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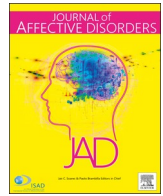
Research paper

Early versus late wake therapy improves mood more in antepartum versus postpartum depression by differentially altering melatonin-sleep timing disturbances

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ABSTRACT

Background: Peripartum major depression (MD) disables mothers and impairs emotional and neurocognitive development of offspring. We tested the hypothesis that critically-timed wake therapy (WT) relieves peripartum MD by altering melatonin and sleep timing, differentially, in antepartum vs. postpartum depressed patients (DP).

Methods: In a university clinical research center, we initially randomized 50 women – 26 antepartum (17 healthy comparison-HC, 9 DP) and 24 postpartum (8 HC, 16 DP) – to a cross-over trial of one night of early-night wake therapy (EWT: sleep 3:00–7:00 am) vs. late-night wake therapy (LWT: sleep 9:00 pm–01:00 am). Ultimately, we obtained mood, overnight plasma melatonin and polysomnography for: 15 antepartum women receiving EWT, 18 receiving LWT; 15 postpartum women receiving EWT, 14 receiving LWT.

Results: EWT improved mood more in antepartum vs. postpartum DP in conjunction with reduced (normalized) melatonin-sleep phase-angle differences (PADs) due to delayed melatonin onsets and advanced sleep onsets, and increased (from baseline) total sleep times (TST). LWT improved mood more in postpartum vs. antepartum DP in conjunction with increased TST.

Limitations: Small samples potentially rendered the study underpowered to detect group differences, making confirmation with larger samples essential. Sufficient follow-up data were not available in most women to document the duration of the mood response to wake therapy.

Conclusions: EWT benefitted antepartum DP more by realigning melatonin and sleep timing, whereas LWT benefitted postpartum DP more by increasing TST. Thus, consistent with precision medicine aims, maximum mood benefits accrue from timing sleep/wake interventions to specific peripartum circadian pathophysiologies.

1. Introduction

Antepartum major depression (MD) increases the risk for post-partum MD, and peripartum MDs may impair neurocognitive and socio-emotional development and sleep in infants and toddlers, while elevating risks of mental and medical disorders in mothers and their children later in life. Treatment of maternal MD reduces these risks (Andersson et al., 2006; Halligan et al., 2007a,b; Murray et al., 2006; Nulman et al., 2002; Swartz et al., 2016; Weissman et al., 2006a,b), highlighting the importance of treating depression during the puerperium. Women and clinicians seek alternatives to pharmacological interventions given their potential side effects on mother and child (Parry, 2009), or psychotherapeutic interventions given their time and expense.

A single night of total or partial "wake therapy" (WT) produces a rapid, albeit transient, antidepressant response in 40–60% of patients (Giedke and Schwarzler, 2002; Gillin, 1983; Leibenluft and Wehr, 1992; Schilgen and Tolle, 1980; Wirz-Justice et al., 2005, 2013; Wirz-Justice and Terman, 2012; Wirz-Justice and Van den Hoofdakker, 1999; Wu and Bunney, 1990). Early-Night Wake Therapy (EWT: i.e., remaining awake until 3:00 am, then sleeping from 3:00 – 7:00 am), or Late-Night Wake Therapy (LWT: i.e., sleeping from 9:00 pm – 01:00 am and remaining awake thereafter), can be as effective as total WT (Parry and Wehr, 1987; Wirz-Justice et al., 2013). LWT is more efficacious than EWT in some, but not all, MDs (Leibenluft and Wehr, 1992; Parry and Wehr, 1987; Wirz-Justice et al., 2013).

Abbreviations

CBT	Cognitive-Behavioral Therapy
D1	Day 1 (after wake therapy)
D2	Day 2 (after recovery sleep)
DLMO	Dim Light Melatonin Onset
DLMOff	Dim Light Melatonin Offset
DP	Depressed Patient(s)
EWT	Early Wake Therapy (remain awake until 3:00 am, then sleep from 3:00–7:00 am)
GCRC	General Clinical Research Center
HC	Healthy Comparisons
HRSD	Hamilton Rating Scale for Depression
LWT	Late Wake Therapy (sleep from 9:00 pm–01:00 am, then remain awake thereafter)
MD	Major Depression

MST	Mid-Sleep Time
PAD	Phase Angle Difference
PDT	Pacific Daylight Time
PST	Pacific Standard Time
PSG	Polysomnography
SIGH-ADS	Structured Interview Guide for the Hamilton Rating Scale for Depression with Atypical Depression Supplement
SE	Sleep Efficiency
SET	Seep End
SOT	Sleep Onset Time
SWA	Slow Wave Activity
SynOff	Melatonin Synthesis Offset
TST	Total Sleep Time
UCSD	University of California San Diego
WT	Wake Therapy

Misaligned circadian rhythms characterize mood disorders (Goel et al., 2013; Monteleone et al., 2011; Srinivasan et al., 2006; Wehr and Wirz-Justice, 1982). Compared with matched healthy comparison (HC) women, we found decreased melatonin amplitude plus phase-advanced (shifted earlier) melatonin timing in premenstrual dysphoric disorder (PMDD) (Parry et al., 1990, 1997) and antepartum depression, but increased morning melatonin amplitude in postpartum depression (Parry et al., 2008b), and increased amplitude plus phase-delayed (shifted later) melatonin offset in peri-menopausal depression (Parry et al., 2008c). Thus, women's depressions during different reproductive epochs coincide with different – even opposite – disturbances in melatonin quantity and timing relative to clock and sleep times.

Based on these findings and our work confirming wake therapy efficacy in PMDD (Parry et al., 1995; Parry and Wehr, 1987) and peripartum depressions (Parry et al., 2000), we tested the hypothesis that critically-timed WT improves mood in peripartum depressions by differentially altering melatonin-sleep *phase-angle differences* (PADs: i.e., temporal intervals between melatonin and sleep timing). As melatonin timing was relatively *phase-advanced* in antepartum depressed patients (DP) vs. HC, but relatively *phase-delayed* (vs. antepartum DP) in postpartum DP (Meliska et al., 2013; Parry et al., 2008b), we hypothesized that EWT (which phase-delays sleep) would improve mood more in antepartum than in postpartum depression, while LWT (which phase-advances sleep and melatonin (Parry et al., 2008a) would improve mood more in postpartum than in antepartum depression. We expected mood benefits of EWT and LWT to correlate with changed melatonin-sleep PADs that approached those of HC (see Fig. 1).

The study aims were (1) to compare efficacy of EWT vs. LWT treatment in peripartum MD; and (2) to relate differences in mood outcomes to chronobiological differences underlying antepartum and postpartum MD. We hypothesized that mood improvement after EWT and LWT would correlate with differential effects on melatonin, sleep, and melatonin-sleep PADs.

2. Methods

The University of California San Diego Institutional Review Board approved the protocol, and all participants gave written informed consent after procedures had been explained fully. We described the details of participant screening and recruitment procedures previously (Parry et al., 2008a; Meliska et al., 2013, and under eMaterials Methods, in the Supplementary Online Content). In brief, we telephone-screened pregnant (up to 34 weeks) and postpartum (up to 11 months) San Diego women who did not smoke or use medications that could interfere with neuroendocrine measures for multiple overnight hospital stays in the General Clinical Research Center (GCRC), where they were allowed to bring a child with them if needed. They had laboratory tests for clinical chemistry, thyroid indices, and complete blood count, urinalysis and urine toxicology screens. Women were without alcohol abuse, significant medical illness or medication that would interfere with study measures.

To establish DSM-IV-TR (APA, 2000) entrance and baseline criteria, trained clinicians used a structured psychiatric interview, the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1995) and two baseline evaluation ratings with the Structured Interview Guide for the
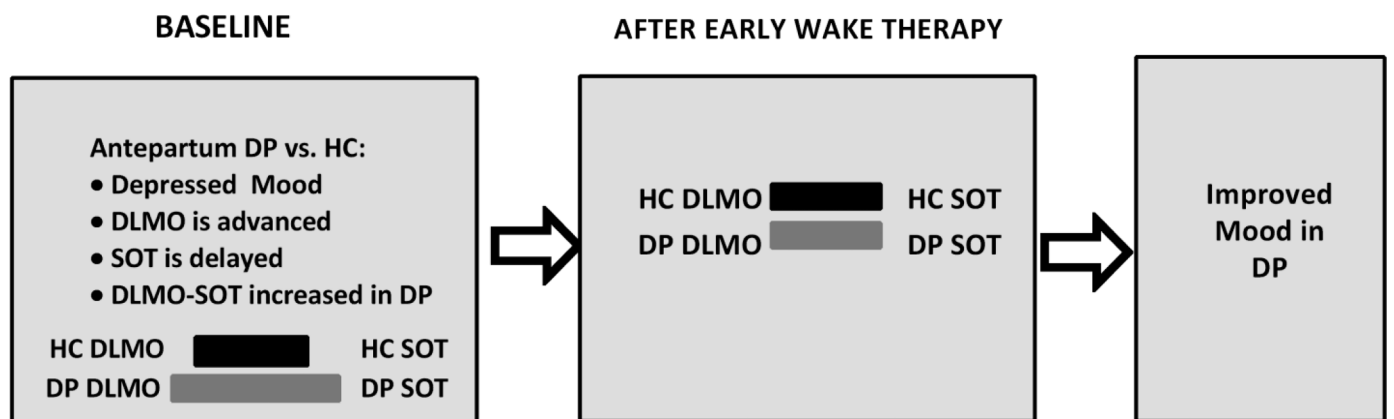

Fig. 1. Conceptual Model: At baseline, antepartum depressed patients (DP) vs. healthy comparison (HC) participants have phase-advanced Dim Light Melatonin Onset (DLMO) time plus phase-delayed Sleep Onset Time (SOT). After Early Wake Therapy, DLMO is delayed while SOT is advanced, thereby normalizing the DLMO_SOT phase angle difference (PAD) in association with improved mood in DP.

21-item Hamilton Depression Rating Scale (HRSD), Seasonal Affective Disorders, using the HRSD + Atypical (SIGH-ADS) version (Williams et al., 1994); the Beck Depression Inventory (BDI) (Beck et al., 1961); and the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987) also validated for use during pregnancy (Hewitt et al., 2009). From the pool of volunteers we obtained mood data on clinically depressed patients (DP) and essentially asymptomatic, healthy control (HC) women using the SIGH-ADS. We excluded patients with bipolar or primary anxiety disorders.

2.1. Participants

We described participant recruitment, methods and baseline observations elsewhere (Meliska et al., 2013; Parry et al., 2008b). In brief, after diagnostic (First et al., 1995) and mood (Hamilton, 1967) assessments in 50 psychoactive-drug free women – 26 antepartum (17 HC, 9 DP) and 24 postpartum (8 HC, 16 DP) – we initially randomized women to a cross-over trial of one night of either EWT or LWT separated by at least seven days, followed by a night of recovery sleep (sleep 10:30 pm-6:30 am). Due to missing data, failure to complete both arms of the cross-over protocol, and dropouts from the study, we subsequently modified the protocol for data analyses, recasting it as a between subjects design, based on: antepartum women – 15 receiving EWT, 18 receiving LWT; and postpartum women – 15 receiving EWT, 14 receiving LWT. We provide an extensive explanation and rational for protocol changes in Supplemental eTable 1.

We obtained, pre- and post-treatment: (1) Interview-based mood assessments using the Structured Interview Guide for the Hamilton Rating Scale for Depression (HRSD) with Atypical Depression supplement (SIGH-ADS) (Williams and Terman, 2003); (2) plasma melatonin (sampled in dim light/dark) at 30-min intervals from 6:00 pm to 11:00 am; and (3) polysomnography (PSG).

2.2. Test procedures

To monitor ambient light and bodily movement, beginning 7 days before the intervention, we required women to wear a wrist actigraph (Actillume) (Jean-Louis et al., 2001), which they wore throughout testing. We admitted participants to the GCRC at 16:00 h local time where they remained at bed rest in a single room; double doors and heavy window drapery blocked extraneous light, producing dim (< 30 lx) daytime light exposure from 16:00 to 11:00 h. Licensed nurses and sleep technicians entered the room only when using a pen-size dim red flashlight. They prepared women for PSG recording using standard methods (see details in *Supplementary Online Content*). After an adaptation night, nurses inserted an intravenous catheter at 17:00 h and drew blood (3 cc) every 30 min from 18:00 to 11:00 h through a catheter threaded through a porthole from an adjoining room. Participants slept in darkness with an eye mask and returned home after each baseline and intervention session. We instructed them not to nap during the interval before the next mood evaluation and we monitored compliance, objectively, using their wrist actigraph records, and

subjectively, with daily Work, Location and Sleep logs. Examination of these sources revealed no substantial deviations from the research protocol. The baseline DLMO night was obtained the day after the adaptation night, and again, on the evening before the second intervention. We measured PSG-derived Sleep Onset Time (SOT), Sleep End Time (SET), Total Sleep Time (TST), Sleep Latency (SL), Sleep Efficiency (SE), and Wake after Sleep Onset (WASO). We also performed Fast Fourier Transform (FFT) analyses to identify possible intervention effects on slow wave activity (SWA) in DP vs. HC.

Melatonin Parameters: We converted local time measures obtained during Pacific Daylight Time (PDT) to Pacific Standard Time (PST) to analyze temporal effects on melatonin parameters. As described previously (Parry et al., 2008c), we defined the *dim light melatonin onset* (DLMO) as the first time that the slope (dy/dt) of the log-transformed melatonin concentration curve became steeply positive for at least three consecutive time points relative to the slope of the points immediately preceding it; *synthesis offset* (SynOff) as the first time after the melatonin peak when the slope of the descending log-transformed melatonin curve became steeply negative for three consecutive time points; *dim light melatonin offset/return to baseline* (DLMOff) as the first time when the slope of the descending log-transformed melatonin curve approached zero for at least three consecutive time points; *synthesis duration* as (SynOff – DLMO); *synthesis AUC* (SynAUC) as the integrated area under the melatonin curve between DLMO and SynOff.

2.3. Response criteria

We compared frequencies of DP achieving the stringent response criterion of 60% reductions from baseline HRSD score after WT, plus the remission criterion of post-intervention HRSD scores ≤ 8 (Terman et al., 1989).

2.4. Statistics

Based on our previous findings showing opposite disturbances in melatonin timing and amplitude in antepartum vs. postpartum DP (Meliska et al., 2013; Parry et al., 2008b), we tested hypotheses using univariate analyses of variance (ANOVA; IBM SPSS Statistics, Version 23) for melatonin timing parameters under dim light: *Dim Light Melatonin Onset* (DLMO), *Dim Light Melatonin Offset/*return to baseline (DLMOff), and melatonin *Synthesis Offset* (SynOff); PSG Sleep Quality (*total sleep time*-TST, *sleep onset time*-SOT, *sleep end time*-SET, *sleep efficiency*-SE, *mid-sleep time*-MST); and all possible melatonin-sleep timing PADs (see *Online Supplement*), using analysis of covariance (ANCOVA) when a covariate, e.g., day length, was significant at the $p < .10$ level; and t-tests to evaluate whether changes from baseline after WT differed from zero. We protected against Type 1 error by initially examining group effects based on stated research hypotheses (e.g., regarding baseline PAD differences, EWT vs. LWT effects). When following up initial findings and subsequently testing differences in related variables (e.g., in SOT, TST, etc.), we based two-tailed paired comparisons (each with a true alpha value of $p = .05$, at least) on univariate ANOVA (or

Table 1
Proportions of antepartum and postpartum depressed patients (DP) who were responders and remitters following early wake therapy (EWT) and late wake therapy (LWT).

Group	A. Responders[a] @EWT	@LWT	p-value	B. Remitters[b] @EWT	@LWT	p-value
Antepartum	4/6 = 66.7%	2/6 = 33.3%	.248	4/6 = 66.7%	3/6 = 50.0%	.558
Postpartum	2/11 = 18.2%	6/9 = 66.7%	**.028[c]**	2/11 = 18.2%	4/9 = 44.0%	.202
p-value	**.046[d]**	.205	–	**.046[d]**	pp = .833	–

[a] Achieving 60% Reduction in Hamilton Rating Scale for Depression-HRSD Score.
[b] Achieving HRSD Score ≤ 8 on Day 2 After Recovery Sleep.
[c] In Postpartum DP, response rate was significantly greater in LWT vs. EWT ($p = .028$).
[d] Response and remission rates to EWT were significantly greater in Antepartum vs. Postpartum DP ($p = .046$).
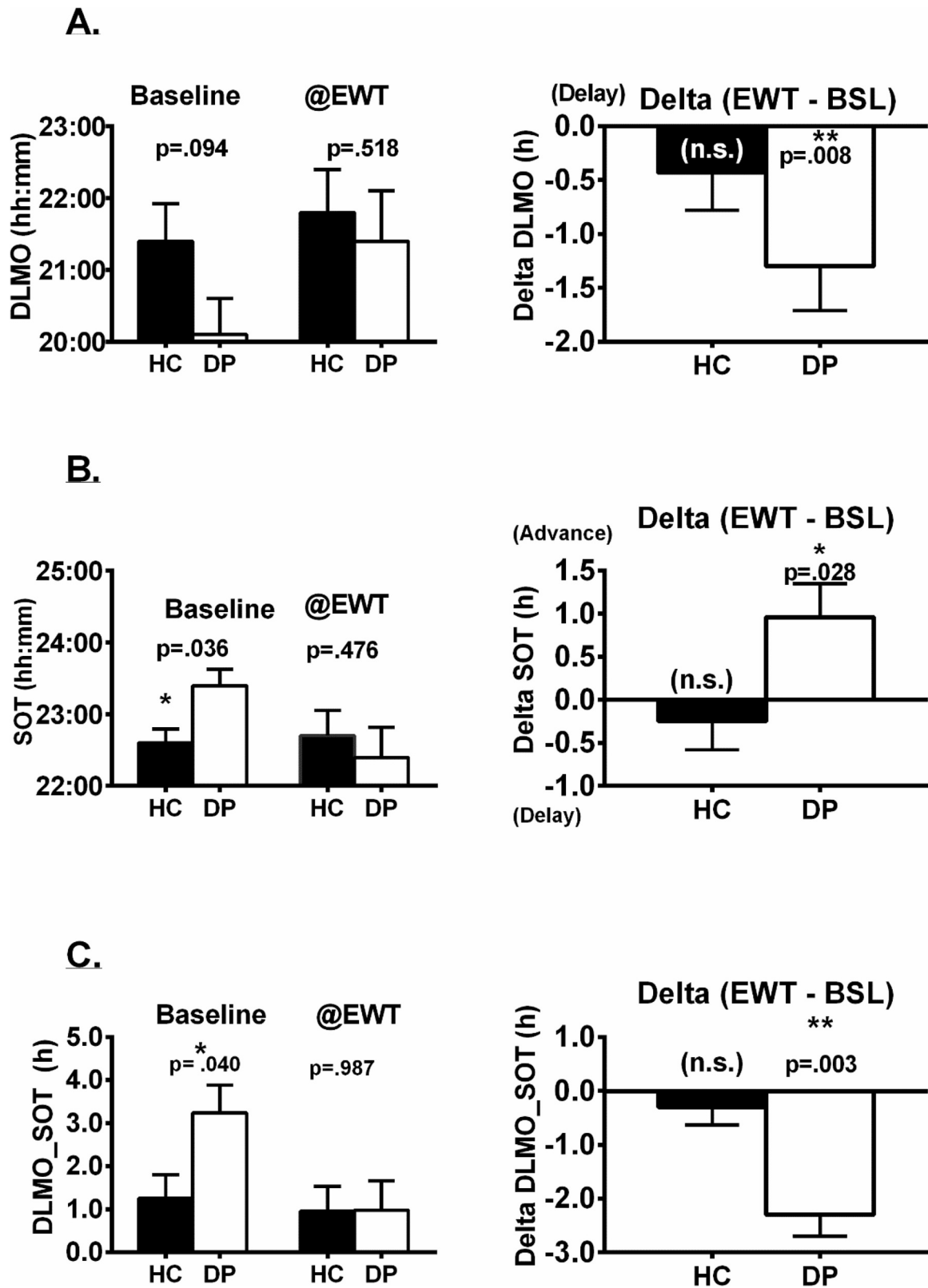
Fig. 2. Melatonin-Sleep Timing Changes after Early Wake Therapy in Antepartum Depressed (DP) vs. Healthy Comparison (HC) women. Values represent means ± SEMs for antepartum healthy comparison (HC; *N* = 7) and depressed participants (DP; *N* = 5) at baseline, and after Early Wake therapy (EWT). By convention, phase-advances are listed as positive values, phase-delays as negative values. (Delta scores represent changes from baseline after EWT)
(A): Dim Light Melatonin Onset (DLMO) in HC vs. DP at baseline (BSL) and after Early Wake Therapy (@EWT);
(B) Sleep Onset Time (SOT) in HC vs. DP, at baseline and after EWT;
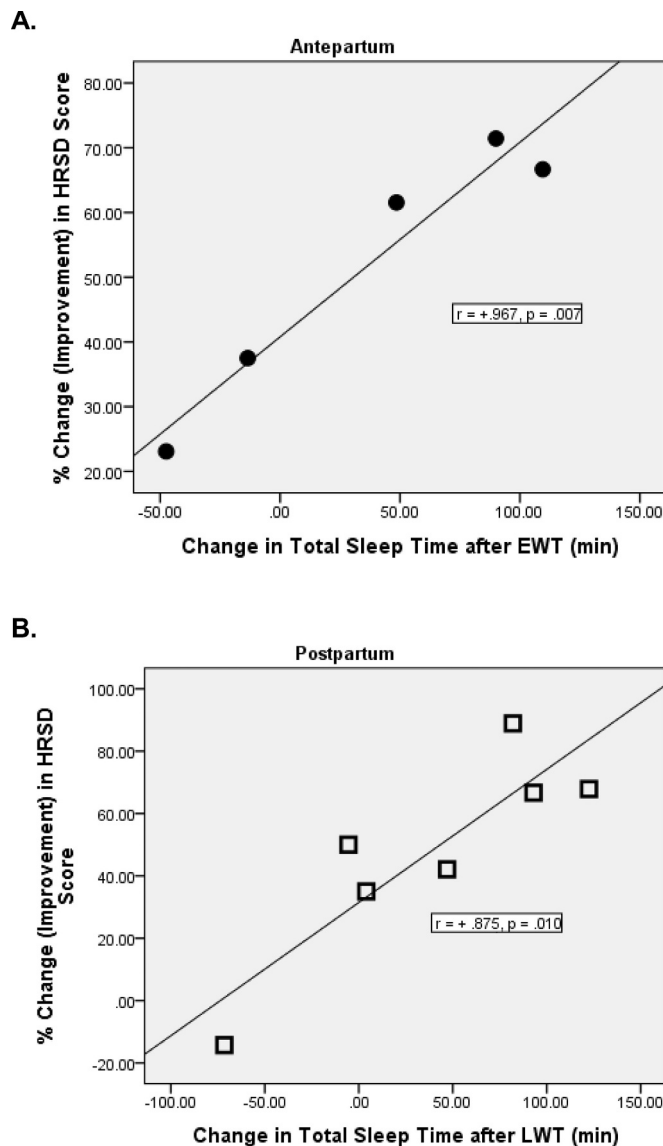(C) DLMO_SOT Phase Angle Difference in HC vs. DP, at baseline and after EWT.

3. Results

Participant demographic characteristics: see supplemental eTable 2.

3.1. EWT vs. LWT effects on mood

Response criteria. After EWT, significantly greater mood improvement (decrease in HRSD score) occurred in antepartum vs. postpartum DP (mean ± SD = 53.4 ± 18.9 vs. 27.3 ± 34.8%, p = .022) by univariate ANCOVA with covariate = ambient day length during testing. Mood improvement of at least 60% from baseline occurred more often in antepartum vs. postpartum DP after EWT ($p = .046$; Table 1A), but not after LWT ($p = .205$). In contrast, response rate after LWT vs. EWT was significantly greater in postpartum ($p = .028$), but not in antepartum DP ($p = .248$).

Remission criteria. The proportion of DP achieving remission (HRSD score ≤ 8) was greater in antepartum vs. postpartum DP after EWT ($p = .046$; Table 1B), but not after LWT ($p = .833$). EWT vs. LWT did not differ significantly in the proportions achieving remission in either antepartum ($p = .558$) or postpartum DP ($p = .202$).

3.2. EWT effects on melatonin, sleep and PAD timing in relation to mood

1. Antepartum women

Overview: EWT reduced depression severity in antepartum women, primarily in conjunction with reduction in the DLMO_SOT PAD due to delays in DLMO and advances in SOT.

Melatonin timing

Baseline. At baseline, the mean DLMO was **non-significantly** advanced (by 78 min) in clock time (corrected for PDT) in antepartum DP vs. HC (means ± SD = 20:06 ± 1:51 vs. 21:24 ± 0:54 hh:mm, $p = .094$; *Fig. 2*A), **and essentially equivalent** in postpartum DP vs. HC (means ± SD = 20:45 ± 1:30 vs. 20:09 ± 0:53 hh:mm, $p = .478$).

EWT effects. EWT phase-delayed DLMO significantly in antepartum DP (mean ± SD = −1 h, 18 min ± 46 min, $p = .008$), but not HC (mean ± SD = −26 ± 64 min, p > .05; Fig. 2A); SynOff and DLMOff were not altered significantly by EWT in either DP or HC ($p > .05$).

Correlation with mood. Percent change/improvement in HRSD score after EWT in antepartum DP correlated negatively with DLMO change (r(partial) = −0.677, $p = .022$) when day length was included in the regression model; i.e., greater mood improvement was associated with greater phase-delay (normalization) in DLMO, and with longer day length.

Responders vs. non-responders. Change in melatonin timing in antepartum DP after EWT was not different in responders vs. non-responders for all timing measures (all $p > .05$).

PSG measures: DP

Baseline. Baseline SOT was delayed (by 43 min) in antepartum DP vs. HC (means ± SD = 23:20 ± 0:39 vs. 22:37 ± 0:23 hh:mm, $p = .036$; Fig. 2B). Baseline MST, SET and TST did not differ significantly in DP vs. HC (all $p > .05$).

EWT effects. EWT phase-advanced SOT in antepartum DP (mean ± SD = + 58 ± 38 min, $p = .028$) but not HC (mean ± SD = −8 ± 59 min, $p = .862$; Fig. 2B). EWT did not significantly alter MST, SET or TST in DP vs. HC (all $p > .05$). A FFT on PSG data revealed no significant group, intervention, or group X intervention interaction effects relating to SWA.

Correlation with mood. After EWT in antepartum DP, mood improved on D2, in association with increased recovery sleep TST (Pearson r = + 0.967, $p = .007$; see Fig. 3A) and increased SE

Fig. 3. Changes in Total Sleep Time (TST) after Wake Therapy in Antepartum and Postpartum Depressed women. Significant positive correlations occurred between change in mood (Hamilton Rating Scale for Depression; HRSD) and change in TST in (A) Antepartum depressed women after Early Wake Therapy (EWT; closed circles) and in (B) postpartum depressed women after Late Wake Therapy (LWT; open squares).

ANCOVA) after obtaining a significant omnibus MANOVA for those variables. Because we made inferential comparisons which involved only two levels of the independent variables, corrections (e.g., with Bonferroni or Sidak) were not required.

Main dependent variables were baseline HRSD, melatonin, PSG, PAD measures, and post-intervention changes. Clinicians assessed mood responses post-intervention on day 1 (D1) after wake therapy and day 2 (D2) after recovery sleep. As we found mood improvement was equivalent or significantly greater ($p < .05$) on D2 vs. D1 (see *Supplemental eFigure 2*), as observed in some studies (Matussek et al., 1974; Sack et al., 1988; Wirz-Justice et al., 1976), we report only D2 results here. We determined the relationships of HRSD scores to melatonin, PSG and PAD measures using Pearson correlations and stepwise linear regression with the "backward" entry method, setting $p < .10$ for elimination of variables from the model.

(r = + 0.942, p = 0.017).

Responders vs. non-responders. In antepartum DP, TST increased significantly more after EWT in responders vs. non-responders (mean ± SD = + 82.7 ± 31.2 vs. − 30.5 ± 24.0 min, p = .046). Relative to baseline, SOT also advanced significantly in responders (mean ± SD = +1 h, 15 min ± 27 min, p = .012), but delayed non-significantly in non-responders (mean ± SD = − 25 ± 17 min, p = .300).

Melatonin-sleep PADs

Baseline. At baseline, DLMO_SOT PAD mean duration was almost 2 h (118 min) longer in antepartum DP vs. HC (means ± SD = 3 h, 14 min ± 2 h, 4 min vs. 1 h, 16 min ± 46 min, p = .040; see *Fig. 2*C).

EWT effects. EWT decreased the DLMO_SOT PAD significantly in antepartum DP (mean ± SD = − 2 h, 26 min ± 1 h, 6 min, p = .010), but only slightly in HC (mean ± SD = − 18 ± 40 min, p = .300, see Fig. 2C and Supplemental eFig. 1). Notably, along with the changes in DLMO_SOT PAD, five of the remaining eight melatonin-sleep PAD values were also significantly altered (p < .05) in antepartum DP after EWT (see Supplemental eTable 3).

Responders vs. non-responders. EWT significantly decreased the DLMO_SOT PAD in antepartum DP responders (mean ± SD = − 2 h, 22 min ± 10 min, p = .027), but not in non-responders (mean ± SD = − 1 h, 40 min ± 46 min, p = .201).

2. Postpartum women
Melatonin, sleep and PAD timing

Baseline. Prior to EWT, melatonin, sleep, and PAD indices were not abnormal in postpartum DP compared with HC (all p > .05), nor were these measures correlated with baseline mood, with one exception: Baseline HRSD score was negatively correlated with TST (r = − 0.734, p = .024); thus, greater depressed mood was associated with shorter sleep time in postpartum DP.

EWT effects. Unlike in antepartum participants, EWT did not significantly alter melatonin timing, sleep timing, or melatonin-sleep PAD indices in the postpartum DP or HC, separately, or in DP vs. HC; nor were HRSD changes correlated with changes in timing relationships; nor were these measures different after EWT in postpartum responders vs. non-responders (all p > .05).

3.3. EWT in antepartum vs. postpartum DP: relation to changes in mood and DLMO_SOT PAD

After EWT, reduction in the DLMO_SOT PAD was substantially greater in antepartum vs. postpartum DP (means = − 2 h, 26 min ± 1 h, 11 min vs. -10 ± 61 min, p = .046) when the covariate of day length during testing was included in the analysis. Furthermore, reduction in DLMO_SOT PAD after EWT correlated significantly with percent change/improvement in HRSD score in Antepartum + Postpartum DP combined (regression analysis controlling for day length, r(partial) = − 0.749, p = .013; see Fig. 4). Thus, greater mood improvement after EWT was associated with greater reduction in DLMO_SOT PAD in antepartum + postpartum DP, after controlling for day length during testing.

3.4. LWT effects on melatonin, sleep, and PAD timing in relation to mood

1. Antepartum women

LWT effects. Responses to LWT were not significantly different from baseline in antepartum DP vs. HC for melatonin timing, sleep timing, or melatonin-sleep PADs (all p > .05). Correlations between changes in these variables and mood changes in DP also were non-significant, and responders to LWT were not significantly different from non-responders in melatonin, sleep or PAD effects (all p > .05).

2. Postpartum women

Overview: LWT reduced depression severity more in postpartum than in antepartum DP, primarily in conjunction with increased TST. Mood improvement after LWT was associated with greater sleep improvement in responders than non-responders, but was unrelated to change in melatonin timing and melatonin-sleep PADs.

Melatonin timing

LWT effects. Although LWT phase-advanced melatonin timing modestly in postpartum DP, changes were only marginal for DLMOff (mean ± SD = + 1 h, 23 min ± 1 h, 56 min, p = .089), and non-significant for SynOff and DLMO; LWT effects on postpartum HC melatonin were also non-significant (all p > .05).

PSG measures

LWT increased TST significantly from baseline in postpartum DP (mean ± SD = + 56.7 ± 51.6 min, p = .043) but not in HC (mean ± SD = + 5.8 ± 65.9 min, p = .837). Changes in SOT, SET and MST after LWT were non-significant in both postpartum DP and HC (all p > .05). A FFT analysis of PSG data revealed no significant group, intervention, or group X intervention interaction effects relating to SWA.

Correlation with mood. After LWT, mood improved in postpartum DP on D2 in association with increased recovery sleep TST (r = + 0.875, p = .010; see Fig. 3B).

Responders vs. non-responders. In postpartum DP at baseline, responders slept less than non-responders, with shorter TST prior to LWT (Means ± SD = 295.8 ± 45.9 vs. 387.4 ± 46.8 min, p = .049). After LWT, TST increased significantly more in postpartum responders vs. non-responders (means ± SD = + 107.8 ± 20.9 vs. − 2.0 ± 4.9 min, p = .019).
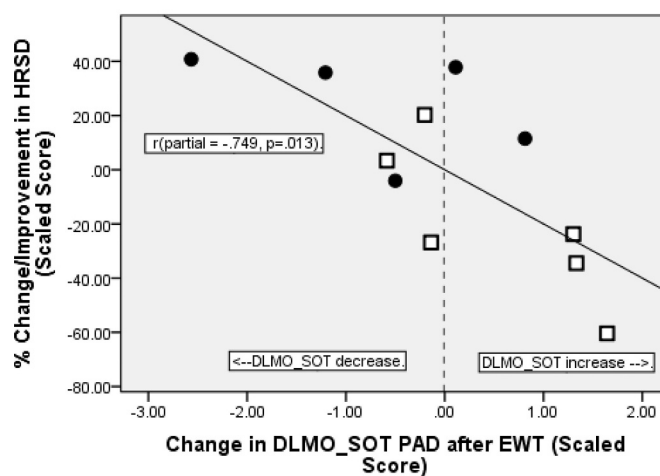

Fig. 4. Percent Change/Improvement in HRSD scaled score vs. change in phase angle difference (PAD; scaled score) of Dim Light Melatonin Onset time (DLMO) - Sleep Onset Time (SOT) (DLMO_SOT PAD) after Early Wake Therapy (EWT) in antepartum and postpartum depressed patients (DP). Partial regression (controlling for baseline day length) showed a significant association between percent change/improvement in scaled scores on Hamilton Rating Scale for Depression (HRSD) and change in DLMO_SOT PAD in the combined antepartum and postpartum DP (r(partial) = − 0.749, p = .013). Reduction in DLMO_SOT PAD after EWT, evident more often in antepartum DP, was associated with greater mood improvement, while increase in DLMO_SOT PAD, evident more often in postpartum DP, was associated with smaller mood improvement.

Melatonin-sleep PADs

After LWT, changes in postpartum PADs did not reach significance in DP or HC, or in DP vs. HC; nor were mood and PAD changes correlated significantly (all *p* > .05). Responders vs. non-responders were not different in baseline PAD values or in response to LWT (all *p* > .05).

5. Discussion

These findings confirm the rapid antidepressant effects of wake therapies in peripartum women. A night of critically-timed partial wake therapy improved mood and sleep in one day. EWT improved mood more in antepartum, while LWT improved mood more in postpartum DP. In antepartum DP after EWT, mood improvement was associated with reducing – and thereby normalizing – the time between melatonin and sleep onsets. In contrast, in postpartum DP after LWT, mood improvement was related primarily to increased total sleep time.

Wake therapy provides a rapid-onset intervention for peripartum depression, which can impair offsprings' cognitive and socioemotional development (Murray et al., 2006), IQ and language (Nulman et al., 2002), in association with increased mood, anxiety, substance use disorders, medical morbidity and mortality in mothers and offspring (Halligan et al., 2007b; Weissman et al., 2006b). Remission of maternal depression reduces children's symptoms; in mothers who remain depressed, rates of their children's disorders increase (Swartz et al., 2016; Weissman et al., 2006a). Pharmacological interventions may be limited by increased risks for adverse infant outcomes (McDonagh et al., 2014; Parry, 2009; Wisner et al., 2009) and psychotherapies by time, expense or trained clinician availability. Light treatment improves mood, but peripartum benefits may take weeks (Corral et al., 2000, 2007; Epperson et al., 2004; Oren et al., 2002; Wirz-Justice et al., 2011).

Due to design limitations, missing data, dropouts from the study and non-compliance issues, we were unable to satisfactorily verify persistence of mood benefits after Day 2 of the interventions. Previous results suggest that a single night of wake therapy typically produces temporary mood improvements, but can have more lasting effects when administered repeatedly or in combination with other interventions, including light, phase-advance of the sleep/wake cycle, psychotherapy, and medication (e.g., Gillin, 1983; Leibenluft and Wehr, 1992; Giedke and Schwarzler, 2002; Wirz-Justice et al., 2013). Evidence from more than 30 studies of more than 1000 patients demonstrates one night of critically-timed therapeutic wake therapy may be the most safe and reliable means of producing rapid antidepressant benefits (Dallaspezia and Benedetti, 2011; Luca et al., 2013; Wirz-Justice et al., 2013). Using strict criteria, our findings that after one night, two-thirds of pregnant DP responded and remitted to EWT, and two-thirds of postpartum DP responded to LWT, compare favorably with the 46% remission rate achieved with antidepressants and 48% with psychotherapy after 10–16 weeks in DP, and with the 34–35% increased remission likelihood with CBT for peripartum women (O'Connor et al., 2016; Siu et al., 2016).

Regarding mechanisms, we found an interaction between wake therapy timing and reproductive status: Antepartum DP, whose baseline melatonin circadian rhythms were shifted earlier relative to healthy women, responded better to EWT that delays sleep, whereas postpartum DP, whose melatonin circadian rhythms were shifted later relative to antepartum DP responded better to LWT that advances sleep. In antepartum DP after EWT, melatonin onset was shifted later and sleep onset was shifted earlier, thereby providing a corrective phase-shift and restoring a more normal timing interval between melatonin and sleep. Sharkey et al. (2013) followed third trimester antepartum women with previous, but not current, depression (and therefore at risk for recurrence), through 6 weeks postpartum and found, like us, a longer duration between melatonin and sleep onset in antepartum vs. postpartum states, in association with more depressive symptoms postpartum (but not meeting MD criteria). We found the time from

melatonin onset to sleep onset was nearly two hours longer in antepartum DP vs. HC. After EWT, SOT shifted earlier by nearly one hour, advancing significantly in EWT responders but not non-responders. By delaying melatonin onset and advancing sleep onset, EWT reduced ('normalized') the baseline melatonin/sleep misalignment, making the difference in DP vs. HC negligible. Thus, an increased DLMO_SOT duration at baseline could represent an identifiable "biosignature predicting treatment responsiveness" (Day and Williams, 2012). Reducing/normalizing an abnormally long interval between melatonin and sleep onset with EWT improved antepartum mood, whereas in postpartum DP, further increasing that interval with EWT did not improve or even worsened mood, thereby implicating a potential neurobiological target for therapeutic intervention.

In contrast, after LWT in postpartum DP, mood improved as total sleep time increased significantly more in responders vs. non-responders. LWT response was predicted by reduced baseline TST. Thus, LWT provided a different corrective pathway than shifting melatonin-sleep timing relationships to restore sleep quality. Increased TST after wake therapy may reflect increased homeostatic drive (Borbely, 1982), possibly deficient in depressed patients. The purpose of this investigation was to assess the impact of critically timed WT on changes in circadian rhythms in relation to sleep and associated changes in mood. Our results suggest critically-timed sleep restriction produced alterations in circadian timing in relation to sleep which was a prerequisite for improved sleep and mood in both antepartum and postpartum DP. As circadian factors do not operate on sleep in isolation from homeostatic factors, changes in one domain will necessarily impact the other in ways that are difficult to identify statistically. Therefore, homeostatic sleep drive must also be considered in interpreting the changes in sleep and mood we observed. As noted by Jones and Benca (2015), non-circadian, homeostatic processes of sleep play important roles in emotional regulation, as we report here for both antepartum and postpartum depression.

That TST increase, not PAD change, was critical for mood improvement in postpartum DP after LWT supports the hypothesis that antepartum vs. postpartum DP have different underlying circadian pathophysiologies and responses to treatment, informing the next DSM (First et al., 2017).

Although antidepressant benefits of WT are typically temporary, numerous studies report mood benefits are sustained by repeating WT, combining with antidepressant medications, bright-light therapy or phase-advance of the sleep wake cycle (see Wirz-Justice et al., 2013 for review). Using combined strategies, 70% of mood disorder patients improved rapidly and 57% remained euthymic for 9 months (Wirz-Justice, 2011).

Study strengths include rigorous diagnostic assessments, frequent plasma melatonin sampling for circadian phase estimation, sleep measured objectively by polysomnography, and inclusion of HC in both antepartum and postpartum groups. Study limitations include small samples in both WT groups, leaving the study potentially underpowered to detect group differences and making confirmation with larger samples essential. *We also were unable to adequately document duration of mood benefits beyond those initially obtained after wake therapy.* Future studies are needed to rigorously evaluate the persistence of mood benefits beyond the initial response to wake therapy. As wake therapy can precipitate mania in bipolar patients, our sample necessarily excluded bipolar DP (Wehr et al., 1987).

6. Conclusions

We found objective mood and sleep benefits were greater in antepartum DP after EWT, but greater in postpartum DP after LWT. These interventions provided specific, differential corrections to underlying chronobiological pathophysiologies: Phase-advanced melatonin timing in antepartum DP responded to phase-delaying EWT that normalized melatonin-sleep timing intervals. In contrast, in postpartum DP, LWT

improved mood primarily in conjunction with improvement in objective sleep quality. These results support our hypothesis of differential pathophysiologies and responses to treatment in antepartum vs. postpartum depression. As "precision medicine" (Collins and Varmus, 2015) aims to "ensure that the right treatment is delivered to the right patient at the right time" (Hey and Kesselheim, 2016), this approach could represent a welcome alternative to pharmacological or psychotherapeutic interventions for pregnant or lactating depressed women. Hopefully, these novel findings will encourage clinicians to utilize wake therapy in peripartum DP, and provide chronobiological targets for treatment interventions.

Clinical application

A valuable resource for clinicians who want to use these interventions is the book by Wirz-Justice, Benedetti and Terman, "Chronotherapeutics for Affective Disorders: A Clinician's Manual for Light and Wake Therapy" which includes a curriculum and additional resources and rating scales in the appendix.

To convince patients of the potential efficacy of wake therapy, we review how nurses, observing sleep times of mood disorder inpatients, noted that before switching from a depression into a mania, patients stayed up most of the night. Subsequent work demonstrated that wakefulness during only part of the night (4 h) was necessary to obtain anti-depressant effects. It also helps to ask patients if they recall having gotten up several hours earlier (e.g., to catch an airplane flight), and afterward feeling more activated and energized, rather than fatigued. Emphasizing that the intervention – lasting only 4 h for 1-night – can immediately improve mood without long-term adverse effects often persuades patients to participate. This sustained 4-h wakefulness intervention is distinctly different from tossing and turning during restless hours of sleep. Over 1000 patients in over 30 studies have benefitted from this intervention, demonstrating that patients experience both improved mood and sleep the following day and night. Thomas Wehr also reported benefits of having periods of quiet wakefulness during the night (Wehr, 1992). Patients often engage in pleasurable activities (e.g., reading, watching movies, or knitting) to sustain wakefulness, and their partners have offered to share the experience with them.

Author statements

IRB

The protocol was approved by the University of California San Diego Institutional Review Board, and all participants gave written informed consent after procedures had been explained fully.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2018.11.064.

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