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Insomnia as a Moderator of Response to Time in Bed Restriction for Augmenting Antidepressant Treatment: A Preliminary Investigation

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Abstract

Background—There are complex, bidirectional associations between major depressive disorder and insomnia. In the present study, we evaluated insomnia as a moderator of response to antidepressant therapy in the context of a sleep manipulation (time in bed restriction) for major depressive disorder.

Methods—Fifty-eight adults with major depressive disorder received 8 weeks of fluoxetine 20–40 mgs and were randomized to 8 hours' time in bed (8h TIB) or 6 hours' time in bed (6h TIB) for the first 2 weeks (participants in the 6h TIB condition were further randomized to a delayed bedtime (Late Bedtime) or advanced risetime (Early Risetime) group). Insomnia was assessed at baseline using the Insomnia Severity Index. Depression symptom severity was determined by the clinician-rated 17-item Hamilton Rating Scale for Depression (HAM-D-17), completed weekly.

Results—A group by time interaction was observed whereby HAM-D-17 scores were higher for participants assigned to the 6h TIB group (without insomnia, weeks 3 through 7; with insomnia from week 3 through 6, $p < .05$) relative to participants without insomnia assigned to the 8h TIB group. There were no differences in HAM-D-17 scores for participants with insomnia in the 6h TIB group relative to the 8h TIB group.

Conclusion—These preliminary findings suggest that response to fluoxetine may be hindered by TIB restriction in individuals without insomnia. Individuals with insomnia respond similarly to fluoxetine regardless of whether their TIB is restricted. Limitations include exclusive use of self-report measures to categorize insomnia, and small sample sizes in several of the subgroups.

Sleep disturbances are exceedingly common in depression. Nearly 85% of adults with major depressive disorder (MDD) subjectively report at least one symptom of insomnia (Sunderajan et al., 2010). The number of nights with insomnia symptoms and frequency of nighttime awakenings are associated with depression severity (Taylor, Lichstein, Durrence, Reidel, & Bush, 2005). Depression is also associated with objective sleep disturbances, including shorter REM onset latency, less slow wave sleep, and less efficient sleep (Arfken

et al., 2014). The associations between MDD and insomnia are complex, bidirectional, and reflected throughout the course of depression. In a large retrospective study of more than 14,000 adults, insomnia symptoms preceded new-onset mood disorders in 41% of cases, and preceded relapse to a mood disorder in 56.2% of the cases (Ohayon & Roth, 2003). Longitudinal studies further confirm sleep disturbance as a significant risk factor in the development of new-onset depression (Breslau, Roth, Rosenthal, & Andreski, 1996; Fernandez-Mendoza et al., 2015; Ford & Kamerow, 1989). This relationship is observed across the lifespan, in adolescents (Johnson, Roth, & Breslau, 2006), young adults (Breslau et al., 1996), and through older adulthood (Cole & Dendukuri, 2003). Difficulties with sleep are also the most common residual symptoms after depression has remitted (Iovieno, van Nieuwenhuizen, Clain, Baer, & Nierenberg, 2011) and predict depression recurrence (Buysse et al., 2008; Dombrovski et al., 2008).

Response to depression treatment is also affected by sleep disturbances. Greater REM percent and less stage 2 sleep were associated with poorer response to combination pharmacotherapy and psychotherapy in older adults (Dew et al., 1997). An abnormal EEG sleep profile, marked by reduced REM latency, increased REM density, and decreased sleep efficiency, predicted poorer response to cognitive behavior therapy (Thase, Simons, & Reynolds, 1996) and interpersonal psychotherapy (Thase et al., 1997). In a more recent study, longer sleep onset latency and shorter sleep duration, measured by EEG, and subjectively reported insomnia were associated with poor treatment response to pharmacotherapy and/or psychotherapy (Troxel et al., 2012). In older adults with depression, subjectively reported sleep problems were associated with persistence of depression across a 12-month period, despite treatment (Pigeon et al., 2008).

Given its interrelationship with mood, sleep is an important target for depression therapies. To date, there are no studies examining the influence of insomnia on response to antidepressant therapy in the context of an experimental sleep manipulation. Sleep deprivation protocols and adaptations of these protocols (including partial sleep deprivation) are among the most widely studied sleep-based depression therapies (Gillin, 1983). Our group recently completed a randomized controlled trial comparing the mood effects of two weeks of restricted time in bed (6 hours' time in bed; 6h TIB) to no time in bed restriction (8 hours' time in bed; 8h TIB) administered adjunctively to the antidepressant fluoxetine in adults with major depressive disorder. As late night sleep deprivation (advanced rise time) has been demonstrated to be superior to early night sleep deprivation (delayed bedtime) for depression (Sack, Duncan, Rosenthal, Mendelson, & Wehr, 1988), but not studied in repeated partial sleep deprivation, 6h TIB participants were further randomized to a delayed bedtime (Late Bedtime) or advanced risetime (Early Risetime) condition to evaluate the effects of timing of partial sleep deprivation. Participants took fluoxetine daily and were followed for 8 weeks. The main findings indicated that the 8h TIB group demonstrated a superior response to fluoxetine relative to the 6h TIB group (Arnedt et al., in press). In the present study, we conducted a secondary data analysis to determine whether the presence of insomnia affected response to fluoxetine and adjunctive time in bed restriction. We hypothesized that participants with insomnia assigned to the 6h or 8h TIB condition would evidence higher levels of depression on a clinician-rated measure of depression symptom severity (suggestive of a poorer response to antidepressant treatment) relative to participants

without insomnia assigned to the 6h or 8h TIB condition. We further hypothesized that among participants with insomnia, those assigned to the 6h TIB condition would evidence lower levels of depression (suggestive of a better response to antidepressant treatment) relative to those assigned to the 8h TIB condition, as the 6h TIB would likely lead to sleep consolidation, which could improve mood in turn. A secondary, exploratory aim of this study was to examine whether depression symptom severity across the study differed according to insomnia status and the timing of TIB restriction (i.e., Late Bedtime vs. Early Risetime).

Method

Participants

Participants were recruited for the study via advertisements and clinical referrals from September 2009 to December 2012. All participants provided written informed consent. Study procedures were approved by the University of Michigan Medical School Institutional Review Board. To be eligible for the study, participants had to meet the following criteria: (1) 18–65 years old; (2) DSM-IV diagnosis of MDD of at least moderate severity (≥ 18 on the 17-item Hamilton Rating Scale for Depression, HAM-D-17 (Hamilton, 1960)); and (3) habitual TIB of 7–10 hours nightly. Participants were ineligible for the study if they met any of the following conditions: (1) lifetime DSM-IV diagnosis other than MDD or generalized anxiety disorder; (2) past 6-month DSM-IV alcohol abuse diagnosis; (3) medical conditions associated with depression or interfering with sleep; (4) sleep disorder other than insomnia; (5) prescription or non-prescription medication for sleep or depression; (6) failed fluoxetine trial within the past six months; (7) overnight shift work; (8) pregnancy, breastfeeding, or inadequate contraception in women of childbearing potential; (9) known contraindication to fluoxetine; and (10) blood biochemistry not within normal limits. Participants had to be free of antidepressants for ≥ 2 weeks (≥ 4 weeks for longer-acting antidepressants). In-laboratory screening was completed to assess for psychiatric, medical, and sleep conditions. Participants were also screened for sleep disorders other than insomnia using in-laboratory polysomnography following recommended guidelines (Ilber, Ancoli-Israel, Chesson, & Quan, 2007).

Study Design and Procedures

The study was a randomized, controlled parallel trial design. All participants received open-label fluoxetine, 20–40 mgs, for 8 weeks. Participants were randomized (1:1:1) to the following experimental TIB conditions for the first 2 weeks of fluoxetine: (1) 8h TIB (n = 17); (2) 6h TIB (n = 41), with a two-hour delay of bedtime (Late Bedtime, n = 18); or (3) 6h TIB with a 2-hour advance of rise time (Early Risetime, n = 23). Participants maintained a regularized 8-hour time in bed schedule at home for 5–7 days after enrollment to ensure adequate sleep opportunity and stabilization of the circadian system. Napping and alcohol/drug use were prohibited. Habitual caffeine intake was allowed prior to 12 pm. Participants began 20 mg of fluoxetine the morning after their first night on the experimental TIB condition and then daily for 8 weeks, with a possible dose increase to 40 mg after Week 4. At the end of the second week, participants were allowed to self-select their sleep schedule for the remainder of the study. Adherence to the two-week experimental TIB condition was

assessed using wrist actigraphy, analyzed in conjunction with daily sleep diaries. Additional details regarding the design and methods of the parent trial are described elsewhere (Arnedt et al., in press).

Measures

The HAMD-17 was used to measure depression symptom severity. The three sleep items were removed from the total score for outcomes in the present study. Total scores on this measure range from 0 to 46. Clinicians trained to reliability on the HAMD-17 administered the HAMD-17 to participants at weekly intervals throughout the study. Clinicians were blinded to TIB condition assignment.

Insomnia was assessed using the Insomnia Severity Index (ISI) at study entry. The ISI is a validated 7-item measure of insomnia symptom severity over the previous two weeks; scores range from 0 to 28 (Bastien, Vallieres, & Morin, 2001). A cutoff score of 10 was used to classify participants as experiencing insomnia, based on previous work showing that 10 is the optimal cutpoint to identify cases of insomnia in community-based samples (Morin, 2011).

Statistical Analyses

All statistical analyses were conducted using SPSS 22.0 software (IBM Corporation, Armonk, NY). All significance testing was set at 0.05. All analyses were intent-to-treat in design. To evaluate the primary aim, participants were classified into the following groups, according to their insomnia status and TIB condition: No insomnia/8h TIB; No insomnia/6h TIB; Insomnia/8h TIB; and Insomnia/6h TIB. To evaluate the secondary aim, participants were classified into the following groups: No insomnia/8h TIB (n = 8); No insomnia/Early Risetime (n = 17); No insomnia/Late Bedtime (n = 7); Insomnia/8h TIB (n = 9); Insomnia/Early Risetime (n = 6); Insomnia/Late Bedtime (n = 11).

Descriptive and inferential statistics analyses were conducted in SPSS 22.0 software (IBM Corporation, Armonk, NY). Stata 13 (StataCorp LP, College Station, TX) was used for the linear mixed models.

One-way ANOVAs and chi-square tests evaluated differences on demographic characteristics and baseline HAMD-17 score by group. For the primary aim, multilevel linear mixed models for repeated measures evaluated the main effects of insomnia status/TIB condition group (No insomnia/8h TIB; No insomnia/6h TIB; Insomnia/8h TIB; and Insomnia/6h TIB), time (week of study; as a linear and quadratic function), and their interaction (insomnia/TIB condition group $\times$ time) on HAMD-17 score (minus the three sleep items). The model was adjusted for education, sex, adherence (compliant within 30 minutes of assigned schedule based on actigraphy), and baseline HAMD-17 score. An unstructured covariance structure was utilized, with a random intercept per participant and a random slope associated with time. Post-hoc pairwise comparisons, adjusted by Holm's sequential Bonferroni procedure (Holm, 1979), assessed differences on HAMD-17 score at each week by insomnia/TIB condition group.

A similar linear mixed model was utilized to evaluate the secondary aim; however, this model included three groups for the TIB condition (8 h TIB, Late Bedtime, Early Risettime). All other elements were identical to the model described above.

Results

Participant Characteristics

Fifty-eight participants were enrolled in the study. All participants completed the first 4 weeks of the study. Four participants were lost to follow-up after week 4 (1 from the No insomnia/6h TIB group; 2 from the Insomnia/8h TIB group; and 1 from the Insomnia/6h TIB group). Participant demographic data and HAMD-17 and ISI scores at study entry are summarized in Table 1. The proportion of participants with insomnia were roughly equivalent in each TIB condition (52.9% in the 8h TIB group, 45% in the 6h TIB group; $\chi^2(1) = .64, p = .58$). The Insomnia/8h TIB group reported significantly more education relative to the Insomnia/6h TIB and No insomnia/6h TIB groups. There were no other group differences on other demographic characteristics or HAMD-17 score at study entry. The proportion of participants who received an increased dose of fluoxetine were not significantly different across groups (37.5% in the No insomnia/8h TIB group, 65.2% in the No insomnia/6h TIB group, 55.6% in the Insomnia/8h TIB group, and 58.8% in the Insomnia/6h TIB group; $\chi^2(3) = 1.89, p = .59$). As assessed by actigraphy, across the two-week experimental period, TIB was 8.0 ± 0.5 hours for participants assigned to the 8h TIB condition and 6.9 ± 1.2 hours ($t = 3.8, df = 56, p < .001$). A greater proportion of participants assigned to the 8h TIB condition (82.4%) relative to those assigned to the 6h TIB condition (53.7%) were within 30 minutes of their assigned schedule per actigraphy throughout the two-week experimental period ($\chi^2 = 4.2, df = 1, p < .04$); for further detail, see Arnedt et al. (Arnedt et al., in press).

Depression Outcomes

Weekly mean HAMD-17 scores (minus the three sleep items) by group are shown in Table 2. For our primary aim, linear mixed model results showed an interaction between insomnia status/TIB condition group and time (see Table 3). Means from the linear mixed model with the quadratic term for week (adjusted for education, sex, adherence, and baseline HAMD-17 score) at each week of study are plotted by group in Figure 1. Participants in the No insomnia/8h TIB condition had the greatest decline in depression symptom severity scores across time. In contrast, the rate of decline was slower and very similar in the No insomnia/6h TIB and Insomnia/6h TIB groups. The Insomnia/8h TIB group showed a curvilinear response, with an initial decline in symptom severity followed by an increase in severity starting around week 6, through the final week. Post-hoc tests, using Holm's sequential Bonferroni procedure to correct for multiple comparisons, revealed that relative to participants without insomnia assigned to the 8h TIB condition, participants without insomnia assigned to the 6h TIB condition and participants with insomnia assigned to the 6h TIB condition had significantly higher HAMD-17 scores beginning in week 3, sustained through week 7 of the study ($p < .05$). Relative to participants without insomnia assigned to the 8h TIB condition, participants with insomnia assigned to the 6h TIB condition had significantly higher HAMD-17 scores beginning in week 3, sustained through week 6 ($p < .05$).

05). There were no differences in HAMD-17 scores between the following groups at any weeks: 8h TIB with insomnia relative to 8h TIB without insomnia; 6h TIB with insomnia relative to 8h TIB with insomnia; 6h TIB without insomnia relative to 6h or 8h TIB with insomnia.

For our secondary aim, results were similar to those from the primary aim analysis, with an interaction between insomnia status/sleep timing group and time ($F(4, 88.09) = 2.69, p = 0.036$). Among participants without insomnia, those in the 8h TIB condition had lower HAMD-17 scores relative to those in the Early Risettime condition starting at week 3 ($p = .012$), sustained through week 8 ($p = .002$). Participants without insomnia in the 8h TIB condition also demonstrated lower HAMD-17 scores relative to participants without insomnia in the Late Bedtime condition starting at week 4 ($p = .023$), sustained through week 8 ($p = .008$). There were no differences in HAMD-17 scores among participants with insomnia assigned to the 8h TIB relative to those assigned to the Early Risettime and Late Bedtime conditions. There were no differences in HAMD-17 scores between participants with or without insomnia assigned to the Early Risettime group relative to the Late Bedtime group.

Discussion

The present study was the first to evaluate time in bed restriction and insomnia status in adults with depression as predictors of treatment response when starting an antidepressant. We observed an interaction effect whereby the response trajectory differed by insomnia status and TIB condition. Visual inspection of these trajectories suggest that participants without insomnia assigned to the 8h TIB condition had the best response to fluoxetine overall. Our hypothesis that participants with insomnia assigned to the 6h or 8h TIB condition would respond more poorly to fluoxetine relative to those without insomnia assigned to the 6h or 8h TIB condition was partially supported. Participants with insomnia in the 6h TIB group had a poorer treatment response when compared to participants without insomnia who were assigned to an 8h TIB schedule. However, the response trajectory of participants with insomnia was equivalent to those of participants without insomnia whose time in bed was restricted when starting fluoxetine. Our hypothesis that participants with insomnia would respond more favorably to fluoxetine when assigned to a 6h TIB condition was not supported, as there were no differences in response trajectory by TIB condition among participants with insomnia.

Within the subgroup of participants without insomnia, differences in treatment response by experimental TIB condition were initially observed at 3 weeks. Of note, this separation in response trajectories occurred earlier than the typical response time to a selective serotonin reuptake inhibitor, which averages 4 to 6 weeks (Nierenberg et al., 2000). Despite returning to their preferred time in bed schedule after the first 2 weeks of the study, participants without insomnia who were assigned to a 6h TIB schedule continued to evidence a much slower response trajectory, whereas those who maintained an 8h TIB for the first 2 weeks had a rather rapid decline in symptoms for the remaining 6 weeks.

Overall, these preliminary findings are generally consistent with studies of insomnia as a moderator of response to traditional depression therapies (e.g., antidepressants or psychotherapy), which have shown that insomnia predicts poorer response to these treatments (Dew et al., 1997; Pigeon et al., 2008; Thase et al., 1997; Thase et al., 1996; Troxel et al., 2012). However, none of these studies were designed to evaluate the experimental manipulation of TIB and evaluate effects on treatment response in the context of starting a depression treatment. Intriguingly, participants without insomnia who were assigned to a restricted time in bed showed a nearly identical antidepressant treatment response as those with insomnia. A possible interpretation of this unexpected finding is restricting time in bed when starting an antidepressant hinders treatment response in individuals who do not have sleep difficulties, whereas it has no effect on individuals with insomnia. However, this finding requires replication and further research is needed to understand the mechanisms by which repeated restriction of time in bed hinders antidepressant treatment response in this population.

There are several limitations to the present study. First, a self-report measure (the ISI) was used to categorize insomnia status. Although the ISI is well-validated against diagnostic measures of insomnia, there may not be perfect overlap between our categorization of participants with insomnia and those obtained from a full diagnostic assessment. Second, our sample was homogenous, consisting of younger adults, the majority of whom were white. Thus, our findings may not generalize to other populations. Third, participants were aware of their TIB condition assignment, and their expectancies regarding treatment effects may have influenced the results. Fourth, the use of sleep diary information in conjunction with actigraphy to define adherence to the assigned TIB means that actigraphy is not truly an objective measure of TIB. Fifth, participants were allowed to determine their own time in bed schedule following the second week of the study. Sleep was also not monitored after the second week of the study. Thus, we do not know how changes in sleep patterns in the last 6 weeks affected treatment response. Finally, several of our subgroups had small sample sizes. Therefore, the failure to detect differences in treatment response in the group of participants with insomnia may be due to Type II error.

Taken as a whole, these preliminary findings provide further evidence of considering habitual sleep patterns (specifically, the amount of time devoted to sleep) and sleep problems in individuals with depression, as curtailing time in bed when starting an antidepressant may negatively affect treatment response in adults who do not have insomnia. Individuals who are not experiencing clinically significant insomnia may have a more robust response to antidepressant medications when they devote an adequate amount of time to sleep while initiating the medication. Replication of these findings with larger sample sizes is important to provide further support for the clinical implications from this preliminary study.

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Figure 1.

Estimated weekly mean HAMD-17 score (minus sleep items) by group, adjusted for education, sex, adherence, and baseline HAMD-17 score.

+ = Scores are significantly lower in the No Insomnia/8h TIB group relative to the No Insomnia/6h TIB group and the Insomnia/6h TIB group.

= Scores are significantly lower in the No Insomnia/8h TIB group relative to the No Insomnia/6h TIB group.

Table 1

Participant demographic characteristics M (SD) or n (%)

	No Insomnia/8h TIB <i>n</i> = 8	No Insomnia/6h TIB <i>n</i> = 24	Insomnia/8h TIB <i>n</i> = 9	Insomnia/6h TIB <i>n</i> = 17	Total Sample <i>N</i> = 58
Age	25.5 (8.3)	23.9 (3.9)	19.2 (1.9)	20.5 (2.8)	25.8 (7.1)
Sex					
Male	6 (75)	11 (45.8)	3 (33.3)	7 (41.2)	27 (46.6)
Female	2 (25)	13 (54.2)	6 (66.7)	10 (58.8)	31 (53.4)
Race					
White	6 (75)	20 (83.3)	7 (77.8)	13 (76.5)	46 (79.3)
Black/African American	2 (25)	2 (8.3)	1 (11.1)	2 (11.8)	7 (12.1)
Other	0	2 (8.3)	1 (11.1)	2 (11.8)	5 (8.6)
Education (years) ^a	15.3 (2.3)	14.3 (1.5)	16.2 (1.2)	14.8 (1.7)	14.9 (1.8)
Employment Status					
Full time	1 (12.5)	4 (16.7)	2 (22.2)	2 (11.8)	9 (15.5)
Part time	4 (50.0)	9 (37.5)	4 (44.4)	6 (35.3)	23 (39.7)
Unemployed	3 (37.5)	11 (45.8)	3 (33.3)	9 (52.9)	26 (44.8)
Marital Status					
Never married	7 (87.5)	20 (83.3)	7 (77.8)	12 (70.6)	46 (79.3)
Married/Partnered	1 (12.5)	4 (16.7)	2 (22.2)	2 (11.8)	9 (15.5)
Separated/Divorced	0	0	0	3 (17.6)	3 (5.2)
HAMD-17 Score-Study Entry ^b	20 (2.9)	19.8 (1.7)	19.2 (1.9)	20.5 (2.8)	20 (2.3)
ISI Score ^c	6.9 (2.8)	5 (2.3)	12 (3.1)	15.4 (3.9)	9.4 (5.4)

Note.

^aThe Insomnia/8h TIB group reported significantly more education relative to the Insomnia/6h TIB and No Insomnia/6h TIB groups ($F(3,57) = 2.93, p < .05$).^bTotal score, including the sleep items.^cThere was a significant difference among the groups on ISI scores ($F(3, 55) = 41.30, p < .001$).

Table 2

Unadjusted HAMD-17 means without sleep items for by week of study by group

	n	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
No insomnia/8h TIB	8	17 (5.56)	12.75 (4.43)	12.13 (3.68)	7.29 (3.73)	5.75 (4.4)	5.71 (3.9)	2.57 (2.88)	3.14 (3.67)	2.5 (1.6)
No insomnia/6h TIB	24	15.75 (4.84)	15.29 (3.58)	12.83 (4.82)	11.62 (4.13)	11.18 (4.52)	10.64 (6)	8.78 (5.19)	9.9 (5.61)	6.91 (4.33)
Insomnia/8h TIB	9	16.78 (3.38)	13.63 (3.85)	10.56 (3.21)	6.57 (3.55)	10.89 (5.49)	8.67 (5.22)	7 (5.35)	9.71 (5.35)	9.63 (8.01)
Insomnia/6h TIB	17	17 (4.95)	14.13 (4.75)	15.35 (5.77)	12.12(5.93)	10.71 (6.22)	10.56 (7.08)	8.6 (5.87)	7.36 (6.46)	7.4 (5.48)

Note. N = 58

Table 3

Estimates of fixed effects from linear mixed models predicting depression severity

Depression severity (HAMD-17)		
	B	SE
Intercept	14.19	6.94 *
Participant (Level 2)		
Education	0.18	0.30
Sex	0.25	0.99
Adherence ^a	0.54	1.09
Baseline depression	0.15	0.22
Group^b		
Insomnia/8h TIB	-1.35	2.77
Insomnia/6h TIB	-2.15	2.41
No insomnia/6h TIB	-3.69	2.36
Week of study (Level 1)		
Week (linear)	-4.00	0.72 ***
Week (quadratic)	0.22	0.07 ***
Week (linear) × Group^b		
Insomnia/8h TIB	0.46	0.99
Insomnia/6h TIB	2.27	0.87 **
No insomnia/6h TIB	2.88	0.84 ***
Week (quadratic) × Group^b		
Insomnia/8h TIB	0.04	0.09
Insomnia/6h TIB	-0.16	0.08 *
No insomnia/6h TIB	-0.21	0.08 **

Note. B = unstandardized coefficient; SE = standard error. Level 2 N = 58 people; Level 1 N = 484 group-weeks.

^aParticipants were considered adherent if they maintained an average time in bed within 30 minutes of their assigned time in bed (per actigraphy).

^bThe No Insomnia/8h TIB was used as the reference in group for all models.

* $p < .05$,

** $p < .01$,

*** $p < .001$.