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Discussion of a Well-Designed Clinical Trial Which Did Not Demonstrate Effectiveness: UIC Center for Botanical Dietary Supplements Research Study of Black Cohosh and Red Clover

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Abstract

The performance of a clinical trial for pharmaceutical agents is usually undertaken only after there is likely benefit demonstrated from the use of the putative agent. The consideration of botanical products as pharmaceutical agents must similarly go through a rigorous evaluation process. The present work reviews the recently published Phase II study evaluating the effectiveness of black cohosh and red clover in a randomized trial with conjugated equine estradiol/medroxyprogesterone acetate and placebo for the treatment of menopausal symptoms. We analyze the possible reasons why this study failed to show benefit for either botanical product in reducing menopause-related vasomotor symptoms.

Keywords

Menopause; vasomotor symptoms; hormone; botanical; black cohosh; red clover

Introduction

Menopause is associated with a wide variety of physiological, anatomical and clinical changes that mark the end of reproductive capacity, usually as result of the gradual cessation of ovarian sex steroidigenesis, but also resulting from the premenopausal surgical removal of the ovaries or the impact of specific chemotherapeutic or pelvic radiation therapeutic interventions in premenopausal women. These profound changes are primarily, but not exclusively, associated with the loss of physiological levels of estrogen. Indeed, it has been the use of estrogen-based therapies that has been associated with the most consistent improvement in many of these symptoms, regardless of whether they are systemic or local in nature.

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However, studies have demonstrated that such hormonal therapies may not be associated with a consistently satisfactory resolution of menopausal symptoms [1,2]. In addition, after the release of the initial outcomes of the Women's Health Initiative study of hormone therapy in menopausal women in 2002 [3], ongoing concerns regarding the safety of menopausal hormone therapies along with considerations of suboptimal effectiveness resulted in a profound reduction in the use of all hormonal menopausal interventions. The decreasing use of hormonal interventions for menopausal symptoms led women to seek non-hormonal regimens to reduce those symptoms. Unfortunately, the marketing of non-pharmaceutical products, including botanical dietary supplements, frequently prey upon symptomatic and, sometimes, desperate women who are willing to try (and spend money to obtain) products that are endorsed by celebrities. Such products are frequently marketed as though they had been scientifically evaluated or supported by “spontaneous” endorsements of “satisfied customers,” though most if not all such products had not been evaluated in a robust or rigorous clinical trial. Accordingly, it behooves us to investigate the use of alternative therapeutic options that could improve the overall health and well-being of menopausal women in a manner, ensuring that the process is similar to the scientific and clinical approach used to approve the use of pharmaceutical agents. Included in this are botanical dietary supplements that have been considered to be potential therapeutic regimens for the relief of menopausal symptoms [4,5].

The determination of the effectiveness and safety of a pharmaceutical agent is the outcome of a series of studies and trials that serve to provide the necessary information to support the benefits of use of the agent as well as providing an accurate assessment of the safety of the regimen. This process is supervised in the U.S. by the Food and Drug Administration (FDA), which is the ultimate arbiter as to whether the agent is effective and safe in treating the symptoms or disorders for which it is intended. The effectiveness aspect of such studies involves the determination of an optimal dose and its impact on the proposed clinical outcome within a given time frame. The safety process includes a thorough evaluation of minor side effects such as dry mouth and rhinorrhea, as well as life-threatening events such as stroke and myocardial infarction.

The planning and performance of a clinical trial for such therapeutic agents is usually undertaken only after considerable experience has been accumulated and has indicated that there is likely an overall clinical benefit from the use of the putative agent. That experience invariably encompasses pharmacokinetic studies (Phase I studies), as well as preliminary clinical studies that are used to determine an optimal dose and regimen to be studied in a large and robust trial, as well as providing initial information concerning side effects and safety (Phase II studies). An evaluation of the agent in a larger population is accomplished in a Phase III study; if such studies demonstrate that benefit far outweighs risk and the agent is approved for use, then a study evaluating the agent's use in a general population outside of a study protocol is commonly performed (Phase IV study).

While preliminary experience can, at times, be extensive, the ultimate determination of clinical effectiveness and safety is dependent on the outcome of that larger and more comprehensive trial that can take on many forms, including but not limited to a randomized, placebo-controlled trial or a cross-over study. In this FDA-regulated environment, the

performance of a more rigorous study of the effectiveness and safety of a botanical dietary supplement may differ somewhat from a study of a synthetic pharmaceutical agent. Specifically, a botanical dietary supplement may not require the same level of toxicity testing used for synthetic pharmaceutical agents because of many such products have a history of extensive human use [6]. However, botanical products do require a similarly rigorous and robust assessment of effectiveness; their wide commercial use and "patient testimonials" do not provide the necessary clinical approbation for effectiveness of such products, given the surprisingly high level of response in study subjects randomized to placebo in some botanical dietary supplement studies, including the study reviewed in this paper [7–9]. While anecdotal experience and observational trials of botanical dietary supplements may provide some expectation of success, the ultimate determination of the product's effectiveness and safety can only be achieved with a rigorous comparison trial, either to placebo or to a known positive control. Indeed, the performance of such a study may demonstrate certain clinical outcomes not previously observed in more limited studies. Such examples may include a more or less profound clinical benefit in individuals of certain racial or ethnic groups, safety issues not previously observed in smaller and more limited studies, or even an entirely different clinical outcome than that observed in other studies. The reasons for such differences can range from different pharmacogenomic characteristics of the study populations, to specific inclusion and exclusion criteria of the studies that later may impact the actual type of subjects evaluated in subsequent studies, to specific definitions of clinical outcomes specific to each study.

While the investigators may have some expectation of beneficial results based on earlier studies, all investigators should initiate that more extensive trial without any preconceived notions and be ready to accept the outcomes of their study. If profound differences with expected outcomes occur, investigators should examine the aspects of their study that may have lead to such differences rather than consider the results of the current study or earlier studies to be erroneous. To this end, the present works reviews the recent study from the University of Illinois at Chicago Center for Botanical Dietary Supplements Research (UIC Study) [9], which sought to assess the safety and effectiveness of two botanical dietary supplements for the management of menopausal vasomotor symptoms.

Background

In the UIC Study, researchers sought to evaluate the safety and efficacy of black cohosh (*Cimicifuga racemosa* (L.) Nutt.) and red clover (*Trifolium pratense* L.) for the relief of menopausal symptoms because of their popularity among women seeking alternative (and ostensibly non-hormonal) interventions for such adverse clinical events. The menopausal symptom that most commonly leads women to seek relief are hot flushes that result from the vasomotor instability associated with the decline of physiologic levels ovarian-produced estradiol, which is a critical factor in development of female secondary sexual characteristics, the menstrual cycle and reproductive capacity [10].

The below ground parts of Black cohosh have long been used as a treatment for menopausal-derived hot flushes; its mechanism of action appears to be serotonergic in nature with little to no estrogenic activity [11]. Conversely, the aerial parts of red clover are rich in estrogenic

isoflavones, suggestive of an estrogenic mechanism for the relief of estrogen-deprivation symptoms. The results of clinical studies of black cohosh for the relief of menopausal hot flushes have been mixed with some showing benefit, while others fail to demonstrate benefit [9]. Studies of red clover have been less supportive of a beneficial effect in the reduction of hot flushes, with those affirmative studies demonstrating a modest benefit, at best [12].

The UIC Study was developed to assess the effectiveness and safety of an ethanolic extract of black cohosh roots/rhizomes and an ethanolic extract of the aerial parts of red clover in a randomized, 4-armed, double-blinded, placebo-controlled trial with 0.625 mg conjugated equine estrogens (CEE)/2.5 mg medroxyprogesterone acetate (MPA; Prempro™; Wyeth Pharmaceuticals, Philadelphia, PA) serving as a positive control. It was agreed that only menopausal women with an intact uterus would be recruited for the trial, thus requiring the use of an estrogen/progestin regimen for the positive control group. The primary outcome was selected as a reduction in vasomotor symptoms, and the sample size calculation was based on clinical outcomes in prior research studies. The study was powered only to compare each botanical product and positive control with placebo, but not to each other.

Recruitment of patients was undertaken at the clinical centers of the University of Illinois at Chicago and the Feinberg School of Medicine of Northwestern University, both in the city of Chicago. All study subjects maintained a written diary of their medication use and symptoms throughout the course of the study. In addition to the primary outcome measures, secondary outcomes were also evaluated including safety assessments, relief of somatic symptoms including insomnia, joint pain, sleep and fatigue, mood changes (depression and anxiety), sexual dysfunction (vaginal dryness, dyspareunia, libido, anorgasmia) and health related quality-of-life. Validated instruments used to evaluate secondary outcome measures included the Greene Climacteric Scale (somatic symptoms and quality-of-life), Pittsburgh Sleep Quality Index, the Positive and Negative Affect Schedule, and the Kupperman Index. More detail of the materials and methods of the study can be found in the body of the original report [9].

The authors found that only the positive control, CEE/MPA, showed a significant reduction in hot flushes compared to placebo. Reductions in vasomotor symptoms over the 12-month study period for the 4 study groups were as follows: CEE/MPA 94%, black cohosh 34%, red clover 57% and placebo 63%, with the symptom reduction in the placebo group being somewhat higher than expected [9]. There was no increased incidence of safety issues for either of the botanical study groups, with no anticoagulant effect being observed in the subjects in the red clover group and no hepatotoxicity observed among subjects in the black cohosh group. Previously, both adverse outcomes had either been attributed to the use of a specific botanical product (black cohosh) [13,14] or had been considered a biologically plausible adverse event given the presence of anticoagulant coumarins in red clover [15]. These findings were important given the high usage of both botanical dietary supplements by women seeking relief from menopausal symptoms and other indications. In addition, there was no evidence of an adverse effect on breast tissue or endometrial thickness for either botanical preparation [9].

With regard to secondary outcomes, red clover users showed a reduction in anxiety over the course of the 12-month study compared to placebo. Surprisingly, while users of CEE/MPA demonstrated a significant reduction in vasomotor symptoms, there was no improvement in sleep quality or in any other secondary clinical outcomes for those hormone therapy users. While no other beneficial secondary outcomes were observed in the study, save for the reduction of anxiety among red clover users, it is important to recognize that the study was not powered to properly evaluate these diverse secondary clinical outcomes.

Discussion

The UIC Study of black cohosh and red clover is a phase II trial that failed to demonstrate significant reduction in vasomotor symptoms for either botanical dietary supplement. In assessing the findings of this trial, one must recognize that the existing literature does not demonstrate overwhelming support for a beneficial effect for either botanical dietary supplement in the reduction of menopausal-derived vasomotor symptoms. As such, the findings of this study can be viewed as confirming a lack of clinical benefit for black cohosh or red clover for the relief of menopausal vasomotor symptoms.

However, one should equally consider some specifics of this study in evaluating the clinical outcomes. First, this study recruited a much higher frequency of non-Caucasian women than in most other menopausal studies. This could have led to the study cohorts having women with genomic differences from those women historically included in menopausal studies and, thus, leading to different clinical outcomes. Second, this study lasted for a 12-month period, longer than many other symptomatic menopausal studies. However, no significant differences in primary or secondary outcomes for any of the study groups were observed at any of the interim study assessments. Third, and possibly most important, is that the botanical products used in this study were authenticated and chemically and biologically standardized. Earlier studies may not have necessarily used study botanical intervention materials that underwent such rigorous production and analysis, potentially allowing for the presence of other phytochemical constituents, or even adulterants, in those study products that could have altered clinical outcomes. Indeed, the authors reviewed the botanical intervention materials before and after the completion of the study to ensure that no adulterations or changes of the study products had occurred that could have impacted the clinical outcomes of the trial.

Certain other study characteristics are unique to this study, but are not likely to have played a role in the distinctive outcomes of the study. Compliance issues were not associated with any of the clinical outcomes of each study group, as study participants in all groups were very highly compliant with their study regimen as demonstrated by the subject diaries. There were very few “dropouts” in any of the study groups, with an overall high retention rate not typically observed in such studies. Indeed, had one or both of the botanical study products been shown to have a significant benefit in reducing vasomotor symptoms, these characteristics would have been used to “explain” the observed salutary outcome, given the equivocal results from earlier published studies for the reduction of menopausal vasomotor symptoms by black cohosh or red clover [12, 16]

In conclusion, well performed studies of botanicals may demonstrate novel clinical outcomes because earlier studies may not have been as rigorously performed as the current study. Other factors, from the study participants to the criteria for participation to the actual therapeutic formulations used in the trial, may considerably impact the clinical outcomes of the study and the implications for clinical care. Regardless of the actual clinical findings, the outcomes of a robust and rigorous clinical trial usually take precedence over observational studies. However, the outcomes of those observational studies still provide important information in the overall assessment of a drug or therapeutic regimen. When the results of observational studies differ from more rigorous clinical trials, one set of trial results are not necessary “better” or “more important” than the other. In such cases, further analysis of the studies is needed to determine the reasons for the results of all trials and determine the need for and configuration of future studies. Conversely, one can arrive at an evidence-based assessment of the literature and determine an appropriate role, if any, of the drug or therapeutic regimen in clinical care. Nonetheless, the results of the UIC phase II trial do not support a larger phase III trial of either botanical dietary supplement for the relief of menopausal vasomotor symptoms.

In the UIC study of black cohosh and red clover, the findings are not wholly unexpected given the outcomes of earlier studies of these botanical dietary supplements. However, some outcomes may be different from those observed in those earlier studies and possibly be considered unexpected by some readers. While expectations are an important aspect in the assessment of scientific literature, they should not guide the analysis of the data of clinical trials. Using those expectations to evaluate disparate studies for differences is an appropriate approach to analyze such studies; however, interpretations of those studies and the use of those outcomes to guide clinical care should be made on the outcomes alone and not perceptions. In this case, the UIC Study clearly shows that black cohosh and red clover failed to reduce hot flushes in symptomatic menopausal women. While a larger trial does not appear to be a logical next step, further studies could be of value to determine if there are specific populations that may find these botanical interventions of clinical value. For example, evaluating these botanical products in a study with primary and secondary clinical outcomes different from the ones used in the UIC study, or determining if earlier studies used botanical intervention materials that may have contained different active compounds, may result in clinical outcomes different from those reported in the UIC study. In this way, valuable clinical information may be obtained that would otherwise be unnoticed and thus help improve the lives of women during menopause and at other times of their lives.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Kronenberg F, Fugh-Berman A. Complementary and alternative medicine for menopausal symptoms: a review of randomized, controlled trials. Ann Intern Med. 2002; 137:805–13. [PubMed: 12435217]
2. Maki PM, Rubin LH, Fornelli D, et al. Effect of botanicals and combined hormone therapy on cognition in postmenopausal women. Menopause. 2009; 16:1167–77. [PubMed: 19590458]

3. Roussow JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA. 2002; 288:321–33. [PubMed: 12117397]

4. Carlson S, Peng N, Prasain JK, Wyss JM. Effects of botanical dietary supplements on cardiovascular, cognitive, and metabolic function in males and females. Gen Med. 2008; 5(Suppl A):S76–S90.

5. Garcia JT, Gonzaga F, Tan D, et al. Use of a multibotanical (Nutrafem) for the relief of menopausal vasomotor symptoms: a double-blind, placebo-controlled study. Menopause. 2010; 17:237–8. [PubMed: 20142786]

6. van Breeman RB, Fong HHS, Farnsworth NR. Ensuring the safety of botanical dietary supplements. Am J Clin Nutr. 2008; 87(suppl):509S–13S. [PubMed: 18258648]

7. Maclennan A, Broadbent J, Lester S, Moore V. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. Cochrane Database Syst Rev. 2004:CD002978. [PubMed: 15495039]

8. Low Dog T. Menopause: a review of botanical dietary supplements. Am J Med. 2005; 118(suppl 12B):98–108. [PubMed: 16414334]

9. Geller SE, Shulman LP, van Breeman RB, et al. Safety and efficacy of black cohosh and red clover for the management of vasomotor symptoms: a randomized controlled trial. Menopause. 2009; 16:1156–66. [PubMed: 19609225]

10. Shulman, LP. The Menstrual Cycle. In: Hatcher, R.; Trussel, J.; Nelson, A., et al., editors. Contraceptive Technology. 20th ed. Ardent Media, in press

11. Burdette JE, Liu J, Chen SN, et al. Black cohosh acts as a mixed competitive ligand and partial agonist of the serotonin receptor. J Agric Food Chem. 2003; 51:5661–70. [PubMed: 12952416]

12. Nelson HD, Vesco KK, Haney E, et al. Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. JAMA. 2006; 295:2057–71. [PubMed: 16670414]

13. Lontos S, Jones R, Angus P, Gow P. Acute liver failure associated with the use of herbal preparations containing black cohosh. Med J Aust. 2003; 179:390–1. [PubMed: 14503910]

14. Mahady G, Low Dog T, Barrett M, et al. Pharmacopeia review of the black cohosh case reports of hepatotoxicity. Menopause. 2008; 15:628–38. [PubMed: 18340277]

15. Abebe W. Herbal medication: potential for adverse interactions with analgesic drugs. J Clin Pharm Ther. 2002; 27:391–401. [PubMed: 12472978]

16. Newton K, Reed S, LaCroix A, et al. Treatment of vasomotor symptoms of menopause with black cohosh, multibotanicals, soy, hormone therapy, or placebo: a randomized trial. Ann Intern Med. 2006; 145:869–79. [PubMed: 17179056]