

A Synergistic Effect of a Daily Supplement for 1 Month of 200 mg Magnesium plus 50 mg Vitamin B₆ for the Relief of Anxiety-Related Premenstrual Symptoms: A Randomized, Double-Blind, Crossover Study

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ABSTRACT

To investigate single and combined effects of daily dietary supplementation with 50 mg of vitamin B₆ and 200 mg magnesium (as MgO) for one cycle for the relief of mild premenstrual symptoms, a randomized, double-blind, placebo-controlled, crossover design was used. Forty-four women with an average age of 32 years took part in the study. Each woman was randomly assigned, according to a Latin square design, to take consecutively all four of the following treatments daily for one menstrual cycle: (1) 200 mg Mg, (2) 50 mg vitamin B₆, (3) 200 mg Mg + 50 mg vitamin B₆ and (4) placebo. Throughout the study, each volunteer kept a daily record of symptoms using a 5-point ordinal scale in a menstrual diary of 30 symptoms. Symptoms were grouped into six categories: anxiety, craving, depression, hydration, other, and total. Urinary magnesium output for 24 hours was estimated using the Mg/creatinine concentration ratio. ANOVA showed no overall difference between individual treatments, but predefined treatment comparisons using factorial contrasts in ANOVA showed a significant effect of 200 mg/day Mg + 50 mg/day vitamin B₆ on reducing anxiety-related premenstrual symptoms (nervous tension, mood swings, irritability, or anxiety) ($p = 0.040$). Urinary Mg output was not affected by treatment. A small synergistic effect of a daily dietary supplementation with a combination of Mg + vitamin B₆ in the reduction of mild premenstrual anxiety-related symptoms was demonstrated during treatment of 44 women for one menstrual cycle. In view of the modest effect found, further studies are needed before making general recommendations for the treatment of premenstrual symptoms. The study indicated that absorption from MgO was poor and daily supplementation for longer than 1 month is necessary for tissue repletion.

INTRODUCTION

ADVERSE SYMPTOMS, INCLUDING CHANGES in mood, behavior, fluid retention, and certain

aspects of mental or physical functioning, are common among women in the luteal phase of the menstrual cycle. Various reports, many of a preliminary nature, or based on clinical experience,

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suggest that these symptoms are related to diet, in particular to high intakes of sugar or to deficiency of certain vitamins and minerals or to both.

Several studies have been reported since the 1970s on the effect of high-dose vitamin B₆ supplementation on the relief of premenstrual symptoms, but most of these were open trials without placebo. Three double-blind, placebo-controlled, crossover studies, carried out on a total of 166 women,¹⁻³ reported significant reduction in symptoms with daily doses of vitamin B₆ ranging from 50 to 150 mg/day. Despite some methodological shortcomings, these studies have done much to influence clinicians to use high-dose vitamin B₆ as first-line treatment for premenstrual syndrome (PMS). However, the possibility of pharmaceutical doses of vitamin B₆ causing reversible peripheral neuropathy has led the U.K. government into a controversial debate about possible withdrawal of over-the-counter sales of this vitamin in daily doses greater than 9 mg.⁴

Abraham⁵ was the first to propose magnesium (Mg) deficiency as an etiological factor in the development of premenstrual symptoms because of the potential of the sedative properties of Mg to counter neuromuscular excitability. Several articles have been published to support this view, including a double blind, placebo-controlled study,⁶ which showed a significant reduction in premenstrual low mood after administration of a supplement of 360 mg Mg/day in the luteal phase of the cycle for 4 months. However, we were unable to confirm an effect of a supplement of 200 mg Mg/day for 2 months on premenstrual mood symptoms in a double-blind, placebo-controlled study of 38 women,⁷ although we were able to show a marked reduction in the premenstrual symptom of hydration (fluid retention) during the second month of supplementation.

An adequate intake of vitamin B₆ is required for maintenance of normal intracellular Mg concentration, as the vitamin plays an important role in Mg transport across the cell membrane.⁸ Hence, a synergistic effect between low Mg and low vitamin B₆ status has been postulated in the etiology of premenstrual symptoms.^{5,9,10} As there are no reports of this hypothesis having been tested, the study presented here was designed to investigate possible synergy of a combined daily dietary supplement of Mg and vitamin B₆ for relief of mild premenstrual symptoms, rather than the more severe symptoms classified as PMS.

Scrutiny of the literature, including a critical appraisal of the uncontrolled, retrospective study of Dalton and Dalton¹¹ on which the proposed withdrawal of high-dose vitamin B₆ sales in the U.K. was heavily dependent, led us to the conclusion that 50 mg/day would be a safe dose, without side effects. The dose of Mg (200 mg as MgO) was chosen to match that which had already shown relief of premenstrual symptoms in our previous study.⁷

MATERIALS AND METHODS

Subjects

Volunteers suffering adverse premenstrual symptoms but otherwise in good health were recruited through a feature article in a local weekly newspaper. Their participation in the study required agreement from the volunteer's general medical practitioner. Each woman underwent two screening stages to assess her suitability as a participant in the study. The first stage assessed her response to a menstrual health questionnaire (MHQ) modified from Warner and Bancroft.¹² This instrument was intended to investigate a woman's experience of her last premenstrual phase and was applied irrespective of the stage of her current cycle. Only those women whose premenstrual total symptoms scores in the MHQ were at least 30% higher than their postmenstrual total symptoms scores were entered into the second screening. The second stage assessed the symptoms scores recorded in the baseline (without treatment) menstrual diary. Exclusion criteria included those already taking any dietary vitamin and mineral supplements and those taking regularly prescribed medication, apart from oral contraceptives.

Experimental design

The protocol for the study was scrutinized and allowed by the University of Reading Ethics and Research Committee. The duration of the study was five menstrual cycles, and baseline data were collected in the first cycle. For the following four cycles, volunteers were randomized according to a Latin square design to take a daily supplement of either 200 mg Mg (as MgO heavy precipitate), 50 mg vitamin B₆, 200 mg Mg + 50 mg vitamin B₆, or placebo for one menstrual cycle, com-

mencing on the first day of the second cycle. Each woman changed to a different supplement according to this design on day 1 of her next cycle, and so on, until all possible combinations had been administered. These supplements were supplied by Boots the Chemists (City Gate, Nottingham, U.K.).

Throughout all five menstrual cycles of the study, the following information was recorded from each volunteer. Daily symptoms using a 30-item menstrual diary were scored on a 5-point ordinal scale with categories 0–4, corresponding to none, mild, moderate, severe, and very severe symptoms, respectively. To assess typical nutrient intake, volunteers were asked to fill in a validated food frequency questionnaire (FFQ) during the baseline cycle.¹³ During cycles in which supplements were taken, the volunteers were required to provide a urine sample on approximately day 20 for analysis of Mg and creatinine.

Analysis

Urine samples were diluted appropriately and analyzed for creatinine and Mg by Vitros 750XRC Clinical Chemistry Slide (Ortho Clinical Diagnostics, Amersham, Buckinghamshire, U.K.). Urinary Mg output was calculated from a ratio of Mg/creatinine concentration, and 24-hour urinary output of Mg was estimated based on a normal creatinine output for women of 18 mg/kg body weight for 24 hours.¹⁴

Data analysis

Data were entered into the computer database DataEase 4.0 (Sapphire DataEase Ltd., Ilford, Essex, U.K.) and analyzed using SAS (SAS Institute Inc., Cary, NY). The completed FFQ were analyzed for nutrient intake using Tinuviel Software 1993 (Tinuviel Software 2, Warrington, Cheshire, U.K.) upgraded to 1994.

As mentioned, a second screening stage to assess the suitability of a volunteer for the study was conducted using the baseline (cycle 1) menstrual diary. For this purpose, the 30 symptoms specified in the baseline menstrual diary were summarized into six symptom categories: anxiety, craving, depression, hydration, other, and total (Table 1). Within these symptom categories, for each subject, the total premenstrual score was calculated for 7 days before the onset of menstruation together with the total postmenstrual score for days 8–14 of the baseline cycle. If the difference between these scores for total symptoms was <10, the subject was excluded from the study. Otherwise, the subject was randomized to a combination of treatments.

To statistically analyze the scores recorded in the menstrual diary records during the four treatment cycles, the scores were grouped into the six symptom categories. The scores were again summed within each symptom category for the premenstrual scores only. Each of the symptom category scores was then treated as if forming

TABLE 1. CLASSIFICATION OF 30 SYMPTOMS IN THE MENSTRUAL HEALTH QUESTIONNAIRE (MHQ) AND IN THE MENSTRUAL DIARY (MD)

| <i>Premenstrual symptom category^a</i> | <i>Symptoms</i> | <i>MHQ maximum score</i> | <i>MD maximum score</i> |
|--|---|--------------------------|-------------------------|
| Anxiety | Nervous tension, mood swings, irritability, anxiety | 16 | 112 |
| Craving | Headache, craving for sweets, increased appetite, heart pounding, fatigue, dizziness or faintness | 24 | 168 |
| Depression | Depression, forgetfulness, easy crying, confusion, insomnia, violent feelings | 24 | 168 |
| Hydration | Weight gain, swelling of extremities, breast tenderness, abdominal bloating | 16 | 112 |
| Other | Cramps, backache, general aches/pains, change in bowel habit, passing water frequently, infections (e.g., colds), allergic reactions, hot flushes or cold sweats, nausea/sickness, spots (e.g., acne) | 40 | 280 |
| Total | Sum of scores of all categories | 120 | 840 |

^aBased on ref. 5.

data on an interval scale. Frequency plots of these scores showed a skewed distribution. Thus, a transformation of these data (square root) was necessary to satisfy a normal distribution. Following data transformation, all symptom category scores were analyzed using ANOVA for a four-period Latin square design. The factors included in the general linear model were subject, diary, treatment, carryover, and interaction between diaries and treatment to enable within-subject comparisons to be made. If the effect of carryover from one cycle to the next or the interaction between diaries and treatment was found to be nonsignificant, these effects were removed from the model. The ANOVA was extended to enable predefined within-subject factorial contrasts of Mg and vitamin B₆ alone and in combination to be made.

Values for the estimated 24-hour urinary output of Mg (mg/day) were also found to be skewed. Hence, these data were transformed (log_e) and analyzed using ANOVA, with similar model effects to those described.

RESULTS

Fifty-eight women completed baseline cycle 1, 44 completed cycle 2, 40 completed cycle 3, 39 completed cycle 4, and 37 completed cycle 5. The main reason for differences in numbers between completion of baseline and completion of cycle 2 was that 11 women failed to satisfy the inclusion criteria set for stage 2 of the screening process. Although volunteers were not specifically asked about adverse side effects, none were reported spontaneously.

The MHQ provided information on the background of the women ($n = 44$) included in the study. Their mean age was 32 years, and 64% had given birth to one or more children. Most (61%) reported regular menstruation with an average duration of 5 days, with medium blood loss (57%). A small minority (18%) were oral contraceptive (OC) users. Respondents ($n = 40$) reported suffering from premenstrual symptoms for an average of 6.3 years (range 1–15 years). About two thirds of the women (64%) reported having stressful lives. The primary statistical analysis of this study was conducted per protocol and, thus, included 44 women who met the inclusion criteria and completed cycle 2. Summary statistics for the premenstrual scores and the difference between the premenstrual and postmenstrual symptom scores in the MHQ for the 44 women are shown in Table 2 for each grouped symptom category.

Premenstrual symptoms

Summary statistics for the premenstrual scores and the difference between the premenstrual and postmenstrual scores recorded in the baseline menstrual diary for the 44 women included in the primary analysis are shown in Table 3 for each grouped symptom category. The small differences between the premenstrual and the premenstrual minus the postmenstrual scores indicate that the majority of symptoms were suffered in the premenstrual and not the postmenstrual phase of the cycle. It is also evident from the standard deviations presented that there is considerable variability in these data.

The mean and median for the raw premen-

TABLE 2. PREMENSTRUAL SYMPTOM SCORES FROM RESPONSES TO THE MHQ WITH AND WITHOUT ADJUSTMENT FOR POSTMENSTRUAL SCORES

| <i>Premenstrual symptom category</i> | <i>Premenstrual scores</i> | | | <i>Premenstrual minus postmenstrual scores</i> | | |
|--------------------------------------|---------------------------------|--|----------------------------|--|-------------------------------|----------------------------|
| | <i>Mean</i> (<i>n</i> = 44) | <i>SD</i> ^a (<i>n</i> = 44) | <i>% of maximum scores</i> | <i>Mean</i> (<i>n</i> = 44) | <i>SD</i> (<i>n</i> = 44) | <i>% of maximum scores</i> |
| Anxiety | 10.5 | 3.5 | 66 | 9.5 | 3.6 | 59 |
| Craving | 8.7 | 4.9 | 36 | 7.5 | 4.8 | 31 |
| Depression | 9.9 | 6.2 | 41 | 8.6 | 5.6 | 36 |
| Hydration | 7.8 | 3.8 | 49 | 6.6 | 3.7 | 41 |
| Other | 9.0 | 6.4 | 23 | 7.6 | 5.9 | 19 |
| Total | 45.9 | 20.1 | 38 | 39.8 | 19.1 | 33 |

^aSD, standard deviation.

TABLE 3. PREMENSTRUAL SYMPTOM SCORES FROM BASELINE MENSTRUAL DIARY RECORDS WITH AND WITHOUT ADJUSTMENT FOR POSTMENSTRUAL SCORES

| Premenstrual symptom category | Premenstrual scores | | | Premenstrual minus postmenstrual scores | | |
|-------------------------------|---------------------|--------------------------|---------------------|---|--------------------------|---------------------|
| | Mean (n = 44) | SD ^a (n = 44) | % of maximum scores | Mean (n = 44) | SD ^a (n = 44) | % of maximum scores |
| Anxiety | 29.3 | 29.3 | 26 | 23.2 | 24.2 | 21 |
| Craving | 24.5 | 25.0 | 15 | 20.3 | 23.1 | 11 |
| Depression | 19.6 | 24.0 | 12 | 17.0 | 21.1 | 10 |
| Hydration | 27.0 | 25.6 | 24 | 26.2 | 25.3 | 23 |
| Other | 23.3 | 26.2 | 8 | 18.3 | 25.1 | 9 |
| Total | 123.7 | 111.1 | 13 | 105.6 | 99.9 | 12 |

^aSD, standard deviation.

strual scores reported in the menstrual diaries for each of the six symptom categories for each treatment are presented in Table 4. The differences between these mean and median scores clearly

show the skew from the normal distribution mentioned previously. The ANOVA performed on the transformed premenstrual scores for each of the symptom categories showed there was no

TABLE 4. MEAN 7-DAY PREMENSTRUAL SYMPTOM SCORES AFTER 1 MONTH OF DAILY SUPPLEMENTATION WITH 200 MG MG OR 50 MG VITAMINS B₆ SINGLY AND IN COMBINATION, COMPARED WITH PLACEBO TREATMENT AND BASELINE VALUES

| Premenstrual symptom category | Stage of study | Treatment | Number of women | Mean score | Median score | % of baseline scores | Adjusted mean (Latin square mean ²) |
|-------------------------------|----------------|-----------------------------|-----------------|------------|--------------|----------------------|---|
| Anxiety | Baseline | | 44 | 29.3 | 22.0 | | |
| | Treatment | Mg | 42 | 22.0 | 16.0 | 75 | 15.7 |
| | | Vitamin B ₆ | 40 | 21.8 | 10.5 | 74 | 14.9 |
| | | Mg + vitamin B ₆ | 38 | 16.3* | 9.0 | 56 | 11.3 |
| | | Placebo | 40 | 19.8 | 11.5 | 68 | 11.8 |
| Craving | Baseline | | 44 | 24.5 | 14.0 | | |
| | Treatment | Mg | 42 | 19.5 | 12.5 | 80 | 15.0 |
| | | Vitamin B ₆ | 40 | 20.5 | 13.0 | 84 | 15.0 |
| | | Mg + vitamin B ₆ | 38 | 14.9** | 11.0 | 61 | 11.3 |
| | | Placebo | 40 | 17.5 | 11.5 | 71 | 13.0 |
| Depression | Baseline | | 44 | 19.5 | 12.0 | | |
| | Treatment | Mg | 42 | 17.1 | 9.0 | 88 | 15.2 |
| | | Vitamin B ₆ | 40 | 20.8 | 7.5 | 107 | 16.0 |
| | | Mg + vitamin B ₆ | 38 | 17.1 | 9.5 | 88 | 12.9 |
| | | Placebo | 40 | 16.4 | 9.5 | 84 | 12.4 |
| Hydration | Baseline | | 44 | 27.0 | 20.0 | | |
| | Treatment | Mg | 42 | 20.9 | 15.5 | 77 | 10.7 |
| | | Vitamin B ₆ | 40 | 21.8 | 12.5 | 81 | 10.4 |
| | | Mg + vitamin B ₆ | 38 | 17.4 | 15.5 | 64 | 9.8 |
| | | Placebo | 40 | 16.8 | 10.0 | 62 | 9.7 |
| Other | Baseline | | 44 | 23.3 | 16.5 | | |
| | Treatment | Mg | 42 | 20.1 | 16.5 | 86 | 15.6 |
| | | Vitamin B ₆ | 40 | 18.7 | 13.0 | 80 | 15.5 |
| | | Mg + vitamin B ₆ | 38 | 18.7 | 10.5 | 80 | 14.9 |
| | | Placebo | 40 | 19.3 | 14.0 | 83 | 13.3 |
| Total | Baseline | | 44 | 123.7 | 83.0 | | |
| | Treatment | Mg | 42 | 99.5 | 67.5 | 80 | 84.6 |
| | | Vitamin B ₆ | 40 | 103.5 | 67.0 | 84 | 83.9 |
| | | Mg + vitamin B ₆ | 38 | 84.4 | 62.0 | 68 | 71.4 |
| | | Placebo | 40 | 89.9 | 60.5 | 73 | 69.4 |

ANOVA using factorial contrast: * $p = 0.040$; ** $p = 0.056$.

TABLE 5. DAILY DIETARY INTAKE OF SELECTED NUTRIENTS FOR WOMEN INCLUDED IN THE STUDY

| | Energy (kcal) | Protein (g) | Fiber (g) | Na (mg) | K (mg) | Ca (mg) | Mg (mg) | P (mg) | Vitamin D (μ g) | Vitamin E (mg) | Vitamin B ₆ (mg) |
|------------------|-------------------|----------------|--------------|------------|-----------|------------|------------|-----------|----------------------------|----------------------|-----------------------------------|
| Mean | 1817 | 70 | 21 | 2028 | 3131 | 902 | 289 | 1213 | 3.2 | 4.3 | 1.9 |
| SD ^a | 422 | 13 | 7.5 | 677 | 697 | 221 | 70 | 289 | 1.8 | 1.4 | 0.5 |
| RNI ^b | 1940 ^c | 45 | 18.0 | 1600 | 3500 | 700 | 270 | 550 | 10 ^d | >3.0 | 1.2 |

^aSD, standard deviation.

^bRNI, reference nutrient intake.¹⁵

^cEstimated average requirement for women 19–50 years old.¹⁵

^dOnly for those with limited exposure to the sun and severe vegans.¹⁵

carryover effect of the treatments or interaction between treatments and diaries. Consequently, these effects were removed from the model. The adjusted mean premenstrual scores for each premenstrual symptom category and treatment calculated from the final model are also shown in Table 4.

The premenstrual symptom category scores, as a percentage of baseline scores (menstrual diary 1) for the various treatments (menstrual diaries 2–5), are presented in Table 4. All treatments led to a reduction in scores for each premenstrual symptom category compared with baseline, including placebo, with the exception of vitamin B₆, which showed an increase in the depression score.

ANOVA showed no overall treatment effect in any symptom category, but extension of the analysis to investigate predefined factorial treatment contrasts of the adjusted mean scores showed a significant interaction effect of Mg and vitamin B₆ supplementation for reducing anxiety-related symptoms ($p = 0.040$) and a nonsignificant reduction trend in craving-related symptoms ($p = 0.056$). Hence, when administered for only one cycle, Mg at the low dose of 200 mg/day

was beneficial for reducing anxiety and craving symptoms only in combination with a dose of 50 mg/day vitamin B₆, and vice versa.

Intake and output of Mg

The dietary intake of Mg and selected nutrients of the 44 women calculated from the FFQ is shown in the Table 5. The average diet of the women included a daily energy intake of 1817 Kcal, on Mg intake of 289 mg/day, and a daily intake of 1.9 mg of vitamin B₆.

Values for the estimated 24-hour urinary output of Mg for the various treatments are shown in Table 6. The lowest mean output of Mg occurred when subjects were taking placebo (85.6 mg/day), and the highest was for the combined treatment (101.2 mg/day). However, the standard deviations show clearly the wide variability in these data, and, thus, no significant differences between treatments were evident when tested in ANOVA.

No correlations between dietary intake of Mg or vitamin B₆ and urinary Mg output were found while the subjects were on placebo.

TABLE 6. MEAN ESTIMATED 24-HOUR URINARY MG OUTPUT OF WOMEN AFTER 1 MONTH OF DAILY SUPPLEMENTATION WITH 200 MG MG OR 50 MG VITAMIN B₆ SINGLY OR IN COMBINATION, COMPARED WITH PLACEBO

| Treatment | Number of subjects | Estimated 24-hour urinary output of Mg (mg) (mean) | SD ^a |
|-----------------------------|--------------------|--|-----------------|
| Mg | 42 | 94.9 | 44.9 |
| Vitamin B ₆ | 42 | 91.4 | 44.0 |
| Vitamin B ₆ + Mg | 38 | 101.2 | 45.5 |
| Placebo | 43 | 85.6 | 36.5 |

^aSD, standard deviation.

DISCUSSION

The scores (% maximum scores) for premenstrual symptoms were rated higher in the MHQ (Table 2) than in the baseline menstrual diary (Table 3). This result was as expected, as a single score in the MHQ for a premenstrual experience scored retrospectively is likely to be rated as the worst-case scenario, whereas prospective scoring over 7 days in a menstrual diary will embrace day-by-day variation in severity of symptoms. Nevertheless, parallels can be drawn between the results from the two methods of scoring. In particular, anxiety-related symptoms were the most prevalent category in both the MHQ and menstrual diary scoring systems, followed by hydration-related symptoms.

The dominance of anxiety-related and hydration-related symptoms compared with depression-related and cravings related symptoms among the 44 women taking part in this double-blind, crossover study is typical of recruits to other studies.¹⁶ Both the MHQ and the menstrual diary instruments yielded differences in premenstrual and postmenstrual symptoms scores, which confirmed that most of the symptoms experienced by the women were in the premenstrual phase of the cycle. This strengthens the view that the incidence of everyday symptoms of poor health can be differentiated from premenstrual symptomatology using both of these instruments. The high scores for premenstrual symptoms indicate that many of the women volunteers may have been suffering from PMS, as previously described,^{17,18} as opposed to just mild premenstrual symptoms, even though most of them had not been specifically diagnosed with PMS.

Mean placebo premenstrual symptom scores from the menstrual diaries for all categories showed a substantial reduction from baseline after 1 month of administration, varying from 16% for depression-related symptoms to 38% for hydration-related symptoms (Table 4). This is a similar response to the reduction in signs and symptoms commonly encountered as a result of placebo treatment in double-blind trials of disease conditions with a psychological element, such as benign prostatic hyperplasia. Indeed, the placebo effect was comparable to that previously shown in PMS studies similar to this one.^{19,20}

ANOVA of factorial contrasts for premenstrual scores from menstrual diaries showed that a daily

dose of 200 mg Mg + 50 mg vitamin B₆ was effective in relieving anxiety-related premenstrual symptoms ($p = 0.040$) after administration for only one cycle. In addition, this treatment combination showed a nonsignificant trend ($p = 0.056$) to reduce symptoms of premenstrual craving compared with the other treatments. Neither Mg nor vitamin B₆ supplementation alone showed any significant benefit compared with the other treatments after 1 month of supplementation.

The lack of effect of a single supplement of Mg in this study appears to be contradictory to the findings of our previous double-blind, crossover study,⁷ which showed that a similar 200 mg daily dose of Mg (as oxide) caused a significant reduction in hydration-related premenstrual symptoms in a group of 38 women when compared with placebo. However, there were differences between these studies. The women in the earlier study were younger, and the daily Mg supplementation was for 2 months compared with 1 month in this study. In the earlier study, the effect of Mg supplementation on premenstrual hydration symptoms was evident only in the second and not in the first month of the study.

There are indications from this present study of a synergistic effect of vitamin B₆ and Mg supplementation in the relief of premenstrual symptoms, as suggested by Abraham.⁵ Nevertheless, as the differences were small, further work will be needed to confirm this finding, using a larger dose of Mg over a longer time and making adequate allowance for carryover effect. Although no carryover was shown in this study, administration of each treatment for longer than 1 month is likely to result in carryover, as our previous study showed.⁷

If Mg from MgO is poorly absorbed, which seems likely from the results of this study, more than 1 month of daily administration of a dose of 200 mg may be necessary for full repletion of deficit. An additional confounding point in comparing our two studies is that hydration-related premenstrual symptoms may be more prevalent in younger women, as found in the earlier study.⁷ Also, because of the multiple roles of Mg in metabolism, the benefit of Mg supplementation in deficient states for the relief of hydration-related and anxiety-related premenstrual symptoms may operate through different mechanisms and, hence, be independent of each other.²¹

Clearly, Mg supplementation is most likely to

be of benefit to the health of women whose diets are deficient in this nutrient. The reference nutrient intake (RNI) for Mg according to the Department of Health in the U.K. is 270 mg/day for women.¹⁵ In other countries, dietary recommendations are higher (400 mg/day is not unusual), being based on balance studies that point to a negative Mg balance at intakes below 6 mg/kg.²² Analysis of the FFQ in this study showed that volunteers had average Mg intakes of 290 mg/day (Table 5). Hence, although a proportion of the women in the study met the U.K. RNI, they may not necessarily have been replete in Mg and may have benefited from dietary Mg supplementation.

If, as has been postulated, vitamin B₆ supplementation is to enhance Mg absorption, this is likely to occur only in vitamin B₆ deficiency.^{9,10} The RNI for vitamin B₆ in the U.K. is currently 1.2 mg/day, and the average intake of the women in this study was 1.9 mg/day (Table 5). Therefore, the fact that most of the women were replete in the vitamin may account for a lack of effect of a supplement of 50 mg vitamin B₆/day on enhancing mean 24-hour urinary Mg output.

In healthy, Mg-replete individuals, enhanced urinary Mg output is regarded as a useful estimate of bioavailability of supplementary Mg preparations.²³ The lack of a significant difference in estimated 24-hour urinary output of Mg in this study between those on Mg supplementation and those on placebo contrasts with the significant difference found in the previous study using the same dose.⁷ Again, this initially appears to be contradictory, particularly as in both studies, Mg was administered as MgO (heavy precipitate). However, the longer period of supplementation in the earlier study may be an important factor (2 months compared with 1 month). Taken together, the results of these studies indicate that Mg absorption from MgO is slow and that chronic administration of more than a month may be necessary to replenish tissue deficit (Mg is primarily an intracellular cation) before urinary stabilizes.

Few studies have reported on the bioavailability of different preparations of Mg using human subjects, and none of the preparations have been administered chronically. In support of our findings, Bohmer et al.²³ found Mg from the oxide to have poor bioavailability, although, in contrast to the present study, their study concerned only acute administration to a small number of human subjects. *In vitro* incubation of Mg citrate indicates

that this is more soluble than MgO²⁴ and may be more suitable for future studies on Mg.

In conclusion, we have found evidence of a synergistic effect of a daily supplement of 200 mg Mg + 50 mg vitamin B₆ after 1 month of administration for the relief of anxiety-related premenstrual symptoms in women and a nonsignificant reduction trend ($p = 0.056$) in craving-related symptoms. The total number of statistical tests applied to the outcome data were all predefined in the study protocol. For reported treatment tests, there were three basic factorial contrasts made for each symptom score and total symptom score (18 tests) and one for the urine data. Although the total number of significance tests were kept to a minimum, the probability that significant results have arisen by chance cannot be excluded. Considering this and as the differences are small, further studies are required to confirm these observations before making general recommendations for treatment of premenstrual symptoms.

In developing protocols for future studies, it should be borne in mind that 2 or more months of daily administration of Mg as MgO may be necessary for full efficacy of treatment of premenstrual symptoms because of the poor bioavailability of this form of Mg. Alternatively, the use of Mg citrate may be a better option for dietary supplementation.

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