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## Commentary on Black Cohosh for Treatment of Menopausal Disorders

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Black cohosh as a possible treatment for menopausal symptoms reflects an increasing interest in the use of non-conventional or “alternative” medicines for amelioration of many disorders. However, it has often been difficult to distinguish between the purported benefits of herbal medicines and vitamins from the effects associated with a variety of placebos. To promote research in this area, an Office of Alternative Medicine was established at the National Institutes of Health in 1992. The Institute of Medicine (IOM) published a report on Complementary and Alternative Medicine in 2005<sup>1</sup>. Given the popularity of alternative medicines, objective examination of the effectiveness of these remedies as well as the possible interactions with conventional prescription medications is very important. The IOM recommended that “the same principles and standards of evidence of treatment effectiveness apply to all treatments, whether currently labeled as conventional medicine or complementary and alternative medicines. Implementing this recommendation requires that investigators use and develop as necessary, common methods, measures, and standards for the generation and interpretation of evidence necessary for making decisions about the use of complementary and alternative medicines and conventional therapies”.

In this context, the report by Reame et al<sup>2</sup> in this issue of *Menopause* on the effects of black cohosh on LH pulse frequency, estradiol levels, hot flashes and brain activation patterns measured by Positron Emission Tomography (PET) is a potentially valuable contribution to an often contradictory and inconclusive literature on alternative medicines for treatment of menopausal symptoms<sup>3</sup>. The rhizome of the black cohosh (*Cimicifuga racemosa*) is thought to contain estrogen-like compounds and to offer a natural alternative to estrogen therapy. One major finding was that 12 weeks of treatment with a commercial preparation of black cohosh (Remifemin, 40 mg/day) in 6 menopausal women did not change the pulse frequency of luteinizing hormone (LH) or levels of estrogen from pre-treatment baseline levels. No significant changes in the average number of hot flashes were detected. This was an open trial in a small sample of menopausal women and there was no placebo control treatment. However, this finding is consistent with previous reports that black cohosh had no discernable effect on the vaginal epithelium, endometrium, LH, FSH or estradiol during one year of treatment in a double-blind, placebo-controlled trial in women with vasomotor symptoms<sup>4</sup>. Similarly, a double-blind, cross-over trial comparing 4 weeks of black cohosh treatment with placebo did not detect any effect on the incidence of hot flashes<sup>5</sup>. A one year, double-blind, placebo-controlled trial reached similar conclusions<sup>6</sup>. There are several reports of liver toxicity associated with black cohosh treatment<sup>7-10</sup> as well as transient gastrointestinal disturbances and headache<sup>11</sup>. Given the apparent lack of efficacy of black cohosh as an estrogen substitute for the treatment of menopausal symptoms, the several risks associated with its use assume increased importance.

It was once believed that hot flashes were associated with changes in release of LH, and by inference hypothalamic luteinizing hormone-releasing hormone (LHRH), but this association is not invariant<sup>12,13</sup>. If black cohosh increased estrogen levels and this in turn decreased LH

pulsatile release, this might influence the incidence of hot flashes. However, analysis of LH pulse frequency before and after chronic treatment with black cohosh did not reveal any significant differences. LH pulse amplitude was not reported, although an increase in LH pulse amplitude rather than an LH pulse frequency is associated with increases in LH during menopause<sup>14</sup>.

It is well established that LHRH control of LH release is under endogenous opioid control<sup>15-17</sup>. Accordingly, blockade of endogenous opioid peptides by *acute* administration of an opioid antagonist such as naltrexone, nalmefene or naloxone produces a dramatic increase in LH in premenopausal women but not in postmenopausal women.<sup>18-20</sup> However, Reame et al<sup>2</sup> report that an 8-hour infusion of naloxone led to a decrease in LH pulse frequency in their post-menopausal subjects. The authors interpret this finding as evidence of interactions between black cohosh and the endogenous opioid peptide system. Alternatively, the significant increase in cortisol during the naloxone infusion suggests that “stress” associated with the procedure also may have contributed to the decrease in LH. An increase in cortisol is an index of activation of the hypothalamic-pituitary-adrenal (HPA) axis, and “stress” reliably disrupts the menstrual cycle<sup>21,22</sup>.

PET scans of brain activation patterns in five of the six subjects before and after *chronic* treatment with black cohosh also failed to reveal significant differences. Rather the activation patterns measured after black cohosh were similar to those in previous studies of placebo effects<sup>23</sup> or estradiol administration<sup>24</sup>.

Given the lack of effect on objective measures of estrogen levels, LH pulse frequency or self-reports of hot flashes, the risks associated with chronic use of black cohosh appear to outweigh the benefits for treatment of menopausal symptoms.

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