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## CLINICAL VIGNETTE

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# A Case of Herbal Medicine as Alternative Therapy for Menopausal Hot Flashes

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### *Introduction*

Hot flashes affect between 65 to 80 percent of menopausal women typically lasting approximately 5 years, but may persist for 10 years in one-third of postmenopausal women.<sup>1,2</sup> Hormonal and other pharmacotherapy are used to help alleviate these symptoms, however, between 45 to 75 percent of menopausal women explore alternative therapies as part of their symptom management.<sup>3,4</sup> These complementary and alternative therapies include, but are not limited to acupuncture, plant-based therapies, herbal medicine, and over-the-counter supplements. Presented here is a patient with a history of hormone-induced venous thrombosis with menopausal hot flashes effectively treated with herbal medicine as an alternative therapy.

### *Clinical Case*

A 58-year-old postmenopausal woman with a long-standing history of hot flashes presented with worsening hot flashes and night sweats. Her hot flashes were present during both day and night but were worse at night and associated with night sweats. The nocturnal hot flashes and night sweats woke her from her sleep nightly. The hot flashes were previously treated with hormonal therapy, but this was discontinued due to the development of lower leg deep venous thrombosis which was treated with anticoagulation.

Physical examination revealed a body mass index of 29.4 kg/m<sup>2</sup>. Lifestyle modifications, including avoiding alcohol, hot and spicy foods, and caffeine, were recommended. She initially received a trial of acupuncture treatments but did not experience significant improvement in her menopausal symptoms. She was subsequently started on the Chinese herbal medicine Zhi Bai Di Huang Wan (Anemarrhena Phellodendron and Rehmannia Pill, Beijing Tong Ren Tang, China) twice daily.

At 2 week follow up, she reported significant improvement in nocturnal hot flashes with mild improvement in daytime hot flashes. She also reported a reduction in night sweats from 90 percent of the night to 20 percent. Due to the decrease in hot flashes and night sweats, she was able to sleep longer during the night. The improvement in her symptoms persisted and remained stable on the herbal medicine at one year with no reported side effects. Follow-up laboratory studies of liver and kidney function tests were normal.

### *Discussion*

The goal in managing menopausal hot flashes is to decrease severity and frequency of hot flashes after factoring in a patient's medical history, comorbid conditions, and personal preferences. Mild vasomotor symptoms that do not affect daily activities usually do not need medical therapy. Behavioral interventions such as temperature control with fans and air conditioning, layered clothing that can be easily removed, and avoiding triggers may help reduce the frequency of symptoms. Triggers that may aggravate frequency or severity of hot flashes include tobacco use, alcohol, hot or spicy foods, caffeine, stress, hot drinks, and warm temperature environments.<sup>5</sup> Body mass index greater than 30 kg/m<sup>2</sup> increases the risk of moderate to severe hot flashes compared with women with a normal body mass index less than 25 kg/m<sup>2</sup>.<sup>5</sup> As such, weight loss may help reduce hot flashes in overweight and obese pre- and postmenopausal women.<sup>6</sup> Participation in a yoga program for 8 to 10 weeks has also been shown to decrease hot flash frequency and severity.<sup>7,8</sup>

For moderate to severe hot flashes, daily activities are somewhat to frequently affected. In this case, medical intervention is appropriate. Current hormonal therapies include menopausal hormone therapy (MHT) and tissue selective estrogen complexes (TSECs) which combine a selective estrogen receptor modulator with an estrogen.<sup>9</sup> Due to the potential risks associated with MHT, perimenopausal and menopausal women considering MHT should be evaluated to determine if they are good candidates based on history and risks for breast cancer, coronary heart disease, and venous thromboembolism.<sup>10</sup> "Bioidentical hormones," or exogenous hormones with the same or similar molecular structure as endogenous hormones, are custom-compounded hormones through specialty pharmacies that has gained popularity as an alternative to MHT under claims of better safety and efficacy, however, there is no evidence to date to support these claims.<sup>11</sup> Nonhormonal pharmacotherapies include selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs), antiepileptics such as gabapentin and pregabalin, and clonidine which have been shown to be effective and are alternatives to MHT.<sup>12</sup>

Between 45 to 75 percent of postmenopausal women explore complementary and alternative therapies to help manage their menopausal symptoms.<sup>3,4</sup> The evidence for these therapies is not well established and is limited by the quality of the studies. It is important to evaluate therapies against placebo in

randomized controlled trials as the placebo effect may reduce hot flashes by as much as 20 to 50 percent.<sup>12-14</sup>

Evidence for the use of acupuncture in menopausal hot flashes is conflicting. In a meta-analysis performed by Dodin, et al. in *Cochrane Database of Systematic Reviews* in 2013, 16 randomized controlled trials were reviewed totaling 1155 women. Eight studies compared acupuncture with sham acupuncture with no significant difference between acupuncture and sham acupuncture in reducing hot flush frequency. Three studies compared acupuncture to MHT showing acupuncture to be associated with less reduction in hot flush frequency than MHT. One study compared electroacupuncture to relaxation and showed no significant difference in hot flush frequency. Four studies compared acupuncture to no treatment showing a significant reduction in hot flush severity. Based on the review, acupuncture appeared to be beneficial compared to no treatment, but less effective compared to MHT, however, the studies were limited by the lack of sham acupuncture and placebo MHT, respectively.<sup>15</sup>

Natural products include plant-based therapies and herbal medicines. Of these, phytoestrogens are the most commonly used of which there are 3 types: isoflavones, lignans, and coumestans. Phytoestrogens and estrogen are not structurally related; however, phytoestrogens contain a phenolic ring which allows them to bind to estrogen receptors. As a result, they may mimic endogenous estrogen or exhibit antiestrogen effects similar to selective estrogen receptor modulators. Two specific isoflavones, genistein and daidzein, are found in soybeans, chickpeas, and lentils and are the most potent of the phytoestrogens.

Various phytoestrogens and herbal medicines have been studied evaluating their effectiveness at reducing menopausal hot flashes, however, the evidence is conflicting. Soy and soy isoflavones are the most commonly used phytoestrogens and studies have shown a modest decrease in hot flash frequency and severity.<sup>16,17</sup> In a study by Kaari, in 2006, soy extract containing 60 mg of isoflavones 2 times a day was noted to be comparable to conjugated estrogens 0.625 mg daily.<sup>18</sup> Although conflicting evidence shows no benefit of soy extracts for hot flashes, it appears at least 15 mg of genistein isoflavone daily is needed to consistently show positive results.<sup>19-21</sup> Black cohosh (*Rhizoma Cimifugae*) does not bind to estrogen receptors like phytoestrogens, but may act as a serotonin receptor agonist. In the commercial form *Remifemin* (Phytopharmica/Enzymatic Therapy), black cohosh showed significant reduction in hot flash frequency compared to placebo and was comparable to low dose transdermal estradiol 25 mcg every 7 days and conjugated equine estrogen 0.625 mg.<sup>22,23</sup> In contrast, other formulations do not demonstrate significant reduction in hot flash frequency compared to placebo.<sup>24,25</sup> Red clover (*Trifolium pratense*) contains isoflavones and preliminary studies suggest benefit for hot flashes, however, most studies including a pooled analysis in 2016 showed no significant reduction in hot flashes compared to placebo.<sup>25-28</sup> Sage (*Salvia officinalis*) contains geraniol, which is believed to contain estrogenic

activity. It has been shown to significantly reduce hot flashes, however, only the use of thujone-free sage is advised as thujone can be toxic.<sup>29,30</sup> Evidence for Asian or red ginseng (*Panax ginseng*) for menopausal hot flashes is conflicting with low dose shown to have no effect, although higher doses at 1000 mg 3 times a day appear to significantly reduce hot flashes.<sup>31,32</sup> Dong quai (*Radix Angelicae sinensis*) and St John's wort as single ingredients, wild yam, chasteberry, flaxseed, wheat germ, and primrose oil, have not demonstrated reliable evidence as being effective at reducing menopausal hot flashes.<sup>25,33-37</sup>

Combination herbal ingredients better reflects how herbal medicine is used in traditional Chinese Medicine and the Chinese herbal medicine (CHM) Zhi Bai Di Huang Wan used in the case is one of the most commonly used herbal medicines for menopausal hot flashes in Taiwan.<sup>38</sup> In a small study by Kwee, in 2007, 31 peri- and postmenopausal Dutch women received 12 weeks of treatment with CHM Zhi Bai Di Huang Wan containing *Rhizoma Anemarrhenae*, *Cortex Phellodendri*, *Radix Rehmannia preparata*, *Fructus Corni*, *Radix Dioscoreae*, *Poria cocos*, *Cortex Moutan*, *Rhizoma Alismatis* and modified with the addition of *Os Draconis*, *Concha Ostreae*, *Fructus Lycii*, hormone replacement therapy (HRT), or placebo with a 4 week non-treatment follow up observation period. The placebo group showed a 30% decrease in hot flushes compared to the start of the study. The CHM group showed a 59% decrease in hot flushes ( $P < 0.05$ ) while the HRT group showed a nearly 80% decrease in hot flushes ( $P < 0.05$ ), or almost 29% and 50% reduction compared with placebo, respectively. During the non-treatment follow up period, the placebo group continued to report a 30% decrease in hot flushes, while both the CHM and HRT groups showed an increase in hot flushes in the absence of treatment.<sup>39</sup> In contrast, in a small study by Davis, in 2001, 55 postmenopausal Australian women received 12 weeks of treatment with a CHM combination of *Radix Rehmannia preparata*, *Fructus Corni*, *Radix Dioscoreae*, *Poria cocos*, *Cortex Moutan*, *Rhizoma Alismatis* with *Pericarpium Citrus reticulate*, *Cortex Lycium*, *Cortex Albizziae*, *Semen Zizyphus*, *Herba Eclipta*, and *Fructus Ligustrum*, or placebo. There was no significant difference between the placebo and CHM group at the end of 12 weeks ( $P = 0.09$ ).<sup>40</sup> In the study by Kwee, et al., a modified version of CHM Zhi Bai Di Huang Wan was used, however, in the study by Davis, et al., the studied CHM used similar ingredients to Zhi Bai Di Huang Wan in *Radix Rehmannia*, *Fructus Corni*, *Radix Dioscoreae*, *Poria cocos*, *Cortex Moutan*, *Rhizoma Alismatis*, but lacked *Rhizoma Anemarrhenae* and *Cortex Phellodendri* which characterizes CHM Zhi Bai Di Huang Wan and was included by Kwee. In a review by Wang, in 2019, 16 randomized controlled trials totaling 1594 women with menopausal symptoms treated with the CHM Erxian decoction containing *Rhizoma Circulinginis*, *Herba Epimedii*, *Radix Morindae*, *Radix Angelicae sinensis*, *Cortex Phellodendri*, and *Rhizoma Anemarrhenae* were reviewed. One study showed improvement in hot flashes compared to placebo, while others showed either contradictory results or showed positive results compared to or when used with hormone therapy. Assessment of the evidence,

however, was limited by the low-quality of the studies.<sup>41</sup> No evidence is available evaluating *Rhizoma Anemarrhenae* or *Cortex Phellodendri* as monotherapy.

### Summary

While there are studies showing positive results for plant-based therapies and herbal medicines in reducing menopausal hot flashes, low-quality studies and conflicting evidence limit our understanding of their role as alternative therapies for reducing vasomotor symptoms. For many menopausal women, alternatives to hormonal and other pharmacotherapies continue to be used due to medical necessity or personal choice. Further high-quality research is needed to better understand these therapies and to evaluate their safety and effectiveness as alternatives for the management of menopausal hot flashes.

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