Magnesium Extended Abstract

Primary literature: Article #1

Facchinetti F, Borella P, Sances et al. Oral Magnesium Successfully Relieves Premenstrual Mood Changes. *Obstet Gynecol.* 1991 Aug; 78(2):177-81. http://www-ncbi-nlm-nih-gov.proxy.lib.uwaterloo.ca/pubmed/2067759.

- **Study objectives**
  - To evaluate the effects of an oral Magnesium (M) preparation on premenstrual symptoms.
- **Methods**
  - Design:
    - Initial 2 months of the study: Double blind, randomized placebo controlled study
    - 2nd part of the study: Open label design
  - Allocation
    - After 2 months of baseline recording, 32 eligible women were randomly assigned to one of two intervention groups with 4 drop-outs.
    - First 2 months: Mg group (n=14), placebo group (n = 14) group
    - Subsequent 2 months: both groups received Mg
  - Blinding
    - Double blind (first 2 months). Open label for 2nd part of the study.
  - Follow-up period
    - 4 menstrual cycles total.
  - Setting
    - Information on study setting not provided other than the fact that it was in Italy.
  - Participants
    - 32 Women age 24-39 years old, with PMS confirmed with the Moos Menstrual Distress Questionnaire (lists of 47 symptoms rate on a severity scale of 1-6 with 1 being no experience of the symptom) according to the DSM III-R criteria. The main inclusion

criterion was history of *severe* PMS affecting social and work activity. The total premenstrual score was at least 30% above that of supposed asymptotic period.

- Exclusion criteria were:
  - Major psychiatric and behavioural disorders including anxiety and depression
  - Kidney or hepatic disease
  - Oral contraceptive use
- Out of the 32 initial participants, there were 4 drop outs (1 for pregnancy, 1 lost to follow up and 2 for side effects of headache and diarrhea

- Intervention:
  - Group 1 received Mg pyrrolidone carboxylic acid 360 mg in 3 divided doses
  - Group 2: placebo three times a day.
  - The tablets were taken from the 15th day of the menstrual cycle to the onset of menstrual flow for 2 menstrual cycles.
  - Oral magnesium was then supplemented in an open design for the next 2 months. Standardization not explained but patients received 360 mg of elemental magnesium daily.
  - Blood samples for Mg measurement were drawn before menses, at baseline and in the 2nd and 4th months of treatment.
  - The Menstrual Distress Questionnaire was administered at baseline, and second and fourth cycles of treatment.
  - Data was grouped into 2 periods: premenstrual period (from day -10 to -1 with respect to the next menstrual flow) and inter-menstrual period (from day +5 to +13)
- Outcomes
  - The primary outcome measure was the relief of peri-menstrual migraine.
  - Overall outcome measures were based on changes in Symptom Cluster and Total Menstrual Distress Questionnaire which looked at the effect of Magnesium on pain, inability to concentrate, behavioral changes, autonomic reactions, water retention, negative affect and arousal.
  - Comparison was made between patient's recorded data at baseline, 2 months and 4 months.
- Patient follow-up
  - 4 months.

- **Main results**

- The number of days with headache was only reduced in patients receiving magnesium ($p < 0.01$)
- The cluster "pain score" was significantly reduced in the second month in both groups ($P<0.05$)
- Treatment had a significant effect on both the total menstrual Distress Questionnaire score ($P = .04$) and the cluster "negative affect" ($P <.02$)
- By the end of the fourth month cycle of treatment, the Mg group had shown a further decrease in in the total Distress Questionnaire score ($P <.05$) and in the categories of "pain" ($P < .04$) and "water retention" ($P < .03$)

- **Conclusions**
  - The results of study indicate that Mg supplementation could represent an effective treatment of premenstrual symptoms related to pain, water retention and mood changes.
- **Comments/critical appraisal (including assessment of internal and external validity)**
  - Study design:
    - The main strength of the study is that it was it was a double blinded and randomized study, at least for the first 2 months.
    - Participants were largely similar at the beginning of the study (ie similar clinical and biochemical features, the PMS distress questionnaire scores for different clusters of symptoms at baseline did not differ significantly).
  - Limitations:
    - Intention to treat protocol was not used in this study as data from the 4 drop-outs were not included in final analysis.
    - This was a very small sample size ($n = 32$).
    - Adverse effects were not discussed (except for the 2 drop outs due to headache and diarrhea).
    - Setting of the study was not clear and this is an important omission as the setting may affect adherence, selection bias or other factors such as participants diet which may affect the outcome.
    - The primary inclusion criterion was for women with "severe" PMS symptoms; the results may not thus be generalized to women suffering from less than severe PMS.

Primary literature: Article #2

Walker AF, De Souza MC, Vickers MF et al. Magnesium supplementation alleviates premenstrual symptoms of fluid retention. *J womens Health*. 1998 Nov; 7(9):1157-65 PMID: 9861593 http://www.ncbi.nlm.nih.gov/pubmed/9861593

- **Study objectives**

  To investigate the effect of daily magnesium supplement on the severity of premenstrual symptoms.

- **Methods**
  - Design:
    - Randomized, double blind, placebo controlled, crossover study.
  - Allocation
    - Volunteers were randomly divided into a treatment or placebo group for 2 months
    - This was followed by a switch-over for two more cycles.
  - Blinding
    - Double blind (first 2 months). Open label for 2nd part of the study.
  - Follow-up period
    - 4 menstrual cycles
  - Setting
    - Conducted in a University community
  - Participants
    - 54 women volunteers (mean age: 18-25) were recruited from University of Reading faculty and student body based on a retrospective questionnaire data on 27 PMS symptoms. Women who had 30% or more difference in pre and postmenstrual scores on questionnaires were included in the study.
    - Exclusion criteria:
      - There were no restrictions placed on oral contraceptive use, medical conditions, or medication use.
    - 38 of 54 subjects completed the study and reasons for withdrawal were not provided.
  - Intervention:
    - A daily supplement of 200 mg of magnesium oxide or placebo was administered for 2 menstrual cycles.
    - At the start of the 3rd menstrual cycle, the daily supplement was crossed over for each subject such that those taking Mg were requested to take placebo, and vice versa and to continue to do so till the end of the 4th cycle.

- Volunteers kept a daily record of their symptoms in a 22-item item menstrual diary based on the Moos questionnaire using a 4-point scale (from 0: none;1:mild, 2: moderate; 3: severe – disabling, unable to function)

  - Outcomes
    - The main outcome measure was the reduction of premenstrual symptomsgrouped into sex categories:
      - PMS – A (anxiety),
      - PMS – C (craving),
      - PMS – D (depression),
      - PMS – H (hydration),
      - PMS – O (other), and
      - PMS – T (Total overall symptoms).
  - Patient follow-up
    - 4 months.
    - Out of the 32 initial participants, there were 4 drop outs (1 for pregnancy, 1 lost to follow up and 2 for side effects of headache and diarrhea)

- **Main results**
  - At 1 month: Analysis of variance for 38 women showed no effect of Mg supplementation compared with placebo in any category.
  - In the second month: there was greater reduction ($p = 0.009$) of PMS_H (weight gain, swelling of extremities, breast tenderness, abdominal bloating) with Mg supplementation compared with placebo.
  - In the 2^{nd} cycle of intervention: Mg was found to reduce mild premenstrual symptoms of fluid retention.
  - Compliance to Mg supplements was confirmed by the greater than estimated 24-hr urine output of Mg ($p =0.013$). It was 108mg output in Mg group vs. 74.1 mg in the placebo group.
- **Conclusions**
  - Magnesium oxide is superior to placebo in the treatment of mild premenstrual symptoms.
- **Comments/critical appraisal (including assessment of internal and external validity)**
  - Study design:
    - It was a randomized double blind control trial.

- Unlike with the above mentioned studies, this study made an attempt to ensure treatment adherence by measuring Mg urine output during supplementation.

  - Limitations:
    - The majority of subjects (72%) were college students who suffered only mild premenstrual symptoms that were not severe enough to be classified as PMS.
    - Furthermore, this age group (18-25 years old) the incidence of PMS tends to be lower than in the older age group; making this the study results not generalizable to the general population of PMS sufferers.
    - Reasons for study withdrawals were not explored and neither were characteristics between the groups discussed. The fact that medication or medical history was not accounted for may indeed have affected the study results.
    - The inclusion of women on oral contraceptives may have also affected the results due to their potential effect on PMS
    - This was also a small study with only 38 (out of 54) participant data obtained and a lower dose of Mg (compared to previous studies) was used.

Primary literature: Article #3

Fathizadeh N, Ebrahimi E, Valiani M et al. Evaluating the effect of magnesium and magnesium plus vitamin B6 supplement on the severity of premenstrual syndrome. Iran J Nurs Midwifery Res. 2010 December; 15(Suppl1): 401-5. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3208934/

- **Study objectives**
  - To determine the effect of magnesium (Mg), combination of vitamin B6 and Mg, and placebo on the severity of PMS.
- **Methods**
  - Design:
    - Double blind, randomized placebo controlled study
  - Allocation
    - Subjects were assigned to one of two intervention groups and one control group, each consisting of 50 participants.

- Mg group, Mg plus vitamin B6 group, and placebo group

- Blinding
  - Double blind
- Follow-up period
  - The entire study spanned over 4 months but the actual treatment intervention was carried out in 2 menstrual cycles.
- Setting
  - Ten selected health centers associated with Isfahan University Medical Centres
- Participants
  - Women age 15-45 years old, referred to the selected health centers and who, after completing a PMS daily symptom record for 2 months, were diagnosed with PMS according to the criteria of American Psychiatry Association. Out of the 150 initial study participants, 116 of them completed the study.
  - Additional inclusion criteria included:
    - Having a regular menstrual cycle
    - No history of depression or anxiety
    - No acute or chronic disease
    - No concurrent medication or supplements
    - Not partaking in regular exercise
  - Exclusion criteria were:
    - Pregnancy
    - Possibility of concurrent hormonal treatment, including contraceptive products
    - Not taking the drug/placebo or filling out the symptom questionnaires regularly
    - Discontinuation of (study) treatment
- Intervention:
  - Group 1 received Mg 250 mg po OD
  - Group 2: Mg (250 mg po OD) plus Vit B6 (40 mg po OD). Vit tab looked like a Mg tab
  - Group 3: placebo OD. Placebo tablet looked like Mg and Vit B6 tablets
  - The tablets were to be taken from the first day of menstrual cycle to the start of the following cycle.

- Participants were asked to record their daily symptoms during treatment period

- Outcomes
  - The main outcome of the study was reduction in the mean score of PMS symptoms
  - The severity of symptoms was determined using daily symptom record form and symptom rating.
  - They were rated as follow: zero (no symptom), 1 (mild – does not interfere with daily activities), 2 (moderate) and 3 (severe – prevents daily activities)
  - Outcome was determine by comparing the Mean PMS scores from before and after intervention
- Patient follow-up
  - 2 months. Results of the study were also evaluated 2 months after the end of the intervention

- **Main results**
  - The findings showed that while the mean score of the 3 groups were not statistically significant before treatment ($p>0.76$), they were significantly different by the end of the treatment ($p<0.001$).
  - After intervention, the mean score was reduced in all groups but the combination of Mg plus Vit B6 was more effective than Mg alone and placebo in lowering the mean score of PMS symptoms ($p<0.05$)
  - The mean score reduction from baseline to post-intervention were
    - Mg + Vit B6 group: went from 37.8 to 15.63 (reduction of 22.17 $p <0.001$)
    - Mg group: went from 36.89 to 22.22 (reduction of 14.67, $p<0.001$)
    - Placebo group: went from 35.8 to 28.41 (reduction 7.39, $p<0.001$)
  - When the 30 symptoms were analyzed in 5 sub-groups of craving, depression, hydration anxiety and somatic. The ones with statistically significant mean reduction were depression, hydration and anxiety ($p <0.001$)
- **Conclusions**
  - The results of the study indicated that the combination of Mg and vitamin B6 was more effective than Mg alone and placebo on decreasing PMS symptoms.
  - By the same token, the study did show that Mg alone is more effective than placebo in the reduction of PMS symptoms.
- **Comments/critical appraisal (including assessment of internal and external validity)**
  - Study design:

- The main strength of the study is that it was it was double blinded and randomized. In order to eliminate potentially confounding factors, participants in the 3 groups were also matched with respect to their educational level, contraception method, job, body weight, height menstrual cycle and age of menarche.

- Limitations:
  - One of the study weaknesses is that intention to treat protocol was not utilized. It is not clear how data from the 34 (out of the original 150) participants who did not complete the study was handled.
  - The sample size of 50 subjects per group is relatively small and confidence intervals were not provided along with their tabulated results.
  - The study did not specify which Mg salt was used and neither did it discuss the adverse effects reported.
  - The fact that this study excluded women using hormonal contraceptives means that the study findings may not be generalized to the high number of women in North American who use such contraceptive measures.
  - It was not clear whether or not the study actually took place in the specified centres or if the health centres are where only the recruitment took place. If this was an out-patient study, it would be difficult to confirm treatment adherence.
  - The follow up period of 2 months post-intervention was considered reasonable given that the effect of Mg on PMS symptoms is expected after at least 2 months. A longer study and follow up duration would have however been ideal.

    Results point to higher efficacy of magnesium 250 mg daily as well as that of the combination of magnesium and vit B6 compared to placebo, however given weaknesses of the study and some unanswered questions, I would recommend further research.

Secondary literature: Article #4 (systematic review)

Whelan AM, Jurgens TM, Naylor H. Herbs, Vitamins and Minerals and the Treatment of Premenstrual Syndrome: a Systematic Review. *Can J clin Pharmacol.* 2009 Fall; 16(3):e407-29. http://www.ncbi.nlm.nih.gov/pubmed/19923637

- **Study objectives**

  To identify herbs, vitamins and minerals advocated for the treatment of PMS and/or PMDD and to systematically review evidence from randomized controlled trials (RCTs) to determine their efficacy in reducing severity of premenstrual symptoms.

- **Scope (ex. patients, interventions, outcomes, duration, etc…)**

- Subjects with symptoms of PMS and/or PMDD were one of the inclusion criteria for studies to include in the systematic review.
- Additional inclusion criteria included therapies containing only one herb, vitamin or mineral (no combination products), and outcome measure of change in severity of PMS/PMDD symptoms.
- Outcome measures were excluded if they solely based on patient satisfactory surveys.
- The number of patients ranged from 19 to 617
- The duration of the trials ranges from 1 to 12 months.

- **Methods (how studies were identified, # and type of trials included, and any other relevant information regarding the methods)**
  - Literature searches were conducted from database inception to April 2008 in Clinical Evidence, the Cochrane Library, Mayoclinic, Medscape, Medline Plus, Natural Medicines Comprehensive Database and the internet, using Google search engine.
  - Key search terms included "premenstrual syndrome," "PMS," "premenstrual dysphonic disorder", "PMDD", "natural health products", "herb", "vitamin", "mineral", "dietary supplement" and "alternative medicine." The search was limited to English and French language references.
  - When an herb, vitamin or mineral was indexed under more than one name, each name was included in the search. (ie "Chasteberry" also searched as "Chaste Tree")
  - Searches were limited to randomized controlled trials
  - Two investigators conducted screening and relevance assessments, with discrepancies resolved by a third investigator.
  - A search of the literature identified 29 RCTs meeting inclusion criteria for the following 10 herbs, vitamins and minerals: chasteberry, evening primrose oil, ginkgo, saffron, St. John's Wort, soy, vitamin B6, vitamin E, calcium and magnesium
- **Main results**
  - Approximately 62% of the 29 RCTs provided sufficient detail to allow selection of a product comparable to the natural product used in the study; however, only 40% of RCTs included in the review were considered to be of sufficient overall quality to warrant applying the results to practice.
  - Results from the RCTs support the use of calcium as a treatment for PMS.
  - Data suggests that vitamin B6 and chasteberry are possibly effective.
  - For the remainder of: gingko, magnesium (pyrrolidone and carboxylic acid), saffron, St John's Wort, soy and vitamin E have preliminary data suggesting benefits but more study is needed to confirm their place in therapy.

- Results from the appraised studies failed to detect symptom improvement with evening primrose oil or magnesium oil.

- **Conclusions**

From the 10 products included in the systematic review, only calcium had good quality evidence to support its use in PMS. Further research is needed, using RCTs of adequate length, sufficient sample size, well-characterized products and measuring the effect on severity of individual PMS symptoms.

- **Comments/critical appraisal**
  - Strengths:
    - This review searched a number of reputable databases using the right search terms
    - A great variety of natural products were evaluated.
    - Only RCTs were selected for use in the review and data was reviewed by 3 people
  - Weaknesses:
    - The majority of the trials were of poor quality
    - There was considerable heterogeneity not only between study designs of different products but even with the same precuts.
    - Different methods to diagnose PMS were used as well as different instruments (scales) to measure study outcomes.
    - Only 4 of the 29 studies included in the review used predetermined definitions of clinical response.
    - Different strengths or salts of various minerals were used in different studies

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Tertiary literature: Reference # 5 (Internet Database)

Natural Medicines Comprehensive Database (NMCD). Magnesium Monograph. www.naturaldatabase.com. Last updated on July/03/2013. Accessed July/17/2013

- **Source description**

NMCD is a reliable and reputable source of evidence-based information on natural health products. NMCD provides information on product use, efficacy, safety, interactions as well as supporting evidence (references) for the claims. There is a textbook as well as an online version. Effectiveness ratings range from |"Effective, likely effective, possibly effective, possibly ineffective, likely ineffective, ineffective".

- **Summary**

  According to NMCD: Magnesium (all the available salts listed under magnesium) is rated:

"**Possibly Effective" for PMS**: "Taking magnesium orally seems to relieve symptoms of PMS. There is some evidence that magnesium supplementation can improve symptoms including mood changes and fluid retention in some patients with PMS. Taking magnesium orally also seems to prevent premenstrual migraine"

- **Comments/Critical appraisal**
  - NMCD supports its claim about the use of magnesium on PMSs with the use of various RCTs and systematic reviews, some of which were appraised above.
  - It does not claim that it will work for certain but rather that it may "possibly" be effective as the evidence suggests.
  - Although further below the website states which magnesium salts have been studies in the context of PMS, it would be better to include it along with the effectiveness information so that it is easier to know which product to purchase, for those wishing to give it a try.