A Pilot Study to Compare Fluoxetine, Calcium, and Placebo in the Treatment of Premenstrual Syndrome

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Abstract: Serotonin reuptake inhibitors and calcium supplements ameliorate symptoms of premenstrual syndrome. A comparison of these agents to placebo may guide treatment selection. The goal of this pilot study was to compare fluoxetine and calcium to placebo.

We enrolled 39 women with at least 3 moderate to severe premenstrual symptoms and functional impairment. The trial compared fluoxetine (10 mg twice daily), calcium carbonate (600 mg twice daily), and placebo over the course of 4 menstrual cycles. The Inventory of Depressive Symptomatology, Premenstrual Tension Scale, Clinical Global Impression–Severity and –Improvement scales, and Daily Record of Severity of Problems were used to measure symptoms.

Symptom improvement was greatest for the fluoxetine group, although significance was achieved only for the Daily Record of Severity of Problems ($\beta = -0.28$; 95% confidence interval, -1.70 to -0.35; $P = 0.02$) and the Clinical Global Impression–Improvement ($\beta = -1.03$; 95% confidence interval= -1.70 to -0.35; $P = 0.04$). The Cohen *d* effect sizes for fluoxetine relative to placebo were between 0.80 and 2.08, whereas the effect sizes for calcium were only between 0.10 and 0.44.

Fluoxetine had clear therapeutic benefit for premenstrual syndrome, whereas the effect of calcium was much smaller. Results of this pilot do not support the need for a larger study that would compare these compounds.

Key Words: premenstrual syndrome, calcium, fluoxetine

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Moderate to severe premenstrual syndrome (PMS), including premenstrual dysphoric disorder (PMDD), is characterized by depressed mood, mood swings, flashes of anger, irritability, and changes in sleep and appetite; symptoms occur at the end of the premenstrual phase and the first few days of menses.[1,2] The efficacy of serotonin reuptake inhibitor (SRI) treatment of moderate to severe PMS and PMDD is now well established[3] and suggests that abnormalities in monoamine, particularly serotonin signaling or functioning contribute to the condition.[1] An interesting property of SRIs is that they alter the metabolism of progesterone. Some posit that PMS results from inadequate production of selected progesterone metabolites ("neurosteroids"), and thus the efficacy of SRIs may relate to their effects on neurosteroid production.

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Research also supports the effectiveness of calcium (1200 mg/d in divided doses) for the treatment of moderate to severe PMS,[4–6] although it is not clear whether calcium is as effective a treatment as an SRI. The utility of calcium treatment is based not on a theory of primary serotonin dysfunction, but instead on dysregulated calcium homeostasis that alters neurotransmitter synaptic receptors and intracellular second messenger systems.[7] Altered calcium homeostasis in women with PMS has been supported by findings such as lower ionized calcium in serum and 1,25 dihydroxyvitamin D levels, lower urine calcium excretion,[8] and lower insulinlike growth factor 1 concentrations in symptomatic as compared with nonsymptomatic women.[9] It is noteworthy that correction of calcium homeostasis such as that found in primary hyperparathyroidism reduces affective symptoms.[7] Accordingly, our aim in this pilot study was to estimate the efficacy of the SRI fluoxetine and calcium each as compared with placebo for treatment of moderate to severe PMS.

MATERIALS AND METHODS

This was a parallel, double-blind study that compared fluoxetine, calcium, and placebo over the course of 4 menstrual cycles. We originally included a fifth cycle that added calcium to either fluoxetine or placebo and continued calcium for participants in that cell, but subject attrition led to data that were insufficient for meaningful analysis.

Recruitment

The majority of recruitment occurred through on-site screening in private gynecologic practices, although we also recruited via advertisements and posters placed in the community in Providence, RI, and New Haven, Conn. Recruitment occurred between 2001 and 2005 in Providence and between 2001 and 2009 in New Haven. Potential subjects provided consent for screening and assessment. Those who were not pregnant and met preliminary, retrospective criteria for moderate to severe PMS were given the opportunity to select participation from one of several ongoing treatment protocols including the pilot study reported herein. The appropriate consent was obtained at that time. Women were then given forms to monitor symptoms daily across the menstrual cycle. We used the 21-item Daily Record of Severity of Problems (DRSP)[10] formatted into weekly forms. Possible participants were given self-addressed return envelopes and asked to return forms either by mail or fax. After completion of 1 month of daily ratings, women were contacted again. If ratings did not show the necessary premenstrual pattern, and they stated it was an unusual month, they were invited to chart symptoms for an additional month; otherwise, they were thanked for participation. Women with symptom patterns consistent with moderate to severe PMS (see below) were invited to participate in further face-to-face evaluation.

Inclusion/Exclusion Criteria

Women were potentially eligible if they (1) were between the ages of 18 and 48 years; (2) had regular menses; (3) met criteria for moderate to severe PMS (as defined by the presence

of at least 3 of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) symptoms problematic enough to warrant treatment, one of which is a functionally impairing affective symptom); (4) retrospectively reported symptoms of moderate to severe PMS in at least 9 of 12 menstrual cycles during the year before screening; (5) in the investigators' opinion were using an adequate method of contraception, including hormonal contraceptives, if treatment had endured a minimum of 6 months; and (6) had the capacity to provide verbal and written consent.

Women were ineligible if they (1) fulfilled *DSM-IV* criteria for another serious Axis I disorder (psychotic disorders, bipolar disorder, major depressive disorder, bulimia and anorexia, obsessive-compulsive disorder, panic disorder, or substance abuse disorder in the prior month); (2) posed a significant risk of suicide; (3) were taking an ongoing medication that, in the opinion of the investigator, could either treat her PMS symptoms (eg, gonadotropin-releasing hormone agonist, calcium, or other psychotropic agent) or were contraindicated during fluoxetine or calcium therapy (digitalis, select antiarrhythmic drugs, select antihistamines); (5) had a history of hypersensitivity or adverse reaction to fluoxetine or calcium; (6) were lactating, pregnant, or imminently planning to become pregnant; or (7) had a clinically significant medical condition that could render participation unsafe (eg, hepatic failure, renal disease, parathyroid disease, active peptic ulcer disease, or malabsorption).

Daily Rating Criteria

We required daily ratings for at least 1 month that showed a minimum of 3 premenstrual symptoms and functional impairment. Mean luteal-phase scores were at least moderate (≥3.0 on a 6-point scale) during the final 5 luteal-phase days; the follicular phase scores were no greater than a mean of 2 on these same items. Participants endorsed impairment on at least 1 of 3 functional impairment items as indicated by a score of greater than 2 on at least 2 luteal-phase days.

Visit Procedures

The trial included a baseline evaluation (visit 1) and 4 additional assessments that were conducted at approximately monthly intervals after randomization. Visits 1, 2, and 5 were conducted face-to-face, whereas visits 3 and 4 were completed over the phone. At visit 1, participants underwent a psychiatric evaluation and were administered symptom severity measures. If they met entrance criteria and did not meet exclusion criteria (eg, another serious psychiatric condition), they were randomized at this visit. Women who did not meet criteria were provided referral for treatment outside the trial and participation ended.

Randomized subjects returned or were telephoned, as close to onset of menses as possible, ideally between days 1 and 5, for the following 4 months. Information on premenstrual symptoms and adverse events was collected at each visit.

Medication and Allocation

Medication was dispensed in 2 bottles and used a double-dummy design. Participants took 1 pill from each bottle, twice daily, throughout the menstrual cycle. The first bottle included either active fluoxetine capsules, 10 mg each, or similar-appearing placebo. This medication was provided by Eli Lilly and then Warner-Chilcott and was the same as the Sarafem brand of fluoxetine. The second bottle included either calcium carbonate tablets, 600 mg, or similar-appearing placebo. The calcium preparation was provided by Smith Kline Beecham and is the same preparation as TUMS™ brand antacids. The dose has previously been found effective for treatment of PMS.[6]

Subjects were randomly assigned to 1 of 3 conditions: fluoxetine, calcium, or placebo. The statistician assigned the group using block sizes of 6. Allocation was concealed from the research staff and patients using sequentially numbered containers. The allocation was made when a subject was given a study number; each site had separate randomization schedules. Bottles were prepared by staff not involved with the project and did not identify the contents as either active medication or placebo. The staff responsible for filling and dispensing bottles would fill bottles with the appropriate medication from a preprepared stock bottle and would place the subject number on the bottle. This bottle would be given to other study staff to dispense to the subjects. Study visits are shown in Figure 1.

At each assessment, a blinded research staff administered the Premenstrual Tension Scale (PMTS)[11] and the Inventory of Depressive Symptomatology (IDS)[12]; an on-site investigator assigned a Clinical Global Impression (CGI)–Severity and –Improvement Scale score.[13] The subject rated her improvement as compared with the premenstrual phase before visit 1. The investigator reviewed daily ratings and collected information about adverse events and concurrent medication use to determine safety issues and whether the participant should continue in the trial. At face-to-face visits, the research assistant collected bottles, recorded the number of remaining pills, dispensed study drug, collected information on adverse events, and scheduled the next appointment.

Study Measures

The DRSP was used to collect prospective symptom ratings and determine eligibility.[14] It has 21 items for which the participant provided a rating from 1 to 6 for 11 symptom clusters, as well as functional impairment in any of 3 domains; subjects also recorded the date of menses. The scale includes the most common premenstrual symptoms, the *DSM-IV* criteria for PMDD, and functional impairment items. It also has the advantage of being short, which bolsters its acceptability, and is externally reliable with other measures (correlation of 0.8).[14] It was completed by participants throughout the trial.

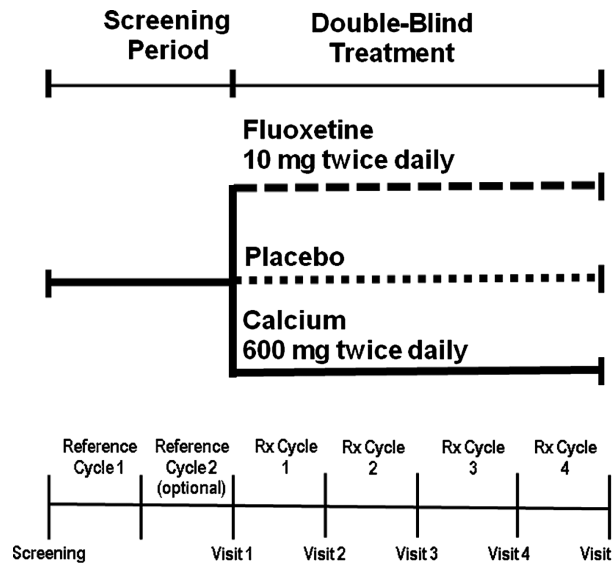

FIGURE 1. Study design.

At visit 1, concurrent exclusionary psychiatric diagnoses were determined by administration of the Mini-International Neuropsychiatric Interview (MINI-CR).[15] The MINI-CR is a 120-item, closed-ended instrument developed to assess 17 Axis I disorders and 10 subtypes, along with suicide risk and 1 Axis II disorder.[15] Diagnoses given by the MINI-CR correlate highly with the Structured Clinical Interview for *DSM-IV*[16] (range, 0.43–0.90) and the Composite International Diagnostic Interview[17] (range, 0.36-0.82), but the MINI-CR has the advantage of being shorter and easier to administer.[15]

Symptomatic distress during the previous (last luteal-phase) week was evaluated with the Premenstrual Tension Syndrome Observer Rating Scale,[11] a clinician-administered retrospective scale developed for the study of PMS. It includes items for irritability-hostility, tension, efficiency, dysphoria, motor coordination, mental-cognitive function, eating habits, social impairment, sex drive, and physical symptoms. The scale has very good internal consistency (Cronbach $\alpha = 0.89$) and good external reliability with daily measures of premenstrual mood disturbance (correlation of 0.63–0.74 with a visual analog scale that measured premenstrual mood, tension, mood swings, and irritability scores).[11] Depressive symptoms during the previous premenstrual phase were also measured through administration of the IDS—Clinician-Rated version (IDS-C_{30}).[12] The IDS-C has high internal consistency; Cronbach α in a sample of symptomatic depressed patients, remitted patients, and control subjects was 0.94.[12] It is sensitive to change during treatment for mood disorders and shows appropriate changes between the follicular and luteal phases of the menstrual cycle in patients with PMS/PMDD.

A blinded rater assigned a global measure of illness severity through use of the CGI scale,[13] a scale widely used in psychopharmacology research. The time frame for the rating was the week before menses. Overall severity (1 = normal, 7 = among the most critically ill) of illness is by the severity subscale, whereas the improvement subscale measured change from the visit 1 baseline to each follow-up assessment (1 = very much better, 7 = very much worse).

Subject Compensation

Participants were reimbursed $25 for 1 month of daily ratings, $15 for each of the 4 face-to-face visits, and $10 for each of the 2 phone visits. Women who completed the entire trial were offered a $150 bonus for their time and effort. The above procedures were approved by human subjects' boards at the Yale School of Medicine and Women's and Infant's Hospital.

Statistical Approach

We computed average differences between luteal and follicular phase symptom severity according to DRSP data. For each symptom and cycle, we used days 6 to 10 after the onset of menses to measure severity in the follicular period and the 5 days before the onset of menses to measure severity in the luteal phase. Scores were averaged for each phase. The mean in the follicular phase was subtracted from the mean in the luteal phase to obtain the mean difference for each symptom. Finally, the means for each symptom were averaged to obtain the grand mean and mean symptom difference. This statistic was modeled as a repeated measure (for each cycle) by subject.

We evaluated differences in treatment effects between groups using linear mixed-effects regression for main outcomes of IDS scores, PMTS scores, the DRSP mean symptom differences, and CGI severity scores. Mixed-effects regression allows for incomplete visit data for subjects. We compared mean changes over time between groups with models that contained a group-by-time interaction. Because CGI improvement is inherently a measure of change, we simply compared mean scores between groups and did not include a group-by-time interaction. In modeling outcomes, we followed CONSORT guidelines and made no correction for baseline differences in demographic characteristics or symptom severity. All data analyses were performed on the intention-to-treat cohort.

For each measure, Cohen *d* effect sizes were calculated by subtracting the difference between changes in the fluoxetine (or calcium) group between visits 1 and 5 and changes in the placebo group between visits 1 and 5, all divided by the SD in the placebo group at visit 5.

A final analysis evaluated response to treatment. For DRSP, IDS, and PMTS, a binary "response" measure was calculated, to classify the participants by whether they experienced 50% improvement between visits 1 and 5. To account for attrition and missing data, we used a last-observation-carried-forward method but also conducted a sensitivity analysis that assessed study completers only.

RESULTS

One thousand women were screened, of whom 951 did not qualify, did not wish to participate or did not complete daily symptom charting for the study. Forty-nine women were randomized, and 39 women completed at least 2 visits and thus had sufficient data to be included in the analysis. The analytic cohort used all informative data for randomized participants without regard to medication compliance or visit attendance beyond the first visit and follow-up visit.

Demographic characteristics of the study groups are shown in Table 1. The majority of women were between ages 30 and 45 years, married, and white. Demographic characteristics were relatively balanced between treatment groups, although the calcium and placebo groups had larger numbers of women with 2 or more pregnancies and more women with self-reported PMS for greater than 10 years. Luteal-phase scores from the DRSP were higher in the fluoxetine group. Concurrent use of an oral contraceptive was roughly equal among groups.

Outcome trends by group are shown in Figure 2. All groups, including the placebo group, showed some improvement after visit 1. For each measure, the improvement was greatest in the fluoxetine group, followed by improvement in the calcium group.

Estimated group differences and effect sizes are shown in Table 2. Estimated differences were marginally significant for fluoxetine improvement relative to placebo for all measures ($0.02 \leq P \leq 0.10$). Between visit 1 and visit 5, the Cohen *d* effect sizes for improvement for fluoxetine relative to placebo were very large, between 0.80 and 2.08. In the calcium group during this period, there were no significant differences relative to placebo. The effect sizes for calcium were small, between 0.10 and 0.44.

Response to treatment (ie, 50% improvement) is shown in Table 3. A higher proportion of women in the fluoxetine group responded to treatment, compared with the other groups. The difference was somewhat more pronounced as measured by the IDS and in the visit-wise analysis.

Adverse event data were available only for the Yale site. There were no severe adverse events. As can be seen in Table 4, events were uncommon and occurred in all 3 groups with a numerically higher number in the calcium group.

DISCUSSION

The results of this pilot study are consistent with other research showing the efficacy of daily fluoxetine as a treatment

TABLE 1. Demographics Characteristics of Study Participants

	Fluoxetine (n = 13)	Calcium (n = 13)	Placebo (n = 13)
Characteristics	**n (%)**	**n (%)**	**n (%)**
Age, y			
25–29	1 (8)	1 (8)	2 (15)
30–39	11 (85)	6 (46)	7 (54)
40–45	1 (8)	6 (46)	4 (31)
Marital status			
Married	7 (58)	8 (62)	9 (69)
Single/divorced/widowed	5 (42)	5 (38)	4 (31)
Not collected	1	0	0
Race/ethnicity			
White	8 (67)	10 (91)	10 (83)
Black	1 (8)	0 (0)	0 (0)
Hispanic	1 (8)	0 (0)	1 (8)
Other/mixed	2 (17)	1 (9)	1 (8)
Not collected	1	2	1
No. pregnancies			
0	6 (46)	3 (23)	5 (38)
1	3 (23)	1 (8)	0 (0)
2+	4 (31)	9 (69)	8 (62)
Years with PMS			
<4	6 (50)	2 (15)	6 (46)
5–10	3 (25)	6 (46)	1 (8)
>10	3 (25)	5 (38)	6 (46)
Not collected	1	0	0
Ever spoken to a doctor about PMS	4 (31)	5 (38)	6 (46)
Obstetrician-gynecologist asked about PMS	2 (15)	5 (38)	2 (15)
Thought about getting help for PMS	7 (54)	7 (54)	6 (46)
Concurrent oral contraceptive use	4 (31%)	3 (23%)	3 (23%)
Baseline Symptom Scores	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
IDS	31.85 (9.14)	30.92 (7.62)	28.85 (9.97)
PMTS	24.15 (5.40)	21.58 (3.73)	20.85 (6.62)
DRSP	2.16 (0.86)	1.12 (0.38)	1.29 (0.60)
CGI-S	4.92 (0.95)	4.46 (1.27)	4.15 (1.28)

The IDS, PMTS, and CGI-Severity were scored on the basis of severity during the prior premenstrual phase. The DRSP score was generated by subtracting average follicular phase severity from average luteal-phase severity and averaging these phase change means across symptoms.

for moderate to severe PMS and PMDD,[18–28] even though our sample size was small, and we required prospective confirmation of a minimum of 3 symptoms rather than 5 as would be required for PMDD. Our findings suggest a small benefit for calcium. However, the estimated effect for fluoxetine was much higher than that of calcium. The placebo response in this study (17%–33% depending on the measure) is in line with reported range of placebo response rates (11.8%–50%) in similar studies.[29]

Our results for calcium efficacy are consistent with the small effect sizes seen for the largest clinical trial that examined calcium compared with placebo for treatment of premenstrual symptoms.[6] In that study of 466 participants, we estimated the luteal-phase Cohen *d* effect sizes for calcium relative to placebo from data presented and found that they ranged from 0.16 to 0.33 between baseline and the end of the third treatment cycle. Estimates for the effect of calcium relative to placebo from our study ranged between 0.10 and 0.44 for the various dependent measures.

Our effect sizes for fluoxetine were also relatively consistent with the literature. We calculated Cohen *d* effect sizes from data presented in a randomized clinical trial of 313 participants with PMDD.[22] These estimates ranged from 0.61 to 0.83. Our data suggest that this effect could be even larger, from 0.80 to 2.08, for women who have PMS and a minimum of 3 symptoms.

The above results are in line with pathophysiologic theories of PMS. Women with PMS are posited to have an increased sensitivity to monthly hormone fluctuations. Fluctuating estrogen levels can alter serotonin receptor availability, binding, and hence neurotransmission, which in turn can lead to premenstrual mood symptoms.[30] It has been proposed that increased extracellular calcium after calcium supplementation may affect monoamine metabolism and reverse serotonin dysregulation.[7] Our data, although preliminary, would suggest that if calcium is working on this pathway, it is less effective than fluoxetine.

Our estimates were limited by several factors. First, the fluoxetine group had greater baseline severity on the DRSP.

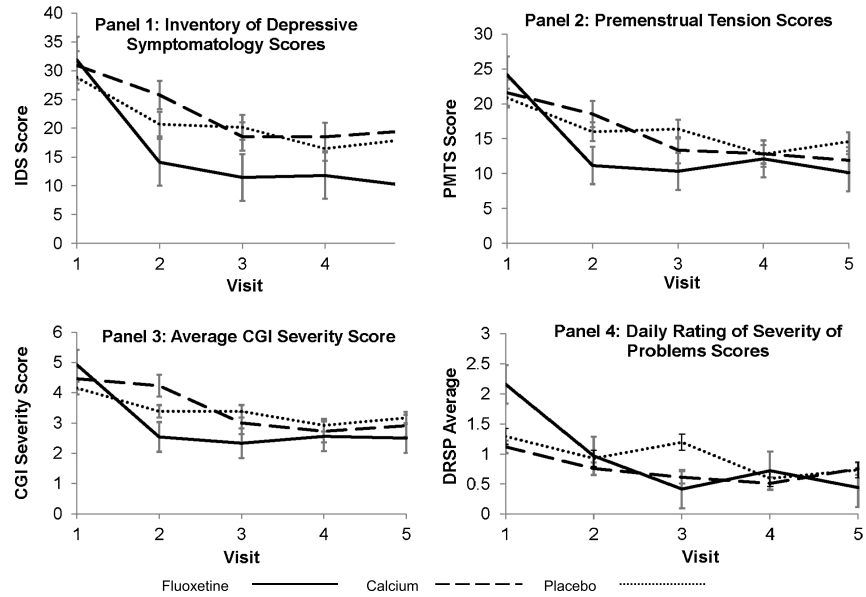

FIGURE 2. Visit-wise outcome of major outcome measures. Mean daily scores for the 3 groups over time. Results include visits attended only.

Because the trial was double-blind and the sample size was small, it is likely that these differences were due to chance imbalances. Still, baseline differences render it more difficult to assess change over time as groups may not have been ideally comparable. The initial severity in the fluoxetine group was much less pronounced in other measures. The difference between concurrent symptom ratings and the measures collected by researchers a few days after menses began may be attributable to recall bias. It may also be a result of individual variations in how women rank the severity of their symptoms.

Second, the sample size for this pilot may not be sufficient to draw definitive conclusions about treatment efficacy. However, our findings echo previous work and are strengthened by the fact that study participants were subjected to the same study conditions, other than treatment assignment. Third, there was somewhat higher attrition in the fluoxetine group compared

TABLE 2. Change in Symptom Scores Among Groups

Group	*B*	95% Confidence Interval	*P*	Effect Size*
IDS†				
Fluoxetine	−2.63	−5.51 to 0.24	0.07	1.15
Calcium	−0.10	−2.85 to 2.65	0.94	0.10
Placebo (reference)	referent			
PMTS†				
Fluoxetine	−1.63	−3.60 to 0.34	0.10	1.06
Calcium	−0.81	−2.71 to 1.09	0.40	0.37
Placebo (reference)	referent			
CGI Severity†				
Fluoxetine	−0.35	−0.73 to 0.03	0.07	0.92
Calcium	−0.17	−0.54 to 0.20	0.36	0.44
Placebo (reference)	referent			
DRSP†				
Fluoxetine	−0.28	−0.53 to −0.04	0.02	2.08
Calcium	0.06	−0.16 to 0.28	0.58	0.18
Placebo (reference)	referent			
CGI Improvement‡				
Fluoxetine	−1.03	−1.70 to −0.35	0.04	0.80
Calcium	−0.20	−0.86 to 0.46	0.54	0.32
Placebo (reference)	referent			

*Effect size was calculated as change relative to placebo from baseline to Visit 5.

†Differences in changes over time between groups.

‡Differences in mean scores.

TABLE 3. Response to Treatment

Response (50% Improvement)	Fluoxetine	Calcium	Placebo	*P*
DRSP LOCF* response	8/10 (80%)	5/12 (42%)	5/12 (42%)	0.15
IDS LOCF* response	10/13 (77%)	4/13 (31%)	4/13 (31%)	0.05
PMTS LOCF* response	8/13 (62%)	4/12 (33%)	2/13% (16%)	0.06
DRSP visit-wise response†	5/5 (100%)	4/8 (50%)	2/6 (33%)	0.09
IDS visit-wise response†	8/8 (100%)	4/11 (36%)	4/12 (33%)	0.005
PMTS visit-wise response†	6/8 (75%)	4/11 (36%)	2/12 (17%)	0.04

*The last observation carried forward (LOCF) response analysis includes data from all subjects with the LOCF to visit 5.

†Visit-wise response considers participants who remained in the study until visit 5 and provided data for the visit. For fluoxetine, calcium, and placebo groups, 8, 11, and 12 participants remained in the trial until visit 5. However, visit 5 DRSP calendars were missing for an additional 3 subjects in the fluoxetine group and for 1 subject in each of the calcium and placebo cells.

with the other groups. If women in this group discontinued as a result of ineffective treatment, the effect of fluoxetine may have been overestimated, although mixed models accounted for discontinuation and partial data profiles. Fourth, SRIs are often used only during the luteal phase rather than daily, as administered in this study. Thus, it is possible that we overestimated the effect of fluoxetine. However, studies generally show luteal-phase and daily dosing are equally effective for treatment of premenstrual symptoms.[31–33]

Some studies suggest that decreased vitamin D levels may be associated with premenstrual symptoms,[34,35] and a study has suggested that calcium 500 mg and vitamin D 200 mg taken twice daily during the luteal phase were superior to placebo.[36] Because vitamin D can enhance calcium absorption, it is possible that results would have been improved if adjunctive calcium had been administered with vitamin D.

Finally, while we initially attempted to recruit from gynecologic practices to obtain a representative sample of women with PMS, we ultimately needed to recruit via media advertisements. We found that very few women were willing to risk taking a placebo and instead elected to participate in an open-label protocol that was being offered concurrently. Other women did not want to complete daily ratings or did not have symptoms sufficiently severe to qualify for this protocol. Given that we screened 1000 women and slightly less than 5% were willing to participate in this protocol, generalizability may be an issue with our results.

In summary, our preliminary findings suggest a large benefit of fluoxetine and small or no benefit of calcium as compared with placebo as a treatment for PMS. These results do not support the need for a larger-scale study to compare the SRI fluoxetine to calcium as a treatment for PMS. However, calcium or calcium in conjunction with vitamin D may be useful as dietary supplements for overall health in women and may show mild improvement of premenstrual symptoms.

TABLE 4. Adverse Events Reported by Study Subjects*

Description	Fluoxetine	Calcium	Placebo
Feeling spacy	0	2	0
Abdominal ache	0	1	0
Burping	0	1	0
Difficulty concentrating	0	1	0
Constipation	1	0	0
Cramps	1	0	0
Decreased appetite	0	0	1
Decreased sex drive	0	1	0
Diarrhea	1	0	0
Dizziness	1	2	0
Dry mouth	2	0	0
Fatigue	0	1	1
Headache	1	3	2
Irritability	0	0	1
Nausea	1	4	2
Sweating	0	1	0
Vertigo	0	1	0

*n = 5, 2, and 8 Subjects reported no adverse events, whereas n = 0, 1, and 1 had insufficient time under observation. No adverse event data were available for Brown subjects.

AUTHOR DISCLOSURE INFORMATION

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