Evening Primrose Oil Extended Abstract

Primary literature: Article #1

Collins A, Cerin A, Coleman G and Landgren B. Essential fatty acids in the treatment of premenstrual syndrome. Obstet and Gynecol. 1993; 81(1): 93-98.

- **Study Objectives**

To investigate the effectiveness of essential fatty acid supplementation using evening primrose oil for the treatment of PMS in a randomized, double-blind, crossover trial. A second goal of the study was to compare menstrual cycle characteristics between women with PMS and symptom free controls.

- **Methods**

- **Design**
  - Randomized, double-blind, placebo-controlled, cross-over study
- **Allocation**
  - 27 women diagnosed with PMS were assigned to placebo first or drug-first by the pharmacy team using a completely randomized design
- **Blinding**
  - Double-blind
- **Follow-up period**
  - The study duration included 10 menstrual cycles over 10 months
  - Participants completed daily mood and symptom ratings
- **Setting**
  - Outpatients in the Stockholm County districts of Solna and Sundyberg
- **Participants**
  - 27 women aged 30-45 with diagnosed PMS

- 22 symptom free controls
- There were no statistical differences between the control and study group in regards to social demographics.

- **Intervention**
  - Efamol – 12 capsules each day (each capsule contained 4.32g linolenic acid and 0.54g gamma-linolenic acid) x 4 cycles
- **Outcomes**
  - PMS symptoms assessed using daily self-ratings
  - Rating scale used was a modified version of a validated scale constructed by Hammarback et al.
  - Rating scale included 16 mood states and symptoms, to be filled out on a 10-cm visual analogue scale with end points of 0 (absence of symptoms) and 10 (maximum level of symptoms). Four of the symptoms were physical and 12 were psychological. Patients were to complete the rating scales at the end of the day before going to bed.
- **Patient follow-up**
  - The study duration was 10 months but there was no mention of frequency of follow-up.

- **Main results**

A multivariate analysis of variance showed no significant effects of evening primrose on PMS symptoms. There was a significant effect of time regardless of which compound the women took; suggesting a placebo effect or an effect due to the expectation of improvement. There were no major side effects reported. The most frequent reported were perceived weight gain and difficulty swallowing the large number of tablets. However, the authors did not state if this was attributed to the treatment or placebo or both.

- **Conclusions**

Evening primrose is not effective in the treatment of PMS.

- **Comments/Critical Appraisal**

Internal validity: The participants were randomized to receive placebo-first or drug-first in a double-blind fashion. However, the authors failed to describe the randomization and blinding processes used. They used a cross-over design which decreases

confounding factors as each patient serves as their own control; however, they did not have a wash-out period between treatments.

External validity: Appropriate inclusion and exclusion criteria were used to identify subjects. However, there were very few subjects included in the study with a large number of drop outs (30) which makes it hard to generalize the results to the population as a whole.

Bottom line: Despite the limitations of this trial, the evidence suggests evening primrose oil is ineffective in the treatment of PMS.

Primary literature: Article #2

Puolakka J, Makarainen L, Viinikka L and Ylikorkala O. Biochemical and clinical effects of treating the premenstrual syndrome with prostaglandin synthesis precursors. The Journal of Reproductive Medicine. 1985; 30(3): 149-153.

- **Study Objectives**

  To study the effects of a prostaglandin synthesis precursor, Efamol, on women with severe PMS.

- **Methods**

- **Design**
  - Randomized, placebo controlled cross-over
- **Allocation**
  - Half of the women were randomized to start treatment with Efamol and half were randomized to start placebo
- **Blinding**
  - Not reported
- **Follow-up period**
  - 4 months
- **Setting**

- Outpatients from Helsinki, Finland

- **Participants**
  - 30 women aged 25 to 47 with severe incapacitating PMS
- **Intervention**
  - Efamol 500mg capsule – 6 capsules daily (daily dose contained 2.16g cis-linoleic acid and 0.27g γ-linolenic acid) starting on the 15th cycle day and continued until the next menstrual period x 4 cycles
- **Outcomes**
  - Participants recorded their symptoms before and during the trial on the last treatment day using a questionnaire
  - The baseline PMS scores were similar in both treatment groups (those starting Efamol and those starting placebo)
- **Patient follow-up**
  - 4 months

- **Main Results**

The authors found both Efamol and placebo significantly decreased PMS symptoms ($P<0.001$) and the decrease was greater with Efamol treatment. Depression was the only symptom that improved more with Efamol than placebo ($P<0.01$).

- **Conclusions**

Both Efamol and placebo significantly reduced PMS symptoms in general; however, Efamol significantly reduced depression symptoms more than placebo. Efamol may be effective in the treatment of PMS symptoms and should be further investigated at larger doses and longer durations.

- **Comments/Critical Appraisal**

Internal validity: The participants were randomized to receive placebo-first or drug-first in a double-blind fashion. However, the authors failed to describe the randomization and blinding processes used. They used a cross-over design which decreases confounding factors as each patient serves as their own control; however, they did not have a wash-out period between treatments. The authors did not specify how or if PMS was diagnosed. There were also no reports on compliance or drop-out rates. The trial was sponsored by the manufacturers of Efamol which questions the validity of the results.

External validity: The authors did not state their inclusion or exclusion criteria and did not provide any information regarding the patient demographics making it difficult to apply the results to other populations. The very few number of subjects in the trial decreases the power of the study and decreases the possibility that a difference can be detected.

Due to the small sample size and large number of methodological flaws the results of this study cannot considered valid. More research is warranted to determine the role of evening primrose in the treatment of PMS.

Secondary literature: Article #3 (systematic review)

Stevenson C and Ernst E. Complementary/alternative therapies for premenstrual syndrome: A systematic review of randomized controlled trials. AJOG 2001; 185(1): 227-234.

- **Study Objectives**

To determine if the use of current complimentary/alternative therapies for PMS are supported by evidence of effectiveness from clinical trials.

- **Scope**

Only randomized controlled trials (RCTs) were included in the review. A total of 27 trials were investigated, 4 of the trials used evening primrose as the intervention. Two of the four were double-blinded crossover studies, one was a double-blinded parallel study and one was a non-blinded crossover study. The comparison in all trials was placebo with evening primrose as the intervention; although, one study used evening primrose and a multi-nutrient supplement as the intervention. The number of patients in the trials ranged from 10 to 38. The dosages used ranged from 3-6 grams and duration ranged from 2 to 6 menstrual cycles. The primary outcome measures included: symptom scale, subjective rating, beck depression inventory, Salkind morbid anxiety inventory and modified version of visual analog scale.

- **Methods**

Articles on PMS and complementary/alternative therapies were identified using the following databases: MEDLINE, EMBASE, BIOSIS, CINAHL, PsycholNFO, The Cochrane Library and CISCOM. Reference lists of the articles were also checked for further relevant publications and manufacturers of herbal preparations were asked for any additional trials. Only RCTs published in a peer-reviewed journal were included in the r review. Articles were read in full and data extracted in a predefined manner by one author, and checked by a second author. No quantitative assessment of the methodological quality of the included trials was performed but comments on the rigor of the studies were included.

- **Main Results**

Of the 4 RCTs of evening primrose all failed to a difference in overall symptoms when compared to placebo. One paper reported a positive finding for cardinal symptoms although there were many limitations to this trial including lack of blinding.

- **Conclusions**

Due to the small sample size of the available studies the results are inconclusive. The current low quality evidence suggests that there is of little if any value of evening primrose for PMS treatment.

- **Comments/Critical Appraisal**

The objective of the study was clear and focused. The authors included only RCTs published in peer-reviewed journals; however, very few restrictions were used. For instance, the authors included all studies regardless of quality and they did not perform a quantitative assessment of methodologic quality. The authors provided comments about each study but this does not provide an accurate assessment of the quality of each study. The authors used a wide range of search strategies to identify studies and it is unlikely that relevant studies were missed. The data abstraction was only done by one author and checked by a second. The second author should have also extracted the data and then compared the results to ensure all relevant data was obtained. The authors used a table to extract data in a standard and predefined manner allowing reproducibility of their assessments of the studies.

There are a number of limitations to this systematic review; however, due to a lack of high quality studies the authors provided an accurate review of the available evidence.

Secondary literature: Article #4 (systematic review)

Whelan AM, Jurgens TM and Naylor H. Herbs, vitamins and minerals in the treatment of premenstrual syndrome: a systematic review. Can J Clin Pharmacol 2009; 16(3):e407-e429.

- **Study Objectives**

To identify natural products used for the treatment of PMS and review evidence from RCTs to determine their efficacy.

- **Scope**

The authors included only RCTs in their review. Sixty two natural products were identified of which only 10 were assessed in RCTs. Three RCTs were included on evening primrose. Two were double-blind, placebo controlled crossover designed studies whereas one was not blinded but a placebo controlled crossover. The number of subjects in the evening primrose RCTS ranged from 27 to 38. Doses ranged from 0.27g and 0.36 g to 6.48 g of γ linolenic acid per day. The length of the studies ranged from 4 to 10 months. The primary outcome measured in all studies was a change in the rating of severity of PMS symptoms.

- **Methods**

The authors identified articles by conducting a literature search using the following databases: Clinical Evidence, the Cochrane Library, Mayoclinic, Medscape, MEDLINE Plus, Natural Medicines Comprehensive Database and the internet. Using the search terms "premenstrual syndrome", "PMS", "premenstrual dysphoric disorder", "natural health products", "herb", "vitamin", "mineral", "dietary supplement" and "alternative medicine", the authors identified 29 RCTs articles that met their inclusion criteria. Of the articles included 21% described the process of randomization, 7% described allocation concealment and 50% provided reasons for participants dropping out.

- **Main Results**

The articles were identified by the authors that examined the efficacy of evening primrose for the treatment of PMS symptoms. There was no significant reduction in total PMS symptoms detected by any of the trials. Two studies were determined

to be of sufficient quality to apply the results to practice. One study found a statistically greater reduction in PMS symptoms with the use of evening primrose but this study was judged to be of lesser quality.

- **Conclusions**

Based on the results of the 3 RCTs included in the systematic review, evening primrose does not seem to be effective for the treatment of PMS symptoms.

- **Comments/Critical Appraisal**

The objective of the study was clear and focused. The authors used appropriate inclusion and exclusion criteria. Both high and low quality studies were included; however, the authors addressed the quality in their analysis and overall conclusion. A wide range of databases were used to identify studies and thus it is unlikely that relevant studies were missed. The authors stated their judgment of the quality of the studies included and explained a method for how the quality was assessed but they did not provide the questions that the investigators used to assess the quality. Thus when they listed a study to be of poor quality there was no way to determine what specifically made the study poor quality. Two separate investigators were used to screen for and assess the studies and a third investigator was used to resolve discrepancies. The authors used a table to extract data in a standard and predefined manner allowing reproducibility of their assessments of the studies. There was a large amount of heterogeneity between the studies as the women had varying severities of PMS with varying methods used to define and/or diagnose PMS. The studies also used a variety of scales to measure the study outcomes of changes in symptom severity. This makes it difficult to come to clinically relevant conclusions when comparing the different studies.

Tertiary literature: Reference # 5 (Internet Database)

Natural Standard. Evening Primrose Oil. Natural Standard Monograph. 2013. www.naturalstandard.com. Accessed July 16, 2013.

- **Source Description**

Natural Standard is an electronic tertiary reference published by an impartial group not supported by any interest group, professional organization or product manufacturer. Content is updated regularly when ne clinically relevant data is available. And regular updates with renewed searches occur every 3-18 months. The last update was July 17, 2013. Search strategies include many databases such as AMED, CANCERLIT, EMBASE, Medline, etc. No restrictions are placed on language. Data analysis and extraction is conducted by healthcare professionals and is verified by a second reviewer. Their review process includes a blinded review of monographs by a multidisciplinary team. A three-member panel of the Editorial Board addresses conflicts and consults experts when applicable. All references are listed for each topic and include an extensive list of primary, secondary and tertiary resources through a systematic review of the literature.

- **Summary**

Evening primrose is used by many women around the world for the treatment of PMS. Despite its popularity there is a lack of evidence to support its efficacy. Most trials are generally limited by low power and methodological flaws but as a result there is no conclusive evidence to support a recommendation for evening primrose in the treatment of PMS symptoms.

- **Comments/Critical Appraisal**

The authors completed an extensive literature search to obtain all the available evidence for the use of evening primrose. Data was retrieved from a review of relevant RCTs, literature reviews and meta-analysis and likely all relevant data was assessed. The resource itself appears to be valid. The founders, editorial board and authors are made up of many multidisciplinary healthcare providers. Appropriate contact information is available on the website. The material is current and updated regularly with references provided. The site had no sponsors or advertisers to suggest any biased information. In conclusion, Natural Standards is a valid resource providing an overview of the available information and evidence on the effectiveness of evening primrose for the treatment of PMS. Due to the lack of quality evidence to support its use, evening primrose should not be recommended for the treatment of PMS.