Tibolone for postmenopausal women: systematic review of randomized trials

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Authors’ objectives
To assess the effect of tibolone on climacteric symptoms, sexual function, endometrial and breast tissue, lipid metabolism and bone mineral density.

Searching
MEDLINE, Galen II (a digital library), EMBASE and the Cochrane Library were searched for articles published from January 1981 to August 2001. The keywords included: 'tibolone', 'Livial', 'postmenopausal women', 'hormone replacement therapy', 'climacteric symptoms', 'sexual function', 'osteoporosis', 'breast cancer', 'lipid metabolism' and 'cardiovascular effects'. The search was not restricted to articles published in the English language. Conference proceedings and the bibliographies of the identified studies were manually searched. Articles in press were obtained from Organon (the manufacturer of tibolone).

Study selection
Study designs of evaluations included in the review
Retrospective analyses, non-randomised and open-label studies were excluded. Double-blind randomised controlled trials (RCTs) were included in the review.

Specific interventions included in the review
Comparisons of tibolone (2.5 mg/day) with a control therapy were eligible. Trials in which the use of a placebo was not specifically stated were reported as being excluded, but this intent does not seem to have been adhered to. The included studies compared tibolone with either placebo, E2 valerate (E2V) or a combination of E2 and norethisterone acetate (NETA). The duration of trials ranged from 6 to 104 weeks.

Participants included in the review
Postmenopausal women were eligible. Premenopausal women were excluded. The selection criteria for all of the included randomised controlled studies were hot flushes, sweating and other postmenopausal symptoms. The participants ranged from 27 to over 65 years of age and included women after a surgical menopause. Individual primary studies excluded the following groups of women: those with a previous history of gynaecological cancer, renal or liver disease; those with hypertension; those with any cardiovascular or cerebrovascular disease; those with thromboembolic disease; those on medication known to affect coagulation, fibrinolysis, or lipid or bone metabolism; and smokers.

Outcomes assessed in the review
The inclusion criteria were not defined a priori in terms of the outcomes. The outcomes assessed were: climacteric symptoms such as hot flushes, sweating, mood and irritability; sexual function; endometrial tissue (using vaginal bleeding); breast tissue (using breast density); lipid metabolism; and bone mineral density (BMD). Lumbar BMD was assessed using computed tomography and dual-energy X-ray absorptiometry. Sexual function was assessed using the McCoy Sex Scale Questionnaire and the Swedish version of this questionnaire. Hot flushes, sweating and vaginal dryness were assessed using 3- or 5-point scales. Changes in mood, irritability and sexual function were measured using different scores and scales. Adverse events were also assessed.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
No formal validity assessment was performed but only double-blind RCTs were included in the review.
**Data extraction**
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

The following information was tabulated: author and year of publication; the treatments compared; study design; the number and age of the participants; study duration; and main outcomes.

**Methods of synthesis**
How were the studies combined?
A narrative synthesis was undertaken.

How were differences between studies investigated?
Differences between the studies were discussed in the text of the review.

**Results of the review**
Twenty-one RCTs (approximately 2,745 women) were included.

The trials differed with regard to the patients’ age and demographics, and the inclusion and exclusion criteria.

Climacteric symptoms: 6 RCTs (305 women) compared tibolone with placebo, 1 RCT (20 women) compared tibolone with E2V, and 3 RCTs (974 women) compared tibolone with E2-NETA.

Compared with placebo, most RCTs reported a significant reduction in hot flushes and sweating in women taking tibolone. The magnitude of the change was not reported for all of the studies.

There was no difference between tibolone and hormone replacement therapy in terms of the change in hot flushes. The magnitude of the improvement could not be ascertained.

The reported changes in the other postmenopausal symptoms varied among the studies. Two trials were of a very short duration (6 and 24 weeks) and two trials did not describe the methods used to measure the symptoms. One small RCT (20 women) found that tibolone and E2V were associated with a similar improvement in mood.

Sexual function.

The results from 2 RCTs comparing tibolone with placebo were inconsistent. One RCT found no significant improvement in libido for women on tibolone, while the other found a significant improvement with tibolone.

Two of the 3 RCTs comparing tibolone with E2-NETA assessed changes in biochemical measures. The 1 RCT that assessed improvement in sexual function had a large drop-out rate (30%) and did not report any reasons for this.

Vaginal bleeding.

One RCT (94 women) found that tibolone was associated with significantly more vaginal bleeding than placebo: 51% with tibolone versus 22% with placebo (P<0.05). Two RCTs (255 women) found that tibolone was associated with approximately half the rate of vaginal bleeding as E2-NETA: 34 versus 58% (P<0.0001) and 25 versus 50%.

Lipids and clotting factors: 7 RCTs compared tibolone with placebo, while 2 RCTs compared tibolone with E2-NETA.

The clinical implications of the effects of tibolone on lipids and clotting factors was unclear. Hence, definite conclusions could not be drawn from the trials on the risks for cardiovascular disease or venous thromboembolism.

Osteoporosis.

Four of the 5 RCTs measuring BMD reported a significant increase in BMD for tibolone when compared with placebo.
One small RCT compared tibolone with E2-NETA and reported only biochemical levels. The trials were small, relatively short in duration (less than 2 years) and provided no data on fracture risk.

Breast cancer.

One small RCT involving 44 women with normal breast tissue found no effect on breast density after 1 year of treatment with tibolone, control or hormone replacement.

Adverse effects.

Adverse effects and drop-out rates due to adverse effects were not reported in the placebo-controlled trials.

**Authors' conclusions**

Tibolone significantly reduced hot flushes and sweating and increased BMD in postmenopausal women. Other effects of tibolone in postmenopausal women, such as its influence on lipid metabolism, haemostasis and sexual function, were less certain. In addition, the long-term effects of tibolone, particularly in reducing fractures, breast cancer and cardiovascular disease, are still unknown.

**CRD commentary**

This was a clearly written and presented review, although it lacked details of the methods used to conduct the review. The aims were stated, and the exclusion criteria were defined in terms of the study design and participants. The inclusion criteria were not defined a priori in terms of the outcomes, and although it was stated that studies in which 'the use of placebo was not specifically stated' were excluded, trials that compared tibolone with alternative hormone replacement therapies were included. The search was adequate and included attempts to locate unpublished material. However, the methods used to select the studies were not described. Validity was not assessed although the included studies of effect were restricted to randomised controlled double-blind trials. Relevant data were presented in tabular format, but the methods used to extract the data were not described. A narrative synthesis was appropriate given the small number of studies comparing similar interventions and reporting equivalent outcomes. Attention was drawn to the limited evidence available from methodologically flawed studies.

The evidence presented supports the authors' conclusions.

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

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

Research: The authors state that large trials should be used to assess the effect of tibolone on the risk of breast cancer, sexual function, vaginal bleeding and postmenopausal osteoporosis. In addition, future trials comparing tibolone with placebo should comprehensively report any adverse events in the treatment groups.

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