VITAMIN B6 EXTENDED ABSTRACT

Primary literature: Article #1

Kashanian M, Mazinani R, Jalalmanesh S. Pyridoxine (vitamin B6) therapy for premenstrual syndrome. Int J Gynaecol Obstet. 2007 Jan;96(1):43-44. PMID: 17187801

- **Study Objectives**
  - To determine the efficacy of pyridoxine in the treatment of premenstrual syndrome.
- **Methods**
  - Design:
    - Double-blind, randomized, placebo-controlled trial
  - Allocation:
    - Women were randomly allocated to receive pyridoxine (N=46) or placebo (N=48)
  - Blinding:
    - Double-blind
  - Follow-up period:
    - 3 menstrual cycles
  - Setting:
    - Iran
  - Participants:
    - 160 female university students who were from the same dormitory
    - Only 94 women who complied with the trial's protocol were analyzed
    - Diagnosed with PMS with at least 1 behavioural and 1 somatic symptom (listed in the American Psychiatric Association (APA) questionnaire which included 17 symptoms – 11 behavioural and 6 somatic)
    - Spent 3 menstrual cycles recording their symptoms prior to receiving treatment
    - No statistically significant differences between the treatment and placebo groups with regards to the number of symptoms and severity of PMS

        - Most prevalent symptoms in both groups were irritability (87%) and depression (87.5%)
    - Intervention:
        - Daily tablet of either 80 mg pyridoxine or placebo, starting on the first day of the fourth cycle through the next 2 cycles
        - Pyridoxine and placebo tablets were manufactured by the same factory and had the same colour, shape, and taste.
        - Recorded PMS symptoms (from APA questionnaire) during the treatment period
    - Outcomes:
        - Reduction in the symptoms of PMS listed in the APA questionnaire
    - Patient follow-up
        - Patients recorded their symptoms for 3 menstrual cycles after the initiation of treatment and were followed up with thereafter
- **Main Results**
    - In the pyridoxine treated group, there was a significant decrease in moodiness, irritability, anxiety, depression, forgetfulness, unreasonable crying, dizziness, fatigability, candy craving, increased appetite, palpitations, breast tenderness, bloating, and edema. Of these symptoms, symptoms of anxiety had the greatest reduction (mean ± SD reduction, −0.22 ± 0.35).
    - In the placebo group, there was a significant decrease in moodiness, anxiety, depression, unreasonable crying, fatigability, increased appetite, palpitations, and bloating. Of these symptoms, anxiety showed the greatest reduction (-0.15 ± 0.35).
    - The severity of psychiatric symptoms significantly decreased in both pyridoxine and placebo groups (paired t-test, $P<0.05$), but the reduction was significantly greater in the pyridoxine group (−1.26±1.91 with pyridoxine vs. −0.60 ± 1.78 with placebo).
    - The severity of somatic symptoms significantly decreased in both pyridoxine and placebo groups (−0.54 ± 0.63 pyridoxine vs. −0.33 ± 0.70 placebo, paired t-test, $P<0.05$), but there was no significant difference between groups.

- There was a significant reduction in total PMS severity in both pyridoxine and placebo groups (−1.80 ± 2.36 pyridoxine vs. −0.93 ± 2.33 placebo, paired t-test, $P<0.05$), but there was a significantly greater reduction in the pyridoxine group ($P<0.05$).

- **Conclusions**
  - Pyridoxine can be suggested as a treatment for the psychiatric symptoms of PMS.
- **Comments/Critical Appraisal**

The most positive aspect of the study is that it is a double-blind, randomized, placebo-controlled trial. Furthermore, patients had to meet the inclusion criteria of 1 behavioural and 1 somatic symptom of PMS and spent three months recording their symptoms prior to receiving treatment. The trial states that there are no significant differences between groups, but the baseline characteristics of both groups were not specifically outlined, which is poor. Other limitations of the study include a small sample size and no description of the randomization process. The APA questionnaire was subjective and the results of the questionnaires including the incidence of specific behavioural and somatic symptoms was not recorded in the paper both prior to and after treatment. What was given to the reader was only an overall incidence of behavioural and somatic symptoms, which is too generalized.

With regards to external validity, it is difficult to apply this study to Canadian patients as the study took place in Iran, was a small sample size, and included only university women. The generalized results don't suggest which specific symptoms of PMS pyridoxine can be recommended to treat. Furthermore, the study cannot be applied to older and younger women.

Primary literature: Article #2

Diegoliu MS, da Fonseca AM, Diegoli CA, Pinotti JA. A double-blind trial of four medications to treat severe premenstrual syndrome. Int J Gynaecol Obstet. 1998 July;62(1):63-7. PMID: 9722128

- **Study Objectives**

- To determine the efficacy of fluoxetine, alprazolam, propanolol, and pyridoxine in the treatment of severe premenstrual syndrome.

- **Methods**
  - Design:
    - Double-blind, randomized, placebo-controlled trial
  - Allocation:
    - Women were randomly allocated to receive fluoxetine (N=30), alprazolam (N=30), propanolol (N=30), or pyridoxine (N=30) for 3 months plus placebo for 3 months.
  - Blinding:
    - Double-blind
  - Follow-up period:
    - 6 months
  - Setting:
    - Sao Paulo University Medical Center, Brazil
  - Participants:
    - 120 patients meeting inclusion criteria randomized into 4 groups of 30
    - Initially answered a questionnaire, ranking the intensity of various PMS symptoms from 0 to 3
    - Patients scoring above 20 points were included in the trial
  - Intervention:
    - Group 1: pyridoxine 300 mg daily from the 15^{th} day of menstrual cycle until the last day of menstruation
    - Group 2: alprazolam 0.25 mg TID from the 15^{th} day of menstrual cycle until the last day of menstruation
    - Group 3: fluoxetine 10 mg daily
    - Group 4: propanolol 20 mg daily (40 mg during the menstrual period)
    - Each group received 3 months of placebo and 3 months of the active drug
  - Outcomes:
    - Decreased intensity of PMS symptoms as measured by the questionnaire used for initial screening
  - Patient follow-up

        - 3 months after treatment with placebo and again in 3 months after treatment with an active drug
- **Main Results:**
    - Pyridoxine treated patients were not statistically different than the placebo
        - In the pyridoxine treated group, pyridoxine caused a 45.3% mean reduction of symptoms while placebo caused a 46% mean reduction of symptoms
        - Pyridoxine primarily reduced tachycardia (55.5%), insomnia (60.5%), acne (61.1%), and nausea (72.2%)
    - Alprazolam, fluoxetine, and propanolol treated groups were statistically different than placebo
        - Alprazolam caused a 55.6% mean reduction of symptoms, fluoxetine caused a 65.4% mean reduction of symptoms, and propanolol caused a 58.7% mean reduction of symptoms
    - Covariation analysis found a statistically significant difference between pyridoxine and the other groups (P=0.025)
    - Of the patients treated with pyridoxine, 43.3% preferred pyridoxine while 56.7% preferred placebo
        - the active drug was preferred over placebo for all other treatment groups
    - Only 36.7% of patients treated with pyridoxine had remission rates equal to or above 50%
        - 63.4% of patients receiving alprazolam, 90% receiving fluoxetine, and 73.4% receiving propanolol had remission rates equal to or above 50%

- **Conclusions**
    - Pyridoxine does not decrease severe PMS symptoms more than placebo
    - Based on the results of the study, 10 mg of fluoxetine daily may be considered as a first line option in the treatment of severe PMS

- **Comments/ Critical Appraisal:**

The positive attributes of this study include double blinding, randomization, and use of placebo by every patient enrolled. It is also great that other treatments were studied as it helps determine how pyridoxine compares to other therapeutic options. Poor aspects of the trial include a small sample size (30 patients per treatment) and inadequate reporting of patient attributes and symptom reduction with placebo use. It is unknown if the patients in each group were similar and if randomization was properly done to distribute confounders equally among groups. The study poorly reported placebo results

as it included the average reduction of symptoms using data from all treatment groups rather than showing results of placebo use by each of the four groups on their own. For this reason, it is very difficult to compare the efficacy of specific symptom relief for each treatment group.

With respect to external validity, this study cannot be usefully applied to patients in Canada. Because the study was conducted in Brazil, cultural differences affect the application of results to Canadians. Furthermore, the dose of pyridoxine used in the study (300 mg daily) is above the recommended maximum dose of 100 mg daily. The study also used a dosage regimen that is not commonly used; Patients in the study were given pyridoxine from the 15th day of their menstrual cycle through to the last day of menstruation. In Canadian patients, vitamin B6 would generally be recommended continuously once daily, particularly for convenience and ease of use, so this is another reason why the external validity is poor

---

Secondary literature: article #3 (systematic review)

Whelan AM, Jurgens TM, Naylor H. Herbs, vitamins and minerals in the treatment of premenstrual syndrome: a systematic review. Can J Clin Pharmacol. 2009 Fall;16(3):e407-29. Epub 2009 Oct 29. PMID: 19923637

- **Study Objectives**
  - To identify vitamins, minerals, and herbs recommended for the treatment of premenstrual syndrome and to systematically review evidence from randomized controlled trials to establish their effectiveness in lowering the severity of PMS symptoms.
- **Scope**
  - 13 studies that met the inclusion criteria for the review were included
  - All studies were randomized controlled trials, 12/13 were double-blind and placebo-controlled, and 7/13 were crossover studies
  - The number of participants included ranged from 1 to 434 women

- The duration of the studies ranged from 3 to 12 months
- The amount of vitamin B6 given varied and ranged from 50mg/day to 500mg/day
- Outcomes were a decrease in the amount or severity of PMS symptoms

Study/Design	**Participants**	**Duration**	**Intervention(s)**	**Outcome(s)**	**Benefit Shown**
Stokes J, et al. Double-blind (DB), placebo-controlled (PC)	13 women with premenstrual tension-depression	8-12 months	Vitamin B6 (or placebo) 50mg/day for 18 days during the premenstrual and beginning of the menstrual phase	Moos menstrual distress questionnaire	No
Abraham GE, et al. DB, PC, crossover	25 women diagnosed with PMS symptoms	6 months	Vitamin B6 (or placebo) 500mg/day ER for 3 months	Abraham's MSQ	Yes
Mattes J, et al. DB, PC, crossover	1 woman with premenstrual depression	8 months	Vitamin B6 (or placebo) 50mg/day 10 days before expected menses	Self-reported change in premenstrual depression	Yes
Barr W, et al. DB, PC, crossover	48 women with PMS symptoms	4 months	Vitamin B6 (or placebo) 100 mg/day from day 10 of one cycle to day 3 of the next for 2 months	Effect on 9 symptoms (depression, irritability, tiredness, swollen breasts, swollen abdomen, swollen fingers/ankles, headache, stomach ache)	Yes
Williams MJ, et al. DB, PC	434 women diagnosed with PMS	3 months	Vitamin B6 100mg/day initially (could decrease to 50mg/day or increase to	Investigator rated change in patient's symptoms	Mixed

			200mg/day) or placebo		
Hagen I, et al. DB, PC, crossover	34 women with PMS symptoms	4 months	Vitamin B6 (or placebo) 100mg/day for 2 months	VAS used to rate severity of global symptoms	No
Smallwood J, et al. DB, PC, crossover	42 women with severe mastalgia during the premenstrual half of cycle	4 months	Vitamin B6 100mg BID for 2 months, then placebo for 2 months (or vice-versa)	Assessed monthly by clinician; Subjective responses measured by linear analogue scale, daily breast pain and tenderness chart and acetaminophen tablet requirements	No
Kendall KE, et al. DB, PC	55 women with PMS symptoms	3 months	Vitamin B6 (or placebo) 150mg/day for 2 months	Moos menstrual distress questionnaire	Yes
Doll H, et al. DB, PC, crossover	37 women with PMS symptoms	7 months	Vitamin B6 (or placebo) 50mg/day for 3 months	Daily severity rating of 3 groups of PMS symptoms: emotional, somatic and menstrual	Yes
Lauritzen CH, et al. DB	127 women with premenstrual tension syndrome	3 months	Placebo on days 1-15; Vitamin B6 200mg/day on days 16-35 of the menstrual cycle for 3 months; Other group: chasteberry	PMTS scale and CGI scale	Yes
Diegoli MSC, et al. DB, PC	120 women diagnosed with PMS	8 months	Vitamin B6 300mg/day from day 15 of last day of menstruation for 3 months; Other groups: alprazolam, fluoxetine, propranolol	Intensity of PMS symptoms (Abraham's MSQ)	No

De Souza MC, et al. DB, PC, crossover	37 women with symptoms of PMS	5 months	Vitamin B6 50mg/day for 1 cycle; Other groups: magnesium, magnesium+B6, placebo	Daily rating of severity of 30 PMS symptoms	No
Kashanian M, et al. DB, PC	94 women diagnosed with PMS symptoms	5 months	Vitamin B6 80mg/day or placebo	Daily recording of 17 symptoms listed in the American Psychiatric Association questionnaire	Yes

- **Methods**
  - Literature was searched to identify randomized controlled trials that advocated for the use of vitamins, minerals, or herbs in the treatment of PMS
  - The search included: Clinical Evidence, the Cochrane Library, Embase, IBID, IPA, Mayoclinic, Medscape, MEDLINE Plus, Natural Medicines Comprehensive Database and the Internet using Google as a search engine
  - Search included literature from the inception of the database up to and including April 2008
  - Literature was limited to those published in English or French
  - Inclusion criteria:
    - RCT
    - English or French
    - Subjects with symptoms of PMS and/or PMDD
    - Therapies containing only one herb, vitamin, or mineral (no combination products)
    - Outcome measure of change in severity of PMS/PMDD symptoms
  - Exclusion criteria:
    - Patient satisfaction survey as sole outcome measure
    - Not compared to placebo or recognized therapy
  - 13 studies on Vitamin B6 met the inclusion criteria and were included in the review

- **Main Results**
  - 5/13 studies reported no benefit for the use of Vitamin B6 in the reduction of PMS symptoms
  - 1 study reported an overall improvement in the patient's condition as assessed by the investigator, but there was no self-reported improvement. This study also allowed the use of analgesics, which could have influenced the outcome.
  - 7/13 studies reported some benefit with Vitamin B6
    - One study had only one participant making it impossible to extrapolate the evidence to a large population
    - 3 trials used doses less than or equal to 100mg, 2 trials used a dose between 100 and 200mg, and 1 trial used a dose of 500mg
      - No association between dose and response
    - 4 trials reported improvement in symptoms associated with mood
    - 2 trials reported an overall improvement in symptoms
    - 3 trials did not report adverse events. It is not known whether this is because the participants did not report any or if they were not monitored in the study.
    - 2 trials report that no women experienced any adverse events
    - 1 trial reported adverse events experienced by 4 of the 66 patients: feeling of lump in the throat (N=1), abdominal discomfort (N=1), reoccurrence of ulcerative colitis (N=1), and persistent bleeding (N=1).
    - Upon critical appraisal of the studies, benefit was shown in one good quality study (Lauritzen et al.) and 3 studies of average quality (Abraham et al., Kendall et al., and Doll et al.)
    - Studies by Barr et al. and Kashanian et al. showed benefit for Vitamin B6, but were shown to be of poor quality upon critical appraisal.

- **Conclusions**
  - Vitamin B6 is possibly effective in the reduction of PMS symptoms, particularly those related to mood. The results of the review are inconclusive as the findings are limited by the poor quality of the studies included. Limited evidence proposes that vitamin B6 may improve mood symptoms at a dose of 100mg/day for 3 months. While higher doses have shown benefit, they are not recommended as doses greater than 200mg/day may cause toxicity.

- **Comments/Critical Appraisal**

  This was an excellent systematic review as it was very thorough and provided detailed descriptions of their search methods and critical appraisal process. There was an exhaustive list of inclusion and exclusion criteria used in the analysis of studies related to the use of vitamin B6 in PMS. All studies that were analyzed were randomized controlled trials and most were double-blind and placebo-controlled, positively impacting the review's internal validity. Furthermore, 13 studies on vitamin B6 were included in the review and this large amount also increases the review's internal validity. All of the studies showing benefit were critically appraised to determine their quality. Out of 13 studies, benefit was shown in one good quality study and 3 average quality studies. This information is very useful when explaining the available evidence to patients. A limitation of the review is that there was little detail as to why the studies were of good or poor quality. Furthermore, there was no indication of the quality of evidence in the studies that did not show benefit. The review provided a great deal of information on the adverse effects experienced in all trials which is extremely useful in the application of the results to patients in practice.

Tertiary literature: Reference # 4 (Micromedex Database)

Premenstrual syndrome. In: DISEASEDEX™ - General Medicine [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated June 20, 2013.

- **Source Description:**
  - Micromedex is a clinical database that provides comprehensive, evidence-based, unbiased, and referenced information about drugs, alternative medicine, toxicology, diseases, and patient education
  - Provides healthcare practitioners with the information they need to make informed diagnosis and treatment decisions based on current clinical evidence
  - The resource provides a wide-range of information on premenstrual syndrome including: background, history and physical, diagnosis, treatment, prognosis, disposition, related information, and references
  - The page on premenstrual syndrome was last updated on June 20, 2013
- **Summary:**

- Vitamin B6 may benefit some patients with PMS, beyond a placebo effect
- Data from 9 clinical trials propose that vitamin B6 reduces PMS symptoms and alleviates depression, but the trials are of poor quality and are inadequate to make strong conclusions
- Doses of 100mg/day are safe and should not be exceeded as large doses may cause peripheral neuropathy

- **Comments/Critical Appraisal:**

Micromedex is a great database to search clinical information because it is entirely evidence-based, unbiased, and provides references. The information provided can be trusted to be accurate and supported with evidence. While the last update was on June 20, 2013, the information on vitamin B6 is outdated from 1999 and 2000. The information provided agrees with more current studies (as discussed in the systematic review by Whelan et al. above), but Micromedex should update its references to increase its validity. Because the evidence provided by Micromedex on vitamin B6 is from systematic reviews that analyzed randomized controlled trials, it can be concluded that they have provided the best possible evidence (although outdated) for the clinical information on vitamin B6 as it relates to PMS.

Tertiary literature: Reference # 5 (Textbook)

Mulherin K, Brown T. Premenstrual syndrome. In: Repchinsky C, ed. *Patient self-care*. 2nd ed. Ottawa, ON: Canadian Pharmacists Association; 2010:782-791.

- **Source Description**
  - Patient Self-Care is a book published by the Canadian Pharmacists Association to provide healthcare practitioners with evidence-based information in order to make educated recommendations for the treatment of minor ailments.
  - Each chapter presents a different therapeutic topic and includes the pathophysiology, patient assessment, goals of therapy, nonpharmacologic therapy, pharmacologic therapy, monitoring of therapy, and patient information.
  - All information is referenced and based on the best available evidence.
  - The book is written by 56 expert authors and reviewed by 40 experts to ensure the information is unbiased and accurate.

- **Summary**
  - Pyridoxine is used in the treatment of PMS because it is a cofactor in the synthesis of dopamine and the metabolism of tryptophan. It also acts to increase the inhibitory to excitatory amine ratio, which may reduce symptoms of PMS as many are attributed to an excitatory state of the central nervous system.
  - Some evidence supports the use of vitamin B6 in the treatment of PMS
    - It is likely beneficial in the treatment of premenstrual symptoms and premenstrual depression
  - Vitamin B6 can be recommended in doses of 50-100 mg/day. Doses above 200 mg/day are associated with peripheral neuropathy and are not to be recommended.

- **Comments/Critical Appraisal**

Patient Self-Care is a great resource for pharmacists because it provides evidence-based information that is clear, organized, and concise, making it simple to provide patients with correct recommendations in a timely manner. However, because the chapters cover so much information and really just provide the bottom-line, the readers do not know the quality of the studies used as evidence, unless they look them up. With regards to pyridoxine use in premenstrual syndrome, the evidence provided was from a meta-analysis and a systematic review analyzing randomized controlled trials, which is a good source of evidence-based information. The book was published in 2010 and the references used on vitamin B6 are from 1999-2007, so the evidence provided may no longer be up-to-date. Furthermore, the authors of the chapter are pharmacists and some of the information provided may be expert opinion although references are provided for all evidence related to pyridoxine.