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# Symptom-Onset Dosing of Sertraline for the Treatment of Premenstrual Dysphoric Disorder: A Multi-Site, Double-Blind, Randomized, Placebo-Controlled Trial

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## Abstract

**Importance—**Serotonin reuptake inhibitors (SRIs) are efficacious treatments for premenstrual dysphoric disorder (PMDD) when given either daily or for half the menstrual cycle during the luteal phase. Preliminary studies suggest SRI treatment can be shortened to the interval between symptom-onset and the beginning of menses.

**Objective—**Determine the efficacy of symptom-onset dosing with sertraline for treatment of PMDD.

**Design, Setting, and Participants—**A double-blind, placebo-controlled trial conducted between 2007 and 2012 at three university medical centers. Women with PMDD were instructed to start pills at symptom onset and continue until the first few days of menses for six menstrual cycles.

**Intervention—**Placebo or sertraline 50–100 mg daily during the symptomatic interval

**Main Outcome Measures—**Premenstrual Tension Scale (PMTS)(Primary outcome measure), Inventory of Depressive Symptomatology– Clinician-Rated (IDS-C), Daily Record of Severity of

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Problems (DRSP) (total and subscales), Clinical Global Impression (CGI) scales and Michelson SSRI Withdrawal Symptoms Scale.

**Results—**125 participants were randomized to sertraline and 127 to placebo. The improvement in IDS-C scores was greater in the sertraline than the placebo group (F(6,1183)=2.6; p=.02; estimated mean difference between intake and endpoint of 5.14 points between groups (95% CI=1.97–8.31)). Group differences in PMTS scores were at a trend level (F(6,448)=2.1; p=.06; estimated mean difference from intake to endpoint of 1.88 between groups (95% CI=0.01–3.75) points). Compared to the placebo group, those assigned to sertraline showed greater improvement on the Total (estimated mean difference of 1.09 points (95% CI=0.96–1.25) and Anger/Irritability subscale of the DRSP (estimated mean difference of 1.22 (95% CI=1.05–1.41) and were more likely to respond ((77 (67%) for sertraline and 65 (53%) for placebo, ($X^2$(1)=5.23; p=0.02)). The number of symptomatic days before pill taking diminished over time (F(5,814)=5.3, p<.001) in both groups with no group differences on the Michelson SSRI Withdrawal Symptoms Scale.

**Conclusions and Relevance—**Women with PMDD may benefit from SRI treatment limited to the interval between the onset of premenstrual symptoms and the first few days of menses. Abrupt treatment cessation at the end of each cycle does not increase risk of discontinuation symptoms.

**Trial Registration—**ClinicalTrials.gov **Identifier** NCT00536198

## Introduction

A wealth of evidence supports the use of serotonin reuptake inhibitors (SRIs) in the management of PMDD[1] either as a daily treatment or one that is restricted to the luteal phase of the menstrual cycle.[1–14] However, symptoms are typically present for only 4–7 days before the onset of menses,[15–17] leading to questions about the potential efficacy of treatments that fit this shorter time frame. Indeed, small studies show that use of an SRI for only one week,[8, 14] or initiated at symptom onset, is therapeutic.[14, 18–23] There are currently no large, randomized, placebo-controlled trials that assessed the efficacy and response parameters of symptom-onset dosing for PMDD.

With this unique treatment format come questions about feasibility and adverse events. Many women experience difficulty anticipating the onset of symptoms or attribute symptoms to environmental stressors rather than PMDD.[15] This can complicate a woman's ability to determine the optimal time to commence treatment. Additionally, a number of reports cite difficulties with abrupt cessation of SRIs and the emergence of a discontinuation syndrome.[24–26] Intermittent treatment for PMDD, by definition, includes treatment that is abruptly stopped although this occurs after a short treatment interval. Thus, a clinical trial of an intermittent treatment would benefit from evaluation of feasibility and risk of discontinuation symptoms.

Herein we report the results of a clinical trial that evaluated symptom-onset dosing of sertraline for the treatment of PMDD. Sertraline is an effective treatment when given only in the luteal phase at doses of 50–100 mg/day.[24–26] Our *a priori* hypothesis was that sertraline, dosed flexibly between 50 mgs and 100 mgs per day during the symptomatic interval, would be feasible and more effective than placebo in the treatment of PMDD. Our assessment

includes secondary outcome data on improvement according to emotional and physical domains. Process outcomes, including the interval between symptom onset and pill taking over the course of the trial as a measure of feasibility, and possible discontinuation symptoms are also reported.

## METHODS

### Study Design and Eligibility

This was a double-blind, placebo-controlled, multi-site, parallel group trial that included a minimum two month pre-trial assessment to confirm a diagnosis of PMDD. Randomized participants were allocated to either sertraline or placebo in a 1:1 ratio, to be taken daily during the symptomatic interval for six menstrual cycles (see Figure 1). Women who did not achieve a CGI-S rating of ≤2 after two months at 100mg or the highest tolerated dose were offered removal from the trial alongside daily sertraline "rescue" treatment. Completers were also offered three months of open-label, daily continuation treatment. Ratings during rescue/continuation treatment were not included in the efficacy analysis.

**Participants—**Women were eligible if they: were between 18–48 years; had menstrual cycles 21–35 days and met criteria for PMDD. Women were ineligible if they: currently met criteria for a major depressive episode (MDE) or a substance use condition other than tobacco; had lifetime bipolar disorder, a psychotic illness, or bulimia; had severe suicidal thoughts; were undergoing treatment with a psychotropic medication, an oral contraceptive comprised of drosperinone (an effective treatment for PMDD[27]), a depot hormonal preparation or intrauterine device that could stop menses; used any oral contraceptive for less than six months prior to screening or did not plan to continue the same hormonal contraceptive throughout the study; used an inadequate birth control method; had a history of hypersensitivity to sertraline; were pregnant or lactating; were planning on re-locating during the study period or were unable or unwilling to provide informed consent. The study was approved by human subjects' boards at the collaborating institutions.

**Randomization and Masking—**Randomization and preparation of study pills occurred at Yale. We used a computer-generated randomization list that stratified assignment into block sizes of six and six strata based upon study site and participant use (Y/N) of an oral contraceptive. A research assistant (RA) who had no contact with participants prepared sequentially numbered stock bottles that had no information about the test drug. Sites were sent two lists (Y/N oral contraceptives) specific for their center, and stock bottles. The RA took stock bottles in sequence from the appropriate list and filled a smaller bottle with a medication event monitoring system (MEMS) cap that was given to the participant. The RA replaced pills from the stock bottle at monthly visits, as needed. In this way, masking of study medication was maintained.

### Procedures

This study was conducted in New Haven, Connecticut; New York City, New York and Richmond, Virginia. Participants were recruited via flyers, newspaper advertisements and direct mail sent to women aged 18–40 in local zip codes. Respondents completed a brief

pre-screening phone interview that included verbal consent. Provisionally eligible women attended a screening office visit wherein we obtained written consent, information about premenstrual symptoms, concurrent medical conditions and use of medications. Study staff gave respondents daily symptom rating forms that were returned weekly. Respondents were allowed to chart symptoms for an additional cycle if one of two cycles did not meet criteria. Participants were reimbursed $15 for the study visit and $50 for completion of daily ratings. Women who did not meet criteria were given treatment referrals.

We used the Daily Rating of Severity of Problems (DRSP)[28] to prospectively establish a diagnosis of PMDD. It is comprised of 21 items that reflect the 11 candidate symptoms for PMDD according to DSM IV[29] and DSM 5.[30] Some symptoms are broken into several component items. Each item is scored 1–6. As in past studies,[31] a diagnosis of PMDD required a minimal average luteal phase score of mild (≥ 3 on a 6-point scale) for at least five PMDD symptoms, including at least one mood symptom, during the five most symptomatic of the final luteal phase week and the first two days of menses onset; we required an average follicular phase score be <2 on these same items.

At the baseline visit, subjects were administered the MINI neuropsychiatric interview[32] to determine the presence of exclusionary diagnoses. Premenstrual symptom severity was captured through administration of the Premenstrual Tension Scale(PMTS)[33] and the Inventory of Depressive Symptomatology-Clinician version (IDS-C)[34]. A clinician assigned a Clinical Global Impression Severity (CGI-S)[35] score and obtained urine for a pregnancy test.

Follow-up visits were 5–7 days after onset of menses wherein we administered measures of premenstrual symptom severity, collected daily ratings, assigned CGI-Improvement (CGI-I) and CGI-S scores and obtained urine pregnancy tests. Visits 5 and 6 were completed over the phone while other visits were face-to-face. Information on adverse events was collected at all visits. At face-to-face visits the RA conducted pill counts and reconciled pill taking with the chart and the MEMs cap.

The starting dose of sertraline was 50 mgs per day (two capsules) to be taken once daily during the symptomatic interval. Daily ratings were reviewed at each visit with the participant to estimate when premenstrual symptoms were likely to occur. Participants were instructed to begin taking sertraline when they first noticed onset of their typical premenstrual symptoms and asked to cease taking pills within a few days of their menstrual flow and around the time symptoms typically ended. The MEMS caps recorded whether the bottle was opened and participants recorded the days they took pills.

Participants who had an inadequate response (a CGI-S of >2) were instructed to increase their dose to a maximum dose of four capsules (100 mgs of sertraline). Participants were instructed to titrate by two capsules every two days to the final dose of 4 capsules and follow the reverse schedule to end dosing. Women who reported moderate to severe side effects, were allowed to reduce pills to one capsule (25 mgs of sertraline) but to increase pills at the next cycle unless rate-limiting side effects continued. Participants were reimbursed $65 for time, transportation and completion of daily symptom ratings.

### Outcome measures

The primary outcome measure was the PMTS; secondary measures included the IDS-C, DRSP and the Michelson SSRI Withdrawal Scale. The PMTS is a 10-item scale (range 0–36)[33, 36] that includes items for irritability-hostility, tension, efficiency, dysphoria, motor coordination, mental-cognitive function, eating habits, social impairment, sex drive, and physical symptoms.[33] The IDS-C has 28 items[34] (range 0–84) and detects appropriate variations in mood between follicular and luteal phases in subjects with PMDD.[37] The PMTS and IDS-C were rated for the 7 days prior to menses. The DRSP total score was generated by computing the mean of each item over the final five days of the luteal phase and summing the 21 items.

Secondary outcomes included global change in illness severity and improvement according to the CGI-S and CGI-I scales, respectively.[35] The ranges for both were 1–7, with 7 as most severe and least improvement. Additionally, “responders” were those who achieved a “1 or 2” on the CGI-I scale; remitters achieved a “1”.

We evaluated possible discontinuation symptoms by adding items from the Michelson SSRI withdrawal scale[24] to the daily charting form that contained the DRSP. The Michelson items were summed for the three days after pill taking ended for each menstrual cycle.

The subscales from the DRSP and secondary outcomes were scored using the days and methods outlined above for the full DRSP. Items were grouped into a Depressive symptoms subscale (felt depressed, felt hopeless, felt worthless or guilty, slept more, trouble sleeping, felt overwhelmed), a Physical symptom subscale (breast tenderness, bloating, headache, joint or muscle pain) and an Anger/Irritability subscale (Anger/Irritability, conflicts with people). In prior work, internal consistency of these subscales (Cronbach’s α) were found to be 0.90, 0.76 and 0.90, respectively.[28, 31]

Inter-rater reliability was maintained throughout the trial via videotapes. The intra-class correlation coefficient (ICC) was at 0.8 or higher.

**Statistical Approach—**The distributions of all continuous variables were examined prior to analysis. No transformations were necessary. For the comparison of sertraline and placebo groups, we used linear mixed effects models for the dependent measures of PMTS, IDS-C and DRSP scores (total and subscale scores) and the Michelson Withdrawal Symptom scale. We used generalized estimating equations for the ordinal CGI scales. In each repeated measures model, there were fixed effects of condition (sertraline, placebo), time (month 1–7), the interaction between condition and time, site (Yale, Cornell, VCU) and oral contraceptive use (Y/N). Interactions among the stratification variables, condition and time were considered but dropped from the models when non-significant. The best-fitting correlation structure was selected for each model based on Schwartz Bayesian Information criterion (BIC). Time was treated as a categorical variable, but linear effects of time were tested within each model. Post-hoc comparisons of least square means were performed to explain significant interactions and main effects. For the responder and remission (CGI-I) analysis, we used the observation from the last visit carried forward and the chi square statistic to compare the number of responders by group.

An alpha level of 0.05 was used for all overall tests of main effects and interactions. The sample size calculation was based on the PMTS. We estimated that with 143 subjects per group and a dropout rate of 30%, we had 80% power to detect a medium effect size (d=0.4) for the difference in mean change from baseline to end-point between groups. Such a difference is considered clinically meaningful.

We conducted an exploratory analysis to determine changes in the interval between symptom onset and initiation of pill-taking over the course of the trial. We computed the mean number of symptomatic days from the DRSP after applying the following conventions. A day was considered symptomatic if a woman had at least three symptoms, each with a severity score of at least three. We conducted sensitivity analyses that used five symptoms but the results were not substantially different (data available upon request). The mean number of symptomatic days prior to pill taking in each cycle was compared for groups, over time, by linear mixed effects models.

Adverse events experienced by participants were tabulated and groups were compared with the chi-square test and Fisher's exact test if the cell size was less than five.

## Results

Recruitment occurred between September 2007 and February 2012, the first randomization on November 6, 2007, last randomization on February 20, 2012 and final visit on July 9, 2012. Screening, randomization and retention are illustrated in Figure 1. Participant characteristics are provided in Table 1. We note a slight imbalance between groups in the percentages of participants with at least a college education.

Overall, 75% of participants completed the trial or were moved to rescue treatment. Groups had similar retention, although more participants in the placebo (n=9) than the sertraline (n=3) group were moved to rescue treatment.

The difference between sertraline and placebo in rates of change for the PMTS scores was at a trend level ($F(6,448)=2.1$; $p=0.06$) with an estimated mean group difference in change from baseline to end-point of 1.88 points (95% CI=0.01–3.75). Compared with placebo, those in the sertraline group showed greater improvement in IDS-C scores over time, $F(6,1183)=2.6$; $p=.02$ (Table 2) with an estimated mean difference from intake to endpoint of 5.14 points (95% CI=1.97–8.31).

Secondary outcomes showed that groups did not differ on the CGI severity scale, although the CGI-Improvement scale favored sertraline ($\chi^2(1)=6.7$; $p=0.01$). The changes in the total DRSP and the Anger/Irritability subscale of the DRSP were greater for the active treatment than placebo group (estimated mean difference for change from baseline to end-point of 1.09 (95% CI=0.96–1.24; $p=0.02$) for total DRSP and 1.22 (95% CI=1.05–1.41; $p<0.01$) for irritability, but there were no differences between conditions in the Depression and Physical subscales(Table 4). Seventy seven (67%) and 65 (53%) participants in the sertraline and placebo groups, respectively, responded ($\chi^2(1)=5.23$; $p=0.02$); remission was attained by 48 (43%) and 39 (31%) in the sertraline and placebo group, respectively ($\chi^2(1)=2.73$; $p=0.10$). There was no interaction between treatment response and hormonal contraceptive use on

any of the continuous outcome measures. Table 3 shows that the number of symptomatic days between symptom onset and the initiation of pill-taking shortened significantly for both groups over the course of the trial ($F(5, 814)=5.3$; $p<.001$).

Both groups endorsed fewer and similar symptoms on the Michelson scale as the trial progressed ($F(6,631) = 6.41$, $p < 0.0001$) (eTable 5), suggesting that these scores do not represent medication withdrawal. Adverse events were similar between groups with the following exceptions: 35 (28%) in the sertraline and 15 (12%) in placebo group endorsed nausea ($\chi^2(1)=8.00$, $p = 0.01$); 22 (18%) in the sertraline and 9 (7%) in the placebo group endorsed difficulty sleeping ($\chi^2(1)= 5.45$; $p = 0.02$). No serious adverse events occurred during the trial (eTable 6).

## Discussion

In this first large randomized, placebo-controlled study of symptom-onset dosing with an SRI for PMDD, there was a trend in favor of the efficacy of sertraline using the PMTS (p=. 06). Compared to placebo, symptom improvement was clearly better with sertraline when measured by the IDS and DRSP. DRSP subscale analysis showed that the Anger/Irritability subscale from the DRSP favored active treatment. Secondary outcomes of improvement and response according to the CGI-I Scale were also significantly greater with sertraline. The totality of our findings support our hypothesis that active treatment with sertraline, even administered for about ~6 days during the symptomatic period, is an effective means by which to treat PMDD, particularly the cardinal symptoms of irritability and anger. Our results are also consistent with smaller studies of symptom onset dosing for premenstrual symptoms.[14, 21, 22]

The efficacy signal in this study was not as large as PMDD trials using continuous and full luteal cycle sertraline dosing.[5, 31] Three potential reasons are: we included symptomatic days prior to onset of pill taking in the luteal phase each month; 2) a possible true lack of effect on depression and somatic symptom dimensions included in the PMTS, IDS-C, and total DRSP scales, and 3) a potentially suboptimal maximal dose of sertraline. In addition, the repeated counseling regarding dosage, timing, and expectation effects of starting pill taking each month could have increased the non specific response levels, which at 53%, was 10–25% higher than rates reported in many full-and half cycle dosing SSRI trials.[5, 31] It is also possible that we would have seen significant differences in the PMTS and depression and somatic measures with a larger sample size.

The robust effect on the Anger/Irritability symptoms in this study is in line with other complete luteal phase dosing studies,[12, 38, 39] and the hypothesis that Anger/Irritability symptoms are the hallmark of the condition.[15, 40–42] The higher standard deviation of DRSP subscale scores for depression and somatic symptoms suggest that these symptoms were less consistently severe than irritability.

A strength of this study is the 6-cycle duration, which allowed us to demonstrate the persistence of response and increased accuracy of pill-taking over time. Clinicians and patients may have concerns about determining when to initiate pill taking. Daily ratings of

PMDD symptoms, are likely to familiarize women with their temporal pattern of symptom emergence and enable them to improve recognition of their symptomatic days. We cannot say whether the accuracy of pill taking would have improved without the necessary vigilance that accompanies keeping a daily symptom rating.

Our data support rapid therapeutic action of SRIs for PMDD symptoms.[21, 23] Although a partial response can be seen in MDE within a week,[43, 44] it is not the norm, and there is no evidence that a response occurs within a few days, as seen in PMDD. Suggested mechanisms of a rapid response are greater sensitivity among PMDD patients to the acute increased availability of synaptic serotonin[21, 45, 46] or increased production of allopregnanolone, an anxiolytic neurosteroid produced in greater amounts after SRI treatment.[47, 48] Animal studies demonstrate that SRIs increase activity of 3-α hydroxysteroid dehydrogenase, the rate-limiting enzyme for allopregnanolone synthesis, independent of serotonin reuptake.[49]

Symptom onset dosing was well-tolerated. Attrition rates did not differ between groups and rates of adverse events were generally similar. Of note, there was no evidence of withdrawal symptoms after cessation of sertraline treatment each month.

In summary, in this large, multisite, randomized, placebo-controlled trial, symptom onset dosing of sertraline demonstrated efficacy for PMDD. Irritability symptoms were most responsive to symptom onset treatment.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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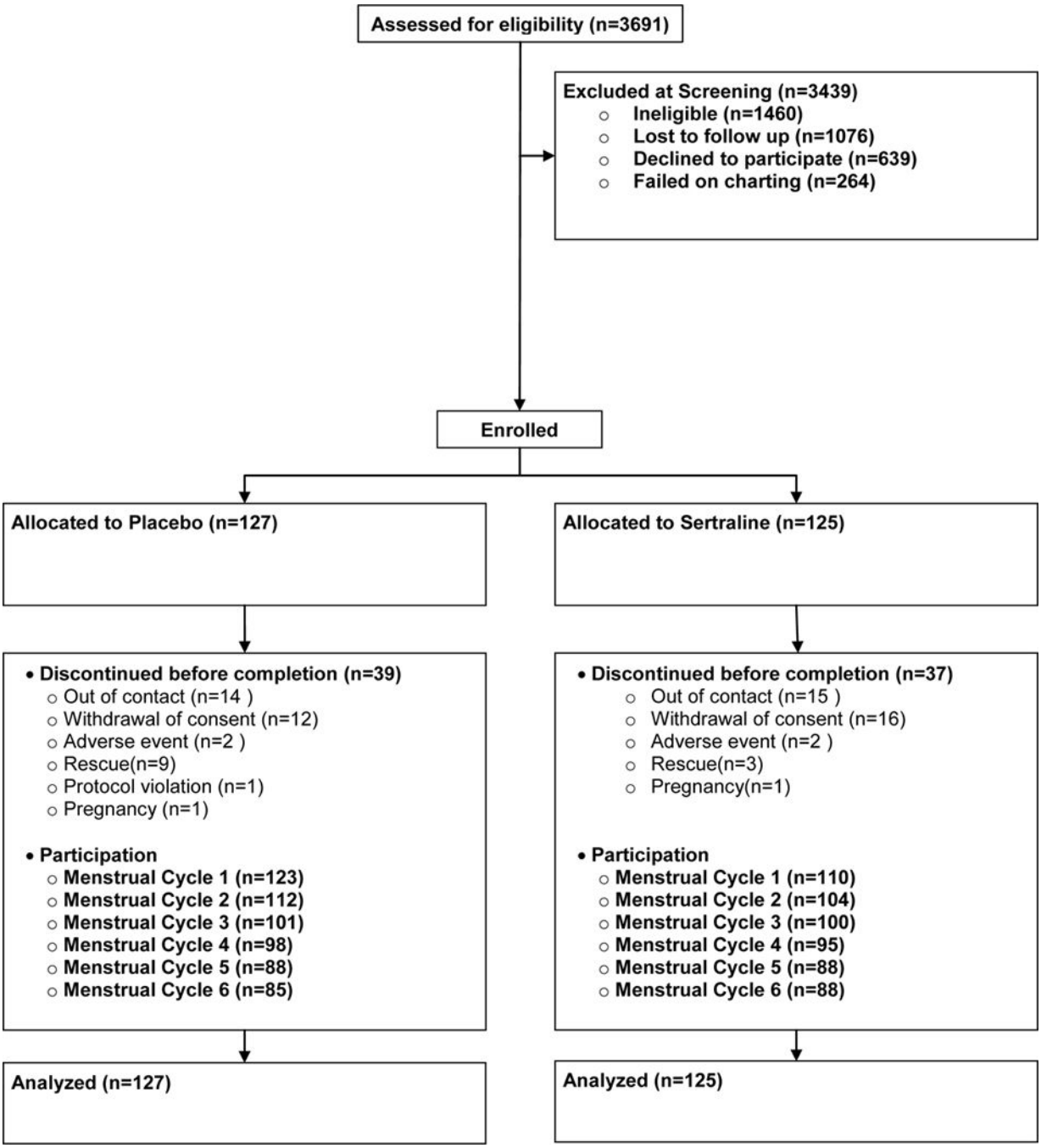


**Figure 1. Study Flow Diagram**

* Randomization occurred between signing consent and the intake visit. Allocation was not disclosed to the participant

## Table 1

Demographic Characteristics, by Random Assignment

| Characteristic | Active (N=125) N (%) | Placebo (N=127) N (%) |
|---|---|---|
| *Age (μ, years)* | 33.7 | 34.6 |
| *Race* | | |
| White | 86 (68.8) | 89 (70.1) |
| Black | 19 (15.2) | 20 (15.7) |
| Hispanic | 15 (12.0) | 13 (10.2) |
| Asian/mixed/other | 5 (4.0) | 5 (3.9) |
| *Education* | | |
| Missing | 1 (0.8) | 0 (0.0) |
| Some high school/high school graduate | 11 (8.8) | 11 (8.7) |
| Some college | 40 (32.0) | 22 (17.3) |
| College/graduate or professional school | 73 (58.4) | 94 (74.0) |
| *Marital status* | | |
| Married | 51 (40.8) | 42 (33.1) |
| Living w partner | 14 (11.2) | 20 (15.7) |
| Divorced/separated | 11 (8.8) | 14 (11.0) |
| Never married | 49 (39.2) | 51 (40.2) |
| *Past Psychiatric Conditions* | | |
| Major Depressive Disorder | 35 (28.0) | 43 (33.8) |
| *Baseline Length of Menstrual Cycle (μ± sd, days)* | 27.9±5.1 | 27.0±4.6 |
| *Baseline Luteal Phase Daily Rating of Severity of Problems Score (μ± sd,)* | 61.2±20.1 | 60.4±17.4 |

**Table 2**

Menstrual Cycle Symptom Scores for Primary and Secondary Outcome Measures, by Random Assignment

| | Number of Participants | | PMTS | | IDS-C | | CGI-S | | CGI-I | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Act.** | **Pla.** | **Active** | **Placebo** | **Active** | **Placebo** | **Active** | **Placebo** | **Active** | **Placebo** |
| Baseline | 125 | 127 | 22.3 (4.8) | 21.4 (4.5) | 35.4 (10.7) | 32.8 (10.4) | 4.5 (0.7) | 4.5 (0.6) | – | – |
| Cycle 1 | 110 | 123 | 15.6 (7.3) | 16.8 (6.0) | 23.7 (12.3) | 24.0 (11.4) | 3.4 (1.0) | 3.8 (0.9) | 2.7 (1.1) | 3.2 (1.0) |
| Cycle 2 | 104 | 112 | 14.1 (6.9) | 15.6 (6.1) | 21.0 (11.7) | 22.8 (10.6) | 3.1 (1.2) | 3.3 (1.1) | 2.4 (1.0) | 2.7 (1.1) |
| Cycle 3 | 100 | 101 | 13.0 (8.0) | 14.0 (5.8) | 19.2 (13.1) | 19.6 (10.0) | 2.8 (1.3) | 3.0 (1.0) | 2.3 (1.3) | 2.4 (1.0) |
| Cycle 4 | 95 | 98 | 12.9 (6.7) | 13.9 (6.3) | 17.3 (11.1) | 19.1 (9.9) | 2.6 (1.2) | 2.9 (1.2) | 2.1 (1.2) | 2.5 (1.3) |
| Cycle 5 | 88 | 85 | 11.4 (6.3) | 12.4 (6.3) | 15.2 (9.9) | 16.7 (10.4) | 2.4 (1.0) | 2.7 (1.1) | 2.0 (1.0) | 2.1 (1.2) |
| Cycle 6 | 88 | 88 | 11.7 (6.8) | 12.8 (6.9) | 15.5 (10.7) | 17.8 (11.0) | 2.2 (1.1) | 2.5 (1.3) | 1.8 (0.9) | 2.2 (1.3) |
| Average Change from Baseline | 88 | 88 | −10.6 (6.6) | −8.9 (7.4) | −20.0 (11.4) | −15.3 (12.5) | −2.3 (1.2) | −1.9 (1.4) | −0.9 (1.2)** | −0.8 (1.4)** |
| Group | | | F(1,249)=1.6, p=0.21 | | F(1,245)=0.4, p=0.54 | | $\chi^2(1)=6.2$, p=0.01 | | $\chi^2(1)=6.7$, p=0.01 | |
| Time | | | F(6,447)=131.8, p<.001 | | F(6,1210)=60.7, p<.001 | | $\chi^2(6)=182.8$, p<.001 | | $\chi^2(5)=29.9$, p<.001 | |
| Group by Time | | | F(6,448)=2.1, p=0.06 | | F(6,1183)=2.6, p=0.02 | | $\chi^2(6)=7.5$, p=0.28 | | | |
| Estimated Mean difference from baseline to end point between active vs. placebo (95% CI) | | | 1.88 (0.01 – 3.75) | | 5.14 (1.97 – 8.31) | | 0.59 (0.30 – 1.19) | | 0.55 (0.30 – 1.02)* | |

* Represents difference between groups at end-point only

** Represents average change from Cycle 1 to end-point

## Table 3

Pill Taking Across the Study, by Random Assignment

| | Number of days pills were taken | | Number of symptomatic[a] days before pills were taken | |
|---|---|---|---|---|
| **Visit** | **Active** | **Placebo** | **Active** | **Placebo** |
| Cycle 1 | 6.5 (3.4) | 6.6 (3.5) | 2.8 (3.0) | 2.6 (3.0) |
| Cycle 2 | 7.4 (3.3) | 6.7 (3.3) | 2.0 (2.2) | 2.7 (3.1) |
| Cycle 3 | 8.2 (3.7) | 7.1 (3.3) | 1.9 (2.8) | 2.0 (2.7) |
| Cycle 4 | 7.0 (3.8) | 6.9 (3.4) | 2.0 (2.7) | 2.0 (2.9) |
| Cycle 5 | 7.6 (4.0) | 6.7 (3.1) | 1.9 (2.9) | 1.8 (2.4) |
| Cycle 6 | 6.9 (3.8) | 6.1 (3.2) | 1.7 (2.3) | 2.0 (3.2) |
| Average Change from Cycle 1 | 0.3 (4.2) | −0.3 (3.6) | −0.7 (3.4) | −1.0 (3.2) |
| Group effect | F(1,208)=1.1, p=0.30 | | F(1,224)=0.1, p=0.80 | |
| Time Effect | F(5,725)=3.6, P<0.01 | | F(5,814)=5.3, p<0.001 | |
| Group by time | F(5,726)=0.6, p=0.73 | | F(5,815)=1.0, p=0.43 | |
| Estimated Mean difference from baseline to end point between active vs. placebo (95% CI) | 1.12 (0.92 – 1.35) | | 1.11 (0.85 – 1.45) | |

[a] Symptomatic days were those that participant experienced at least 3 symptoms at a severity of at least “3”.

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**Table 4**

Total and Subscale Scores for the Daily Rating of Severity of Problems, by Random Assignment

| | Number of Participants | | Total DRSP | | Depression Subscale | | Physical Subscale | | Anger/Irritability Subscale | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Act.** | **Pla.** | **Active** | **Placebo** | **Active** | **Placebo** | **Active** | **Placebo** | **Active** | **Placebo** |
| Baseline | 113 | 115 | 60.3 (19.5) | 59.5 (17.3) | 7.5 (4.0) | 7.2 (3.5) | 10.6 (3.6) | 10.6 (3.9) | 6.4 (2.2) | 6.3 (2.1) |
| Cycle 1 | 104 | 110 | 43.7 (17.4) | 46.1 (17.2) | 5.5 (3.0) | 5.7 (8.4) | 8.4 (3.5) | 8.4 (3.6) | 4.1 (1.9) | 4.6 (2.1) |
| Cycle 2 | 95 | 104 | 38.7 (15.8) | 44.4 (17.5) | 4.8 (2.7) | 4.9 (2.4) | 8.2 (3.7) | 8.8 (3.8) | 3.5 (1.7) | 4.5 (2.3) |
| Cycle 3 | 87 | 89 | 36.8 (15.7) | 40.7 (14.7) | 4.6 (2.7) | 4.6 (2.0) | 7.8 (3.2) | 8.1 (3.4) | 3.3 (1.7) | 4.0 (1.9) |
| Cycle 4 | 81 | 74 | 35.3 (12.2) | 36.9 (11.3) | 4.3 (1.9) | 4.3 (1.5) | 7.4 (3.2) | 7.3 (2.8) | 3.2 (1.4) | 3.8 (1.6) |
| Cycle 5 | 76 | 64 | 31.7 (10.5) | 35.2 (12.7) | 3.9 (1.6) | 4.2 (1.8) | 6.9 (2.7) | 7.1 (3.0) | 2.9 (1.3) | 3.5 (1.7) |
| Cycle 6 | 58 | 51 | 32.2 (10.4) | 36.1 (13.6) | 3.9 (2.0) | 4.2 (2.0) | 6.9 (2.6) | 7.4 (2.9) | 2.8 (1.4) | 3.5 (1.5) |
| Average Change from Baseline | 55 | 49 | −29.7 (18.8) | −22.4 (16.0) | −4.0 (4.0) | −2.7 (3.0) | −4.2 (3.8) | −2.9 (3.5) | −3.7 (2.2) | −2.8 (1.9) |
| Group Effect | | | F(1,273)=0.1, p=0.83 | | F(1,252)=0.8, p=0.37 | | F(1,240)=1.1, p=0.31 | | F(1,228)=11.6, p<.001 | |
| Time Effect | | | F(6,911)=79.5, p<.001 | | F(6,540)=31.8, p<.001 | | F(6,989)=50.0, p<.001 | | F(6,986)=109.4, p<.001 | |
| Group by time | | | F(6,911)=2.5, p=0.02 | | F(6,537)=0.6, p=0.73 | | F(6,989)=1.0, p=0.46 | | F(6,986)=3.2, p<0.01 | |
| Estimated Mean difference from baseline to end point between active vs. placebo (95% CI) | | | 1.09 (0.96 – 1.25) | | 1.08 (0.91 – 1.28) | | 1.09 (0.96 – 1.23) | | 1.22 (1.05 – 1.41) | |

Depressive symptoms included: felt depressed, felt hopeless, felt worthless or guilty, slept more, trouble sleeping, felt overwhelmed. Physical symptoms included breast tenderness, bloating, headache, joint or muscle pain. Anger/irritability included anger/irritability and conflicts with people