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Review

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.

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1. 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 steroidogenesis, 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.

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

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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.

2. 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

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