Critical evaluation of the safety of Cimicifuga racemosa in menopause symptom relief
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CRD summary
This review concluded that extracts of Cimicifuga are safe to use in women with menopausal symptoms. The conclusion was generally in line with the evidence presented. The review had methodological and reporting weaknesses that make it difficult to be certain of the reliability of the conclusions.

Authors' objectives
To assess the safety of Cimicifuga racemosa in women with menopausal symptoms.

Searching
MEDLINE, EMBASE, BIOSIS Previews and SciSearch were searched. Searches were also conducted of the Food and Drug Administration (FDA) and World Health Organization (WHO) adverse event reporting systems, monographs, compendia, and unpublished data from Schnaper and Brummer. The search terms for the FDA database were provided. Reports published in foreign languages were eligible. The reference lists in identified studies were also checked.

Study selection
Study designs of evaluations included in the review
Uncontrolled and controlled preclinical and clinical trials were eligible for inclusion. The review included randomised controlled trials (RCTs) and uncontrolled studies, including post-marketing surveillance reports, preclinical studies, and historical and anecdotal reports.

Specific interventions included in the review
The inclusion criteria were not explicitly stated in terms of the interventions, although it was clear that studies of Cimicifuga racemosa were eligible for inclusion. The review included studies of black cohosh, but the focus was on commercially available extracts of Cimicifuga. The included clinical trials used Cimicifuga in doses ranging from 20 to 40 drops of ethanolic extract twice daily (48 to 140 mg crude drug), to two to four tablets of isopropanolic extract per day (39 to 140 mg crude drug). Where reported, the duration of the studies ranged from 8 to 52 weeks.

Participants included in the review
The inclusion criteria were not explicitly stated in terms of the participants, although it was clear that studies of women with menopausal symptoms were to be included. The included clinical studies were of women with menopausal symptoms, premenstrual tension, pregnancy problems, dysmenorrhoea, amenorrhoea, oligomenorrhoea, hormone-related conditions, breast cancer (including women taking tamoxifen), or hysterectomy; perimenopausal women; and girls with juvenile menstrual disorders.

Outcomes assessed in the review
The inclusion criteria were not explicitly stated in terms of the outcomes, although it was clear that studies that reported adverse effects were eligible for inclusion. Some of the included studies assessed the oestrogenic effect, i.e. cell proliferation, luteinising hormone (LH), follicle stimulating hormone (FSH), prolactin and sex hormone-binding globulin levels.

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

Assessment of study quality
The validity of the studies was not formally assessed. However, some aspects of validity were discussed in the text, such as study design, study duration and the lack of an evaluation of drug exposure.
Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Information on the participants' characteristics, formulation of Cimicifuga, treatment duration and adverse events were tabulated for clinical studies and postmarketing surveillance studies. Details of each adverse event (including event, preparation, ingredients and manufacturer) reported to the FDA were also tabulated, as were adverse events reported to the WHO Collaborating Center. Study parameters, formulation and safety-related outcomes were tabulated for the in vitro and in vivo studies.

Methods of synthesis
How were the studies combined?
The studies were combined in a narrative review under the following headings: historical results; uncontrolled reports; postmarketing surveillance; preclinical safety; and clinical safety. The overall adverse event rate was calculated for clinical studies.

How were differences between studies investigated?
Differences between the studies were not investigated.

Results of the review
Two postmarketing surveillance studies (669 women), 20 clinical trials (2,140 women exposed to Cimicifuga) and 7 studies (more than 389 women) in special populations of women, two of which had been included in the 20 clinical trials, were included. Two of the clinical trials were RCTs (237 women). The review also considered in vitro and animal studies.

Only the results from studies of humans are reported in this abstract.

The FDA reported 9 adverse events, only one of which (headaches and high blood-pressure) occurred with Cimicifuga used alone. The other adverse events were associated with combinations of Cimicifuga and other herbal preparations. The WHO Collaborating Center for International Drug Monitoring reported 35 adverse events (general symptoms not confined to particular organs) in preparations of Cimicifuga alone or in combination with other agents. A monograph from the German Commission E found no drug interactions with Cimicifuga, whereas the FDA and WHO advised caution when using Cimicifuga in combination with other herbal products.

Two reports of postmarketing surveillance showed low adverse event rates: one study of Cimicifuga solution (629 women followed-up for 8 weeks) found short-lived adverse events in 7%, while the other study of isopropanolic Cimicifuga tablets (40 women entered, 28 women followed-up for 3 months) found no adverse events.

The clinical studies found low adverse event rates (5.4%). Most (97%) of the adverse events were minor and did not lead to the withdrawal of Cimicifuga.

Dose-related safety: one RCT (152 women) found similar adverse events for doses of Cimicifuga of 39.0 and 127.3 mg/day for 24 weeks.

Special populations: the evidence was limited on account of the lack of consistent reporting of baseline hormone levels and the lack of placebo controls. Four of the 5 tabulated studies that investigated the effects of Cimicifuga found no change in markers of oestrogenic activity for Cimicifuga taken for between 8 and 24 weeks. One of these, an RCT (85 women with breast cancer) found no change in LH or FSH with either Cimicifuga extract or placebo for 8 weeks. The fifth study (52 women) showed that Cimicifuga significantly reduced LH, but not FSH, after 8 weeks. Another study (not tabulated under the special population heading) found that Cimicifuga was associated with proliferation for vaginal epithelium.
Authors' conclusions
Extracts of Cimicifuga, especially isopropanolic preparations, are safe to use in women with menopausal symptoms. They are also safe in women for whom conventional oestrogen replacement therapy is contraindicated.

CRD commentary
The review did not explicitly state any inclusion criteria, although the review question was clear in terms of the intervention and outcomes. Studies of any design were included. The focus of the review was stated to be menopausal women, but women and girls with other conditions were also included. Several relevant sources were searched for published and unpublished data, and foreign language reports were eligible. Search terms were only reported for the FDA database, while search dates were only reported for the WHO database. No details were given of either the number of reviewers who conducted the searches or the methods used to extract the data; hence, any efforts made to reduce errors and bias cannot be judged. The assessment of study validity was limited to a brief comment on the limitations of uncontrolled studies of short duration. Some relevant information on some of the included studies was tabulated.

A narrative synthesis was appropriate given the nature of the evidence. The authors reported the proportion of patients who reported adverse events in the clinical studies and the proportion of adverse events that were minor, and gave details of severe adverse event rates. Selected studies were described in more detail. The duration of treatment in some studies was short, which limits the evidence. The review showed that few adverse events were reported in a considerable number of studies with a large total population. However, the number of women for whom oestrogens were contraindicated was small and this limited the evidence for this population.

Implications of the review for practice and research
Practice: The authors stated that Cimicifuga appears to be a safe treatment for women with menopausal symptoms.

Research: The authors stated that a large long-term, well-conducted study is required to assess the effect of treatment with Cimicifuga.

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