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ARTICLE CLASS OF EVIDENCE

Bright light therapy for depression in Parkinson disease

A randomized controlled trial

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Abstract

Objective

To assess the efficacy of bright light therapy (BLT) in reducing depressive symptoms in patients with Parkinson disease (PD) and major depressive disorder (MDD) compared to a control light.

Methods

In this double-blind controlled trial, we randomized patients with PD and MDD to treatment with BLT (±10,000 lux) or a control light (±200 lux). Participants were treated for 3 months, followed by a 6-month naturalistic follow-up. The primary outcome of the study was the Hamilton Depression Rating Scale (HDRS) score. Secondary outcomes were objective and subjective sleep measures and salivary melatonin and cortisol concentrations. Assessments were repeated halfway, at the end of treatment, and 1, 3, and 6 months after treatment. Data were analyzed with a linear mixed-model analysis.

Results

We enrolled 83 participants. HDRS scores decreased in both groups without a significant between-group difference at the end of treatment. Subjective sleep quality improved in both groups, with a larger improvement in the BLT group (B [SE] = 0.32 [0.16], $p = 0.04$). Total salivary cortisol secretion decreased in the BLT group, while it increased in the control group (B [SE] = −8.11 [3.93], $p = 0.04$).

Conclusion

BLT was not more effective in reducing depressive symptoms than a control light. Mood and subjective sleep improved in both groups. BLT was more effective in improving subjective sleep quality than control light, possibly through a BLT-induced decrease in cortisol levels.

ClinicalTrials.gov identifier:

NCT01604876.

Classification of evidence

This study provides Class I evidence that BLT is not superior to a control light device in reducing depressive symptoms in patients with PD with MDD.

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Glossary

AUC_G = area under the curve with respect to the ground; **AUC_I** = area under the curve with respect to the index of salivary cortisol change over time; **BLT** = bright light therapy; **CSD** = Consensus Sleep Diary; **DLMO** = dim-light melatonin onset; **DSM-IV-TR** = *Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision*; **HDRS** = Hamilton Depression Rating Scale; **MDD** = major depressive disorder; **MEQ** = Morningness-Eveningness Questionnaire; **mITT** = modified intention-to-treat; **PD** = Parkinson disease; **RCT** = randomized controlled trial.

The prevalence of major depressive disorder (MDD) in patients with Parkinson disease (PD) is 17%, and insomnia occurs in at least 30%.[1,2] Both are associated with a reduced quality of life and poorer daytime functioning.[1–5] A disturbed circadian rhythm may contribute to the development of depression and insomnia in patients with PD.[6,7] Bright light therapy (BLT) can positively influence sleep and mood by supporting the circadian pacemaker and may therefore be an alternative treatment option for depression and insomnia in PD.[8,9] Previous studies on the effects of BLT demonstrate a positive effect on mood, sleep, excessive daytime sleepiness, and motor symptoms.[10–13] To date, however, no study has used a randomized controlled trial (RCT) design to evaluate the effect of BLT on depression in PD. In this RCT, we investigated the hypothesis that BLT is more effective in reducing depressive symptoms in patients with PD and MDD than exposure to a control light. Secondary outcomes were objective and subjective sleep parameters and the circadian rhythm markers melatonin and cortisol.

Methods

The primary research question of this study, providing Class I evidence, was the following: Is BLT more effective in reducing depressive symptoms, as measured with the Hamilton Depression Rating Scale (HDRS), in patients with PD with MDD than a control light device?

Standard protocol approvals, registrations, and patient consents

This study protocol was approved by the medical ethics committee of the VU University Medical Center. The trial was registered on ClinicalTrials.gov on May 17, 2012 (NCT01604876). All participants provided written informed consent.

Study design and procedures

The study protocol of this double-blind RCT was described in detail previously.[14]

After providing informed consent, participants were enrolled by the assessor (S.R.) and randomized to the intervention or control condition by a research coordinator (C.V.). Block randomization was performed per season with a computer-generated random number list (in Excel 2007) to rule out seasonal influences on the treatment effect. The randomization list was managed by the research coordinator. The research coordinator assigned the treatment to a new participant after inclusion by sequentially following the randomization list. Subsequent treatment allocations were therefore not influenced by the previous allocation, and coding of participants did not contain any information about the treatment allocation. This list was stored on a secure and password-protected drive separate from all other data and was not available to the rest of the research team. Both participants and assessors (S.R., O.A.v.d.H.) were blinded to treatment condition. Because the appearance of the device or the characteristics of the emitted light might provide our participants with clues about the treatment condition and influence study outcomes, we did not inform our study participants about the exact details of the 2 light devices and the expected therapeutic effect. Assessments took place at home and in the research facility and outpatient clinic of the VU University Medical Center. After completion of the baseline (T0) assessments, participants were asked to keep a sleep diary and to wear a light sensor and actigraphy watch for the subsequent 7 days. Moreover, they were asked to collect saliva samples at home in the morning and evening on 6 days during their participation in the trial: the day before the start of treatment (T0) and 1 day before each follow-up assessment. The first sample was taken immediately after waking up, followed by 3 more at an interval of 30 minutes. In the evening, samples were collected hourly, starting 3 hours before the intended bedtime. After this, a BLT or control light was installed at the participant's home by the research coordinator or a trained research assistant. Participants were treated at home for 3 consecutive months, after which they entered a 6-month naturalistic follow-up. Assessments were repeated halfway (T1) and at the end (T2) of treatment, and 1 (T3), 3 (T4), and 6 (T5) months after treatment. Before each postbaseline assessment (T1–T5), participants received a package containing questionnaires, a sleep diary, an actigraphy watch, a light sensor, and cotton dental rolls for saliva sampling to perform these measures at home in the week before the assessment visit.

Participants

Study participants were recruited throughout the Netherlands through various strategies, including referral by medical professionals, recruitment through various PD-related organizations, and an advertisement in a Dutch national newspaper. The trial ran between July 2012 and January 2017.

Patients diagnosed with idiopathic PD by a neurologist and meeting MDD criteria according to the DSM-IV-TR[15] were eligible for inclusion. Exclusion criteria were a current

psychosis or (relative) contraindication for BLT such as a bipolar disorder or increased risk of photosensitization due to medication use or a medical disorder.[16,17] Participants had to be on a stable dose of antiparkinsonian and psychopharmacologic agents for at least 4 weeks before inclusion and were asked not to change the medication regimen during the intervention period, unless this was deemed medically necessary.

Intervention

The intervention consisted of BLT with a Brazil Lightbox (Lumie, Cambridge, UK), which emits daylight spectrum light with an intensity of 10,000 lux at a 30- to 40-cm distance. For the control condition, neutral density filters (Lee Filters, type 209.03ND, Hampshire, UK) were installed in the light device, reducing the transmission to 200 lux. At this light intensity, no substantial effect on circadian rhythmicity was expected.[18] Participants were treated at home daily for 30 minutes in the morning and evening for 3 consecutive months. Timing of the morning treatment was based on the score on the Morningness-Eveningness Questionnaire (MEQ), as recommended by the Center for Environmental Therapeutics (see table in AutoMEQ at cet.org), within a time frame of 6:00 AM and 8:15 AM.[19,20] The evening session took place 9.5 hours before the morning BLT to allow 8 hours of nighttime sleep.

Outcome measures

Primary outcome

The primary outcome measure of this study was the severity of depression at T2, as measured with the 17-item version of the HDRS.[21]

Secondary outcomes

The secondary outcome measures of this study included the following:

1. The total score on the 30-item Geriatric Depression Scale.[22]
2. The proportion of participants in each treatment group who fulfilled the DSM-IV criteria for a "depressive disorder in full remission."[15]
3. Subjective quality of sleep, as measured with the Scales for Outcomes in Parkinson's Disease–Sleep.[23] Both total score and the scores on the subscales rating daytime sleepiness, nighttime sleep, and subjective sleep quality were used.
4. Actigraphic estimates of total sleep time and sleep fragmentation, i.e., the number of wake bouts per hour (GENEActiv Sleep; GENEActiv, Huntingdon, UK).
5. Circadian rhythm markers derived from salivary concentrations of melatonin and cortisol. Using the cortisol concentrations in the morning, we calculated the area under the curve with respect to the ground (AUC_G) and the area under the curve with respect to the index of salivary cortisol change over time (AUC_I) (2003).[24] The morning AUC_G is an estimate of the total cortisol secretion throughout the day, whereas the AUC_I is a measure of the cortisol awakening response. Melatonin concentrations were used to calculate the dim-light melatonin onset (DLMO) with the hockey-stick method.[25]

Exploratory outcomes

There were 8 exploratory outcomes as follows:

1. Subjective quality of sleep, rated by the Consensus Sleep Diary (CSD).[26]
2. Actigraphic estimation of sleep efficiency, defined as the percentage of time spent asleep between going to bed and getting up in the morning.
3. Evening cortisol secretion, calculated as both the AUC_G and AUC_I.
4. Global cognitive function, assessed with the Mini-Mental State Examination.[27]
5. Motor symptoms, assessed with Part III of the Unified Parkinson's Disease Rating Scale.[28]
6. The score on the MEQ.[19]
7. The score on the World Health Organization Quality of Life assessment.[29]
8. Caregiver burden, assessed with the Zarit Burden Interview.[30]

Confounding factors

To control for factors that might influence the association between treatment and the outcome measures, we corrected our analyses for age; treatment expectancy, as measured with the Credibility/Expectancy Questionnaire[31]; compliance with treatment, measured with an occupancy data logger (HOBO occupancy/light logger, Onset Computer Corp, Bourne, MA); exposure to environmental light, assessed with a light sensor (Actiwatch Light, Cambridge Neurotechnology Ltd, Cambridge, UK); dose of dopaminergic medication converted to the levodopa equivalent daily dose[32]; and the use of antidepressants and hypnotic/anxiolytic medications.

Tolerability and safety

Participants were screened for possible adverse effects, on the basis of previous reports, after 6 weeks of treatment.[20,33] After treatment, all participants were asked to rate their appreciation of the therapy on a visual analog scale of 0 to 100.

Statistical analysis

Sample size calculation

We calculated the necessary sample size for a mixed-model analysis,[34] aiming at sufficient sensitivity for a minimal standardized effect size of Cohen d = 0.6 and intraparticipant correlation of assessments of $\rho = 0.6$. For a statistical power of 80% and a 2-tailed significance level of $p < 0.05$, we required 35 participants per treatment group. To correct for a maximum dropout rate of 1 of 6 (16.7%), we would need 7 additional participants per group, resulting in a total sample size of 84 participants.

Efficacy analysis

Analyses were performed on the modified intention-to-treat (mITT) population, consisting of all participants who received

at least 1 week of treatment and provided at least 1 postbaseline assessment of the HDRS. Linear mixed-model analyses were used to analyze the effect of the intervention on the different outcome variables. Mixed-model analyses were used to adjust for the dependency of the repeated observations within the patient. The linear mixed models included the intervention variable, time (treated as a categorical variable and represented by dummy variables), the interaction between the intervention and time, and the baseline value of the particular outcome variable. With this model, we estimated the differences between the groups at T2 (end of treatment) and T5 (end of study). Because of the adjustment for the baseline value of the particular outcome variable, the differences between the groups at T2 and T5 are equal to the differences in the changes in the outcome between baseline and T2 and between baseline and T5. For all analyses, both crude and adjusted results, adjusted for all potential confounders, were estimated. Statistical significance was defined as a value of $p < 0.05$. All statistical analyses were performed with IBM SPSS Statistics 22 (IBM, Armonk, NY).

Data availability statement

All published and unpublished anonymized data from this study will be shared by request from a qualified investigator.

Results

Participants

The trial ran between July 2012 and January 2017. The figure provides a flowchart of the study. Of the 389 patients assessed for eligibility, 306 were excluded, resulting in a sample size of 83. Three participants withdrew before randomization, and another 8 withdrew within the first week of treatment, resulting in an mITT population of 72 participants.

Table 1 gives the demographic and clinical characteristics of the mITT population at baseline. Mean age was 64.4 [SD 9.2] years, and 44% of the study participants were female. The majority of participants (58%) were in Hoehn & Yahr stage 2. Mean HDRS score was 14.6 [SD 3.6], indicating that most study participants had moderately severe depression.

As a result of an error in the salivary melatonin concentration measurement, analyses on the DLMO could not be performed. Because the assay used to determine the salivary cortisol concentration had a minimum detection limit of 2.0 pg/mL, some of the concentrations were nondetectable. We imputed these with a value of 1.9 pg/mL. Because the number of cortisol concentrations in the evening was considered too low to calculate a reliable AUC_I and AUC_G, we instead calculated the mean evening cortisol concentration using the salivary cortisol concentration at bedtime and 1 and 2 hours before bedtime.

Efficacy analyses

Table 2 demonstrates the results of our crude efficacy analyses corrected only for baseline value of the outcome variable. The adjusted analyses, corrected for confounders, are presented in table 3.

During the intervention, the HDRS total score decreased in both the intervention and control groups. At T2, there was no significant between-group difference in our primary outcome ($p = 0.59$). At T5, the HDRS score was significantly lower in the control group than the intervention group ($p = 0.03$).

In terms of the secondary outcomes, the mean 30-item Geriatric Depression Rating Scale score decreased in both groups, with no significant between-group difference. The percentage of participants who achieved clinical remission of the depressive episode at T2 was 63% in the intervention group and 52% in the control group, corresponding to an absolute risk reduction of 0.11 and a number needed to treat of 9. At T5, 72% of participants in the experimental group had recovered from their depressive episode vs 87% of the control group (absolute risk reduction 0.15, number needed to treat 7). At both time points, this difference was statistically not significant (p = NS).

The score on the total Scales for Outcomes in Parkinson's Disease–Sleep and its subscales decreased in both groups during the intervention, with no significant between-group differences. Between T0 and T2, total sleep time decreased in both groups. Sleep fragmentation increased in the control group, while it remained relatively stable in the intervention group (between-group difference at T2 and T5, p = NS).

The mean AUC_G of the morning salivary cortisol concentrations in the intervention group decreased between T0 and T2, while it increased in the control group, resulting in a significant difference at T2 ($p = 0.04$). At T5, this difference was not significant. There were no significant between-group differences for the AUC_I.

The exploratory analyses showed no significant between-group differences except for the subjective quality of sleep at T2, which was rated better on the CSD in the intervention group ($p = 0.04$).

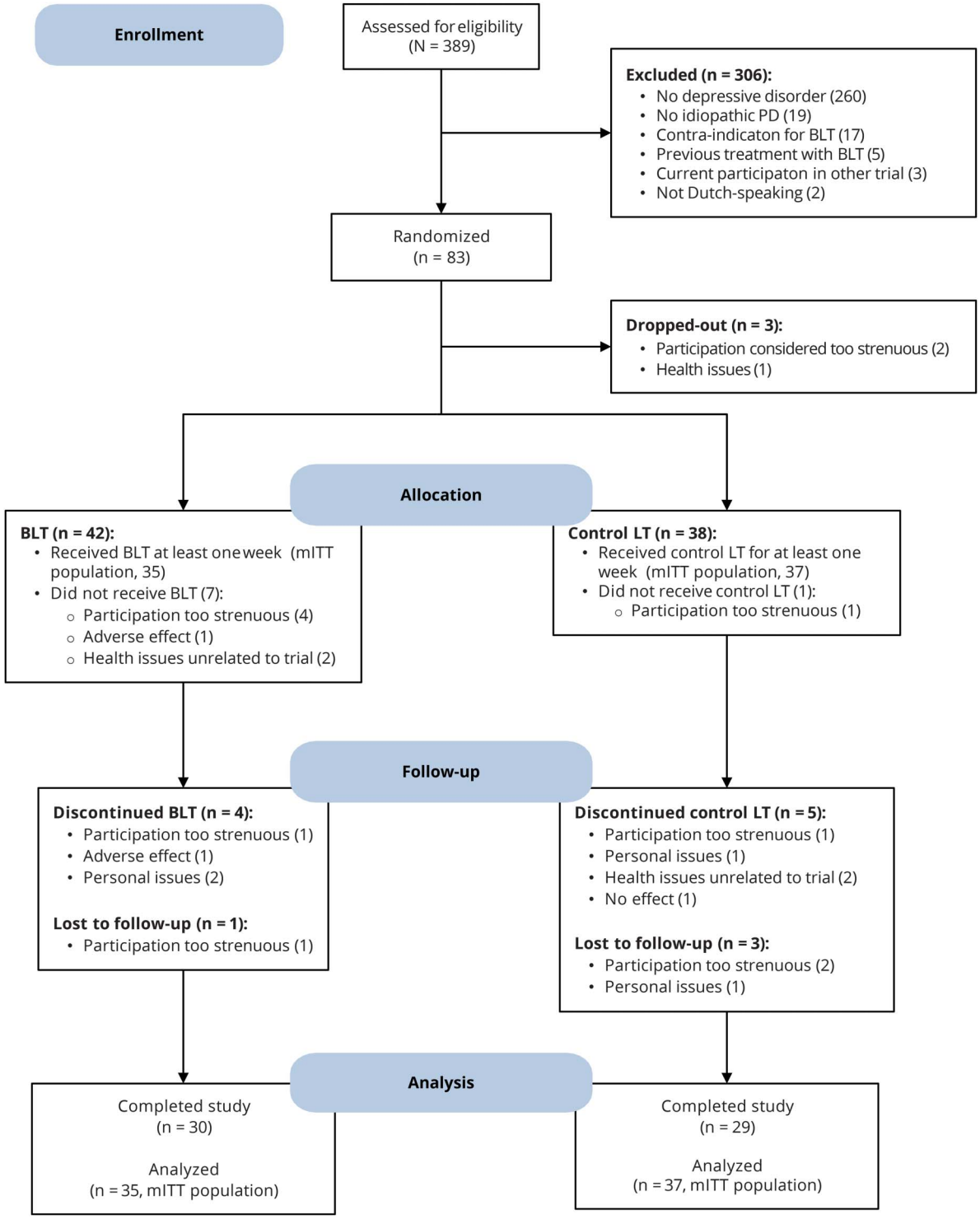
Adverse effects and treatment satisfaction

In the intervention group, 66% experienced adverse effects compared to 46% of the control group ($\chi^2 = 2.68$, $df = 1$, $p = 0.10$). Ocular symptoms, headache, and gastrointestinal complaints were reported most often. All adverse effects were mild and transient. There were no significant between-group differences in the occurrence of adverse events or in the appreciation of duration and timing of light therapy sessions.

Discussion

In this RCT, we studied the effects of BLT on depression severity as the primary outcome in patients with PD and MDD. This interventional study provides Class I evidence that BLT

Figure Flowchart



BLT = bright light therapy; LT = light therapy; mITT = modified intention-to-treat; PD = Parkinson disease.

(10,000 lux) is not superior to a control light device (200 lux) in reducing depressive symptoms, as measured with the HDRS, in patients with PD with MDD (B [SE] = −0.58 [1.06], 95% confidence interval −2.66 to 1.51, $p = 0.59$). Comparison of this RCT and previous studies on the effects of BLT on depressive symptoms in patients with PD is difficult because prior studies differed in study design, study population, control condition, and measuring instruments, as well as in type, duration, and timing of light exposure. Previous studies, however, showed a positive effect of BLT on mood.[10–12] In a case series of 12 patients with PD and insomnia and/or depressive symptoms, 2 to 5 weeks of 1,000- to 1,500-lux

Table 1 Demographic and clinical characteristics of the mITT population at baseline

	Control group			BLT group		
Variable	**No.**	**Mean [SD]**	**Range**	**No.**	**Mean [SD]**	**Range**
Age, y[a]	37	65.8 [8.6]	46.3 to 82.7	35	58.9 [8.5]	36.3 to 83.8
Female, % (n)	37	46 (17)		35	43 (15)	
Use of antidepressants, % (n)	37	18.9 (7)		35	20.6 (7)	
Use of melatonin supplements, % (n)	37	0 (0)		35	5.7 (2)	
LEDD	37	700 [434]	0 to 2,125	35	590 [407]	0 to 1,940
UPDRS-III score	37	23.9 [10.5]	8 to 55	35	20.7 [8.8]	8 to 50
H&Y stage, % (n)	37			35		
1.0		3 (1)			11 (4)	
1.5		3 (1)			0 (0)	
2.0		51 (19)			66 (23)	
2.5		19 (7)			11 (4)	
3.0		19 (7)			6 (2)	
4.0		3 (1)			6 (2)	
5.0		3 (1)			0 (0)	
MMSE score	37	28.0 [1.7]	24 to 30	35	28.4 [2.3]	21 to 30
HDRS score	37	14.5 [3.8]	8 to 25	35	14.7 [3.5]	9 to 24
GDS-30 score	37	17.1 [5.9]	3 to 28	35	17.9 [5.9]	6 to 28
DSM-IV-TR classification comorbid conditions, % (n)	37			35		
Cognitive disorder[a]		5 (2)			9 (3)	
Anxiety disorder[b]		43 (16)			60 (21)	
Substance-related disorder[b]		3 (1)			0 (0)	
SCOPA-SLEEP score	37			35		
Nighttime sleep		7.9 [4.3]	0 to 15		9.3 [3.8]	1 to 15
Daytime sleepiness		6.7 [5.0]	0 to 18		6.2 [4.3]	0 to 15
Sleep quality rating		3.5 [1.8]	0 to 6		4.3 [1.5]	0 to 6
Total score		14.5 [7.1]	2 to 33		15.5 [6.3]	2 to 28
CSD subjective sleep rating	36	2.0 [0.8]	0 to 3	35	1.7 [0.6]	1 to 3
TST, min	29	391 (57)	254 to 524	35	386 (67)	246 to 533
SF, wake bouts/h	29	7.0 (4.1)	1.7 to 18.1	35	6.2 (2.8)	2.5 to 15.6
SE, %	29	86 [6]	71 to 94	35	87 [9]	63 to 97
MEQ total	37	54.0 [8.5]	38 to 74	34	56.0 [9.1]	35 to 72
Chronotype, % (n)	37			34		
Moderate evening type		8 (3)			3 (1)	
Neutral type		57 (21)			65 (22)	
Moderate morning type		30 (11)			24 (8)	
Distinct morning type		5 (2)			9 (3)	
Cortisol, pg/L						

Continued

Table 1 Demographic and clinical characteristics of the mITT population at baseline *(continued)*

Variable	Control group			BLT group		
	No.	Mean [SD]	Range	No.	Mean [SD]	Range
AUC_G	24	25.0 [10.2]	9.2 to 39.4	22	21.8 [10.2]	10.7 to 52.3
AUC_I	24	3.3 [9.3]	−14.0 to 21.9	22	5.7 [9.2]	−6.8 to 24.5
Mean evening concentration	20	2.3 [0.5]	1.9 to 3.9	20	2.7 [1.6]	1.9 to 5.6
WHO-QOL score	37	80.7 [11.9]	58 to 112	35	79.0 [13.1]	46 to 106
ZBI score	31	25.3 [12.6]	3 to 56	29	23.3 [16.4]	3 to 62

Abbreviations: AUC_G = area under the curve with respect to the ground; AUC_I = area under the curve with respect to the index of salivary cortisol change over time; BLT = Bright light therapy; CSD = Consensus Sleep Diary; GDS-30 = 30-item Geriatric Depression Rating Scale; HDRS = Hamilton Depression Rating Scale; H&Y = Hoehn & Yahr; LEDD = levodopa equivalent daily dose; MEQ = Morningness–Eveningness Questionnaire; mITT = modified intention-to-treat; MMSE = Mini-Mental State Examination; SCOPA-SLEEP = Scales for Outcomes in Parkinson's Disease–Sleep; SE = sleep efficiency; SF = sleep fragmentation; TST = total sleep time; UPDRS-III = Unified Parkinson's Disease Rating Scale Part III; WHO-QOL = World Health Organization Quality of Life assessment; ZBI = Zarit Burden Interview.
[a] Obtained from the medical history provided by the general practitioner or neurologist.
[b] Established with the Structured Clinical Interview for DSM-IV Axis I Disorders.

BLT for 60 to 90 minutes before normal bedtime resulted in a noticeable improvement of mood, as well as sleep-onset latency and sleep continuity.[12] An open-label study on the effects of 4,000- to 6,000-lux BLT for 60 minutes before bedtime in 120 patients with PD resulted in less anxiety and improved mood in patients with good compliance.[11] In an RCT in 36 patients with PD, 2 weeks of 7,500-lux BLT for 30 minutes each morning resulted in a stronger improvement of mood and daytime sleepiness compared to 950-lux placebo light.[10] In a recent RCT, 31 patients with PD were treated for 2 weeks with 10,000-lux BLT or 300-lux dim-red light twice daily for 60 minutes.[13] BLT resulted in significant improvements of excessive daytime sleepiness and subjective sleep quality.

Because we observed a large improvement of mood and sleep in our trial in both the group treated with BLT and the group treated with a control light device, we assessed the effect of time on our outcomes in a post hoc linear mixed-model analysis (table 4). There was a significant effect of time on depression, as measured with the HDRS (after intervention $p < 0.001$, after follow-up $p < 0.001$). There are several possible explanations for this finding. The first is a spontaneous remission. In ±50% of the depressed patients with PD in a 5-year longitudinal cohort study, depression showed a nonpersistent course.[35] Although our treatment phase lasted only 3 months, some participants may have shown a spontaneous remission of their depression. A second possibility is a placebo effect. The average placebo response rates in placebo-controlled antidepressant trials, defined as a ≥50% reduction in HDRS score from baseline, are 35% to 40%.[36] A post hoc analysis showed that the response rate in our control group was 44% compared to 56% in the intervention group, which is a bit higher than in antidepressant trials. A final possible explanation is that the decrease in depressive symptoms was due to structuring of the sleep-wake cycle as a result of the scheduling of light therapy. All study participants had to get up at a fixed time for their morning light therapy and were advised to go to bed ±1 hour after evening light therapy. According to the social zeitgeber hypothesis, mood can be improved by restoring the circadian rhythm by re-establishing daily routine such as bed and wake-up time.[37] To explore this hypothesis, we performed a post hoc analysis, correlating the change in HDRS score to the change in average SD of bedtime and time of getting up between T0 and T2. This correlation was not significant. Our study, however, was not designed to test the effects of improvement of the sleep-wake rhythm on depressive symptoms. To disentangle the effects of structuring the sleep-wake cycle from the effects of BLT, a future study design should have 3 additional treatment arms: 2 in which BLT and control light are administered at random times and 1 in which the participants apply a scheduled sleep-wake cycle without receiving light therapy.

Subjective sleep improved significantly in both groups during the intervention (table 4). The CSD subjective sleep rating increased significantly more in the intervention group compared to the control group. This finding supports the hypothesis that BLT has a positive effect on subjective sleep in PD, as also shown in previous studies.[11–13]

In terms of circadian rhythm markers, the AUC_G decreased in the BLT group during treatment, while it increased in the control group, resulting in a significant between-group difference at T2. In previous studies in individuals without PD, BLT led to a decrease in total cortisol secretion throughout the day.[38] Because increased cortisol levels are associated with light sleep,[39] we hypothesize that the improvement of subjective sleep in the BLT group is related to decreased cortisol levels. Unfortunately, our own data could not support this hypothesis: a post hoc correlation between the change in AUC_G and the change in CSD subjective sleep rating between T0 and T2 was not significant, possibly because the number of calculated AUC_G changes was too small.

This RCT had several limitations. Our power analysis indicated a necessary sample size of 84 participants. Because we were able

Table 2 Results of the crude treatment efficacy analyses corrected for baseline value

	Baseline (T0)		After intervention (T2)					After follow-up (T5)				
	Control, mean [SD] (n = 37)	BLT, mean [SD] (n = 35)	Control, mean [SD] (n = 34)	BLT, mean [SD] (n = 33)	Group difference			Control, mean [SD] (n = 29)	BLT, mean [SD] (n = 30)	Group difference		
					B [SE]	95% CI	*p* Value			B [SE]	95% CI	*p* Value
HDRS score	14.5 [3.8]	14.7 [3.5]	8.3 [4.3]	7.6 [5.0]	−0.58 [1.06]	−2.66 to 1.51	0.59	5.9 [3.0]	8.5 [4.6]	2.39 [1.10]	0.23 to 4.57	0.03
GDS-30 score	17.1 [5.9]	17.9 [5.9]	14.9 [6.3]	13.7 [6.9]	−1.36 [1.39]	−4.08 to 1.37	0.33	12.3 [7.0]	13.2 [6.6]	0.36 [1.40]	−2.40 to 3.11	0.80
Remission, % (n)[a]	0 (0)	0 (0)	52 (17)	63 (20)	0.57 [0.51]	0.43 to 1.57	0.26	87 (26)	72 (21)	−0.91 [0.68]	−2.24 to 0.42	0.18
SCOPA-SLEEP score												
Nighttime sleep	7.9 [4.3]	9.3 [3.8]	5.1 [3.3]	5.5 [3.5]	−0.52 [0.72]	−1.94 to 0.90	0.47	4.4 [3.7]	6.1 [3.2]	0.83 [0.87]	−0.88 to 2.55	0.34
Daytime sleepiness	6.7 [5.0]	6.2 [4.3]	5.6 [3.8]	5.5 [3.6]	0.07 [0.76]	−1.44 to 1.57	0.93	5.3 [4.0]	5.1 [3.8]	0.24 [0.77]	−1.28 to 1.76	0.76
Sleep quality rating	3.5 [1.8]	4.3 [1.5]	2.2 [1.5]	2.3 [1.5]	−0.24 [0.33]	−0.90 to 0.42	0.48	2.4 [1.7]	2.8 [1.5]	0.04 [0.34]	−0.62 to 0.71	0.91
Total score	14.5 [7.1]	15.5 [6.3]	10.8 [5.5]	10.9 [6.0]	−0.62 [1.23]	−2.93 to 1.90	0.67	9.7 [6.1]	11.2 [5.4]	0.99 [1.24]	−1.44 to 3.43	0.42
CSD subjective sleep rating	2.0 [0.8]	1.7 [0.6]	2.1 [0.7]	2.2 [0.8]	0.32 [0.16]	0.01 to 0.62	0.04	2.2 [0.77]	2.0 [0.62]	0.00 [0.16]	−0.32 to 0.32	0.98
TST, min	391 [57]	386 [67]	349 [39]	371 [56]	26.71 [13.51]	0.08 to 53.35	0.05	363 [69]	375 [67]	−6.11 [14.51]	−34.72 to 22.50	0.68
SF, wake bouts/h	7.0 [4.1]	6.2 [2.8]	8.2 [5.6]	6.3 [2.9]	−0.51 [0.68]	−1.86 to 0.84	0.46	8.0 [3.3]	6.1 [2.8]	−0.48 [0.73]	−1.92 to 0.97	0.52
SE, %	86 [6]	87 [9]	84 [8]	86 [7]	1.73 [1.32]	−0.88 to 4.34	0.19	81 [8]	85 [9]	2.11 [1.43]	−0.71 to 4.93	0.14
UPDRS-III score	23.9 [10.5]	20.7 [8.8]	24.1 [10.1]	18.2 [7.4]	−2.76 [1.81]	−6.35 to 0.83	0.13	23.0 [12.0]	21.3 [11.0]	1.34 [1.92]	−2.46 to 5.13	0.49
MMSE score	28.0 [1.7]	28.4 [2.3]	28.0 [2.8]	28.3 [2.7]	−0.02 [0.49]	−0.98 to 0.95	0.97	28.1 [2.6]	28.2 [2.7]	0.06 [0.50]	−0.94 to 1.05	0.91
MEQ total score	54.0 [8.5]	56.0 [9.1]	53.9 [6.7]	57.4 [7.9]	1.37 [1.33]	−1.24 to 3.99	0.30	55.3 [6.6]	57.3 [6.8]	0.76 [1.34]	−1.89 to 3.40	0.57
Cortisol, pg/L												
AUC_G	25.0 [10.2]	23.1 [10.2]	26.9 [19.6]	19.6 [7.8]	−8.11 [3.93]	−15.77 to −0.35	0.04	28.4 [17.5]	27.2 [10.8]	−0.96 [3.96]	−8.77 to 6.85	0.81
AUC_I	3.3 [9.3]	5.6 [9.2]	8.0 [15.2]	3.0 [7.9]	−4.95 [3.98]	−12.81 to 2.92	0.22	3.8 [12.8]	5.7 [14.4]	1.59 [4.03]	−6.36 to 9.54	0.69
Mean evening concentration	2.3 [0.5]	2.7 [1.6]	7.2 [19.1]	3.9 [5.2]	−3.43 [2.72]	−8.82 to 1.95	0.21	2.7 [0.9]	2.1 [0.5]	−0.52 [2.93]	−6.31 to 5.27	0.86
WHO-QOL score	80.7 [11.9]	79.0 [13.1]	83.2 [11.8]	83.3 [13.6]	0.48 [2.55]	−4.57 to 5.54	0.85	83.1[13.5]	85.5 [12.6]	2.65 [2.59]	−2.48 to 7.77	0.31
ZBI score	25.3 [12.6]	23.3 [16.4]	20.7 [10.1]	21.1 [15.8]	1.44 [2.52]	−3.57 to 6.45	0.44	21.7 [16.2]	19.9 [13.5]	−1.28 [2.56]	−6.37 to 3.81	0.62

Abbreviations: AUC_G = area under the curve with respect to the ground, AUC_I = area under the curve with respect to the index of salivary cortisol change over time; BLT = bright light therapy; CI = confidence interval; CSD = Consensus Sleep Diary; GDS-30 = 30-item Geriatric Depression Rating Scale; HDRS = Hamilton Depression Rating Scale; MEQ = Morningness-Eveningness Questionnaire; MMSE = Mini-Mental State Examination; SCOPA-SLEEP = Scales for Outcomes in Parkinson's Disease–Sleep; SE = sleep efficiency; SF = sleep fragmentation; TST = total sleep time; UPDRS-III = Unified Parkinson's Disease Rating Scale Part III; WHO-QOL = World Health Organization Quality of Life assessment; ZBI = Zarit Burden Interview.
[a] Analyzed with logistic regression analysis.

Table 3 Results of the treatment efficacy analyses corrected for baseline value and confounders

	Baseline (T0)		After intervention (T2)					After follow-up (T5)				
	Control, mean [SD] (n = 37)	BLT, mean [SD] (n = 35)	Control, mean [SD] (n = 34)	BLT, mean [SD] (n = 33)	Group difference			Control, mean [SD] (n = 29)	BLT (n = 30), mean [SD]	Group difference		
					B [SE]	95% CI	*p* Value			B [SE]	95% CI	*p* Value
HDRS score	14.5 [3.8]	14.7 [3.5]	8.3 [4.3]	7.6 [5.0]	0.01 [1.15]	−2.25 to 2.27	0.99	5.9 [3.0]	8.5 [4.6]	2.93 [1.22]	0.53 to 5.34	0.02
GDS-30 score	17.1 [5.9]	17.9 [5.9]	14.9 [6.3]	13.7 [6.9]	−0.42 [1.60]	−3.57 to 2.74	0.80	12.3 [7.0]	13.2 [6.6]	0.21 [1.65]	−3.04 to 3.46	0.90
Remission, % (n)[a]	0 (0)	0 (0)	52 (17)	63 (20)	−0.23 [0.83]	−1.86 to 1.40	0.78	87 (26)	72 (21)	−1.53 [1.18]	−3.84 to 0.78	0.20
SCOPA-SLEEP score												
Nighttime sleep	7.9 [4.3]	9.3 [3.8]	5.1 [3.3]	5.5 [3.5]	0.31 [0.88]	−1.42 to 2.05	0.72	4.4 [3.7]	6.1 [3.2]	0.94 [0.99]	−1.02 to 2.90	0.34
Daytime sleepiness	6.7 [5.0]	6.2 [4.3]	5.6 [3.8]	5.5 [3.6]	0.94 [0.83]	−0.69 to 2.58	0.26	5.3 [4.0]	5.1 [3.8]	1.44 [0.86]	−0.26 to 3.14	0.10
Sleep quality rating	3.5 [1.8]	4.3 [1.5]	2.2 [1.5]	2.3 [1.5]	0.05 [0.38]	−0.70 to 0.80	0.89	2.4 [1.7]	2.8 [1.5]	0.06 [0.40]	−0.72 to 0.85	0.87
Total score	14.5 [7.1]	15.5 [6.3]	10.8 [5.5]	10.9 [6.0]	1.22 [1.36]	−1.46 to 3.89	0.37	9.7 [6.1]	11.2 [5.4]	2.41 [1.41]	−0.37 to 5.18	0.09
CSD subjective sleep rating	2.0 [0.8]	1.7 [0.6]	2.1 [0.7]	2.2 [0.8]	0.36 [0.18]	0.01 to 0.70	<0.05	2.2 [0.77]	2.0 [0.62]	0.14 [0.19]	−0.23 to 0.51	0.46
TST, min	391 [57]	386 [67]	349 [39]	371 [56]	27.51 [15.53]	−3.17 to 58.18	0.08	363 [69]	375 [67]	2.59 [17.00]	−30.98 to 36.16	0.88
SF, wake bouts/h	7.0 [4.1]	6.2 [2.8]	8.2 [5.6]	6.3 [2.9]	−0.42 [0.82]	−2.04 to 1.20	0.61	8.0 [3.3]	6.1 [2.8]	−0.69 [0.89]	−2.44 to 1.06	0.44
SE, %	86 [6]	87 [9]	85 [8]	86 [7]	1.06 [1.55]	−1.99 to 4.12	0.49	81 [8]	85 [9]	3.16 [1.70]	−0.20 to 6.51	0.07
UPDRS-III score	23.9 [10.5]	20.7 [8.8]	24.1 [10.1]	18.2 [7.4]	−2.31 [2.29]	−6.85 to 2.24	0.32	23.0 [12.0]	21.3 [11.0]	3.75 [2.51]	−1.24 to 8.73	0.14
MMSE score	28.0 [1.7]	28.4 [2.3]	28.0 [2.8]	28.3 [2.7]	0.00 [0.43]	−0.85 to 0.86	0.99	28.1 [2.6]	28.2 [2.7]	−0.21 [0.47]	−1.14 to 0.73	0.66
MEQ total score	54.0 [8.5]	56.0 [9.1]	53.9 [6.7]	57.4 [7.9]	1.40 [1.72]	−1.98 to 4.79	0.42	55.3 [6.6]	57.3 [6.8]	0.93 [1.75]	−2.53 to 4.38	0.60
Cortisol, pg/L												
AUC_G	25.0 [10.2]	23.1 [10.2]	26.9 [19.6]	19.6 [7.8]	−13.45 [5.17]	−23.69 to −3.22	0.01	28.4 [17.5]	27.2 [10.8]	−6.36 [5.33]	−16.91 to 4.20	0.24
AUC_I	3.3 [9.3]	5.6 [9.2]	8.0 [15.2]	3.0 [7.9]	−0.94 [5.73]	−12.28 to 10.39	0.87	3.8 [12.8]	5.7 [14.4]	1.32 [5.91]	−10.38 to 13.02	0.82
Mean evening concentration	2.3 [0.5]	2.7 [1.6]	7.2 [19.1]	3.9 [5.2]	2.12 [1.65]	−1.16 to 5.39	0.20	2.7 [0.9]	2.1 [0.5]	2.07 [1.91]	−1.73 to 5.87	0.28
WHO-QOL score	80.7 [11.9]	79.0 [13.1]	83.2 [11.8]	83.3 [13.6]	−0.34 [2.90]	−6.27 to 5.59	0.91	83.1 [13.5]	85.5 [12.6]	1.16 [3.11]	−5.02 to 7.35	0.71
ZBI score	25.3 [12.6]	23.3 [16.4]	20.7 [10.1]	21.1 [15.8]	1.91 [3.22]	−4.51 to 8.34	0.55	21.7 [16.2]	19.9 [13.5]	−1.28 [3.61]	−8.50 to 5.93	0.72

Abbreviations: AUC_G = area under the curve with respect to the ground, AUC_I = area under the curve with respect to the index of salivary cortisol change over time; BLT = bright light therapy; CI = confidence interval; CSD = Consensus Sleep Diary; GDS-30 = 30-item Geriatric Depression Rating Scale; HDRS = Hamilton Depression Rating Scale; MEQ = Morningness–Eveningness Questionnaire; MMSE = Mini-Mental State Examination; SCOPA-SLEEP = Scales for Outcomes in Parkinson's Disease–Sleep; SE = sleep efficiency; SF = sleep fragmentation; TST = total sleep time; UPDRS-III = Unified Parkinson's Disease Rating Scale Part III; WHO-QOL = World Health Organization Quality of Life assessment; ZBI = Zarit Burden Interview.
[a] Analyzed with logistic regression analysis.

Table 4 Results of the post hoc analyses: A mixed-model analysis on the effect of time for the mITT population

	Baseline (T0), mean [SD] (n = 72)	After intervention (T2) (n = 67)				After follow-up (T5) (n = 59)			
		Mean [SD]	B [SE]	95% CI	*p* Value	Mean [SD]	B [SE]	95% CI	*p* Value
HDRS score	14.6 [3.6]	8.0 [4.6]	−6.5 [0.6]	5.3 to 7.6	<0.001	7.2 [4.0]	−7.1 [0.6]	5.8 to 8.3	<0.001
GDS-30 score	17.4 [5.9]	14.3 [6.6]	−2.9 [0.6]	1.6 to 4.1	<0.001	12.7 [6.8]	−4.2 [0.6]	3.0 to 5.5	<0.001
SCOPA-SLEEP score									
Nighttime sleep	8.6 [4.1]	5.3 [3.4]	−3.2 [0.4]	2.4 to 4.0	<0.001	5.3 [3.5]	−3.1 [0.4]	2.3 to 3.9	<0.001
Daytime sleepiness	6.4 [4.7]	5.6 [3.7]	−0.8 [0.4]	0.1 to 1.6	0.04	5.2 [3.9]	−1.2 [0.4]	0.4 to 2.0	<0.01
Sleep quality rating	3.9 [1.7]	2.2 [1.5]	−1.7 [0.2]	1.3 to 2.0	<0.001	2.6 [1.6]	−1.3 [0.2]	1.0 to 1.7	<0.001
Total score	15.0 [6.7]	10.9 [5.7]	−4.0 [0.6]	2.8 to 5.3	<0.001	10.5 [5.8]	−4.3 [0.6]	3.1 to 5.6	<0.001
CSD subjective sleep rating	1.8 [0.7]	2.2 [0.7]	0.3 [0.1]	−0.5 to −0.2	<0.001	2.1 [0.7]	0.2 [0.1]	−0.4 to −0.1	<0.01
TST, min	388 [63]	360 [50]	−14.5 [6.9]	0.8 to 28.2	0.04	370 [68]	−2.7 [7.2]	−11.5 to 16.9	0.71
SF, wake bouts/h	6.6 [3.5]	7.2 [4.5]	0.1 [0.4]	−0.6 to 0.9	0.69	6.9 [3.2]	0.2 [0.4]	−0.5 to 0.9	0.62
SE, %	86.9 [7.7]	85.6 [7.4]	0.3 [0.7]	−1.1 to 1.7	0.67	83.2 [8.4]	3.2 [0.8]	1.7 to 4.7	<0.001
UPDRS-III score	22.4 [9.8]	21.2 [9.3]	−1.2 [1.0]	−0.8 to 3.1	0.23	22.2 [11.5]	0.5 [1.0]	−1.5 to 2.5	0.62
MMSE score	28.2 [2.0]	28.1 [2.7]	−0.05 [0.2]	−0.4 to 0.5	0.85	28.2 [2.6]	−0.03 [0.2]	−0.4 to 0.5	0.89
MEQ total score	54.9 [8.8]	55.7 [7.5]	0.1 [0.6]	−1.3 to 1.1	0.83	56.3 [6.7]	0.7 [0.6]	−1.9 to 0.5	0.27
Cortisol, pg/L									
AUC_G	24.1 [10.1]	23.7 [15.9]	0.5 [2.0]	−3.5 to 4.5	0.82	27.9 [14.9]	3.4 [2.0]	−7.4 to 0.7	0.10
AUC_I	4.6 [9.4]	5.8 [12.7]	0.9 [2.4]	−5.6 to 3.8	0.70	4.6 [13.4]	0.5 [2.4]	−4.3 to 5.2	0.84
Mean evening concentration	2.4 [0.9]	5.6 [14.0]	3.3 [1.5]	−6.2 to −0.3	0.03	2.4 [0.7]	0.1 [1.6]	−3.3 to 3.0	0.94
WHO-QOL score	79.9 [12.4]	83.2 [12.7]	2.6 [1.3]	−5.1 to −0.1	0.04	84.3 [13.0]	3.1 [1.3]	−5.7 to −0.6	0.02
ZBI score	24.3 [14.4]	20.9 [15.9]	−2.9 [1.3]	0.3 to 5.4	0.03	20.7 [14.7]	3.3 [1.3]	0.7 to 5.8	0.013

Abbreviations: AUC_I = Area under the curve with respect to the index of salivary cortisol change over time; AUC_G = area under the curve with respect to the ground; CI = confidence interval; CSD = Consensus Sleep Diary; GDS-30 = 30-item Geriatric Depression Rating Scale; HDRS = Hamilton Depression Rating Scale; MEQ = Morningness–Eveningness Questionnaire; mITT = modified intention-to-treat; MMSE = Mini-Mental State Examination; SCOPA-SLEEP = Scales for Outcomes in Parkinson's Disease–Sleep; SE = sleep efficiency; SF = sleep fragmentation; TST = total sleep time; UPDRS-III = Unified Parkinson's Disease Rating Scale Part III; WHO-QOL = World Health Organization Quality of Life assessment; ZBI = Zarit Burden Interview.

to enroll only 83 participants and our dropout rate was higher than expected, we had insufficient power for our follow-up analyses. Moreover, we were unable to collect all data from all study participants on objective sleep parameters and salivary melatonin and cortisol concentrations. In particular, the collection of saliva samples at set times was experienced as stressful by the participants, and these samples were not collected on all 6 days by all participants. We therefore think that we were underpowered for some of the analyses of the secondary outcomes. However, the sample size was sufficiently large for the postintervention analysis of our primary outcome.

Our study participants had a mean HDRS score of 14.6 [SD 3.6] at baseline, which makes generalizability of our results to patients with PD with more severe depression questionable. However, all participants met criteria for MDD according to the DSM-IV-TR.

We cannot rule out that the decrease of depressive symptoms in the control group was due partially to a therapeutic effect of the control light because a study in healthy participants suggests that a light intensity of ±100 lux is already sufficient to influence the circadian rhythm.[40] However, the participants in that study were exposed to 100 lux for 6.5 hours,[40] while our controls were exposed to only 30 minutes of 200 lux twice daily.

At the end of the trial, the HDRS score was significantly lower in the control group. We chose a naturalistic follow-up design because we found it unethical to withhold treatment from patients with remaining depressive symptom for 6 months. Because the number of participants with persistent MDD in the control group was larger after the intervention, more participants in this group may have been inclined to seek treatment during follow-up. This is reflected by the medication use of our

participants during follow-up. At the end of the intervention, 7 of 34 (20.6%) participants in the experimental group and 8 of 30 (26.7%) in the control group used antidepressants. During follow-up, the number of users of antidepressants decreased more strongly in the experimental group, to 4 of 29 (13.8%) vs 6 of 32 (18.8%) in the control group at the end of the trial. While we corrected our efficacy analyses for the use of antidepressants or anxiolytic/hypnotic medications, we were unable to correct for the effect of psychotherapeutic or behavioral interventions. This might explain the larger improvement of depressive symptoms at follow-up in the control group.

Finally, we encountered some issues in the collection and analysis of the saliva samples during our trial, which precluded us from calculating reliable values for the DLMO and evening AUC_G and AUC_I.

BLT was not more effective in reducing depressive symptoms than exposure to control light. Both the intervention and control group showed a significant improvement of depression and subjective sleep. However, BLT was more effective in improving subjective sleep quality than control light, possibly through a BLT-induced decrease in cortisol levels.

Author contributions

Sonja Rutten: design and conceptualization of the study, statistical analysis and interpretation of the data, drafting the manuscript for intellectual content. Chris Vriend: design and conceptualization of the study, revising the manuscript for intellectual content. Jan H. Smit, Henk W. Berendse, and Eus J.W. van Someren: conceptualization of the study, revising the manuscript for intellectual content. Adriaan W. Hoogendoorn: analysis of the data, revising the manuscript for intellectual content. Jos W.R. Twisk: analysis and interpretation of the data, revising the manuscript for intellectual content. Ysbrand D. van der Werf and Odile A. van den Heuvel: design and conceptualization of the study, revising the manuscript for intellectual content.

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