Does Black Cohosh Improve Anxiety/Depression Symptoms in Women Who Are Postmenopausal?

Priya Patel
Philadelphia College of Osteopathic Medicine, Priyapat@pcom.edu

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Does Black Cohosh improve anxiety/depression symptoms in women who are postmenopausal?

Priya Patel, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences- Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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ABSTRACT

OBJECTIVE: The objective of this systematic review is to determine is Black Cohosh effective for reducing anxiety/depression symptoms in postmenopausal women?


DATA SOURCES: Randomized, double blind, placebo-controlled trials comparing Black Cohosh to placebo or hormonal therapies were found using PubMed and Cochrane databases.

OUTCOMES MEASURED: Each of the three trials assessed the efficacy and clinical improvement in anxiety symptoms with the use of Black Cohosh. Studies utilized to measure change in anxiety symptoms included Harrison Anxiety Rating (HAM), Symptom Rating Test (SRT), and Kupperman Test.

RESULTS: Two double-blind randomized controlled trials were included in this review. Results from the Amsterdam et al study indicates that Black Cohosh use had little vasomotor or anxiolytic activity, however the sample size in this study was small. The second study by Nappi et al concluded that after the use of Black Cohosh reduced anxiety/depression as well as vasomotor symptoms in postmenopausal women to the same degree as hormone therapy. The third study by Vermes et al showed a reduction in anxiety/depression symptoms. The Kupperman index scores also decreased over the duration of the study. All three trials demonstrated that Black Cohosh does contribute reduction in anxiety/depression in menopausal women.

CONCLUSIONS: All of the RCT and Clinical Trial demonstrate that Black Cohosh use is effective at reducing anxiety/depression. Black Cohosh seems to be the same effectiveness as Hormonal therapy available for anxiety/depression in postmenopausal women.

KEY WORDS: Black Cohosh (Remifemin, Cimicifuga racemosa), anxiety, depression
INTRODUCTION

Menopause is defined as occurring 12 months after your last menstrual period and marks the end of menstrual cycles. Menopause can happen in your 40s or 50s. Postmenopausal is after one has undergone menopause. There are many symptoms associated with menopause, such as anxiety and depression that can make life challenging.\(^1\) Anxiety can be described as a sense of foreboding, such as feeling as if something is wrong. Women can experience palpitations, shortness of breath, trembling, lightheadedness, as well as other symptoms due to anxiety.\(^2\) Additionally, women approaching menopause are at increased risk for depression, which may be from hormonal changes.\(^2\) This paper evaluates two randomized, double blind control trials and one clinical trial comparing the efficacy of Black Cohosh to placebo/hormone replacement therapy.

Anxiety and Depression in postmenopausal women is relevant to the Physician Assistant profession due to its high rates of prevalence today. It is estimated that 65% - 85% of women experience vasomotor symptoms related to menopause, and 30% seek medical attention for these symptoms.\(^2\) Although vasomotor symptoms are most pronounced during the initial years of menopause, nearly 64% of women will continued to experience vasomotor symptoms up to 5 years after menopause, and 26% of women will have symptoms lasting up to 10 years.\(^1\) Currently Black Cohosh is highly affordable since it is available without a prescription. The cost of a one-month supply of the product ranges from $16 to $60 depending upon the dosage.\(^1\)

Hormone replacement therapy (HRT) has been the mainstay for treatment. Benzodiazepine have become treatment of choice for anxiety symptoms, despite the presence of BZ-induced dependence and antidepressant-induce sexual side effects, weight gain, and withdrawal. These side effects are why women are seeking alternative medicine, Black Cohosh,
remedies for their climacteric symptoms.\textsuperscript{2}

Menopause can cause a number of physical changes that may cause anxiety themselves. It is well known that menopause appears to increase risk for panic attacks but the cause and effect is not exactly clear. Menopausal anxiety can be hormone mediated, hormone exacerbated, or simply menopausal related. \textsuperscript{1}

Usual methods used to treat menopausal anxiety include Hormone Replacement Therapy, such as Medroxyprogesterone. Additionally, antidepressants are used in combination with Hormonal Replacement Therapy, such as, fluoxetine, paroxetine, and venlafaxine, can be used to control anxiety and other menopausal symptoms. Among the pharmacological treatment, benzodiazepines, Xanax, are the drug of choice for anxiety in postmenopausal women. Also, other Complementary Alternative Medications, dong quai, black cohosh, St. Johns wort, and ginkgo biloba, are becoming popular due to the side effects of pharmacologic treatment. \textsuperscript{3}

The above treatments are effective options for postmenopausal women suffering from anxiety and efficacy of the treatment varies from patient to patient. Women with comorbidities or history of past breast or uterine cancer, blood clots, liver disease, and stroke are not good candidates for Hormone Replacement Therapy. Black Cohosh may be a natural anxiolytic alternative to these regimens in reducing anxiety in postmenopausal women and will be discussed further in this review. \textsuperscript{3}

\textbf{OBJECTIVE}

The objective of this selective EBM review is to determine whether or not “Does Black Cohosh improve anxiety/ depression symptoms in women who are postmenopausal?”
METHODS

The three studies utilized in this review include two randomized control trials and one clinical trial, which met the following criteria: The population consisted of postmenopausal women with symptoms of anxiety. The intervention used was Black Cohosh 64mg, 40mb/day. The treatment group receiving Black Cohosh versus the experimental group receiving either visually matched placebo or HRT.\textsuperscript{3,4} Outcomes measured include the efficacy of Black Cohosh for the treatment of Anxiety or depression incidences in postmenopausal women.

Key word used to locate the literature consisted of Black Cohosh (Black Cohosh (Remifemin, Cimicifuga racemosa), anxiety, and depression. All articles were published in English and published in peer-reviewed journals. The articles were searched via PubMed and were selected based on their relevance to my clinical question and if they included patient oriented outcomes (POEMS). Inclusion criteria consisted of randomized controlled trials and clinical trials with postmenopausal women. Exclusion criteria consist of previous hormone therapy or contraindications to hormonal therapy. Statistics that were reported and utilized are relative risk reduction (RRR), absolute risk reduction (ARR), numbers needed to treat (NNT), Standard Deviation, p-values, baseline tests, ANOVA.\textsuperscript{3,4,5}

Demographics and characteristics of the studies utilized for review are displayed in Table 1.
<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th># Pts</th>
<th>Age</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>W/D</th>
<th>Interventions</th>
</tr>
</thead>
</table>
| Amsterdam (2009) | Randomized Control Trial | 34    | >40       | -Women who were either postmenopausal for more than 12 months or perimenopausal [with amenorrhea lasting 2 to 11 months in the proceeding year] were included  
- Women with prior hysterectomy an uncertain menopausal status had a serum follicle stimulating hormone level greater than or equal to 40 mIU/l.  
- Other CAM remedies, oral estrogen, estrogen cream, or phyto-estrogen preparation was not permitted. Perimenopausal women employed a medically proven, nonhormonal form of contraception and had a negative pregnancy test. | Axis I diagnosis of Major Depressive Disorder, Bipolar Disorder, Panic Disorder Phobic Disorder, Obsessive-compulsive Disorder, Post-traumatic Stress Disorder, Acute Stress Disorder, Substance-induced Anxiety Disorder, Schizophrenia, Dementia, or Substance Abuse or Dependence Disorder within the preceding 3 months. | 6    | -64 mg Black cohosh BID for first 2 weeks  
- 4 capsules daily of 128 mg Black cohosh by study week 4 with less than or equal to 50% reduction in total baseline HAM-A score. |
| Nappi (2005)  | Randomized Control Trial | 64    | 45-55     | -Spontaneous menopausal status of at least 6 months with follicle-stimulating hormone [FSH] level > 30 mU/l  
- Presence of hot flushes [at least five per day] and endometrial thickness <5 mm. | Previous hormone therapy or contraindications to hormonal treatments | 4    | 40 mb/day of isopropanolic aqueous CR extract for 3 months |
| Vermes (2005) | Clinical Trial      | 2016  | 45-65     | Kupperman index (20), refusal or contraindication for estrogen therapy | Pts on HRT | 140  | Remifemin tablets BID PO x 12 weeks                                         |
OUTCOMES MEASURED

All outcomes measured in the trials were based on patient oriented evidence that assessed the efficacy and clinical improvement in anxiety as well as other menopausal symptoms in women. The Amsterdam et al study primarily used HAM-A scores between the two groups to measure outcomes. Secondary outcomes used in Amsterdam et al study included Beck Anxiety Inventory (BAI) and Green Climacteric Scale (GCS). Nappi et al measured the change in anxiety and depression using the Symptoms Rating Test (SRT). Lastly, Vermes et al also used the Kupperman index, which utilized the severity of the symptoms. This was evaluated at the start of the study and throughout the study.

RESULTS

The results for the Amsterdam et al study was that 34 patients were originally enrolled in the study and 6 patients were screen failures who withdrew consent to participate. The patients were randomized to either black cohosh or placebo. 75% of patients completed all study visits and were used for the results. The final results of the study showed that the HAM-A score at study endpoint had no significant difference. There was a greater reduction in total GCS scores favoring placebo (-4.45 (95% CI= (-8.59, 3.12; p= 0.035)).

Table 2 Characteristics of Black Cohosh and Placebo groups

<table>
<thead>
<tr>
<th></th>
<th>Black Cohosh (n=15)</th>
<th>Placebo (n=13)</th>
<th>p-value **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian (%)</td>
<td>71.43</td>
<td>61.54</td>
<td>0.78</td>
</tr>
</tbody>
</table>
Table 3: Estimated difference in Overall change for treatment groups using regression model

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Est. Change Diff in Groups (60β)</th>
<th>95% CI for Change Diff</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAM-A</td>
<td>-1.58</td>
<td>-4.53 to 1.37</td>
<td>0.294</td>
</tr>
<tr>
<td>BAI</td>
<td>-1.07</td>
<td>-6.14 to 1.96</td>
<td>0.578</td>
</tr>
<tr>
<td>GCS total</td>
<td>-4.45</td>
<td>-8.59 to -3.12</td>
<td>0.035</td>
</tr>
<tr>
<td>GCS psychological</td>
<td>-2.68</td>
<td>-5.51 to .15</td>
<td>0.063</td>
</tr>
<tr>
<td>GCS anxiety</td>
<td>-1.52</td>
<td>-3.44 to .4</td>
<td>0.121</td>
</tr>
<tr>
<td>GCS depression</td>
<td>-1.17</td>
<td>-2.76 to .42</td>
<td>0.148</td>
</tr>
<tr>
<td>PGWB</td>
<td>11.06</td>
<td>-3.63 to 25.75</td>
<td>0.140</td>
</tr>
</tbody>
</table>

*Mean (SD)/range; **Pearson x2 test (binary variables) or Wilcoxon Rank sum test (continuous variables)
Table 4: Estimated values in overall change for treatment groups using regression model (2)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Est. Change Diff Cohosh</th>
<th>Est. Change diff Placebo</th>
<th>Effect Size</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAM-A</td>
<td>-2.56</td>
<td>-4.90</td>
<td>0.72</td>
<td>0.294</td>
</tr>
<tr>
<td>BAI</td>
<td>-1.17</td>
<td>-4.46</td>
<td>0.34</td>
<td>0.578</td>
</tr>
<tr>
<td>GCS Total</td>
<td>0.56</td>
<td>-3.94</td>
<td>0.85</td>
<td>0.035</td>
</tr>
<tr>
<td>GCS anxiety</td>
<td>0.0084</td>
<td>-1.93</td>
<td>0.55</td>
<td>0.121</td>
</tr>
<tr>
<td>GCS depression</td>
<td>-0.19</td>
<td>-0.98</td>
<td>0.54</td>
<td>0.148</td>
</tr>
</tbody>
</table>

Table five for the Nappi et study shows the baseline characteristics of the women treated with Black Cohosh (CR) and low dose TTSE.

Table 5 [CR (n = 32)] [TTSE2 (n = 32)] p Value

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>50.5 +/- 2.1</th>
<th>50.9 +/- 1.8</th>
<th>0.37</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menopause (months)</td>
<td>9.0 +/- 2.9</td>
<td>9.1 +/- 3.0</td>
<td>0.87</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>22.9 +/- 2.2</td>
<td>22 +/- 2.1</td>
<td>0.40</td>
</tr>
</tbody>
</table>
As shown in Figure 1, Black Cohosh (CR) was significantly effective in reducing both anxiety (p<0.001) and depression (p<0.001) measured by SRT following three months of treatment. The results for the Vermes et al study showed that the Kupperman index scores decreased through the course of the study. The decline was most extreme during the first 4 weeks of treatment. The total mean score decreased at a constant rate of from one evaluation period to the next, decreasing first at 8.12, then by 5.56, and finally by 3.96 points.

Table 6. Changes in the Kupperman Menopause Index in the Course of Treatment

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Week 0</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>1.77</td>
<td>3.53</td>
<td>1.29</td>
<td>0.96</td>
</tr>
</tbody>
</table>
Discussion

Many menopausal and postmenopausal women are searching for CAM remedies to relieve their menopause related symptoms. CAM therapies are becoming more popular due to their decreased concern about drug toxicity and side effects, cultural attitudes, and the stigma of having a psychological disorder.\textsuperscript{3,5} The primary solution for the symptoms of menopause is HRT, however, many patients are afraid of the risk of breast cancer and deep vein thrombosis associated with it.\textsuperscript{5} Nappi et al. compared the efficacy of Black Cohosh compared to HRT in reducing menopausal symptoms and found a significant reduction in menopause-related psychological symptoms. Nappi et al. study was limited by the absence of a placebo group.\textsuperscript{4} With the Amsterdam et al. study there are several caveats that need to be considered in their findings. There was a lower than expected subject enrollment and small sample size with limited ability to detect difference between treatment condition, which provides no clinical meaningfulness.\textsuperscript{3} Additionally, in the Vermes et al. study the Kupperman index was used and a mean 17.64 point decrease was observed during the twelve weeks of treatment. This finding is suggestive that the extract of C racemosa (Remifemin) reduces the intensity of menopausal symptoms effectively. Additionally, drug tolerability was considered excellent by the patients themselves and their physicians. The limitations for Vermes et al. study include that the study was not a placebo-controlled trial. Second, he findings were based on an assessment of changes in subjective symptoms rather than objective symptoms.\textsuperscript{5}

Conclusion
According to the Amsterdam et al. study Black Cohosh appears to be effective in reducing the vasomotor symptoms of menopause and minimal activity for anxiolytic symptoms. However, Amsterdam et al. study noted that the sample size was extremely small, and the choice of Black Cohosh preparation dosage had limited their ability to identify the clinical meaningfulness of Black Cohosh over placebo. Nappi et al. study concludes that Black Cohosh (40mg/day) can be considered a consistent and safe option to counteract specific symptoms in postmenopausal women. In conclusion Vermes et al. study states that Remifemin may effectively reduce the severity of symptoms of menopause and Remifemin shows promise as an effective therapeutic choice for menopausal complaints.
References:


