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SCIENTIFIC INVESTIGATIONS

Circadian Preference as a Moderator of Depression Outcome Following Cognitive Behavioral Therapy for Insomnia Plus Antidepressant Medications: A Report From the TRIAD Study

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Study Objectives: We previously presented results from a randomized controlled trial that examined the effects of antidepressant medication plus cognitive behavioral therapy for insomnia (CBT-I) among patients with major depressive disorder (MDD) and insomnia. The current secondary analysis aims to examine whether circadian preference moderated the reduction in depression and insomnia symptom severity during this trial.

Methods: A total of 139 adult participants with MDD and insomnia disorder were treated with antidepressant medication and randomized to receive 7 sessions of CBT-I or a control therapy (CTRL). Circadian preference (eveningness) was measured using the Composite Scale of Morningness (CSM). Depression symptom severity was assessed using the Hamilton Depression Rating Scale (HDRS); insomnia symptom severity was assessed using the Insomnia Severity Inventory (ISI). The moderating role of circadian preference on changes in HRSD and ISI was assessed via latent growth models within the framework of structural equation modeling.

Results: Greater evening preference was associated with smaller reduction in HDRS (P = .03) from baseline to week 6 across treatment groups. The interaction between CSM and treatment group was also significant (P = .02), indicating that participants with greater evening preference in the CTRL group had significantly smaller HDRS reduction than those with greater evening preference in the CBT-I group. Circadian preference did not share significant associations with ISI (all P > .30).

Conclusions: Individuals with MDD and insomnia who have an evening preference are at increased risk for poor response to pharmacological depression treatment augmented with either CBT-I or CTRL behavioral insomnia treatment. However, evening types have better depression outcomes when treated with CBT-I than with CTRL for insomnia.

Keywords: CBT-I, circadian, depression, eveningness, insomnia

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Evening circadian preference is associated with increased vulnerability to both depression and insomnia and evidence that one of the benefits of cognitive behavioral therapy for insomnia is reduction in depressive symptom severity. Prior research indicates that eveningness may be associated with less reduction in depressive symptom severity following cognitive behavioral therapy for insomnia.

Study Impact: This is the first study to investigate the role of circadian preference in response to treatment for depression and insomnia in a randomized controlled treatment trial. The present study findings suggest that clinical care using antidepressant medications for individuals with comorbid depression and insomnia could be enhanced by (1) evaluating circadian preference and (2) augmenting antidepressant medications with cognitive behavioral therapy for insomnia for those expressing an evening circadian preference.

INTRODUCTION

Sleep and its regulatory systems, including the circadian and arousal systems, are closely related to mental illness and mental health treatments.[1] During major depressive episodes, as many as 67% to 84% of adults report difficulties initiating or maintaining sleep.[2–4] Insomnia symptoms are associated with greater functional impairment[5] and depressive symptom severity.[6] Poor sleep is a risk factor for a future depressive episode among nondepressed individuals[7] and those who are in remission from a previous depressive episode.[8]

Circadian preference for rest and activity is also relevant to depression. An *evening circadian preference,* also referred to as *eveningness,* is characterized by a preference for later sleep onset and offset. Individuals with evening preference have higher suicide risk[9,10] and greater depressive symptoms severity.[11–13] These associations were found in community,[14–16] clinically depressed,[10,17] and admitted psychiatric inpatient[18]

samples. In an observational study of 253 individuals with major depressive disorder (MDD) recruited from a psychiatric outpatient clinic, eveningness was associated with higher risk of nonremission from depression at 5-year naturalistic follow-up, independent of insomnia severity.[19] In a small study of 30 adults with depressive disorder who received fluoxetine, sleep duration and timing were experimentally manipulated in order to examine effects on circadian timing relative to sleep onset and on depressive symptoms.[20] The study randomized participants to one of three sleep conditions: (1) 8 hours in bed at habitual bed time, (2) 6 hours in bed with a 2-hour advance of habitual rise time, or (3) 6 hours in bed with 2-hour delay of habitual rise time. Sleep restriction with delayed timing was associated with a poorer antidepressant treatment response across 8 weeks of the study relative to the habitual sleep duration and timing condition.[20] These studies suggest that preference for delayed schedule are relevant to depression severity and response to antidepressant treatment.

Eveningness is also associated with worse self-reported sleep quality,[10,21,22] shorter sleep duration, and more nonrefreshing sleep on working days.[23,24] Among adults with insomnia, those with evening preference report more variability in their sleep schedules and greater distress than expected in association with the level of reported insomnia severity. Despite reporting more total sleep time, they also report more concern about the consequences of insomnia and their ability to control sleep.[25] These studies suggest that individuals with evening preference might be more sensitive to the effects of sleep loss or more averse to perceived sleep disruption than individuals with higher scores on measures of circadian preferences. These observations further suggest that having a circadian preference toward eveningness may affect responses to cognitive behavioral therapy for insomnia (CBT-I), which typically includes changes in bedtime, wake time, and/or total time in bed.

Evidence indicates that evening preference is associated with increased vulnerability to both depression and insomnia, and that one of the benefits of CBT-I is reduction in depressive symptom severity.[26–28] Thus, we previously examined the possibility that evening preference might dampen this benefit. In a large sample of outpatients with insomnia receiving group CBT-I in a sleep disorder center, we found that sleep improved among individuals of all circadian preferences, but greater preference toward eveningness was associated with significantly less reduction in depressive symptom severity.[29] However, because there was no control therapy, it was not possible to ascertain whether those with eveningness benefit less in terms of depression severity than those not receiving CBT-I. Thus, although the aforementioned studies suggest that circadian preference may be an important factor to consider when treating depression, no study to date has investigated the role of circadian preference in response to treatment for depression in the context of a well-powered randomized controlled treatment trial.

The current study is a secondary analysis of data collected during the Treatment of Insomnia and Depression (TRIAD) study. The primary aim of the TRIAD study was to examine whether CBT-I enhances depression treatment outcomes among patients with comorbid MDD and insomnia. Although insomnia symptoms were significantly improved by the addition of CBT-I compared to a control insomnia therapy, there was no differential improvement in remission from depression.[30] This negative finding underscores the need for identifying potential moderators of treatment response. The present study aims to examine whether circadian preference moderated reductions in both depressive and insomnia symptoms following CBT-I or control treatment within the TRIAD study sample.

METHODS

Details regarding the design and methods of the TRIAD study are published elsewhere.[31] We include here methodological information that is most relevant to the current investigation. TRIAD was a three-site randomized controlled trial conducted at Duke University (Durham, North Carolina), Stanford University (Palo Alto, California), and the University of Pittsburgh (Pittsburgh, Pennsylvania).

Participants

Recruitment occurred between March 2009 and August 2013, using community advertisements. Eligible participants were (1) 18 to 75 years of age, (2) fluent in English, (3) met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) MDD criteria based on the Structured Clinical Interview for DSM-IV,[30] (4) scored higher than 15 on the 17-item Hamilton Rating Scale for Depression,[32] (5) met DSM-IV-TR criteria for insomnia (primary insomnia or insomnia due to another mental disorder) based on the Duke Structured Interview for Sleep Disorders,[33] and (6) scored higher than 10 on the Insomnia Severity Index (ISI).[34] Participants were excluded if they were involved in another active treatment for depression or insomnia, had failure or intolerance for past adequate trials of all study medications, had a history of treatment with CBT-I, and had conditions incompatible with study pharmacotherapy (eg, pregnancy). If participants had another sleep disorder, most relevant to this article, individuals with severe circadian rhythm sleep-wake disorders (CRSWD) such as advanced sleep-wake phase disorder or delayed sleep-wake phase disorder with extreme habitual bedtimes and rise times (outside of 8:00 PM to 3:00 AM and 4:00 AM to 11:00 AM respectively) they were excluded. Participants with a fixed night shift work schedule between midnight and 5:00 AM and those with rotating work schedules that require night shifts were also excluded. For other sleep disorder exclusion criteria see the main article for more details.[31] Individuals were also excluded if they consumed more than 3 cups of caffeinated beverages per day, more than 14 alcoholic drinks per week, or reported using any illicit drugs; had conditions that would have necessitated medical care not included in the study or confounded the interpretation of study results or took medications with known impact on mood or sleep (see main article appendix for more details);[31] or had current active suicidal potential, psychotic features, seasonal pattern of depression, or onset of current depressive episode within 2 months of childbirth. In the current study, nine participants who did

not complete circadian preference assessment were excluded from analyses. Missing participants did not differ in Hamilton Rating Scale for Depression (HRSD) or ISI and were equally distributed by treatment arm.

Procedures

Study protocols were approved by each University's institutional review board and were identical for all three sites. After providing written consent, participants were screened for study eligibility. Eligible participants were randomized centrally (1:1 in random blocks of two and four, stratified by study site) to either 8 weeks of CBT-I or control therapy. Participants in both treatment conditions received antidepressant medication, managed by a study psychiatrist during medication management visits conducted every 2 weeks over 16 weeks (8 visits in total, including the baseline visit when medications were dispensed).

Following principles used in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, pharmacotherapy allowed choice of the first medication to be tried and one switch to another medication.[35] Medications prescribed were escitalopram, sertraline, and desvenlafaxine. Medications were equally distributed across treatment groups.[31] Study psychiatrists were masked to treatment condition and did not address sleep issues.

Both the CBT-I and control therapy were conducted in individual, in-person format by licensed therapists who were trained by authors RM and JE to competency in delivery. CBT-I components included sleep education, sleep restriction, stimulus control, strategies for reducing somatic and sleep-related cognitive arousal, cognitive restructuring of sleep-related thoughts, and relapse prevention.[36–38] The control therapy included the sleep education module from the CBT-I condition, and systematic pairing of sleep-related distressing situations with emotionally neutral images, a treatment previously used as a credible insomnia control therapy.[27,39] Sleep therapists in both arms did not discuss issues unrelated to sleep or adherence with treatment recommendations. In particular, therapists did not discuss depressive cognitions.

Following the 16-week treatment phase, participants were transitioned to community care and were followed up for assessments every 4 months over 2 years.

Measurements

Depression Symptom Severity

The 17-item HRSD[32] is an interviewer-administered semistructured interview and is one of the most widely used measures in depression treatment studies.[40,41] Higher scores on the HRSD indicate greater depressive symptom severity. In this study, the HRSD was administered by blind raters, and the Cronbach α for the HRSD ranged from .72 to .84 across all time points. The HRSD was collected at baseline, biweekly during the acute treatment phase (nine repeated assessments in total). The HRSD scores used in this study excluded the sleep items.

Insomnia Symptom Severity

The seven-item ISI[34] is an index of the global severity of insomnia, including perceived daytime consequences and distress from sleep difficulties; higher scores on the ISI indicates greater insomnia severity. In this study, Cronbach α for the ISI ranged from .87 to .90 across all time points.

Circadian Preference

The 13-item Composite Scale of Morningness[42] (CSM) assessed preferred timing for various activities and ease of rising in the morning, with higher scores indicating greater morning preference. Each item was given a score from 1 to 4 when the response patterns were limited to four and from 1 to 5 for all the items implying five response patterns; the final score was cumulative and varied from a minimum of 13 to a maximum of 55, with lower scores representing a stronger evening preference. CSM was treated as a linear variable in all analyses. Circadian preference was assessed only at baseline. The Cronbach α in the study sample was .85.

Statistical Analyses

Changes in depression symptom severity (HRSD) and insomnia symptom severity (ISI) were assessed by latent growth models within the framework of structural equation modeling. These analyses did not include treatment arm. Changes in ISI and HRSD from baseline to the end of the intervention were nonlinear, with faster reductions in both symptom types early in treatment, and slower changes later in treatment. To address this nonlinear pattern, the latent growth factors included two linear "slopes" representing the rates of change over time during the earlier (slope 1; baseline to week 6) and later (slope 2; week 6 to the end of treatment) phases of the intervention respectively. The models also included an intercept representing pre-treatment symptom severity. The "bend" defining earlier and later phases was determined by comparing the model fit for inflections at weeks 4, 6, and 8. For both the ISI and HRSD, the model with a "bend" at week 6 was the best fit, and was therefore chosen for the final models. Time scores (ie, latent factor loadings) were specified such that unstandardized estimates of the slopes can be interpreted as changes in raw outcome scores per 2-week period. To examine whether CSM scores moderated the effects of CBT-I on HRSD, and separately on ISI trajectories, latent growth models with CSM, treatment condition (Arm), and their interaction were used to predict slope 1 and slope 2, with age and sex as covariates. Significant interactions, which indicate moderating effects, were further examined using simple slope analyses to test whether the individual simple slopes of the models differ.

RESULTS

Sample Characteristics

We included a total of 139 participants in the analyses (66.2% females, age mean 43.4 years, standard deviation [SD] 12.9). The parent study enrolled 150 participants. For this article, we excluded 9 participants who did not complete CSM and 2 participants whose postrandomization data revealed they were enrolled in error; psychotic symptoms developed in one participant before treatment began and bipolar symptoms developed in the other participant at week 4 (see primary outcome

Table 1—Correlations among baseline variables.

	CSM	Age	HRSD	ISI	Bedtime	WASO	SOL	Wake Time	TST	SE
CSM	1.00									
Age	.31	1.00								
HRSD	−.03	−.04	1.00							
ISI	.08	.06	.31	1.00						
Bedtime	−.45	−.24	.06	−.24	1.00					
WASO	.15	.15	−.07	.20	−.36	1.00				
SOL	−.13	−.02	.03	.23	−.18	.16	1.00			
Wake Time	−.51	−.33	−.06	−.22	.72	−.21	.00	1.00		
TST	−.20	−.22	−.15	−.34	.25	−.14	−.32	.57	1.00	
SE	−.16	−.23	−.16	−.43	.37	−.28	−.56	.37	.60	1.00

CSM = Composite Scale of Morningness, HRSD = Hamilton Rating Scale for Depression, ISI = Insomnia Severity Index, SE = sleep efficiency, SOL = sleep onset latency, TST = total sleep time, WASO = wake after sleep onset.

paper).[31] Of the participants in the current study, 90.6% were Caucasian, 45.7% were employed, and 37.0% were married or living with a partner. The average baseline HRSD was 17.29 (SD = 3.36), and the average baseline ISI was 18.91 (SD = 4.15). Sleep diary data revealed the following mean baseline values: sleep efficiency was 66.8% (SD = 16.2), total sleep time was 5.7 hours (SD = 1.2), Bedtime was 12:10 AM (SD = 1.5; in hours past 00:00) and rise time was 7:36 AM (SD = 1.8; in hours past 00:00). Mean CSM score was 31.1 (SD = 7.7), classifying those with scores that were one standard deviation above the mean as having "morningness" and those with scores that were one standard deviation below the mean as having "eveningness" resulted in 13.7% classified as "Eveningness" (n = 19), 79.9% as "intermediate" type (n = 111), and 6.5% as "Morningness" type (n = 9). Circadian preference categories were used in order to illustrate the direction of findings for the continuous CSM variable. We chose to define preference categories based on one SD of CSM scores rather than based on traditional CSM cutoffs because in our sample, which excluded individuals with advanced sleep-wake phase disorder and delayed sleep-wake phase disorder in the context of extremes of sleep onset and offset times, the traditional cutoff yielded small cell sizes for the evening and morning types, particularly morning types, which would have rendered the results unstable. Traditional cutoffs for CSM define a score 22 or lower as eveningness chronotype, whereas in our classification the cutoff score was 23 or lower. Traditional cutoffs for CSM defined morningness type is a score of 44 or higher, whereas in our classification the cutoff was 38 or higher. Across the 16-week and 9 time points, data completion rate for the HRSD (the primary outcome) was 73.5%.

As shown in **Table 1**, at baseline, morning preference was associated with older age, earlier bedtime and wake time, and shorter total sleep time. CSM was not significantly associated with HRSD or ISI scores at baseline.

Insomnia and Depressive Symptom Change Trajectory

Piecewise latent growth models with two slopes bending at week 6 provided good fit for both HRSD and ISI data (HRSD: χ^2 [36] = 44.90, P = .15, Confirmatory Fit Index = 0.98, Root Mean Square Error of Approximation = 0.042, Standardized Root Mean Square Residual = 0.079. ISI: χ^2 [35] = 64.71, P = .02, Confirmatory Fit Index = 0.96, Root Mean Square Error of Approximation = 0.078, Standardized Root Mean Square Residual = 0.074). Model estimated trajectories are summarized in **Table 2**.

During the first 6 weeks, HRSD decreased at a rate of 2.14 points every 2 weeks, followed by a slower rate of 0.50 points every 2 weeks thereafter. Both slopes for HRSD were significantly less than 0 (P < .01), suggesting that for the overall sample, depressive symptom severity decreased significantly during both early and later treatment.

Similar to the HRSD trajectory, ISI decreased at a rate of 1.91 points every 2 weeks during the first 6 weeks, followed by a slower rate of 0.85 points every 2 weeks thereafter. Both slopes were significantly less than 0 (P < .01), suggesting that overall, insomnia symptom severity decreased significantly during both early and later treatment.

The Role of Circadian Preference in Depression Symptom Change Trajectory

The moderation analysis revealed that greater evening preference (ie, lower score on CSM) was significantly associated with less reduction in HRSD (ie, smaller slope; P = .03) from baseline to week 6 across the whole sample (main effect). The interaction between CSM scores and Arm was also significant (P = .02), indicating that insomnia treatments had differential effects on depression symptom reduction during the first 6 weeks of treatment, depending on CSM scores. To illustrate this interaction term we categorized CSM, classifying those with scores that were 1 SD above the mean as "morningness" and those with scores that were 1 SD below the mean as "eveningness." **Figure 1** displays that, during the first 6 weeks of treatment, those in the "eveningness" category had better depression outcome if assigned to CBT-I compared with CTRL and that the CTRL was particularly ineffective in reducing depression symptoms those with "eveningness."

From week 6 onward, CSM did not have either a main effect, or a moderating effect on HRSD change trajectory (both P > .30). From week 6 to end of treatment sex did significantly

Table 2—Overall growth model without covariates.

		ISI	HRSD
Baseline	Means	18.88 (18.19, 19.56)	17.16 (16.61, 17.71)
	Variances	12.27 (7.82, 16.71)	5.00 (1.32, 8.69)
Slope 1	Means	−1.91 (−2.24, −1.58)	−2.14 (−2.47, −1.82)
	Variances	2.53 (1.56, 3.51)	1.57 (0.59, 2.56)
Slope 2	Means	−0.85 (−1.08, −0.61)	−0.50 (−0.74, −0.25)
	Variances	1.18 (0.72, 1.64)	0.87 (0.37, 1.36)

Unstandardized coefficients (95% confidence interval) are presented to assist changes in the raw ISI and HRSD scores. Model includes all treatment time points, allowing two slopes: slope 1 from baseline to week 6, slope 2 from week 6 to end of treatment. All values of $P < .01$. HRSD = Hamilton Rating Scale for Depression, ISI = Insomnia Severity Index.

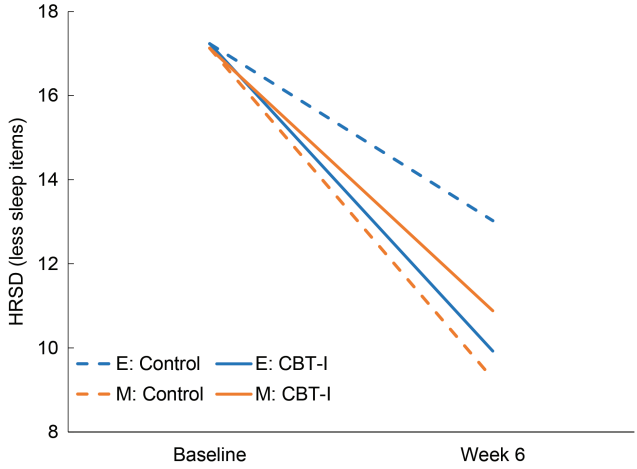
moderate HRSD change trajectory ($P = .04$), such that women had less steep change in depression symptom trajectory.

The Role of Circadian Preference in Insomnia Symptom Change Trajectory

Controlling for age and sex, final models evaluated both the main and moderating effect of CSM in ISI reduction related to insomnia treatment. As shown in **Table 3**, CSM scores did not share significant associations with ISI score trajectory based on either baseline ISI or its two change slopes (all $P > .30$). The interaction between CSM scores and treatment arm was also not significant for either ISI change slopes ($P = .11$ and .41 respectively), suggesting that insomnia treatment effects on ISI did not depend on CSM scores.

From baseline to week 6, sex significantly moderated ISI change trajectory ($P = .04$), such that women had a steeper change in insomnia symptom trajectory.

Figure 1—Simple slopes for model-adjusted values with age held at its mean and effect of sex weighted based on sample proportion.



This figure is designed to illustrate the interaction term between CSM and "treatment arm" that were found in the main analyses, using CSM as a continuous variable. Categories of circadian preference were based on one standard deviation above and below the mean CSM scores. E = CSM scores ≤ 23; evening preference; M = CSM scores ≥ 38; morning preference. CBT-I = cognitive behavioral therapy for insomnia, CSM = Composite Scale of Morningness, HRSD = Hamilton Rating Scale for Depression

DISCUSSION

Using data from the TRIAD study, a randomized controlled trial that examined the effects of antidepressant medication plus CBT-I among patients with MDD and insomnia, we found that stronger evening preference was associated with higher depressive symptom severity at 6 weeks unless the patient was randomized to CBT-I; the CTRL treatment was particularly ineffective among those with stronger evening preference. This suggests that offering CBT-I to those with greater eveningness (eg, those with scores 23 or lower on the CSM) may mitigate their risk for poor response to antidepressant medications alone.

There are several possible explanations for this finding. One reason that treatment of insomnia may be particularly relevant to those with evening circadian preference is the possibility that among those with evening preference, CBT-I leads to greater reduction in distress about poor sleep than the control therapy. This assertion is based on past findings that those with evening circadian preference are more distressed by sleep difficulties, even when their sleep is not objectively worse than that the other circadian types.[10,21,22,25] To test this potential explanation, we conducted exploratory moderation analyses of the effect of circadian preference on the daytime symptoms of insomnia (derived from relevant items on the ISI) but found no significant main or interaction effects. However, because this study was not optimally designed to test this potential mechanism we cannot rule out the possibility that differential effect on distress plays a role in explaining the findings. Another possible reason that treatment of insomnia may be particularly relevant to those with greater evening preference is that CBT-I aims to regularize sleep schedule, usually leading to an earlier rise time that could result in increased morning light exposure. Both more regular rise time and morning light exposure are tied to alignment between sleep/wake behaviors and circadian rhythms, which has been previously linked to depression symptom severity among those with a delayed sleep schedule.[43] A shift to a more regular and advanced sleep schedule may strengthen the amplitude of the circadian rhythm and may result in circadian phase advance, both of which are circadian factors associated with improved depression symptoms and both of which may be

Table 3—Summary of final models for predicting insomnia and depression trajectories.

		ISI	*P* value	HRSD	*P* value
Baseline	Age	0.07 (−0.14, 0.27)	.51	−0.04 (−0.28, 0.20)	.74
	Sex	0.14 (−0.06, 0.33)	.17	0.16 (−0.07, 0.39)	.18
	Chronotype	0.04 (−0.16, 0.24)	.70	−0.02 (−0.26, 0.22)	.86
Slope 1	Age	0.17 (−0.04, 0.37)	.11	0.16 (−0.14, 0.46)	.29
	Sex	−0.21 (−0.42, −0.01)	.04 *	−0.12 (−0.43, 0.19)	.43
	Baseline	−0.09 (−0.37, 0.20)	.55	0.50 (−0.22, 1.23)	.17
	Arm	−0.38 (−0.57, −0.20)	< .001 ***	−0.09 (−0.34, 0.15)	.44
	Chronotype	0.16 (−0.15, 0.47)	.30	−0.46 (−0.85, −0.06)	.02 *
	Chronotype x Arm	−0.24 (−0.54, 0.05)	.11	0.45 (0.10, 0.81)	.01 *
Slope 2	Age	−0.04 (−0.27, 0.19)	.74	0.08 (−0.21, 0.36)	.60
	Sex	−0.01 (−0.23, 0.21)	.95	0.29 (0.02, 0.57)	.04 *
	Baseline	−0.31 (−0.57, −0.05)	.02 *	−0.64 (−1.06, −0.23)	.003 **
	Arm	0.01 (−0.20, 0.23)	.91	0.06 (−0.19, 0.32)	.62
	Chronotype	−0.07 (−0.42, 0.27)	.67	0.18 (−0.22, 0.59)	.37
	Chronotype x Arm	0.14 (−0.19, 0.47)	.41	−0.20 (−0.58, 0.17)	.29

Values are presented as standardized coefficients (95% confidence interval) and values of *P*. Standardized coefficients are used to assist comparisons of effects among predictors. Baseline represents the latent intercept for ISI in the insomnia model, and latent intercept for HRSD for the depression model. All associations are assessed at the same time on top of the growth model in Table 2. * = $P < .05$, ** = $P < 01$, *** = $P < .001$. HRSD = Hamilton Rating Scale for Depression, ISI = Insomnia Severity Index.

particularly relevant for evening types.[44–47] Through advancing rise time, CBT-I often leads to greater morning light exposure, which has demonstrated antidepressant effect and might have a particularly significant antidepressant effect among those with an evening circadian preference.[48,49]

The current study is the first to directly assess whether circadian preference moderated reduction in depressive symptoms following combined treatment with antidepressant and CBT-I. We found only one other study that examined eveningness tendency as a predictor of depression severity outcome following CBT-I. In this sample of 419 adult patients with insomnia disorder from a sleep disorders clinic, greater eveningness was a risk factor for nonremission of depression following group CBT-I, independent of baseline depression symptom severity.[29] This previous study did not include individuals with comorbid MDD and insomnia (although comorbid psychiatric disorders were not excluded), did not provide antidepressant treatment, although some patients may have received it as part of their usual care, and did not include a control condition to assess the differential effect of CBT-I. Given the paucity of research in this area, further research is needed to (1) replicate the findings in the current secondary analysis of the TRIAD study and (2) identify and test possible mechanisms driving the moderation effect of circadian preference on depression treatment outcome.

We found that circadian preference did not moderate insomnia symptom severity trajectory. In other words, participants benefitted from insomnia treatment regardless of circadian preference. This finding is consistent with the sleep disorders clinic sample study, which also found that all circadian types benefited from CBT-I.[29] It also indicates that insomnia symptom severity differences are likely not the mechanism by which circadian preference moderates antidepressant medication treatment response.

Interestingly, we found that baseline subjectively assessed circadian preference was not associated with more severe depression or insomnia symptoms. Previous studies found that individuals with eveningness have similar insomnia severity (or sleep symptom severity) but greater depression severity in both depressed patient samples and patient samples with insomnia.[25,29] In the current study the correlation between depression severity and eveningness scores was weak ($P = .08$); however, there is a signal in the same direction. It is important to note that the sample in the current study had greater eveningness type than the sample from our sleep disorders clinic database[29] (mean CSM in the clinic study was 35.70 (SD 9.13) and 31.14 (SD 7.71) in the current sample) and the standard deviation in CSM scores was lower. It is also possible, based on the substantial differences between the two samples, that a sample with comorbid depression and insomnia is more likely to have greater eveningness; this is another important area for future research.

Although we did not have a priori hypotheses regarding sex as a moderator of depression or insomnia symptom trajectories, we found that women had greater insomnia symptom improvement than men during the first 6 weeks of treatment, and less depression symptom improvement than men in the latter half of treatment. Of note, there were more women (n = 108) than men (n = 40) in the sample and there were no baseline differences in depression or insomnia severity between men and women in the sample. These unexpected findings are difficult to interpret. There are some limited data that suggest women respond better to selective serotonin reuptake inhibitors than men.[50,51] It is possible that women responded more quickly to the selective serotonin reuptake inhibitors than men, thus improving their insomnia symptoms and depression symptoms in the first 6 weeks. Although sex was not a significant moderator of depression symptom change from baseline to week 6 ($P > .05$)

there was a negative slope; see **Table 3** from baseline to week 6. While speculative, it is possible that this initial "bump" in treatment response was then followed by slower depression symptom improvement in the latter half of treatment. This finding requires more future research to be adequately contextualized.

Several limitations should be noted in the current study. The TRIAD study excluded some comorbid sleep and psychiatric disorders, including CRSWD, and most of the sample was Caucasian; particularly relevant to this article, we excluded two individuals because they met criteria for CRSWD and three additional people who did not meet criteria for CRSWD, who had extreme bedtimes/rise times. These exclusions limit the generalizability of the findings to those with severe CRSWD and/or more extreme sleep/wake schedules, other racial/ethnic groups and some psychiatric comorbid presentations. The current study was underpowered to detect differences between the treatment arms by circadian preferences and therefore results from simple slope analyses of differences between categorical morningness and eveningness in the CBT-I versus CTRL are not interpretable. Another potential limitation to generalizability is the demanding screening process, resulting in randomization of only 40% of consenting participants. Most individuals with depression report poor sleep, but may not meet criteria for insomnia disorder. Although evening preference is a risk for insomnia disorder, it is not clear if the results will generalize to individuals with depression and evening preference who do not meet criteria for insomnia. It is also not clear if the results will generalize to augmentation of antidepressant medications with pharmacotherapy for insomnia, or augmentation of psychotherapy for depression with insomnia therapy.

In conclusion, using a well-characterized clinical sample of individuals with depression and insomnia and standardized treatment protocols for both disorders, delivered simultaneously, the current study found that individuals with comorbid depression and insomnia and an evening preference are at increased risk for poor response to antidepressant medications and do better when their insomnia is treated with CBT-I. Given that the main outcome article from the TRIAD study did not find that CBT-I augmented depression treatment outcome, it is clinically relevant to better understand which patients could benefit from the addition of CBT-I treatment. Identifying individuals who are most likely to benefit from CBT-I is especially important given the additional cost and time commitment required for the patient and the health system. The findings from the current study suggest that circadian preference may be a salient dimension in treatment planning for individuals with MDD and insomnia. Moreover, the findings suggest that clinical care using antidepressant medications for individuals with comorbid depression and insomnia could be enhanced by (1) evaluating circadian preference and (2) augmenting antidepressant medications with CBT-I for those identified as having a more evening circadian preference.

ABBREVIATIONS

CBT-I, cognitive behavioral therapy for insomnia
CSM, Composite Scale of Morningness
CTRL, control therapy
HRSD, Hamilton Rating Scale for Depression
ISI, Insomnia Severity Index
MDD, major depressive disorder
TRIAD, Treatment of Insomnia and Depression study

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