Bright Light Therapy in the Morning or Midday for the Treatment of Nonseasonal Depression in Bipolar Disorder (LuBi):

A Dose-Escalation Phase 1/2 Randomized Double-Blind Trial

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Abstract

Objective: This dose-escalation study aimed to evaluate the tolerance (hypomanic symptoms) and efficacy of bright light therapy (BLT) in depressed patients with bipolar disorder (BD) with mood stabilizers, using different schedules (duration and escalation), applied in morning or midday.

Methods: Patients with BD I or II (*DSM-IV-TR*) followed a 1-week placebo phase and were randomized to morning or midday BLT with dose escalation from 7.5 to 45 minutes/d, until September 2023. Inter- and intrasubject escalation were performed, with dose adjustments based on dose-limiting toxicities (DLTs) to determine the maximum tolerated dose (MTD) and target ceiling dose (TCD) of BLT exposure. The primary outcome measure, DLT, was assessed weekly after each dose initiation or increase and defined as a hypomanic switch (Young Mania Rating Scale [YMRS] score ≥12/60) or subsyndromic hypomanic symptoms (YMRS score 8–12).

Results: Both groups reached the starting dose of 45 minutes without reaching the MTD or TCD, enrolling 38 patients (morning = 18 and midday = 16) and demonstrating good tolerance and acceptability. Two patients (6%) experienced a hypomanic switch at 45 minutes: 1 in the morning group (week 1) and 1 in the midday group (week 4). Five patients had subsyndromic hypomania. All symptoms improved within 3 days after dose reduction. Depressive symptoms (Montgomery-Asberg Depression Rating Scale, $P = .007$) and Clinical Global Impression (CGI) scores ($P < .001$ for severity, $P = .01$ for improvement) significantly improved over time. A cumulative exposure effect was observed on CGI improvement ($P = .038$), alongside a starting dose effect over the weeks on CGI severity ($P < .001$) and the Flexibility Circadian Type Inventory ($P = .042$). The comparison between groups shows a higher CGI improvement score in the morning group ($P = .035$).

Conclusions: BLT is a viable antidepressant strategy for BD, safely starting at 45 minutes regardless of timing. Occurring hypomanic symptoms, if any, resolve quickly after dose reduction, provided there is careful monitoring.

Trial Registration: ClinicalTrials.gov identifier: NCT03396744.

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The use of light for its antidepressant effects dates back to antiquity, and in recent decades, a growing body of evidence has supported bright light therapy (BLT) as an effective treatment for depression.[1,2] Initially used for seasonal affective disorder (SAD),[3] defined by annual recurring depressive episodes,[4] BLT has also shown efficacy in treating nonseasonal depression in both unipolar and bipolar disorders (BD).[1,5] Light acts on mood by influencing biological rhythms through the suprachiasmatic nuclei (SCN)-dependent pathway, as well as through direct, SCN-independent pathways such as the serotonergic system, emotion regulation brain regions, the homeostatic sleep process, and the wake system by "enhancing alertness."[6] These developments align with new insights into the pathophysiology of BD, including disruptions in biological rhythms, homeostatic sleep processes, wake systems, and monoaminergic systems.[7–12]

Clinical Points

- Bright light therapy (BLT) is well tolerated in bipolar disorder, starting at 45 minutes/day, regardless of timing, with only 6% of patients experiencing a hypomanic switch and 13% experiencing subsyndromic symptoms, which resolved quickly after dose reduction.
- BLT significantly improves depressive symptoms and overall clinical status over time, with a cumulative exposure effect, emphasizing the need for careful monitoring.

Despite these new insights, the management of BLT in BD remains debated.[1] An international BD task force concluded that current evidence supports BLT's efficacy in BD despite heterogeneous study designs and various light parameters used and emphasized the need for larger, longer trials to determine optimal parameters.[13] Available randomized controlled trials report a low manic switch rate with BLT, yet the antidepressant switch potential and additional clinical, animal, and epidemiologic data linking light exposure with mania led the International Society for Bipolar Disorder (ISBD) task force to recommend against LT during acute manic or mixed states.[13] In addition to these safety concerns, nonadherence remains a critical challenge in BD treatment, particularly due to side effects.[14] Switch rates with BLT have ranged from 0% to 18.8%, depending on assessment methods and patient characteristics.[15] Early reports suggest that midday exposure may lower the risk of manic switching.[16] A 6-week double-blind, placebo-controlled trial provided further support for midday BLT as effective and safe, with no manic switches observed; although a majority of enrolled patients (82%) had seasonal and nonseasonal depression, the sample size (N = 46) and lack of replication to date limited generalization.[17] Historical reviews indicate that manic switches may occur independently of treatment type,[15] and the lack of direct comparisons among dose-titration protocols highlights the need for more reliable evidence-based guideline.[18] These challenges underscore the importance of conducting additional dose-finding, safety, and efficacy trials for BLT in depressed patients with BD to refine treatment protocols and ensure its safe implementation in clinical practice.[16]

In this context, we conducted a phase 1/2 study to evaluate, in patients with BD and nonseasonal depression, the effect of the characteristics of BLT administration (duration, escalation, and morning and midday exposure, all not codified) on tolerance (hypomanic symptoms) using an intrasubject dose escalation scheme with 2 groups randomly exposed to either morning or midday BLT. We hypothesized that BLT would be well tolerated, effective in reducing depressive symptoms, and associated with low rates of hypomanic switching. Given prior findings, we also anticipated that morning exposure might yield greater antidepressant effects but could be associated with a higher risk of manic switching compared to midday exposure.

METHODS

Aims of the Study

This phase 1/2 study aimed to evaluate the effects on treatment tolerance of escalation protocols for morning and midday BLT in nonseasonal bipolar depression. The primary goal was to determine the maximum tolerated dose (MTD) of BLT across 2 groups exposed to BLT in the morning or at midday. Secondary objectives included (1) identifying the optimal duration for acute BLT, (2) assessing feasibility and (3) acceptability, (4) assessing efficacy and identifying clinical markers linked to BLT response, (5) evaluating tolerance and its acceptability at 6 months, and testing (6) placebo glasses for future randomized trials.

Study Oversight

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2013. All procedures involving human subjects/patients were approved by the French Committees of Protection of Persons (CPP de Ouest 6 – CPP 1002 – DM2) June 20, 2017, and authorization from the French National Drug and Health Product Agency on December 12, 2017. It is registered on ClinicalTrials.gov (NCT03396744). A Data Safety Monitoring Board (independent members from investigators) and a Steering Committee were established to oversee the study's progress and safety.

Following an information and screening visit, patients with bipolar depression (major depressive episode with bipolar disorder subtype I or II, nonseasonal, and already treated with mood stabilizers) from 5 participating French university-affiliated psychiatric departments were included, until September 2023, after providing written informed consent. Patients initially received similar placebo glasses emitting light at 50 lux (close to ambient light) for 1 week into morning or midday exposure groups. They were then exposed to active BLT with an escalating dose protocol (inter- and intrasubject), increasing from 7.5 to 45 minutes over 10 weeks. Patients were assessed again 6 months postintervention, with no other antidepressant strategies allowed during the 10-week intervention. Patients were included by cohorts of 3 with inclusions delayed of at least 3 days for safety reasons. This study follows the CONSORT recommendations.

Outcomes

The primary outcome was dose-limiting toxicity (DLT), assessed weekly using the Young Mania Rating Scale (YMRS) after each dose initiation or increase. Any hypomanic switch (YMRS score ≥12/60) or subsyndromic hypomanic symptoms (YMRS score between 8 and 12) counted as a DLT. The occurrence of DLTs defined both the dose (duration of exposure) of the intrasubject dose escalation (regardless of the morning or midday group) and the intersubject dose escalation, ie, the dose of the next patient cohort.

Secondary outcomes included the 10-week change in depressive symptoms, measured by the Montgomery-Åsberg Depression Rating Scale (MADRS) and Clinical Global Impression (CGI); as well as effects on suicidal ideation as assessed by the Columbia Assessment Scale on Suicidal Risk Severity (C-SSRS), sleep quality assessed by the Pittsburgh Sleep Quality Index (PSQI), the chronotype assessed by the Composite Scale of Morningness (CSM), the Circadian Type Inventory (CTI), and the daytime sleepiness assessed by the Epworth Sleepiness Scale (ESS). All assessment tools used in this study were validated French versions (C-SSRS, PSQI, CSM, CTI, ESS), ensuring linguistic and cultural validity. The CTI scores are composite measures assessing Languid/Vigorous and Flexibility/Rigidity of circadian rhythms, with higher scores indicating a greater languid circadian type or increased flexibility. For a more detailed description of these measures and their methodological considerations, we refer readers to our previously published methodological study.[18] Secondary outcomes were assessed at baseline, at each weekly visit up to week 10, and at the 6-month follow-up.

Eligibility Criteria

Participants were eligible if they were between 18 and 55 years old, inpatients or outpatients receiving psychiatric care for a major depressive episode, and diagnosed with BD type I or II according to *DSM-IV* criteria, as confirmed by the Structured Clinical Interview for *DSM* (SCID),[19] with a MADRS total score of ≥20. Additionally, they must have been on treatment with mood stabilizers for at least 4 weeks at a standard dosage,[20] including lithium with levels controlled by serum lithium concentration >0.5 mEq/L for immediate-release 250 mg and ≥0.8 mEq/L for slow-release 400 mg; sodium divalproate with serum level >40 mg/L; valpromide with serum level >40 mg/L; carbamazepine with dosage ≥150–800 mg; or second-generation antipsychotics such as quetiapine (≥150–800 mg), aripiprazole (≥15–30 mg), or olanzapine (≥10–20 mg). Written informed consent was required for participation.

Intervention, Light Device

The BLT was administered using Luminette glasses, a medical device produced by Lucimed (EAN: 0702382929671). It provided daily exposure to fluorescent light with a perceived intensity of 10,000 lux, included a UV filter, and met CE standards. For this study, the Luminette glasses were set at intensity 2/3, emitting blue-enriched light at 1,000 lux, equivalent to 10,000 lux in traditional BLT.[21] A placebo exposure was established using the same Luminette device, adhering to CE standards, but emitting a fluorescence of 50 lux, similar to ambient light and considered ineffective. It aims to provide a zero-dose measurement of light therapy and to allow the patient to become accustomed to the device.

The detailed study design has been previously published,[18] and a summary is available in Supplementary Materials (Appendix 1, Supplementary Methods).

Statistics

A sample of approximately 20 subjects was targeted, accounting for the 5 possible dose levels per subject and the inclusion of 3 subjects per cohort, as commonly used in oncology phase 1 dose-escalation studies. This sample size allowed for the inclusion of up to 3 additional subjects at each dose level in case of DLT, aiming to include at least 15 ± 6 patients per group (morning or midday).

Statistical analysis used a modified intention-to-treat (mITT) population, whereby each enrolled subject was analyzed within their assigned randomization group, regardless of treatment completion, unless there were contraindications, withdrawal of consent, or the patient's decision to discontinue.

Mixed effects models were applied to model the effects of the starting dose effect (duration), the cumulative doses, and morning vs midday exposure pattern, on the YMRS score and the secondary outcomes incorporating the subject effect (random).[22] We used a mixed effects model with random intercepts to account for intraindividual variability. Normality was assessed using the Shapiro-Wilk test.

For all statistical analyses, we report effect size estimates along with *P* values, including the estimated β coefficients and SEs for regression models. This approach ensures a more comprehensive interpretation of the study findings, beyond statistical significance alone.

Missing data were handled using a last-observation-carried-forward approach where appropriate. All scale scores were treated as continuous variables except for categorical assessments such as hypomanic switch events.

Covariates included in the model were age, sex, and baseline YMRS score, with a type I error rate at 0.05 for statistical significance.

The same measures were used at the 6-month follow-up, and results were interpreted relative to baseline and week 10 values.

Table 1.

Demographic and Clinical Characteristics of Patients at Inclusion

Characteristics	Total (n = 34)	Morning group (n = 18)	Midday group (n = 16)
Age, median [IQR], y	42.5 [31.3, 53.2]	41.5 [31.5, 53.2]	45.2 [31.6, 52.1]
Male sex, n (%)	14 (41%)	8 (44%)	6 (38%)
Weight, median [IQR], kg	75 [61.1, 83]	76 [60, 82]	75 [62.2, 90]
BMI, kg/m^2, median [IQR]	24 [21.7, 29.1]	23.4 [21.7, 29.1]	24.4 [22.3, 28.1]
Marital status, n (%)			
Single	16 (47%)	8 (44%)	8 (50%)
Married	11 (32%)	6 (33%)	5 (31%)
Separated	4 (12%)	3 (17%)	1 (6%)
Divorced	3 (9%)	1 (6%)	2 (12%)
Activity, n (%)			
Craftsmen, retailer, head of company	2 (6%)	2 (11%)	0
Employee	8 (24%)	4 (22%)	4 (25%)
Intermediate occupations	1 (3%)	1 (6%)	0
Executive, intellectual profession	7 (21%)	2 (11%)	5 (31%)
Unemployed	11 (32%)	7 (39%)	4 (25%)
Not applicable	5 (15%)	2 (11%)	3 (19%)
Type of activity, n (%)			
Permanent contract	13 (45%)	7 (44%)	6 (46%)
Fixed-term contract	4 (14%)	2 (12%)	2 (15%)
Retired	2 (7%)	1 (6%)	1 (8%)
Student not in paid employment	2 (7%)	0	2 (15%)
Not applicable	8 (28%)	6 (38%)	2 (15%)
NA	5	2	3
No. of years of studies (from first year of primary school), n (%)			
9 y	3 (9%)	2 (11%)	1 (6%)
12 y	9 (26%)	3 (17%)	6 (38%)
>12 y	22 (65%)	13 (72%)	9 (56%)
Smoking, n (%)			
No	15 (44%)	8 (44%)	7 (44%)
Actually	13 (38%)	7 (39%)	6 (38%)
Ex-smoker	6 (18%)	3 (17%)	3 (19%)
Episodes of depression, n (%)	34 (100%)	18 (100%)	100%
No. of depressive episodes, median [IQR]	7 [4, 11]	9 [4, 10]	7 [3.5, 18] (3, 36)
Manic episodes, n (%)	17 (50%)	9 (50%)	8 (50%)
No. of manic episodes, median [IQR]	2 [1, 4]	2 [2, 4]	2.5 [1, 5.5]
Hypomanic episodes, n (%)	28 (82%)	14 (78%)	14 (88%)
No. of hypomanic episodes, median [IQR]	4 [2, 6]	4 [2.2, 5.8]	4 [2, 6] (2, 10)
At least 1 with mixed characteristics, n (%)	18 (53%)	11 (61%)	7 (44%)
Bipolar subtype, n (%)			
Type I	17 (50%)	9 (50%)	8 (50%)
Type II	17 (50%)	9 (50%)	8 (50%)
Rapid cycle (more than 4 episodes/y)	6 (18%)	3 (17%)	3 (19%)
Age at first episode	19.5 [17, 29]	19.5 [16.5, 23.8]	19.5 [17, 32.2]
Age at first treatment	29 [21.5, 33.5]	29 [18.8, 34]	26 [22, 33.5]
Number of hospitalizations	4 [1, 8]	4.5 [1, 7.2]	3 [1, 9]
Age at first hospitalization	30 [22.2, 37]	29.5 [23.2, 34.2]	30 [22.2, 38.5]
Total length of hospital stay (weeks)	6 [2, 34]	8 [3.5, 39]	6 [2, 26]

All analyses were conducted using SAS software (SAS Inc, Cary, NC) and R version 4.1.1 (https://www.R-project.org/).

RESULTS

Population

A total of 38 patients were included in 6 centers (Supplementary Table 1) between September 30, 2019, and February 14, 2023. Four patients with no data regarding the exposure period were excluded (1 due to contraindication, 2 for personal reasons, and 1 withdrawal of consent). The flowchart is displayed in Supplementary Figure 1. The mITT included 34 subjects, including 18 patients allocated to the morning group and 16 to the midday group. Sociodemographic and clinical characteristics of these patients are detailed in Table 1. Information regarding psychotropic medication intake at the time of inclusion

Table 2.

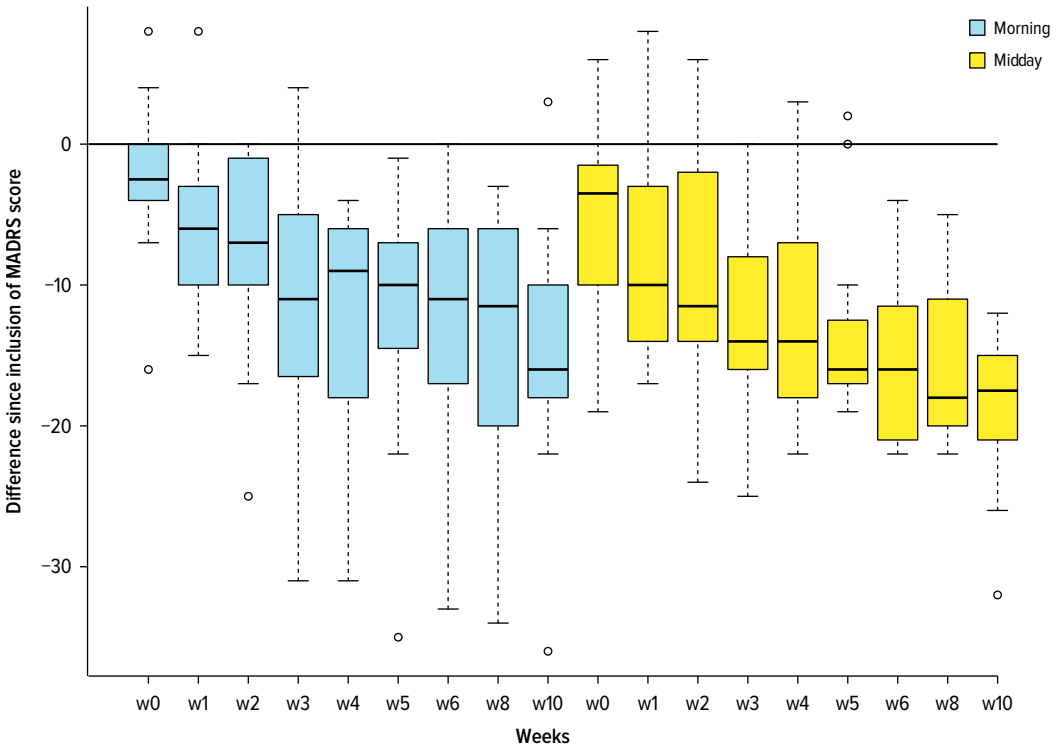
Estimated Effects of Time (Week), Starting Allocated Dose (Duration), Randomization (Morning vs Midday), and Current Dose With Potential Heterogeneity in Effect Over Time of Both Starting Dose and Randomization, on Primary and Secondary Outcomes[a]

	Estimated β (SE) with *P* value					
	Week	Starting duration	Morning vs midday	Current dose	Interaction week: starting dose	Interaction week: morning vs midday
Primary outcome						
YMRS score	−0.159 (0.101), *P* = .12	−0.010 (0.022), *P* = .66	-0.231 (0.533), *P* = .67	0.013 (0.013), *P* = .32	0.003 (0.003), *P* = .41	0.086 (0.071), *P* = .23
Secondary outcomes						
MADRS score	**−1.049 (0.383), *P* = .007**	−0.020 (0.098), *P* = .84	−0.568 (2.505), *P* = .82	−0.012 (0.050), *P* = .81	0.008 (0.012), *P* = .48	−0.130 (0.269), *P* = .63
CGI score (severity)	**−0.295 (0.054), *P* < .001**	−0.020 (0.015), *P* = .171	−0.099 (0.380), *P* = .796	0.011 (0.007) *P* = .114	**0.006 (0.002), *P* < .001**	0.053 (0.038), *P* = .166
CGI score (global improvement)	**−0.150 (0.058), *P* = .01**	−0.017 (0.013), *P* = .19	0.249 (0.325), *P* = .45	**0.016 (0.008), *P* = .038**	0.002 (0.002), *P* = .18	0.007 (0.041) *P* = .87
CGI score (therapeutic index)	−0.379 (0.225), *P* = .09	−0.003 (0.053), *P* = .95	1.241 (1.314), *P* = .35	0.028 (0.029), *P* = .343	0.005 (0.007), *P* = .50	−0.068 (0.158), *P* = .67
C-SSRS score	−0.039 (0.033), *P* = .24	−0.010 (0.006), *P* = .12	−0.042 (0.144), *P* = .77	0.005 (0.004), *P* = .19	0.001 (0.001), *P* = .24	0.015 (0.024), *P* = .53

[a]Statistically significant results shown in shaded cells with bold *P* values.
Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale, CGI-I = Clinical Global Impression—Global Improvement, CGI-S = Clinical Global Impression—Severity, CGI-TI = Clinical Global Impression—Therapeutic Index, MADRS = Montgomery-Åsberg Depression Rating Scale, YMRS = Young Mania Rating Scale.

Figure 1.

Distribution of the Absolute Variation of MADRS Score From Inclusion Over Weeks, in Both Randomized Groups[a]



[a]w0 refers to the beginning of the first 7-day period in which all patients received the placebo (baseline score).
Abbreviation: MADRS = Montgomery-Åsberg Depression Rating Scale.

Table 3.

Evolution and Comparison of Assessments Scores Between Inclusion and Week 10 by Morning and Midday Groups

	Median [IQR] difference from inclusion to week 10			
	Total (n = 34)	Morning group (n = 18)	Midday group (n = 16)	*P* value
Manic symptoms (YMRS)	0 [−2, 0]	0 [−1, 0]	−1 [−2, 0]	.64
Suicidal ideation (C-SSRS)	0 [−0.5, 0]	0 [0, 0]	0 [−0.8, 0]	.42
Depressive symptoms (MADRS)	−17 [−18, −12]	−16 [−18, −10]	−17.5 [−20.2, −15.5]	.19
Severity of the disorder (CGI1)	−2 [−3, −0.5]	−2 [−3, −1]	−2 [−3.8, −0.2]	.95
Global improvement (CGI2)	1 [0, 2]	1 [0, 1]	2 [2, 2]	.035
Therapeutic index (CGI3)	−4 [−8, 0]	−4 [−8, 0]	−6 [−8, 0]	.76
Sleep quality (PSQI)	−1 [−2, 0]	−1 [−2, 0]	−1.5 [−2.8, −0.8]	.25
Excessive daytime sleepiness (ESS)	0 [−2.5, 1]	−0.5 [−1.8, 0.8]	0 [−4, 1]	.62
Chronotype (CSM)	−1 [−2.2, 2.5]	−1.5 [−3, −1]	1.5 [−1.2, 4]	.18
Circadian type flexible/rigid (CTI)	0.5 [−2, 4.2]	0.5 [−2, 2.5]	0.5 [−1.5, 5.8]	.73
Circadian type languid/vigor (CTI)	0 [−2, 3]	1.5 [0, 3]	−2 [−5, 1]	.079

Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale, CGI = Clinical Global Impression, CSM = Composite Scale of Morningness, CTI = Circadian Type Inventory, ESS = Epworth Sleepiness Scale, MADRS = Montgomery-Åsberg Depression Rating Scale, PSQI = Pittsburgh Sleep Quality Index, YMRS = Young Mania Rating Scale.

is provided in Supplementary Table 2. Twelve patients (6 in each group) prematurely discontinued treatment (complete study flowchart of the LuBi study: Supplementary Figure 1).

Main Outcome

Two patients (6%) experienced a hypomanic switch. One patient in the morning group experienced a DLT after being exposed to 45 minutes of light therapy in the 1st week. This patient with BD type II was treated with lithium and lamotrigine. No new DLTs occurred in the subsequent morning cohort that also started at 45 minutes. The other hypomanic switch occurred for 1 patient in the midday group after being exposed for 45 minutes in the fourth week. This patient with BD type I was treated with lithium, lamotrigine, and an antidepressant serotonin-norepinephrine reuptake inhibitor. As such, neither the MTD nor the TCD was reached for any of the 2 groups.

Notably, 5 patients experienced subsyndromic hypomanic episode, none during the 1st week: 3 in the morning group (all at 45 minutes, 2 with BD type II, and 1 with BD type I) and 2 in the midday group (all at 30 minutes and with BD type II). These 5 patients were treated with lithium, in combination with lamotrigine for 3 cases. Additionally, 3 patients received antidepressants, 1 was prescribed methylphenidate, 1 melatonin, and 1 pramipexole. Overall, 20.6% of participants (7/34) exhibited either subsyndromic or full-blown hypomania.

All these patients experienced a reduction in their hypomanic symptoms within 3 days following dose reduction, with no hypomanic symptoms observed at the 3-day follow-up visit.

No significant associations were found between manic symptoms (YMRS score) and the week of treatment, the starting dose, the cumulative dose, or the morning vs midday exposure (Table 2). Similarly, we observed no significant effects of the starting exposure duration or the morning/midday group allocation on the YMRS score over the weeks (Table 2).

Secondary Outcomes

Secondary outcomes are shown in Table 2.

Depressive symptoms. Figure 1 shows the median of variation after baseline of the MADRS over week according to the group. The MADRS score decreased over weeks ($P = .007$), whichever the randomization (morning vs midday) ($P = .63$) or the starting exposure duration ($P = .48$).

Clinical Global Impression. The CGI severity score significantly decreased over weeks ($P < .001$), and this was more pronounced in those who initially received a long duration ($P < .001$). The CGI improvement score decreased over weeks ($P = .010$), as well as with the exposure duration ($P = .038$).

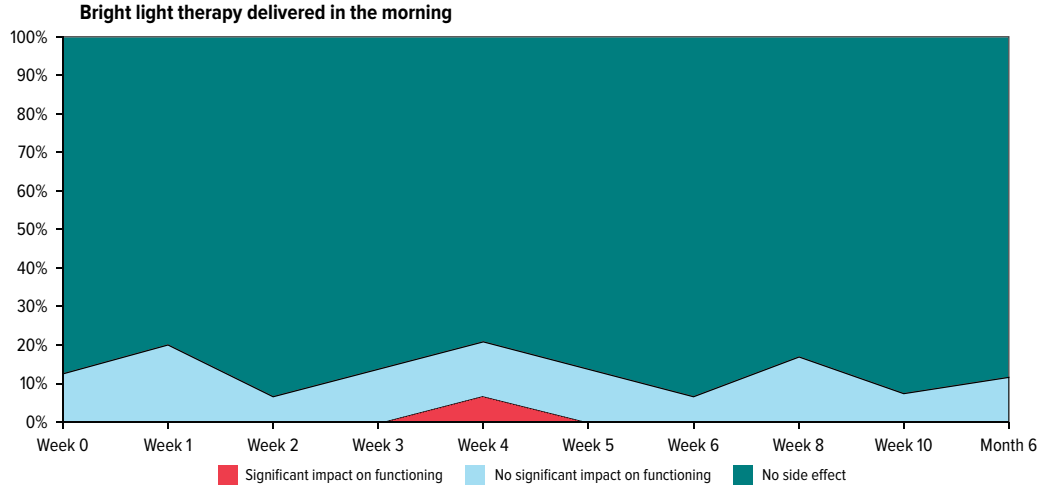
Suicidal ideation. There was no evidence of BLT effect on the mean of suicidal ideations assessed by the clinician (C-SSRS, $P = .24$), nor any significant effects of other features.

Other secondary end points. No statistically significant effects were observed on the global sleep quality and chronotype (Supplementary Table 3). An association was observed regarding the Circadian Type Inventory (FR) score and the midday group ($P = .031$), meaning the flexibility circadian type was increased with the midday exposure. Moreover, the Flexibility Circadian Type Inventory modification over the week depended on the starting duration ($P = .042$). For the daytime sleepiness, no statistically significant effects were found.

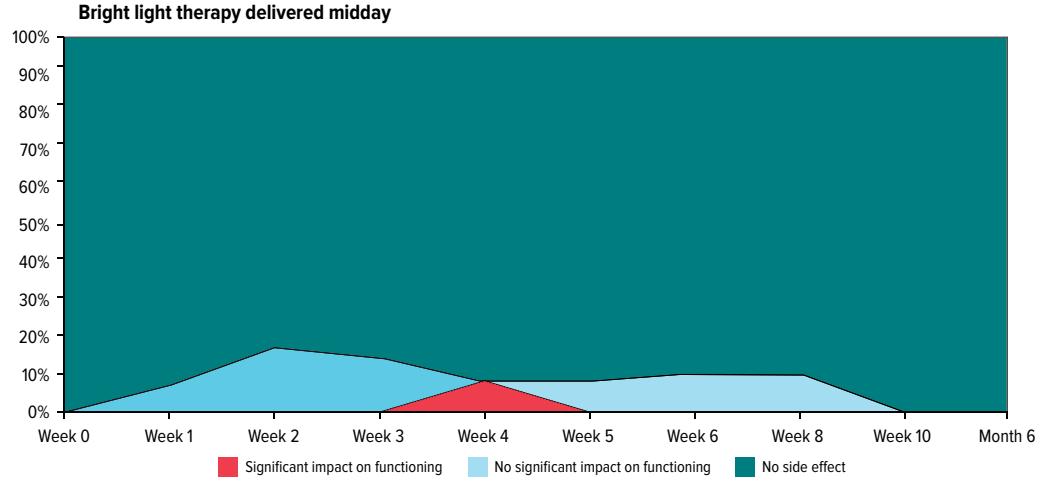
Figure 2.

(A) Prevalence and Impact of Side Effects Observed During 6 Months in a Group of Patients Treated with 10 Wk of Bright Light Therapy (BLT) and (B) Acceptability of Bright Light Therapy over Weeks for the Morning and Midday Groups with Bipolar Disorder

A. Prevalence and Impact of Side Effects



Side effects (prevalence, %)	Week 0 (baseline)	Week 1 (placebo)	Week 2 (BLT)	Week 3 (BLT)	Week 4 (BLT)	Week 5 (BLT)	Week 6 (BLT)	Week 8 (BLT)	Week 10 (BLT-End)	Month 6
Side effect with a significant impact on functioning	0	0	0	0	7	0	0	0	0	0
Side effect with no significant impact on functioning	13	20	7	14	14	14	7	17	8	12
No side effect	87	80	93	86	79	86	93	83	92	88

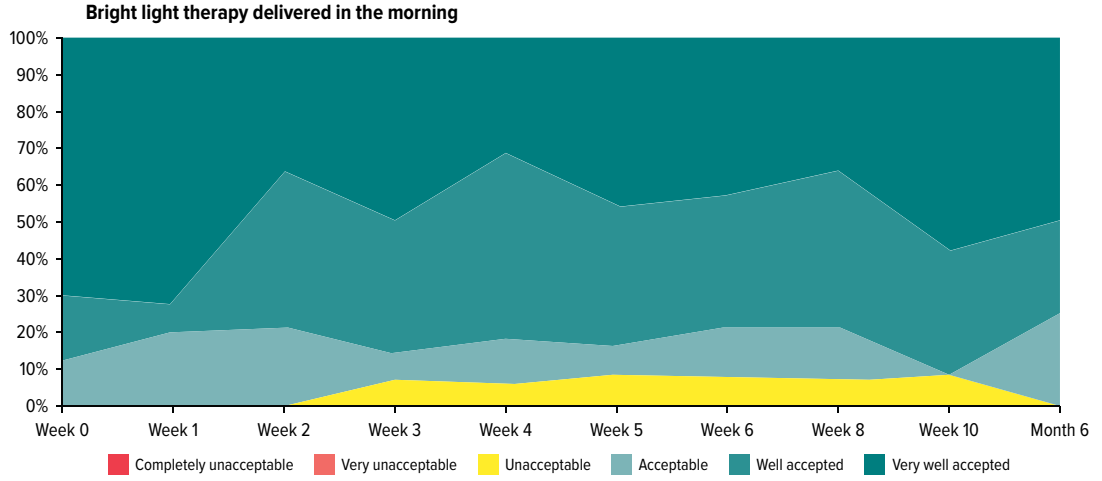


Side effects (prevalence, %)	Week 0 (baseline)	Week 1 (placebo)	Week 2 (BLT)	Week 3 (BLT)	Week 4 (BLT)	Week 5 (BLT)	Week 6 (BLT)	Week 8 (BLT)	Week 10 (BLT-End)	Month 6
Side effect with a significant impact on functioning	0	0	0	0	8	0	0	0	0	0
Side effect with no significant impact on functioning	0	7	17	14	0	8	10	10	0	0
No side effect	100	93	83	86	92	92	90	90	100	100

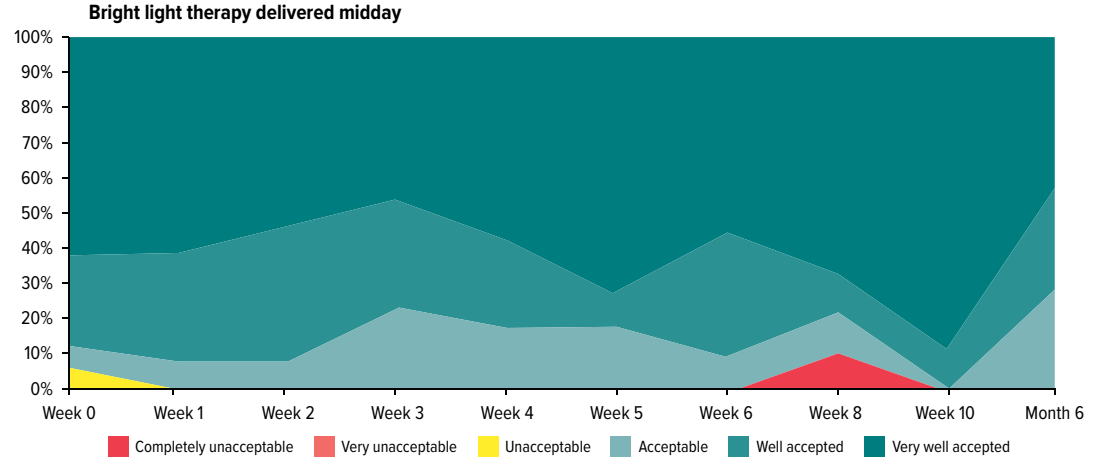
Abbreviation: BLT = bright light therapy.

Figure 2.
(Continued).

B. Acceptability of Bright Light Therapy



Acceptability (prevalence, %)	Week 0 (baseline)	Week 1 (placebo)	Week 2 (BLT)	Week 3 (BLT)	Week 4 (BLT)	Week 5 (BLT)	Week 6 (BLT)	Week 8 (BLT)	Week 10 (BLT-End)	Month 6
Completely unacceptable	0	0	0	0	0	0	0	0	0	0
Very unacceptable	0	0	0	0	0	0	0	0	0	0
Unacceptable	0	0	0	7	6	8	7	7	8	0
Acceptable	12	13	21	7	12	8	14	14	0	25
Well accepted	18	4	43	36	50	38	36	43	33	25
Very well accepted	71	47	36	50	31	46	43	36	58	50



Acceptability (prevalence, %)	Week 0 (baseline)	Week 1 (placebo)	Week 2 (BLT)	Week 3 (BLT)	Week 4 (BLT)	Week 5 (BLT)	Week 6 (BLT)	Week 8 (BLT)	Week 10 (BLT-End)	Month 6
Completely unacceptable	0	0	0	0	0	0	0	11	0	0
Very unacceptable	0	0	0	0	0	0	0	0	0	0
Unacceptable	6	0	0	0	0	0	0	0	0	0
Acceptable	6	8	8	23	17	18	9	11	0	29
Well accepted	25	31	38	31	25	9	36	11	11	29
Very well accepted	62	62	54	46	58	73	55	67	89	43

Comparison of These Evolutions of Clinical Scale Scores Between the Morning and Midday Groups

No differences were observed between the morning and midday groups regarding evolutions of clinical scale scores at week 10 from baseline, except for the CGI global improvement score, which was on average higher for the morning group (P = .035) (Table 3).

Tolerance

Both the morning and midday groups demonstrated excellent tolerance to BLT, with over 80% reporting no side effects and 7%–20% reporting side effects without significant impact on functioning, depending on the week. Only 1 patient in the morning group reported a significant impact at week 4, experiencing a subsyndromic hypomanic switch, while 1 patient in the midday group, also at week 4, experienced a hypomanic episode switch (Figure 2A).

Otherwise, the device was well tolerated, as illustrated by the placebo week (week 1), with reports comparable to those during the active BLT weeks.

Acceptability

Both the morning and midday groups demonstrated high acceptability, with fewer than 10% of patients reporting unacceptability throughout the study period (Figure 2B).

Similarly, the placebo intervention showed comparable acceptability, with only 6% of patients reporting it as unacceptable.

DISCUSSION

This first dose-escalation study provides insights into the use BLT in BD for managing depressive symptoms, emphasizing that a carefully monitored, dose-escalated approach induces manageable side effects, while achieving therapeutic benefits. Key findings reveal that BLT at both morning and midday is generally well-tolerated up to 45 minutes, with only a small proportion of patients experiencing transient hypomanic symptoms. Notably, no mania cases occurred, and only 6% of participants experienced a full hypomanic switch, which resolved promptly with dose reduction, including patients with subsyndromic hypomania. Furthermore, depressive symptoms significantly improved as measured by MADRS and CGI, with a cumulative exposure effect observed on CGI scores, suggesting sustained benefits with ongoing treatment. Morning BLT showed a slightly greater CGI improvement than midday exposure, potentially guiding optimal timing. These findings suggest that BLT, when carefully escalated and monitored, is a viable antidepressant strategy in BD, improving mood and clinical impression, with hypomanic symptoms resolving quickly after dose reduction.

Findings from this study align with previous research on the benefits of BLT in BD[13] but expand on the applicability of BLT in BD by focusing on dose-escalation protocols and tolerance. For instance, Sit et al[16] previously reported that morning light exposure could improve depressive symptoms in BD though with a risk of hypomanic switching. Our structured escalation approach addresses this risk through controlled dose adjustments and close monitoring of hypomanic symptoms. Our study shows that any full-blown or subsyndromic hypomania quickly decreases after dose reduction, without requiring additional intervention or antimanic treatment, but it therefore emphasizes the need for close monitoring of BD symptoms, even when mood stabilizers are present at effective antimanic dosages.

Studies traditionally demonstrate that morning BLT has a greater antidepressant effect than afternoon exposure.[23,24] The enhanced effectiveness of morning BLT is thought to be due to its impact on circadian rhythms, aligning them with natural daylight cycles.[25] Our study reported that both morning and midday BLT schedules can improve depressive symptoms, although a slight significant benefit in global clinical improvement was noted with morning exposure. These results align with the findings of Burgess et al,[26] which highlighted the complex relationships between phase shifts induced by bright light and the antidepressant response. They reported nonsignificant correlations between changes in depression severity scores and phase shifts, noting that depressive symptoms decreased regardless of whether patients' circadian rhythms were delayed, advanced, or unchanged. This suggests that the antidepressant effects of BLT are not solely mediated through the SCN-dependent circadian pathway; rather, BLT engages multiple signaling pathways that influence mood, potentially depending on individual phenotypic characteristics and underlying pathophysiological mechanisms of depression. Building on this idea, Terman et al[23] emphasized that the effects of light extend beyond merely synchronizing the biological clock. They found that certain individuals respond preferentially to light depending on its timing. For instance, some patients prefer evening light, while others derive greater benefit from morning exposure, and some show no significant difference in their responses between morning and evening light. This underscores the importance of considering individual differences when evaluating the impact of light therapy on mood and the need for further research comparing different timing protocols, particularly in BD and its subtypes, including the chronotype, insomnia or hypersomnolence complaints, seasonal patterns, rapid cycling, gender, etc. Regarding the issue of suicidal behavior, a known concern with

conventional antidepressants, previous case reports have highlighted the potential for emergent suicidal ideation in patients treated with light therapy alone. Specifically, a report described 3 cases—2 individuals with BD experiencing seasonal depression and 1 with unipolar SAD—where suicidal ideation emerged during the first week of treatment, resulting in suicide attempts in 2 of the cases.[27] However, a more recent study focused on the effects of light therapy on suicidality in patients with SAD (both unipolar and bipolar) observed a protective effect; nearly half of the 191 participants experienced a reduction in suicidal ideation, with worsening reported in only 6 cases.[28] This antisuicidal effect has also been demonstrated in studies combining light therapy with other treatments in unipolar[29] and bipolar disorders.[30] In our study, we observed no significant effects, either positive or negative, on suicidal behaviors over the 10-week period, with no differences between the morning and midday exposure groups.

Our findings confirm that BLT in BD during depression was well tolerated[31] and highly acceptable over the 10 weeks of intervention and during the extended 6-month follow-up period. Both the morning and midday BLT groups reported excellent safety profiles, with over 80% experiencing no side effects and the majority of those who did reporting mild effects without significant functional impact. Additionally, the placebo intervention, which used dim-light exposure, demonstrated comparable tolerability and acceptability, underscoring also its credibility as a control condition. As with prior studies, the possibility of hypomanic switches in patients with BD remains a potential risk, manifesting in symptoms such as tachypsychia, logorrhea, increased energy and activity, irritability, or aggression.[16,32] Other rare side effects of light therapy include headache, eye strain, nausea, and agitation.[24,33,34] However, these occurrences were infrequent, and no retinal toxicity was observed, consistent with existing literature.[35] Overall, these results emphasize the safety and acceptability of BLT and highlight its suitability for patients with BD when administered with appropriate precautions and monitoring. In addition to its favorable safety profile, BLT presents a promising adjunctive treatment to pharmacotherapy in BD, particularly for patients with inadequate response to mood stabilizers or those seeking nondrug alternatives. While not a substitute for conventional treatments, BLT aligns with the ISBD guidelines, which recognize its potential as a first-line treatment.[13,36] Given its high acceptability and good efficacy, future research should explore its broader applications in BD subtypes and other mood disorders, including postpartum depression, premenstrual syndrome, and rapid cycling.

One limitation of our study is the relatively small sample size, which, while appropriate for a rigorous dose-escalation study, limits broader interpretation, particularly regarding other clinical dimensions. However, the design allowed for accurate monitoring of dose tolerance and escalation, providing insights into the safety of BLT in BD. Additionally, this study was not powered to detect potential differences in response rates, side effects, or hypomanic risk based on sex or study site. Future research with larger sample sizes is needed to explore these potential interactions. Moreover, the short follow-up duration limits our understanding of BLT's long-term effects on mood stability in BD, a common limitation in current research that highlights the need for extended follow-up studies.[37–39] Nonetheless, the intensive observation period allowed us to assess short-term tolerance and effectiveness, supporting BLT's safety profile in the initial treatment phase. Future research should investigate the long-term effects of BLT, including sustained antidepressant efficacy and recurrence rates over extended follow-up periods. Another limitation is that the study focused primarily on BD patients receiving stable mood stabilizers, potentially narrowing generalizability to those not receiving concurrent medication. This focus, however, ensures that observed effects are more directly attributable to BLT, strengthening the internal validity of our findings.

CONCLUSION

In conclusion, BLT stands out as a safe and viable nondrug strategy for managing depressive symptoms in BD, with evidence supporting its initiation at 45 minutes regardless of timing. Any hypomanic symptoms, if they occur, appear transient and resolve quickly with dose reduction, provided that careful monitoring is ensured. Findings from this study strengthen the case for incorporating BLT as an effective adjunctive therapy to mood stabilizers in BD, a field where existing treatments often have limitations. These results highlight new opportunities for optimizing treatment strategies and improving patient outcomes.

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The Journal of Clinical Psychiatry

Supplementary Material

Article Title: Bright Light Therapy in the Morning or Midday for the Treatment of Nonseasonal Depression in Bipolar Disorder (LuBi): A Dose-Escalation Phase 1/2 Randomized Double-Blind Trial

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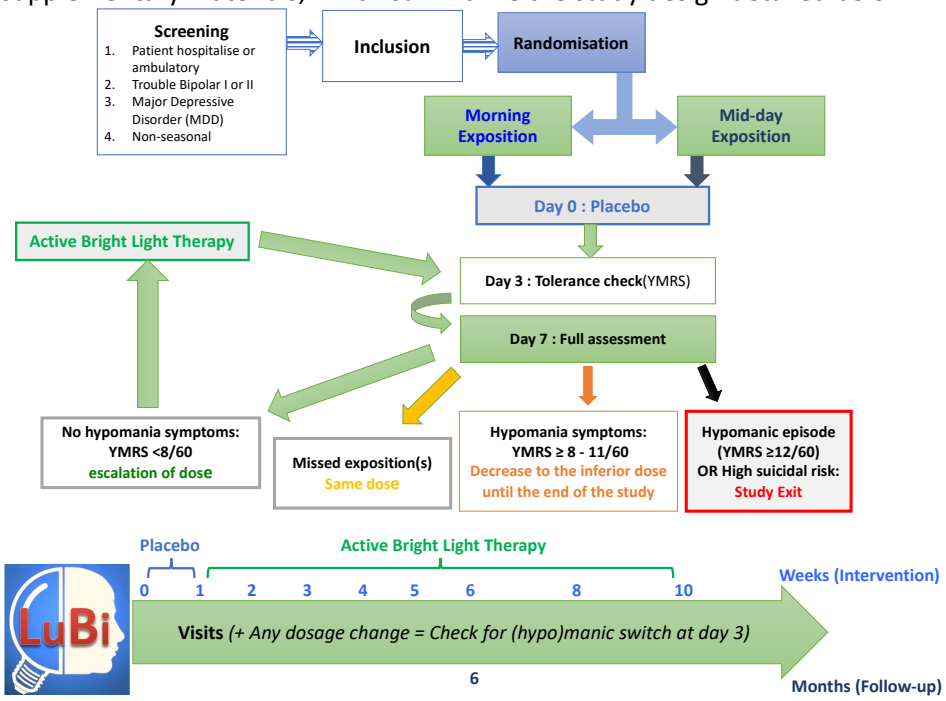
LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

Appendix 1. Supplementary Methods: Study Design

This is a dose-finding study, with the dose defined as the duration of light exposure, using both inter- and intra-subject dose to determine the maximum tolerated dose (MTD) of bright light therapy (BLT) in bipolar depression. Five dose levels were evaluated (7.5, 10, 15, 30, and 45 minutes), with participants randomly assigned in a 1:1 ratio to either morning or mid-day BLT groups. The dosage depended on the therapeutic escalation. It was based on the definition of several intra-subject dose escalation schemes, with different initiation dose among 5 dose levels (7.5, 10, 15, 30 and 45 min). The intra-subject escalation scheme had to be done at most once a week.

This approach accounts for both inter- and intra-individual variability in tolerance and response, enabling cumulative toxicity modeling and maximizing each patient's likelihood of receiving an effective dose. Refer to the intra-patient dose escalation rules and figures in the supplementary materials, which summarize the study design detailed below.



Inter- and Intra-Subject Escalation

The inter-subject escalation scheme aimed to estimate the maximum tolerated dose (MTD) of the BLT, as measured on hypomanic switch, and was based on the standard '3+3' design. The first three participants (Cohort A) began with the starting dose level of 7.5 minutes. If no dose-limiting toxicity (DLT) was observed among all three, the starting dose for the next cohort (Cohort B) was increased to the next level (10 minutes). Inter-subject escalation depended on observing no DLTs in all three subjects of a cohort, or at most 1 in 6. If one participant exhibited a DLT, a second identical cohort would start at the same starting dose, and escalation to a higher dose level would only proceed if no DLT was observed in this supplemental cohort. The MTD was defined if two or three subjects in the same cohort exhibited a DLT, or if two separate cohorts at the same dose initiation level each had one participant with a DLT. If only one participant in the first cohort showed a DLT, a second cohort at the same starting dose was started to confirm the safety of that dose. This process was repeated for subsequent cohorts.

The intra-subject escalation scheme aimed to account for individual variability in the definition of the MTD [34], allowing each subject to receive the maximum dose that he(she) tolerates. The intra-subject dose escalation occurred only once a week for each patient. The intra-patient dose escalation took into account any DLTs (ie, hypomanic switches) observed during the escalation on the previous cohorts, through the observation of so-called "Target Ceiling Dose" (TCD)[35].

Rules for this escalation were summarized in the supplementary materials. If a patient presented a DLT during this escalation, the escalation was abandoned for this patient and the dose defined the DLT for this patient. If 2 DLTs occurred at a same dose, the "Target Ceiling Dose" (TCD) was defined -which is the highest theoretical dose that can be administered to a patient [35]- and lead to a maximum dose for all participants at a dose below the TCD such as the dose level immediately lower if it exists.

The TCD concept guided both intra- and inter-subject escalations (i.e., between cohorts of three patients starting at the same dose), where no cohort could begin at a dose equal to the TCD. Intra-subject escalation could be interrupted at the dose where a patient reached his(her) DLT or when a TCD was defined for two patients in the study, after which the TCD was applied to subsequent cohorts. TCDs determined during intra-subject escalation were promptly communicated to investigators upon inclusion, with real-time updates sent to the site and clinicians alerted by email as needed (*see supplemental Figures 1 to 4*).

Intrapatient dose escalation rules

- All patients start with a first week with a placebo for 10 minutes. This week with placebo aims to have a zero-dose measurement of light therapy; it also allowed the patient to get used to the device.
- In the absence of DLT (YMRS score < 8), active treatment at the initial dose was started.
- If the subject has DLT (YMRS score ≥ 8) within one week after treatment onset, the patient had to discontinue the treatment with planned management of the mood episode; this DLT was recorded and used for the following cohorts.
- Otherwise, an intra-subject escalation of the dose administered on the next week to the upper level (immediately above) occurred.
  - If YMRS score < 8 has been observed in the patient, escalation was proposed to the higher dose (if available) after 1 week at the same dose.
  - If YMRS score between 8 and 12, defining sub-syndromic hypomanic symptoms, the intensity of light therapy was reduced to the previous level (de-escalation to the lower dose, if it existed, and if not, this resulted in the study termination).
  - If YMRS score between 12 and 20, the light therapy was interrupted, and the study ended for the subject with planned management of the thymic episode (see below).
  - If YMRS score ≥ 21, it defined a manic episode, this led to the same result as a previously described hypomanic episode, namely the treatment discontinuation and usual psychiatric hospital care.

Intervention

The BLT was administered using Luminette® glasses, a medical device produced by Lucimed (EAN: 0702382929671). The device weighed 0.6 kg and measured 22 x 11 x 11 cm. It provided daily exposure to fluorescent light with a perceived intensity of 10,000 Lux, included a UV filter, and met CE standards. For this study, the Luminette® glasses were set at intensity 2/3, emitting blue-enriched light at 1000 Lux, equivalent to 10,000 Lux in traditional BLT [32].

A Placebo exposure was established using the same Luminette® device, adhering to CE standards, but emitting a fluorescence of 50 Lux, similar to ambient light and considered ineffective.

The modes of administration were the same for the subjects exposed in the morning and those exposed at mid-day, and was done at a fixed time and common to all centers: i) BLT in the morning: 8 am ± 30 min; ii) BLT at midday: 12 hours (noon) ± 30 min; during which patients could continue normal activities.

Patients received instructions on using the Luminette®, with adherence tracked through daily logs. This method, proven effective in recent studies, required no prior training [33]. The device's simple operation involved a push-button for on/off and a rechargeable battery.

An independent nurse, blinded to the treatment assignment and not involved in patient evaluations, administered either the active or placebo device. Patients remained blinded to their assigned condition throughout the study. Furthermore, the investigator responsible for patient evaluations was also blinded to the type of device used, as it was distributed solely by the independent nurse.

Supplementary Table 1: Centers

Center	**Total (n=34)**	**Morning (n=18)**	**Mid-day (n=16)**
Paris - Bichat - Psychiatry	20 (59 %)	10 (56 %)	10 (62 %)
Paris - Fernand Widal - Psychiatry	7 (21 %)	4 (22 %)	3 (19 %)
Lille - Fontan - Psychiatry	3 (9 %)	2 (11 %)	1 (6 %)
Montpellier - Lapeyronie - Psychiatry	2 (6 %)	1 (6 %)	1 (6 %)
Colombes - Louis Mourier - Psychiatry	1 (3 %)	1 (6 %)	0
Paris - Sainte Anne - Psychiatry	1 (3 %)	0	1 (6 %)

Supplementary Table 2: Psychotropic medications

Treatment	**Total (n=34)**	**Morning (n=18)**	**Mid-day (n=16)**
Mood stabilizer	**27 (79%)**	**14 (78%)**	**13 (81%)**
Lithium	22	11	11
Lamotrgine	7	3	4
Valpromide	3	2	1
Valproate	1	0	1
Atypical antipsychotic	**18 (53%)**	**10 (56%)**	**8 (50%)**
Aripiprazole	7	3	4
Quetiapine	7	5	2
Olanzapine	2	1	1
Risperidone	1	1	0
Amisulpride	1	0	1
Clozapine	1	1	0
Benzodiazepine/ Anxiolytic	**13 (38%)**	**6 (33%)**	**7 (44%)**
Antidepressant	**11 (32%)**	**6 (33%)**	**5 (31%)**
SSRIs (Selective Serotonin Reuptake	7	3	4
ŠNŘIs (Serotonin-Norepinephrine Reuptake Inhibitors)	4	3	1
Typical (Conventional) antipsychotic	**2 (6%)**	**1 (6%)**	**1 (6%)**
Melatonin	**1 (3%)**	**0**	**1 (6%)**

Supplementary Table 3. Estimated effects of time (week), initial allocated dose (duration), randomization (Morning vs Mid-Day) and current dose with potential heterogeneity in effect over time of both initial dose and randomization, on secondary outcomes - Statistically significant results depicted in colored-cells

Estimated β (SE) ; p-value	Week	Initial duration	Morning vs Mid-Day	Current dose	Interaction week: Initial dose	Interaction week: Morning vs Mid-Day
PSQI score	0.089 (0.114) p=0.43	0.069 (0.037) p=0.068	-1.550 (1.007) p=0.13	-0.021 (0.015) p=0.17	-0.006 (0.003) p=0.080	-0.020 (0.081) p=0.81
CSM score	-0.276 (0.205) p=0.18	-0.010 (0.110) p=0.93	0.061 (3.152) p=0.98	-0.008 (0.027) p=0.77	0.012 (0.006) p=0.056	-0.021 (0.145) p=0.88
CTI (FR)	-0.121 (0.129) p=0.35	0.020 (0.052) p=0.71	3.329 (1.475) **p=0.031**	-0.027 (0.017) p=0.11	0.008 (0.004) **p=0.042**	0.069 (0.090) p=0.44
CTI (LV)	0.218 (0.173) p=0.209	0.018 (0.075) p=0.81	-1.029 (2.133) p=0.63	-0.010 (0.023) p=0.65	-0.007 (0.005) p=0.22	0.085 (0.120) p=0.48
ESS score	-0.073 (0.177) p=0.68	0.022 (0.063) p=0.73	-1.097 (1.751) p=0.53	0.033 (0.023) p=0.14	-0.001 (0.005) p=0.84	0.043 (0.119) p=0.72

Supplementary Figure 1: Study flowchart of the LuBi study