BMD in women with low bone density who had discontinued HT within the past 3 months. Among treatment options for preventing bone loss on HT discontinuation for which there were data from RCTs, alendronate appeared the most promising, either preventing BMD loss or increasing BMD.

CRD commentary
This review was based on clear inclusion criteria and a wide search for both published and unpublished data. The review would, however, have benefited from some assessment of study quality, although the authors limited data to RCTs which constitute the highest level of evidence. The findings of the review are limited by the paucity of data concerning treatment after HT discontinuation, as well as the heterogeneity observed between the included studies. There were also some discrepancies between the data in the tables and in the text, which make interpretation of the authors' findings difficult. Although the authors made some attempt to examine the effects of potential confounders (age, baseline BMD levels and treatment duration) on their findings, there may be additional confounders which have not been considered. The potential adverse effects of treatment were also not considered. Given these limitations and the authors' recommendations for further research, the review findings are rightly cautious.

Implications of the review for practice and research
Practice: The authors stated that women who are discontinuing HT should be counselled about potential bone loss and effective treatment options. These women should be monitored closely, with BMD testing, after they discontinue HT. Measurements should be carried out immediately after discontinuation to provide a baseline and approximately 12 months later to detect any changes.

Research: The authors stated that further RCTs are necessary to definitively address the extent, if any, of the benefit that other agents (apart from alendronate) may have in preventing BMD loss.

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