https://doi.org/10.5664/jcsm.9648

JCSM | Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Change in circadian preference predicts sustained treatment outcomes in patients with unipolar depression and evening preference

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Study Objectives: Eveningness is associated with worse outcomes in depression. It remained unclear if eveningness could be altered with chronobiological therapy and whether such a change would predict long-term outcomes of depression.

Methods: Data from a randomized controlled trial of 5-week adjunctive bright light therapy with a gradual advance protocol conducted in 91 adult patients with nonseasonal unipolar depression and eveningness (Morningness-Eveningness Questionnaire, score ≤ 41) was examined. "Change of eveningness" was defined by Morningness-Eveningness Questionnaire score over 41 at posttreatment week 5 and "persistent change of eveningness" was defined as maintenance of Morningness-Eveningness Questionnaire score > 41 throughout the follow-up period from week 5 to posttreatment 5 months.

Results: Thirty-three participants (36%) had change of eveningness at week 5. Generalized estimating equations models showed that a change of eveningness at week 5 predicted a 2-fold increase in remission of depression over the 5-month follow up (odds ratio = 2.61 95% confidence interval 1.20–5.71, $P = .016$). Twenty-five participants (75.7%) had a persistent change and were more likely to achieve a remission of depression over the 5-month follow up (odds ratio = 3.18, 95% confidence interval: 1.35–7.50, $P = .008$).

Conclusions: One-third of the patients with depression changed their evening-preference after 5-week of chronotherapeutic treatment, and such change predicted a higher likelihood of depression remission over 5 months of follow-up.

Clinical Trial Registration: Registry: Chinese Clinical Trial Registry; Name: Adjunctive light treatment in major depressive disorder patients with evening chronotype-A randomized controlled trial; URL: https://www.chictr.org.cn/showprojen.aspx?proj=11672; Identifier: ChiCTR-IOR-15006937.

Keywords: depression, eveningness, chronotype, persistent change, remission

Citation: Chan JWY, Chan NY, Li SX, et al. Change in circadian preference predicts sustained treatment outcomes in patients with unipolar depression and evening preference. *J Clin Sleep Med*. 2022;18(2):523–531.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Eveningness is associated with worse outcomes in depression. It remained unclear if eveningness could be altered with chronobiological therapy and whether such a change would predict long-term outcomes of depression.

Study Impact: Our results showed that one-third of the depressed patients with eveningness at baseline changed to non-eveningness after 5-week of chronotherapeutic treatment, and such a change at week 5 was associated with a 2-fold higher probability of depression remission over 5 months of follow-up. Those with a milder degree of eveningness were found to be more amenable to treatment than those with extreme eveningness. Chronotherapeutic treatment should be considered for all the depressed patients with eveningness, and more intensive chronotherapeutic measures may be needed for those with more extreme eveningness.

INTRODUCTION

Our sleep and activity are influenced by the circadian preference, which is referred to as the individual differences in one's optimal timing for rest and activity.[1] It could be measured by a self-reporting questionnaire, such as the Morningness-Eveningness Questionnaires (MEQ).[2] Based on the MEQ scores, individuals could be categorized as morning-type (known as "larks"), intermediate-type, and evening-type (or "night owls").[2] Circadian preference has been viewed as a stable trait by some researchers, eg, the morningness-eveningness personality.[3] The trait nature of circadian preference is supported by a twin study on which genetics was found to account for around 50% of the variance.[4] A genome-wide association study also found that sleep timing (but not duration) was associated with chronotype loci (chronotype was classified by self-report of being a morning type or evening type), which was further associated with depression.[5] However, it is well-known that circadian preference changes with age, with a surge of eveningness in teenage to early adulthood, followed by progressively increasing morningness tendency toward the older age.[6] Circadian preference could also be modulated by sex,[7] circadian preference of the family members,[8] sunset time,[9] and seasonality.[10] These suggest that the circadian preference, as influenced by both genetic and

environmental factors, may potentially be modulated by external factors.

Circadian preference, as assessed by the MEQ, was found to correlate with endogenous circadian markers, such as dim light melatonin onset and core body temperature.[11,12] These observations suggested that self-reported eveningness might serve as a proxy-marker of circadian phase delay which has been linked in turn to depression.[13–15] Emerging research suggested that circadian rhythm plays an important role in the pathogenesis of depression.[16,17] Previous research has found that eveningness was associated with depressive symptomatology in both clinical and community-based samples.[18–23] Eveningness is associated with a higher risk of depression[19–23] and poorer outcomes of depression, including nonremission and a higher risk of suicidality.[18] However, there was limited longitudinal data on the intraindividual stability of circadian preference in patients with depression. A shift in circadian preference toward morningness was found in 24% of the participants with major depression (n = 721) following 8 weeks of agomelatine treatment, and such a change in circadian preference was found to be associated with better treatment response.[24] In contrary, no change in MEQ score was found in a small sample of hospitalized patients with nonseasonal depression (n = 19), despite a significant improvement of depression.[25] Given the limited and mixed findings in the existing literature, there was a need to further examine the stability of circadian preference and its prognostic implications in patients with depression. We hypothesized that 1) evening-preference could be altered by the chronotherapeutic treatment and 2) the change of eveningness could predict treatment outcomes.

METHODS

Participants

The current study was a secondary analysis of the data collected in a randomized controlled trial of adjunctive bright light therapy in patients with nonseasonal depression and concomitant eveningness. Patients with depression and with eveningness were targeted because they were found to have more severe depressive symptoms and poorer response to conventional psychiatric treatment in our previous study.[18] Bright light therapy has been shown to be an efficacious treatment for nonseasonal depression[26] and light therapy has also been used for advancing circadian phase in patients with delayed sleep-wake phase disorder.[27] As such, it was expected that depressed patients with eveningness might benefit from this circadian-focused treatment. For the details of the methodology of this randomized controlled trial, please refer to our previous publication.[28] In brief, 93 adult patients with moderate unipolar depression were recruited from an university-affiliated psychiatric clinic. The diagnosis of nonseasonal major depressive disorder was confirmed by Mini-International Neuropsychiatric Interview (M.I.N.I.)[29] and the seasonal pattern specifier of *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5).[30] A score of 14 or above on the 17-item Hamilton Depression Score (17-HDS) of the Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement (SIGH-ADS)[31] represented moderate severity of depression. Circadian preference was assessed by the MEQ,[2] in which lower scores indicates a higher tendency toward eveningness (morning type: 59–86; intermediate type: 42–58; evening type: 16–41). All the participants were classified as evening-type if scoring 41 or less on the MEQ at baseline. Those with a history of substance abuse, manic or hypomanic episode, schizophrenia, personality disorder, mental retardation, and organic mental disorder were excluded. Participants with eye disease, using photosensitizing agents; taking medication(s) or having a condition (eg, shift work, trans meridian flight) that might interfere the circadian rhythm were also excluded. The study procedure was approved by the institutional clinical research ethics committee and the trial was registered with the Chinese clinical trial registry (ChiCTR-IOR-15006937). All the participants gave written informed consent.

Intervention

Eligible participants were randomized to either 1) 10,000 lux bright white light therapy with gradual advance in timing (BLT group) or 2) 50 lux dim red light therapy (DRL group) with the same gradual advance protocol for 5 weeks. Both types of light therapy were carried out at home for 30 minutes a day as an adjunct to their usual psychiatric treatment. The prescription of light therapy start time was based on a gradual advance protocol for both groups, such that the start time was advanced 30 minutes weekly if the participants were able to adhere to the prescribed light treatment. Adherence was defined as receiving greater than 50% of the total weekly duration of light therapy over the past treatment week, with timing overlapped with or earlier than the prescribed timing of light therapy. Each participant was followed up weekly during the 5-week light therapy (from week 1 to week 5), and at posttreatment 1 week, 1 month, 2 month, and 5 month.

Assessment

At baseline, data on demographics, sleep, and clinical characteristics of the participants were collected. At each follow-up, participants were assessed for their circadian preference, sleep pattern, and clinical outcomes.

Outcomes

The primary outcome was the remission of depression as defined by 17-HDS score of 7 or less.[28] Other clinical outcome measures included Hamilton Anxiety Rating Scale (HAM-A), Hospital Anxiety and Depression Scale (HADS), Insomnia Severity Index (ISI), Beck's Scale for Suicide Ideation (BSSI), Chalder Fatigue Scale (CFS), Short-form 36-item Health Survey (SF36), and the Young Mania Rating Scale (YMRS). Details of the clinical outcomes in the trial were reported elsewhere.[28] In the present study, the focus was on the prospective relationship between the change of eveningness and the depression remission during follow up. The "change of eveningness" was defined as having a MEQ score greater than 41 (the range of nonevening type) at week 5 upon the completion of chronotherapeutic treatment. "Persistent change of eveningness" was defined as a MEQ score greater than 41 throughout the follow

up period from week 5 to 5 month. Sleep-wake variables were recorded by weekly sleep diary.

Statistical analysis

The data were analyzed on a modified intention-to-treat basis, including all the participants with at least 1 follow-up assessment. Those who dropped out before the outcome end-point (posttreatment 5 month) were analyzed using the last observation carried forward approach. Chi-square test and *t*-test were employed to compare the demographic and baseline clinical characteristics between the participants who remained as evening type (eveningness group) and those who had a change of eveningness at week 5 (change to noneveningness [CNE] group). One-way repeated measures analysis of variance was used to compare the weekly changes of sleep and clinical parameters from baseline to the end of treatment (week 5), stratified by the 2 groups (eveningness group and CNE group) to examine the changes with time along the course of treatment within the respective group. To test the impact of the change of eveningness after treatment on the remission status at the follow-up visits (week 5 and 1-week, 1-month, 2-month, and 5-month posttreatment), generalized estimating equation models were used. Binary outcomes of depression remission status were entered as the dependent variables. Age, sex, light treatment group, MEQ score, 17-HDS score, and ISI score at baseline as well as potential confounding variables with $P < .1$ in the univariate analyses were entered as covariates. In Model 1: the "change of eveningness" at week 5 was entered as the independent variable. In Model 2, the "persistent change of eveningness" was entered as the independent variable. Two-sided tests were used and a P value of less than .05 was considered to be statistically significant. The data were analyzed using Statistical Package System for Windows v25.0 (SPSS, IBM Corp, Chicago, IL). To examine the correlations between the magnitude of change in MEQ and sleep timing and the depression outcomes, ie, the 17-HDS score and the modified 17-HDS score without the 3 sleep items, we have conducted repeated-measures correlations using the *rmcorr* package of R.[32] The *rmcorr* is a statistical technique for determining the common within-individual association for paired measures over repeated time points. It has the advantage over simple regression/correlation in that it considers the nonindependence of the data with a greater power and can detect associations between variables that might otherwise be obscured due to aggregation (taking the mean change) or being treated as nonindependent values.[33] Like the Pearson correlation coefficient, the *rmcorr* coefficient (r_{rm}) is bounded by −1 to 1 and represents the strength of correlation between the 2 variables.[33]

RESULTS

Baseline characteristics

As 2 participants did not have at least 1 follow-up assessment, the final number of participants included in the analyses was 91. The average age of the participants was 46.3 ± 11.8 years (mean ± standard deviation) and 79% were female. Demographics and clinical characteristics are presented in **Table 1**. At the end of light treatment (week 5), 33 out of 91 (36%) participants had a change of eveningness to the noneveningness range (MEQ > 41). The MEQ score for all 33 participants changed from eveningness to intermediate range. None of the participants changed to morning type following the treatment. There were no differences in the demographic features between those who changed to non-evening type (CNE group) and those who remained as evening type (eveningness group). The duration of depressive illness was comparable for both groups. 17-HDS score at baseline appeared slightly lower in the CNE group but the difference did not reach a statistical significance (mean ± standard deviation: 17.5 ± 6.8 vs 20.3 ± 6.7, $P = .07$). MEQ score at baseline was higher in the converted (CNE) group (mean ± SD: 37.0 ± 4.8 vs 31.6 ± 5.3, $P < .01$), and a higher percentage of participants in the CNE group were prescribed benzodiazepines (58% vs 35%, $P = .03$). Other clinical parameters, including ISI, HAMA, HADS, BSSI, CFS, SF36, and YMRS scores at baseline, did not differ between the 2 groups.

Treatment profile

Table 2 shows the treatment profile of the 2 groups. Forty-six participants and forty-five participants were randomized to the BLT group and DRL group, respectively. There was a trend toward a higher percentage of participants in the CNE group who had received BLT compared to the eveningness group (CNE group 64% vs eveningness group 43%, $P = .06$). Among the participants in the BLT group, 21 (46%) changed to non-evening type, while 12 (27%) participants in the DRL group also changed to non-evening type. There was also a trend toward an earlier light therapy start time in the CNE group at week 5 (9:22 ± 1:36 vs10:11 ± 2:02, $P = .09$). There were no significant differences in the season of enrolment to the study and the adherence to light treatment between the 2 groups.

Changes in sleep and clinical parameters

Table 3 compares the changes of sleep and clinical parameters from baseline to the end of treatment (week 5). The magnitude of change of MEQ score in the eveningness group and CNE group was 1.4 ± 4.4 and 10.2 ± 6.5, respectively. In the eveningness group, rise time was significantly advanced and wake after sleep onset was significantly reduced, whereas for the CNE group, rise time and the time to fall asleep were both significantly advanced and sleep efficiency was significantly improved. Both groups had a significant reduction of ISI, 17-HDS, and modified 17-HDS scores (without the sleep items) after treatment.

Prediction of depression remission by the change of circadian preference

Table 4 shows the generalized estimating equation analyses of the effects of the change of eveningness on the depression remission status. As the proportion of participants using benzodiazepines at baseline was significantly higher in the CNE group, the use of benzodiazepines was entered into the generalized estimating equation as a covariate. In Model 1, a change of eveningness at week 5 was significantly associated with the

Table 1—Demographics and baseline clinical characteristics of participants who remained as evening-type at week 5 (eveningness group) and those who had a change to noneveningness (CNE group).

	Eveningness Group (n = 58)	CNE Group (n = 33)	*P*
Demographics			
Age, years, mean ± SD	45.2 ± 12.6	48.3 ± 9.9	.21
Sex, female (%)	48 (83)	24 (73)	.26
Education, n (%)			.62
Primary	6 (10)	5 (15)	
Secondary	33 (57)	20 (61)	
Tertiary	19 (33)	8 (24)	
Living status, n (%)			.58
Alone	9 (14)	6 (18)	
With others	50 (86)	27 (82)	
Monthly income in HKD, n (%)			.75
< 10,000	22 (38)	11 (33)	
10,001–20,000	15 (26)	11 (33)	
> 20,001	21 (36)	11 (33)	
Baseline Clinical Characteristics			
Duration of illness, years, mean ± SD	13.3 ± 11.7	14.4 ± 10.2	.65
MEQ, mean ± SD	31.6 ± 5.3	37.0 ± 4.8	< .01
Extreme eveningness, n (%)	26 (45)	4 (12)	< .01
17-HDS, mean ± SD	20.3 ± 6.7	17.5 ± 6.8	.07
Modified 17-HDS, mean ± SD	16.7 ± 6.1	14.2 ± 6.3	.06
SIGH atypical score, mean ± SD	6.0 ± 3.5	5.3 ± 3.3	.34
ISI, mean ± SD	17.3 ± 5.7	17.2 ± 6.7	.95
HAMA, mean ± SD	22.3 ± 10.3	20.6 ± 11.5	.48
HADS, mean ± SD	21.7 ± 6.70	20.8 ± 5.20	.54
BSSI, mean ± SD	12.0 ± 6.8	11.0 ± 5.5	.53
CFS, mean ± SD	20.9 ± 6.49	19.0 ± 7.60	.23
SF36, mean ± SD	280.2 ± 110.3	298.1 ± 91.6	.44
YMRS, mean ± SD	0.60 ± 1.08	1.18 ± 4.98	.13
Antidepressant, n (%)	44 (76)	26 (79)	.75
Antipsychotics, n (%)	14 (24)	8 (24)	.99
Benzodiazepine, n (%)	20 (35)	19 (58)	.03
Hypnotics, n (%)	16 (28)	9 (27)	.97
Mood stabilizer, n (%)	4 (7)	4 (12)	.45‡

A change of eveningness is defined as MEQ score over 41 at week 5. Extreme-eveningness is defined as MEQ score of 30 or below. ‡Fisher exact test. BSSI = Beck's Scale for Suicidal Ideation, CFS = Chalder Fatigue Scale, CNE = change to noneveningness, Extreme-eveningness = MEQ score 30 or less, HADS = Hospital Anxiety Depression Scale, HAMA = Hamilton Anxiety Rating Scale, 17-HDS = 17-item Hamilton Depression Score component of the SIGH with Atypical Depression Supplement, HKD = Hong Kong Dollar, ISI = Insomnia Severity Index, MEQ = Morningness-Eveningness Questionnaire, Modified 17-HDS = total 17-HDS score excluding the 3 sleep items, SF-36 = Short-form 36-item Health Survey, SIGH = Structured Interview Guide for the Hamilton Depression Rating Scale, YMRS = Young Mania Rating Scale.

remission of depression over the 5-month follow-up (odds ratio = 2.61 95% confidence interval [CI]: 1.20–5.71, *P* = .016), after adjusting for age; sex; light treatment group; baseline scores of MEQ, ISI, 17-HDS; and benzodiazepine use. Twenty-five of 33 participants (75.7%) in the CNE group were found to have "persistent change of eveningness". In Model 2, the "persistent change of eveningness" was associated with a greater odds of remission of depression (odds ratio = 3.18, 95% CI: 1.35–7.50, *P* = .008).

Repeated measures correlation between MEQ and depressive symptoms

The *rmcorr* was used to assess the correlations between MEQ and 17-HDS scores at each time point during treatment (from

Table 2—Treatment profile of the eveningness group and CNE group.

	Eveningness Group (n = 58)	CNE Group (n = 33)	*P*
Treatment, n (%)			.06
Dim red light	33 (57)	12 (36)	
Bright light therapy	25 (43)	21 (64)	
Season of Enrollment, n (%)			.41
Spring summer	23 (40)	16 (48)	
Autumn winter	35 (60)	17 (52)	
Light Therapy			
Start time at week 1, HH:MM	10:48 ± 2:21	10:17 ± 2:04	.30
Start time at week 5, HH:MM	10:11 ± 2:02	9:22 ± 1:36	.09
Adherence, %	42 ± 22	48 ± 27	.25

Adherence was defined as the overall percentage of the total duration of light therapy carried out as recorded by the sleep diary with timing overlapped with or earlier than the prescribed timing over the 5 treatment weeks. CNE = change to noneveningness.

baseline and the weekly assessments from week 1 to 5). The *rmcorr* coefficient (r_{rm}) between MEQ scores and 17-HDS scores was −0.24, 95% CI = −0.32 to −0.15, $P < .001$. Higher MEQ scores were associated with lower 17-HDS scores. For the modified 17-HDS score without sleep items, a weaker but significant correlation was found with an $r_{rm} = -0.14$, CI = −0.23 to −0.05, $P = .002$. The sleep midpoint also showed significant correlations with the 17-HDS and modified 17-HDS score, with $r_{rm} = 0.21$, CI = 0.12 to 0.30, $P < .001$ and $r_{rm} = 0.20$, CI = 0.11 to 0.29, $P < .001$, respectively. Later sleep midpoint was found to be associated with higher 17-HDS and modified 17-HDS scores. The *rmcorr* plot of the above correlations are depicted in **Figure S1**, **Figure S2**, **Figure S3** and **Figure S4** in the supplemental material.

Table 3—Changes of sleep and clinical parameters from baseline to end of treatment.

	Eveningness Group (n = 58)			CNE Group (n = 33)		
	Baseline	Week 5	*P*	Baseline	Week 5	*P*
Sleep Parameters, HH:MM						
Bedtime	01:45 ± 01:48	01:37 ± 01:36	.46	00:39 ± 01:38	00:12 ± 01:08	.11
Time to fall asleep	02:21 ± 01:45	02:11 ± 01:38	.34	01:16 ± 01:28	00:32 ± 01:08	.001
Wake time	09:57 ± 02:17	09:50 ± 02:20	.29	08:49 ± 02:16	08:38 ± 01:36	.84
Rise time	10:41 ± 01:59	10:19 ± 02:12	.02	09:55 ± 01:58	09:10 ± 01:34	.003
Time in bed	08:56 ± 1:21	08:44 ± 1:24	.28	09:15 ± 01:55	08:55 ± 01:28	.56
WASO	00:36 ± 00:42	00:21 ± 00:29	.003	00:23 ± 00:23	0:11 ± 00:15	.04
Actual sleep duration	07:38 ± 01:26	07:45 ± 01:27	.63	07:38 ± 01:51	08:05 ± 01:29	.44
Sleep efficiency	0.85 ± 0.11	0.89 ± 0.10	.06	0.83 ± 0.13	0.91 ± 0.10	.003
Sleep midpoint	06:08 ± 01:56	05:55 ± 01:47	.13	05:03 ± 01:39	04:35 ± 01:11	.06
Clinical Parameters, mean ± SD						
MEQ	31.6 ± 5.3	32.8 ± 5.6	.08	37.0 ± 4.8	47.2 ± 4.3	< .001
Changes of MEQ scores	1.4 ± 4.4			10.2 ± 6.5		
ISI	17.3 ± 5.7	15.9 ± 6.8	.001	17.2 ± 6.7	13.1 ± 7.1	.003
17-HDS	20.2 ± 6.7	14.1 ± 7.3	< .001	17.5 ± 6.8	10.8 ± 7.9	< .001
Modified 17-HDS	16.7 ± 6.1	11.8 ± 6.6	< .001	14.2 ± 6.3	9.3 ± 6.9	< .001

Time in bed = bedtime to rise time. Actual sleep duration = wake time – time to fall sleep – WASO. Sleep efficiency = actual sleep time/time in bed. Sleep midpoint = midpoint time between time to fall sleep and rise time. Only data at the baseline and week 5 (end of treatment) is presented here. Data from week 2 to week 4 will be available upon request. CNE = change to noneveningness, 17-HDS = 17-item Hamilton Depression Score component of the Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement, ISI = Insomnia Severity Index, MEQ = Morningness-Eveningness Questionnaire, Modified 17-HDS = total 17-HDS score excluding the 3 sleep items, WASO = wake after sleep onset.

Table 4—GEE analyses: longitudinal associations between change of eveningness and remission of depression.

	Independent Variable	*P*	Odds Ratio	95% CI
Model 1†	Change of eveningness‡	.016	2.61	1.20–5.71
Model 2†	Persistent change of eveningness§	.008	3.18	1.35–7.50

Dependent variable = remission of depression was defined as 17-HDS of 7 or less. †Model adjusted for age, sex, light treatment group, MEQ score at baseline, 17-HDS score at baseline, ISI score at baseline, baseline use of benzodiazepines. ‡Improvement of eveningness is defined as MEQ scored greater than 41 at week 5. §Persistent improvement of eveningness is defined as MEQ scored greater than 41 throughout week 5 to posttreatment 5-month follow up. CI = confidence interval, GEE = generalized estimating equation, 17-HDS = 17-item Hamilton Depression Score component of the Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement, ISI = Insomnia Severity Index, MEQ = Morningness-Eveningness Questionnaire.

DISCUSSION

The aim of this study was to investigate if eveningness could be changed by chronotherapeutic treatment and whether such a change could predict treatment response in depression. Our study demonstrated that about one-third of evening-type patients had a change of circadian preference as measured by the MEQ after 5-week of chronotherapeutic treatment, and such a change predicted a 2.6-fold increase in depression remission during 5-month posttreatment follow-up after controlling for baseline clinical characteristics. The significant improvement of eveningness in our study might be related to the use of circadian-focused treatment for depression (ie, combination of light treatment and gradual advance protocol). It has been suggested that circadian phase delay could be a contributing factor in depression, and phase advance by behavioral change in sleep-wake cycle has been advocated as a therapeutic strategy.[34–36] Our findings were consistent with other studies that demonstrated the possibility of advancing the circadian preference toward morningness in different clinical samples using circadian-related treatments (eg, in sleep-disturbed military veterans receiving behavioral interventions,[37] in youth with eveningness,[38] and in patients with depression[24,39]). Corruble et al[24] found that 24.3% of the patients with major depressive disorder had a change toward morningness after 8-week agomelatine treatment, and the percentage of eveningness patients significantly reduced in the group that showed treatment response. A clinical trial on bright light treatment for youth depression also found that a shift toward morningness had a significant influence on the improvement of depressive symptoms at posttreatment.[39] In addition, in a study of total sleep deprivation and light therapy in patients with bipolar depression, a phase advance of the activity-rest rhythm as measured by actigraphy was also shown to correlate with the antidepressant response.[40] Moreover, a strong correlation was found between the advance of dim light melatonin onset and the improvement in depression in an open trial of multimodal chronobiological intervention for youth depression.[41] Collectively, the evidence suggested that an advance in both subjective circadian preference and objective actigraphic/biological markers were associated with more favorable treatment response. While these studies focused on the short-term outcome after treatment, our study extended the existing knowledge by demonstrating that an improvement of eveningness with a brief period of chronotherapeutic treatment could predict long-term outcomes even after the cessation of treatment up to posttreatment 5 months. Although baseline late chronotype did not predict persistent depression at the 4-year follow-up in a study that involved 505 patients with a depressive and/or anxiety disorder diagnosis,[42] there has been a dearth of data to examine the improvement of eveningness as a predictor to treatment response. Our data further demonstrated the possibility that eveningness could be subjected to change with treatment, and such a change may have prognostic implication of predicting longer term outcomes.

Several items shared by both MEQ and Composite Scale of Morningness (CSM)[43] were connected to morning mood characteristics (ie, MEQ items 4, 5, 7, 9) and was termed "Morning Affect" by some researchers.[44,45] In our current study, we observed not only an increase in the MEQ total score but also a concurrent advance in the time to fall asleep and rise time in the CNE group. These results may suggest that the change in circadian preference was not merely due to an improvement in morning affect upon the effect of morning bright light and was consistent with an advance in the overall circadian preference. Further factor analyses may be helpful to delineate if particular items in the MEQ drive the change of circadian preference in future study with a larger sample size. On the other hand, it might also be possible that a shift toward morningness reflected an advance in the endogenous rhythm that facilitated earlier sleep timing in these patients. Of note, our results showed a positive correlation between sleep midpoint and the measure of depression severity at successive time points during the treatment phase, but whether there was a change in the endogenous biomarker accompanying the change in sleep-wake cycle would require further investigation in future study.

Out of 33 participants who had an improvement of eveningness at week 5, 25 (75.7%) maintained as persistent non-evening type at their subsequent follow-ups, even after the cessation of light therapy. Importantly, this sustained change predicted an even higher odds of remission in depression. This observation had a major implication in understanding the stability of circadian preference and challenged the view that circadian preference is an unmodifiable trait. For those who had changed to the non-evening type at week 5, they showed a milder degree of eveningness at baseline (a higher MEQ score 37.0 ± 4.8 vs 31.6 ± 5.3, $P < .01$). This could not be explained by the presence of insomnia, as the baseline ISI scores were similar between the 2 groups. Our data led us to the speculation that the

circadian preference for those with a milder form of eveningness (about one-third) might be more a state-related condition in depression, hence their circadian preference could be advanced with chronotherapeutic treatment and the improvement was associated with a higher odds of remission. The circadian preference for those with more extreme-eveningness (two-thirds) might be more trait related and was less amenable to the chronotherapeutic treatment, which was evident by the minimal change in the MEQ scores after treatment (31.6. ± 5.3 vs 32.8 ± 5.6). It is possible that the more-extreme evening-type patients might need longer duration of treatment or more intensive chronotherapeutic intervention, for example, a combination of partial sleep deprivation with sleep phase advance and light therapy, which has been demonstrated to rapidly advance the circadian rhythm in patients with bipolar depression.[46] The use of lithium, which inhibits glycogen-synthase kinase 3 and influences the amplitude and period of the circadian clock,[47] may also warrant further investigation. Interestingly, in a cross-sectional study examining the MEQ score among 53 patients with bipolar disorders, patients on lithium were shown to have less eveningness tendency compared to those who were not on lithium (mean MEQ score 56.0 on lithium vs 46.9 with no lithium, $P = .007$).[48] A recent study conducted in the patients with bipolar disorders also found that lithium responders reported a higher level of morningness tendency at baseline when compared to lithium nonresponders.[49] Adequate assessment of circadian preference and sleep-wake activity are imperative for patients with depression. Further developments of intervention and biological phenotyping would be needed to determine the best treatment strategy for those patients with extreme evening chronotype.

In this study, both BLT and DRL groups were subjected to a gradual advance in timing of the light therapy by a blind prescriber. Hence, the light therapy start time was advanced at week 5 in both groups. The proportion of participants who received BLT was apparently higher in the CNE group than the eveningness group (64% vs 43%) with a near-significance, $P = .06$. Timed bright light was known to effectively shift the circadian rhythm.[50] It is interesting that 12 out of 45 participants in the DRL group also had a change of circadian preference despite that DRL was suggested to have little phase-shifting effect.[51] This was likely as a result of earlier rise time related to a gradual advance protocol. Our findings were consistent with those of randomized controlled trials conducted in patients with delayed sleep-wake phase disorder, in which sleep onset time was also found to be advanced with gradual advancement irrespective of the type of light.[52,53] In the patients with major depressive disorder, it was found that those with evening type, compared to the morning type, had significantly better response in the "morning-stream" of an integrated day treatment program.[54] Altogether, the evidence suggested that by scheduling rise time or providing the treatment at an earlier timing might already be beneficial to the evening-type patients with depression. It is also possible that the improvement of mood might be related to the concomitant earlier exposure to the environmental light, regularization of social rhythm, and reduction of circadian misalignment; further research on the underlying mechanism is needed.

Strengths and limitations

The main strengths of this study included a prospective evaluation of the change of circadian preference along the course of depression upon the chronotherapeutic treatment. The follow-up duration was up to 5 months after treatment, which provided important long-term data with prognostic implications beyond the acute treatment effect. Nonetheless, several limitations should be noted. First, as the present study focused exclusively on the patients with depression with eveningness at baseline, we were not able to discern the influence of change of circadian preference in the patients with morning or non-evening type. Second, an advance in sleep-wake cycle may be associated with changes in other zeitgebers (eg, more environmental light exposure and social engagements), which might potentially improve mood. The potential mediating/moderating role of social rhythm stimulation could not be tested in this study. It was also difficult to differentiate the effect of social stimulation on circadian rhythm independent of their role in regulating light exposure.[55] Third, the change of circadian preference as defined by MEQ scores was based on the original cut-off by Horne and Ostberg.[2] This cut-off was employed as we found MEQ scores distributed normally within the cohort of patients with unipolar depression in the previous studies.[18,25] It was recognized that cut-off scores of circadian preference scales might be influenced by sex, age, and culture, and the determination of cut-off scores on a continuous variable has often been considered as a problem in psychometrics.[45] Nonetheless, this cut off is the most widely used and it enables the comparison across studies. In addition, the repeated-measures correlations also demonstrated that the change of MEQ correlated with the change of depressive symptoms as a continuous outcome. Lastly, biological markers were not measured in this study, but the correlations between MEQ and endogenous biological markers have been demonstrated.[12,56,57] In addition, the group of patients with a change to noneveningness also reported a concurrent advance in time to fall asleep, which was not seen in the group of patients that remained as evening types. Further study using different instruments or measurements of sleep-wake activity and endogenous biological rhythm is needed.

CONCLUSIONS

In summary, our study demonstrated that one-third of the evening-type patients had a change of circadian preference after 5-week of phase-advancing treatment, and such a change predicted better clinical outcomes in depression. Those with a milder degree of eveningness were found to be more amenable to treatment than those with extreme eveningness. Assessment of sleep and circadian preference is important in management of depression. Chronotherapeutic treatment should be considered for all the patients with depression with eveningness, and more intensive chronotherapeutic measures may be needed for those with more extreme eveningness.

ABBREVIATIONS

BSSI, Beck's Scale for Suicide Ideation
BLT, bright light therapy

CFS, Chalder Fatigue Scale
CI, confidence interval
CNE, change to non-eveningness
DRL, dim red light
HAM-A, Hamilton Anxiety Rating Scale
HADS, Hospital Anxiety and Depression Scale
17-HDS, 17-item Hamilton Depression Score
ISI, Insomnia Severity Index
MEQ, Morningness-Eveningness Questionnaire
SF-36, Short Form 36-item Health Survey

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Submitted for publication June 14, 2021
Submitted in final revised form September 1, 2021
Accepted for publication September 1, 2021
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DISCLOSURE STATEMENT

All authors have seen and approved this manuscript. Work for this study was performed at the Department of Psychiatry, The Chinese University of Hong Kong. This study was funded by the Health and Medical Research Fund, The Food and Health Bureau, The Government of Hong Kong Special Administrative Region (Ref 12131131). This was not an industry-supported study. YKW reported grants from General Research Fund of University Grants Committee, Health and Medical Research Fund, Hong Kong SAR, received personal fees for delivering a lecture from Eisai Co., Ltd and sponsorship from Lundbeck HK Limited. JWYC received personal fees for participating in an expert panel meeting from Eisai Co., Ltd. All other authors report no conflicts of interest.