Adjunctive light treatment in major depressive disorder among evening chronotype: a randomised controlled trial (abridged secondary publication)

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KEY MESSAGES

1. Home-based bright light therapy is a feasible adjunctive treatment with a highly tolerable adverse effect profile.
2. Home-based bright light therapy with gradual timing advance improves clinical outcome, with a quicker treatment effect, which is evident from a higher remission rate at week 2 of treatment and a higher cumulative remission rate for 5 months after treatment.
3. Adjunctive bright light therapy for patients with unipolar non-seasonal depression and evening-chronotype may be used in clinical practice to improve clinical outcomes.

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Introduction

Major depressive disorder (MDD) is a common mental illness with significant morbidities and mortalities. In patients with MDD, the non-remission rate (as defined by a Hamilton Depression Rating Scale-17 [HRSD 17] score of ≥8 and the presence of a major depressive episode by the Mini International Neuropsychiatric Interview) was 42.3%, despite active treatment.[1] About 20% of subjects were evening chronotype as classified by the Morningness and Eveningness Questionnaire (MEQ), and they had more severe insomnia, worse depressive symptoms, and higher suicidality.[1] The evening-type patients also had higher non-remission rate (65.3%) than the morning-type (38.7%) or intermediate-type (35.9%). Non-remission of depression is associated with a range of adverse outcomes. A more intensive alternative or adjunctive treatment to improve the outcomes in this subgroup of patients is needed.

Light therapy has been demonstrated to be effective in two randomised controlled trials on non-seasonal depression.[2,3] Both studies showed that light therapy was associated with lower depressive symptoms score and a higher remission rate. Apart from improving mood symptoms, light is effective in phase-shifting the human circadian rhythm. Evening chronotype patients may be additionally benefited from the phase advancing effect of the light therapy. This study aims to examine the effectiveness of adjunctive light therapy with gradual advanced timing in evening-type patients with non-seasonal depression. We hypothesised that the bright light treatment (BLT) group would have a higher remission rate and a lower depression score than the dim red light (DRL) group.

Methods

Patients were recruited from the psychiatric outpatient clinic of the university-affiliated hospital. Ethical approval was obtained from the Joint CUHK-NTEC Clinical Research Ethics Committee (reference no: 2014.505-T) and the trial was registered with the Chinese clinical trial registry (ChiCTR-IOR-15006937).

This study was a home-based, randomised, assessor- and prescriber-blind trial. Usual psychotropic medications prescribed from the outpatient clinic, including antidepressants and hypnotics, and the prescriptions for the general medical conditions were allowed. Eligible subjects were randomly assigned to either the bright light therapy (BLT) group or the dim red light (DRL) group. Light therapy was prescribed for 30 minutes daily at their habitual wake time, which was based on the 1-week sleep diary before the start of treatment. Subjects were required to record the timing of light therapy daily. Compliance was defined on two levels: (1) day-compliance: the percentage of the number of days with light therapy over the past week, irrespective of the timing and (2) appropriately timed light therapy defined as >50% of the total weekly duration of light therapy received over the past treatment week with timing overlapped with or earlier than the prescribed time of light therapy.

TABLE 1. Baseline characteristics, medication use, and sleep parameters of the dim red light group and bright light treatment group

	Dim red light group (n=45)*	Bright light treatment group (n=46)*	P value
Age, y	45.2±12.0	47.4±11.5	0.38
Female sex, %	88.9	69.6	0.02
Duration of depression, y	13.5±11.2	13.9±11.0	0.86
Hamilton Rating Scale for Depression	19.9±5.90	18.6±7.63	0.35
Insomnia Severity Index	16.8±5.56	17.7±6.43	0.49
Hamilton Anxiety Rating Scale	22.9±9.80	20.8±11.4	0.27
Morningness Eveningness Questionnaire	34.7±7.05	36.0±6.56	0.34
Beck Scale for Suicide Ideation	11.5±7.06	11.8±5.65	0.85
Chalder Fatigue Scale	20.3±6.34	20.2±7.51	0.81
Short-Form 36 Health Survey	266.2±99.2	306.2±106.5	0.07
Hospital Anxiety and Depression Scale	22.4±6.08	20.4±6.22	0.13
Young Mania Rating Scale	0.80±1.45	0.83±1.52	0.93
Expectation score	59.1±17.1	62.9±21.7	0.35
Medications, %			
Antidepressants	77.3	76.1	0.89
>1 type of antidepressant	31.8	23.9	0.40
Antipsychotics	22.7	26.1	0.71
Mood stabilisers	4.5	13.0	0.16
Benzodiazepines	40.9	45.7	0.65
Hypnotics	29.5	26.1	0.71
Sleep parameters			
Time to go to bed	01:24±02:00	01:18±01:39	0.80
Time to sleep	02:03±1:59	01:53±1:26	0.63
Wake up time	09:37±2:23	09:31±2:22	0.98
Time getting up from bed	10:29 ±02:00	10:21±02:02	0.77
Time in bed	8:59±1:25	9:07±1:43	0.72
Wake after sleep onset	0:37±0:40	0:35±0:45	0.98
Actual sleep time	7:38±1:30	7:40±1:39	0.92
Sleep efficiency	0.85±0.13	0.84±0.11	0.86
Sleep midpoint	5:50±2:02	5:41±1:45	0.72

* Data are presented as mean standard deviation or % of patients

The timing of light therapy was gradually advanced 30 minutes each week if the subject was able to reach 50% appropriately timed light therapy until a desirable wake time was achieved. If the subject was not able to adhere to the prescription, the timing would be kept the same and no advancement would be made. A prescriber reviewed the sleep diary and light therapy record weekly. An independent clinical assessor assessed the patients at baseline and at each follow-up (weekly during the 5-week treatment period, and at 1 week, 1 month, 2 months, and 5 months after treatment). Both the prescriber and assessor were blinded to the group allocation. The study subjects were instructed not to reveal their allocated treatment to both prescriber and assessor.

The primary outcomes measures were the rate of remission (as defined by HRSD 17 scoring ≤7) and the change of HRSD 17 score. Secondary outcomes included anxiety symptoms measured by Hamilton Anxiety Rating Scale, Hospital Anxiety and Depression Scale, insomnia symptoms by Insomnia Severity Index, suicidal ideation by Beck Scale for Suicide Ideation, fatigue by Chalder Fatigue Scale, and quality of life by Short Form-36 Health Survey. Adverse outcomes were monitored by a modified adverse event checklist. Young Mania Rating Scale was used to monitor for possible hypomanic/manic symptoms. At baseline, subjects were asked to give an expectation score towards treatment efficacy in reducing depressive symptoms on a Likert scale from 0 to 100; higher scores indicated higher positive expectations.

All analyses were based on a modified intent-to-treat model: subjects with at least one follow-up assessment were included. Chi squared analysis and *t* tests were used to compare baseline characteristics. Treatment effects on the outcome variables were analysed using repeated measure ANOVA. All tests were based on a 0.05 level of significance. The differences between the DRL group and BLT group in terms of rates of remission and response were tested by binary logistic regression. Statistical analyses were performed using SPSS (IBM Corp, Armonk [NY], US).

Results

The DRL and BLT groups were comparable in terms of baseline clinical characteristics, medication use, and sleep parameters, except that there was a female preponderance in the DRL group (88.9% vs 69.6%, P=0.023, Table 1).

Compared with the DRL group, the BLT group had higher (but not significantly) remission and response rates at all time points, except that at week 2 of treatment the remission rate was significantly higher (37.0% vs 13.3%, Table 2) based on both unadjusted regression model (P=0.012) and adjusted regression model (P=0.034) controlled for the baseline HRSD 17 score, age, sex, and season of enrolment. From baseline to 5 months after treatment, all clinical symptom measures had a reduction of score over time (P<0.001 for time), except for Young Mania Rating Scale and Short Form-36. However, the differences in the changes of these clinical measures between the two groups for 5 months were not significant (P>0.05 for time × intervention).

Using Kaplan-Meier curve analyses, cumulatively 31 (67.4%) of patients in the BLT group achieved remission of depression (HRSD17 score

TABLE 2. Change in clinical measures between bright light treatment (BLT) group and dim red light (DRL) group

	Intervention period						Follow-up period after treatment				P value for time	P value for time × intervention
	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	1 week	1 month	2 month	5 month		
Remission, %												
DRL	0	13.3	13.3	20.0	24.4	20.0	28.9	22.2	20.0	26.7		
BLT	0	15.2	37.0	39.1	34.8	32.6	37.0	34.8	23.9	32.6		
Hamilton Depression Rating Scale											0.001	0.41
DRL	19.8±5.91	16.3±7.68	15.2±8.04	14.9±8.10	13.6±7.48	14.0±7.53	13.4±7.80	14.7±7.69	15.2±8.14	13.7±8.01		
BLT	18.6±7.63	16.2±7.30	12.1±7.91	11.5±7.72	12.0±8.67	11.8±7.66	10.7±7.41	11.0±7.28	12.6±7.12	12.2±8.26		
Hamilton Anxiety Rating Scale											0.001	0.51
DRL	22.9±9.80	19.0±10.4	17.8±10.2	19.4±10.8	17.6±9.94	17.6±9.23	17.4±10.7	18.8±10.7	18.0±11.0	17.4±10.7		
BLT	20.4±11.4	19.2±10.0	16.2±11.7	15.3±10.5	16.3±10.4	15.6±10.1	14.3±9.55	15.0±9.51	16.6±10.4	16.4±10.9		
Young Mania Rating Scale											0.66	0.86
DRL	0.80±1.45	0.75±1.35	0.64±1.17	0.91±1.33	0.73±1.19	0.80±1.48	0.80±1.86	0.64±1.31	1.04±2.12	0.93±1.66		
BLT	0.82±1.52	0.76±1.51	0.93±2.58	0.94±2.23	0.93±2.05	1.26±2.90	1.22±2.59	1.21±2.59	1.28±2.53	0.98±2.18		
Insomnia Severity Index											0.001	0.33
DRL	16.8±5.56	17.0±6.52	15.7±5.95	15.4±6.67	15.1±6.70	15.4±6.92	15.3±7.07	15.3±6.47	14.8±6.61	15.0±6.73		
BLT	17.7±6.43	16.7±6.40	15.6±6.62	15.1±6.08	15.4±5.98	14.5±7.08	14.1±6.60	14.1±7.04	14.8±7.09	14.3±6.28		
Hospital Anxiety and Depression Scale											0.001	0.22
DRL	22.4±6.08	22.1±6.28	21.7±6.60	21.6±6.26	20.6±6.79	20.2±6.47	21.2±6.83	21.4±7.30	21.4±6.38	21.6±6.45		
BLT	20.4±6.22	19.2±7.98	18.7±6.99	18.4±7.79	17.0±8.27	17.1±7.82	16.6±7.76	16.6±8.21	17.0±8.07	17.9±8.44		
Beck Scale for Suicide Ideation											0.001	0.38
DRL	11.5±7.06	10.7±6.89	9.98±6.98	10.3±7.15	9.43±6.59	9.24±6.91	9.76±6.98	9.48±6.97	9.81±7.12	9.43±6.80		
BLT	11.8±5.65	10.1±5.95	10.1±5.95	8.95±6.00	8.62±6.38	8.52±6.37	8.71±6.16	8.76±6.90	8.83±6.19	9.02±6.68		
Chalder Fatigue Scale											0.001	0.09
DRL	20.4±6.33	-	-	-	-	18.5±7.57	-	19.5±7.14	18.7±7.18	18.7±7.55		
BLT	20.0±7.50	-	-	-	-	16.8±7.81	-	15.5±7.52	17.3±8.10	16.1±6.83		
Short Form-36 Health Survey											0.06	0.58
DRL	244.1±92.9	-	-	-	-	266.7±114	-	272.8±156	267.7±127	272.6±145		
BLT	316.2±116	-	-	-	-	355.2±161	-	333.2±139	326.1±147	349.9±144		

≤7) at any follow-up, whereas 21 (46.7%) patients in the DRL group achieved remission (P=0.04, log rank test, Fig).

Discussion

In evening-chronotype patients, the overall remission rate was lower than that reported in other bright light trials,[2,4] consistent with our previous finding that evening-chronotype tended to be associated with a higher rate of non-remission of depression.[1] The rate of remission was significantly higher in the BLT group than in the DRL group (37.0% vs 13.3%) at week 2 in both unadjusted and adjusted models. This indicates that BLT has a quicker anti-depressant effect. Survival analysis also revealed significantly higher cumulative remission rate in the BLT group than in the DRL group (67.4% vs 46.7%).

The improvement in clinical symptom measures was greater (but not significantly) in the BLT group than in the DRL group. Several reasons may explain the lack of significant difference between groups. First, the relative short duration of light therapy may not be adequate to discern the

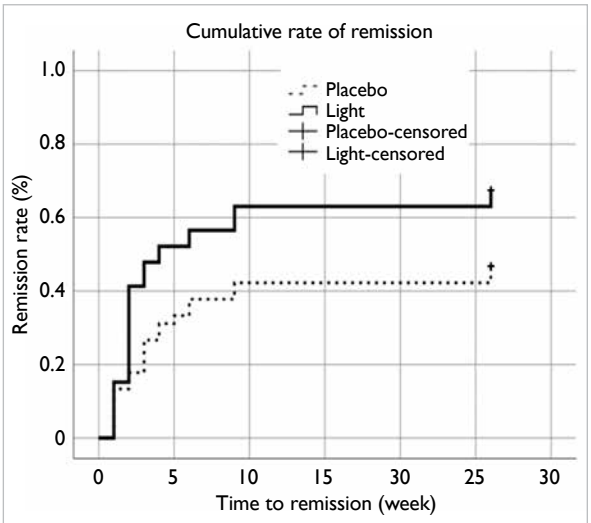

FIG. Kaplan-Meier curve analysis on depression remission between bright light treatment group and dim red light group

full effect of BLT. The duration of treatment that effectively achieved remission was 6 to 8 weeks.[2,3] In patients with bipolar depression, the remission rate greatly increased by 30% only after 4 weeks of treatment.[3] Likewise, a longer duration of each light therapy session may improve treatment outcomes. Second, the DRL group is not a pure placebo group. This group also underwent a gradual advance in light therapy and had a small advancement in their time to sleep, wake-up time, and sleep midpoint. The sleep advancement of the DRL group was comparable to that of the BLT group. This gradual advance may signify a stabilisation of sleep-wake rhythm; subjects were able to maintain a more regular and gradually advanced sleep-wake cycle. With an earlier wake time, subjects might be exposed to more environmental sunlight beneficial for the mood condition. Third, we used a more stringent definition of compliance, taking into account both the number of days with light therapy and adherence to the exact treatment timing. The overall compliance in terms of the number of days with light therapy was 66.3% and 73.5% in the DRL and BLT groups, respectively, whereas the compliance rate in other studies (albeit without precise definition) was 80% to 90%.[2-4] The inability to detect the outcome differences may be attributed to the lower compliance rate. The relatively lower compliance could be related to the recruitment of exclusive evening-type subjects who were known to be associated with poorer self-regulation.[5] Nevertheless, BLT was highly tolerable, with few adverse events. No subject had a hypomanic or manic swing. BLT is a viable adjunctive treatment, with no drug-drug interactions and with few contra-indications.

Conclusion

Adjunctive BLT with gradual timing advancement is useful in patients with non-seasonal depression and evening-chronotype, with a quicker and potentially augmented antidepressant effect.

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Disclosure

The results of this research have been previously published in:

1. Chan JW, Lam SP, Li SX, et al. Adjunctive bright light treatment with gradual advance in unipolar major depressive disorder with evening chronotype: a randomized controlled trial. Psychol Med 2020:1-10.
2. Chan JW, 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 2021 Sep 21.

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