Vitex agnus castus: a systematic review of adverse events
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CRD summary
This review assessed the safety of Vitex agnus castus (VAC) monopreparations. The authors concluded that the available data indicate that VAC is not associated with serious health risks, but further rigorous studies are needed. The authors’ conclusion about adverse event rates may be optimistic given the paucity of well-controlled studies, but the need for further rigorous studies is supported.

Authors' objectives
To evaluate the safety of Vitex agnus castus (VAC) monopreparations.

Searching
MEDLINE, AMED, CINAHL, EMBASE, PsycINFO and the Cochrane Library were searched (September 2004) for relevant articles; the search terms were reported and no language restrictions were applied. In addition, personal files and the references of identified articles were checked. Twelve manufacturers of VAC, identified from references texts, were also contacted. Data from a number of spontaneous schemes, including the WHO Collaborating Centre for International Drug Monitoring, and from herbal organisations were also requested.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs), non-randomised controlled trials, case reports, case series, surveys and postmarketing surveillance studies were included in the review.

Specific interventions included in the review
Studies assessing monopreparations of VAC were eligible for inclusion. Studies of VAC used in combination with other herbs or homeopathic preparations of VAC were excluded. Where reported, the comparators included pyridoxine, fluoxetine, vitamin B, placebo and no treatment.

Participants included in the review
All but two of the studies included in the review involved women. Women with premenstrual syndrome, luteal phase defects as a result of hyperprolactinaemia, premenstrual dysphoric disorder, corpus luteum insufficiency, bleeding abnormalities, and breast-feeding or lactating women were included in the review, as were men and women with acne, and healthy men.

Outcomes assessed in the review
Studies reporting any adverse event were eligible.

How were decisions on the relevance of primary studies made?
One reviewer assessed the identified articles for eligibility; the decisions were independently checked by at least one other reviewer.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data were extracted according to predefined criteria, including number and type of adverse event reported.
Methods of synthesis
How were the studies combined?
A narrative summary was presented.

How were differences between studies investigated?
The studies were grouped by study design.

Results of the review
Thirty-three studies were included in the review; five of these were RCTs (n=498) and four were non-randomised controlled trials (n=1,098).

RCTs.
Two of three placebo-controlled trials reported on diverse events. One study reported that no adverse events were observed. The remaining trial found that the occurrence of adverse events was comparable across the treatment groups (4.7% in the VAC group and 4.8% in the placebo group). In the two trials with active controls, one study found a comparable adverse drug reaction rate between VAC and fluoxetine (40% and 42.8%, respectively); the other study found a higher adverse drug reaction rate in the VAC treatment group (19.7%) compared with pyridoxine (7.7%). The most frequent adverse events recorded were nausea, acne, allergic reactions, headaches and stomach disturbances.

Non-RCTs.
Two studies did not provide any data on adverse events. Of the remaining studies, one study (n=817) reported 15 cases of pruritus, exanthema and urticaria, and some cases of early menstrual period; the other study (n=20) reported adverse events in 18 men, but the correlation between VAC treatment was judged to be 'uncertain' in most cases.

Other study designs.
The results from uncontrolled studies, postmarketing surveillance studies, surveys and spontaneous reporting schemes were described. Overall, a low incidence of adverse events was reported: adverse event rates of 1.9 to 5% and withdrawals due to adverse effects of 0.9 to 1.1% in 6 postmarketing studies.

Authors’ conclusions
The available data indicate that VAC is not associated with serious health risks, although further rigorous studies are needed.

CRD commentary
The broad review question was not well supported in terms of inclusion and exclusion criteria, which may reflect the lack of literature in this area. Several electronic databases were searched, unrestricted by language, and some attempt was made to locate unpublished material. Methods were used to minimise errors and bias in the selection of studies, but it was unclear whether similar steps were taken when extracting the data from the primary studies; the quality of the primary studies was not assessed. The included studies were heterogeneous in terms of their study design, intervention, comparators and population, thus the narrative summary was appropriate. The authors’ conclusion that VAC is not associated with serious adverse events may be overstated given the paucity of rigorous trials. However, the stated need for further trials is supported.

Implications of the review for practice and research
Practice: The authors stated that VAC should be avoided during pregnancy and lactation because of the lack of data on its safety.

Research: The authors stated that further rigorous studies are needed to assess the safety of VAC.
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