St John's Wort Extended Abstract

Primary Literature: Article #1

Stevinson C and Ernst E. A pilot study of *Hypericum perforatum* for the treatment of premenstrual syndrome. *Brit J Obstet Gynaec* 2000; 107: 870-6.

Study Objectives

To investigate whether St. John's Wort (SJW) could relieve symptoms of PMS in a small group of women in order to establish a hypothesis and to test methods for conducting a future RCT of SJW for the treatment of PMS.

Methods

- **Design:** Prospective, open label, uncontrolled, observational study
- **Allocation:** All participants took 900 mg SJW daily for 2 complete menstrual cycles.
- **Blinding:** There was no blinding used in this study.
- **Follow up period** Participants were followed for 4 menstrual cycles (cycle 1 – screening; cycle 2 -- baseline measures; cycle 3 and 4 -- treatment cycles).
- **Setting:** Department of Complementary Medicine, University of Exeter, Exeter, UK
- **Participants:** Participants were recruited through advertisements and publicity in the local media and given a preliminary screening interview by telephone. 25 participants gave informed consent and 6 dropped out of the trial. 3 withdrew for personal reasons, 1 underwent a hysterectomy, 1 became pregnant and one withdrew for feeling jittery. 19 participants completed the protocol and were included in the analysis.
    - Inclusion criteria
        - Self-reported PMS symptoms for > 6 months
        - Self-reported impairment of occupational, family or personal functioning
        - Age between 18-50
        - Informed consent

- Exclusion criteria
    - Existing use of SJW
    - Known contraindications to SJW
    - Current major psychiatric disorder
    - Current history of serious health problems (eg. cancer, epilepsy, conditions requiring steroid therapy)
    - Use of psychotropic medications (eg. antidepressants, anxiolytics, hypnotics)
    - Concomitant treatments for PMS including vitamins and supplements if they could not be stopped for the trial
    - Current or planned pregnancy
    - Current lactation
    - Hysterectomy
    - Not using adequate contraception
    - Irregular menstrual cycles
    - History of substance abuse in previous 12 months
    - Participation in another clinical trial

- **Intervention:** All participants took 900 mg SJW daily for 2 complete menstrual cycles
- **Outcomes:**
    - Primary outcomes:
        - Daily Symptom Report (DSR)
        - A checklist of 17 PMS symptoms rated from 0-4 according to their severity throughout the menstrual cycle
        - Included a tick box to indicate when tablet was taken
    - Secondary outcome measures:
        - The modified, self-reported Social Adjustment Scale (SAS-M), for assessing occupational, social and personal functioning, and the Hospital Anxiety and Depression Scale (HAD)
        - These outcomes were measured at baseline and after 1 and 2 cycles of treatment
- **Patient Follow Up:** Following the preliminary screening interview, the next follow-up came mid-cycle to confirm a diagnosis of PMS through a physician appointment. The second visit occurred at the end of the second cycle to complete baseline

measures for the HAD and SAS-M. DSR were completed throughout the entire duration of the study and participants were informed to mail in their booklets.

Main Results

There were significant reductions in all outcome measures. The degree of improvement in overall PMS scores between baseline and the end of the trial was 51%; with over two-thirds of the sample demonstrating at least a 50% decrease in symptom severity. Tolerance and compliance with the treatment were encouraging.

Conclusions

There is a scope for conducting a randomized, placebo-controlled, double-blinded trial to investigate the value of SJW as a treatment for PMS.

Comments/Critical appraisal

- **Strengths**
  - Prospective
  - All patients underwent the same follow-up and were treated similarly
- **Limitations**
  - Participants were not blinded to treatment, all patients received SJW and because they were using self-reported outcomes there was a huge bias present in the evaluation of the therapy
  - Since there was only one treatment used for all participants, there is a possibility of bias introduced by the investigators who were responsible for the analysis of the results
  - Although the authors indicated that the purpose of the study was to demonstrate that there was a role for further investigation of the use of SJW for PMS, their results mainly focused on the improvement on symptoms seen, despite poor study design for this purpose
  - The only intervention was SJW, thus there was no comparator and perhaps if placebo had been used in these same patients, the same results would have been seen

- The baseline characteristics of the participants were not outlined, so it makes it difficult to determine what patient population would be appropriate for future study
- Participants were asked to complete daily DSRs over a period of 4 cycles, however, it is possible that some patients completed these retroactively as there was no mention of how often these reports were submitted to the investigators
- Only 19 patients were included in the study

- **Bottom line**

  It may be appropriate to conduct further investigations to assess the role of SJW in the treatment of PMS.

Primary literature: Article #2

Hicks SM, Walker AF, Gallagher J, Middleton RW and Wright J. The Significance of "Nonsignificance" in Randomized Controlled Studies: A Discussion Inspired by a Double-Blinded Study on St. John's Wort (*Hypericum perforatum* L.) for Premenstrual Symptoms. *J Altern Complem Med* 2004; 10: 925-32.

Study Objectives

To investigate whether SJW is more beneficial than placebo treatment in relieving symptoms of PMS.

Study Objectives

- **Design:** Randomized, double-blinded, placebo-controlled trial
- **Allocation:** Patients were randomized (by an external party) to receive either 2 tablets daily of SJW (600 mg total) or 2 placebo tablets daily for the last 2 cycles of the study.
- **Blinding:** This trial was double-blinded.
- **Follow up period**: The duration of the study was 3 menstrual cycles (cycle 1 -- no treatment, gathering baseline data; cycles 2 and 3 -- treatment cycles)
- **Setting:** The University of Reading, Berkshire, England

- **Participants:** Participants were recruited nationally from newspaper and magazine articles aimed at volunteers suffering from PMS symptoms. Respondents then completed a Menstrual Health Questionnaire (MHQ). Inclusion criteria included symptoms of PMS that were at least 30% more severe in the week preceding menstruation than in the week after menstruation and this was confirmed using the MCQ and later with prospectively recorded data. 169 women were recruited into the study, with 125 completing the protocol and being included in the analysis. There were 82 patients assigned to placebo and 87 assigned to SJW, with 64 completing the protocol in the placebo group after accounting for dropouts and 61 in the SJW group.
    - Exclusion criteria
        - Psychiatric illness
        - Major endocrine abnormalities (eg. thyroid disease)
        - Pregnant or had given birth within last year
        - On psychotropic medications or prescribed medications for PMS
        - On oral contractive pills
- **Intervention:** The two treatment groups were 600 mg SJW (standardized to 1800 μg hypericin) and placebo.
- **Outcomes:**
    - Primary Outcome
        - Anxiety subgroup of symptoms of the Menstrual Diary (MD)
        - Consisting of 25 symptoms scored daily with a new MD started on day 1 of each menstrual cycle
        - Symptoms were clustered into subgroups for analysis, based on Abraham's classification of PMS symptoms
        - Individual symptoms were scored using visual analogue scales (VAS)
        - MD scores were read using automatic data capture software which converted the participants marks into a score on a scale of 0-10
        - For each symptom subgroup a PMS score was derived and was used to assess treatment effects (higher score = greater severity)
- **Patient Follow Up:** The study does not outline how often the MDs were collected for analysis. This was the only form of follow-up aside from a post-trial questionnaire for adverse reactions.

Main Results

After averaging the effects of treatment over both treatment cycles it was found that there was a trend for SJW to be superior to placebo. However, this finding was not statistically significant. Although no serious side effects were reported for SJW, more subjects withdrew from the study because of side effects in this group versus placebo.

Conclusions

It is possible that this non-significant finding resulted from insufficient statistical power in the study, rather than a lack of efficacy of SJW. In future, similar studies should be powered to detect a minimum clinically relevant difference between treatments.

Comments/Critical appraisal

- **Strengths**
  - Participants were randomized by an external source
  - This study was double-blinded and placebo-controlled
  - No conflicts of interest identified
  - Relatively large study size compared to other trials investigating the role of SJW in PMS
  - MD scores were read using automatic data capture software, which reduces the possibility of bias being introduced if an investigator was to score the results
- **Limitations**
  - Baseline characteristics have not been outlined for the *individual* treatment groups, thus baseline heterogeneity may have existed
  - Exclusion criteria did not account for other herbal or OTC medications being used to treat PMS
  - The average age of subjects was 37.2, limiting the applicability of the results to a younger patient population
  - This trial was insufficiently powered due to inappropriate assumptions made by the investigators (overestimated treatment difference between SJW and placebo)
  - Study took place at a single centre (as opposed to multi-centre design) limiting the applicability of the results to the general population
  - All outcome measures were subjective self-reported measures, however, this is likely the only option for symptoms of this nature related to PMS

- Although patients were asked to complete their MDs daily it is possible that some participants completed theirs retrospectively
- The diagnosis of PMS came strictly from self-reported measures on the MHQ and there was no direct patient interaction to confirm diagnosis by a medical professional

- **Bottom line**

  Due to the limitations of this trial (especially that it was insufficiently powered) and the non-significant results, it is unclear whether there is a role for SJW in PMS.

Primary literature: Article #3

Canning S, Waterman M, Orsi N et al. The Efficacy of Hypericum perforatum (St John's Wort) for the Treatment of Premenstrual Syndrome A Randomized, Double-Blind, Placebo-Controlled Trial. CNS *Drugs* 2010; 24(3): 207-25.

Study Objectives

To investigate whether SJW 900 mg/day is more beneficial than placebo treatment in relieving symptoms of mild PMS.

Methods

- **Design:** Randomized, double blind, placebo-controlled, crossover study
- **Allocation:** All participants received both treatments throughout the course of the investigation, as this was a crossover study. The probability of assignment to treatment groups was equal and a randomization code was generated using a random permuted block-method. The allocation codes were kept from the principal investigator until after the last participant completed the trial.
- **Blinding:** After 3 untreated screening cycles women who met a prospective PMS diagnosis underwent a single-blind placebo run-in phase of 2 menstrual cycles. Following this, women were randomized to receive 2 cycles of double-blind treatment

with SJW or placebo. A single-blind placebo-treated washout cycle followed, after which women were crossed over to placebo or SJW for an additional 2 cycles.

- **Follow up period**: Women were followed over 10 menstrual cycles.
- **Setting:** Institute of Psychological Sciences, University of Leeds, Leeds, UK.
- **Participants:** Participants were recruited between November 2005 and August 2006 via advertisements and publicity in the local media that requested volunteers experiencing premenstrual symptoms. Participants were women aged 18-45 who had regular menstrual cycles (25-35 days) and who were able to make frequent study visits. 36 participants were randomized and 34 completed the protocol.

    - Inclusion criteria: Women deemed to be in good physical and psychological health entered the screening phase. Women had to demonstrate at least a 30% increase between their follicular and luteal Daily Symptom Report total scale scores in at least 2/3 cycles to be eligible to continue in the study. Follicular scores were obtained by averaging the DSR total scale scores from cycle days 5–10, with day 1 being the first day of menstruation. Luteal scores were obtained by averaging the DSR total scale scores from the 6 days prior to the onset of menstruation. Since PMS should be limited to the luteal phase, the investigators included exclusion criteria for elevated anxiety and depression in the follicular phase.
    - Exclusion criteria:
        - photosensitive
        - using hormonal contraception or treatment
        - pregnant or breastfeeding
        - taking prescribed (eg. estrogens, progestogens, danazol, gonadotropin-releasing hormone agonists) or OTC (eg. calcium, evening primrose oil, vitamin B6, *Vitex agnus castus*) medication for PMSreporting menstrual cycle irregularity
        - taking prescribed drugs known to interact with SJW
        - elevated anxiety and depression levels in their follicular phase
        - average total score exceeding the clinical threshold for ‘caseness for depression’ (≥12) on the Beck Depression Inventory (BDI) and/or an average total score that exceeded the upper 90% probability limit for the general

adult population (≥51) on the Trait scale of the State-Trait Anxiety Inventory (STAIS) were excluded from the placebo run-in phase

- **Intervention:** Women who remained eligible after 3 screening cycles (n = 36) underwent a 2-cycle placebo run-in phase. They were then randomly assigned to receive SJW tablets 900 mg/day (standardized to 0.18% hypericin; 3.38% hyperforin) or identical placebo tablets for 2 menstrual cycles. After a placebo-treated washout cycle, the women crossed over to receive placebo or SJW for 2 additional cycles.
- **Outcomes:**
    - Primary outcomes:
        - Daily Symptom Report (DSR):
        - DSR is a checklist of 17 PMS symptoms
        - Symptoms are rated from 0 (not present at all) to 4 (severe: symptom is overwhelming and/or unable to carry out daily activity)
        - DSR is comprised of 4 subscales that describe mood, behavioural, pain and physical symptoms
        - Women were asked to complete DSRs throughout the duration of the trial
        - On the DSR participants were to make note whether they had their period and included a tick box to confirm they had taken their study medication that day
    - Secondary outcome measures:

        - Trait scale of the State-Trait Anxiety Inventory (STAIS)
        - Beck Depression Inventory (BDI)
        - Aggression Questionnaire (BPAQ)
        - Barratt Impulsiveness Scale version 11 (BIS-11)
    - These outcome measures were completed weekly throughout the trial
    - All self-reported measures were provided to participants in diary booklets sent biweekly throughout the trial
- **Patient follow-up**

Participants were instructed to begin a new diary booklet on the first day of each menstrual cycle and to complete the weekly measures from their previous booklet if applicable. They were asked to return each diary booklet immediately upon completion.

Women were required to visit the principal investigator at the Institute of Psychological Sciences, University of Leeds, during the follicular and luteal phases of study cycles 3,5,7,8 and 10. During these visits, blood samples were obtained to assess hormone (follicle stimulating hormone, luteinizing hormone, estradiol, progesterone, prolactin and testosterone) and cytokine (IL-1β, IL-6, IL-8, IFNγ and TNFα) levels. Each week participants were also asked to provide information regarding any adverse events they experienced and/or concomitant medications taken in their diary booklet. Adverse events were also assessed at each study visit through a semi-structured interview and blood pressure was also recorded.

Main Results

SJW was statistically superior to placebo in improving physical and behavioural symptoms of PMS ($p < 0.05$). There were no significant effects of SJW compared with placebo treatment for mood- and pain-related PMS symptoms ($p>0.05$). Plasma hormone and cytokine levels, and weekly reports of anxiety, depression, aggression and impulsivity, also did not differ significantly during the SJW and placebo cycles ($p > 0.05$).

Conclusions

Daily treatment with SJW was more effective than placebo treatment for the most common physical and behavioural symptoms associated with PMS. These benefits were apparent during the first menstrual cycle in which SJW was taken and occurred with minimal adverse effects. As pro-inflammatory cytokine levels did not differ significantly between SJW and placebo treatment, these beneficial effects are unlikely to be produced through this mechanism of action alone. Further work is needed to determine whether pain- and mood-related PMS symptoms benefit from longer treatment duration.

Comments/Critical appraisal:

- **Strengths**
    - Patients were randomized to treatment order using a random permuted block-method
    - The two groups were similar at the start of the trial in terms of baseline characteristics
    - The two treatment groups were treated similarly, receiving identical follow-up by the investigators
    - No conflict of interest in terms of funding
    - Double-blinded, crossover design was used

- Prospective

- **Limitations**
  - The study size was quite small (n=36)
  - Study took place at a single centre (as opposed to multi-centre design) limiting the applicability of the results to the general population
  - All outcome measures were subjective self-reported measures, however, this is likely the only option for symptoms of this nature related to PMS
  - This trial only examined patients with symptoms of mild PMS, so the findings are not applicable to those with moderate to severe symptoms
  - As mentioned by the authors, it is possible that some participants did not have PMS but rather a psychiatric condition that was not directly assessed given that many women who present with PMS are found not to have the syndrome but rather a premenstrual exacerbation of a psychiatric disorder and although all participants were deemed to be in good psychological health it would have been more accurate to administer a structured clinical interview such as the Structured Clinical Interview for DSM-IV
  - Trial participants were provided with diary booklets that contained 7 DSRs on a weekly basis and although participants were informed to complete one DSR each evening it is very likely that some participants completed their DSR in a retrospective manner and furthermore some women may have been biased by their previous DSR ratings from earlier in the week
  - All women who completed the trial were of Northern European origin with the exception of one British-born Asian and one Eastern European, which limits the applicability of the results to those of other descent
  - The average age of participants was 35.3 years, limiting the applicability of the results to younger patients suffering from PMS

- **Bottom line**

This was a fairly well designed double-blinded, placebo-controlled crossover study. However, given the small study population and other limitations discussed above, the use of SJW for physical and behavioural symptoms of PMS requires further investigation before any definitive conclusions for its place in therapy can be drawn.

Secondary literature: Article #4 (systematic review)

Dante G and Facchinetti. Herbal treatments for alleviating premenstrual symptoms: a systematic review. ***Journal of Psychosomatic Obstetrics & Gynecology*** **2011; 32(1): 42–51**

Objective

To analyze the effects of herbs in the management of PMS or PMDD in medical practice.

Scope

Studies included in the analysis were all RCTs examining the use of herbal medications in the treatment of PMS or PMDD. Inclusion criteria are outlined below. The study duration and patient characteristics differed greatly amongst included studies.

Methods

Systematic literature searches (from January 1980 to September 2010) were performed in September 2010 in the following electronic databases:

- Medline
- Amed
- The Cochrane Library
- PDR for Herbal Medicines

An extensive number of search terms were used as outlined in the article. No language restrictions were imposed and further relevant papers were identified by hand searching the references of recent systematic reviews. Only human studies were included. Exclusion criteria included data from herbal treatments in combination with other herbs, animal studies, *in vitro* investigations and Chinese

herbal remedies. In situations of dual publications, the more recent and detailed paper was used. The Jadad method was used to evaluate the quality of the identified articles. Studies with a Jadad score <3 were considered of poor quality and excluded from the analysis. Studies were also evaluated according to the method used for the clinical diagnosis, using the definition for PMS given by the American College of Obstetrics and Gynecologists and that for PMDD given by the American Psychiatric Association. In addition, the diagnosis of PMS is generally accepted when performed by a prospective evaluation of symptoms through validated questionnaires for at least 2 menstrual cycles and only studies using these standard criteria were included. All identified sources were read by one author and successively independently checked by the other author. After applying the search criteria and eliminating results based on exclusion criteria, only 10 RCTs were included in the systematic review.

Main results

Hicks et al. investigated a SJW extract standardized to 0.3% of hypericin in volunteers recruited through newspaper advertisements, followed by an interview. Although minor adverse effects are reported, 5 subjects in the SJW group, and 1 in the placebo group withdrew because of this. Averaging both treatment cycles there was only a trend for SJW to be superior to placebo.

Canning et al. also recruited through advertisements but employed a different extract titrated to 0.18% hypericin and 3.38% hyperforin. The subject evaluation included 3 observational run-in cycles, followed by 2 placebo-cycles before randomization, allowing few, very selected subjects to be treated. Minor adverse effects were reported both in placebo and SJW group. In a sophisticated multivariate analysis, SJW was not different than placebo on overall PMS symptoms. Sub-analyses revealed SJW efficacy for physical and behavioural symptoms. Unexpectedly, SJW did not relieved mood symptoms.

Conclusions

Some herb remedies seem useful for the treatment of PMS. However, more RCTs are required to account for the heterogeneity of the syndrome.

As a whole, SJW did not show an efficacy different than placebo. Small benefits were seen for physical, but not psychological symptoms.

Comments/Critical Appraisal

- **Strengths**

- No conflicts of interest were identified
- The authors completed a comprehensive search, using extensive search terms and examining the references of other recent systematic reviews for additional articles
- The search was not limited to English language only
- The authors used a consistent method (Jadad method) to determine the quality of the articles for inclusion in the review
- Only RCTs were included in the review

- **Limitations**
  - Only two trials investigating SJW were included in this systematic review
  - The outcomes were not very clearly identified, other than "effectiveness" in PMS/PMDD
  - The search strategy only included text words and not MESH terms
  - Different scales were used to assess the effectiveness of the herbal remedies in the treatment of PMS/PMDD which limits the quality of the conclusions drawn by the authors
  - The authors calculated a reduction in symptoms versus baseline as a percent change in overall symptoms, but since different scoring methods were used in different studies these numbers are not directly comparable
  - For some of the included articles, it was not even possible to calculate a reduction in symptoms versus baseline again limiting the author's conclusions
  - The authors did not adjust for heterogeneity between the trials

Bottom Line

Given the limited number of trials included assessing SJW and the many limitations outlined above, this systematic review does not contribute much to the current understanding of the inconclusive role of SJW for the treatment of PMS.

Tertiary literature: Reference # 5 (Internet Database)

Natural Standard. St. John's Wort Professional Monograph. Accessed from www.naturalstandard.com. Accessed on July 17, 2013.

Source Description

Natural Standard is a database founded by healthcare providers and researchers to provide high-quality evidence-based information about complementary and alternative medicines and their role in various health conditions. The SJW monograph makes no reference as to when it was last updated.

Summary

"There is currently insufficient evidence to determine if SJW is an effective treatment for PMS. Preliminary evidence from a case series merited follow-up with a controlled trial. The one controlled trial was perhaps underpowered to determine clinically relevant differences between treatments. Well-designed clinical trials are still needed in this field."

SJW has been generally well tolerated at recommended doses for up to 1-3 months based on published literature. The most common adverse effects include gastrointestinal symptoms, skin reactions, fatigue, restlessness or anxiety, photosensitivity, sexual dysfunction, dizziness, headache and dry mouth. However, recent analyses have concluded that adverse event rates are comparable to placebo. SJW has the potential to reduce the systemic bioavailability of many conventional drugs and to date the variable effects of SJW on various conventional drugs and the mechanisms by which these effects may operate remain inconclusive.

Comments/Critical Appraisal

The evidence to support the recommendation surround the use of SJW comes from only 2 trials dating back to 2004:

- Hicks SM, Walker AF, Gallagher J, Middleton RW, and Wright J. The significance of "nonsignificance" in randomized controlled studies: a discussion inspired by a double-blinded study on St. John's wort (*Hypericum perforatum L.)* for premenstrual symptoms. *J Altern Complement Med* 2004; 10(6): 925-32.

-Stevinson C and Ernst E. A pilot study of *Hypericum perforatum* for the treatment of premenstrual syndrome. *British Journal of Obstetrics and Gynaecology* 2000; 107(7): 870-6.

Thus, more recent studies have not been included in the review of this evidence. Given the preliminary nature of the evidence for the use of SJW for this indication and the uncertainty surrounding potential drug interactions and long-term safety it may be best to avoid this medication until further high quality trials are completed.