Published in final edited form as:

Psychiatry Res. 2008 October 30; 161(1): 76–86. doi:10.1016/j.psychres.2007.11.017.

Late, but not early, wake therapy reduces morning plasma melatonin: relationship to mood in premenstrual dysphoric disorder

Barbara L. Parry^{a,b,*}, Charles J. Meliska^a, L. Fernando Martínez^a, Ana M. López^a, Diane L. Sorenson^a, Richard L. Hauger^{a,b}, and Jeffrey A. Elliott^a

^aDepartment of Psychiatry, University of California, San Diego

^bSan Diego Veterans Affairs Healthcare System

Abstract

Wake therapy improves mood in Premenstrual Dysphoric Disorder (PMDD), a depressive disorder in DSM-IV. We tested the hypothesis that the therapeutic effect of wake therapy in PMDD is mediated by altering sleep phase with melatonin secretion.

We measured plasma melatonin every 30 minutes (18:00 - 09:00 h) in 19 PMDD and 18 normal control (NC) women during mid follicular (MF) and late luteal (LL) menstrual cycle phases, and during LL interventions with early wake therapy (EWT) (sleep 03:00–07:00 h)(control condition) versus late wake therapy (LWT) (sleep 21:00–01:00 h)(active condition).

Melatonin offset was delayed and duration was longer in the symptomatic LL vs. asymptomatic MF phase in both NC and PMDD subjects. LWT, but not EWT, advanced offset and shortened duration vs. the LL baseline, although they improved mood equally. Later baseline LL morning melatonin offset was associated with more depressed mood in PMDD patients, and longer melatonin duration in the MF phase predicted greater mood improvement following LWT.

That LWT, but not EWT, advanced melatonin offset and shortened duration while they were equally effective in improving mood suggests that decreasing morning melatonin secretion is not necessary for the therapeutic effects of wake therapy in PMDD.

Keywords

Sleep deprivation; circadian rhythms; affective disorders; reproduction

1. INTRODUCTION

Premenstrual Dysphoric Disorder (PMDD) is defined as a depressive disorder in DSM-IV (American Psychiatric Association, 1994). Abnormalities in melatonin secretion characterize women with PMDD. In two separate studies, our laboratory reported low amplitude circadian rhythms of nocturnal plasma melatonin (Parry et al., 1990; Parry et al., 1997). In the initial pilot study (Parry et al., 1990), we also observed an earlier (phase-advanced) offset of melatonin secretion, which contributed to a shorter secretion duration and a decreased area under the curve (AUC) during four menstrual cycle phases (early and late follicular; mid and late luteal) in eight PMDD compared with eight normal control (NC)

Address correspondence to: Barbara L. Parry, M.D., Professor of Psychiatry, University of California, San Diego, Mailcode 0804, 9500 Gilman Dr., La Jolla, CA 92093-0804, Phone: 619 543-5592, Fax: 619 543-7519, bparry@ucsd.edu.

women. In a follow-up study, melatonin onset time was delayed, duration was compressed and AUC was decreased during the luteal compared with the follicular menstrual cycle phase in 21 PMDD subjects (Parry et al., 1997). In contrast, melatonin rhythms did not change with the menstrual cycle in 11 NC subjects, as also reported by Brzezinski et al. (1988) and Berga and Yen (1990).

Total and partial sleep deprivation (currently referred to as wake therapy) improve mood in PMDD (Parry and Wehr, 1987; Parry et al., 1995). The mechanisms by which wake therapy exerts antidepressant effects in PMDD are unknown, but we found the intervention altered the biological rhythms of sleep (Parry et al., 1999), thyroid-stimulating hormone, prolactin (Parry et al., 1996) and cortisol (Parry et al., 2000). In the present study, we tested the hypothesis that wake therapy exerts antidepressant effects in PMDD by altering the internal temporal relationship between the circadian rhythms of sleep and melatonin secretion. If the phase relationship between sleep and melatonin is pathogenic in PMDD, then shifting sleep with respect to melatonin should thereby improve mood.

Previous studies of the effects of wake therapy on melatonin amplitude measures showed primarily no effect (Jimerson et al., 1977; Touitou et al., 1992; von Treuer et al., 1996; Leproult et al., 1997; Goichot et al., 1998; Kudo et al., 1999; Redwine et al., 2000), although some observed an increase (Akerstedt et al., 1979; Salin-Pascual et al., 1988; Goh et al., 2001), and some a decrease (Rao et al., 1996; Shilo et al., 1999; Cajochen et al., 2003). These disparate results may be due to different methodologies employed, including the timing and frequency of the melatonin measurements in relation to sleep deprivation, light and activity conditions, the use of plasma versus urinary or salivary measures, the duration and timing of the change in sleep phase or sleep deprivation, and the method used to analyze melatonin amplitude or phase. In the present study, as is standard procedure in other wake therapy studies (see review, Giedke and Schwarzler, 2002), we used midnight as the focal point, and shifted sleep onset time either three hours earlier (to 21:00 h) or three hours later (to 03:00 h). Consistent with our earlier interventions (Parry et al., 1995), we truncated sleep to four hours, as allowing more than this amount of sleep does not improve mood in depressed patients (see review, Giedke and Schwarzler, 2002).

Thus, the present study was designed to test whether systematically advancing or delaying sleep would differentially alter melatonin and its timing relationship to sleep in PMDD vs. NC subjects. A second aim was to assess whether experimentally induced alterations in melatonin amplitude or phase relationships were associated with changes in depressed mood in PMDD patients.

2. METHODS

2.1. Subjects

As described elsewhere (Parry et al., 1995), subjects were screened extensively over 2–3 months by prospective evaluation using daily mood ratings, a structured menstrual assessment questionnaire, the 21-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1967), the Beck Depression Inventory (BDI) (Beck et al., 1961) the Structured Clinical Interview for DSM-IV (SCID – Patient version) (First et al., 1995), a psychiatric interview, physical examination, and laboratory tests. After screening, 41 subjects (23 PMDD + 18 NC subjects) entered the study. Seventeen PMDD and 18 NC completed the mid follicular (MF) and late luteal (LL) studies; 13 PMDD and 12 NC the late-night wake therapy (LWT) and early-night wake therapy (EWT) studies. Mean menstrual cycle length was 28.5 ± 3.1 (range 26–33) days for NC vs. 25.4 ± 2.8 (range 25–30) days for PMDD patients; mean BMI was 22.9 ± 1.6 for NC vs. 25.2 ± 5.0 vs. PMDD. Winter was identified as “my worst season” by 35.4% of NC and 50.0% of PMDD subjects. The mean age of

PMDD patients was 36.0 ± 4.1 years (range 29–43) and of NC subjects 37.2 ± 5.8 years (range 24–45). PMDD and NC subjects did not differ significantly in age, education, marital status, BMI, menstrual cycle length, “worst season,” or parity (all $p > .05$). Descriptions of mood rating scales, the nature and severity of depressive symptoms, sleep characteristics and certain hormonal treatment responses of these subjects have been published previously (Parry et al., 1995; Parry et al., 1996; Parry et al., 1999; Parry et al., 2000).

The Institutional Review Board for the Human Subjects Committee of the University of California, San Diego approved the protocol and all subjects gave written informed consent after the procedures had been explained fully.

2.2. Procedures

Using a within-subjects design, subjects underwent one night of baseline study with undisturbed sleep at their habitual times during two menstrual cycle phases: 1) MF, day 6–10 after menses, and 2) LL, two to four days prior to the onset of menses based on the mid-cycle luteinizing hormone (LH) surge, assuming a 14-day luteal phase (See Figure 1). The timing of the mid-cycle LH surge was determined by a colorimetric urinary immunoassay (Ovustick Company, Irvine, CA). Subjects also were studied during two subsequent luteal menstrual cycle phases for a randomized crossover trial of EWT with wake until 03:00 h and sleep from 03:00–07:00 h, versus LWT with sleep from 21:00–01:00 h and wake from 01:00 h until the following night of sleep. Each night of therapy was followed by a night of recovery sleep from 22:30–06:30 h.

During study nights, subjects were admitted to the General Clinical Research Center from 16:00 to 09:00 h. Ambient lighting at bedside was maintained at 30 lux or less as measured by a LM631 Digital Light Meter (Meterman Tools, Everett, WA 98203). Subjects slept in the dark with an eye mask, essentially at 0 lux. Nurses inserted an intravenous catheter at 17:00 h, and drew blood every 30 minutes from 18:00 to 09:00 h through a catheter, threaded through a porthole to an adjoining room during sleep. Blood sampling was obtained during MF, LL, EWT and LWT nights.

As described previously (Parry et al., 1995), for screening, diagnosis and mood ratings in different menstrual phases, we used the 21-item HDRS. As standard procedure, for assessments of the mood effects of sleep alterations, we omitted items that could not be meaningfully related to the subject’s condition during a brief wake therapy protocol, including three questions related to sleep. Trained clinicians administered mood ratings (HDRS, BDI) between 16:00–18:00 h during baseline MF and LL studies, and the day before, of, and after EWT, LWT and recovery nights of sleep. Technicians recorded the sleep polysomnogram (PSG) during MF, LL, wake therapy and subsequent nights of recovery sleep.

2.3. Melatonin assay

Blood samples were placed in ethylenediaminetetracetic acid-containing plastic tubes, centrifuged, frozen immediately, and stored at -70°C until assayed. All samples for the same subject were run in the same assay. Plasma melatonin concentrations were measured by radioimmunoassay (IBL Immuno-Biological Laboratories, Hamburg, Germany) with an intra-assay coefficient of variation of approximately 8% and an interassay coefficient of variation of approximately 15%. The standard range is from 3.0 – 300 pg/ml, with an assay sensitivity of 2.5 pg/ml.

2.4. Methods of estimation of melatonin parameters

As there is no universally accepted method for determining melatonin timing parameters, we compared threshold (Lewy et al., 1985; Parry et al., 1990; Klerman et al., 2002), pharmacokinetic (Gamst et al., 2004), curve-fitting (Straume et al., 1991) and a visual inspection method (Wehr et al., 2001). The later defined onset as the time of the first elevated point when the slope (dy/dt) of the melatonin concentration curve became steeply positive for at least three consecutive time points relative to the slope of points immediately preceding it; offset as the first time when the slope of the descending melatonin curve approached zero for at least three consecutive time points, and synthesis offset, based on Lewy et al. (1999), as the first time after the melatonin peak when the slope of the descending melatonin curve became steeply negative for three consecutive time points. We elected to use visual inspection in subsequent data analyses because it yielded the most reliable and accurate estimates of melatonin timing parameters, while minimizing the number of missing values, outliers and spurious values obtained with other methods. For all estimates we used the median of three visual inspection values derived from independent raters, blinded to each subject's group. Cross correlation analyses showed visual inspection yielded inter-rater reliabilities ranging from $r = .913$ to $.999$ for melatonin onset, from $r = .801$ to $.925$ for melatonin offset and from $r = .816$ to $.930$ for synthesis offset.

The duration was defined as the difference in hours between onset and standard offset, while synthesis duration was defined as the difference in hours between onset and synthesis offset. We also defined the peak concentration as the single highest concentration during the nocturnal secretory episode, and area under the curve (AUC) as the integrated melatonin concentration (pg/ml/h) from onset to standard offset.

2.5. Statistical analyses

We addressed four primary questions (Q): 1) Did melatonin measures change differentially between PMDD and NC from the follicular to the luteal menstrual cycle phase? 2) Did sleep interventions with LWT vs. EWT differentially alter melatonin parameters? 3) To what degree were changes in melatonin measures correlated with changes in mood during the different conditions? 4) Did alterations in the phase-angle between melatonin and sleep correlate with mood changes?

Tests on PSG and standard melatonin timing (Onset, Offset, Duration) and quantitative (AUC and Peak) measures, as well as measures based on synthesis offset (Synthesis Offset, Synthesis Duration, and Synthesis AUC) were carried out with two-factor "mixed" (one between, one within) multivariate analyses of variance (MANOVA), followed by univariate ANOVA with the Geisser-Greenhouse correction for sphericity of repeated measures, performed only on factors found to be significant by MANOVA. For Q1, tests of the effects of Diagnosis (NC vs. PMDD) x Menstrual Cycle Phase (MF, LL) were performed. For Q2, a Diagnosis (NC vs. PMDD) x Condition (LL vs. LWT vs. EWT) MANOVA was performed, with Condition as the repeated (within subjects) factor. For Q3, Pearson correlations were used to assess relationships of melatonin measures to mood (HDRS, BDI scores) in PMDD patients. For Q4, phase angles (melatonin onset time – sleep onset time; melatonin onset time – sleep end time; sleep onset time – melatonin offset time; sleep offset time – melatonin offset time; sleep onset time – melatonin synthesis offset time; and melatonin synthesis offset time – sleep end time) were analyzed similarly. Signs of the difference scores were adjusted so that a positive value indicated the sleep measure occurred after the melatonin measure, while a negative value indicated the sleep measure occurred before the melatonin measure. We also assessed the effect of Treatment Order (LWT first vs. EWT first) by including Treatment Order as a factor in the analyses. Post hoc analyses of significant main effects were done using pair-wise comparisons, uncorrected for number of

comparisons, due to the preliminary and exploratory nature of the data analyses, and the limited number (three) of post-hoc comparisons performed.

3. RESULTS

3.1. Standard melatonin variables

Q1 (MF vs. LL): Based on our previous studies comparing MF and LL melatonin measures (Parry et al., 1990; Parry et al., 1997), and our observation that other subject groups (e.g., postpartum and menopausal women) showed differences in melatonin secretion between symptomatic and asymptomatic groups at baseline, we tested the a priori hypothesis that PMDD and NC women would differ in melatonin measures in the asymptomatic (MF) and symptomatic (LL in PMDD) menstrual cycle phases. For the standard melatonin timing measures (Onset, Offset, and Duration), the overall MANOVA showed a significant main effect of menstrual cycle phase ($p = .048$). Univariate ANOVA showed the transition from the MF to the LL phase was associated with no significant change in melatonin onset time ($p = .738$), but a delay in melatonin offset [$F(1,33) = 4.28, p = .046$] and a corresponding increase in melatonin duration [$F(1,33) = 6.64, p = .015$]. The main effect of diagnosis ($p = .730$) and the phase $\times$ diagnosis interaction ($p = .634$) were not significant, indicating that the melatonin timing changes occurred in both PMDD and NC subjects.

Q2 (LL, LWT, EWT): The overall, repeated measures MANOVA of Diagnosis (NC vs. PMDD) $\times$ Condition (LL vs. LWT vs. EWT) was significant for Condition ($p = .002$), but not Diagnosis ($p = .697$) or the Diagnosis $\times$ Condition interaction ($p = .333$). Univariate ANOVA showed condition was significant for the standard melatonin timing measures of offset (return to baseline) [$F(2,46) = 6.84, p = .003$] and duration [$F(2,46) = 5.01, p = .012$], but not onset [$F(2,46) = 0.471, p = .478$]. Paired comparisons showed melatonin offset occurred earlier (was advanced) by LWT (when sleep was advanced, i.e., shifted earlier) relative to the LL baseline ($p = .045$; effect size = .434). See Figure 2. As a consequence, duration was shorter in the LWT than in the LL condition ($p = .014$; effect size = .512). See Figure 3. Relative to EWT, LWT offset was earlier ($p = .002$; effect size = .732) and duration was shorter ($p = .005$; effect size = .618). EWT did not significantly alter onset, offset or duration relative to the LL baseline (both $p > .05$). AUC and peak concentration were not significantly affected by Condition (all $p > .05$). The effect of treatment order (LWT first vs. EWT first) on melatonin timing and quantitative measures was non-significant for all analyses, as were the interactions between main effects and treatment order (all $p > .05$).

3.2. Melatonin synthesis variables

The effect of diagnosis ($p = .367$), condition ($p = .870$), and the diagnosis $\times$ condition interaction ($p = .451$) were statistically non-significant by MANOVA. A power/sample size analysis for these measures was performed. It showed that, given sample sizes of 18 and 17 and the mean values obtained in the present study, effect sizes were estimated at 0.385 and .224 for synthesis offset and synthesis duration, respectively; samples of $N = 85$ for synthesis offset and $N = 249$ for synthesis duration, **equivalent to effect sizes of .846 with N's of 17/18**, would be required to detect a differences between NC and PMDD with 80% power. Thus, the absence of significant effects with these synthesis offset parameters appears to be related to small effect sizes, not to inadequate sample sizes.

3.3. Mood ratings

To summarize previously published results (Parry et al., 1995): Compared with the pretreatment baseline, PMDD patients' mood ratings after recovery sleep decreased (improved) significantly following both types of wake therapy. Significant reductions in

HDRS scores occurred after both LWT (mean = -6.5 units, $p = .0005$) and EWT (mean = -6.3 units, $p = .008$), along with reductions in BDI scores for both LWT (mean = -10.1 units, $p = .0002$) and EWT (mean = -10.9 units, $p = .0001$). The differences between LWT and EWT post-treatment ratings were not significant for HDRS (mean = .13 units, $p > .05$) or BDI (mean = .80 units, $p > .05$).

3.4. Phase Angles between Melatonin and Sleep Timing Measures

We expected the sleep alterations imposed during the LWT and EWT conditions to significantly alter phase angles between melatonin and sleep timing measures on those nights. In fact, the Diagnosis x Condition repeated measures MANOVA showed a highly significant main effect of Condition ($p = .001$); the Diagnosis effect and the Diagnosis x Condition interaction were statistically non-significant ($p > .05$). Univariate ANOVA showed the main effect of Condition was significant for all phase angles tested: melatonin onset—sleep onset; melatonin onset—sleep end time; sleep onset—melatonin offset; sleep end time—melatonin offset; sleep onset—synthesis offset; and synthesis offset—sleep end time (all $p < .01$). As expected, paired comparisons showed phase angles during LWT and EWT were significantly different from those during MF and LL phases; MF and LL did not differ significantly ($p > .05$) from each other for any phase angles. (See Table 1.)

3.5. Correlations of melatonin measures with mood ratings (Q3)

Given the significant changes in melatonin timing measures that occurred in the luteal compared with the follicular menstrual cycle phase, we calculated Pearson correlations relating melatonin offset time and duration to changes in mood from the MF to the LL phase in PMDD subjects. Baseline LL melatonin offset time was positively correlated with the changes (increases) in HDRS ($r = .603$, $p = .017$) and BDI ($r = .565$, $p = .028$) depression scores that accompanied the transition from the asymptomatic MF to the symptomatic LL phase (see Figure 4 for HDRS); PMDD patients with later luteal phase melatonin offset times had greater increases in HDRS and BDI depression scores (worsening of mood) from the MF to the LL phase, compared with patients with earlier offsets.

In relation to treatment interventions, baseline MF melatonin duration was negatively correlated with change in HDRS score from LL to LWT ($r = -.748$, $p = .003$, where negative change means improvement); PMDD patients with longer MF baseline melatonin durations had greater improvement in mood (reduction in HDRS scores) after LWT recovery sleep than patients with shorter melatonin durations. (See Figure 5.)

Change in HDRS score following LWT recovery sleep was negatively correlated with change in melatonin offset time ($r = -0.637$, $p = .014$) and change in duration ($r = -.557$, $p = .039$) during LWT. Patients whose melatonin offsets or durations changed the least during LWT had the greatest reductions in HDRS scores (improvements in mood) after LWT. Change in HDRS score after EWT was not correlated significantly with change in offset time ($r = -.217$, $p = .476$) or change in duration ($r = -.397$, $p = .179$).

3.6. Correlations between melatonin-sleep phase angles and mood ratings (Q4)

As we observed significant wake therapy effects on phase angles between melatonin and sleep timing measures, we tested the relationship of phase angles to mood indices. Mood measures obtained in the evening immediately preceding wake therapy were significantly correlated with melatonin-sleep phase angles on the LWT treatment night: The phase angle between melatonin onset time and sleep onset time was negatively correlated with the pre-treatment HDRS ($r = -.632$, $p = .012$) and BDI scores ($r = -.567$, $p = .028$); the higher the HDRS and BDI depression scores, the later the melatonin onset time relative to sleep onset time. Similarly, the phase angle between the melatonin onset time and sleep end time was

negatively correlated with the pretreatment baseline HDRS ($r = -.712$, $p = .003$) and BDI scores ($r = -.550$, $p = .034$); the higher the HDRS and BDI depression score, the later the melatonin onset time relative to sleep end time. Furthermore, the phase angle between sleep onset time and melatonin synthesis offset time was negatively correlated with the pretreatment HDRS score ($r = -.546$, $p = .035$) and BDI score ($r = -.835$, $r = .001$); the higher the depression score the later the melatonin synthesis offset relative to sleep onset time. The phase angle between melatonin synthesis offset and sleep end time also was negatively correlated with HDRS ($r = -.633$, $p = .011$) and BDI score ($r = -.848$, $p = .001$); the higher the depression score the later the melatonin synthesis offset relative to sleep end time.

4. DISCUSSION

The most important finding from this study is that early and late wake therapy produced different effects on melatonin timing parameters, while producing essentially the same level of improvement in mood. LWT, but not EWT, advanced the phase and shortened the duration of melatonin secretion. As Boivin et al. (1997) observed regarding the interaction of circadian phase and wakefulness, even moderate changes in the timing of the sleep-wake cycle may have profound effects on subsequent mood. As wakefulness is paralleled by strong changes in circadian pacemaker activity that regulates melatonin secretion (Deboer et al., 2003), it may be the timing of wakefulness that accounts for the differential effect of LWT and EWT on melatonin. The findings also could be consistent with the two-process model of sleep regulation (Borbely, 1982) in that LWT had effects on a circadian process C, whereas EWT had effects on a homeostatic process S. We cannot rule out, however, the possible effects of dim light with differential timing of wake in ≤ 30 lux vs. sleep with the mask in 0 lux.

The internal coincidence and desynchronization models for sleep deprivation and depression (Wehr and Wirz-Justice, 1981) propose that the therapeutic effects of wake therapy are mediated by the realignment of sleep with underlying circadian rhythms such as melatonin (Wirz-Justice and Van den Hoofdakker, 1999). The phase-angle (timing relationship) between sleep and circadian rhythms may be critical in inducing therapeutic responses to treatment interventions. In this model, a phase advance of melatonin and/or sleep may have therapeutic effects, in part, through resulting change in the temporal relationships among these rhythms. The findings from these studies partially are consistent also with a critical interval hypothesis of depression (Wirz-Justice et al., 1995), in which sleep occurring during a critical interval of hormonal secretion at a specific circadian phase can be depressogenic. Accordingly, by truncating and shifting the sleep-wake cycle earlier with LWT, the resulting realignment of sleep with the circadian rhythm of melatonin should be sufficient to improve mood in PMDD patients. This hypothesis, however, was not supported in this study in that both LWT and EWT improved mood, while only LWT acutely altered the timing of melatonin rhythms.

A longer duration of melatonin secretion and a later (phase-delayed) offset occurred in both NC subjects and PMDD patients during the symptomatic luteal menstrual cycle phase. This effect may be attributable to the phase-delaying effects of progesterone secretion on circadian rhythms in the luteal phase (Albers, 1981; Albers et al., 1981; Axelson et al., 1981; Davis et al., 1983) if this effect is manifest more on the timing of melatonin offset than on onset. In women predisposed to depression, these melatonin timing alterations might be expected to exacerbate luteal phase depressive symptoms. That melatonin duration also increased significantly in NC subjects without worsening mood suggests that delayed luteal phase melatonin offset does not invariably lead to symptoms of depression. Conceivably, PMDD patients may be more vulnerable to depression due to luteal increases in melatonin

duration than asymptomatic women. A longer duration of melatonin secretion also occurs in primarily women patients with seasonal affective disorder (SAD)(Wehr et al., 2001), postmenopausal (Tuunainen et al., 2002; Kripke et al., 2003) or other major depressive disorders (Sekula et al., 1997; Blaicher et al., 2000), and there is high comorbidity in patients with PMDD and SAD (Maskall et al., 1997; Praschak-Rieder et al., 2001; Portella et al., 2006). As in animal models, it may be that depressed patients are more sensitive to changes, rather than in absolute levels, of melatonin duration (Carter and Goldman, 1983; Bartness et al., 1993).

Truncating melatonin secretion may improve mood in some depressed patients. The reduction of early morning melatonin secretion with exposure to bright light or propranolol administration improved mood in SAD (Rosenthal et al., 1984; Terman et al., 1989; Wehr et al., 2001; Youngstedt et al., 2004), in PMDD, but not in NC subjects (Parry et al., 1989; Parry et al., 1993; Parry et al., 1997), and in Seasonal Premenstrual Syndrome (Parry et al., 1987). Nevertheless, the occurrence of significant mood improvement following EWT in the present study, despite no significant changes in offset and duration, indicates that acute truncation of melatonin secretion is not necessary for the mood improvements produced by wake therapy.

The data correlating melatonin measures with HDRS scores at baseline support the hypothesis that delayed offset of melatonin secretion accompanies depressive mood changes. In PMDD patients, a later LL phase melatonin offset time was associated with a larger increase in depression ratings from the MF to the LL phase (Figure 4). Also, the longer the melatonin duration during the MF phase, the greater the mood improvement after recovery sleep from LWT (but not from EWT) (Figure 5). This finding suggests that a longer duration of melatonin secretion at baseline may predict clinical response to LWT. Findings generated from analyses of changes in phase angles between melatonin and sleep also are consistent with this theory: At baseline, the later the melatonin onset time relative to either sleep onset or end time, the higher the depression score. The higher the depression score before EWT, the later the melatonin offset relative to sleep end time on that night. Our finding that after LWT, the patients with the greatest changes in phase of melatonin offset had the least improvement in mood is inconsistent with this analysis, and suggests, as in SAD patients (Thompson et al., 1997), that symptomatic individuals show greater circadian phase instability in response to treatment interventions than healthy controls.

That melatonin offset, but not onset, changed during the luteal phase and as a consequence of LWT is consistent with a two-oscillator model of melatonin secretion in which onset (evening oscillator) and offset (morning oscillator) are differentially regulated by light (Pittendrigh and Daan, 1976b; 1976a; Vanecek and Illnerova, 1982; Buresova et al., 1992; Elliott and Tamarkin, 1994). Delayed offset, but not onset, of urinary measures of melatonin also characterized depressed postmenopausal women (Tuunainen et al., 2002).

Similar to Benloucif et al. (2005), we found that the standard melatonin offset (return to baseline) was a more relevant clinical marker than synthesis offset. Perhaps the synthesis offset best reflects the circadian phase of the suprachiasmatic nuclei, while the time when melatonin concentration reaches a minimal value may more closely represent a functional change in melatonin waveform (duration), which in turn relates to deactivation of melatonin receptors, e.g., in pars tuberalis or the arcuate nucleus. Thus, a phase marker chosen to best reflect SCN timing might not be the best predictor of changes in melatonin-mediated responses, especially those related to melatonin duration, at the target tissue level.

Some, but not all, studies report greater therapeutic benefit with LWT than with EWT (Gillin, 1983; Parry and Wehr, 1987; Wu and Bunney, 1990; Kuhs and Tolle, 1991;

Leibenluft and Wehr, 1992; Van den Hoofdakker, 1994). As EWT was designed as the control intervention in this study because sleep phase is shifted in the opposite direction to that of LWT, we cannot rule out the contribution of placebo effects to the responses of EWT or LWT (Parry et al., 1995).

Although changes in melatonin phase and amplitude often parallel each other, our findings do not support previous studies of circadian rhythms in PMDD and other depressive disorders in which amplitude disturbances were the primary abnormality (Souetre et al., 1989; Parry et al., 1990; Parry et al., 1996; Parry et al., 1997). Our results also contrast with studies that reported no effect of sleep deprivation on melatonin secretion (Jimerson et al., 1977; Touitou et al., 1992; von Treuer et al., 1996; Leproult et al., 1997; Goichot et al., 1998; Kudo et al., 1999; Redwine et al., 2000), and studies showing melatonin amplitude, but not phase, changes (Akerstedt et al., 1979; Salin-Pascual et al., 1988; Rao et al., 1996; Shilo et al., 1999; Goh et al., 2001; Cajochen et al., 2003). We cannot explain why the melatonin phase and amplitude results of our current study differ from our previous baseline studies. Our radioimmunoassay sensitivity is greater in the current study, but that would not account for group differences. Our sample size also is larger in this study than in our initial pilot study and our melatonin assay and analytical methods are more precise.

In conclusion, findings from the present study show that LWT advances melatonin offset time and shortens duration in the critical early morning hours in the luteal phase in both NC and PMDD subjects. While truncation of melatonin secretion may have antidepressant effects in some disorders, our results argue against this effect mediating wake therapy-induced mood improvement in PMDD, as EWT was equally effective in reducing depressive symptoms in the absence of comparable melatonin changes. It remains possible, however, that antidepressant effects in EWT vs. LWT may be generated by different mechanism(s), including a placebo response. It also may be that sleep restriction, per se, is critical in eliciting therapeutic effects of EWT and LWT, even though altered melatonin timing, which was related to PMDD symptoms, was only acutely affected by LWT. Pathogenic effects may need to be distinguished from treatment effects. Alternatively, LWT and EWT may alleviate depression by altering the phase of sleep with the phase of circadian rhythms other than melatonin. Consistent with this hypothesis are findings that LWT vs. EWT differentially phase-advanced circadian rhythms of cortisol (Parry et al., 2000) and prolactin (Parry et al., 1996).

Acknowledgments

Daniel F. Kripke, M.D. provided valuable expertise as scientific consultant and Alan Turken provided valuable technical support in performing biochemical assays.

Funding/Support: Supported by NIH Grant No. MH-063462, NIH Research Center (CRC) Grant No. M01-RR-00827, and MIRECC and VA Merit Review (RH).

REFERENCES

- Akerstedt T, Froberg JE, Friberg Y, Wetterberg L. Melatonin excretion, body temperature and subjective arousal during 64 hours of sleep deprivation. *Psychoneuroendocrinology* 1979;4:219–225. [PubMed: 515290]
- Albers HE. Gonadal hormones organize and modulate the circadian system of the rat. *Am J Physiol* 1981;241:R62–R66. [PubMed: 7246802]
- Albers HE, Gerall AA, Axelsson JF. Effect of reproductive state on circadian periodicity in the rat. *Physiol Behav* 1981;26:21–25. [PubMed: 7195042]
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Washington, D. C.: American Psychiatric Association; 1994.

- Axelsson JF, Gerall AA, Albers HE. Effect of progesterone on the estrous activity cycle of the rat. *Physiol Behav* 1981;26:631–635. [PubMed: 7196588]
- Bartness TJ, Powers JB, Hastings MH, Bittman EL, Goldman BD. The timed infusion paradigm for melatonin delivery: what has it taught us about the melatonin signal, its reception, and the photoperiodic control of seasonal responses? *J Pineal Res* 1993;15:161–190. [PubMed: 8120796]
- Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* 1961;4:561–571. [PubMed: 13688369]
- Benloucif S, Guico MJ, Reid KJ, Wolfe LF, L'Hermite-Baleriaux M, Zee PC. Stability of melatonin and temperature as circadian phase markers and their relation to sleep times in humans. *J Biol Rhythms* 2005;20:178–188. [PubMed: 15834114]
- Berga SL, Yen SS. Circadian pattern of plasma melatonin concentrations during four phases of the human menstrual cycle. *Neuroendocrinology* 1990;51:606–612. [PubMed: 2112733]
- Blaicher W, Speck E, Imhof MH, Gruber DM, Schneeberger C, Sator MO, Huber JC. Melatonin in postmenopausal females. *Arch Gynecol Obstet* 2000;263:116–118. [PubMed: 10763839]
- Boivin DB, Czeisler CA, Dijk DJ, Duffy JF, Folkard S, Minors DS, Totterdell P, Waterhouse JM. Complex interaction of the sleep-wake cycle and circadian phase modulates mood in healthy subjects. *Arch Gen Psychiatry* 1997;54:145–152. [PubMed: 9040282]
- Borbely AA. A two process model of sleep regulation. *Hum Neurobiol* 1982;1:195–204. [PubMed: 7185792]
- Brzezinski A, Lynch HJ, Seibel MM, Deng MH, Nader TM, Wurtman RJ. The circadian rhythm of plasma melatonin during the normal menstrual cycle and in amenorrheic women. *J Clin Endocrinol Metab* 1988;66:891–895. [PubMed: 3129448]
- Buresova M, Dvorakova M, Zvolsky P, Illnerova H. Human circadian rhythm in serum melatonin in short winter days and in simulated artificial long days. *Neurosci Lett* 1992;136:173–176. [PubMed: 1641185]
- Cajochen C, Jewett ME, Dijk DJ. Human circadian melatonin rhythm phase delay during a fixed sleep-wake schedule interspersed with nights of sleep deprivation. *J Pineal Res* 2003;35:149–157. [PubMed: 12932197]
- Carter DS, Goldman BD. Antigonadal effects of timed melatonin infusion in pinealectomized male Djungarian hamsters (*Phodopus sungorus sungorus*): duration is the critical parameter. *Endocrinology* 1983;113:1261–1267. [PubMed: 6617572]
- Davis FC, Darrow JM, Menaker M. Sex differences in the circadian control of hamster wheel-running activity. *Am J Physiol* 1983;244:R93–R105. [PubMed: 6849422]
- Deboer T, Vansteensel MJ, Detari L, Meijer JH. Sleep states alter activity of suprachiasmatic nucleus neurons. *Nat Neurosci* 2003;6:1086–1090. [PubMed: 12958601]
- Elliott JA, Tamarkin L. Complex circadian regulation of pineal melatonin and wheel-running in Syrian hamsters. *J Comp Physiol [A]* 1994;174:469–484.
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JB. *Biometrics Research Dept. New York: New York State Psychiatric Institute; 1995. Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (SCID-I/Pm, version 2.0).*
- Gamst A, Wolfson T, Parry B. Local polynomial regression modeling of human plasma melatonin levels. *J Biol Rhythms* 2004;19:164–174. [PubMed: 15038856]
- Giedke H, Schwarzler F. Therapeutic use of sleep deprivation in depression. *Sleep Med Rev* 2002;6:361–377. [PubMed: 12531127]
- Gillin JC. The sleep therapies of depression. *Prog Neuropsychopharmacol Biol Psychiatry* 1983;7:351–364. [PubMed: 6137031]
- Goh VH, Tong TY, Lim CL, Low EC, Lee LK. Effects of one night of sleep deprivation on hormone profiles and performance efficiency. *Mil Med* 2001;166:427–431. [PubMed: 11370208]
- Goichot B, Weibel L, Chapotot F, Gronfier C, Piquard F, Brandenberger G. Effect of the shift of the sleep-wake cycle on three robust endocrine markers of the circadian clock. *Am J Physiol* 1998;275:E243–E248. [PubMed: 9688625]
- Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol* 1967;6:278–296. [PubMed: 6080235]

- Jimerson DC, Lynch HJ, Post RM, Wurtman RJ, Bunney WE Jr. Urinary melatonin rhythms during sleep deprivation in depressed patients and normals. *Life Sci* 1977;20:1501–1508. [PubMed: 559896]
- Klerman EB, Gershengorn HB, Duffy JF, Kronauer RE. Comparisons of the variability of three markers of the human circadian pacemaker. *J Biol Rhythms* 2002;17:181–193. [PubMed: 12002165]
- Kripke DF, Youngstedt SD, Rex KM, Klauber MR, Elliott JA. Melatonin excretion with affect disorders over age 60. *Psychiatry Res* 2003;118:47–54. [PubMed: 12759161]
- Kudo Y, Uchiyama M, Okawa M, Shibui K, Kamei Y, Hayakawa T, Kim K, Ishibashi K. Correlation between the circadian sleep propensity rhythm and hormonal rhythms under ultra-short sleep-wake cycle. *Psychiatry Clin Neurosci* 1999;53:253–255. [PubMed: 10459703]
- Kuhs H, Tolle R. Sleep deprivation therapy. *Biol Psychiatry* 1991;29:1129–1148. [PubMed: 1873374]
- Leibenluft E, Wehr TA. Is sleep deprivation useful in the treatment of depression? *Am J Psychiatry* 1992;149:159–168. [PubMed: 1734735]
- Leproult R, Van Reeth O, Byrne MM, Sturis J, Van Cauter E. Sleepiness, performance, and neuroendocrine function during sleep deprivation: effects of exposure to bright light or exercise. *J Biol Rhythms* 1997;12:245–258. [PubMed: 9181436]
- Lewy AJ, Cutler NL, Sack RL. The endogenous melatonin profile as a marker for circadian phase position. *J Biol Rhythms* 1999;14:227–236. [PubMed: 10452335]
- Lewy AJ, Sack RL, Singer CM. Immediate and delayed effects of bright light on human melatonin production: shifting "dawn" and "dusk" shifts the dim light melatonin onset (DLMO). *Ann N Y Acad Sci* 1985;453:253–259. [PubMed: 3865585]
- Maskall DD, Lam RW, Misri S, Carter D, Kuan AJ, Yatham LN, Zis AP. Seasonality of symptoms in women with late luteal phase dysphoric disorder. *Am J Psychiatry* 1997;154:1436–1441. [PubMed: 9326828]
- Parry BL, Berga SL, Kripke DF, Klauber MR, Laughlin GA, Yen SS, Gillin JC. Altered waveform of plasma nocturnal melatonin secretion in premenstrual depression. *Arch Gen Psychiatry* 1990;47:1139–1146. [PubMed: 2244799]
- 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;12:47–64. [PubMed: 9104690]
- Parry BL, Berga SL, Mostofi N, Sependa PA, Kripke DF, Gillin JC. Morning versus evening bright light treatment of late luteal phase dysphoric disorder. *Am J Psychiatry* 1989;146:1215–1217. [PubMed: 2764181]
- Parry BL, Cover H, Mostofi N, LeVeau B, Sependa PA, Resnick A, Gillin JC. Early versus late partial sleep deprivation in patients with premenstrual dysphoric disorder and normal comparison subjects. *Am J Psychiatry* 1995;152:404–412. [PubMed: 7864267]
- Parry BL, Hauger R, LeVeau B, Mostofi N, Cover H, Clopton P, Gillin JC. Circadian rhythms of prolactin and thyroid-stimulating hormone during the menstrual cycle and early versus late sleep deprivation in premenstrual dysphoric disorder. *Psychiatry Res* 1996;62:147–160. [PubMed: 8771612]
- Parry BL, Javeed S, Laughlin GA, Hauger R, Clopton P. Cortisol circadian rhythms during the menstrual cycle and with sleep deprivation in premenstrual dysphoric disorder and normal control subjects. *Biol Psychiatry* 2000;48:920–931. [PubMed: 11074230]
- Parry BL, Mahan AM, Mostofi N, Klauber MR, Lew GS, Gillin JC. Light therapy of late luteal phase dysphoric disorder: an extended study. *Am J Psychiatry* 1993;150:1417–1419. [PubMed: 8352356]
- Parry BL, Mostofi N, LeVeau B, Nahum HC, Golshan S, Laughlin GA, Gillin JC. Sleep EEG studies during early and late partial sleep deprivation in premenstrual dysphoric disorder and normal control subjects. *Psychiatry Res* 1999;85:127–143. [PubMed: 10220004]
- Parry BL, Rosenthal NE, Tamarkin L, Wehr TA. Treatment of a patient with seasonal premenstrual syndrome. *Am J Psychiatry* 1987;144:762–766. [PubMed: 3296791]
- Parry BL, Wehr TA. Therapeutic effect of sleep deprivation in patients with premenstrual syndrome. *Am J Psychiatry* 1987;144:808–810. [PubMed: 3592005]

- Pittendrigh CS, Daan S. A functional analysis of circadian pacemakers in nocturnal rodents IV entrainment: Pacemaker as clock. *J Comp Physiol* 1976a;106:291–331.
- Pittendrigh CS, Daan S. A functional analysis of circadian pacemakers in nocturnal rodents V.: Pacemaker structure: A clock for all seasons. *J Comp Physiol* 1976b;106:333–355.
- Portella AT, Haaga DA, Rohan KJ. The association between seasonal and premenstrual symptoms is continuous and is not fully accounted for by depressive symptoms. *J Nerv Ment Dis* 2006;194:833–837. [PubMed: 17102707]
- Praschak-Rieder N, Willeit M, Neumeister A, Hilger E, Stastny J, Thierry N, Lenzinger E, Kasper S. Prevalence of premenstrual dysphoric disorder in female patients with seasonal affective disorder. *J Affect Disord* 2001;63:239–242. [PubMed: 11246102]
- Rao ML, Pelzer E, Papassotiropoulos A, Tiemeier H, Jonck L, Moller HJ. Selective slow-wave sleep deprivation influences blood serotonin profiles and serum melatonin concentrations in healthy subjects. *Biol Psychiatry* 1996;40:664–667. [PubMed: 8886302]
- Redwine L, Hauger RL, Gillin JC, Irwin M. Effects of sleep and sleep deprivation on interleukin-6, growth hormone, cortisol, and melatonin levels in humans. *J Clin Endocrinol Metab* 2000;85:3597–3603. [PubMed: 11061508]
- Rosenthal NE, Sack DA, Gillin JC, Lewy AJ, Goodwin FK, Davenport Y, Mueller PS, Newsome DA, Wehr TA. Seasonal affective disorder. A description of the syndrome and preliminary findings with light therapy. *Arch Gen Psychiatry* 1984;41:72–80. [PubMed: 6581756]
- Salin-Pascual RJ, Ortega-Soto H, Huerto-Delgadillo L, Camacho-Arroyo I, Roldan-Roldan G, Tamarkin L. The effect of total sleep deprivation on plasma melatonin and cortisol in healthy human volunteers. *Sleep* 1988;11:362–369. [PubMed: 3206055]
- Sehula LK, Lucke JF, Heist EK, Czambel RK, Rubin RT. Neuroendocrine aspects of primary endogenous depression. XV: Mathematical modeling of nocturnal melatonin secretion in major depressives and normal controls. *Psychiatry Res* 1997;69:143–153. [PubMed: 9109182]
- Shilo L, Dagan Y, Smorjick Y, Weinberg U, Dolev S, Komptel B, Balaum H, Shenkman L. Patients in the intensive care unit suffer from severe lack of sleep associated with loss of normal melatonin secretion pattern. *Am J Med Sci* 1999;317:278–281. [PubMed: 10334113]
- Souetre E, Salvati E, Belugou JL, Pringuey D, Candito M, Krebs B, Ardisson JL, Darcourt G. Circadian rhythms in depression and recovery: evidence for blunted amplitude as the main chronobiological abnormality. *Psychiatry Res* 1989;28:263–278. [PubMed: 2762432]
- Straume, M.; Frasier-Cadoret, SG.; Johnson, ML. Least squares analysis of fluorescence data. In: Lakowicz, JR., editor. *Topics in Fluorescence Spectroscopy*. New York: Plenum; 1991. p. 117–240.
- Terman M, Terman JS, Quitkin FM, McGrath PJ, Stewart JW, Rafferty B. Light therapy for seasonal affective disorder. A review of efficacy. *Neuropsychopharmacology* 1989;2:1–22. [PubMed: 2679625]
- Thompson C, Childs PA, Martin NJ, Rodin I, Smythe PJ. Effects of morning phototherapy on circadian markers in seasonal affective disorder. *Br J Psychiatry* 1997;170:431–435. [PubMed: 9307692]
- Touitou Y, Benoit O, Foret J, Aguirre A, Bogdan A, Clodre M, Touitou C. Effects of a two-hour early awakening and of bright light exposure on plasma patterns of cortisol, melatonin, prolactin and testosterone in man. *Acta Endocrinol (Copenh)* 1992;126:201–205. [PubMed: 1574947]
- Tuunainen A, Kripke DF, Elliott JA, Assmus JD, Rex KM, Klauber MR, Langer RD. Depression and endogenous melatonin in postmenopausal women. *J Affect Disord* 2002;69:149–158. [PubMed: 12103461]
- Van den Hoofdakker RH. Chronobiological theories of nonseasonal affective disorders and their implications for treatment. *J Biol Rhythms* 1994;9:157–183. [PubMed: 7873775]
- Vanecsek J, Illnerova H. Effect of light at night on the pineal rhythm in N-acetyltransferase activity in the Syrian hamster *Mesocricetus auratus*. *Experientia* 1982;38:513–514. [PubMed: 7084426]
- von Treuer K, Norman TR, Armstrong SM. Overnight human plasma melatonin, cortisol, prolactin, TSH, under conditions of normal sleep, sleep deprivation, and sleep recovery. *J Pineal Res* 1996;20:7–14. [PubMed: 8648563]

- Wehr TA, Duncan WC Jr, Sher L, Aeschbach D, Schwartz PJ, Turner EH, Postolache TT, Rosenthal NE. A circadian signal of change of season in patients with seasonal affective disorder. *Arch Gen Psychiatry* 2001;58:1108–1114. [PubMed: 11735838]
- Wehr, TA.; Wirz-Justice, A. Internal coincidence model for sleep deprivation and depression. In: Koella, WP., editor. *Sleep 1980*. Basel: Karger; 1981. p. 26-33.
- Wirz-Justice A, Krauchi K, Brunner DP, Graw P, Haug JH, Leonhardt G. Circadian rhythms and sleep regulation in seasonal affective disorder. *Acta Neuropsychiatrica* 1995;7:41–43.
- Wirz-Justice A, Van den Hoofdakker RH. Sleep deprivation in depression: what do we know, where do we go? *Biol Psychiatry* 1999;46:445–453. [PubMed: 10459393]
- Wu JC, Bunney WE. The biological basis of an antidepressant response to sleep deprivation and relapse: review and hypothesis. *Am J Psychiatry* 1990;147:14–21. [PubMed: 2403471]
- Youngstedt SD, Leung A, Kripke DF, Langer RD. Association of morning illumination and window covering with mood and sleep among post-menopausal women. *Sleep and Biological Rhythms* 2004;2:174–183.

Figure 1.

Flow diagram showing Baseline and Treatment Conditions over the three-month study period after the evaluation phase. Mood, sleep and melatonin (MLT) sampling were carried out during one Mid Follicular (MF) and three consecutive Late Luteal (LL) phases. Interventions during Months 2 and 3 included Late Wake Therapy (LWT) or Early Wake Therapy (EWT), presented in a randomized, crossover design.

Figure 2.

Mean melatonin offset time ($\pm$ SEM) during Late Luteal baseline, Late Wake Therapy (LWT), and Early Wake Therapy (EWT) conditions in patients with Premenstrual Dysphoric Disorder (PMDD; closed bars, $N = 13$) and Normal Control (NC; open bars, $N = 12$) subjects. P-values identify significant differences between LWT and LL baseline ($p = .045$), and LWT and EWT ($p = .002$); EWT did not differ from LL baseline ($p > .05$).

Figure 3.

Mean melatonin duration ($\pm$ SEM) during Late Luteal baseline, Late Wake Therapy (LWT), and Early Wake Therapy (EWT) conditions in patients with Premenstrual Dysphoric Disorder (PMDD; closed bars, $N = 13$) and Normal Control (NC; open bars, $N = 12$) subjects. P-values identify significant differences between LWT and LL baseline ($p = .014$), and LWT and EWT ($p = .005$); EWT did not differ from LL baseline ($p > .05$).

Figure 4. Change in Hamilton Depression Rating Scale (HDRS) score from the mid follicular (MF) to the late luteal (LL) menstrual cycle phase in relation to Melatonin Offset Time during the LL baseline phase in patients with Premenstrual Dysphoric Disorder (PMDD, N = 14).

Figure 5. Change (improvement) in Hamilton Depression Rating Scale (HDRS) score after Late Wake Therapy Recovery (LWT-R) sleep as a function of melatonin duration during the mid follicular (MF) phase in patients with Premenstrual Dysphoric Disorder (PMDD, N = 14).

Table 1

Melatonin - Sleep Phase Angles Mean ($\pm$ SD h) in Premenstrual Dysphoric Disorder (PMDD) (N = 11) and Normal Control (N = 6) Subjects. (A positive value indicates the sleep measure occurred after the melatonin measure; a negative value indicates the sleep measure occurred before the melatonin measure.)

PHASE ANGLE	MID-FOLLICULAR	LATE LUTEAL	LATE WAKE** THERAPY	EARLY WAKE** THERAPY
Melatonin Onset Time – Sleep Onset Time				
Normal Controls	3.04 ($\pm$ 1.49)	3.05 ($\pm$ 0.98)	0.83 ($\pm$ 0.74)	6.62 ($\pm$ 0.92)
PMDD	3.48 ($\pm$ 1.19)	2.96($\pm$ 1.28)	1.62 ($\pm$ 1.24)	6.00 ($\pm$ 2.07)
Melatonin Onset Time – Sleep End Time				
Normal Controls	10.35 ($\pm$ 1.76)	10.43 ($\pm$ 1.02)	4.34 ($\pm$ 0.69)	10.48 ($\pm$ 0.94)
PMDD	10.61($\pm$ 1.18)	10.19 ($\pm$ 1.26)	5.19 ($\pm$ 1.20)	10.50 ($\pm$ 1.52)
Sleep Onset Time – Melatonin Offset Time				
Normal Controls	-16.29 ($\pm$ 0.78)	-15.80 ($\pm$ 1.38)	-14.42 ($\pm$ 1.18)	-19.53 ($\pm$ 1.05)
PMDD	-16.07 ($\pm$ 1.75)	-15.65 ($\pm$ 0.99)	-14.62 ($\pm$ 1.82)	-18.36 ($\pm$ 1.78)
Sleep End Time – Melatonin Offset Time				
Normal Controls	-0.40 ($\pm$ 0.90)	-0.82 ($\pm$ 1.29)	-6.07 ($\pm$ 1.06)	-0.61 ($\pm$ 1.04)
PMDD	-0.79 ($\pm$ 1.40)	-1.13 ($\pm$ 0.85)	-5.80 ($\pm$ 1.76)	-1.14 ($\pm$ 0.92)
Sleep Onset Time – Melatonin Synthesis Offset				
Normal Controls	-5.37 ($\pm$ 0.86)	-4.87 ($\pm$ 0.82)	-6.33 ($\pm$ 0.70)	-0.72 ($\pm$ 1.71)
PMDD	-3.93 ($\pm$ 1.56)	-4.17 ($\pm$ 1.50)	-5.84 ($\pm$ 2.04)	-1.22 ($\pm$ 1.69)
Melatonin Synthesis Offset – Sleep End Time				
Normal Controls	1.93 ($\pm$ 1.04)	2.51 ($\pm$ 0.90)	-2.82 ($\pm$ 0.66)	3.14 ($\pm$ 1.73)
PMDD	3.21($\pm$ 1.27)	3.05 ($\pm$ 1.35)	-2.26 ($\pm$ 1.99)	3.27 ($\pm$ 1.69)

** Asterisks denote significance of differences between Late Luteal and Late Wake Therapy ($p < .01$), and Late Luteal and Early Wake Therapy ($p < .01$) phases.