



Relationships between circadian measures, depression, and response to antidepressant treatment: A preliminary investigation

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ABSTRACT

Few studies have examined relationships between circadian rhythms and unipolar major depressive disorder. Further, no study to date has examined circadian markers as predictors of response to depression treatment. In the present study, we examined associations between circadian timing and its alignment with sleep and depression severity in 30 adults with major depressive disorder who completed a randomized controlled trial of two weeks of time in bed (TIB) restriction administered adjunctive to fluoxetine, with a focus on sex differences. Thirty adults with major depressive disorder received 8 weeks of fluoxetine 20–40 mgs and were randomized to 8 h TIB or 6 h TIB for the first 2 weeks. Participants in the 6 h TIB condition were further randomized to a delayed bedtime or advanced risetime group. Circadian measures included dim light melatonin onset (DLMO) and the difference between DLMO and midsleep point (i.e., phase angle difference). Depression was assessed using the Hamilton Rating Scale for Depression. For females, a phase delay after 2 weeks of fluoxetine and the experimental TIB manipulation was associated with a poorer response to fluoxetine, and depression severity was negatively correlated with phase angle difference, whereas males showed a positive correlation between depression severity and phase angle difference.

1. Introduction

Circadian rhythm dysregulation is implicated in the pathogenesis and course of many affective disorders (Jones and Benca, 2015). However, most empirical investigations in this area have focused on seasonal affective disorder (Lewy et al., 2006). Emerging evidence from the last decade has provided preliminary support for early hypotheses linking circadian rhythms to unipolar major depressive disorder (MDD).

Several studies have established associations between an evening preference (e.g., evening chronotype), measured by self-report, and depression severity. In a cross-sectional study of 100 adults with MDD, participants with an evening chronotype had more severe suicidal ideation and greater functional impairment relative to those with morning or neither chronotypes (Gaspar-Barba et al., 2009). Further, in a naturalistic follow-up study of adults with major depressive disorder, a self-reported evening preference was predictive of more severe depression symptoms, and significantly greater odds of non-

remission of depression (Chan et al., 2014).

Beyond chronotype, two recent studies have examined the role of misalignment between objective markers of the circadian pacemaker (e.g., dim light melatonin onset, or DLMO) and the timing of sleep in MDD (Emens et al., 2009; Hasler et al., 2010). In a cross-sectional study of 18 females with MDD who had persistent symptoms of depression despite antidepressant treatment, depression severity was negatively correlated with the amount of time between dim light melatonin onset (DLMO) and midsleep (i.e., phase angle difference; PAD), such that a shorter PAD (corresponding to a phase delay) was associated with more severe depression (Emens et al., 2009). In a comparison of circadian and sleep markers in 18 adults with depression and 19 healthy controls, the group with depression had a later mean sleep onset and a later mean midsleep point relative to the control group (Hasler et al., 2010). Although a delay in core body temperature minimum relative to midsleep and DLMO was correlated with depression severity, no relationship was observed between the DLMO-midsleep PAD in this study (Hasler et al., 2010). Although these

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studies have relatively small, homogenous samples, their findings suggest that further exploration of misalignment between the circadian and sleep timing systems in MDD is warranted. In particular, no studies to date have examined circadian measures as predictors of response to antidepressant therapy. This line of inquiry is critical to the development of personalized treatment approaches to enhance outcomes for individuals with MDD.

One of the most well-established sleep-based therapies for depression, sleep deprivation (Giedke and Schwarzler, 2002; Schilgen and Tölle, 1980) is hypothesized to improve depression by directly influencing the sleep homeostatic and circadian systems. Sleep deprivation treatments for MDD includes single-night total deprivation, single-night partial deprivation, and repeated partial sleep deprivation. In partial deprivation, an advanced wake time (i.e., wakefulness during the second half of the night) is generally more effective than a delayed bedtime (i.e., wakefulness during the first half of the night (Sack et al., 1988)). Our group recently completed a randomized controlled trial designed to compare depression remission rates and time to depression remission for two weeks of 6 h' time in bed (6 h TIB) to 8 h TIB delivered adjunctive to fluoxetine in adults with MDD (Arnedt et al., 2016). Participants completed the 2-week TIB condition protocol at home and were assigned to 8 h TIB, 6 h TIB with delay of bedtime (Late Bedtime), or 6 h TIB with advance of rise time (Early Rise time). It was hypothesized that participants assigned to the Early Rise time condition would report the greatest symptom improvement relative to those assigned to the Late Bedtime or 8 h TIB conditions. Contrary to hypotheses, participants assigned to the 8 h TIB group had lower depression severity, greater remission rates, and earlier onset of remission relative to both 6 h TIB groups (Arnedt et al., 2016).

In the present study, we conducted a secondary analysis of the parent randomized controlled trial to explore change in circadian timing from baseline to post-experimental TIB manipulation and to examine the role of circadian timing and its alignment with sleep as a predictor of depression severity and treatment response. We note that the parent trial was specifically designed to minimize the effects of the TIB schedule on the circadian system. To this end, participants were instructed to remain in dim light and to engage in only quiet, sedentary activities during the period of sleep deprivation. Thus, although we assessed whether circadian measures changed from baseline to post-experimental TIB manipulation, we did not have specific hypotheses regarding the effects of the different TIB schedules on circadian measures. However, based on previous findings, we hypothesized the following: 1. Baseline DLMO would be positively correlated with depression severity (i.e., later DLMO would be associated with more severe depression); 2. Baseline PAD (defined as DLMO – midsleep) would be negatively correlated with depression severity (i.e., a shorter PAD would be associated with more severe depression); 3. Delay in DLMO from baseline to post-experimental TIB manipulation (indicating a shift towards eveningness) would predict poorer response to fluoxetine across the 8-week study (i.e., more severe depression symptoms). Upon further considerations of the possible ways to analyze the data, associations between post-experimental TIB manipulation DLMO, PAD, and depression severity were analyzed, sex differences were examined, and quadratic (parabolic) analyses were added.

2. Methods

2.1. Participants

The parent trial was an 8-week randomized, controlled trial with 68 participants (Arnedt et al., 2016). All participants in the parent trial completed the dim light melatonin saliva sample collection procedure (except for the last 5 participants, who did not complete the procedure due to financial considerations); however, due to financial constraints, for this secondary analysis, saliva samples were assayed for melatonin

in a subsample of 30 participants randomly selected from parent trial. The study was approved by the University of Michigan Medical School Institutional Review Board. Recruitment occurred from September 2009 to December 2012; participants were recruited through advertisements for the study and clinical referrals. Written informed consent was obtained from all participants. The eligibility criteria for the parent trial was as follows: (1) 18–65 years of age; (2) diagnosis of major depressive disorder per DSM-IV plus a score of ≥ 18 on the 17-item Hamilton Rating Scale for Depression (HAM-D-17 (Hamilton, 1960)); and (3) habitual time in bed of 7–10 h per night. Participants were excluded from participation for any of the following: (1) current or past history of DSM-IV diagnosis other than major depressive disorder or generalized anxiety disorder; (2) diagnosis of DSM-IV alcohol abuse in the past 6 months; (3) presence of medical conditions associated with depression or affecting sleep; (4) sleep disorders other than insomnia; (5) use of medication (prescription or over-the-counter) for sleep or depression; (6) use of fluoxetine in the past 6 months; (7) night shift work; (8) pregnancy or breastfeeding; (9) known contraindication to fluoxetine; or (10) blood biochemistry not within normal limits. All participants were free of antidepressant medications for ≥ 2 weeks (≥ 4 weeks for longer-acting antidepressants). Participants completed an in-laboratory screen to assess for eligibility, including overnight polysomnography to screen for sleep disorders (Iber et al., 2007). A similar number of participants were enrolled in the study in the fall/winter (53.33%) and spring/summer (46.67%).

2.2. Study design and procedures

In the study preparatory phase, participants maintained a consistent 8-h time in bed (TIB) schedule at home, based on their habitual sleep schedule, for 5–7 days. To assess for melatonin levels, saliva samples were collected in dim light at Baseline (for more detail, see Measures below). Through random assignment, participants were then allocated 1:1:1 to one of three TIB conditions for the first 2 weeks of the study (experimental phase): (1) 8 h TIB ($n = 10$; 7 males, 3 females); (2) 6 h TIB ($n = 20$), with a 2-h delay of habitual bedtime (Late Bedtime, $n = 10$; 3 males, 7 females); or (3) 6 h TIB with a 2-h advance of habitual rise time (Early Rise time, $n = 10$; 4 males, 6 females). Participants began open-label fluoxetine 20 mgs daily the morning after their first experimental phase night; doses could be increased to 40 mgs after Week 4. Participants assigned to the 6 h TIB conditions were instructed to remain in dim light conditions for the 2 h period of sleep deprivation (e.g., a participant assigned to the Late Bedtime condition with a habitual bedtime of 10 pm would remain in dim light from 10 pm to 12 pm) during the first 2 weeks of the study to minimize direct effects on the circadian system. Participants wore a wrist actigraph with an integrated light meter (Philips Respironics Actiwatch-2) on their non-dominant wrist during the preparatory and experimental phases of the study; they were instructed to keep the face of the actigraph uncovered by clothing at all times. Actigraphy data were collected at a 60-second sampling rate. Actigraphy were scored according to established procedures (Ancoli-Israel et al., 2015) using Actiware® – Sleep software (Version 5.0) in conjunction with daily sleep/wake diaries. Participants were prohibited from using drugs and alcohol and napping during the preparatory and experimental phases of the study. They were allowed to use their habitual amount of caffeine prior to 12 pm.

Participants underwent overnight polysomnography in the laboratory for the first 3 nights of the study (respectively, screening/adaptation (8 h TIB), Baseline (8 h TIB), and first experimental night (6 h or 8 h TIB)) and again for 2 consecutive nights at the end of the experimental phase ((the final experimental night (6 h or 8 h TIB)) and an 8 h TIB recovery night; Week 2); polysomnography results are reported in the parent trial (Arnedt et al., 2016). On the final experimental night, participants again completed a saliva sample collection protocol in dim light to assess melatonin levels (for more detail, see Section 2.3 below).

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