Short and long term effects of tibolone in postmenopausal women (Review)

Formoso G, Perrone E, Maltoni S, Balduzzi S, D'Amico R, Bassi C, Basevi V, Marata AM, Magrini N, Maestri E

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2012, Issue 2

http://www.thecochranelibrary.com

[Intervention Review]

Short and long term effects of tibolone in postmenopausal women

Giulio Formoso[1], Enrica Perrone[1], Susanna Maltoni[2], Sara Balduzzi[3], Roberto D'Amico[3], Chiara Bassi[1], Vittorio Basevi[1], Anna Maria Marata[1], Nicola Magrini[1], Emilio Maestri[1]

[1]CeVEAS, NHS Centre for the Evaluation of the Effectiveness of Health Care, WHO Collaborating Centre for Evidence-based Research Synthesis and Guideline Development in Reproductive Health, Modena Local Health Authority, Emilia Romagna Regional Health System, Modena, Italy. [2]Regional Agency for Health and Social Care, Emilia-Romagna Region, Bologna, Italy. [3]Statistics Unit, Department of Oncology, Hematology and Respiratory Diseases, University of Modena and Reggio Emilia, Modena, Italy

Contact address: Giulio Formoso, CeVEAS, NHS Centre for the Evaluation of the Effectiveness of Health Care, WHO Collaborating Centre for Evidence-based Research Synthesis and Guideline Development in Reproductive Health, Modena Local Health Authority, Emilia Romagna Regional Health System, Viale Muratori 201, Modena, 41124, Italy. g.formoso@ausl.mo.it.

Editorial group: Cochrane Menstrual Disorders and Subfertility Group.
Publication status and date: New, published in Issue 2, 2012.
Review content assessed as up-to-date: 17 July 2011.

Citation: Formoso G, Perrone E, Maltoni S, Balduzzi S, D'Amico R, Bassi C, Basevi V, Marata AM, Magrini N, Maestri E. Short and long term effects of tibolone in postmenopausal women. *Cochrane Database of Systematic Reviews* 2012, Issue 2. Art. No.: CD008536. DOI: 10.1002/14651858.CD008536.pub2.

ABSTRACT

Background

Tibolone is an option available for the treatment of menopausal symptoms, based on short-term data on its efficacy. However, there is a need to consider the balance between the benefits and risks of tibolone as there are concerns about breast and endometrial cancer as well as stroke.

Objectives

To evaluate the effectiveness and safety of tibolone in treating postmenopausal women.

Search methods

We searched the Cochrane Menstrual Disorders and Subfertility Group (MDSG) Specialised Register (19 April 2011), Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, 2nd Quarter), MEDLINE (from inception to 19 April 2011), EMBASE (1980 to week 3 April 2011), PsycINFO (1806 to week 3 April 2011), Clinical Trials.gov (30 April 2011). Individual researchers and the current manufacturer of tibolone were contacted to identify unpublished and ongoing trials.

Selection criteria

Randomised controlled trials (RCTs) that compared tibolone versus placebo, estrogens or combined hormone replacement therapy (HT) by assessing the percentage of women with menopausal symptoms, the severity of those symptoms and the occurrence of safety outcomes in postmenopausal women.

Data collection and analysis

Four review authors independently extracted information from the articles, resolving discrepancies by consensus. All outcomes studied were dichotomous. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using the random-effects model. Heterogeneity of studies was taken into account before deciding to combine the data.

Main results

When compared to placebo, tibolone was more effective in relieving the frequency of vasomotor symptoms (two RCTs, n = 847; OR 0.42, 95% CI 0.25 to 0.69), although only the 2.5 mg/day dose of tibolone was significantly better than placebo; but with increased vaginal bleeding (seven RCTs, n = 7462; OR 2.75, 95% CI 1.99 to 3.80). When compared to equipotent doses of combined HT, tibolone reduced vaginal bleeding (15 RCTs, n = 6342; OR 0.32, 95% CI 0.24 to 0.42) but was less effective in relieving the frequency of vasomotor symptoms (two RCTs, n = 545; OR 4.16, 95% CI 1.50 to 11.58).

As for long term safety, two major RCTs of tibolone versus placebo provided the most relevant data. An RCT of 3098 women with breast cancer and menopausal symptoms was halted after 3.1 years because of increased tumour recurrence (OR 1.50; 95% CI 1.21 to 1.85). However, in another RCT that selected osteoporotic women with negative mammograms (n = 4506) tibolone was associated with a reduction in breast cancer compared to placebo after 2.8 years (OR 0.32, 95% CI 0.13 to 0.79) although the trial was not specifically designed to assess that outcome and the number of overall events was low. In the same RCT, an excess risk of stroke was observed (OR 2.18, 95% CI 1.12 to 4.21). There was no clear evidence of a tibolone effect on endometrial cancer compared with placebo given the low number of events (seven RCTs, n = 8152; OR 1.98, 95% CI 0.73 to 5.32).

There was no evidence of a difference in long term safety between tibolone and combined HT.

Authors' conclusions

Tibolone, used at the daily dose of 2.5 mg, may be less effective than combined HT in alleviating menopausal symptoms although it reduced the incidence of vaginal bleeding. There was evidence that treatment with combined HT was more effective in managing menopausal symptoms than was tibolone. Available data on the long term safety of tibolone is concerning given the increase in the risk of breast cancer in women who had already suffered from breast cancer in the past and in a separate trial the increase in the risk of stroke in women whose mean age was over 60 years. Similar concerns may exist for estroprogestins but their overall benefit-risk profile is better known and is more directly related to women with menopausal symptoms.

PLAIN LANGUAGE SUMMARY

Combined hormone therapy is more effective than tibolone on menopausal symptoms. Tibolone may increase the risk of recurrent breast cancer and stroke

The authors analysed 33 clinical trials to evaluate whether tibolone, compared to placebo or combined hormone replacement therapy (HT), was effective in alleviating menopausal symptoms and the risks associated with the longer term use of HT. Limited evidence suggested that tibolone was less effective than combined HT in the treatment of menopausal symptoms, although fewer women suffered vaginal bleeding. In two separate trials, prolonged use of tibolone (for one or more years) increased the risk of breast cancer in women who had already suffered from breast cancer in the past and increased the risk of stroke in women whose mean age was over 60 years. The risk profile of this drug is not well defined but it is concerning enough that its longer term use should not be supported.