Chasteberry Extended Abstract

Systematic Review - Tertiary Resource #1

Whelan, AM, Jurgens, TM, Naylor, H. Herbs, Vitamins and Minerals in the Treatment of Premenstrual Syndrome: a Systematic Review. *Can J Clin Pharmacol*. 2009; 16(3). http://www.jptcp.com/. Accessed 07/07/13.

- **Study Objectives**

  To identify natural health products (NHP) advocated for the treatment of premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) and to systematically review the evidence from random controlled trials (RCTs) for the use of the identified NHPs in treating or alleviating symptoms in PMS and PMDD.

- **Scope**

  The article reviewed RCTs which studied the efficacy of 10 different NHPs in the treatment of PMS. 2 RCTs were reviewed for calcium, 4 RCTs were reviewed for chasteberry, 13 RCTs were reviewed for vitamin B6, 2 RCTs were reviewed for vitamin E, 3 RCTs were reviewed for magnesium, 1 RCT was reviewed for saffron, 1 RCT was reviewed for ginkgo, 1 RCT was reviewed for St. John's Wort, 1 RCT was reviewed for soy, and 3 RCTs were reviewed for evening primrose oil. One article studied both magnesium and vitamin B6 while another article compared chasteberry and vitamin B6. Most of the studies compared the NHP to placebo, and outcomes included relieve of mood, physical, and depressive symptoms.

  For the trials investigating chasteberry, comparison treatments used included placebo, vitamin B, and fluoxetine. Chasteberry was investigated for its efficacy in PMS and PMDD in the different trials. Study participants in the trials identified had different types and severities of PMS and PMDD.

- **Review Methods**

  The review was focused on a number of RCTs and a search on trials conducted up to April 2008 was performed using Clinical Evidence, the Cochrane Library, Embase, IBID, IPA, Mayoclinic, Medscape, MEDLINE Plus, and the Natural Medicines Comprehensive Database. Study abstracts were screened for relevance and only full articles where abstracts were determined to be relevant to the review was retrieved. Only trials published in English and French were included, and studies were

excluded if the comparator was not placebo or recognized therapy, if the outcome measure was patient satisfaction, or if the therapies studied were combination products.

57 abstracts were screened for relevance whereby 19 abstracts were excluded due to the exclusion criteria. 38 articles were then assessed for relevance where another 9 articles were excluded due to lack of randomization, use of combination products, duplication publication, or improper outcome measures. 29 RCTs that meet the inclusion criteria were identified and trials investigating a number of NHPs including chasteberry, evening primrose oil, ginkgo, saffron, St. John's Wort, soy, vitamin B6, vitamin E, calcium, and magnesium were reviewed.

- **Main Results**

Most of the trials reviewed found that chasteberry had beneficial effects in reducing symptoms of irritability, mood, anger, breast fullness and tenderness, headache, cramps, water retention, swelling, and food cravings. The RCTs reviewed all used different preparations of chasteberry such as crude extracts as well as extracts standardized to casticin. Chasteberry may be possibly effective in treating symptoms of PMS.

- **Conclusions**

From the review, only calcium had good quality evidence for its use in PMS. However, chasteberry has a possibly effective rating in treating symptoms of PMS. Most trials have shown beneficial effects with mild adverse events, but further research may be required in order to better understand its effects on PMS symptoms.

- **Comments**

There was a good procedure and review in place to select and analyze relevant articles. There was a clear inclusion/exclusion criteria, and the process of study selection was conducted by two investigators, where discrepancies were resolved by a third investigator. An assessment instrument previously developed by the investigators was used to critically appraise each study. As well, in order to determine whether the RCTs could support a meta-analysis for each NHP, data from each trial were examined for homogeneity of patient population, duration of trials, outcome measures, product content, as well as doses.

Of the 29 trials included in the review, 28 were RCTs and 11 were crossover studies. There was heterogeneity in trial design such as product content, outcome measures, and length of the trials. There were language and publication biases in place as only English and French articles were reviewed and publications had to be published prior to April 2008. Also, the RCTs used

were of poor quality which limited comparison between RCTs to understand the true efficacy of NHPs on PMS or PMDD. For the use of chasteberry in PMS, it is difficult to utilize the results from this review in recommending chasteberry to patients, as study populations as well as diagnosis criteria for PMS and PMDD used in individual trials were inconsistent.

Natural Standard Database - Secondary Resource #1

Natural Standard. Natural Standard Professional Monograph <Chasteberry>. 2013. http://www.naturalstandard.com.proxy.lib.uwaterloo.ca/databases/herb supplements/all/chasteberry.asp?. Last updated 07/07/13. Accessed 07/06/13.

- **Source**

  Natural Standard is an international research collaboration which aims to provide evidence-based healthcare information through systematic scientific evidence reviews on complementary and alternative medicine. The monograph on chasteberry was last updated on July 7, 13 and was completed with the collaboration of a number of authors and editors consisting of pharmacists and doctors. Blinded peer review was also performed by the Natural Standard Editorial Board.

- **Summary**

  Natural Standards has given chasteberry an evidence grade of C for its use in premenstrual syndrome (PMS). A grade of C means that there is either unclear or conflicting scientific evidence for the use of chasteberry in the investigated condition. It has a grade of C as well for other conditions such as premenstrual dysphoric disorder (PMDD), luteal phase deficiency, cyclic mastalgia, and irregular menstrual cycles. For hyperprolactinemia, it has an evidence grade of B suggesting that chasteberry has good scientific evidence for its use in hyperprolactinemia.

  Chasteberry has been studied to inhibit prolactin secretion by binding to dopamine receptors in a competitive manner and has also been shown to be well tolerated with minimal side effects. It is likely safe when used in PMS as well as when used concomitantly with hormone replacement therapy and contraceptives. However, its long-term safety and effects are not well established. Chasteberry is likely unsafe when used in pregnant or lactating patients, and is possibly unsafe when used with dopamine agonists or antagonists. There is insufficient evidence to recommend its use in children, and one case of multiple follicular development after taking a supplement containing chasteberry was reported. Mild skin reactions such as eczema, itching, rash, and allergic exanthema have also been reported in clinical trials.

- **Comments**

  The monograph was compiled by reviewing a number of controlled trials and pre-clinical studies. All of the studies suggest that chasteberry has the ability to inhibit prolactin secretion. However, it was recognized that many of the studies identified for

PMS have poor study design, and further study may be required in order to assess whether chasteberry is truly beneficial for the management of PMS.

As well, there is no universal standardization for chasteberry extracts currently. The optimal therapeutic dose is currently unknown, and clinical effects of different brands studied are difficult to compare due to the different content and part of the plant used to make the extract. In one study, administration of low dose chasteberry led to a small increase in prolactin secretion, whereas a high dose of chasteberry led to a small decrease in prolactin secretion. However, overall, the effects of dosing on clinical effects are not well understood.

Traditional dosing even uses alcoholic extracts, tinctures, dried extracts and dried fruit. Chasteberry has shown to have hormonal effects, but its reported effects on prolactin levels in humans are variable. Chasteberry also seems to have *in vitro* activity against *Staphylococcus aureus, Streptococcus faecalis, Salmonella, E. coli, Candida albicans, C. tropicalis, C. pseudotropicalis,* and *C. kruesi*. It also exhibits high levels of toxicity against a number of other microorganisms.

With an evidence grade of C, the monograph suggests that chasteberry may be safe but not necessarily recommended for use in PMS. More studies will be beneficial in further understanding the effects of chasteberry on PMS.

Systematic Review - Tertiary Resource #2

Van Die, MD, Burger, HG, Teede, HJ, Bone KM. Vitex agnus-castus Extracts for Female Reproductive Disorders: A Systematic Review of Clinical Trials. *Planta Med.* 2013; 79: 562-575. https://www.thieme-connect.com/ejournals/pdf/10.1055/s-0032-1327831.pdf. Accessed 07/07/2013.

- **Study Objectives**

  To critically assess the evidence for the efficacy and safety of *Vitex* extracts (chasteberry) from RCTs in women's health such as premenstrual syndrome (PMS), premenstrual dysphoric disorder (PMDD), and latent hyperprolactinaemia.

- **Scope**

  In the review, 13 RCTs were identified where 12 were included. Eight of the studies identified studied the use of *Vitex* extracts in PMS, two in latent hyperprolactinaemia and mastalgia, and two in PMDD. There were small sample sizes in some studies and reference treatments differed. As well, the methodological quality of the studies and the conditions investigated in the studies varied. A number of different research settings were used, including clinical, community, and university settings. In the studies baseline symptoms were either diagnosed according to the DSM-III or DSM-IV criteria, by general practitioners, or the participant self-diagnosed and self-rated their own condition. The ages of the participants in the studies were generally around 30 to 40 years old. The studies used sample sizes ranged from 55 to 120 patients per arm. Outcome measures investigated in the studies included luteal phase serum prolactin levels, self-reported VAS, mood alterations, headache, bloating, breast fullness, increased appetite, Mood Menstrual Distress Questionnaire, work interests, and HAM-D.

  Placebo, pyridoxine (vitamin B6), and magnesium were utilized as comparison treatments for studies investigating PMS, fluoxetine was compared to *Vitex* extracts for studies investigating PMDD, and bromocriptine as well as placebo were used in studies investigating efficacy of chasteberry in latent hyperprolactinaemia.

- **Methods**

  Electronic databases such as Medline, PubMed, EMBASE, the Cochrane Library, CI-NAHL, Ovid, Google scholar, and Web of Science were used to identify studies for this review. A number of different search terms were utilized and only randomized, controlled trials studying the effects of *Vitex* extracts in female reproductive conditions were included. Studies that investigated multi-component herbal formulations and homeopathic preparations were excluded.

Overall 106 articles were located but only 14 articles met the selection criteria which were reviewed by two investigators. The Jadad scales, Cochrane risk of bias, and CONSORT were used to critically assess the articles. Due to duplication in publication and a lack of data for a placebo arm in two articles, in the end 12 RCT articles were reviewed.

- **Main Results**

  Seven of the eight RCTs investing the use of *Vitex* extracts in PMS in the review found the extracts to be superior to the reference treatments. For PMDD there were conflicting results as one study showed that the extracts and fluoxetine were equally efficacious in alleviating symptoms while in another study fluoxetine was superior to the extracts. For latent hyperprolactinaemia, one study found the extracts to be superior to placebo in its therapeutic hormonal effects while another found the extracts to be comparable to bromocriptine in ameliorating cyclic mastalgia and reducing prolactin levels in the blood.

- **Conclusions**

  Overall, the RCTs reviewed suggest that *Vitex* extracts have beneficial effects in the treatment of PMS, PMDD, and latent hyperprolactinaemia.

- **Comments**

  Overall, rigorous and systematic review was performed in selecting relevant articles and a variety of articles were gathered for review. There were no language restrictions imposed in the search for articles, but data from studies investigating homeopathic preparations as well as multicomponent herbal formulations were excluded. Although 106 articles related to the investigation of the efficacy of chasteberry in female reproductive disorders were identified, only 12 articles were selected for review. In data extraction and quality assessment, each trial was reviewed by two reviewers who utilized the Jadad scale as well as the CONSORT checklist to determine the validity of eligible RCTs. When an agreement could not be reached by the two reviewers, a third reviewer would be consulted.

  The selected articles were all RCTs, however methodological quality of the studies still varied and a meta analysis could only be performed on 2 of the selected articles. The review article acknowledged that performance bias was present in many of the studies, where blinding of participants and study personnel were inadequately described, and at times random sequence

generation and blinding of outcome assessment were also unclear. As well, the plant component used to prepare the *Vitex* extract was not reported in one study.

Although the review suggests that *Vitex* extracts have beneficial effects, results are at times not consistent from one study to another, and above all it is difficult to achieve a good comparison between studies when the comparison treatments used are different. As well, the use of comparison treatments which do not have established efficacy in female reproductive disorders make study results less valuable. The study populations in the different studies also differ, not so much in age but in their conditions, which may lead to a challenge in the application of study results to patients.

The lack of common outcome measures, clearly defined patient populations, and transparency in reporting in the 12 articles make it difficult to utilize the data analyzed in the review for clinical practice.

Double Blinded RCT - Primary Resource #1

Zamani, M, Neghab, N, Torabianm S. Therapeutic Efffect of *Vitex Agnus Castus* in Patients with Premenstrual Syndrome. *Acta Medica Iranica*. 2012; 50(2): 101-106. http://journals.tums.ac.ir/upload_files/pdf/_/20208.pdf. Accessed 07/07/13.

- **Study Objectives**

  To investigate and compare the therapeutic effects of *Vitex agnus castus* against placebo in women with PMS.

- **Methods**

  Design: Randomized, placebo-controlled, double-blind, cross-over study

  Allocation: A computer generated schedule into control and experiment groups was used to randomly divide patients into control and experiment groups.

  Blinding: Double blinded (study participants as well as investigators); however, the drug store which dispensed the placebo and the extracts as well as the clinician who gave out prescriptions for the treatments were not blinded, as there was a sign in the prescription of those who were in the control group.

  The extract and placebo bottles had identical appearance and medications were labeled either Clinical A or Clinical B. An identification number was noted in a protocol to allow a subsequent identification after the completion of the study and statistical analysis. Information on the placebo and the active substance became available to the investigators and volunteers after the completion of the study and after statistical analysis was performed.

  Follow-up period: 6 menstruation cycles, where study participants were visited and filled out a second questionnaire and self assessment. The first questionnaire and assessment were completed at the beginning of the study.

  Setting: Hamedan University of Medical Sciences, the Fatemie Hospital Clinic affiliated with Hamedan University Hospital, as well as community drugstores

  Participants: Females of child bearing age referred to the Fatemie Hospital Clinic in Hamedan, Iran from December 2006 to January 2007 were evaluated using the DSM-IV criteria for PMS. Inclusion criteria for the study were women of reproductive

age, menstrual cycles lasting 25 to 34 days, and diagnosis of PMS using the DSM-IV criteria in the two menstrual cycles prior to study initiation. Patients who were pregnant, breast feeding, had a history of drug and alcohol abuse, had pituitary problems, those who had used hormone products other than oral contraceptive pills, those with concomitant serious medical conditions, those allergic to *Vitex agnus*, as well as those who had previously tried *Vitex agnus* were excluded from the study. 146 women were screened whereas 128 patients were evaluated. The mean age of females in the experimental group was 30.77 (SD = 4.37) and the mean age of females in the control group was 30.89 (SD = 4.02).

Intervention: 40 drops of *Vitex agnus* extracts or placebo were administered for 6 days before menses for 6 consecutive cycles. Participants were prohibited from using other medications concomitantly during the study.

Outcomes: Improvements and alleviations in symptoms of PMS such as headache, anger, irritability, depression, breast fullness, bloating, and tympani were studied using patient self assessment questionnaires. Items were rated using a visual analogue scale (VAS).

Patient follow-up: 128 women of the 146 screened completed the study.

- **Main Results**

  No adverse effects were reported, and although PMS VAS scores dropped in both the experimental group and control group, the decrease was more significant in the control group. Decrease in VAS scores reported for headache, nervousness, restlessness, depression, breast swelling and pain, as well as bloating and tympani in the treatment group as compared to placebo were found to be significant ($P<0.0001$).

- **Conclusions**

  The study concluded that *Vitex agnus* can be considered as an effective and well tolerated treatment for relief of mild and moderate PMS symptoms.

- **Comments**

  In this study by Zamani *et al*., an intake of 40 drops of *Vitex agnus* extract was shown to be an effective and well tolerated treatment for relief of mild and moderate PMS symptoms. The article has clearly defined inclusion and exclusion criteria and a good duration of treatment of 6 menstruation cycles. It was mentioned that a similar trial was performed by Berger *et al.*,

which also used 40 drops of *Vitex agnus* extract but had implemented a daily use regimen for a 4 month period. Zamani *et al*. used a 6 cycles duration and the treatment was administered 6 consecutive days before menses. Analysis was also performed to ensure that study population in the treatment and control groups were comparable.

However, this study also had a number of weaknesses. A previous similar study had already been performed and Zamani *et al.* had only prolonged treatment period by 2 cycles and had implemented cyclic use instead of daily use of the treatment. The study does not mention the strength of extract serum used, which makes it difficult in the implementation of the results of this trial in actual population. The study also does not elaborate on participant drop out or how follow-up was performed, so it is not apparent whether or not intention to treat analysis was used in the study. The study also does not mention any adverse effects which participants may have experienced. A relatively small sample size was used, and there is an overall lack of transparency in the data that was collected.

The study was performed in Iran and due to differences in population characteristics, standards of care, lifestyle, and cultural differences leading to possible differences in interpretation of symptoms in the completion of self-assessment scales, the data collected may not accurate reflect the efficacy of this agent when used on female population in Canada.

Double Blinded RCT - Primary Resource #2

Schellenberg, R, Zimmermann, C, Drewe, J, Hoexter, G, Zahner, C. Dose-dependent Efficacy of the *Vitex agnus castus* extract Ze 440 in patients suffering from premenstrual syndrome. *Phytomedicine*. 2012; 19:1325-1331. http://journals1.scholarsportal.info.proxy. lib.uwaterloo.ca/tmp/7063361011606461221.pdf. Accessed 07/07/13.

- **Study Objectives**

  To investigate and compare the clinical effects of three different *Vitex agnus* castus (VAC) extract Ze 440 doses (8mg, 20mg, and 30mg) to placebo in patients suffering from PMS.

- **Methods**

  Design: Multicenter, double-blinded, placebo-controlled, randomized, parallel-group study

  Allocation: Randomization where blocks of 8 patients were allocated to the treatment group using a validated computer program.

  Blinding: Patient blinded; does not describe how investigators are blinded

  Follow-up period: Patients were followed over a 3 menstrual cycle period. There were at least 1 baseline visit and 1 visit at week 12. There are additional visits with physicians but the study did not describe the frequency study participants received follow-up.

  Setting: Patient outpatient clinics in Germany

  Participants: 162 female patients with PMS aged 18 to 45 years

  Intervention: Placebo or different doses of Ze 440, a 60% (m/m) ethanolic extract prepared from VAC fruits at dosages 8mg, 20mg, and 30mg over three menstrual cycles. All tablets used were identical in size, color and appearance and were all film-coated. Study participants were instructed to take one tablet once daily un-chewed with liquid at meals for a 3 menstrual cycle period. Patients received 126 tablets at their first visit and patient compliance was assessed and taken into regard in data

analysis. Certain concomitant medications were prohibited in the study as well as certain physical or psychotherapeutic measures such as acupuncture and hypnosis.

Outcomes: Improvements and alleviations in symptoms of PMS such as irritability, mood alteration, anger, headache, bloating, and breast fullness were studied using patient self assessment questionnaires. Items were rated using a visual analogue scale (VAS).

Patient Follow-up: 142 of 162 patients were followed to the end of the study.

- **Main Results**

  Improvement in total symptom score (TSS) was measured as the outcome. The 20mg group showed the most improvement in TSS as compared to the placebo and 8mg treatments. However, the 30mg treatment group did not experience significant decrease in symptoms compared to the 20mg group. The results also corresponded with observed single PMS symptom scores. All of the treatments were well tolerated.

- **Conclusions**

  The study has shown that a daily dose of VAC extract Ze 440 20mg was effective in relieving symptoms of PMS.

- **Comments**

  This study had a novel objective to investigate dose-dependency of VAC in alleviating PMS symptoms. The study protocols and data reporting were transparent, and conflicts of interest were disclosed as well. The study had clearly defined inclusion and exclusion criterias and the study population also included patients who had used oral contraceptives, which is interesting because some studies had excluded this population due to the possibility of data distortion from oral contraceptive intake. However, the study also mentions that a statistical evaluation was performed on the 23% study population taking oral contraceptives and concluded that oral contraceptives have no significant effect on investigated parameters.

  The study utilized a number of different tools and training in order to enhance the data that was collected from the study. Pre-study training in using study instruments was given to all attending physicians to enhance inter-and intra-centre consistency and all assessments were performed by the same individual in each clinic. There was also a rigorous screening strategy used to recruit suitable study participants. Patient compliance was also taken into consideration in data analysis, and documentation on

concomitant medication use was documented at each visit. A safety assessment was performed at the beginning and end of the study and results were documented. The preparations which were used were adequately described and the treatments used were standardized.

The study also had a number of weaknesses. Although the study mentioned that intention to treat analysis was used, those who had withdrawn from the study after study initiation were not taken into account and therefore intention to treat analysis had not been performed. As well, a longer study period greater than 3 menstrual cycles may be beneficial in observing long term effects of dose on PMS symptoms as well as side effects related to use of the extract. It is unknown whether the German population will respond in a similar manner as the Canadian population to the use of chasteberry in the management of PMS.

References

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