Clinical Intervention Study Protocol

FULL PROTOCOL TITLE

Alternative Treatments for Premenstrual Dysphoric Disorder

(Subtitle: A randomized, masked, 40-subject clinical trial of combination wake and light therapy in the treatment of Premenstrual Dysphoric Disorder)

Study Chairman or Principal Investigator:

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Tool Revision History

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Summary of Revisions Made: These final revisions are our biostatistician's (Shahrokh Golshan, Ph.D.) response to NCCAM queries from 8/30/13.

Version Number: 5
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Summary of Revisions Made: These final revisions amend the memo format of the language in section 6.2.6 to be in line with the standard protocol template; and also to reflect that we will perform secondary analyses on completers.

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PRÉCIS

Study Title

Alternative Treatments for Premenstrual Dysphoric Disorder

Objectives

The primary aim of this study is to examine the effects of co-administered wake therapy followed by light treatment on mood and circadian rhythms to test the hypothesis that critically timed chronotherapy improves mood by correcting phase disturbances in melatonin and sleep in women with Premenstrual Dysphoric Disorder (PMDD).

Design and Outcomes

40 women with Premenstrual Dysphoric Disorder ages 18-45 will be randomized to a cross-over design contrasting one night of Late Wake Therapy followed by 7 days of morning Bright-White Light (LWT+AM BWL) vs. one night of Early Wake Therapy followed by evening Bright-White Light (EWT+PM BWL) administered in the luteal phase of two separate menstrual cycles. Treatment will be preceded by 2 evaluation months to determine diagnosis and collect baseline mood, sleep, actigraphy and endocrine measures. To lessen the patient's burden, the 1-night EWT or LWT and the following 7-day BWL interventions will be conducted at home, given at a fixed point in each menstrual cycle, from day 1 to 7 after the mid-cycle LH surge. We anticipate that LWT+7 days of AM BWL (vs. EWT+PM BWL) will produce much greater mood benefits and larger physiological responses, than the one-time light pulses used in our earlier phase-shift studies. [1, 2]

Interventions and Duration

Using a randomized cross-over design, in the luteal phase of their menstrual cycles, PMDD women will receive either 1) one night of LWT (sleep 21:00-01:00 h, followed by wakefulness) plus 7 days of AM BWL (light-emitting diode-LED administered for 60 minutes, starting within 30 minutes of habitual wake time) or 2) EWT (wakefulness until 03:00 h, then sleep 03:00-07:00 h) plus 7 nights of PM BWL (administered 90 minutes before habitual sleep onset, for 60 minutes). Following this first intervention, patients will undergo one washout month with no intervention. The second intervention will be completed in the luteal phase of the following month and will be the treatment opposite the one previously performed. Total study duration, including evaluations and washout, will be 5 months (see Figure 1, Section 3, for detailed study flow diagram).

Sample Size and Population

In order to achieve the targeted enrollment goal of 40 completed subjects allowing for a 20% drop-out rate, 48 PMDD women ages 18-45 will be recruited to participate in the study.

1. STUDY OBJECTIVES

1.1 Primary Objective

We will assess the effects of the proposed study interventions on mood, urinary melatonin, sleep and activity to test the following specific hypothesis:

For PMDD patients in the symptomatic luteal phase, LWT+AM BWL, compared

with EWT+PM BWL, will: A) Improve mood on rating scales; B) Phase-advance urinary melatonin timing measures in relation to clock time and sleep measures; C) The magnitude of the mood change will correlate with the magnitude of the phase-advance in melatonin.

1.2 Secondary Objectives

We will assess the effects of the proposed interventions on reproductive hormones. In addition, we will test the effects of expectation, morningness/eveningness and seasonality on primary outcome measures of mood, melatonin and sleep. We will evaluate subjective assessments of side effects to treatment and effectiveness.

2. BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

PMDD is a devastating illness, causing extensive personal suffering, disruption in interpersonal and family relationships and occupational impairment. It can progress to major depressive disorder (MDD)[3, 4] and exacerbate the course of bipolar illness,[5, 6] pregnancy, postpartum and menopausal depression.[7] The incidence of women with severe premenstrual mood symptoms who meet criteria for a mental disorder has been estimated at 5-8%.[8-10] In addition, 20% to 80% of women report some mood, cognitive, and behavioral disturbances associated with their menstrual cycle.[3] Current treatments of PMDD are marginal (< 60% response).[11] Many women do not want to use, or cannot tolerate, chronic antidepressant medications for a periodic illness. Consequently, enhanced treatment approaches are needed to improve health outcomes.[12] The NIH Office of Research for Women's Health (Planning the Women's Health Agenda for the 21st Century, November, 1997, Bethesda, MD) targeted PMDD as an area for increased research on women's mental health, now mandated by Congress. PMDD was a DSM-IV[8] criterion set designated for further study in the appendix,[13] but will be incorporated into the DSM-5.[14]

Women are underrepresented in studies of sleep and circadian rhythms.[15, 16] A translational comprehensive approach to studying the chronobiological abnormalities in PMDD can serve to develop new, alternative non-pharmacological treatment strategies of sleep and wake therapies. The key to establishing synchronized rhythms associated with healthy mood states is intervention at critical clock times. To achieve this objective, a better understanding of the optimal timing of wake and light interventions is needed. Elucidating the factors contributing to PMDD also will enhance our understanding and treatment of other female-specific mood disorders that involve alteration of reproductive hormones (e.g., pregnancy, postpartum and menopausal depression). Another positive outcome may be optimization of sleep and wake therapies applied to other types of depression with chronobiological disturbances, given the similarity of their phenomenology and possible pathogenic mechanisms.

This proposal is innovative in providing new, alternative and possibly complementary treatment interventions as well as in providing a conceptual model to understand the mechanisms by which wake therapy and light treatment exert their antidepressant effects. The benefits of combined sleep and light therapies have been confirmed in mood disorders,[17-31] but combined wake therapy and light treatment have not been used previously to treat PMDD, or those women who do not respond to, cannot

tolerate, or desire alternatives to antidepressant or other treatments for PMDD. Using wake therapy alone is limited by the relapse that often occurs after subsequent sleep; and light treatment alone in non-seasonal mood disorders is limited by the duration of treatment required to elicit a therapeutic response (at least 4-6 weeks). The combined treatment proposed here is innovative because wake therapy enhances the effect of light treatment and reduces the time needed to elicit a therapeutic response, and light treatment maintains mood benefits of wake therapy lost after subsequent sleep. This approach is in response to a call for the development of novel combination therapies to improve treatment responses.[32] Before combining treatments, it is best that each treatment be tested alone.[32] Our research team previously has applied wake therapy alone or light treatment alone, yet no group has used these combined treatments in PMDD. Thus this proposal represents a reasonable next step and a creative synthesis of the two treatment approaches. Also, although chronobiological mechanisms have been proposed as the neurobiologic basis for mood disorders,[29, 33-35] the chronobiologic basis of PMDD has not been investigated systematically by research groups other than our own. Frederick Goodwin, Peter Whybrow, Anna Wirz-Justice and Siegfried Kasper,[33] as well as a position statement by the Committee on Chronotherapeutics of the International Society for Affective Disorders,[34] endorsed a broader view of chronobiological factors (e.g., circadian phase and sleep disturbances) in mood disorders, emphasizing that sleep and light therapies are rapid and effective antidepressants for first-line treatment of MDD.[30] We designed our proposed study to provide crucial evidence on whether sleep and light therapies in combination provide enhanced benefits in PMDD.

2.2 Study Rationale

Interventions: The wake therapy and light interventions proposed in this application are based on our previous studies in PMDD [36-39] and key published experiments by other investigators that indicate that the combined interventions are efficacious in other mood disorders after one week of treatment and maintained at 9-months follow-up.[17-31] To provide optimal timing of interventions, we will administer wake therapy in the early-night vs. late-night and light pulses in the AM vs. PM at selected times in relation to sleep (within 30 min of waking and 90 min before sleep onset, respectively). These times were selected to examine phase-advance and phase-delay responses without disrupting sleep. Successful light treatment is associated with a phase-shift of the melatonin rhythm as noted by Epperson et al.[40] in a randomized trial of bright light therapy for antepartum depression and by Terman et al.[41] in winter depression. In this proposal focusing on mood effects, we will administer 7 days of AM or PM light after wake and before sleep, respectively, for 60 min using a light-emitting diode (LED) device. The advantage of LEDs over conventional light boxes (fluorescent or incandescent) is that LEDs can be selected to emit light with energy concentrated at wavelengths of 450-480nm to which the human circadian system is most sensitive.[42-44] Thus LEDs are not only more efficient, but smaller and light-weight, further enhancing patient compliance. Clinical effects on mood generally occur within 3-4 days after the onset of treatment, and expire within 3-4 days after discontinuation of treatment.[45, 46]

A crossover treatment design will be employed to compare LWT+AM BWL vs. EWT+PM BWL responses within the same individual. As wake interventions lose effectiveness after 1 day, and light treatment effects after 3-4 days, we anticipate minimal carry-over effects of the wake plus light interventions administered a month

apart. To further ensure no carry-over effects, there will be a month of no-intervention between the 1st and 2nd treatments. Because our previous studies clearly indicated differences between PMDD and NC subjects occurred primarily in the luteal menstrual cycle phase, we will treat during this menstrual cycle phase rather than in the follicular phase.

Melatonin measures: To make the study more clinically feasible on an outpatient basis and to reduce subject burden, instead of plasma melatonin measures requiring now expensive inpatient admissions, we will obtain two overnight collections (30+ h) of urinary 6-sulfatoxymelatonin (6-SMT) pre- and post-intervention. Since light suppresses melatonin acutely (within 30 minutes), melatonin measures will be obtained after completion of the light treatment to avoid confounding the suppressive effects with the phase-shifting effects of light. Based on previous work,[1, 47, 48] we know melatonin profiles are stable and consistent within an individual when measured at different time points. These characteristics make melatonin one of the best markers for circadian rhythmicity in humans in non-constant routine conditions, if light is controlled appropriately. We will not use a constant routine, as it is not needed to obtain informative circadian parameters from rhythms in urinary 6-SMT, is burdensome, not clinically feasible for depressed patients in an outpatient setting, and has less potential therapeutic application. Melatonin is also a very useful marker because it is little masked by exercise, sleep, diet or stress when compared with other circadian parameters such as temperature, cortisol or activity measurements. Measuring 6-SMT in the urine has similar advantageous characteristics, and is less expensive and burdensome to patients compared with plasma measures. Moreover, the power of this method has been clearly and extensively demonstrated at UCSD by our collaborators Drs. Elliott, Kripke and colleagues.[49, 50]

Other biological rhythm measures such as sleep and activity may be independently regulated, but coupled. Therefore, it is informative also to measure these components of the circadian system in order to better quantify and understand the circadian response to treatment and its impact on mood and sleep.

3. STUDY DESIGN

Forty PMDD subjects will be recruited. Menstrual cycle phase will be established by measuring the mid-cycle LH surge using a urinary colorimetric assay (Clearblue® colorimetric LH assay, Princeton, New Jersey). Failure to ovulate will exclude the subject from participating that month, and the study will be postponed until a following month when ovulation can be documented.

Overall Design (see Figure 1): Month 1 consists of a screening evaluation using daily mood ratings (DMR) (see Section 6: Subject Selection). In Month 2, evaluations are continued, the Structured Clinical Interview for DSM-IV (SCID)[51, 52] and documentation of ovulation by the LH surge (approximately menstrual cycle day 14) are performed. In the Month 2 luteal phase, PMDD subjects will collect overnight urine samples for 6-SMT and reproductive hormones (RH) (estradiol, progesterone, FSH, LH, prolactin) starting 8-9 days after the LH surge (approximately menstrual cycle days 22-23). These baseline urine sample collections are timed to coincide with post-intervention measures in months 3 and 5. Starting in Month 3, after the LH surge (luteal phase), subjects will undergo a night of LWT (sleep 21:00-01:00 h, followed by wake) vs. EWT (wake until 03:00 h followed by sleep until 07:00 h) at home. We selected the specific wake and sleep times based on our previous work in

PMDD.[36, 37] The following day, subjects will receive the light intervention for 7 consecutive days: days 1-7 after the LH surge (approximately menstrual cycle days 15-21). We will randomize subjects to 60 min of either AM bright white light (LED of 1350 lux at 20 inches) starting within 30 minutes of their habitual wake time, or PM bright white light ending 30 min before their habitual sleep onset time. After completing seven days of light exposure, subjects again will collect 30+ hours of urine samples over 2 nights (between days 8-9 after the LH surge, approximately menstrual cycle day 22-23). The following Month 4 (Washout) will be a month of no intervention to prevent any carry-over effects from the Month 3 intervention affecting measures in Month 5. Mirroring Month 3 timing, in the luteal phase of Month 5, subjects will receive the alternate wake therapy (LWT or EWT) and light exposure (AM or PM), followed by 2 overnight collections of urinary 6-SMT and RH samples. See Fig. 1, below.

This design allows us to complete the studies at least two days before the next expected menstrual period. Measuring the circadian profile of urinary melatonin over 2 nights for 30+ h will allow us to assess phase, duration and amplitude changes of melatonin reflective of the underlying circadian pacemaker. In addition, we will assess phase-shift responses of melatonin to light in relation to other critical biological rhythm measures of sleep and activity. To document the sleep/wake cycle and exposure to light intensity and spectra, we will use the Actiwatch device (see description below).

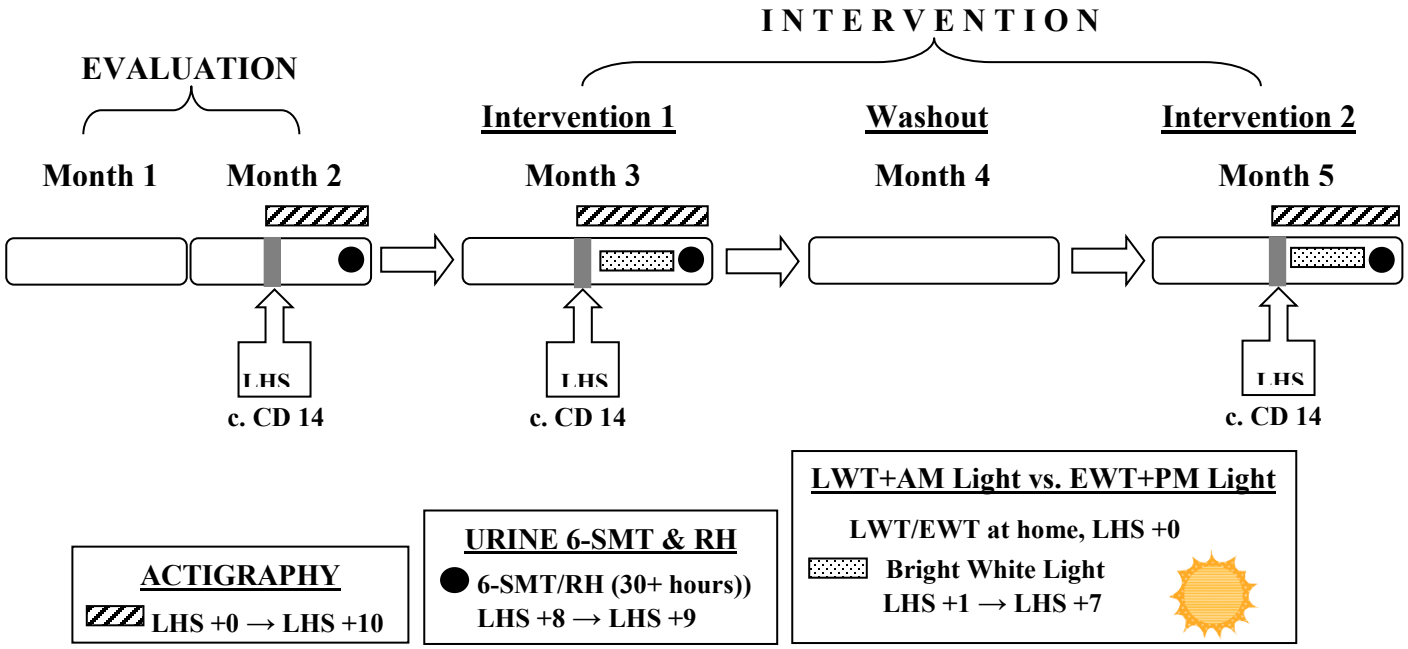


Figure 1. Study flow: The luteinizing hormone surge (LHS) documents ovulation, c. menstrual cycle day (CD) 14. Urine samples for 6-sulphatoxy-melatonin (6-SMT) and reproductive hormones (RHs) will be collected for 30+ hours over 2 nights between days 8-9 after the LH surge (c. CD 22-23) in months 2,3,5; actigraphy will begin the day of LHS and continue until day 10 after the LHS (CD 14-24) of months 2,3,5; late wake therapy (LWT) or early wake therapy (EWT) will be administered at home on the night of the LHS; bright morning (AM) or evening (PM) light will be administered on days 1-7 after the LHS (CD 15-21) in a counterbalanced, cross-over design in months 3 and 5. Mood ratings (HRSD+BDI) will be collected as follows: Months 1 & 2 – once per week; Months 3 & 5 – LHS + 0 (Pre-

LWT/EWT), daily LHS +1 → LHS + 2 and once the evening after last treatment (LHS +7/8). Visual Analogue Scales (VAS) for depressed mood, anxiety, affective lability, irritability (Daily Mood Ratings)(core PMDD symptoms) collected daily during Months 1 & 2, and twice daily on LHS + 0 through LHS + 2 (for wake therapy effects) and daily LHS + 3 through LH + 10 (for light treatment effects) in Months 3 & 5. HRSD will be collected once during Month 4 and a once a month after Intervention 2 to monitor relapse.

Urinary Collections for 6-SMT and RH: For urine collections, subjects will measure and record the time and total volume of each urine voided over a 30-hour interval starting with the last urination before going to bed one evening and ending on the morning of the second day thereafter. Two 2 ml aliquots from each voiding will be frozen at home in duplicate using labeled and numbered vials, and later stored at -70 C in the lab until assay. Subjects will receive thorough instruction regarding accurate recording of time and volume and proper collection and storage of the aliquots associated with each sample, including hands-on experience. Subjects also will be encouraged to drink extra fluids during waking hours (~ 200 ml every 2 hours) to remain well-hydrated and to facilitate more frequent voiding. Subjects will receive an oversupply of duplicate sample vials, each with easily read numbers on the printed label which are repeated on the vial tops to ensure correct identification of each sample with the associated time and volume on the record sheet. They also will be supplied with 1000 ml plastic bottles for refrigerator storage of samples collected during awakenings at night (so that volume measurement and transfer to freezer vials can be postponed until morning). The above urine collection methods have served us well for many years.[49, 50, 53]

Actigraphy Measures: Measures of activity and illumination using the Actiwatch Spectrum device will be obtained for 10 days in the luteal phase starting on the day of the LH surge during the 2nd month of screening evaluation and during each subsequent intervention month. The Actiwatch Spectrum, developed by Respironics®, a subsidiary of Royal Philips Electronics, is a small device (48.5 x 36.7 x 13.8 mm and weighing 29.8 g with band) containing a piezoelectric linear accelerometer (sensitive to 0.003 g and above), log-linear photometric transducer (sensitive from <0.01 lux to >100,000 lux), 3 photon flux and irradiance color sensors in the red, green, and blue bands of visible light, a microprocessor with 2 Mbits RAM memory that allows for 36 days continuous recording of 1-minute epochs, and associated circuitry. The orientation and sensitivity of the accelerometer are optimized for highly effective sleep-wake inference from wrist activity. The illumination measurements are roughly log-linear from a range below moonlight to the brightest summer day at noon. An important innovative feature of this device is an off-the-wrist sensor, which distinguishes when the participant has removed the device for any reason. The Actiwatch Spectrum also allows us to determine spectral composition of light, which may differentially affect phase-shift, and therefore, treatment responses.[45]

Sleep Interventions: Adherence to appropriate sleep and wake times during the EWT and LWT interventions will be documented by actigraphy. Compliance with wake therapy also will be monitored by having patients leave a message on an answering machine once every half-hour while awake. As they are only awake for 4 hours during wake therapy, they will make 8 calls.

Light Interventions: Subjects will sit in front of a portable (5.5” x 6.25”) Litebook ® Model 1.2 light box (an array of 60 cool white light-emitting diodes behind a clear

plastic screen)(The Litebook Company Ltd., Alberta Canada) with an intensity of 1,350 lux and an irradiance of $2.41x10^{-9}$ w/cm^2 at 20 in, and spectral emission peaks at 464 nm and 564 nm. Subjects will gaze at the light source for a minute every few minutes for 30 min. The distance of the subject from the light source will be calibrated individually for each light box by use of a Meterman LM631 Digital Light Meter (Meterman Test Tools, Everett, WA) to produce an intensity of 1,350 lux at 20.0 in. Ambient light intensity and spectra will be documented by the Actiwatch Spectrum. A research assistant will provide a measuring tape to ensure proper distance between light source and patient, check the Actiwatch recordings to ensure compliance, as well as the Litebook's built-in compliance monitor recordings.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

Subjects for these experiments over 5 years will include: Forty women with premenstrual dysphoric disorder (PMDD). As only women have menstrual cycles, only women will be sought. As women generally do not develop significant premenstrual mood symptoms until late adolescence, and the menstrual cycle may become irregular during the perimenopause, only women age 18-45 years will be studied. For these reasons, children and adolescents under the age of 18 and peri- and post-menopausal women will be excluded. All ethnic groups will be represented (Caucasian, Asian, Black, Hispanic and Other). We will focus on recruiting subjects representative of the community: approximately 54% Caucasian, 30% Hispanic, 10% Asian, 5% African American and 1% Other. The UCSD Medical Center serves a clientele in which minorities are over-represented. All subjects will be adults individually competent to execute written informed consent.

Recruitment of minority subjects: We will take pains to recruit women of color and other minorities working with the Women's Center, the Cross Cultural center, the Lesbian, Gay, Bi-Sexual and Transgender (LGBT) Resource Center, Queer People of Color (QPOC) Center and the Native American Student Alliance on the University of California campus.

	Caucasian	Hispanic	Asian	Black	Other
Female	54%	30%	10%	5%	1%

4.1 Inclusion Criteria

PMDD women wishing to participate in this study must meet the following inclusion criteria:

- Age: 18-45 years.
- Women with regular ovulatory menstrual cycles 26-32 days in length (for at least the previous six months).
- A history of a depressive (but not bipolar) mood disorder, but not an ongoing episode (symptom free for the last 12 months).
- Patients must meet DSM-IV criteria for Premenstrual Dysphoric Disorder (that includes irritability).
- Objective ratings: mean of HRSD total scores across evaluation weeks 1-8 $\leq$ 7 for follicular phase (day 5-10 of cycle after menses); mean of total HRSD

scores across evaluation weeks 1-8 ≥ 14 for premenstrual (luteal) phase (6 days prior to onset of menses onward).

- Subjective ratings: mean of Beck Depression Inventory total scores across evaluation weeks 1-8 < 10 follicular phase; ≥ 10 premenstrual (luteal) phase.
- Daily ratings: minimal symptoms (mean less than 50 on 100mm scale) follicular phase; at least a 30% increase in mean affective symptom ratings, premenstrual (luteal) phase.
- By clinical assessment and ratings, the patient has reported a history (for at least the last six months) of recurrent, moderate to severe premenstrual mood symptoms that impair some aspect of social or occupational functioning and that remit within a few days after the onset of menses. This pattern is prospectively documented with subjective daily mood ratings (DMR – visual analogue scale) during at least two consecutive symptomatic cycles. Symptom severity will also be documented with objective and subjective ratings over that time. Patients must demonstrate a consistency of symptoms and a long enough duration of symptoms (7-10 days) to allow for study.
- Subjects willing to endure the rigors of a long-term (up to 6 months) research study.

4.2 Exclusion Criteria

Participants meeting any of the following exclusion criteria at baseline will be excluded from study:

- Subjects with significant medical illness including hepatic (abnormal liver function tests), neurological, renal, cardiac, pulmonary, hematologic, gastrointestinal, or metabolic disorders.
- Subjects who are lactating, are within 6 months postpartum, or have an irregular sleep- wake cycle, e.g., from having very young children in the home.
- Subjects who are using hormonal contraception (within six months prior to the study).
- Subjects using medication that may affect outcome measures of mood, circadian rhythms or hormone levels (6-sulphatoxy-melatonin, estradiol, progesterone, FSH, LH, prolactin) within one month of initiating the study or anytime during the study. Such medications include OTC medication (excluding Tylenol), antidepressants, anti-anxiety, antihypertensive, beta blockers, and asthma medications. Vaccinations, vitamins/mineral supplements (excluding St. John's Wart, melatonin and valerian) and/or short course antibiotics will not be considered exclusionary.
- Subjects with significant psychiatric disorder (schizophrenia, bipolar disorder, anxiety disorders, eating disorders, personality disorders, sleep disorders). An ongoing major depressive episode within the last year is reason for exclusion, although a previous history of a depressive episode is not (using DSM-IV diagnostic criteria for a major depressive episode).
- Subjects with a recent history (within the past year) of drug or alcohol abuse.

- Subjects with a history of anemia, liver, kidney, cardiopulmonary, metabolic or thyroid disease within one year of participation (per patient-reported medical history).
- Subjects with irregular menstrual cycles (cycle lengths vary greater than 3 days or who fail to ovulate for 2 consecutive months).
- Subjects unlikely to cooperate with the requirements of the study.
- Subjects needing frequent or continuous use of any medication or drugs that may affect outcome measures, including alcohol (>1 drink daily) and nicotine (> 5 cigarettes daily).
- Subjects whose prospective DMR ratings do not show cyclic variation in association with the menstrual cycle (as per inclusion criteria).
- Subjects with an irregular sleep schedule, extreme chronotypes or a sleep-wake cycle that does not correspond to the environmental light-dark cycle (e.g., subjects within 2 weeks of transmeridian travel, night shift workers, or those with significant advanced or delayed sleep phase syndromes). To enhance precision of the timing of the light stimulus on circadian phase (temporal resolution), we will exclude women with habitual sleep onset times after midnight or wake times after 9 am.

4.3 Study Enrollment Procedures

Subject Selection: Before entering the study, all subjects undergo a diagnostic evaluation for 2-3 months to establish that they meet criteria for PMDD, as required by DSM-IV:

A. In most menstrual cycles during the past year, five (or more) of the following symptoms were present for most of the time during the last week of the luteal phase, which began to remit within a few days after the onset of the menstrual flow, and were absent in the week post-menses, with at least one of the five symptoms being from among those numbered 1, 2, 3 or 4.

1. markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts
2. marked anxiety, tension, feelings of being "keyed up" or "on edge"
3. marked affective lability (e.g., feeling suddenly sad or tearful or increased sensitivity to rejection)
4. persistent and marked anger or irritability or increased interpersonal conflicts
5. decreased interest in usual activities (e.g., work, school, friends, hobbies)
6. subjective sense of difficulty in concentrating
7. lethargy, easy fatigability, or marked lack of energy
8. marked change in appetite, overeating, or specific food cravings
9. hypersomnia or insomnia
10. a subjective sense of being overwhelmed or out of control
11. other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of bloating," weight gain

B. The disturbance markedly interferes with work or school or with usual social activities and relationships with others (e.g., avoidance of social activities, decreased productivity and efficiency at work or school).

C. The disturbance is not merely an exacerbation of the symptoms of another disorder, such as major depression disorder, panic disorder, dysthymia disorder or a personality disorder (although it may be superimposed on any of these disorders.)

D. Criteria A, B, and C must be confirmed by prospective daily ratings during at least two consecutive symptomatic cycles.

Note: Although the criteria for PMDD are in the main body of the text and formatted slightly differently in DSM-5, the diagnostic criteria for PMDD have not changed between DSM-IV and DSM-5. Thus, no alterations to the DSM-IV SCID criteria are needed to establish diagnosis.

Participants will begin the Evaluation Period at any time during their menstrual cycle. Patients will monitor their cycle days and collect ratings until two consecutive symptomatic menstrual cycles occur, per diagnostic criteria (outlined in pg.16, section 4.3). As we expect variation in menstrual cycle lengths among patients, we cannot establish a strict temporal schedule for this evaluation period. Nevertheless, we anticipate its duration to be no less than 2 (provided evaluation begins proximal to their first cycle day and they have regular, continuously symptomatic cycles) and no greater than 3 months (to allow for detection of 2 full symptomatic cycles). Scheduling the start of this evaluation period according to patients' first cycle day would increase patient burden and be prohibitive to recruitment efforts.

To facilitate understanding of study flow and design (see section 6.1), we refer to the Evaluation Period as Month 1 and Month 2 (as there are 2 full consecutive menstrual cycles within this period).

We recruit subjects through referral sources from the UCSD Dept. of Psychiatry Outpatient Services and Women's Mood Disorders Clinic, the Reproductive and Family Medicine Clinics, the Internal Medicine Group, the Student Health Service and the Counseling and Psychological Service (with all of whom the PI has a longstanding collaborative relationship -- see attached letters). Through the UCSD public affairs office, we place advertisements in local newspapers, mail flyers to local San Diego zip codes, make on-line announcements for UCSD employees/students, and place flyers or brochures at clinics, libraries and on campus bulletin boards in the San Diego area. After subjects complete an initial telephone and written screening questionnaire (Menstrual Assessment Form), we obtain a medical and psychiatric history from every subject selected for possible inclusion in the proposed study. A Clinical Rater (trained clinician) with established inter-rater reliability (kappa coefficient = 0.90) will conduct SCID[52] interviews. During the telephone screening we will inquire on history of anemia, kidney, cardiopulmonary, metabolic, liver or thyroid disease within one year of screening. Those endorsing positive history of any of these conditions will be excluded from participation. No lab test or physical examinations are required to verify history. We will not test for existence of these medical conditions at the time of study since it would be cost prohibitive and an unreasonable burden for patients to obtain labs via outside sources, thus hindering recruitment efforts. We will obtain a urine toxicology screen and a pregnancy test. In addition, each subject will receive a thorough explanation of the study before being asked to personally sign informed written consent under supervision of the UCSD Committee on Investigations Involving Human Subjects.

During an initial 2-3 month evaluation period, subjects will complete twice-daily self ratings of mood (including core PMDD symptoms of depression, anxiety, affective lability, irritability) using a 100 mm visual analogue scale (Daily Mood Ratings form-DMR).[54, 55] Individual items on the DMRs will be measured, scored and plotted using GraphPad Prism (GraphPad Software, Inc. La Jolla, CA) to observe the daily progression of mood symptoms (both in the morning and evening from day to day in the follicular and luteal phase) throughout the evaluation phase and in relation to the woman's menses to ensure proper diagnosis based on DSM-IV criteria. Women also will visit the clinic on a weekly basis where the project coordinator will collect the daily rating forms, and a trained clinician, blind to treatment condition, will interview the subjects using the 24-item Hamilton Rating Scale for Depression (HRSD).[56] At this time the subjects also will complete a Beck Depression and Anxiety Inventory.[57, 58] In addition, we will ask them to complete a screening questionnaire on their sleep patterns, to keep daily sleep logs and to adhere to their habitual sleep schedule. This evaluation period will establish the diagnosis of PMDD and will provide information as to when symptoms are likely to occur. It also helps us to design a study schedule based on each patient's individual symptom patterns, and to establish each individual's sleep schedule prior to interventions. As in our previous studies and those of others,[59] we expect about 5% of patients screened to meet criteria. We especially will recruit women who are non-responsive to other interventions for PMDD, or who seek alternatives to pharmacological or chronic treatments for PMDD.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

Treatment 1 will occur during the menstrual cycle immediately following the 2 menstrual cycles studied in the evaluation period. Washout will occur the following menstrual cycle, and Treatment 2 the menstrual cycle immediately following Washout. As we establish the Evaluation Period as Month 1 and Month 2, we will refer to Treatment 1 as occurring in Month 3, Washout in Month 4, and Treatment 2 in Month 5 (see section 6.1).

During Month 3, qualified participants will sign the Study Consent between cycle days 1 and 10, be randomized to treatment and receive all necessary instructions, forms and equipment to continue with the treatment phase. On the day of their luteinizing hormone (LH) surge (luteal phase), subjects will undergo a night of Late Wake Therapy (LWT) (sleep 21:00-01:00 h, followed by wake) vs. Early Wake Therapy (EWT) (wake until 03:00 h followed by sleep until 07:00 h) at home. We selected the specific wake and sleep times based on our previous work in PMDD.[36, 37] The following day, subjects will receive the light intervention for 7 consecutive days: days 1-7 after the LH surge (approximately menstrual cycle days 15-21). Depending on their randomization schedule, subjects will receive, at home, 60 min of either AM bright white light (LED of 1350 lux at 20 inches) starting within 30 minutes of their habitual wake time (for those undergoing LWT), or PM bright white light ending 30 min before their habitual sleep onset time (for those undergoing EWT). The following Month 4 (Washout) will be a month of no intervention to prevent any carry-over effects from the Month 3 intervention affecting measures in Month 5. Mirroring Month 3 timing, in the luteal phase of Month 5, subjects will receive the alternate wake therapy (LWT or EWT) and light exposure (AM or PM) (see Fig. 1, above).

Sleep Interventions: Appropriate sleep and wake times during the EWT and LWT interventions will be documented by actigraphy. Compliance with wake therapy also will be monitored by having patients leave a message on an answering machine once every half-hour while awake. As they are only awake for 4 hours during wake therapy, they will make 8 calls. The potential risks of wake therapy include fatigue. Subjects will be encouraged to stay at home the day after wake therapy or, if driving, arrange alternative transportation. In previous studies of one night of total wake therapy in PMDD patients, subjects felt energized and wished to return to work or other daily activities. Previous studies also included two consecutive nights of partial wake therapy. We anticipate fewer problems in this study with only one night of partial wake therapy. Sleep and activity measures are non-invasive, but may cause some skin irritation and/or discomfort on the wrist where the Actiwatch Spectrum (Philips Respironics, Bend Oregon) is worn.

Light Interventions: Subjects will sit in front of a portable (5.5" x 6.25") Litebook ® Model 1.2 light box (an array of 60 cool white light-emitting diodes behind a clear plastic screen)(The Litebook Company Ltd., Alberta Canada) with an intensity of 1,350 lux and an irradiance of 2.41×10^{-9} w/cm^2 at 20 in, and spectral emission peaks at 464 nm and 564 nm. Subjects will gaze at the light source for a minute every few minutes for 60 min. The distance of the subject from the light source will be calibrated individually for each light box by use of a Meterman LM631 Digital Light Meter (Meterman Test Tools, Everett, WA) to produce an intensity of 1,350 lux at 20.0 in. Ambient light intensity and spectra will be documented by the Actiwatch Spectrum. A research assistant will provide a measuring tape to ensure proper distance between light source and patient, check the Actiwatch recordings to ensure compliance, as well as the Litebook's built-in compliance monitor recordings. Since most of us are exposed to fluorescent light in our everyday lives, we do not anticipate that exposure to bright light per se will pose any special physical, psychological, social or legal risks. The intensity planned is less intense than bright sunlight, which normally exceeds 10,000-50,000 lux. Although 1,350 lux is more intense than common indoor room lighting during a 16-hour day, the average patient would receive more radiation from room lighting than from 1-2 hours of special lighting. Thus, the treatment is expected to be less hazardous than going for a walk or going to the beach. No special side effects apart from mild sleepiness (the patient needs to be awake for the light exposure and evening light may potentially disrupt sleep onset) are anticipated. It should be noted that sleep deprivation has been reported to benefit depressed patients. The possibility that the bright light treatment might potentiate a depressed patient's risk of switching into mania is recognized, although we have not seen this effect in previous studies of PMDD patients and we will exclude bipolar patients with mania from the study. If hypomania occurs, the light would be discontinued and appropriate referral and treatment with psychotropic medication, if needed, would be given.

Duration: Intervention phase will require a minimum of 3 months, provided patients have regular menstrual cycles and we can detect an LH surge (ovulation) in months 3 and 5. If a patient fails to ovulate in either month 3 or 5, she will be asked to repeat ovulation testing the following month. Two consecutive months with no ovulation will result in discontinuation of participation.

5.2 Handling of Study Interventions

After randomization, the research associate will prepare all necessary equipment and recording logs necessary for patients to complete the study. The study

coordinator and research associate, unmasked to the treatment condition, will provide the necessary instructions to ensure proper administration of treatment.

Light boxes, binders, calendars and checklists will be provided in office to facilitate patient adherence to time-specific study protocols, completion of forms, collection of required measures and at-home self-administration of the study intervention.

5.3 Concomitant Interventions

As we will study mood and endocrine effects of the intervention from baseline to post-treatment, use of hormonal contraception (within six months prior to study) and other medication (within one month prior to study) will be prohibited.

5.3.1 Allowed Interventions

Acetaminophen (Tylenol) 650 mg po every 4 hours prn pain or headache.

5.3.2 Required Interventions

N/A

5.3.3 Prohibited Interventions

Hormonal contraception (within six months prior to study) and other medication (within one month prior to study or at any time during the study) that may affect outcome measures of mood, circadian rhythms or hormone levels (6-sulphatoxy-melatonin, estradiol, progesterone, FSH, LH, prolactin) will be prohibited. Such medications include Over-the-Counter (OTC) medication (excluding Tylenol), antidepressants, anti-anxiety, antihypertensive, beta blockers, and asthma medications. Vaccinations, vitamins/mineral supplements (excluding St. John's Wart, melatonin and valerian) and/or short course antibiotics will not be considered exclusionary.

5.4 Adherence Assessment

Utilizing itemized checklists outlining each study requirement, study staff will review all data collection forms/logs on an ongoing basis for completeness and accuracy as well as compliance to study protocol. Binders, calendars and checklists will be provided to facilitate patient adherence to time-specific study protocols, completion of forms and collection of required measures. Staff will calculate adherence to protocol and continuously tabulate the results to ensure adherence to wake therapy is 100% and light is at least 85% (completing at least 6 of 7 days of light therapy). Appropriate sleep and wake times during the EWT and LWT interventions will be documented by actigraphy. Compliance with wake therapy also will be monitored by having patients leave a message on an answering machine once every half-hour while awake. As they are only awake for 4 hours during wake therapy, they will make 8 calls. To ensure compliance with light protocols, a research associate will provide a measuring tape to ensure proper distance between light source and patient, check the Actiwatch recordings during time of intervention, as well as the Litebook's built-in compliance monitor recordings.

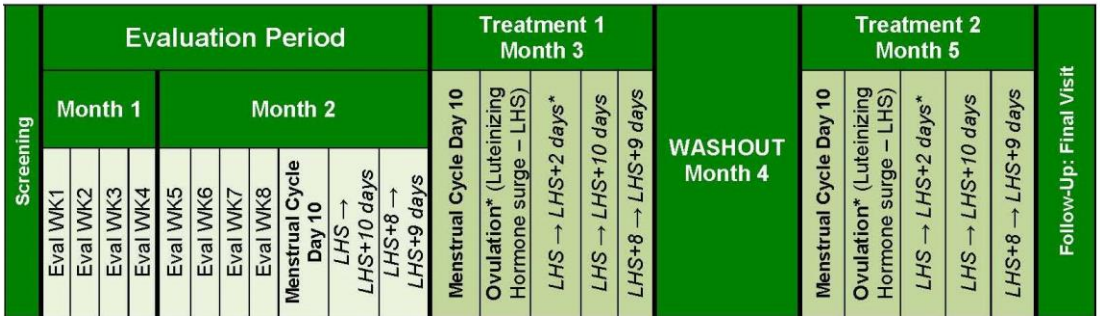
6. STUDY PROCEDURES

6.1 Schedule of Evaluations

	Screening	Evaluation Period											Treatment 1 Month 3					WASHOUT Month 4	Treatment 2 Month 5						Follow-Up: Final Visit
		Month 1				Month 2																			
		Eval WK1	Eval WK2	Eval WK3	Eval WK4	Eval WK5	Eval WK6	Eval WK7	Eval WK8	Menstrual Cycle Day 10	*LHS → LHS+10 days*	*LHS+8 → LHS+9 days*	Menstrual Cycle Day 10	Ovulation* (Luteinizing Hormone surge – LHS)	*LHS → LHS+2 days**	*LHS → LHS+10 days*	*LHS+8 → LHS+9 days*		Menstrual Cycle Day 10	Ovulation* (Luteinizing Hormone surge – LHS)	*LHS → LHS+2 days**	*LHS → LHS+10 days*	*LHS+8 → LHS+9 days*	
Screening Consent	X																								
Urine Toxicology Screen	X																	X							
Menstrual Assessment Questionnaire	X																								
Ovulation Testing (7 days)										X			X						X						
Hamilton		X	X	X	X	X	X	X	X					X	X		X	X		X	X		X	X	X
BDI		X	X	X	X	X	X	X	X					X	X		X	X		X	X		X	X	X
BAI		X	X	X	X	X	X	X	X					X	X		X	X		X	X		X	X	X
PGWI		X	X	X	X	X	X	X	X					X	X		X	X		X	X		X	X	X
Daily Mood Ratings		X	X	X	X	X	X	X	X					X	X					X	X				
SCID									X																
Study Consent													X												
Randomization													X												
SPAQ													X												
Expectation Form													X												
Horne and Ostberg													X												
PSQI					X				X								X							X	
Visual Analogue Scale Sleep Quality Rating					X				X								X							X	
Actigraphy (10 days)											X					X						X			
Urine Collection (30 hrs)												X					X							X	
Side-Effects Checklist																	X							X	
Global Assessment of Treatment Effectiveness																									X

* Evaluations (Hamilton and Becks) over the phone.

6.2 Description of Evaluations



Evaluations will be performed at various times during the multiple steps of this 5-month study: Screening, Evaluation Period (months 1 and 2), Treatment 1 (month 3), Washout (month 4), Treatment 2 (month 5) and Follow-up/Final Visit. In the Schedule of Evaluations figure above, LHS refers to luteinizing hormone surge detected via ovulation testing (performed for 7 days starting on menstrual cycle day 10 in months 2, 3 and 5).

Objective ratings (HRSD and SCID) will be administered, collected, scored and reviewed by the Clinical Rater immediately upon completion by the patient.

Subjective ratings (BDI, BAI, PGWI, Daily Mood Ratings (VAS), SPAQ, Expectation Form, Horne and Ostberg Scale, PSQI, Sleep Quality Ratings, Side Effects Checklists, Global Assessment of Treatment Effectiveness) will be collected and scored by the Research Associate for review by the Clinical Rater upon completion by the patient.

6.2.1 Screening Evaluation

Screening evaluations will be collected weekly in clinic during months 1 and 2. Baseline mood, endocrine and sleep measures will also be collected during evaluation month 2.

Screening

All subjects will be screened via telephone to ensure they meet study criteria as defined in sections 4.1 (Inclusion Criteria) and 4.2 (Exclusion Criteria) above. Those that meet criteria will be scheduled for a screening interview with the Study Coordinator. Inclusion and exclusion criteria must be maintained throughout the study. Any deviation will be reported to the Study Coordinator and conveyed to the PI for evaluation and outcome determination.

During their initial screening visit in clinic, patients will complete a Menstrual Screening Form to assess mood and somatic symptoms, medication use and personal and family medical and psychological history. In addition we will obtain a urine toxicology screen and a pregnancy test.

Consenting Procedure

A written informed Screening Consent will be obtained from each subject at entry into the study to proceed with participation in the evaluation phase. After completion of the evaluation phase, qualified participants will sign a Study Consent before

proceeding with the treatment phase. Informed consent is obtained by the following process:

1. The subject will be asked to review the screening consent form.

2. The PI, Study Coordinator and/or one of their associates will meet with the subject to review the form, to confirm and to answer any questions the subject might have. The UCLA Office of Protection of Research Studies "Evaluation to Sign a Consent form for Research" will be administered to insure that all participants have understood the consent document, before they are asked to sign it.

3. Once the subject demonstrates understanding of the study and agrees to participate in the study, the consent will be signed in the presence of the Study Coordinator or a Research Associate and a witness.

6.2.2 Enrollment, Baseline, and/or Randomization

Baseline Assessments

In accordance with the Schedule of Evaluations (section 6.1 above), baseline measures will be collected in Evaluation Month 2 as follows:

- Hamilton: The Hamilton Rating Scale for Depression (HRSD)[56] (as a validated objective, interview-based assessment of depression). Atypical depression symptoms as part of the Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders version (SIGH-SAD)[60] (as atypical symptoms in particular respond to light treatment[61]) Mania[62] ratings (to document any clinical induction of manic symptoms by the wake or light interventions) – once weekly for 8 weeks,
- Beck Depression Inventory (BDI)[57] (as a validated subjective assessment of depression) – once weekly for 8 weeks,
- Beck Anxiety Inventory (BAI)[58] (as many women with PMDD report anxiety symptoms)[63] – once weekly for 8 weeks,
- The Psychological General Well-Being Index (PGWI)[64] – once weekly for 8 weeks,
- Daily mood self-ratings (DMR)[54] that include core PMDD symptoms of anxiety and irritability – daily for 8 weeks,
- Expectation form measuring patient expectation for change with the interventions (100 mm line from "much worse" to "much better") – completed once,
- Horne-Östberg scales to assess morningness and eveningness[65] – completed once,
- Seasonal Pattern Assessment Questionnaire (SPAQ)[66] – completed once,
- Pittsburgh Sleep Quality Index (PSQI)[67] to assess subjective sleep quality – once in month 1 and month 2,
- Visual analogue scale[68] to assess subjective sleep quality – once in month 1 and month 2,

- Structured Clinical Interview for DSM-IV (SCID)[51, 52] – completed once to establish diagnosis in evaluation week 8,
- Ovulation testing performed for 7 days starting on menstrual cycle day 10 in month 2 to determine luteinizing hormone surge (LHS). Participants will contact Study Coordinator with their time of first menses (cycle day 1) to determine cycle day 10 and schedule appointment for collecting study forms and equipment,
- Actigraphy will be collected for 10 days starting the day of LHS to monitor baseline sleep, light and activity measures at home,
- Urine collection for 30 hrs performed between days 8-9 after LHS.

Enrollment

Enrollment in the evaluation phase of the study occurs at the time of first screening visit when patients sign a Screening Consent form.

Enrollment in the treatment phase occurs during a clinic visit scheduled between cycle days 1 and 10 of the menstrual cycle immediately following successful completion of the evaluation phase (Month 3), provided they are qualified to participate and they sign a Study Consent form. During this visit, they will also be assigned an individual participant identifier (Master Code Number) and be randomized to the first of two treatment conditions. Enrollment ascertainment for the treatment phase and randomization occur at the same time.

Randomization

All subjects for this study will be enrolled in the evaluation phase of the study at the time of the first screening visit when patients sign a Screening Consent form. Enrollment in the treatment phase occurs during a clinic visit scheduled between cycle days 1 and 10 of the menstrual cycle immediately following successful completion of the evaluation phase (Month 3), provided the subject is qualified to participate. During this visit, we will randomize subjects to the first of two treatment conditions. Starting on the day of ovulation, subjects will be randomized to either 1) one night of Late Wake Therapy (LWT: sleep 21:00-01:00 h, followed by wakefulness) plus 7 days of AM Bright White Light (BWL: light-emitting diode-LED administered for 60 minutes, starting within 30 minutes of habitual wake time) or 2) Early Wake Therapy (EWT: wakefulness until 03:00 h, then sleep 03:00-07:00 h) plus 7 nights of PM BWL (administered 90 minutes before habitual sleep onset, for 60 minutes). The problem of randomization imbalance, observed particularly when independent groups (such as group 1 receiving only treatment A and group 2 receiving only treatment B) are used, will be addressed by two processes. First, this study uses a cross-over design and subjects will be assigned to the other treatment in the luteal phase of their next menstrual cycle after a one-month washout period. Second, subjects will be randomized to study treatment group in a 1:1 ratio with variably-sized block design. This randomization will be done using SAS programs that we have used for many of our clinical trial studies. The block sizes are known only to the study statistician. The randomization table will be prepared prior to the initiation of the study.

Note, only subjects who meet all of the inclusion criteria and none of the exclusion criteria after successful completion of the evaluation phase are eligible for randomization into the treatment phase.

In addition to violations of inclusion and exclusion criteria, we also will document in the patient's chart reasons for randomization failure, any protocol deviations and reasons why subjects were lost to follow-up, voluntarily withdrew and/or were terminated from the study.

Participants will be assigned for study between cycle days 1 and 10 of Month 3 and will begin the wake therapy component of Treatment 1 at time of ovulation, which may occur between cycle days 10 and 17. Treatment 2 will occur in Month 5, approximately two months after randomization. If a patient does not ovulate, treatment will be delayed until the following menstrual cycle, thereby increasing the time between randomization and each treatment condition by approximately 1 month, the maximum allowable period.

6.2.3 Blinding

The principal investigator and clinical rater will remain blind to treatment condition until completion or discontinuation of participant from study. As patients will be coded, one statistician and technician and supervisor running assays also will be blind to patient name and treatment condition. Members of the Data Safety Monitoring Committee will review records in which patient names are coded, unless the code needs to be broken in the event of an adverse outcome. All other lab personnel will not be blind to treatment as the study coordinator and research associate prepare patient equipment and instruct patients on proper completion of the treatment protocol, the data manager and quality assurance officer enter all data into the database (including treatment condition). Due to the nature of the treatment (sleep, light intervention), patients will not be blind to condition.

6.2.4 Treatment Visits

In accordance with the Schedule of Evaluations (section 6.1 above), treatment-related measures will be collected in months 3 and 5 as follows:

- Hamilton: The Hamilton Rating Scale for Depression (HRSD)[56] (as a validated objective, interview-based assessment of depression). Atypical depression symptoms as part of the Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders version (SIGH-SAD)[60] (as atypical symptoms in particular respond to light treatment[61]) Mania[62] ratings (to document any clinical induction of manic symptoms by the wake or light interventions) – on ovulation night (LSH), daily on LHS+1 – LHS+2 (during intervention) and once after light treatment on LHS+8-9 (post-intervention assessment).
- Beck Depression Inventory (BDI)[57] (as a validated subjective assessment of depression) – on ovulation night (LSH), daily on LHS+1 – LHS+2 (during intervention) and once after light treatment on LHS+8-9 (post-intervention assessment),
- Beck Anxiety Inventory (BAI)[58] (as many women with PMDD report anxiety symptoms)[63] – on ovulation night (LSH), daily on LHS+1 – LHS+2 (during intervention) and once after light treatment on LHS+8-9 (post-intervention assessment),
- The Psychological General Well-Being Index (PGWI)[64] – on ovulation night (LSH), daily on LHS+1 – LHS+2 (during intervention) and once after light treatment on LHS+8-9 (post-intervention assessment),

- Daily mood self-ratings (DMR)[54] that include core PMDD symptoms of anxiety and irritability – collected daily on LHS+0 through LHS+2 (for wake therapy effects) and daily LHS+3 through LHS+10 (for light treatment effects),
- Pittsburgh Sleep Quality Index (PSQI)[67] to assess subjective sleep quality – once on LHS+8-9 (post-intervention assessment),
- Visual analogue scale[68] to assess subjective sleep quality – once on LHS+8-9 (post-intervention assessment),
- Ovulation testing performed for 7 days starting on menstrual cycle day 10 in months 3 and 5 to determine luteinizing hormone surge (LHS). Participants will contact Study Coordinator with their time of first menses (cycle day 1) to determine cycle day 10 and schedule appointment for collecting study forms and equipment,
- Actigraphy will be collected for 10 days starting the day of LHS to monitor baseline sleep, light and activity measures at home,
- Urine collection for 30 hrs performed between days 8-9 after LHS.

Objective assessments (HRSD) collected during intervention and post-intervention will be performed by telephone, to reduce patient burden, on the same day the patients complete the subjective assessment forms (BDI, BAI, PGWI, DMR, PSQI, sleep quality) during the times indicated above.

6.2.5 Washout

During washout Month 4, subjects will again perform the urine toxicology screening, Hamilton, BDI, BAI and PGWI ratings (once ***during the luteal phase, around the same time in the patient's cycle as the post treatment 2 ratings were collected***).

6.2.6 Follow-up/Final Evaluation

During final visit, subjects will again perform the Hamilton, BDI, BAI and PGWI ratings (once). They will also complete the Global Assessment of Treatment Effectiveness form. Final evaluation of inclusion/exclusion criteria will be performed at this time.

After completion of the study (final visit), participants will be followed up for 1 month to monitor relapse. The Clinical Rater will telephone the patient at home during the luteal phase, around the same time in the patient's cycle as the post treatment 2 ratings were collected, to collect follow-up mood ratings (Hamilton, BDI, BAI and PGWI).

None of the subjects will be excluded from analysis, and their data will be analyzed according to the randomization scheme. Different hypotheses are included for different phases of the study. All subjects will be included in any baseline analyses regardless of their final study status. In addition to the baseline data, at least one other data point is needed in order to provide a valid estimation of a parameter for change throughout the study. The Random Regression Model was selected due to the flexibility of this method that includes all subjects with any valid data point in the analyses, as opposed to a method that is designed to examine just

the completers, such as a Repeated Measures Analysis of Variance. All subjects will be included in the analyses and we will not focus only on subjects who complete the study. Secondary analyses will be performed on data from completers. Our methods for data analyses include all subjects with any valid data points in the analyses (see Section 9.6. General Approach to Data Handling and Statistical Analyses).

7. SAFETY ASSESSMENTS

Participant safety will be monitored once an individual is enrolled for screening in the study.

7.1 Specification of Safety Parameters

Risks to patients in this protocol are low and are detailed as follows:

Affect and Anxiety:

Premenstrual symptoms may become worse leading to depression, anxiety, irritability and rarely suicidality. It is anticipated that these studies will not be greatly different from spending nights at home with some added measurements and interventions. The added measures may add some disruption and anxiety to daily schedules.

Urine Collection, Sleep/Activity:

The risks of urine collection are minimal and may include inconvenience with collection of samples and completion of forms. Sleep and activity measures are non-invasive, but may cause some skin irritation and/or discomfort on the wrist where the Actiwatch is worn.

Effects of Bright Light Treatment:

Since most of us are exposed to fluorescent light in our everyday lives, we do not anticipate that exposure to bright light per se will pose any special physical, psychological, social or legal risks. The intensity planned is less intense than bright sunlight, which normally exceeds 10,000-50,000 lux. Although 1,350 lux is more intense than common indoor room lighting during a 16-hour day, the average patient would receive more radiation from room lighting than from 1-2 hours of special lighting. Thus, the treatment is expected to be less hazardous than going for a walk or going to the beach. No special side effects apart from mild sleepiness (the patient needs to be awake for the light exposure and evening light may potentially disrupt sleep onset) are anticipated. It should be noted that sleep deprivation has been reported to benefit depressed patients. The possibility that the bright light treatment might potentiate a depressed patient's risk of switching into mania is recognized, although we have not seen this effect in previous studies of PMDD patients and we will exclude bipolar patients with mania from the study. If hypomania occurs, the light would be discontinued and appropriate referral and treatment with psychotropic medication, if needed, would be given.

Effects of Wake Therapy or Partial Sleep Deprivation:

The potential risks include fatigue. Subjects will be encouraged to stay at home the day after wake therapy or, if driving, arrange alternative transportation. In previous studies of one night of total wake therapy in PMDD patients, subjects felt energized and wished to return to work or other daily activities. Previous studies also included two consecutive nights of partial wake therapy. We anticipate fewer problems in this study with only one night of partial wake therapy.

The following risk-management procedures will be used:

Depression, Anxiety, Suicidality, Mania:

To guard against adverse effects, all subjects will have a complete psychiatric history administered by a certified clinician. By monitoring mood twice daily and by providing weekly ratings by trained clinicians, we expect to detect any problems with mood before they become severe. Known bipolar patients are excluded to reduce the risk of mania occurring. Suicidal ideation will be monitored by the Clinical Rater at the time of HRSD administration. Patients are instructed to call the Rater, Study Coordinator, Research Associate or on-call psychiatrist if these symptoms occur. Suicidal ideation will be evaluated by both the Clinical rater and PI to determine the best course of action. A licensed psychiatrist will always be on-call to subjects should any psychiatric emergency arise. If needed, patients will be referred for appropriate treatment including inpatient hospitalization if warranted.

Urine Collections:

Trained staff will instruct participants in the proper method of urine collections.

Wake Therapy:

To ensure sufficient wakefulness after the wake therapy interventions, the patient is encouraged to stay at home, not drive or operate machinery and arrange for alternate transportation, for which they will be reimbursed. To avoid the induction of mania, bipolar patients are excluded.

Actiwatch:

Equipment will be checked regularly and its use by subjects overseen by specifically trained personnel to ensure maximum safety and comfort.

Pregnancy:

Subjects are warned not to rely on "time of the month" for contraception.

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

Timing of assessment and reporting of adverse events are detailed in items 7.3 and 7.4 below. We will utilize a Data Safety and Monitoring Committee and will immediately report any unanticipated or adverse events affecting subjects or others to the Institutional Review Board (IRB) of the University of California, San Diego to determine whether further information or protocol changes are needed. Any study modifications required by the IRB would be reported to the NCCAM/NIH program officer immediately.

7.3 Adverse Events and Serious Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject during participation in the clinical study or with use of the experimental agent being studied. An adverse finding can include a sign, symptom, abnormal assessment (laboratory test value, vital signs, electrocardiogram finding, etc.), or any combination of these.

A serious adverse event (SAE) is any adverse event that results in one or more of the following outcomes:

- Death

- A life-threatening event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly or birth defect
- An important medical event based upon appropriate medical judgment

AEs will be categorized according to the likelihood that they are related to the study intervention as follows:

0 – Definitely unrelated:	AE is clearly not related to the investigational agent(s)
1 – Unlikely:	AE is doubtfully related to the investigational agent(s)
2 – Possibly related:	AE may be related to the investigational agent(s)
3 – Probably related:	AE is likely related to the investigational agent(s)
4 – Definitely related:	AE is clearly related to the investigational agent(s)

All AEs (and SAEs) will be recorded by the study coordinator, research associate or other staff member as they occur. Reports that include onset time, duration, severity, etc., will be sent to PI for review to determine actions to be taken, relatedness to study and monitoring of outcomes.

Mood ratings and side effects checklists will be utilized to assess treatment safety.

7.4 Reporting Procedures

As detailed in the Data and Safety Monitoring Plan (DSMP) for an Independent Monitoring Committee, AEs (and SAEs) will be labeled by level of severity in accordance with the grading system stipulated in the U.S. Department of Health and Human Services' Common Terminology Criteria for Adverse Events (CTCAE) – Version 4.0 (v4.03: June 14, 2010).[1] Grades range from 1 to 5 and are based on the AE's impact on the patient as 1) Mild, 2) Moderate, 3) Severe, 4) Life-threatening, and 5) Death. Attribution of each AE will be determined by PI according to the above criteria.

AEs will be followed up weekly for 3 months, once every 2 weeks for 2 months, and once per month for 1 month (total of 6 months).

The Independent Monitoring Committee (IMC), composed of a clinician with expertise in women's mental health and the reproductive cycle, a physician with expertise in clinical trials and a biostatistician will review adverse event rates yearly. A yearly Study Safety Report listing individual AEs, frequency/severity of treatment-related side effects and out-of-range scores will be provided to the IMC, the UCSD IRB and NIH/NCCAM.

[1] U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Center. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 – Published: May 28, 2009 (v4.03: June 14,2010) http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the IMC, IRB and NCCAM in accordance with requirements.

- Unexpected fatal or life-threatening AEs related to the intervention will be reported to the NCCAM Program Officer within 7 days. Other serious and unexpected AEs related to the intervention will be reported to the NCCAM Program Official within 15 days.
- Anticipated or unrelated SAEs will be handled in a less urgent manner but will be reported to the IMC, IRB, NCCAM, and other oversight organizations in accordance with their requirements. In the annual AE summary, the Independent Monitor Report will state that they have reviewed all AE reports.

7.5 Followup for Adverse Events

AEs will be followed weekly for 3 months, once every 2 weeks for 2 months, and once per month for 1 month (total of 6 months).

7.6 Safety Monitoring

The independent monitors comprising the IMC for this study are Dr. James Lohr, with expertise in clinical trials, Dr. Kathryn Hirst, with clinical expertise in women's mental health related to the reproductive cycle and Dr. Wesley Thompson, a biostatistician. They are not associated with this research project and thus work independently of the PI, Dr. Barbara L. Parry. Drs. Lohr, Hirst and Thompson are not a part of the key personnel involved in this grant and are qualified to review the patient safety and data generated by this study because of their expertise in the following areas:

As professor and vice chair of clinical affairs in the UCSD Department of Psychiatry, director of the VA Center of Excellence for Stress and Mental Health, and executive director of the UCSD Psychopharmacology Research Initiatives Center of Excellence, Dr. Lohr has extensive experience in human subjects research monitoring and disease expertise. Dr. Hirst's experience is in Family Medicine and Psychiatry with a focus on women's mental health and the reproductive cycle.

Dr. Thompson's research interests center on the adaptation and application of statistical models of a dynamic covariation of multiple functional processes in order to identify potentially causal relationships between brain function, depression, and physical health. He is also interested in developing statistical models that may explain the underlying mechanisms of healthy cognitive aging.

8. INTERVENTION DISCONTINUATION

If complications develop from the urine collection, sleep, activity or light studies, the procedure would be discontinued and all appropriate measures taken to provide the necessary care and follow up (unless otherwise requested by patient).

Participation in research is entirely voluntary. Patients may refuse to participate or withdraw at any time without jeopardy to the medical care they will receive at this institution or loss of benefits to which they are entitled. The investigator also may withdraw patients from participation if they become pregnant or otherwise loose qualification for participation (see sections 4.1 and 4.2 for inclusion and exclusion criteria, respectively). The PI can

withdraw patients from the study without their consent if they fail to comply with important study requirements, such as keeping appointments or if they become so ill that they need to be referred for outside treatment.

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

The design is a randomized cross-over contrasting LWT+AM bright light vs. EWT+PM bright light administered in the luteal phase of two separate menstrual cycles, and preceded by 2 evaluation months. To lessen the patient's burden, the 1-night EWT or LWT and the following 7-day BWL interventions will be conducted at home, given at a fixed point in each menstrual cycle, from day 1 to 7 after the mid-cycle LH surge. We anticipate that LWT+7 days of AM BWL (vs. EWT+PM BWL) will produce much greater mood benefits and larger physiological responses, than the one-time light pulses used in our earlier phase-shift studies.

The wake therapy and light interventions proposed in this application are based on our previous studies in PMDD and key published experiments by other investigators that indicate that the combined interventions are efficacious in other mood disorders after one week of treatment and maintained at 9-months follow-up. To provide optimal timing of interventions, we will administer wake therapy in the early-night vs. late-night and light pulses in the AM vs. PM at selected times in relation to sleep (within 30 min of waking and 90 min before sleep onset, respectively).

A crossover treatment design is employed to compare LWT+AM BWL vs. EWT+PM BWL responses within the same individual. As wake interventions lose effectiveness after 1 day, and light treatment effects after 3-4 days, we anticipate minimal carry-over effects of the wake plus light interventions administered a month apart. To further ensure no carry-over effects, there will be a month of no-intervention between the 1st and 2nd treatments. Because our previous studies clearly indicated differences between PMDD and NC subjects occurred primarily in the luteal menstrual cycle phase, we will treat during this menstrual cycle phase rather than in the follicular phase.

Hypothesis (H) 1: For PMDD patients in the luteal phase, LWT+AM BWL, compared with EWT+PM BWL, will A) Decrease scores on SIGH-SAD, BDI, BAI, and DMR, and increase global assessment of treatment effectiveness from baseline to post-intervention; B) Phase-advance urinary melatonin timing measures (acrophase, onset and offset time) in relation to clock time and to sleep measures (onset, end time and mid-sleep times); C) The magnitude of the phase-advance (B, above) will correlate with the magnitude of the symptom changes (A, above) by linear regression.

9.2 Sample Size and Randomization

For our primary outcome measures of mood, based on our earlier data reflecting

seven days of light exposure alone[2] (i.e., without the 'priming' effect of wake therapy), we predict the following changes in mood in PMDD subjects (N = 40) after Late Wake Therapy plus AM Light vs. Early Wake Therapy plus PM Light: A significantly greater improvement (decrease in raw score) will be detected at the p = .05 level with (a) 71% power in Hamilton Rating Scale for Depression (HRSD) Score (Mean difference 3.15±9; effect size = .324); (b) > 99% power in atypical score (Mean difference 4.45±5; effect size = .78); (c) > 99 % power in Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders (SIGH-SAD) Items (Mean difference 7.0±11; effect size = .627); (d) 86% power in Beck Depression Inventory (BDI) score (Mean difference 6.30±15; effect size = .378).

For the recovery criterion of ≥ 50% decrease from baseline (Chi Square analyses): (a) 97% power for HRSD score (difference in proportions: .44); (b) 70% power for atypical score (difference in proportions: .30); (c) 86% for SIGH-SAD score (difference in proportions: .325); and (d) 93% power for BDI score (difference in proportions: .40). For the remission criterion of reduction to a score of ≤ 8 (Chi Square analyses): (a) 89% power for the SIGH-SAD score; (b) 44% power for the BDI score. All tests are two-tailed.

We also performed power analyses for the primary hypotheses, incorporating the longitudinal nature of the design for the proposed Random Regression model (also known as Multilevel Models, or Growth Curve Models). Procedures describes by Hedeker et al.[69] for Random Regression Models, with the above data, was used for the proposed study to estimated needed sample size. We assume a Type-I error level (alpha-level) of 0.05, drop-out rate of 10% to 15% and an autoregressive covariance structure, with correlation between sequential assessments set at 0.45 (based on our previous data). We are confident based on our results from these two separate approaches that the proposed study will have minimum power of 80% to yield a statistically significant result for a medium effect size. Here, medium effect size is defined as a treatment difference increasing linearly from 0 at baseline to .5 SD units at the last time point. Type 1 error will be controlled by correcting the p-value per domain.

Treatment Assignment Procedures

We will study subjects pre- and post-intervention to determine the optimal phase-relationship between melatonin and sleep. Using a randomized cross-over design, PMDD and NC in the luteal phase will receive either 1) one night of LWT (sleep 21:00-01:00 h, followed by wakefulness) plus 7 days of AM BWL (light-emitting diode-LED administered for 60 minutes, starting within 30 minutes of habitual wake time) or 2) EWT (wakefulness until 03:00 h, then sleep 03:00-07:00 h) plus 7 nights of PM BWL (administered 90 minutes before habitual sleep onset, for 60 minutes). Subjects will be cross-over to the other treatment in the luteal phase of their next menstrual cycles after one month of washout period.

Study statistician, Dr. Golshan, will prepare randomization table prior to startup of

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[2] Parry BL, Berga SL, Mostofi N, Klauber MR, Resnick A. Plasma melatonin circadian rhythms during the menstrual cycle and after light therapy in premenstrual dysphoric disorder and normal control subjects. *J Biol Rhythms.* 1997;12(1):47-64.

the study.

For blinding, see section 6.2.3 above.

9.3 Definition of Populations

Forty women with DSM-IV diagnoses of premenstrual dysphoric disorder (PMDD) will be selected for the study. Before entering the study, patients will be screened using standardized questionnaires and the Structured Clinical Interview for Diagnosis (SCID), complete daily mood self-ratings for two months (required to confirm a DSM-IV diagnosis) and visit our clinic weekly for Hamilton, Beck, atypical and mania ratings to observe individual changes in symptoms over the menstrual cycle that include symptoms of anxiety, irritability, mood lability and physical discomfort. Eligibility, inclusion and exclusion criteria are listed below. All subjects with valid baseline and at least one post baseline measurement will be included in the analysis.

PMDD Subjects: Eligibility, Inclusion and Exclusion Criteria:

Inclusion criteria

1) Age: 18-45 years.
2) Women with regular ovulatory menstrual cycles 26-32 days in length (for at least the previous six months).
3) A history of a depressive (but not bipolar) mood disorder, but not an ongoing episode (symptom free for the last 12 months).
4) Patients must meet DSM-IV criteria for Premenstrual Dysphoric Disorder (that includes irritability).
5) Objective ratings: mean of HRSD total scores across evaluation weeks 1-8 $\leq$ 7 for follicular phase (day 5-10 of cycle after menses); mean of total HRSD scores across evaluation weeks 1-8 $\geq$ 14 for premenstrual (luteal) phase (6 days prior to onset of menses onward).
6) Subjective ratings: mean of Beck Depression Inventory total scores across evaluation weeks 1-8 < 10 follicular phase; $\geq$ 10 premenstrual (luteal) phase.
7) Daily ratings: minimal symptoms (mean less than 50 mm on 100mm scale) follicular phase; at least a 30% increase in mean affective symptom ratings, premenstrual (luteal) phase.
8) By clinical assessment and ratings, the patient has reported a history (for at least the last six months) of recurrent, moderate to severe premenstrual mood symptoms that impair some aspect of social or occupational functioning and that remit within a few days after the onset of menses. This pattern is prospectively documented with subjective daily mood ratings (DMR – visual analogue scale) during at least two consecutive symptomatic cycles. Symptom severity will also be documented with objective and subjective ratings over that time. Patients must demonstrate a consistency of symptoms and a long enough duration of symptoms (7-10 days) to allow for study.
9) Subjects willing to endure the rigors of a long-term (up to 6 months) research study.

Exclusion Criteria

1) Subjects with significant medical illness including hepatic (abnormal liver function tests), neurological, renal, cardiac, pulmonary, hematologic, gastrointestinal, or metabolic disorders.

2) Subjects who are lactating, are within 6 months postpartum, or have an irregular sleep- wake cycle, e.g., from having very young children in the home.
3) Subjects who are using hormonal contraception (within six months prior to the study).
4) Subjects using medication that may affect outcome measures of mood, circadian rhythms or hormone levels (6-sulphatoxy-melatonin, estradiol, progesterone, FSH, LH, prolactin) within one month of initiating the study or anytime during the study. Such medications include OTC medication (excluding Tylenol), antidepressants, anti-anxiety, antihypertensive, beta blockers, and asthma medications. Vaccinations, vitamins/mineral supplements (excluding St. John's Wart, melatonin and valerian) and/or short course antibiotics will not be considered exclusionary.
5) Subjects with significant psychiatric disorder (schizophrenia, bipolar disorder, anxiety disorders, eating disorders, personality disorders, sleep disorders). An ongoing major depressive episode within the last year is reason for exclusion, although a previous history of a depressive episode is not (using DSM-IV diagnostic criteria for a major depressive episode).
6) Subjects with a recent history (within the past year) of drug or alcohol abuse.
7) Subjects with a history of anemia, kidney, cardiopulmonary, metabolic, liver or thyroid disease within one year of participation (per patient-reported medical history).
8) Subjects with irregular menstrual cycles (cycle lengths vary greater than 3 days or who fail to ovulate for 2 consecutive months).
9) Subjects unlikely to cooperate with the requirements of the study.
10) Subjects needing frequent or continuous use of any medication or drugs that may affect outcome measures, including alcohol (>1 drink daily) and nicotine (>5 cigarettes daily).
11) Subjects whose prospective DMR ratings do not show cyclic variation in association with the menstrual cycle (as per inclusion criteria).
12) Subjects with an irregular sleep schedule, *extreme chronotypes* or a sleep-wake cycle that does not correspond to the environmental light-dark cycle (e.g., subjects within 2 weeks of transmeridian travel, night shift workers, or those with significant advanced or delayed sleep phase syndromes).

9.4 Interim Analyses and Stopping Rules

This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial.

No interim analysis is planned.

9.5 Outcomes

9.5.1 Primary Outcome

- Treatment-Related Mood Rating Changes from Baseline (month 2) to post intervention (months 3,5) :

  Mood ratings include Hamilton Rating Scale for Depression (HRSD), Beck Depression Inventory (BDI), atypical depression symptoms as part of the Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders version (SIGH-SAD), Beck Anxiety Inventory (BAI), mania ratings, the Psychological General Well-Being Index (PGWI) and daily mood self-ratings (DMR) that include core PMDD symptoms of anxiety and irritability as required during diagnostic evaluation, before, during and after each wake and light intervention at the same time of day (between 15:00-17:00 h). To assess more acute effects on mood that may occur more rapidly during the wake interventions, subjects will complete DMRs twice daily beginning the evening before the wake therapy intervention and continuing until the morning after the recovery night of sleep.

- Treatment-Related Urinary 6-sulfatoxymelatonin (6-SMT) Changes from Baseline (month 2) to post intervention (months 3,5) :

  6-SMT is a principal melatonin metabolite that is abundant in urine, well correlated with plasma melatonin, and serves as an excellent marker for circadian phase response.

- Treatment-related changes in objective and subjective sleep measures:

  Using actigraphy, we will obtain objective measures of the sleep/wake cycle to ensure appropriate sleep/wake times during wake therapy, and during the light interventions as it is an important biological rhythm with which to compare the intervention-induced melatonin rhythm changes. To assess subjective sleep quality, we will use the Pittsburgh Sleep Quality Index (PSQI) and a visual analogue scale.

9.5.2 Secondary Outcomes

- Effects of expectation, morningness/eveningness and seasonality on primary outcome measures:

  Prior to entering the study, subjects will complete expectation forms measuring their expectation for change with the interventions (100 mm line from "much worse" to "much better") as well as Horne-Östberg scales to assess morningness and eveningness, as these variables may mediate or moderate primary outcome measures. To determine whether seasonality affects outcome, subjects will complete the Seasonal Pattern Assessment Questionnaire (SPAQ).

- Treatment-related changes from baseline (month 2) and 1-2 days post intervention (months 3,5) in reproductive hormones:

  We will obtain overnight urinary samples for estradiol, progesterone, gonadotropins and prolactin (obtained at the same time of 6-SMT overnight collections in baseline and intervention months).

- Subjective visual analog scale-based global assessment of treatment effectiveness:

Following both treatment interventions, subjects will complete a visual analog scale-based global assessment of treatment effectiveness.

- Subjective assessment of side effects to treatment: collected 1-2 days post intervention (months 3,5)

  Following each treatment interventions, subjects will complete an assessment of side effects using the Side Effects Checklist.

As delineated in our Data and Safety Monitoring Plan, the Independent Monitoring Committee will meet on an annual basis to review outcome data. The committee will be masked to a participant's intervention group assignment.

9.6 Data Analyses

Analysis will be performed on data from subjects qualified for participation in accordance to DSM-IV criteria for PMDD (see section 4.3 for criteria and symptoms) as confirmed prospectively by Daily Mood Ratings (DMR).

Mood and Other Ratings: In study month 3 (first treatment), month 4 (washout), month 5 (second treatment) and month 6 (follow-up), we will examine objective (HRSD, atypical, mania – to evaluate symptom severity) and subjective (Beck– to evaluate symptom severity, visual analogue scale-*DMR*) mood (including irritability and anxiety) and physical symptom ratings as a function of diagnosis and time of wake/light interventions.

6-SMT data processing and circadian analyses: From the 6-SMT concentration, urine volume, and the collection times, the 6-SMT excretion rate (ng/h) is computed for each collection interval (the interval between one voiding and the next). Circadian parameters then are computed from analyses of the full time series of 5-min intervals representing each overnight collection. The best-fitting 24-hour cosine curve (for an assumed period of 24 h) is estimated with a least-squares technique to yield the acrophase time (peak), amplitude (1/2 height) and mesor (mean excretion rate (ng/h)) of the fitted curve. To further describe changes in circadian phase and waveform, we use the actual ng/h curve to estimate the circadian timing of nocturnal 6-SMT onsets and offsets algebraically from upward (onset) and downward (offset) crossings of the cosine mesor.

Reproductive Hormones: Levels will be correlated with circadian measures and mood ratings to determine reproductive hormonal influences on circadian physiology and mood.

Daily Sleep Logs will be analyzed for rhythm stability (consistency of standard deviations of sleep onset and offset times from night to night), before vs. after the interventions.

Actiwatches: Activity and illumination will be examined to determine time-in-bed and any naps that occur during the day. Daily total sleep time, wake time, number of awakenings and distribution of lengths of awakenings for night and day separately in each 24 h period will be determined using the automated sleep-wake scoring algorithm and custom SAS procedures that we have developed.[70] Extended cosinor analyses[70] will be done to determine the mesor, amplitude and acrophase of activity and illumination and the f-statistic (with higher values representing more robust and synchronized rhythms that we expect to correlate with improved mood). The mean and maximum light intensities (in lux) and the number of minutes above 1,000 lux

also will be examined. Analyses then will be done comparing activity, sleep and light exposure between groups and time of light intervention with the light and activity summary variables as continuous covariates. Baseline pre-intervention values and post-intervention activity and illumination values also can be compared for a specific light pulse. These analyses will determine if the following variables predict the magnitude of treatment and phase-shift responses: 1) The timing of activity onset and offset, 2) The amplitude of activity at baseline, 3) The illumination levels at baseline.[1] For young adults, the Actiwatch is an accurate method for recording both the in-bed interval and for estimating the time asleep.[71] Although presumably less accurate on a nightly basis than PSG, the Actiwatch is capable of several weeks of round-the clock recording, which would not be feasible with PSG either in the CTRI or at home.

General Approach to Data Handling and Statistical Analyses: Care will be taken to insure the confidentiality, complete recording, and accurate computerization of the data. Items will be subject to range and relational checks. Crosscheck programs will be used to provide a 100% check of data entry. Descriptive statistics will be calculated on all data items. Distributions, means, medians, standard deviations, ranges, skewness and kurtosis will be calculated for all measurements. Missing data values will be minimized by intensive training of the interviewers in techniques of clarifying answers and checking questionnaires while participants are on-site. When missing values are identified, several approaches such as rescheduling tests or interviews will be used to acquire the necessary data. Furthermore, missing data will be examined to assess randomness. We expect missing data to be randomly distributed and will impute appropriate values. Missing data (i.e. loss to follow-up) will be tested to determine if it is informative, and the methods developed by Diggle[72] and Ridout[73] to test for completely random dropouts will be applied. All available data will be used in our data analysis without any need to estimate missing data (see below).

Specifically, data for hypothesis 1.A. will be analyzed using a Random Regression Model (RRM), a generalized linear model described by Gibbons et al.,[74] Hedeker et al.[69] and Laird.[75] The random effects method has several advantages over more traditional analytic approaches such as a change score, end-point or repeated measures analysis of variance. This method allows the inclusion of subjects with missing data or those who were terminated early in the study, without relying on data imputation procedures. This method provides an estimate of the individual variability around the population trend, the variability of the individual intercepts (baseline values) and slopes (changes across time), and the correlation between them. A fully saturated treatment by time model will be utilized for inference. Co-variance structure will be chosen based on Akaikes Information Criterion (AIC). Random treatment effects also will be evaluated for importance based on the model AIC. This plan allows for any group level effects to be incorporated into the model. Denominator degrees of freedom will be calculated using the Kenward-Roger small sample correction. All subjects will be included in the analyses, and we will not focus only on subjects who complete the study. Our methods for data analyses include all subjects with any valid data points in the analyses. Secondary analyses will be performed on data from completers. Type 1 error will be controlled by correcting the p-value per domain. For hypothesis 1.B, an individual's slope for each of the dependent variables listed above will be calculated and will be used for correlational analysis using the Pearson method. In addition, we will examine the number of responders. The operational definition of the criteria for

response on the mood measures, the HRSD, SIGH-SAD and the BDI, is a decrease of > 50% in the pre-treatment/baseline score, while the remission criterion will be a decline to a value < 8 on the SIGH-SAD and BDI as per Terman et al.[41] We will compare percentages of PMDD subjects achieving the Terman criteria in groups receiving different interventions using Chi Square analysis. Results from Expectation Forms and Horne-Ostberg Scales will be examined in relation to the magnitude of mood change after interventions as assessed by mood ratings, the Psychological General Well-Being Index (PGWI), and side effects checklists. We also will examine the effect of diagnosis and light intervention on measures of subjective sleep quality as measured by the Pittsburgh Sleep Quality Index (PSQI), and differences between groups or intervention on outcome measures as a function of the phase-angle difference (PAD) between melatonin timing (acrophase, onset, offset) and sleep (onset, end-time, mid-sleep) measures. Data for hypothesis 1.C will be analyzed similar to hypothesis 1.B. Data for hypothesis 2.A will be analyzed similar to hypothesis 1.A using RRM. Data from LWT + AM BWL, however, will be used only. Data for hypothesis 2.B will be analyzed similar to hypothesis 1.B by using individual slope in the correlational analysis. Data for hypothesis 3.A will be analyzed similar to hypothesis 1.B, and for hypothesis 3.B, similar to hypothesis 1.A using only EWT +PM BWL treatment data.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Data will be collected according to the schedule outlined in section 6.1. The blind clinical rater will collect all mood forms (Hamilton, BDI, BAI, PGWI, DMRs, SCID, etc.). All other forms (screening, consents, actigraphy, urine collection, side effects, urine toxicology, ovulation, etc.) will be collected by the study coordinator and/or research associate, who are not blind to the study condition. Forms will not contain any patient identifiers; only patient numbers corresponding to each participant in accordance to the confidentiality protocols stipulated in section 11.3 below.

10.2 Data Management

The data monitor will review all data collection forms on an ongoing basis for completeness and accuracy as well as compliance with study protocol. She will enter patient data into a central database, which will be verified against the original source document by independent lab personnel. The quality assurance officer will oversee the completeness and accuracy of this central database prior to proceeding with statistical analyses.

Data forms for this study are as follows:

- Menstrual Assessment Questionnaire to collect patient's menstrual, medical and psychiatric history during screening,
- Hamilton: The Hamilton Rating Scale for Depression (HRSD)[56] (as a validated objective, interview-based assessment of depression). Atypical depression symptoms as part of the Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders version (SIGH-SAD)[60] (as atypical symptoms in particular respond to light treatment[61]) Mania[62] ratings (to document any clinical induction of manic symptoms by the wake or light interventions),

- Beck Depression Inventory (BDI)[57] (as a validated subjective assessment of depression),
- Beck Anxiety Inventory (BAI)[58] (as a subjective assessment of anxiety symptoms)[63],
- The Psychological General Well-Being Index (PGWI)[64] (as a subjective assessment of general well-being),
- Daily Mood Ratings (DMR)[54] (as a subjective 100 mm visual analogue scale that include core PMDD symptoms of anxiety and irritability),
- Expectation form measuring patient expectation for change with the interventions (100 mm line from “much worse” to “much better”),
- Horne-Östberg subjective scales to assess morningness and eveningness[65],
- Seasonal Pattern Assessment Questionnaire (SPAQ)[66] to subjectively assess seasonality,
- Pittsburgh Sleep Quality Index (PSQI)[67] to assess subjective sleep quality,
- Sleep Quality Ratings[68] (a 100 mm visual analogue scale to assess subjective sleep quality),
- Structured Clinical Interview for DSM-IV (SCID)[51, 52] (a detailed objective questionnaire to establish diagnosis),
- Actiwatch Log to record subjective sleep times (bed time, wake time, naps, etc.) and assist in editing and analyzing objective sleep data,
- Urine Collection Log to record time and total urination volume associated with each collected urine sample and necessary for post-assay data analysis,
- Side- Effects Checklist to record potential side effects from treatment. Forms will be used to assess treatment safety,
- Global Assessment of Treatment Effectiveness (subjective assessment).

10.3 Quality Assurance

10.3.1 Training

Laboratory staff members are well experienced in the collection, processing and analysis of all protocol-related data. Nevertheless, as technologies and procedures continue to evolve, the quality assurance officer and study coordinator will ensure that all necessary training in the areas of data collection, processing, analysis, and reporting~~;~~ are routinely performed via specialized training courses offered at the University of California, San Diego.

10.3.2 Quality Control Committee

In accordance with the Data and Safety Monitoring Plan, laboratory personnel will provide yearly study reports to the Independent Monitoring Committee (see section 7.6 for list of committee members) to evaluate data quality, ensure protocol goals are met and recommend any necessary modification to protocol.

10.3.3 Metrics

The Quality Assurance Officer (QAO) will train personnel and implement data collection procedures and practices to ensure maximum consistency, reliability and validity of data acquisition, data entry and data analysis. Immediately after input to computer data files, the QAO will check the data file against the original data source(s) (e.g., paper records) and will examine means and standard deviations of data inputs for outliers, normality/skewness, etc.

A key element in the data acquisition process will be the routine use of check lists and spread sheets which identify individual components, as well as the person(s) responsible for executing each component of the research protocol. The QAO and Clinical Coordinator will examine check lists daily to verify that strict compliance with procedures is achieved.

Mood Measures:

To establish a reliable diagnosis of PMDD, an experienced, Ph.D.-level clinical rater will administer and interpret mood measures over two consecutive menstrual cycles. In consultation with the Principal Investigator, a licensed psychiatrist, diagnoses of PMDD will be established based on DSM-IV criteria. After they are admitted for study, the clinical rater will evaluate patients according to the evaluation schedule outlined in section 6.1 using standard clinical rating instruments, including HRSD, BDI, BAI, etc. before and after treatment (sleep + light). Mood improvement will be determined based on differences between before and after measures. Further, the exit interview will provide an opportunity for the patient express satisfaction with the protocol and to identify issues or problems in data collection, thereby providing valuable feedback for improving procedures. Complaints from participants regarding aspects of the protocol that are too burdensome will be evaluated and alterations considered.

Urine Melatonin:

The Clinical Coordinator will instruct each patient and demonstrate procedures for completing the Urine Log and collecting, transferring urine samples to tubes (using urine kits provided to them prior to cycle day 10 in months 2, 3 and 5) and freezing samples at home. The Research Associate will telephone patients to prompt them to collect samples when menstruation approaches (based on menstruation histories), will collect frozen urine kits and data logs within 3 days of collection (but not before completion of actigraphy measures), catalogue identifying information, and store samples at -70^0 centigrade. On the day the patient transfers samples to the laboratory, missing samples or log entries will be noted and the participant will be instructed on the importance of providing complete samples and records. As urine collections (particularly during mornings) may be problematic for women in school or work, patients that cannot collect some morning/evening urine samples are instructed to record time of missed collections in order to later extrapolate 6-SMT excretion rates before proceeding with analysis. Patients that are completely unable to collect urine will not be excluded from participation in the study as they will still collect mood, activity, light and sleep data for analysis of treatment outcomes.

Sleep Measures:

The Clinical Coordinator will instruct each patient on the proper use of the Actiwatch device and the completion of its accompanying log. Actigraphy devices and logs will be collected by the research associate at the same time as the urine samples. Data will be verified against logs to ensure completeness and accuracy, as well as to monitor compliance with sleep and light protocols. Compliance with wake therapy will be monitored by means of half-hourly message left to a laboratory voice mail. Timing of these messages must correspond to the required treatment time. Failure to comply with wake therapy will result in repetition of wake therapy prior to commencing light treatment.

As precise timing of ovulation is essential to the protocol, Recruitment Officer/Clinic Coordinator will train personnel to read luteinizing hormone (Clearblue®) indicators. The Coordinator and another staff member will independently examine the Clearblue® on the day after the participant phones in with her putative ovulation identification. If both agree that ovulation has occurred, the participant will be advanced to the next phase of testing. If not, further testing will be postponed until clear-cut evidence of ovulation is obtained.

10.3.4 Protocol Deviations

Laboratory staff, particularly the study coordinator and research associate, will monitor and record any deviation from study protocol and immediately report to principal investigator to assess the necessary follow up steps to achieve a resolution. Deviations in study protocol also will be reported to the Independent Monitoring Committee, the UCSD Human Research Protection Program and the NCCAM/NIH Program Official for review and follow up.

10.3.5 Monitoring

Protocol compliance will be monitored via the annual DSMP Study Report for the Independent Monitoring Committee. For detailed monitoring methods, please consult the Data Safety Monitoring Plan.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol, the informed consent documents, and any subsequent modifications will be reviewed and approved by the UCSD Human Research Protection Program responsible for oversight of the study.

11.2 Informed Consent Forms

Written informed consent will be obtained from each subject at entry into the study. For participants who cannot consent for themselves, such as those with a legal guardian (e.g. person with power of attorney), this individual must sign the consent form. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant or legal guardian and this fact will be documented in the participant's record. Informed consent is obtained by the following process:

1. The subject will be asked to review the study consent form.

2. The PI, Study Coordinator and/or one of their associates will meet with the subject to review the form, to confirm and to answer any questions the subject might have. The UCLA Office of Protection of Research Studies "Evaluation to Sign a Consent form for Research" will be administered to insure that all participants have understood the consent document, before they are asked to sign it.

3. Once the subject demonstrates understanding of the study and agrees to participate in the study, the consent will be signed in the presence of the Study Coordinator or a Research Associate and a witness.

11.3 Participant Confidentiality

All of the materials collected are for research purposes only, and data will be kept in strict confidence in accordance to the Health Insurance Portability and Accountability Act (HIPAA). No information will be given to anyone without permission from the subject. The consent form includes the informed consent statement required by the University of California, San Diego. All data will be identified with a randomly generated identification code unique to the subject.

All study data will be secured with password protection. Electronic communication with outside collaborators will involve only unidentifiable information. Source documents including all paper and electronic records for all enrolled subjects (i.e., case report forms, laboratory reports, subject study binders, etc.) will be kept in locked cabinets within locked offices. Data, specimens, forms, reports, and other records that leave the site will be identified only by a participant identification number (PID) to maintain confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using PIDs only. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the IMC and NCCAM.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NCCAM, or other government agencies as part of their duties to ensure that research participants are protected.

12. COMMITTEES

As described in section 7.4, this research protocol has an Independent Monitoring Committee that will oversee data quality and patient safety.

13. PUBLICATION OF RESEARCH FINDINGS

Publication of research findings will be at the discretion of the principal investigator. Findings will be made available to NCCAM and will also be published in ClinicalTrials.gov in accordance to their individual policies and procedures.

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15. SUPPLEMENTS/APPENDICES

I. Procedures Schedule

Consult Schedule of Evaluations (see section 6.1) for specific evaluations, forms and ratings associated with each time point listed below.

1. Screening:
    a. Telephone screening to ensure potential participants meet eligibility criteria and to schedule initial in-office screening visit,
    b. Screening Visit:
        i. Patient signs Screening Consent
        ii. Perform urine toxicology screening
        iii. Complete Menstrual Assessment Questionnaire
        iv. Record most recent start of menses (Cycle Day 1)

2. Evaluation Month 1
    a. Evaluation week 1
        i. Provide patient with binder that includes all required study forms, calendars, checklists and equipment/collection instructions needed in Evaluation Months 1 and 2
    b. Evaluation week 2
    c. Evaluation week 3
    d. Evaluation week 4

3. Evaluation Month 2
    a. Record Cycle Day 1 (patient will call Study Coordinator with date)
    b. Evaluation week 5 – (Steps i – iv below must occur before Cycle Day 10):
        i. Provide Clearblue® ovulation (luteinizing hormone surge-LHS) test kit
        ii. Provide urine collection kit
        iii. Provide Actiwatch Spectrum
        iv. Provide instructions and demonstration of proper form completion, sample collection and equipment use
    c. Evaluation week 6
    d. Evaluation week 7
    e. Evaluation week 8
    f. The following steps are not categorized within the previous 4 evaluation weeks (5-8) as varying menstrual cycle times make it difficult to determine exactly when each of the following events will occur:
        i. Menstrual Cycle Day 10 – commence testing for LHS (7 days of testing)
        ii. Ovulation Day (LHS) – commence actigraphy recording (for 10 days)
        iii. 8-9 Days after LHS (LHS+8 → LHS+9) – commence urine collection (30 hrs)
        iv. LHS+11 – equipment, samples and forms are returned to lab

4. Treatment 1 (Month 3)

a. Record Cycle Day 1 (patient will call Study Coordinator with date and to schedule pre-intervention in-office visit)
b. Pre-Intervention Visit – to be completed between cycle days 1 and 10:
    i. Patient signs the Study Consent
    ii. Patient is randomized to treatment
    iii. Provide ovulation test kit
    iv. Provide urine collection kit
    v. Provide Actiwatch Spectrum
c. Menstrual Cycle Day 10 – commence testing for LHS (7 days of testing)
d. Ovulation Day (LHS) – commence actigraphy recording (for 10 days)
    – commence Wake Therapy (1 night)
e. Day after LHS (LHS+1) – commence first light treatment (for 7 days)
f. LHS+8 → LHS+9 – commence urine collection (30 hrs)
g. LHS+11 – equipment, samples and forms are returned to lab

5. Washout (Month 4)
    a. Perform clinical ratings only

6. Treatment 2 (Month 5)
    a. Record CD1 (patient will call Study Coordinator with date and to schedule pre-intervention in-office visit)
    b. Pre-Intervention Visit – to be completed between cycle days 1 and 10:
        i. Provide ovulation test kit
        ii. Provide urine collection kit
        iii. Provide Actiwatch Spectrum
    c. Menstrual Cycle Day 10 – commence testing for LHS (7 days of testing)
    d. Ovulation Day (LHS) – commence actigraphy recording (for 10 days)
        – commence Wake Therapy (1 night)
    e. LHS+1 – commence first light treatment (for 7 days)
    f. LHS+8 → LHS+9 – commence urine collection (30 hrs)
    g. LHS+11 – equipment, samples and forms are returned to lab

7. Final Visit (can be performed at time of item 6.g. above)
    a. Review side effects to treatment and subjective global assessment of treatment effectiveness.

8. Follow-up (luteal phase in the month following Treatment 2)
    a. Perform clinical ratings per telephone.