

# Critically Appraised Topic

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## Is black cohosh a safe and effective substitute for hormone replacement therapy?

A 50-year-old woman is seeking advice from her primary care PA regarding her progressively worsening hot flashes associated with menopause. The patient reports an average of eight hot flashes per day for the past 7 days; she has difficulty sleeping and is concerned about her loss of interest in sexual activities. She is the mother of two teenagers, so maintaining her emotional stability and energy are important to her. The patient eats a healthy diet, exercises daily, denies tobacco use, and drinks a glass of red wine nightly with dinner. She takes daily vitamins and is more accepting of holistic remedies than prescription medications. She has been researching various herbal products advertised to alleviate the vasomotor symptoms associated with menopause and would like to utilize black cohosh as an alternative to hormone replacement therapy (HRT).

### CLINICAL QUESTION

Is black cohosh a safe and effective substitute for HRT in the treatment of vasomotor symptoms associated with menopause in healthy women?

### BACKGROUND

Approximately 85% of women experience hot flashes and night sweats associated with menopause.<sup>1</sup> These vasomotor symptoms may be associated with diminishing estrogen levels, changes in the potency of the type of circulating estrogen (estradiol vs estrone), and variations in the surges of luteinizing hormone.<sup>2</sup> The gold-standard treatment is HRT; however, recent studies have precluded and discouraged some women from this treatment. The Women's Health Initiative Estrogen-Plus-Progestin

Study, halted in July 2002, demonstrated a decrease in menopausal climacteric symptoms with HRT use but also found an increase in serious adverse events, such as coronary artery disease, stroke, thrombosis, and breast cancer.<sup>1</sup> Black cohosh (*Cimicifuga racemosa*) is an herb commonly used as an alternative to HRT in Europe and is one of the highest selling herbal supplements in the United States.<sup>1</sup> As is the case with approximately half of the herbal supplements sold, black cohosh is not part of the FDA's Generally Recognized as Safe list. However, omission from the list does not necessarily correlate with a lack of safety.

### SEARCH CRITERIA AND RESULTS

Ovid, PubMed, Medline, Cochrane, and Natural Standard databases, through April 2009, were searched using the search terms *black cohosh* AND *menopause* OR *vasomotor* OR *hot flashes*. The results were limited to humans, female, and English language. Twenty-seven final papers were selected based on internal validity (intention-to-treat analysis and minimal bias) and the highest levels of evidence (meta-analyses, systematic reviews, and randomized controlled trials [RCTs]). Articles were excluded if they did not specifically test black cohosh for the relief of vasomotor symptoms. Three systematic reviews and one recent RCT were selected for this review.

### EVALUATING THE EVIDENCE

Borrelli and Ernst published a systematic review of six double-blind clinical RCTs that evaluated the efficacy of black cohosh for menopausal vasomotor symptoms.<sup>3</sup> Measured outcomes

included psychologic as well as physiologic variables, and four of the studies investigated black cohosh (n = 327 participants). Only one of the research designs was placebo-controlled, and this study found no difference between the black cohosh and placebo groups in all outcomes. Several methodologic discrepancies were noted. Specifically, variations in dosing (6.5 mg of extract to 160 mg/d of a multibotanical preparation), participant ethnicity (European, American, and Chinese), and outcome measures (endocrine/metabolic tests and self-report indices) led the authors to conclude that black cohosh does not consistently demonstrate a statistically or a clinically significant effect on relief from menopausal symptoms.<sup>3</sup>

Borrelli also reviewed the adverse effects of black cohosh that included reports from randomized and nonrandomized clinical trials, case series, and marketing surveillance.<sup>4</sup> Eighty adverse events were reported for 2,189 patients in clinical trials, and 54 adverse events were recorded by the voluntary reporting programs. Mild and reversible GI symptoms and rashes were the most common adverse effects, yet the frequency of these adverse events was shown to be comparable to those with placebo (5.4%). In the most recent clinical trials (n = 1,522 participants), 46 adverse events were specifically reported. In three surveillance studies (n = 2,691), 28 adverse events were noted, and 18

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adverse events were reported as case series or single case reports.

Serious complications in patients using black cohosh included liver failure or acute hepatitis (n = 7), cutaneous vasculitis (2), seizures (1), anaphylactic facio-oral edema (5), muscle damage (1), cutaneous pseudolymphoma (1), and death from multiorgan failure (1). However, three of the patients with liver damage and the patient with multiorgan failure ingested known hepatotoxic substances along with the black cohosh. Similarly, the seizure patient had ingested potential seizure-inducing substances. The other patients recovered after discontinuing the herbal remedy or liver transplantation. Furthermore, not all of the cases supplied information about the formulation or dosage of black cohosh used or eliminated other possible causes for the adverse effects. Causal attribution to black cohosh can neither be confirmed nor rejected in these cases.

Palacio and colleagues reviewed 16 RCTs that evaluated the effectiveness of black cohosh in managing menopausal symptoms.<sup>5</sup> The authors highlight the methodological differences in the original research studies that may have contributed to the inconclusive effects of black cohosh. (1) Twelve different rating scales were used to measure outcomes. (2) Not all of the RCTs were of high methodological rigor using the Jadad scoring instrument, which assesses the quality of clinical trials on a scale of 0 to 5 (scores in the Palacio review ranged from 2 to 5). (3) Black cohosh formulations and dosages that were used in the trials varied greatly. Some studies used 20 mg of standardized Remifemin Menopause Tablets daily, some used 40 mg of Remifemin daily, some used 40 mg of *C racemosa*, and other researchers used various multibotanical combinations. (4) Not all the studies were placebo-controlled. Of the nine black-cohosh-versus-placebo studies, only one high-quality study (Jadad = 4) showed significant ( $P < .05$ ) improvement of hot flashes for the Remifemin group.<sup>5</sup> In contrast, the other high quality study (Jadad = 5), conducted by Newton and

colleagues,<sup>6</sup> failed to show significant clinical relief of vasomotor symptoms with black cohosh. Hormone therapy, however, demonstrated a significant decrease of 4.06 vasomotor symptoms per day versus placebo (95% confidence interval, -5.93 to -2.19;  $P < .001$ ).<sup>6</sup>

Most recently, van der Sluijs and colleagues conducted a randomized, double-blind, placebo-controlled study of postmenopausal women (n = 93) to evaluate the efficacy of a Chinese herbal formula containing black cohosh for relieving menopausal vasomotor symptoms.<sup>7</sup> The outcome measures were the quantity and severity of hot flashes. The study also employed two quality-of-life scales: The Greene Climacteric Scale and the Hot Flash Related Daily Interference Scale. The study found that there were no statistically significant differences on any of the outcome measures between the placebo and herbal intervention groups ( $P > .05$  for all comparisons); no adverse medical events associated with the interventions were reported.<sup>7</sup>

The North American Menopause Society has stated that herbal remedies may be used in conjunction with lifestyle changes, but the data are not yet complete.<sup>8</sup> The American Association of Clinical Endocrinologists will not advocate either for or against the use of herbal remedies,<sup>9</sup> and the American College of Obstetricians and Gynecologists does not recommend herbal supplements, citing lack of evidence.<sup>10</sup>

## CLINICAL BOTTOM LINE

Of prime importance when evaluating any treatment plan for a patient is the safety of the intervention. Studies indicate that black cohosh itself is safe but not without potential adverse effects. Definitive conclusions regarding black cohosh efficacy are difficult to reach based on current research methodology, the various preparations of black cohosh in use, and the numerous clinical end points being measured. Current data suggest that herbal formulas containing black cohosh provide no consistent reduction in the quantity or severity of

hot flashes, nor do they provide a statistically measurable improvement in quality of life. Furthermore, according to the Physician Assistant Competencies, PAs are to create an environment for communicating with patients in such a manner that effective information exchange can occur. This includes the directive to make informed decisions about therapeutic interventions based on patient information and preferences, as well as up-to-date scientific evidence. In this case, the PA can intelligently discuss the results of the studies on black cohosh and reference the lack of statistical and clinical data that support a decrease in menopausal symptoms or an improvement in quality of life. Furthermore, the PA should inform the patient that concerns about hepatotoxicity and other adverse side effects have been raised in the medical literature. **JAAPA**

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