Effects of Restricted Time in Bed on Antidepressant Treatment Response:
A Randomized Controlled Trial

J. Todd Arnedt, PhD[a,*]; Leslie M. Swanson, PhD[a]; Richard R. Dopp, MD[a]; Holli S. Bertram, LMSW[a]; Ann J. Mooney, MSW[a]; Edward D. Huntley, PhD[a]; Robert F. Hoffmann, PhD[a]; and Roseanne Armitage, PhD[b]

ABSTRACT

Objective: Antidepressant response onset is delayed in individuals with major depressive disorder (MDD). This study compared remission rates and time to remission onset for antidepressant medication delivered adjunctively to nightly time in bed (TIB) restriction of 6 hours or 8 hours for the initial 2 weeks.

Methods: Sixty-eight adults with *DSM-IV*–diagnosed MDD (mean ± SD age = 25.4 ± 6.6 years, 34 women) were recruited from September 2009 to December 2012 in an academic medical center. Participants received 8 weeks of open-label fluoxetine 20–40 mg and were randomized to 1 of 3 TIB conditions for the first 2 weeks: 8-hour TIB (n = 19); 6-hour TIB with a 2-hour bedtime delay (late bedtime, n = 24); or 6-hour TIB with a 2-hour rise time advance (early rise time, n = 25). Clinicians blinded to TIB condition rated symptom severity weekly. Symptom severity, remission rates, and remission onset as rated by the 17-item Hamilton Depression Rating Scale were the primary outcomes.

Results: Mixed effects models indicated lower depression severity for the 8-hour TIB compared to the 6-hour TIB group overall ($F_{8, 226.9} = 2.1$, $P < .05$), with 63.2% of 8-hour TIB compared to 32.6% of 6-hour TIB subjects remitting by week 8 ($\chi^2_1 = 4.9$, $P < .05$). Remission onset occurred earlier for the 8-hour TIB group (hazard ratio = 0.43; 95% CI, 0.20–0.91; $P < .03$), with no differences between 6-hour TIB conditions.

Conclusions: Two consecutive weeks of nightly 6-hour TIB does not accelerate or improve antidepressant response. Further research is needed to determine whether adequate sleep opportunity is important to antidepressant treatment response.

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[a]Sleep and Circadian Research Laboratory, Department of Psychiatry, University of Michigan, Ann Arbor
[b]When this work was done, Dr Armitage was a faculty member at the University of Michigan.
**Corresponding author:* J. Todd Arnedt, PhD, Associate Professor of Psychiatry and Neurology, Sleep and Circadian Research Laboratory, University of Michigan Medical School, 4250 Plymouth Rd, Ann Arbor, MI 48109-2700 (tarnedt@umich.edu).

Major depressive disorder (MDD) affects roughly 16.5% of US adults in their lifetime[1] and is a leading cause of disease burden. Evidence-based pharmacotherapy is widely available, but treatment response time is delayed and failure rates are as high as 30%–40%.[2–4] Novel therapies are needed to accelerate and improve antidepressant response.

One night of total sleep deprivation improves mood in 60% of MDD patients[5]; however, relapse following recovery sleep occurs in up to 80% of unmedicated patients.[5,6] Serial repetition can sustain the positive mood response to total sleep deprivation, but relapse remains likely, particularly without concomitant antidepressant treatment.[7] More recent studies (eg, Martiny et al[8]) combining total sleep deprivation with other chronotherapeutic interventions (light therapy and sleep schedule adjustments) and medication have shown promise, but these treatments are complex to administer.

Single-night partial sleep deprivation (4–5 hours of sleep) has been explored as an alternative to total sleep deprivation. Research[9] has found next-day response rates to partial sleep deprivation equivalent to total sleep deprivation, with improved patient tolerance. Wakefulness during the second half of the night (late partial sleep deprivation, when rapid eye movement [REM] sleep predominates) is often superior to wakefulness in the first half (early partial sleep deprivation),[10] but perhaps not if total sleep time is equivalent.[11,12] Studies have found that repetition of partial sleep deprivation during the initial 1–4 weeks of antidepressant therapy can accelerate treatment response[13–15] and quality-of-life improvement,[16] but these were conducted in inpatients or in a laboratory setting and did not include sleep control conditions or sufficient follow-up after the partial sleep deprivation procedures. Ideal sleep-focused strategies would be clinically efficacious and maximize patient feasibility by allowing treatments to be carried out safely in the home environment. To date, no study has assessed the effects of a modest repeated restriction of time in bed (TIB) on treatment response in outpatients with depression initiating an antidepressant treatment trial.

The primary aim of the present study was to compare the mood effects of 2 weeks of 6-hour TIB to 8-hour TIB delivered adjunctively to antidepressant therapy in outpatient adults with MDD. A secondary aim was to investigate whether the timing of the TIB restriction was important by randomizing subjects to either a 2-hour delay of bedtime (late bedtime) or a 2-hour advance of rise time (early rise time). We hypothesized that symptom improvement would be greater and remission onset would be earlier for MDD subjects randomized to antidepressant therapy plus 6-hour TIB. We expected that, relative to the 8-hour TIB condition, the late bedtime group would experience an increase in slow-wave sleep, while the early rise time group

Clinical Points

- Effective and practical clinical strategies are critically needed to improve response and remission rates to first-line antidepressant medications.
- Patients initiating a new trial of antidepressant medication should be cautioned against restricting their time in bed.

would experience a reduction in REM sleep. Since most prior studies have shown late night sleep deprivation to be superior to early night sleep deprivation, we hypothesized that symptom improvement would be greater in the early rise time compared to the late bedtime condition.

METHODS

Participants

Participants were recruited from September 2009 to December 2012 through advertisements and clinical referrals. Inclusion criteria were (1) 18–65 years old, (2) *DSM-IV* diagnosis of MDD of at least moderate severity (≥ 18 on the 17-item Hamilton Depression Rating Scale [HDRS-17]), and (3) habitual TIB of 7–10 hours nightly. Exclusion criteria included (1) lifetime *DSM-IV* diagnosis of bipolar disorder, psychotic disorder, substance or alcohol dependence, eating disorder, posttraumatic stress disorder, or obsessive-compulsive disorder; (2) past 6-month *DSM-IV* alcohol abuse diagnosis; (3) medical conditions associated with depression (eg, hypothyroidism) or interfering with sleep; (4) sleep disorder other than insomnia, based on the International Classification of Sleep Disorders, 2nd Edition (ICSD-2)[17]; (5) prescription or nonprescription medication for sleep or depression; (6) failed fluoxetine trial within the past 6 months; (7) overnight shift work; (8) pregnancy, breastfeeding, or inadequate contraception in women of childbearing potential; (9) known contraindication to fluoxetine; and (10) abnormal laboratory values. Subjects had to be free of antidepressants for ≥ 2 weeks (≥ 4 weeks for longer-acting antidepressants). Participants underwent an initial telephone screen and in-laboratory psychiatric, medical, and sleep screening. Study procedures were approved by the University of Michigan Medical School Institutional Review Board, and participants provided written informed consent. The study was registered on ClinicalTrials.gov (identifier: NCT01545843).

Study Design and Procedures

In this randomized controlled parallel trial, participants received open-label fluoxetine 20–40 mg for 8 weeks and were randomized (1:1:1) to 1 of 3 TIB conditions for the initial 2 weeks: (1) 8-hour TIB; (2) 6-hour TIB with a 2-hour delay of bedtime (late bedtime); or (3) 6-hour TIB with a 2-hour advance of rise time (early rise time). After enrollment but prior to the first in-laboratory night, subjects maintained a regularized 8-hour TIB schedule at home for 5–7 days, which was based on their self-reported preferred bedtimes and rise times. Alcohol/drug use and napping were prohibited and habitual caffeine intake was permitted before noon. Schedule compliance was confirmed with daily sleep/wake diaries and with wrist-worn actigraphy (Actiwatch-2, Philips Respironics; Murrysville, Pennsylvania).

Following the at-home 8-hour TIB schedule, participants spent 7 nights and mornings total in the sleep laboratory: 3 before starting fluoxetine, 2 after the 2-week TIB condition, and 2 after 8 weeks of fluoxetine treatment. The first 2 in-laboratory nights before starting fluoxetine were adaptation and baseline nights, respectively. Subjects maintained the 8-hour TIB schedule and were assessed for sleep disorders on the adaptation night using standard procedures.[18] Six subjects were excluded for suspicion of a sleep-related breathing disorder, based on ICSD-2 criteria. On the third night before starting fluoxetine, subjects were randomized to 1 of the 3 TIB conditions (8-hour TIB, late bedtime, early rise time) and maintained this schedule at home for a mean ± SD of 14.0 ± 1.6 nights until returning for 2 additional in-laboratory nights. Participants underwent 2 final in-laboratory nights following the 8-week open-label antidepressant trial.

Subjects took the first 20-mg dose of fluoxetine following the first TIB condition night and then daily for 8 weeks, with a possible dose increase to 40 mg after week 4 based on clinician-rated response. Pills were counted at each in-laboratory visit to evaluate compliance.

Blinded clinician ratings of mood were completed at baseline and weekly thereafter. Subject-rated depression scales were completed at baseline and weeks 1, 2, 4, and 8; quality-of-life ratings were completed at baseline and weeks 4 and 8. A 2-hour neurocognitive test battery was completed in the morning following each in-laboratory sleep assessment (results not reported herein).

Outcome Measures

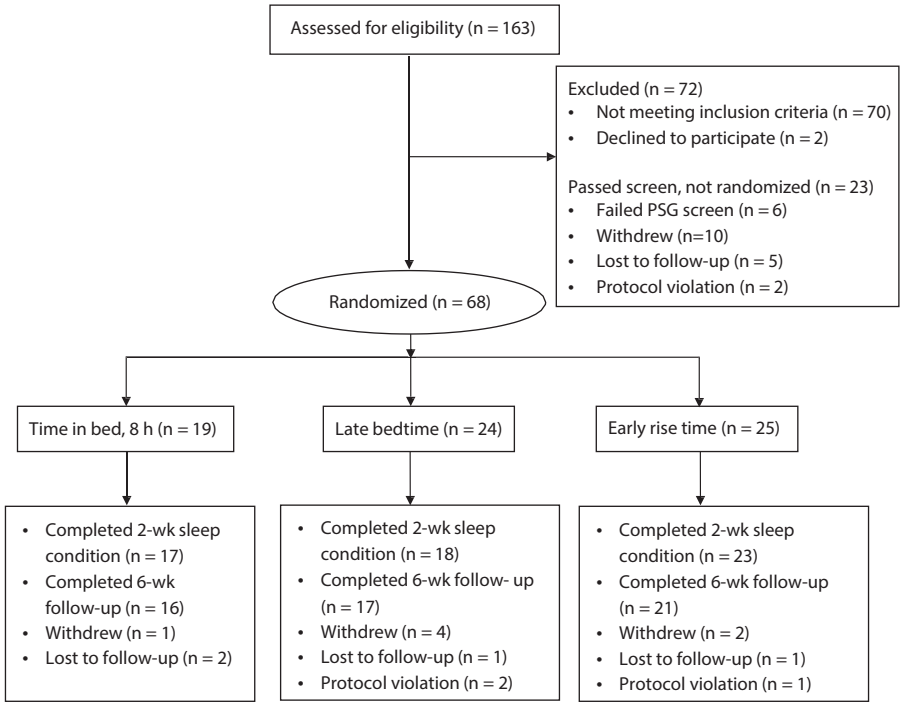
The HDRS-17[19,20] was the primary outcome measure. Symptom changes were evaluated with the total HDRS-17 score minus the 3 sleep items (range, 0–46),[21,22] and remission was defined as a score ≤ 7.[21,22] Removal of the 3 items from the HDRS-17 ensured that any observed mood improvements could not be attributable to sleep-related improvements from the TIB manipulations. The Clinical Global Impressions-Improvement scale (CGI-I)[23] was a secondary measure of clinician-rated improvement.

The 16-item Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR)[24] was the subject-rated symptom severity measure. Symptom severity scores minus the sleep item (range, 0–24) and remission (score ≤ 5) were the primary outcomes.[3]

The 12-item Short-Form Health Survey (SF-12) was included as a quality-of-life measure.[25] The primary dependent variables are the physical and mental composite scores, which range from 0 to 100, with higher scores indicative of better quality of life (mean = 50.0, SD = 10.0).

Polysomnography. Electrophysiological signals were collected via standard polysomnography montage[26] using the

Figure 1. CONSORT Diagram



Vitaport 3 (TEMEC Instruments, The Netherlands) digital polysomnography acquisition system. Polysomnography records were scored visually offline in 30-second epochs using standard criteria[26] by sleep technicians blinded to group assignment. Changes in the following sleep variables from baseline to week 2 were evaluated: total sleep time (total time asleep during the night); sleep efficiency (total sleep time/total recording time × 100); sleep latency (time in minutes to initial sleep onset); number of arousals; percentage of stages 1, 2, slow-wave sleep (stages 3 and 4), and REM; and latency to REM sleep (time in minutes to first REM episode).

Actigraphy. Actigraphs were set at a sampling rate of 1 minute and worn on the nondominant wrist during the prelaboratory baseline nights and during the 2-week TIB condition to assess compliance. Sleep/wake activity was estimated using Actiware-Sleep software (version 5.0) in combination with daily sleep/wake diaries. We followed established procedures for scoring actigraphy.[27] The primary outcomes were TIB and total sleep time.

Statistical Analyses

Continuous variables were analyzed in SPSS 20.0 (IBM Corporation; Armonk, New York), with linear mixed models using Akaike information criterion to evaluate goodness of fit for covariance structures.[28] The main model was parameterized to evaluate the effects of TIB condition (6-hour TIB vs 8-hour TIB), visit (baseline, weeks 1 through 8), and their interaction (condition by visit), adjusting for baseline covariates. Significant main effects or interactions favoring the 6-hour TIB over the 8-hour TIB condition on mood outcomes were further evaluated with post hoc analyses comparing the 3 TIB conditions separately. Because of a priori–hypothesized differences in slow-wave sleep and REM between the two 6-hour TIB conditions, the model analyzing polysomnography outcomes included all 3 levels for TIB condition. Differences in time to remission onset were evaluated using discrete time survival analyses using Stata 13 (StataCorp LP; College Station, Texas). Data are reported as mean ± SD or mean with 95% confidence interval (CI), with significance level set at .05.

RESULTS

Recruitment and Retention

A CONSORT diagram of participant flow through the protocol is shown in Figure 1. Overall, 58 subjects (85.2%) completed the 2-week TIB condition, and 54 subjects (79.4%) completed the 8-week study. Eleven of the 68 randomized subjects (16.2%) discontinued participation (3 8-hour TIB, 5 late bedtime, 3 early rise time), and 3 subjects (4.4%) were discontinued for protocol violations. Dropouts did not differ from completers on demographic or clinical variables.

Descriptive data for all randomized subjects are summarized in Table 1. The 8-hour TIB group had more years of education than the late bedtime and early rise time groups ($P < .005$).

Clinician- and Subject-Rated Symptom Changes

Summary data for clinician- and subject-rated symptom measures are shown in Table 2. Linear mixed models indicated a significant condition-by-visit interaction for

the HDRS-17 ($F_{8,\ 226.9} = 2.1$, $P < .05$). The HDRS-17 ratings were significantly lower (indicating less depression) for 8-hour TIB compared to 6-hour TIB subjects at weeks 3, 5, and 6, with trends at weeks 2, 4, and 7. After 2 weeks, HDRS-17 ratings had improved by 36.0% ± 22.6% versus 22.7% ± 31.0% for the 8-hour TIB and 6-hour TIB groups, respectively, but the proportion of subjects in remission at week 2 did not differ. By week 8, however, 12/19 (63.2%) 8-hour TIB subjects had remitted compared to 16/49 (32.6%) 6-hour TIB subjects ($\chi^2_1 = 4.9$, $P < .05$). Clinician ratings on the Clinical Global Impressions-Improvement scale indicated an overall visit effect ($F_{195.8} = 16.1$, $P < .001$), but no TIB condition-by-visit interaction.

No overall TIB condition-by-visit interaction was evident for QIDS-SR scores, but by week 2, scores were improved by 49.9% ± 31.4% for 8-hour TIB subjects compared to 24.5% ± 43.6% in 6-hour TIB conditions ($t_{56} = 2.2$, $P < .05$). By week 8, symptom improvement was equivalent between the 2 conditions. The SF-12 mental health composite scores were significantly more improved in the 8-hour TIB group by week 8 ($P < .04$), with a trend for significantly more improvement by week 4.

Onset of Symptom Remission

The HDRS-17 remission survival functions for the 8-hour TIB and 6-hour TIB conditions differed significantly (hazard ratio [HR] = 0.43; 95% CI, 0.20–0.91; $P < .03$) (Figure 2). Remission onset occurred after 6.4 ± 2.2 weeks for the 8-hour TIB group compared to 7.3 ± 1.5 weeks for the 6-hour TIB conditions. Onset of QIDS-SR remission (8-hour TIB: 6.7 ± 2.3 weeks vs 6-hour TIB: 7.5 ± 1.8 weeks) was earlier for 8-hour TIB compared to 6-hour TIB subjects, but the survival functions were not significantly different.

Polysomnography

Polysomnography outcomes are displayed in Table 3. Linear mixed models indicated a significant increase in slow-wave sleep percentage at week 2 in the late bedtime condition compared to baseline (β = 8.4, standard error [SE] = 2.4, $P < .001$). Post hoc analyses indicated that, from baseline to week 2, slow-wave sleep percentage *increased* by 4.2% ± 11.2% for late bedtime subjects compared to a 4.0% ± 5.1% *decrease* in the 8-hour TIB condition ($P < .002$). Rapid eye movement sleep percentage at week 2 was significantly lower in the early rise time group compared to baseline (β = −5.3, SE = 2.6, $P < .05$). Post hoc analyses indicated that REM sleep percentage declined more in the early rise time compared to the 8-hour TIB condition (−6.9% ± 5.5% vs −1.2% ± 11.3%, $P < .05$), but not the late bedtime condition. Across sleep conditions, light stage 1 sleep was 3.2% ± 4.4% higher at week 2 relative to baseline (β = 4.4, SE = 1.1, $P < .001$) and REM latency was 45.4 ± 59.9 minutes longer (β = 31.9, SE = 14.0, $P < .03$), findings consistent with the known effects of fluoxetine on sleep.

Table 1. Characteristics of Randomized Participants by Sleep Condition

	Time in Bed, 8 h (n = 19)		Time in Bed, 6 h (n = 49)				Total (n = 68)	
			Late Bedtime (n = 24)		Early Rise Time (n = 25)			
Variable	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age, y	26.4	7.4	24.4	5.6	25.7	7.0	25.4	6.6
Education, y[a]	16.0	2.0	14.4	1.7	14.5	1.5	14.9	1.8
Age at MDD onset, y	17.7	6.1	16.2	6.3	16.2	7.6	16.6	6.7
Current episode, mo	10.2	7.6	14.8	22.2	9.5	8.5	11.6	14.7
	n	%	n	%	n	%	n	%
Sex								
Male	12	63.1	11	45.8	11	44.0	34	50.0
Female	7	36.8	13	54.2	14	56.0	34	50.0
Race								
Black/African American	3	15.8	3	12.5	2	8.0	8	11.8
White	14	73.7	18	75.0	20	80.0	52	76.5
Other	2	10.5	3	12.5	3	12.0	8	11.8
Marital Status								
Unmarried	15	78.9	21	87.5	18	72.0	54	79.4
Married/partnered	4	21.1	2	8.3	5	20.0	11	16.2
Separated/divorced	0	0.0	1	4.2	2	8.0	3	4.4
Employment status								
Full-time employment	4	21.1	4	16.7	3	12.0	11	16.2
Part-time employment	8	42.1	9	37.5	9	36.0	26	38.2
Unemployed	7	36.8	11	45.8	13	52.0	31	45.6
Positive family history of MDD	13	68.4	19	79.2	17	68.0	49	72.1
MDD treatment history[b]								
None	6	33.3	8	34.8	7	30.4	21	32.8
Medication	5	27.8	1	4.3	3	13.0	9	14.1
Psychotherapy	3	16.7	2	8.7	2	8.7	7	10.9
Both	4	22.2	12	52.2	11	47.8	27	42.2
Comorbidity								
Medical	7	36.8	8	33.3	13	52.0	28	41.0
Psychiatric[c]	4	21.0	7	29.2	6	24.0	17	25.0

[a]The 8-hour time in bed group had significantly more years of education than either the late bedtime or early rise time group ($P < .005$).
[b]8-hour time in bed (n = 18), 6-hour late time in bed (n = 23), 6-hour early time in bed (n = 23), total (n = 64).
[c]Lifetime bipolar disorder, psychotic disorder, substance or alcohol dependence, eating disorder, posttraumatic stress disorder, and obsessive-compulsive disorder and post 6-month substance or alcohol abuse were exclusionary.
Abbreviation: MDD = major depressive disorder.

Compliance

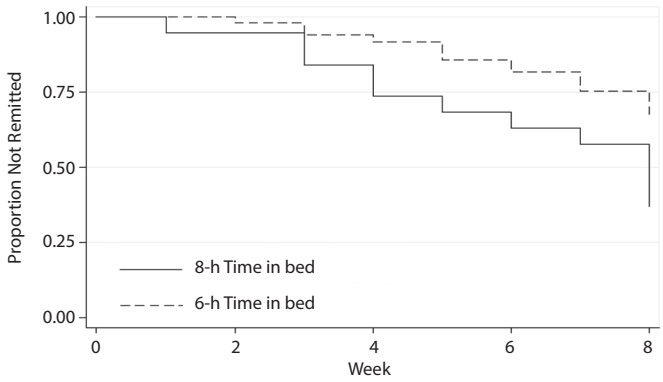
Actigraphy outcomes (n = 58) at baseline and during the 2-week TIB manipulation are shown in Table 4. All 3 groups showed good compliance with the baseline 8-hour TIB schedule, with no significant group differences in any actigraphy parameter. During the 2-week experimental manipulation, TIB was 8.0 ± 0.5 hours for 8-hour TIB subjects and 6.9 ± 1.2 hours for 6-hour TIB subjects (late bedtime = 6.7 ± 1.0 hours, early rise time = 7.0 ± 1.3 hours) ($t_{56} = 3.8$, $P < .001$). Daily deviation from assigned TIB was 0.9 ± 29.7 minutes for the 8-hour TIB group, 41.9 ± 58.8 minutes for the late bedtime group, and 60.1 ± 80.4 minutes for the early rise time group ($P < .01$ for 8-hour TIB vs early rise time). More 8-hour TIB (82.4%) than 6-hour TIB (53.7%) subjects were within 30 minutes of their assigned TIB schedule at the end of the 2-week period ($\chi^2_1 = 4.2$, $P < .04$); however, including compliance as a covariate in analyses of primary outcomes did not change the findings. Actigraphically measured nightly total

Table 2. Clinician- and Subject-Rated Scores on Mood and Clinical Improvement Outcomes by Time-in-Bed Condition

Measure and Assessment	Time in Bed, 8 h (n = 19) Mean	SD	Time in Bed, 6 h (n = 49) Mean	SD	Analysis[a] β Estimate[b]	SE	P Value
Clinician-rated							
HDRS-17 (minus sleep items)[c]							
Baseline	18.2	2.6	18.0	2.2			
Week 1	13.2	4.0	15.1	4.1	2.2	1.6	.20
Week 2	11.3	3.4	13.9	5.3	2.9	1.6	.08
Week 3	6.9	3.5	11.8	5.0	**5.8**	**1.6**	**.001**
Week 4	8.5	5.5	11.0	5.2	2.9	1.6	.07
Week 5	7.2	4.7	10.6	6.4	**3.8**	**1.6**	**.02**
Week 6	4.9	4.8	8.7	5.4	**4.4**	**1.6**	**.006**
Week 7	6.4	5.5	8.9	6.0	2.6	1.6	.09
Week 8	6.1	6.7	7.1	4.7	1.2	1.3	.35
CGI-Improvement							
Week 1	3.2	1.3	3.2	0.7			
Week 2	2.7	0.6	2.9	0.9	0.2	0.3	.66
Week 3	2.1	0.8	2.8	1.1	**0.7**	**0.3**	**.04**
Week 4	2.3	1.2	2.6	1.0	0.3	0.3	.42
Week 5	2.4	1.4	2.5	1.2	0.1	0.3	.67
Week 6	1.8	1.0	2.2	1.0	0.5	0.4	.14
Week 7	1.9	1.1	2.1	0.9	0.3	0.3	.44
Week 8	1.8	1.0	1.8	0.8	0.06	0.3	.84
Subject-rated							
QIDS-SR (minus sleep item)[d]							
Baseline	10.8	3.3	11.4	4.0			
Week 1	6.5	4.4	9.2	4.4	1.9	1.3	.15
Week 2	5.1	2.9	7.8	4.0	2.3	1.3	.07
Week 4	4.9	3.5	6.7	3.8	1.2	1.2	.33
Week 8	3.6	4.4	5.0	3.9	0.8	1.1	.45
SF-12: physical composite							
Baseline	55.8	5.3	54.7	10.0			
Week 4	56.1	4.9	51.9	9.2	−1.2	2.5	.65
Week 8	53.7	6.6	53.3	8.2	1.5	2.6	.56
SF-12: mental composite							
Baseline	24.8	9.1	26.8	8.3			
Week 4	38.5	14.7	34.4	11.2	−6.2	3.5	.08
Week 8	44.8	12.5	40.0	11.2	**−7.9**	**3.8**	**.04**

[a]Boldface type denotes significant findings.
[b]Estimate compares 8-hour time in bed versus combined 6-hour time in bed conditions with baseline as reference (visit 1 reference for CGI-Improvement).
[c]HDRS-17 minus sleep range is 0–46.
[d]QIDS-SR minus sleep range is 0–24.
Abbreviations: CGI = Clinical Global Impressions, HDRS-17 = 17-item Hamilton Depression Rating Scale, QIDS-SR = Quick Inventory of Depressive Symptomatology-Self-Rated, SF-12 = 12-Item Short-Form Health Survey.

Figure 2. Remission Survival Curves Across 8 Weeks for Adults With Major Depressive Disorder Receiving Fluoxetine 20–40 mg and Randomized to 8-Hour Time in Bed or 6-Hour Time in Bed During the Initial 2 Weeks of Therapy



sleep time was 6.6 ± 1.0 for the 8-hour TIB group and 5.9 ± 1.1 for the 6-hour TIB groups (late bedtime = 5.7 ± 0.9 hours, early rise time = 6.1 ± 1.2 hours) ($t_{56} = 2.2$, $P < .03$). During the 2-week experimental phase, sleep latency did not differ between TIB conditions, but wake after sleep onset was significantly longer in the 8-hour compared to the 6-hour TIB condition (44.8 ± 23.2 vs 28.3 ± 18.1 minutes; $t_{55} = 2.8$, $P = .006$).

No differences were evident in medication compliance, in the percentage of participants who increased to fluoxetine 40 mg (8-hour TIB [42.1%] vs late bedtime [54.2%] vs early rise time [48.0%]), or in the timing of fluoxetine dose increase.

DISCUSSION

This randomized controlled trial found that a 6-hour TIB schedule during the first 2 weeks of antidepressant therapy did not augment treatment response in young adults with MDD. Instead, depressed subjects who were provided an 8-hour TIB schedule had greater clinician-rated symptom improvement, were more likely to achieve remission after 8 weeks (63% vs 33%), and experienced symptom remission onset 1 week earlier. These effects were not due to better medication compliance or to a higher medication dose in the 8-hour TIB group. Importantly, objective compliance monitoring indicated that subjects were compliant with the 8-hour TIB schedule, but subjects assigned to the 6-hour TIB schedule were not. To our knowledge, this study is the first to evaluate experimentally a modest repeated TIB restriction on antidepressant treatment response.

The failure of TIB restriction to accelerate or augment antidepressant response contrasts with uncontrolled inpatient repeated partial sleep deprivation studies but is consistent with one of the few randomized controlled trials[29] to evaluate whether 1 night of total sleep deprivation could accelerate response to paroxetine in older adults with depression. Given previous findings, it is conceivable that a nightly TIB restriction dose greater than 2 hours was needed or that a 6-hour TIB schedule of longer than 2 weeks was necessary to produce beneficial mood effects. However, most previous studies[13–15] were conducted in inpatient or laboratory settings, which allow for controlled and safe delivery of sleep deprivation, but which are also impractical for outpatient practice. We were fundamentally interested in evaluating a more modest TIB restriction that has been used in experimental sleep deprivation studies,[30] is commonly used in behavioral sleep medicine outpatient practice,[31] and would be feasible and

Table 3. Polysomnography Outcomes at Baseline and Week 2 by Time-in-Bed Condition

	Time in Bed, 8 h (n = 17)		Time in Bed, 6 h (n = 40)				
			Late Bedtime (n = 18)		Early Rise Time (n = 22)		Time in Bed Condition by Visit, *P* Value[a]
Variable	Mean	SD	Mean	SD	Mean	SD	
Bedtime, hh:mm							**<.001**
Baseline	23:42	1:01	23:42	1:06	23:57	1:02	
Week 2	23:48	1:20	1:42	1:06	23:57	1:02	
Rise time, hh:mm							**<.001**
Baseline	7:42	1:01	7:42	1:06	7:57	1:03	
Week 2	7:42	1:01	7:42	1:06	5:57	1:03	
Total sleep time, min							**<.001**
Baseline	430.1	60.9	439.2	36.3	444.0	19.7	
Week 2	435.4	25.7	337.8	24.7	332.9	17.0	
Sleep efficiency, %							.70
Baseline	89.7	12.6	91.7	7.6	92.8	4.0	
Week 2	90.8	5.3	93.3	5.0	92.9	4.7	
Sleep latency, min							.64
Baseline	25.2	60.2	16.3	32.3	11.5	7.9	
Week 2	17.8	22.2	6.8	13.4	8.3	5.2	
No. of arousals							.17
Baseline	19.2	8.2	18.0	10.8	16.8	7.5	
Week 2	22.0	9.2	17.0	7.6	14.1	7.0	
Stage 1, %							.25
Baseline	5.0	3.0	3.9	3.2	4.5	3.2	
Week 2	9.5	6.1	5.1	4.0	7.3	4.8	
Stage 2, %							**.027**
Baseline	53.8	9.5	54.3	8.1	54.2	7.2	
Week 2	53.1	8.6	49.5	9.0	57.8	8.6	
Slow-wave sleep, %							**.004**
Baseline	14.4	9.7	14.6	6.9	12.8	8.0	
Week 2	11.6	7.1	20.3	12.1	12.8	7.7	
REM sleep, %							.08
Baseline	22.1	7.6	23.5	4.7	25.0	6.1	
Week 2	20.4	5.3	21.0	5.6	18.0	6.1	
REM latency, min							.52
Baseline	98.4	42.5	78.1	33.0	70.3	21.1	
Week 2	130.0	55.8	132.2	61.4	121.1	49.9	

[a]Time in bed condition includes all 3 levels (8-hour time in bed, late bedtime, early rise time). Boldface type denotes significant findings.
Abbreviation: REM = rapid eye movement.

Table 4. Actigraphy Outcomes at Baseline and Week 2 by Time-in-Bed Condition

	Time in Bed, 8 h (n = 17)		Time in Bed, 6 h (n = 41)				
			Late Bedtime (n = 18)		Early Rise Time (n = 23)		8-h vs 6-h Time in Bed, *P* Value[a]
Variable	Mean	SD	Mean	SD	Mean	SD	
Time in bed, hh:mm							
Baseline	8:01	0:06	7:58	0:07	8:00	0:09	.53
Week 2	8:01	0:30	6:42	0:59	7:00	1:20	**<.001**
Total sleep time, hh:mm							
Baseline	6:20	0:50	6:27	0:44	6:39	0:30	.31
Week 2	6:37	1:00	5:41	0:53	6:09	1:10	**.03**
Sleep efficiency, %							
Baseline	79.3	10.6	80.8	9.2	83.2	6.2	.31
Week 2	82.6	10.4	85.3	9.4	88.0	6.5	.10
Sleep latency, min							
Baseline	24.2	26.1	33.2	15.0	22.1	19.3	.63
Week 2	15.2	13.3	10.4	11.2	8.4	8.4	.07
Wake after sleep onset, min							
Baseline	52.4	28.0	43.4	21.4	41.3	23.2	.18
Week 2	44.8	23.2	29.3	17.5	27.5	18.9	**.006**

[a]Boldface type denotes significant findings.

straightforward to deliver in outpatient psychiatric settings.

Our study is the first to demonstrate that adequate sleep opportunity may accelerate and augment treatment response, although further studies are needed to address this question directly. At a minimum, our findings raise the possibility that consideration of TIB may be relevant in the initial stages of antidepressant medication therapy. We compared the trajectory of HDRS-17 score changes in our study with a previous 8-week open label study[2] of fluoxetine 20 mg/d in MDD outpatients. That study found that the onset of treatment response after 2 weeks occurred in 26.0% of subjects; onset was defined as a decrease of at least 30% on the HDRS-17 without a subsequent increase that led to a final decrease of 50% by 8 weeks. Using a similar definition, we found that 8/19 (42.1%) 8-hour TIB subjects compared to only 6/49 (12.2%) 6-hour TIB subjects experienced an onset of response by week 2 ($\chi^2_1 = 7.5$, $P < .006$). These findings suggest that encouraging adequate TIB accelerated the onset of response while restricting TIB delayed it. These findings additionally complement our analyses indicating that remission onset occurred almost 1 week earlier in the 8-hour TIB group. It is notable that the 63% remission rate for the 8-hour TIB group after 8 weeks is higher than most randomized controlled antidepressant trials,[3,32] highlighting the need for replication. In addition, while the overall treatment response and speed of treatment response on the subject-rated depression measure did not differ significantly between groups, a similar pattern of results was evident. The smaller improvement in self-reported versus clinician-rated depression measures has been reported previously,[13,33–36] but this discrepancy could also be related to measurement frequency, as the more frequent clinician measures could increase the sensitivity to detect symptom change. Our findings do highlight the importance of continued clinical follow-up after any sleep manipulation has ended to assess potential longer-term or delayed mood effects.

A secondary aim was to determine the importance of sleep deprivation timing, but we did not analyze the symptom severity effects separately by TIB condition because 8-hour TIB subjects showed greater improvements on all major mood outcomes. Sleep architecture changes with the TIB manipulations, however, were in the expected direction based on objective polysomnography. Specifically, late bedtime subjects had significant increases in slow-wave sleep at week 2, while the early rise time group showed a reduction in REM sleep. The polysomnography findings for the 8-hour TIB group are consistent with previous

studies[37–40] evaluating the effects of fluoxetine on objective sleep parameters in depressed subjects after 2 weeks of medication. Because the 8-hour TIB group had a better mood response, our findings do not support slow-wave sleep increase or REM sleep reduction as likely mechanisms involved in any therapeutic effects of sleep deprivation, although mechanisms associated with restricted TIB may differ from those associated with responses to total and partial sleep deprivation. The existing literature on the role of sleep deprivation–induced sleep architecture changes in antidepressant response is mixed. For example, a landmark study by Vogel and colleagues[41] found that patients deprived of REM sleep for 3 consecutive weeks showed more mood improvement than non-REM–deprived patients, but these results have not been replicated. Similarly, early studies showing that restricting wakefulness to the second half of the night (when REM sleep predominates) was more effective than so-called early partial sleep deprivation (ie, staying awake until 1:30 and then initiating sleep) have since been challenged.[11,12,42] It is notable that the 8-hour TIB group was the only group to experience a reduction in slow-wave sleep at week 2 relative to baseline. In a recent report, Landsness and colleagues[43] used acoustic stimuli to reduce slow-wave sleep by 54% after 1 night relative to baseline (without reducing total sleep time) in 17 nonmedicated depressed adults. The results indicated that next-day clinician- and self-rated depression scores decreased by 27% and 10%, respectively. Thus, future experimental studies are needed to resolve whether total sleep time, specific sleep stages, timing, and/or quality of sleep are involved in antidepressant treatment response.

Actigraphy monitoring indicated good compliance overall with the 8-hour TIB schedule during the 2-week experimental phase (TIB of 8.0 ± 0.5 hours), while subjects in the 6-hour TIB group spent nearly an hour more TIB each night than prescribed, despite showing excellent compliance with their baseline 8-hour TIB schedule before antidepressant therapy initiation. Importantly, however, medication compliance was not different among the groups, and remission rates for the 6-hour TIB conditions at the end of the 8-week trial were consistent with other studies. The TIB schedule noncompliance by 6-hour TIB participants may have contributed to the small group differences in total sleep time (0.7 hours difference on average), particularly between the 8-hour TIB and late bedtime groups. The actigraphy findings highlight the challenge of maintaining a restricted TIB schedule over time, raising questions about the feasibility of more intensive sleep deprivation protocols for depression (eg, repeated wake therapy or chronotherapeutic interventions), despite recent promising findings.[8] In addition to evaluating efficacy, future sleep deprivation studies in depression should monitor and report on adherence with adjunctive therapies (eg, light therapy, sleep time stabilization) to measure the feasibility of these interventions.

The moderate sample size is a limitation, as we could not perform subgroup analyses to evaluate moderators of treatment response. In addition, the sample was largely young, healthy, white men and women with depression; thus our findings may not generalize to other depressed samples. Subjects' knowledge that they were receiving pharmacotherapy may have contributed to the higher response and remission rates. Moreover, we could not blind subjects to TIB schedule assignment; therefore, subject expectancies may have influenced the results. The TIB schedule assignment additionally did not take into account circadian phase information; thus, the timing of the assigned TIB schedule relative to circadian preference could have affected the outcomes. In addition, differential amounts of environmental light exposure among the 3 groups, either during the experimental TIB manipulation or during the subsequent 6 weeks, could have specifically contributed to antidepressant treatment response and should be controlled more closely in future studies. Finally, we included limited measurement of sleep patterns or other potential moderators (eg, comorbid psychiatric symptoms, diurnal mood variation) after week 2; thus, we cannot speculate on potential contributors to group differences between weeks 2 and 8.

In summary, we found that a nightly 6-hour TIB schedule during the initial 2 weeks of antidepressant therapy did not accelerate or augment treatment response in young adults with depression; instead, our findings raise the possibility that adequate TIB duration may positively impact treatment response. Future studies that optimize or extend sleep duration while initiating antidepressant therapy are needed to address this question directly. In addition, more work is needed with larger, more ethnically diverse, and older samples. Future treatment studies should systematically include measures to identify potentially important clinical moderators (eg, diurnal mood variation) and sleep-related moderators (eg, circadian preference, insomnia) of antidepressant treatment response in addition to evaluation of potential mechanisms of adjunctive depression treatments.

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