

Bright Light Treatment in Elderly Patients With Nonseasonal Major Depressive Disorder

A Randomized Placebo-Controlled Trial

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Context: Major depressive disorder (MDD) in elderly individuals is prevalent and debilitating. It is accompanied by circadian rhythm disturbances associated with impaired functioning of the suprachiasmatic nucleus, the biological clock of the brain. Circadian rhythm disturbances are common in the elderly. Suprachiasmatic nucleus stimulation using bright light treatment (BLT) may, therefore, improve mood, sleep, and hormonal rhythms in elderly patients with MDD.

Objective: To determine the efficacy of BLT in elderly patients with MDD.

Design: Double-blind, placebo-controlled randomized clinical trial.

Setting: Home-based treatment in patients recruited from outpatient clinics and from case-finding using general practitioners' offices in the Amsterdam region.

Participants: Eighty-nine outpatients 60 years or older who had MDD underwent assessment at baseline (T0), after 3 weeks of treatment (T1), and 3 weeks after the end of treatment (T2).

Intervention: Three weeks of 1-hour early-morning BLT (pale blue, approximately 7500 lux) vs placebo (dim red light, approximately 50 lux).

Main Outcome Measures: Mean improvement in Hamilton Scale for Depression scores at T1 and T2 using parameters of sleep and cortisol and melatonin levels.

Results: Intention-to-treat analysis showed Hamilton Scale for Depression scores to improve with BLT more than placebo from T0 to T1 (7%; 95% confidence interval, 4%-23%; $P=.03$) and from T0 to T2 (21%; 7%-31%; $P=.001$). At T1 relative to T0, get-up time after final awakening in the BLT group advanced by 7% ($P<.001$), sleep efficiency increased by 2% ($P=.01$), and the steepness of the rise in evening melatonin levels increased by 81% ($P=.03$) compared with the placebo group. At T2 relative to T0, get-up time was still advanced by 3% ($P=.001$) and the 24-hour urinary free cortisol level was 37% lower ($P=.003$) compared with the placebo group. The evening salivary cortisol level had decreased by 34% in the BLT group compared with an increase of 7% in the placebo group ($P=.02$).

Conclusions: In elderly patients with MDD, BLT improved mood, enhanced sleep efficiency, and increased the upslope melatonin level gradient. In addition, BLT produced continuing improvement in mood and an attenuation of cortisol hyperexcretion after discontinuation of treatment.

Trial Registration: clinicaltrials.gov Identifier NCT00332670

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MAJOR DEPRESSIVE DISORDER (MDD) is frequently accompanied by symptoms suggestive of circadian dysfunction,¹ such as abnormal sleep-wake patterns,² altered social rhythms,³ and diurnal mood swings.⁴ These symptoms have, therefore, been related to impaired functioning of the suprachiasmatic nucleus (SCN), the circadian pacemaker of the brain.⁵⁻⁸ Activation of the SCN has been hypothesized as one of the mechanisms of bright environmental light (bright light treatment [BLT]) on mood,^{9,10} sleep,^{11,12} circadian rhythms,¹¹ and hypothalamic-pituitary axis (HPA) ac-

tivity.^{13,14} Light induces specialized light-sensitive retinal ganglion cells to release glutamate in the SCN through a monosynaptic pathway called the retinohypothalamic tract.¹⁵⁻¹⁷ Bright light treatment also targets depression-associated neurotransmitter systems (serotonin, noradrenalin, and dopamine) and targets the same brain structures as antidepressant drug treatments.^{18,19} In primates, subcortical projections of retinal neurons not only involve the SCN but also the serotonergic raphe nucleus.^{20,21} Elderly people expose themselves less frequently to bright environmental light.^{22,23} Moreover, with aging, photoreception declines.²⁴ Concertedly, these age-related changes may re-

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Table 1. Demographic Characteristics of the 89 Randomized Study Patients by Treatment Assignment

Characteristic	Placebo Group (n=47)	BLT Group (n=42)	P Value ^a
Age, mean (SD), y	69.00 (6.6)	69.67 (8.5)	.69
Sex, No. F/M (% female)	30/17 (64)	28/14 (67)	.52
Lives with partner, No. (%)	18 (38)	16 (38)	.52
Body height, mean (SD), m	1.69 (0.08)	1.68 (0.07)	.55
Body weight, mean (SD), kg	76.37 (14.2)	73.88 (15.1)	.45
BMI, mean (SD)	26.79 (4.6)	26.15 (4.6)	.54
MMSE score, mean (SD)	28.47 (1.8)	27.60 (2.0)	.04
CIRS comorbidity scores, mean (SD)			
Total pathology	5.33 (2.8)	4.82 (2.9)	.55
Illness severity composite	0.30 (0.2)	0.24 (0.2)	.33
Comorbidity composite	0.96 (1.1)	0.83 (1.0)	.59
SCID-IV/DSM-IV comorbid diagnoses (DSM-IV code)			
Panic disorder with agoraphobia (300.21)			
Severe	1	0	>.99
Moderate	0	1	>.99
Light	2	1	>.99
Hypochondria (300.7)	0	1	>.99
Social phobia (300.23)	0	1	>.99
Alcohol abuse (305.00)			
Sustained full remission	2	3	>.99
Early partial remission	0	1	>.99
Cannabis abuse (305.20)	0	1	>.99

Abbreviations: BLT, bright light treatment; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CIRS, Cumulative Illness Rating Scale⁶⁵; MMSE, Mini-Mental State Examination; SCID-IV, Structured Clinical Interview for DSM-IV Axis I Disorders.^{44,56}

^aCalculated as comparisons of BLT and placebo, using 2-tailed *t* tests (continuous variables) or χ^2 tests (discrete variables). Statistically significant test values are in bold type.

sult in insufficient stimulation of the SCN,^{22,23} thought to be involved in the attenuated neuronal activity in the SCN at advanced age.²⁵ Bright light treatment could therefore be hypothesized to be particularly suitable in the management of MDD in elderly patients, which is important because of the less favorable adverse-effect profile of antidepressants in this population.

The beneficial effect of BLT in seasonal affective disorder is well accepted,²⁶ with early onset of action²⁷ and mild adverse-effect profiles.²⁸ Results of controlled BLT trials in nonseasonal MDD are promising but inconclusive, especially with respect to efficacy in elderly patients with MDD.^{26,29-35} Reviews emphasize the need for further study because of the great diversity of study designs and the relatively small sample sizes.^{30,36} We showed that bright light attenuated the development of depressive symptoms in elderly residents of group care facilities.¹¹ To our knowledge, double-blind, placebo-controlled, randomized clinical trials of sufficient sample size to evaluate the efficacy of BLT in elderly patients diagnosed as having MDD have not been performed, although some studies suggested BLT might have favorable effects.^{34,35,37,38}

Our hypotheses were 2-fold. First, we expected BLT to lower depressive symptoms. Second, we expected this to be mediated by improved circadian functioning, as indirectly indicated by enhanced sleep and hormone rhythms.

Therefore, we conducted a double-blind, placebo-controlled, randomized clinical trial that included assessment of SCN function from cortisol profiles, rise in evening melatonin levels, and actigraphic sleep estimates.

METHODS

The present study was executed in accordance with the Helsinki Declaration.³⁹ Approvals were obtained from the Dutch authorities and the medical ethical committee (METIGG [Medisch-ethische Toetsingscommissie Instellingen Geestelijke Gezondheidszorg], Utrecht). In particular, the medical ethical committee consented to the blinding procedure and the way information was provided to the patients.

PARTICIPANTS

Based on the literature, a moderate response was expected.⁴⁰⁻⁴² With the use of conventional values for α (.05) and β (.80) for 2-tailed tests with equal groups, the sample size was determined to be 63 patients per arm,⁴³ resulting in a total number of 126 patients. Inclusion started on January 22, 2003, and lasted until August 22, 2007 (4.5 years). By then, 89 patients were included (for depression characteristics, see eTable 1 <http://www.genpsychiatry.com>). Taking into account the conservative power analysis and the limiting resources and perspectives for subsequent inclusion rates, it was decided not to include more patients.

We recruited study participants from outpatient clinics, advertisements, and referrals by general practitioners. Candidates were 60 years or older and first selected using the 15-item version of the Geriatric Depression Scale. Individuals with Geriatric Depression Scale scores of 5 or more were screened by interview (n=444) to establish whether they met the eligibility criteria. Exclusions were categorized as psychiatric (n=154), neurological (n=22), ophthalmological (n=17), research incompatibility (n=101), and miscellaneous (n=9)^{44,54,55} (**Table 1**). In addition, 52 individuals refused to participate.

DIAGNOSIS AND QUANTIFICATION OF SEVERITY

Depression was diagnosed using the Structured Clinical Interview for DSM-IV Axis I Disorders.⁵⁶ Severity was rated with the Structured Interview Guide for the Hamilton Scale for Depression (HAM-D)—Seasonal Affective Disorder Version,^{48,49} a structured interview yielding total score, the original HAM-D score,⁴⁷ the 8-item Atypical Symptom Scale score, and the HAM-D6, the 6-item core version score.^{50,57} Furthermore, the Montgomery-Åsberg Depression Rating Scale⁴⁶ was used to allow comparison of our results with other randomized controlled trials in depression in elderly patients. Interviews were performed by a trained physician (R.L.) and qualified research psychologists (including M.M.A.N.), all blind to assignments (**Table 2**).

STUDY DESIGN

We used a randomized, double-blind, placebo-controlled design to compare the antidepressive effects of BLT and placebo.

Permuted block randomization in subsets of 10 was performed, with separate randomizations for the strata of patients who used and did not use antidepressants. The 2 randomization lists, prepared by an independent researcher (B.M.J.U.) not involved in the recruitment and using a computer-generated table, were transferred to a sequence of sealed opaque envelopes.

Study patients were informed that the primary goal of the study was to investigate spectrum-dependent efficacy differ-

ences between blue and red. Investigators were blinded to the condition because the lamps were delivered at the patients' homes by protocol-blinded instructors, who were also informed that the study aimed for spectrum-dependent efficacy differences. Patients were asked not to discuss any details of their condition with the interviewers. In 2 cases, patients did reveal their assignment, after which the interviewer was replaced. Before the light box was installed, patients completed a 4-item expectations questionnaire (eTable 2).

STUDY INTERVENTION

Patients were randomly assigned to receive bright pale blue or dim red light treatment therapy at home using 2 light boxes (Philips Bright Light Energy HF 3304; Koninklijke Philips Electronics NV, Eindhoven, the Netherlands). Concealed within the light boxes, a single-layer filter was wrapped around the fluorescent tubes: a mist-blue filter (Model 061; Lee Filters, Andover, England) with high-throughput pale blue (7500 lux) for the active condition and a blood-red filter (Model 789; Lee Filters) with low-throughput red (50 lux) for the placebo condition (eFigure 1). Dim red light can be considered to be biologically inactive⁵⁸ (supplementary Appendix A).

Given the proposed interaction between exposure intensity and duration for the efficacy of BLT,⁹ we chose an exposure of 60 minutes in the early morning at about 7500 lux. For BLT of nonseasonal depression in elderly patients, there is no consensus with respect to optimal timing, dosage, and treatment duration. We chose 3 weeks of daily light exposure (**Figure 1**) because most studies thus far used short-term treatment of up to 1 week^{37,41,42,59-69} and because the Cochrane review of studies of BLT in nonseasonal affective disorder concluded that BLT may be effective in as little as 1 week.³¹

OUTCOME MEASURES

Assessments were performed at the following 3 time points (Figure 1): just before the start of light treatment (baseline [T0]), immediately on completion of the 3-week treatment interval (T1), and 3 weeks after the end of the treatment (T2).

The primary outcome was determined to be the change in HAM-D score at T1 relative to T0. Secondary efficacy outcome measures were (1) change in HAM-D score at T2 relative to T0 to investigate whether immediate responses would last after treatment discontinuation and (2) the dichotomized treatment response for T1 relative to T0 and T2 relative to T0 (with responders vs nonresponders defined according to whether the HAM-D score decreased by at least 50%).

Endocrine Outcome Measures

Urinary Cortisol Levels. Urinary free cortisol (UFC) levels during a 24-hour period provide a noninvasive valid estimation of overall daily cortisol production.⁷⁰ Collections were performed at home at T0, T1, and T2. Urine was collected in 3-L polyethylene bottles starting after the first voided urine after awakening and included the first voided urine on the following day. The UFC level was determined by radioimmunoassay using a commercially available antibody kit (Coat-A-Count; Diagnostic Product Corporation, Siemens, Los Angeles, California). Analysis procedures and limits of detection reported for assays performed at the VU University Medical Center Laboratory are published by the manufacturer and available on request. Completeness of collection was ascertained by interviews documenting urine losses. Only complete collections, with creatinine within the normal range of 0.06 to 1.20 mg/dL per 24 hours (to convert to micromoles per liter, multiply by 88.4) were included in analysis.⁷¹ Repeated-measures analysis of vari-

ance (ANOVA) was applied to completers (20 patients in the BLT group and 20 in the placebo group) with the T0 cortisol level as the covariate. To evaluate whether MDD was associated with HPA alterations, age- and sex-matched nondepressed control patients were recruited from general practitioners' offices. We excluded controls with Geriatric Depression Scale⁴⁵ scores larger than 0, a lifetime history of psychiatric disorders, any somatic condition that could interfere with HPA functioning, or any required medications other than sporadic use of aspirin. Valid urine samples were obtained from 8 men and 14 women with a mean (SD) age of 68.9 (6.4) years.

Saliva Cortisol Levels. At T0, T1, and T2, we collected saliva samples using cotton dental rolls (Salivette; Sartstedt Ltd, Numbrecht, Germany), including 4 sequential single samples at 30-minute intervals starting 30 minutes after final awakening and 4 sequential samples at hourly intervals starting 4 hours before the predicted bedtime (supplementary text; available at <http://www.ggzingeest.nl/saliva-sampling>). The samples were collected the following day to be delivered to the laboratory, where they were centrifuged and stored at -85°C. All samples were analyzed in a single batch using a cortisol assay on an immunoanalyzer system (Roche Cobas assay on an Elecsys system; Roche Diagnostics, Mannheim, Germany). The detection limit was 0.07 µg/dL (to convert to nanomoles per liter, multiply by 27.588), and the intra-assay and interassay variability coefficients were less than 10%. For determination of the diurnal time course of saliva cortisol levels, only days with at least 7 of 8 valid samples were included in analyses. A skewed cosine function⁷² was fitted to each day using SPSS statistical software, version 16.0.2 (SPSS, Inc, Chicago, Illinois), providing the most parsimonious rhythmic diurnal curve description that allows for skewness, an undisputed property of the cortisol curve. Areas under the curves for the morning and evening (ie, 9 AM to 1 PM and 5 to 9 PM) were calculated for subsequent analyses.

Saliva Melatonin Levels. At T0, T1, and T2, 4 sequential saliva samples were collected using the cotton dental rolls (Salivette) at hourly intervals starting from 4 hours before predicted bedtime under dim light conditions (supplementary text and Appendix B). The samples were collected the following day to be delivered to the laboratory to be centrifuged and stored at -85°C. Concentrations were determined using an assay with a limit of sensitivity of 0.2 ng/L (to convert to picomoles per liter, multiply by 4.305) (Bühlmann Laboratories AG, Schönenbuch, Switzerland) and intra-assay and interassay coefficients of 2.6% and 20.1%. For determination of a rise in melatonin levels, only days with at least 3 of 4 valid samples were included in the analyses.

Because melatonin levels were so low that commonly applied methods were not applicable, we could obtain a measure of the steepness of the evening rise only, which may have biological relevance and which has been proposed before as a parameter of use.⁷² Therefore, we used a mixed-effect linear regression model to estimate treatment effects on the slope (steepness of melatonin level rise) and intercept (timing of the melatonin level rise) of the evening rise (supplementary Appendix B).

Actigraphic Estimates of Sleep and Light Exposure

Actigraphy, the continuous assessment of activity with a watch-sized nondominant wrist-worn recorder (Actiwatch-L; Cambridge Neurotechnology, Cambridge, England), is a validated technique to obtain estimates of sleep.^{11,73,74} Patients wore actigraphs throughout their participation and were instructed not to remove them when taking a bath or shower. Patients kept a diary of bedtimes and get-up times after final awakening. The sleep analysis software (Sleepwatch; Cambridge Neurotech-

nology) was used to obtain estimates of sleep parameters, including total sleep time, sleep efficiency (ie, the percentage of actual sleep between sleep onset and final awakening), and sleep onset latency (ie, the time between lights out and sleep onset).

A light sensor integrated in the actigraphs was used to evaluate whether treatment adherence was supported by increased intensity recording during the time intervals of BLT and to evaluate compliance with dim-light requirements during saliva sampling for characterization of the evening rise in melatonin levels (supplementary Appendix A).

Adverse Events

At baseline and at the end of every week during treatment, patients were systematically interviewed about 28 possible adverse effects by blinded raters. Each item was rated on a 4-point scale (0 indicates absent; 1, mild; 2, moderate; and 3, severe).

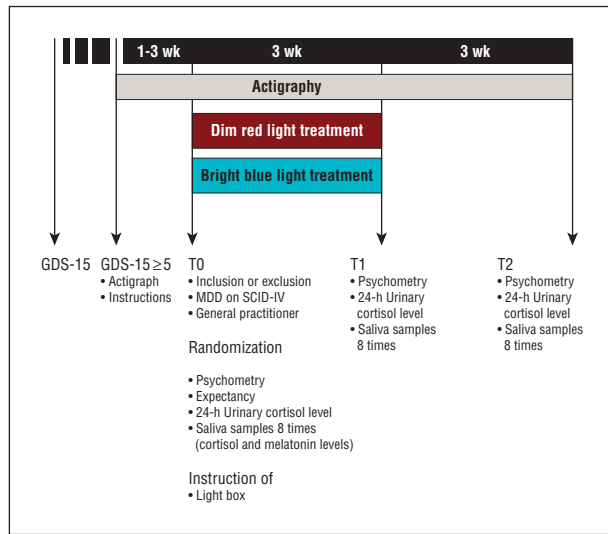


Figure 1. Diagram of the study protocol. Assessments of psychometry and hypothalamic-pituitary axis function and parameters of sleep and circadian rhythmicity were conducted before the start of 3 weeks of light treatment (T0), after 3 weeks of treatment (T1), and 3 weeks after discontinuation of treatment (T2). Wrist actigraphy was continuously measured. GDS-15 indicates 15-item version of the Geriatric Depression Scale; MDD, major depressive disorder; and SCID-IV, Structured Clinical Interview for *DSM-IV* Axis I Disorders.

An adverse event was recorded only if it increased relative to baseline and the previous rating. Group differences in frequencies were compared using χ^2 statistics.

STATISTICAL ANALYSES

Baseline characteristics were compared using 2-sided *t* tests for continuous data and χ^2 statistics and 2-tailed Fisher exact tests for categorical data with the use of SPSS 16.0.2 software (Table 1 and eTable 1).

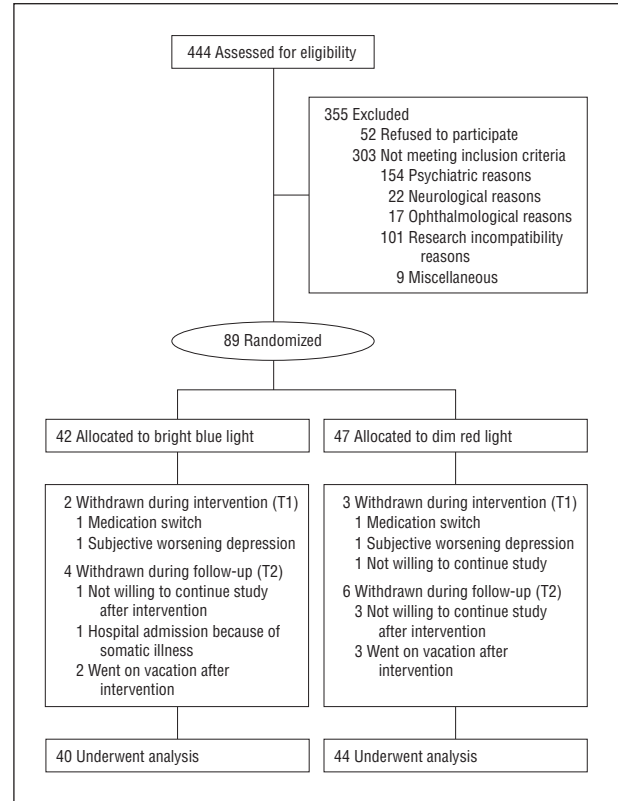


Figure 2. Flow of study patients. Every randomized patient started treatment. Five patients discontinued the intervention and refused follow-up. Analyses fulfill intention-to-treat characteristics because none of the patients assigned to a condition switched to another condition and because analyses involved all available observations of all patients.

Table 2. Outcomes in Depression Ratings^a

Outcome	Placebo Group, Mean (SD)			BLT Group, Mean (SD)			Change From T0 to T1 ^b			Change From T0 to T2 ^b		
	T0	T1	T2	T0	T1	T2	Mean (95% CI) ^b	Test Statistic (P Value) ^c	Cohen d ^d	Mean (95% CI) ^b	Test Statistic (P Value) ^c	Cohen d ^d
HAM-D ^e (n=84)	16.2 (4.6)	10.4 (6.3)	10.8 (6.5)	18.6 (5.7)	10.1 (6.1)	8.6 (6.5)	2.6 (0.3-4.9)	$F_{1,81}=3.94 (.03)^f$	0.50	4.5 (2.4-6.6)	$F_{1,81}=11.39 (.001)^f$	0.93
BCF ^g (n=89)	16.0 (4.7)	10.6 (6.3)	10.9 (6.4)	18.4 (5.6)	10.4 (6.1)	8.9 (6.5)	2.6 (0.3-4.8)	$F_{1,86}=3.18 (.04)^f$	0.48	4.4 (2.3-6.5)	$F_{1,86}=8.846 (.004)^f$	0.80
CA ^g (n=74)	15.7 (4.3)	9.9 (6.1)	10.3 (6.3)	18.5 (5.6)	9.9 (6.1)	8.2 (6.5)	2.7 (0.2-5.2)	$F_{1,71}=3.14 (.04)^f$	0.50	4.9 (2.6-7.1)	$F_{1,71}=11.39 (<.001)^f$	1.01

Abbreviations: BCF, baseline carried forward analysis; BLT, bright light treatment; CA, completers analysis; CI, confidence interval; HAM-D, Hamilton Scale for Depression⁴⁷; T0, baseline; T1, after 3 weeks of treatment; T2, 3 weeks after discontinuation of treatment.

^aOutcome descriptions are given in the "Outcome Measures" subsection of the "Methods" section.

^bIndicates differences between BLT and placebo in the change from T0 to each patient's own end point for the change in depression rating.

^cCalculated as part of the repeated-measures analysis of covariance (ANCOVA), using T0 depression rating and Mini-Mental State Examination scores as covariates. Statistically significant test values are depicted in bold type.

^dComputed as the difference between the means, $M_1 - M_2$, divided by the pooled standard deviation, sigma (σ_{pooled}) of both groups.

^eThe intention-to-treat analysis used the last observation carried forward.

^fWith repeated-measures ANCOVA, using the T0 rating as a covariate was significant.

^gPerformed as a sensitivity analysis.

Treatment effect analyses fulfilled intention-to-treat criteria because none of the patients assigned to one condition switched to another, and analyses involved all observations of all patients until study end or withdrawal. The primary efficacy outcome analysis consisted of repeated-measures ANOVA with baseline HAM-D scores as covariates. Ancillary analyses consisted of analysis of covariance (ANCOVA) on HAM-D scores from T0 to T2 scores. To analyze the interaction effect of antidepressants, it was added to the repeated-measures model. Subgroup analyses of the possible effects of antidepressants, age, sex, melancholy, atypical features, seasonality, recurrent course, treatment resistance, late onset, and duration of depression were preplanned.

Numbers needed for treatment were computed according to the methods of Sacket et al,⁷⁵ with 95% confidence intervals (CIs) computed using the method of Altman.⁷⁶

For dropouts after the T1 assessment, the principle of last observation carried forward was used for depression scales. As secondary sensitivity analyses, we performed a baseline (T0) carried forward analysis and a T2-completers analysis (**Figure 2**).

We used mixed-effect regression analysis (MLwiN software; Institute of Education, London, England) to evaluate treatment effects on saliva cortisol and melatonin levels and diary and actigraphic sleep estimates to account for the variable number of valid days within patients, without having to discard patients because of partially missing data.

Based on the literature finding that dim red light treatment never had a more favorable outcome than BLT on depression ratings,³¹ we justified 1-sided testing on the primary outcome of depression ratings at T1. All other significance levels for effects (ie, at T2) were set at $P < .05$ with 2-sided testing. Means and 95% CIs are provided. Secondary analyses were not adjusted for multiple comparisons and should therefore be regarded as descriptive and exploratory. Where not otherwise indicated, data are expressed as mean (SD).

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

We included and randomized 89 patients, with 42 allocated to the BLT condition and 47 to the placebo condition (Figure 2). There were no hospitalizations or suicides or other deaths.

Randomization was balanced with respect to demographic and comorbidity characteristics and psychiatric comorbid diagnoses (Table 1). Groups were not balanced with regard to Mini-Mental State Examination score (mean placebo group score, 28.5 [1.8]; mean BLT group score, 27.6 [2.0]; $P = .04$) or the pretreatment HAM-D score (mean placebo group score, 16.0 [4.7]; mean BLT group score, 18.4 [5.6]; $P = .03$). Baseline values were therefore used as covariates in all effect analyses. The number of patients who received psychotherapy in the past was smaller in the placebo group than in the BLT group (21 [45%] vs 31 [74%]; $\chi^2 = 7.0$; $P = .007$). Three patients in the placebo group discontinued before T1 and 6 after T1. Two patients in the BLT group discontinued before T1 and 4 after T1 (Figure 2).

EXPECTANCY

None of the 4 expectancy scores differed significantly between the treatment groups (all $P > .05$, ANOVA) or between responders and nonresponders in the BLT or pla-

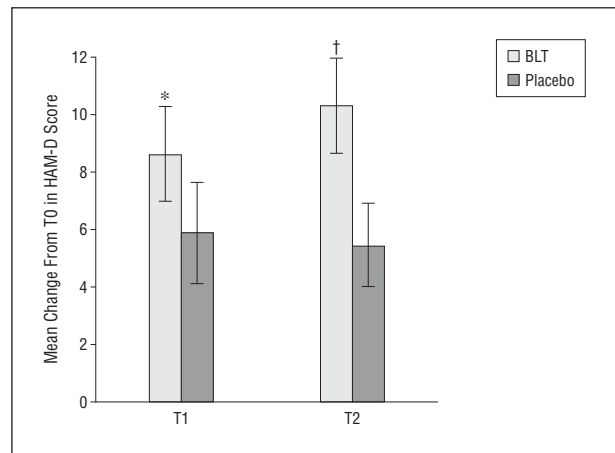


Figure 3. Changes in the Hamilton Scale for Depression (HAM-D) from baseline (T0) in groups receiving bright light treatment (BLT) and placebo for nonseasonal major depressive disorder in elderly individuals. Bars indicate standard deviations. T1 indicates after 3 weeks of treatment; T2, 3 weeks after discontinuation of treatment. * $P < .05$. † $P = .001$.

cebo groups (all $P > .05$, ANOVA). Responders in the BLT group had more pessimistic expectations concerning improvement without treatment than did placebo responders (BLT group, 4.55 [1.14]; placebo group, 3.56 [1.01]; $F_{1,29} = 5.08$; $P = .03$). Mean expectations in nonresponders in the BLT and placebo groups did not differ (all $P > .05$, ANOVA). Expectations did not predict treatment response ($r = 0.03$; $P = .81$) (eTable 2).

TREATMENT ADHERENCE

Adherence to treatment was supported by the fact that only BLT-assigned patients showed elevated light exposure exclusively during the treatment intervals (supplementary Appendix A).

TREATMENT EFFECT ON DEPRESSION RATINGS

The intention-to-treat analysis showed significantly more T0 to T1 improvement in HAM-D scores in patients in the BLT group (43%; 8.5 [95% CI, 6.8-10.3] points) than in the placebo group (36%; 5.8 [4.0-7.6] points), the difference being 7% (4%-23%; $F_{1,81} = 3.94$; 1-sided $P = .03$, with HAM-D and Mini-Mental State Examination scores at T0 as covariates). Ancillary analyses of treatment effects after discontinuation at T2 likewise showed significantly more T0 to T2 improvement in HAM-D scores in the BLT group (54%; 10.0 [95% CI, 8.6-12.0] points) than in the placebo group (33%; 5.4 [3.9-6.9] points), the difference being 21% (7%-31%; repeated-measures ANCOVA, $F_{1,81} = 11.39$; $P = .001$, with HAM-D and Mini-Mental State Examination scores at T0 as covariates) (Table 2 and **Figure 3**).

At T1, 20 patients in the BLT group (50%) were responders vs 18 (41%) in the placebo group ($\chi^2 = 0.70$; $P = .20$) (eTable 3 and **Figure 4**). The difference became significant at T2, with 23 responders in the BLT group (58%) vs 15 in the placebo group (34%) ($\chi^2 = 3.76$; $P = .05$). The number needed to treat for HAM-D score improvement at T2 was 5 (95% CI, 1-151) (eTable 3).

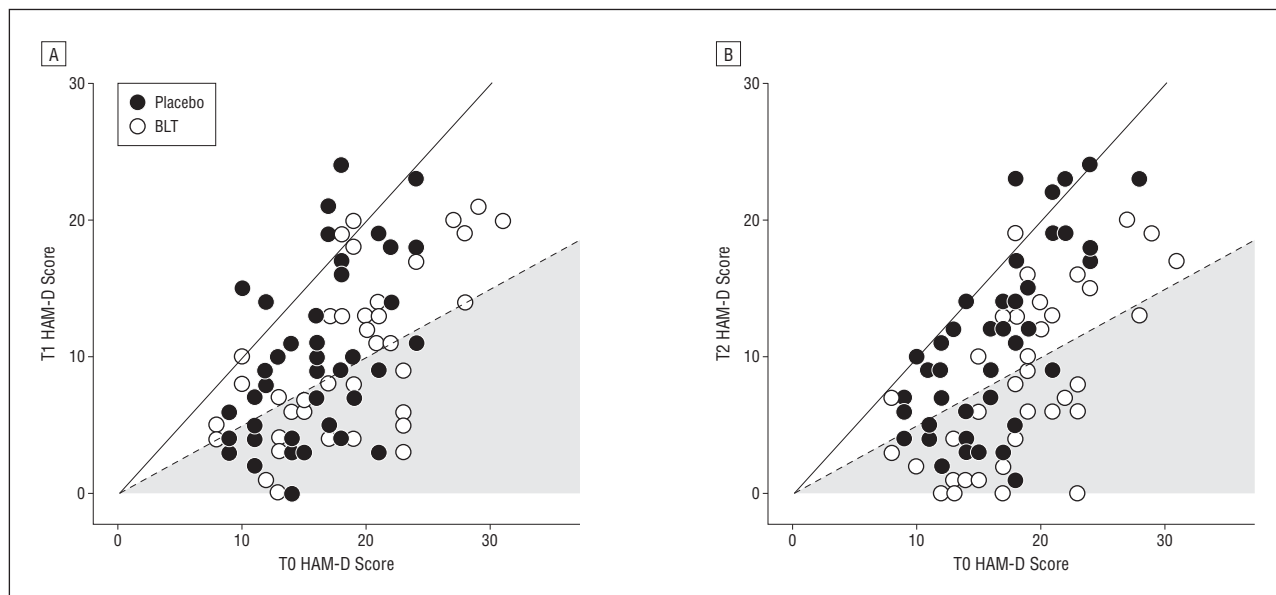


Figure 4. Scatterplots of individual patients' Hamilton Scale for Depression (HAM-D) scores at baseline (T0), after 3 weeks of treatment (T1) (A), and 3 weeks after discontinuation of treatment (T2) (B). Treatment consisted of bright light treatment (BLT) or placebo. Points that fall below the solid diagonal represent patients who improved. Points that fall below the dashed diagonal in the gray shaded area represent patients whose scores were reduced by 50% or more relative to baseline.

As sensitivity analyses, the baseline carried forward and completers analyses showed results comparable to those of the intention-to-treat analysis (Table 2 and eTable 3). Analyses on other depression ratings produced similar results, with some significant and others as trends only (Table 3, eTable 4, and Figure 5).

EFFECT MODIFICATION BY ANTIDEPRESSANT USE AND DEPRESSION SUBTYPE

Fourteen patients in the BLT group (33%) and 18 in the placebo group (38%) used antidepressants. Analyses revealed no effect of antidepressants on the HAM-D scores ($F_{1,71}=1.46$; $P=.24$) or interaction of antidepressants with treatment effect at T2 ($F_{1,71}=0.001$; $P=.98$). Likewise, there was no significant effect on HAM-D score or the interaction of treatment by patient characteristics, including age ($F_{1,71}=0.41$; $P=.67$), sex ($F_{1,71}=0.50$; $P=.61$), melancholy ($F_{2,138}=0.23$; $P=.79$), atypical features ($F_{2,138}=0.59$; $P=.55$), seasonality (Global Seasonality Score; $F_{1,71}=0.85$; $P=.43$), recurrent course ($F_{1,71}=1.13$; $P=.33$), treatment resistance ($F_{2,138}=1.68$; $P=.18$), late onset ($F_{2,138}=1.25$; $P=.29$), or short duration ($F_{2,138}=0.02$; $P=.10$) at T2.

24-HOUR URINARY CORTISOL EXCRETION

Nine patients (10%) refused to collect urine, and 3 others had incontinence. Seventy-two urine collections at T0 and 40 at both T1 and T2 (20 in each group) were considered valid. Mean T0 24-hour UFC excretion was 5.65 (3.73) μg , which was significantly higher than the mean 24-hour UFC excretion of controls (4.31 [2.07] μg ; $P=.01$) (supplementary Appendix C).

From T0 to T1, 24-hour UFC excretion decreased by 7.3% (-0.36 [95% CI, -1.76 to 1.04] μg) in the BLT group and increased by 32.3% (1.49 [0.36-2.61] μg) in the placebo group, a difference that did not yet reach signifi-

cance (ANCOVA, $F_{1,38}=3.663$; $P=.06$). Significance was reached by T2 when the 24-hour UFC level had decreased by 17% (-0.98 [95% CI, -1.73 to 0.24] μg) in the BLT group and had increased by 20% (0.98 [0.16-1.81] μg) in the placebo group, resulting in a difference of 37% (ANCOVA, $F_{2,37}=6.78$; $P=.003$) (Figure 6). At T2, 24-hour UFC excretion of patients undergoing BLT no longer differed from that of the healthy controls ($P=.47$). Thus, in contrast to the placebo group, the mean 24-hour UFC excretion in the BLT group was significantly lowered (supplementary Appendix C and eFigure 3). To investigate whether the increased 24-hour UFC excretion in placebo-treated patients could be explained by nonresponse, placebo nonresponders were compared with placebo responders, which showed that nonresponders had higher 24-hour UFC excretion than responders (5.53 [3.34] vs 3.94 [1.29] $\mu\text{g/dL}$) but without reaching statistical significance ($P=.07$).

SALIVA CORTISOL LEVELS

Seven patients (8%) refused saliva sampling. In sum, 1537 samples from 177 series were used from 5:30 AM until 3:15 AM. The skewed cosine model showed a goodness of fit of $R^2=0.79$ (SD, 0.10). During the course from T0 to T2, the area under the curve during the evening (5-9 PM) showed a stronger decrease with BLT than with placebo, reaching significance for the contrast between T2 and T0 (BLT, 34% decrease from T0 at 0.10 [95% CI, 0.07-0.12] $\mu\text{g/dL}$ per minute to T2 at 0.05 [0.04-0.09] $\mu\text{g/dL}$ per minute; placebo, 7% increase from T0 at 0.08 [0.05-0.11] $\mu\text{g/dL}$ per minute to T2 at 0.10 [0.04-0.15] $\mu\text{g/dL}$ per minute; $P=.02$). The morning area under the curve showed a similar decrease that was stronger during and after BLT than placebo, although the difference did not reach significance (eFigure 4). The findings indicate that BLT accelerated the diurnal decline in saliva cortisol level.

Table 3. Outcomes in Supplementary Depression Ratings^a

Outcome	Placebo Group, Mean (SD)			BLT Group, Mean (SD)			Change From T0 to T1 ^b			Change From T0 to T2 ^b		
	T0	T1	T2	T0	T1	T2	Mean (95% CI) ^b	Test Statistic (P Value ^c)	Cohen d ^d	Mean (95% CI) ^b	Test Statistic (P Value ^c)	Cohen d ^d
HAM-D6 (n=84)	8.9 (2.4)	5.6 (3.2)	5.4 (3.8)	9.3 (3.0)	4.6 (3.3)	4.0 (3.0)	1.3 (-0.1 to 2.7)	F_{1,81}=5.14 (.01)^e	0.41	1.8 (0.4 to 3.1)	F_{1,81}=8.78 (.004)^e	0.58
ATYP-8 (n=84)	6.4 (4.3)	4.2 (3.8)	4.4 (3.2)	7.5 (4.7)	3.8 (2.9)	3.2 (3.9)	1.45 (-0.4 to 3.4)	F _{1,81} =2.25 (.07)	0.33	2.1 (0.2 to 4.1)	F_{1,81}=7.02 (.01)^e	0.52
SIGH-SAD (n=84)	24.4 (8.4)	16.1 (9.2)	16.3 (10.2)	28.1 (9.0)	15.3 (8.9)	12.7 (9.3)	4.5 (0.9 to 8.1)	F_{1,81}=4.84 (.02)^e	0.55	7.7 (4.1 to 11.2)	F_{1,81}=13.13 (<.001)^e	0.95
MADRS (n=84)	25.2 (6.8)	16.9 (9.8)	16.1 (9.2)	24.7 (6.5)	14.4 (0.6)	12.7 (10.6)	2.1 (-1.4 to 5.5)	F_{1,81}=3.04 (.04)^e	0.26	3.3 (-0.5 to 6.9)	F_{1,81}=4.32 (.04)^e	0.41

Abbreviations: ATYP-8, Atypical Symptom Scale; BLT, bright light treatment; CI, confidence interval; HAM-D6, Hamilton Scale for Depression 6-item core version (consisting of depressed mood, self-depreciation and guilt feelings, work and interests, psychomotor retardation, psychic anxiety, and general somatic)⁵⁰; MADRS, Montgomery-Åsberg Depression Rating Scale⁴⁶; SIGH-SAD, Structured Interview Guide for the Hamilton Scale for Depression-Seasonal Affective Disorder Version^{48,49}; T0, baseline; T1, after 3 weeks of treatment; T2, 3 weeks after discontinuation of treatment.

^aOutcome descriptions are given in the "Outcome Measures" subsection of the "Methods" section.

^bIndicates differences between BLT and placebo in the change from T0 to each patient's own end point for the change in depression rating.

^cCalculated as part of the repeated-measures analysis of covariance (ANCOVA), using T0 depression rating and Mini-Mental State Examination scores as covariates. Statistically significant test values are depicted in bold type.

^dComputed as the difference between the means, $M_1 - M_2$, divided by the pooled standard deviation, sigma (σ_{pooled}) of both groups.

^eWith repeated-measures ANCOVA, using the T0 rating as a covariate was significant.

SALIVA MELATONIN LEVEL

Seven hundred fifty-six samples were considered valid. At T1 relative to T0, the steepness of the melatonin rise increased by 109% in the bright blue light condition (from 0.48 [95% CI, 0.27-0.69] to 1.00 [0.50-1.49] ng/L/h), whereas it decreased by 11% in the dim red light condition (from 0.32 [CI, 0.17-0.47] to 0.28 [0.09-0.47] ng/L/h). This differential change, being 81%, was significant ($P=.03$). A similar differential change between T0 and T2 did not reach significance. No significant changes in regression intercept (ie, onset phase) were found (supplementary Appendix B). The findings indicate that BLT enhanced the evening rise in saliva melatonin level.

SLEEP

At baseline, there were no statistically significant group differences with respect to self-reported habitual bedtime (mean, 11:21 PM [1 hour 12 minutes]) or get-up time after final awakening (mean, 8:19 AM [58 minutes]). No significant group changes over time or treatment effects were found for habitual bedtime. Between T0 and T1, get-up time advanced in the BLT group from 8:07 (95% CI, 7:47-8:26) AM to 7:34 (7:19-7:50) AM, which was a significantly stronger advance (7%, $P<.001$) than occurred in the placebo group (from 8:32 [8:11-8:54] AM to 8:04 [7:47-8:22] AM). At T2 relative to T0, get-up times after final awakening in the BLT group (T2, 7:49 [95% CI, 7:25-8:12] AM) were still significantly (3%, $P=.001$) more advanced than in the placebo group (T2, 8:30 [8:07-8:54] AM). No significant group changes over time or treatment effects were found for time in bed.

Valid actigraphy recordings were available on average for 217 (113) hours before T0 as baseline assessment, for 414 (108) hours from T0 to T1, and for 287 (215) hours from T1 to T2. At baseline, there were no statistically significant group differences with respect to actigraphic estimates of total sleep time ($P=.48$), sleep efficiency ($P=.63$), or sleep latency ($P=.37$). From T0 to

T1, total sleep time decreased in the BLT group from 6 hours 52 minutes (95% CI, 6 hours 31 minutes to 7 hours 14 minutes) to 6 hours 37 minutes (6 hours 17 minutes to 6 hours 57 minutes), which was a significantly stronger decrease ($P=.03$) than occurred in the placebo group (from 6 hours 42 minutes [6 hours 23 minutes to 7 hours 1 minute] to 6 hours 22 minutes [6 hours to 6 hours 45 minutes]). No significant differences remained at T2 ($P=.47$). From T0 to T1, sleep efficiency increased in the BLT group from 76.8% (95% CI, 74.1%-79.5%) to 77.9% (75.5%-80.4%), which was a significantly stronger increase (2%, $P=.01$) than the change that occurred in the placebo group (from 75.9% [73.5%-78.4%] to 75.6% [73.2%-78.0%]). No significant differences remained at T2 ($P=.61$). No differential changes occurred in sleep onset latency from T0 to T1 ($P=.53$) or from T0 to T2 ($P=.70$). The findings indicate that BLT decreases total sleep duration by advancing get-up time after final awakening and increases sleep efficiency.

ADVERSE EFFECTS

Bright light treatment and placebo were well tolerated. Their adverse effect profiles did not differ (eTable 5). In the placebo group, more patients reported the emergence or increase in daytime sleepiness (36% vs 24%; $\chi^2=3.95$; $P=.05$) and fatigue (34% vs 19%; $\chi^2=5.11$; $P=.02$).

COMMENT

This is, to our knowledge, the first double-blind, placebo-controlled randomized trial with a sufficient sample size to evaluate the effects of BLT on mood in elderly patients with a DSM-IV diagnosis of nonseasonal MDD. The design appeared successful with respect to treatment adherence and balanced expectations.

Directly after 3 weeks of treatment (T1), BLT improved depressive symptoms better than placebo (43% vs 36%). Three weeks after treatment withdrawal (T2),

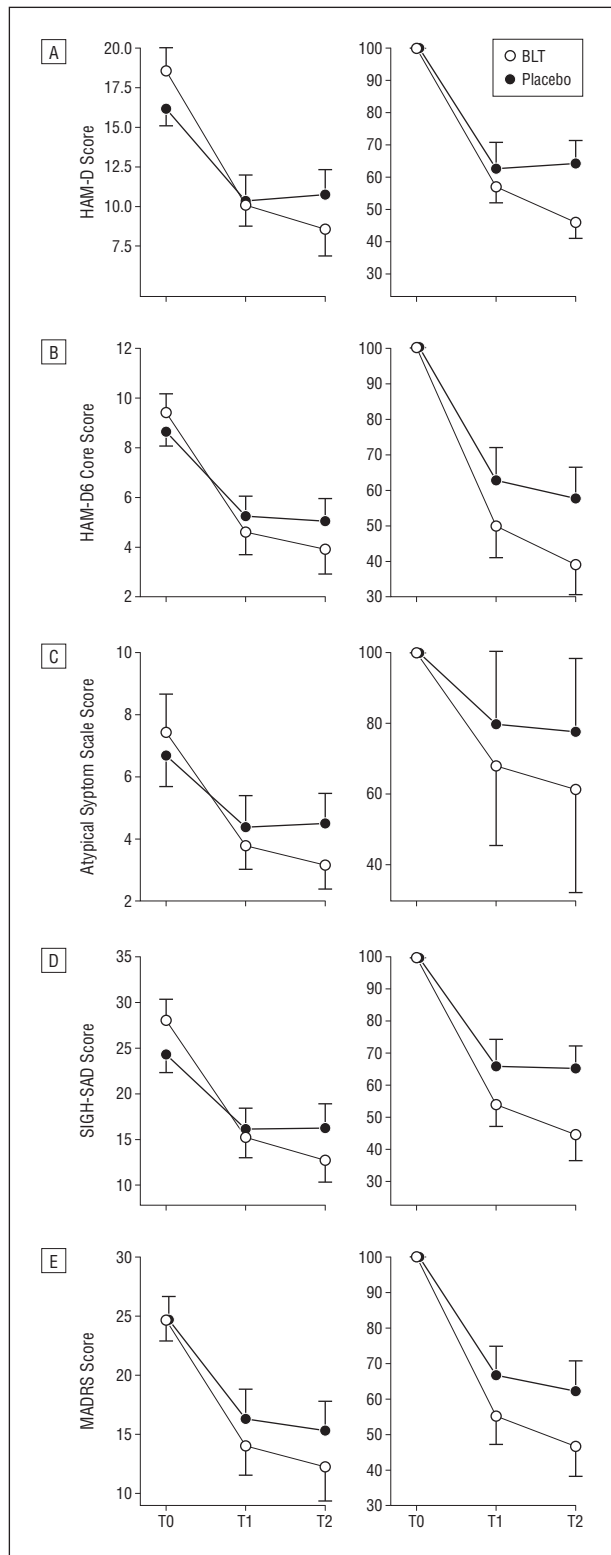


Figure 5. Effects of bright light treatment (BLT) and placebo in elderly patients with nonseasonal major depressive disorder. Data are depicted as means; error bars show the 95% confidence intervals. Absolute values are given on the left side, and the percentage of change from baseline (T0) is shown on the right side. Measures include the Hamilton Scale for Depression (HAM-D) scores (A), the HAM-D6 (the HAM-D 6-item core version) scores (B), Atypical Symptom Scale scores (C), the Structured Interview Guide for the HAM-D–Seasonal Affective Disorder Version (SIGH-SAD) scores^{48,49} (D), and the Montgomery–Åsberg Depression Rating Scale (MADRS) scores (E). T1 indicates after 3 weeks of treatment; T2, 3 weeks after discontinuation of treatment.

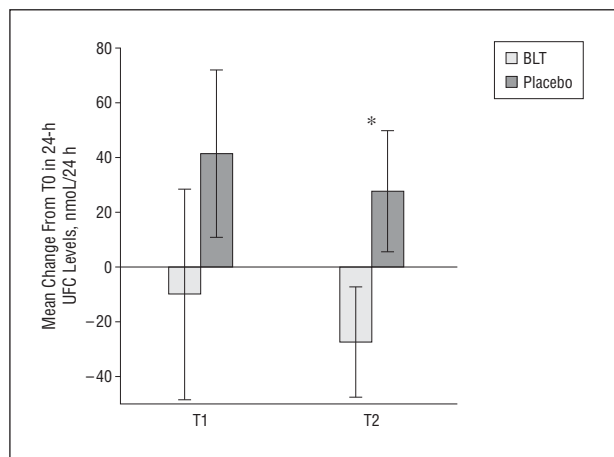


Figure 6. Mean change from baseline (T0) in patients receiving bright light treatment (BLT) and placebo by effects on 24-hour urinary free cortisol (UFC) levels. Data are depicted as mean change from baseline UFC levels; error bars show the 95% confidence intervals. T1 indicates after 3 weeks of treatment; T2, 3 weeks after discontinuation of treatment. * $P = .003$.

symptoms had continued to improve in the BLT group but not in the placebo group (54% vs 33%). Bright light treatment resulted in a good responder rate (ie, $\geq 50\%$ symptom reductions) of 50% vs 41% in the placebo condition at T1 and of 58% vs 36% at T2 (eTable 3 and eTable 4). These effect sizes appear comparable to those reported for antidepressants (number needed to treat, 5), with the noticeable difference that no adverse effect could be demonstrated for BLT (eTable 5). Ancillary analyses on other measures of depression severity showed comparable results (Table 3, eTable 4, and Figure 5).

In contrast to the continuing improvement after discontinuation of treatment in the present study, Martiny et al⁷⁸ found a lack of sustained effect in their study. Four weeks after their treatment period of 5 weeks, the BLT and placebo groups no longer differed regarding remission rates. Martiny et al hypothesized that BLT accelerated remission of symptoms rather than having an augmenting effect. Whereas Martiny et al supplemented BLT with pharmacological treatment, with increasing dosages after the BLT period, our study did not offer a secondary treatment after the BLT period. We therefore conclude that our BLT protocol induced the recovery process that lasted beyond discontinuation of treatment.

Of interest is the finding that effects on depression, 24-hour UFC excretion, diurnal cortisol level, and get-up time after final awakening persisted, improved, or became significant only at T2, whereas the other sleep measures and melatonin levels changed during BLT but returned to baseline at T2. The finding suggests rather acute effects on melatonin levels and sleep, whereas effects on clinical improvement in depression symptoms and cortisol hyperactivity are initiated by the treatment but take longer to develop fully. To the best of our knowledge, we are the first to report that, in elderly patients with MDD, 24-hour UFC and diurnal salivary cortisol levels attenuated after BLT (Figure 6). In contrast, placebo-treated patients continued to increase their 24-hour UFC levels. We hypothesize that the burden and stress of participating in a clinical trial with disappointing treatment effects may have further elevated HPA activity. Alternatively, a continued increase of

24-hour UFC levels may be a characteristic of the developmental time course of MDD in elderly patients.

Several limitations should be discussed. First, at baseline a slight randomization imbalance for outcome was seen for HAM-D scores, indicating that BLT-treated patients had slightly higher pretreatment severity ratings than placebo-treated patients. This difference was not reflected in the other depression severity ratings, in severity distribution, or in other depression characteristics. All analyses took this into account by including baseline severity covariates in the analyses. Significance of the covariate-corrected treatment effects indicated that the antidepressant effects of BLT could not be attributed to HAM-D pretreatment score differences. Second, the monitoring of depression symptoms was limited to T1 and T2. If the developmental course of improvement is the focus of interest, more frequent assessments for more detailed analyses will be required. Moreover, with the positive effect of BLT that we found, more data points would have further increased the statistical significance. Third, our trial investigated only the immediate and 3-week delayed effect of a 3-week BLT treatment duration. Therefore, prolonged effects, or effects of long-term BLT, remain to be investigated. A large study on long-term effects of light treatment on demented elderly patients without MDD suggests preservation of antidepressant effects rather than habituation.¹¹ Fourth, only 89 patients were included from a total of 444 undergoing assessment. This could have been due to several factors, including (1) active case-finding efforts, (2) strict inclusion criteria to fulfill the requirements for a diagnosis of MDD only, and (3) the criterion of absence of seasonal affective disorder. Although the findings of this specific study are thus limited to elderly patients with MDD, efficacy of light treatment in elderly patients with a profile of milder depression is suggested by previous work.¹¹

In conclusion, we showed that BLT had beneficial effects in elderly patients with nonseasonal MDD and found indirect support for the contention that therapeutic effects may in part be mediated by enhancements of circadian system functioning. These results support inclusion of chronotherapeutic strategies in the treatment options for nonseasonal MDD in elderly patients. Bright light treatment may provide a viable alternative for patients who refuse, resist, or do not tolerate antidepressant treatment.

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Supplementary Online Content

Lieverse R, Van Someren EJW, Nielen MMA, Uitdehaag BMJ, Smit JH, Hoogendijk WJG. Bright light treatment in elderly patients with nonseasonal major depressive disorder: a randomized placebo-controlled trial. *Arch Gen Psychiatry*. 2011;68(1):61-70.

eTable 1. Depression characteristics.

eTable 2. Outcome in expectancy questionnaire ratings.

eTable 3. Number of participants with $\geq 50\%$ reduction in HAM-D score from baseline.

eTable 4. Number of participants with $\geq 50\%$ reduction in supplementary depression ratings.

eTable 5. Evaluation of adverse events.

eFigure 1. Spectrophotometry curves.

eFigure 2. Educational figure on melatonin.

eFigure 3. 24-Hour UFC in healthy controls.

eFigure 4. Saliva cortisol levels.

eAppendix A. Supplemental information on depression characteristics, intervention, and compliance.

eAppendix B. Supplemental information on evening melatonin level rise.

eAppendix C. Supplemental information on urinary cortisol excretion and saliva cortisol levels.

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Depression characteristics^a			
	Placebo (n=47)	BLT (n=42)	P Value^b
<i>Subtype</i>			
No subtype specifiable, N (%)	14 (30%)	11 (26%)	.92
Melancholic subtype, N (%)	21 (45%)	21 (50%)	.62
Number of melancholic features, mean (SD)	2.91 (2.0)	3.38 (2.0)	.28
Atypical subtype, N (%)	12 (26%)	10 (24%)	.85
Number of atypical features, mean (SD)	1.48 (1.4)	1.83 (1.6)	.22
<i>Severity estimates</i>			
Number DSM-IV-depression features, mean (SD)	6.43 (1.3)	6.50 (1.3)	.82
GDS-15, mean (SD)	9.62 (2.5)	9.97 (2.7)	.54
HAM-D score, mean (SD)	16.02 (4.7)	18.40 (5.6)	.03
ATYP-8 score, mean (SD)	6.40 (4.1)	7.45 (4.7)	.26
SIGH-SAD score, mean (SD)	24.13 (8.3)	27.95 (8.8)	.04
HAM-D6 subscore ^c , mean (SD)	8.77 (2.45)	9.26 (2.9)	.38
MADRS score, mean (SD)	25.13 (6.8)	24.95 (6.8)	.90
<i>Course estimates</i>			
Recurrent subtype, N (%)	23 (48%)	29 (69%)	.06
Number of previous Episodes, mean (SD)	3.07 (3.6)	4.00 (4.7)	.89
With interepisode recovery, N (%)	15 (32%)	16 (38%)	.52
Without interepisode recovery, N (%)	7 (15%)	11 (26%)	.52
Chronic course, N (%) ^d	1 (2%)	2 (5%)	>.99
Single episode subtype, N (%)	24 (51%)	13 (31%)	.06
Chronic course, N (%) ^e	20 (43%)	12 (29%)	.12
Duration of current depression, months (SD)	56.81 (108.1)	62.20 (94.14)	.81
Short (< 2 years) current episode, N (%)	24 (51%)	17 (41%)	.32
Long (> 2 years) current episode, N (%)	23 (49%)	25 (60%)	.32
<i>Seasonality characteristics</i>			
Atypical Balance ^f , mean (SD)	24.40 (12.7)	25.42 (10.9)	.07
Global Seasonality Score (GSS) ^g , mean (SD)	9.12 (6.4)	8.55 (7.2)	.74
GSS>=11 ^h , N (%)	12 (26%)	9 (21%)	.66
Symptoms are worse in winter months, N (%)	15 (32%)	17 (40%)	.45
Severity seasonality at least moderately problematic, N(%)	13 (28%)	14 (33%)	.71
Fulfilling winter blues criteria to Rosenthal ⁱ , N (%)	7 (15%)	7 (17%)	.84
Fulfilling SAD-criteria according to Rosenthal ^h , N (%)	2 (4%)	4 (10%)	.84
Fulfilling SAD-criteria according to DSM-IV-TR, ¹ N (%) ^h	0 (0%)	0 (0%)	.30
<i>Treatment characteristics</i>			
Never treated with antidepressants, N (%)	27 (57%)	25 (60%)	.75
In past treated with tricyclic antidepressants, N (%)	5 (11%)	9 (21%)	.22
On-going treatment with antidepressants, N (%)	18 (38%)	14 (33%)	.85
SSRI	14	11	
SNRI	4	3	
No AD or benzodiazepine	28 (60%)	22 (52%)	.58
In past treated with SSRI ^j s, N (%)	24 (51%)	22 (52%)	.75
In past treated with psychotherapy, N (%)	21 (45%)	31 (74%)	.007
Current use of benzodiazepines, N (%)	13 (28%)	13 (31%)	.78
Treatment resistance ^k , N (%)	31 (66%)	35 (83%)	.13
Treatment refractoriness ^k , N (%) ^l	15 (32%)	16 (38%)	.69

Abbreviations: BLT, bright light treatment; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition⁴⁴; GDS-15, Geriatric Depression Rating Scale;⁶⁶ MADRS, Montgomery-Åsberg Depression rating Scale;⁵¹ HAM-D, 17-item Hamilton Depression Rating Scale;⁴⁸ ATYP-8, Atypical Symptom Score; SIGH-SAD, Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorder version;^{46, 47} HAM-D6, Hamilton Depression Rating Scale- 6-item core version;^{48, 50, 75} GSS, Global Seasonality Score; SSRI, SD, Antidepressant; Selective Serotonin Reuptake Inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor.

^a All randomized (n=89)

^b BLT and placebo characteristics were compared using analysis of variance (ANOVA) and χ^2 -statistics and Fisher exact tests (when cell sizes were <5)

^c Consists of the depression core items (depressed mood, self-depreciation and guilt feelings, work and interests, psychomotor retardation, psychic anxiety and general somatic.

^d Chronic course of recurrent episode.

^e Chronic course limited to single episode.

^f Atypical balance ([atypical score] / [total SIGH-SAD score] x 100)⁷⁶ is in some studies a strong predictor of response to light

^g Central component of the Seasonal Pattern Assessment Questionnaire (SPAQ), Scale of Rosenthal *et al.*⁷⁷ that measures seasonal variations on six different items (sleep, mood, weight, energy, social activity and appetite).

^h Rosenthal *et al* argues to differentiate between winter blues and SAD using questions 2 & 3 on the SPAQ: GSS > 11 indicates towards SAD while winter blues scores 8<GSS<10, and seasonal changes in mood and behavior is at least a moderate problem on a scale of no problem, mild, moderate, marked, severe, or disabling.

ⁱ DSM-III -IV criteria for the seasonal pattern specifier. However, the specifier is based on the timing of discrete winter major depressive episodes, and does not take into account depressions that, while present across the seasons, show winter exacerbation.

^j nonresponse to >= 1 trial of antidepressant medication during the current episode

^k >= 2 trials of antidepressant medication during the current episode

Statistically significant test values are depicted in bold font.

eTable 2. Outcome in Expectancy Questionnaire Ratings^a

	Placebo (n=47)			BLT (n=42)			Test Statistic <i>P</i> value		
	T	R	NR	T	R	NR	T vs T	R vs. R	NR vs. NR
(1.) Mean (SD)	3.65 (1.37)	3.56 (1.01)	3.78 (1.48)	4.29 (1.30)	4.55 (1.14)	4.09 (1.45)	F _{1,70} =3.96 <i>P</i> =.05	F _{1,29} =5.08 <i>P</i> =.03	F _{1,33} =0.35 <i>P</i> =.56
(2.) Mean (SD)	2.44 (0.86)	2.56 (1.01)	2.46 (0.80)	2.44 (0.88)	2.36 (0.79)	2.58 (1.08)	F _{1,70} =0.00 <i>P</i> =.99	F _{1,31} =0.32 <i>P</i> =.58	F _{1,34} =0.16 <i>P</i> =.70
(3.) Mean (SD)	2.53 (0.76)	2.50 (0.76)	2.59 (0.73)	2.62 (0.70)	2.73 (0.70)	2.40 (0.70)	F _{1,69} =.23 <i>P</i> =.63	F _{1,30} =0.59 <i>P</i> =.45	F _{1,32} =0.48 <i>P</i> =.50
(4.) Mean (SD)	2.90 (1.04)	2.63 (0.74)	3.05 (1.07)	3.00 (0.95)	3.14 (0.96)	2.73 (0.91)	F _{1,66} =0.15 <i>P</i> =.70	F _{1,29} =1.86 <i>P</i> =.18	F _{1,32} =0.71 <i>P</i> =.41

Abbreviations: T = total, R = responder, defined as $\geq 50\%$ reduction in HAM-D score between baseline (T0) and endpoint (T2), NR = nonresponder, defined as $<50\%$ reduction in HAM-D scores.

^a To evaluate the blinding procedure, and in order to assess participants' general expectations for light therapy and their specific expectations with respect to their allocated light boxes, expectations were measured before the light box was set up using a 4-item expectations questionnaire. Briefly, participants were asked to rate, on a 7-point scale (feeling much better = 1, definitely better = 2, feeling slightly better = 3, no change = 4, feeling slightly worse = 5, feeling definitely worse = 6, feeling much worse = 7), how they thought light therapy would affect them on the following 4 questions: (1) To what extent do you expect your problems will improve without treatment? (2) To what extent do you expect your problems will improve with light treatment? (3) To what extent do you expect your problems will improve with blue light treatment? (4) To what extent do you expect your problems will improve with red light treatment?

eTable 3. Number of participants with $\geq 50\%$ reduction in HAM-D score from baseline										
	Baseline to T1					Baseline to T2				
Outcome	Placebo N(%) ^a	BLT N(%) ^a	Test statistic (df) <i>P</i> value	ARR (95% CI)	NNT ^b (95% CI)	Placebo N(%) ^a	BLT N(%) ^a	Test statistic (df) <i>P</i> value	ARR (95% CI)	NNT ^b (95% CI)
HAM-D ITT (n=84) ^c	18 (41%)	20 (50%)	$\chi^2=0.70$ (1) <i>P</i> =.20	9.1% (-12.2 to 30.3)	11 (3 to inf.)	15 (34%)	23 (58%)	$\chi^2=3.76$ (1) <i>P</i>=.05	21.1% (0.2 to 42.0)	5 (1-151)
BCF ^d (n=89)	18 (38%)	20 (48%)	$\chi^2=0.79$ (1) <i>P</i> =.19	9.3% (-11.2 to 29.9)	11 (3 to inf.)	16 (34%)	23 (55%)	$\chi^2=3.90$ (1) <i>P</i>=.05	20.7% (0.5 to 41.0)	5 (2-121)
CA ^e (n=74)	15 (40%)	19 (53%)	$\chi^2=1.32$ (1) <i>P</i> =0.13	13.3% (-9.2 to 35.8)	8 (3 to inf.)	13 (34%)	22 (61%)	$\chi^2=5.37$ (1) <i>P</i>=.02	26.9% (5.0 to 48.8)	4 (2-20)

Abbreviations: HAM-D, 17-item Hamilton Depression Rating Scale;⁴⁷ ITT, intention to treat; BCF, baseline carried forward; CA, completers analysis; ARR, absolute risk reduction; NNT, Number Needed to Treat; CI, confidence interval; T1 rating directly after three weeks treatment; T2 rating directly three weeks after discontinuation of treatment.

^a N(%) Responders defined as $\geq 50\%$ reduction in HAM-D score from baseline

^b NNT-values computed as the inverse of the absolute risk reduction⁷⁷

^c The intention to treat analysis used the last observation carried forward

^d The baseline carried forward analysis was performed as sensitivity analysis

^e The completers analysis was performed as sensitivity analysis.

Statistically significant test values are depicted in bold font.

eTable 4. Number of participants with $\geq 50\%$ reduction in supplementary depression ratings										
	Baseline to T1					Baseline to T2				
Outcome	Placebo N(%) ^a	BLT N(%) ^a	Test statistic (df) <i>P</i> value	ARR (95% CI)	NNT ^b (95% CI)	Placebo N(%) ^a	BLT N(%) ^a	Test statistic (df) <i>P</i> value	ARR (95% CI)	NNT ^b (95% CI)
HAM-D6 (n=84)	17 (39%)	22 (55%)	$\chi^2=2.26(1)$ <i>P</i> =.07	16.4% (-4.7 to 37.5%)	6 (negative CI)	21 (48%)	25 (63%)	$\chi^2=1.85(1)$ <i>P</i> =.17	14.8% (-6.3 to 35.8%)	5 (negative CI)
ATYP-8 (n=84)	16 (36%)	22 (55%)	$\chi^2=2.64(1)$ <i>P</i>=.05	18.6% (-2.3 to 39.6%)	6 (negative CI)	18 (41%)	25 (63%)	$\chi^2=3.54(1)$ <i>P</i> =.06	21.6% (0.7 to 42.5%)	5 (2 to 156)
SIGH-SAD (n=84)	15 (34%)	19 (48%)	$\chi^2=1.56(1)$ <i>P</i> =.10	13.4% (-7.5 to 34.3%)	7 (negative CI)	13 (30%)	23 (58%)	$\chi^2=6.69(1)$ <i>P</i>=.01	28.0% (7.6 to 48.4%)	4 (2 to 14)
MADRS (n=84)	14 (32%)	19 (48%)	$\chi^2=2.16(1)$ <i>P</i> =.07	6.3% (-16.3 to 28.9)	6 (negative CI)	15 (34%)	21 (53%)	$\chi^2=2.90(1)$ <i>P</i> =.09	18.4% (-2.5 to 39.3)	5 (negative CI)

Abbreviations: HAM-D6, Hamilton Depression Rating Scale 6 item core version (comprising depressed mood, self-depreciation and guilt feelings, work and interests, psychomotor retardation, psychic anxiety and general somatic);⁵⁰ ATYP-8, Atypical Symptom Score, SIGH-SAD, Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorder version;^{48,49} MADRS, Montgomery-Åsberg Depression Rating Scale,⁴⁶ ARR, absolute risk reduction; NNT, Number Needed to Treat; CI, confidence interval; T1 rating directly after three weeks treatment; T2 rating directly three weeks after discontinuation.

^a See “Methods” section for Outcome descriptions.

^a N(%) Responders defined as $\geq 50\%$ reduction in HAM-D score from baseline

^b NNT-values computed as the inverse of the absolute risk reduction⁷⁷

Statistically significant test values are depicted in bold font.

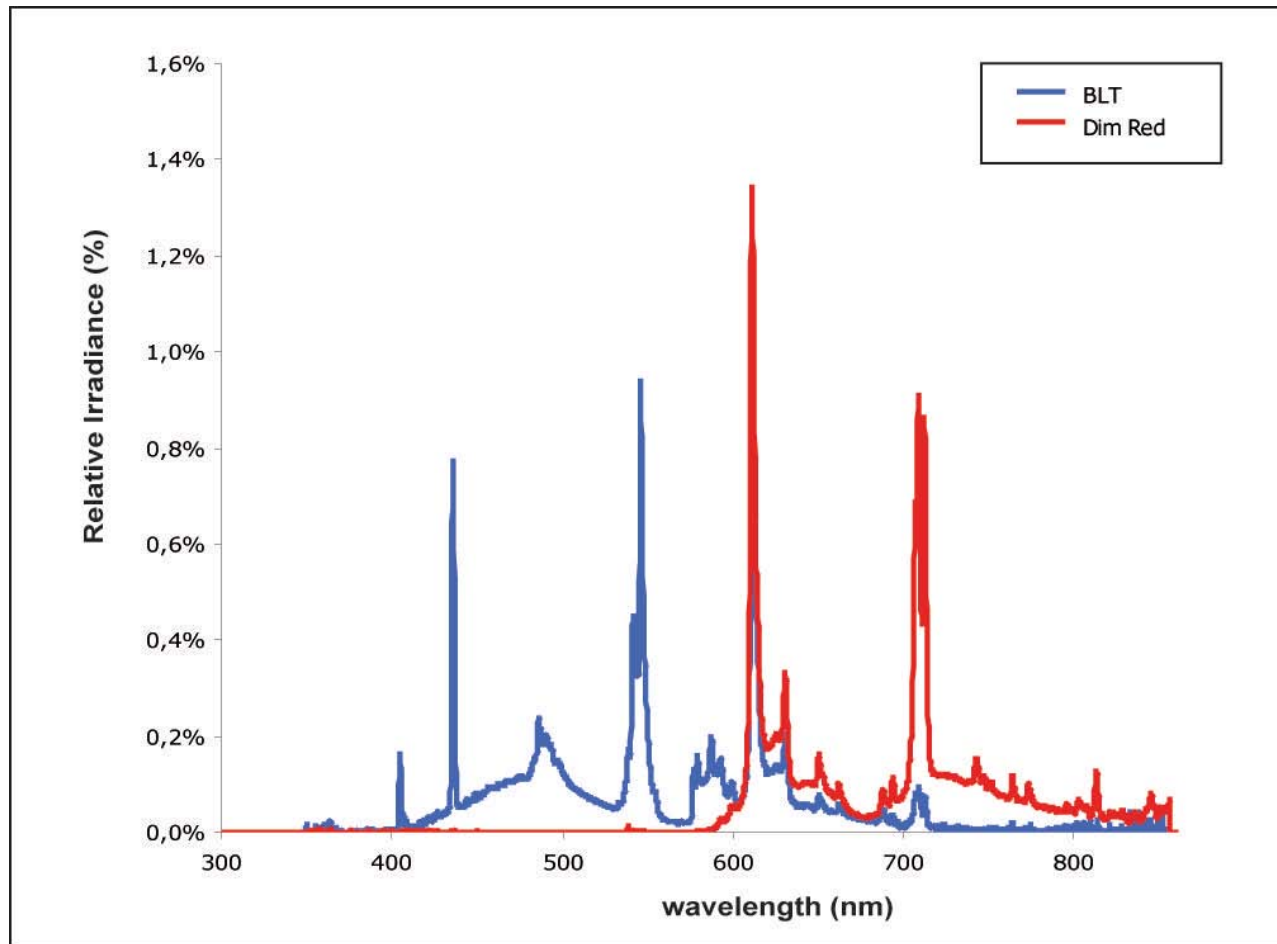
eTable 5. Evaluation of Adverse Events ^a			
Type	No. (%)		P Value
	Placebo (n=47)	BLT (n=42)	
Total, No.	144	149	
Eye strain	8 (17)	7 (17)	.67
Headache	11 (23)	12 (29)	.94
Early awakening	8 (17)	8 (19)	.83
Daytime sleepiness	17 (36)	10 (23)	.05
Fatigue	16 (34)	8 (19)	.02
Drowsiness	5 (11)	4 (10)	.65
Nervousness	8 (17)	7 (17)	.67
Anxiety	4 (9)	5 (12)	.80
Tensions	8 (17)	8 (19)	.89
Irritability	3 (6)	8 (19)	.12
Dizziness	1 (2)	4 (10)	.19
Tight muscles	6 (13)	5 (12)	.66
Viral infection	2 (4)	2 (5)	.95
Fever	0 (0)	1 (2)	.33
Excessive sweating	6 (13)	7 (17)	.85
Hot flushes	4 (9)	6 (14)	.56
Allergy	1 (2)	1 (2)	.96
Rash	3 (6)	1 (2)	.27
Nasal congestion	3 (6)	5 (12)	.51
Nasal drip	3 (6)	2 (5)	.59
Respiratory infections	2 (4)	5 (12)	.27
Dry mouth	7 (15)	11 (26)	.34
Nausea and vomiting	2 (4)	4 (10)	.44
Anorexia	6 (13)	3 (7)	.24
Weight loss	0 (0)	2 (5)	.16
Dyspepsia	4 (9)	4 (10)	.93
Obstipation	1 (2)	4 (10)	.19
Diarrhoea	5 (11)	2 (5)	.20

^a Patients provided a total of 204 adverse events scale ratings, of which 120 were follow-up assessments.

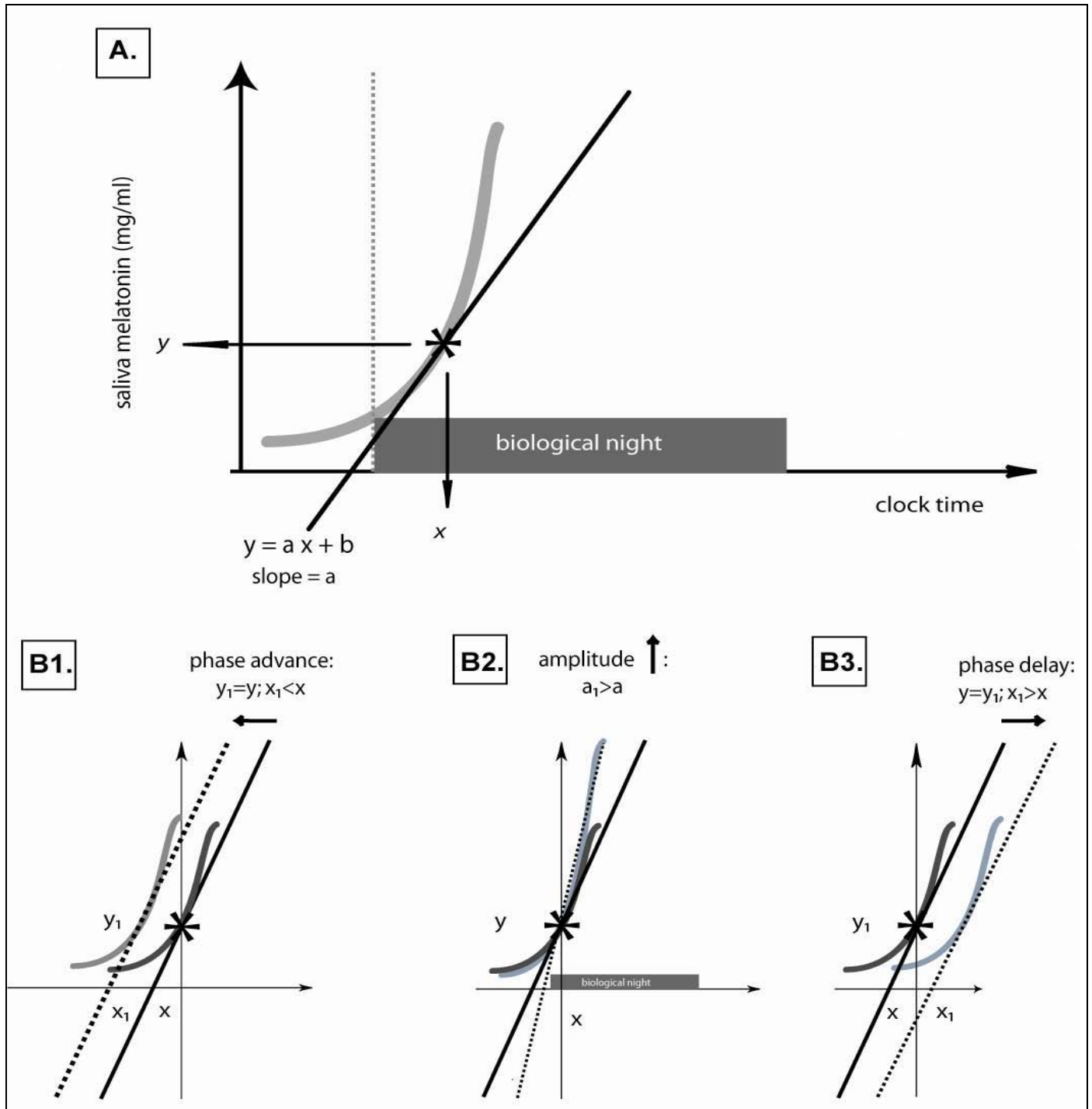
^b Subjects were systematically asked about possible side effects by the blind raters 28 items ratings on a 4-point scale (0=absent, 1=mild, 2=moderate or 3=severe).

^c BLT lowered the ratings on daytime sleepiness and fatigue (depicted in bold font).

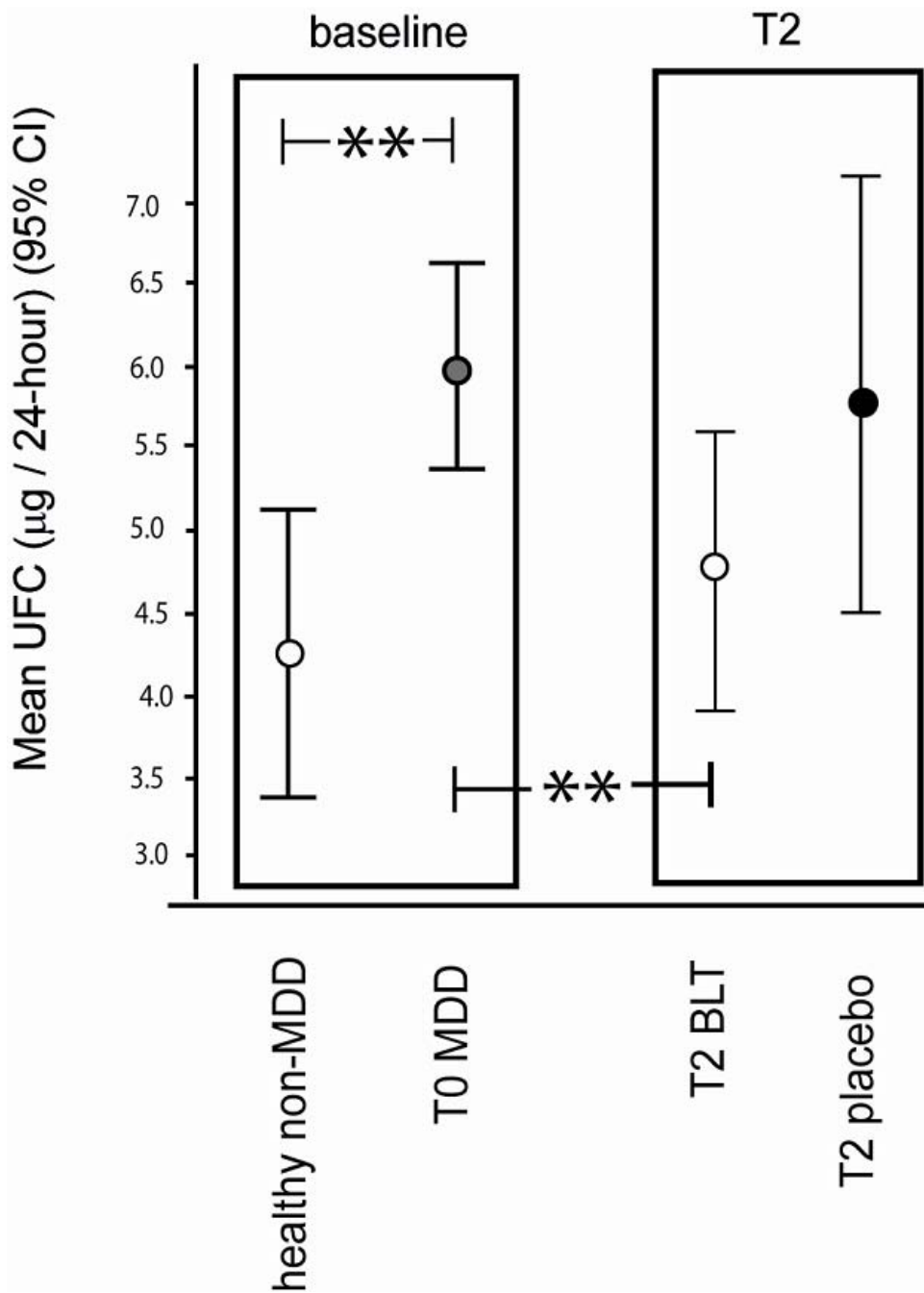
eFigure 1. Spectrophotometry curves. The bright light treatment (BLT) condition is perceived as blue, but the spectrum extended far into the green region. The curves show the percentage irradiance (watt/m²) in each 0.3641 nm bit relative to the total irradiance over the measurement interval of 190 to 860nm. Emitted light spectra and intensities were quantified at 40cm in front of the light box. Lux meter readouts were approximately 7500 lux for the active condition and 50 lux for the placebo condition, measured in gaze direction at eye level.



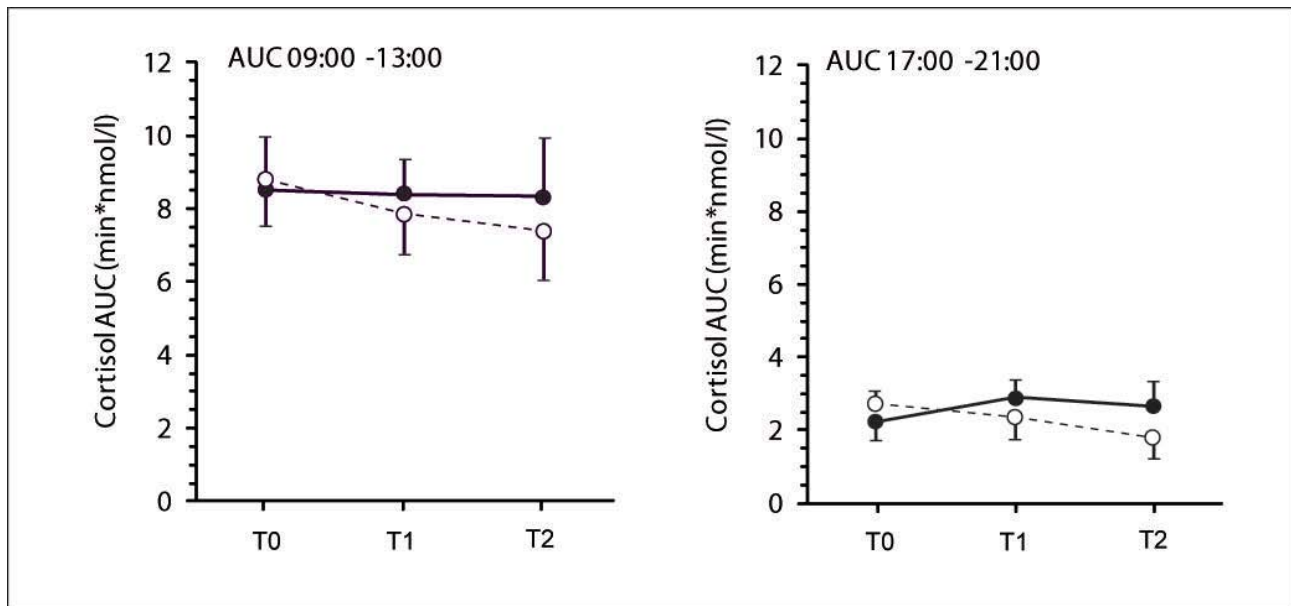
eFigure 2. Educational figure on melatonin. Illustration of the method applied for inferring evening melatonin rise. [A] The upper panel shows the shape of the melatonin level evening rise. Using mixed-effects linear regression model through 4 successive evening saliva samples, referenced to habitual bedtime, at baseline (T0), after 3 weeks of treatment (T1) and 3 weeks after discontinuation (T2) the effects of treatment on the slope (upslope gradient, steepness of melatonin rise) and intercept (timing of the melatonin rise) of the regression lines are compared. The lower panel illustrates the various possible outcomes: An increasing intercept with the y-axis indicates that the melatonin onset curve phase-advances ([B1]), whereas decreasing intercept indicates phase delay ([B3]). [B2] when the slope increases, there is a more pronounced rise of melatonin, and when the slope decreases the melatonin rise is less pronounced.



eFigure 3. 24-Hour urinary free cortisol (UFC) in healthy controls. Baseline (T0) 24-hour UFC levels of 40 patients with major depressive disorder (MDD) are compared with (1) 24-hour UFC levels of 22 age- and sex-matched healthy control subjects (MDD-), and (2) the 24-hour UFC levels after bright light treatment (BLT) or placebo treatment (T2). **: $P < .001$.



eFigure 4. Effects of bright blue light (○) versus dim red light (●) on the daytime saliva cortisol level areas under the Curves (AUC) for the morning and evening: 09:00-13:00hr, and 17:00-21:00hr. Error bars indicate 95% confidence intervals between-subject variance. For the evening level, there was a significant difference between bright light treatment and placebo-treated subjects with respect to their within-subject change from baseline (T0) to 3 weeks after discontinuation (T2). T1 indicates after 3 weeks of treatment.



A. SUPPLEMENTAL INFORMATION ON DEPRESSION CHARACTERISTICS, INTERVENTION, AND COMPLIANCE

Instruction for light therapy:

The exact light bathing-instructions patients received verbally and in written form were: 1) Position yourself near the appliance and place the lamps at a 45° angle so you can comfortably look in the direction of the light; You do not need to sit right in front of the appliance. The agreed usage duration is 60 minutes per session at a distance of about 30cm (that is the length of an A4-paper). 2) Do not look into the light continuously. You can simply engage in other activities such as reading, eating, writing, watch TV, or handicraft while taking a light exposure and look into the light every now and then. 3) Ensure that you sit behind the device every morning at the same time, so that you can get the light during the entire hour. 4) The device will switch-off by itself after 1 hour. You don't need to remove the plug from the electrical outlet.

Ambient lighting during intervention

At instruction, the ambient light conditions were measured using an electronic lux meter. Light intensity during morning hours was measured in the horizontal plane at the eye level, in gaze direction, of every participant who sat at the exact position on the table where they should take their light therapy hours (mean 223; SD, 317; range, 10-1570). Patients who were randomized in the bright light treatment group had mean (SD) ambient light levels of 240 (247) lux, and patients who were randomized in the placebo group had mean (SD) light levels of 206 (378) lux, which did not differ significantly from each other ($P=.746$).

Furthermore, long-term ambient light exposure could be estimated using a light sensor built in the actigraphs that was worn on the wrist. During daytime hours (from 10:00 AM to 3:00 PM) during the intervention weeks the mean wrist-measured light intensity was 315 (SD, 650) lux and BLT and placebo ambient lighting conditions did not differ statistically significant ($P=.06$).

Effect of season

Season of treatment

Forty-six patients (26 BLT and 21 placebo) were treated during the six months with shorter day length (from the end of October 1 to the end of March) and 43 patients (14 BLT and 23 placebo) were treated in the 6 months with longer day length (from April to September) ($\chi^2=2.54$ (1); $P=.11$).

Influence of seasonality

Patients treated with BLT did not differ significantly in mean Global Seasonality scores (GSS) at baseline whether they were included and treated in winter or in summer. Patients treated with placebo did not differ either. Analyses of covariance showed that wintertime did not influence outcome ($F_{1,81}=0.41$; $P=.84$), nor did GSS ($F_{1,71}=0.85$; $P=.43$).

Treatment adherence:

Methods

Four interventions were applied to promote compliance: (1) Patients chose a fixed starting time within 1 hour from their habitual wake-up time. (2) Devices were automatically switched on and off, using clock- power supplies. (3) Patients were asked to note their compliance in their trial diaries, which were discussed during and after the trial. (4) Patients were made aware of compliance assessments using the photocells, that were built in the wrist-worn actimeters they wore during the entire protocol.

Results

Light exposure estimated from a light sensor built in the actigraphs that was worn on the wrist showed that mean maximum light intensity during the planned exposure period was higher during (mean = 247 (SD, 284) lux) than before BLT-weeks (mean = 73 (SD, 102) lux; $P<.001$), or after BLT weeks (mean = 139 (SD, 210) lux; $P=.001$) in the active condition.

In the placebo treated group, there was no difference between luxometry during placebo (mean max lux = 176 (SD, 238) and before (mean 180 (283) lux; $P=.920$) or after (mean 176 (251) lux); $P=.993$).

Conclusion

In conclusion, compliance is supported by the fact that only BLT-assigned patients showed elevated light exposure and exclusively during the treatment.

B. SUPPLEMENTAL INFORMATION ON EVENING MELATONIN RISE

Method:

At baseline (T0), after 3 weeks of treatment (T1) and 3 weeks after discontinuation (T2), 4 evening samples (Salivette, Sartstedt, Germany) were collected at hourly intervals starting 4 hours before predicted bedtime). (For patient instructions, see INSTRUCTIONS APPLIED FOR SALIVA SAMPLING, available at <http://www.ggzingeest.nl/1994258/instructions-saliva-sampling.pdf>). Melatonin concentrations were measured using a direct commercial radioimmunoassay (RIA, Bühlmann Laboratories AG, Schönenbuch, Switzerland. The limit of sensitivity was 0.2pg/ml and intra-assay and interassay coefficients in the measuring range were 2.6% to 20.1%. The melatonin levels in our dataset were so low that commonly applied methods were not applicable, we could only obtain a measure of the steepness of the evening rise, which may have biological relevance and which has been proposed before as a parameter of use. We promoted melatonin samplings to take place during the evening dim light hours. We have several arguments supporting assessment of unmasked melatonin onset:

- (1) First, using a luxmeter, we measured ambient evening light intensity at the eye level in a sample of 12 representative houses in Amsterdam and found at hourly intervals between 6:00 PM to 0:00 AM mean (SD) levels of 13 (7) lux. These results, in combination with the fact that photoreception in advancing age is reduced, reassured us that efforts to reduce ambient lighting – other than providing clear instructions (see (2) below) – were not required.
- (2) Second, participants were instructed, as follows: “Because melatonin in the body is under the influence of light, it is important that you stay in a semi-dim light condition during the whole evening of saliva sampling. Watching TV at some distance is allowed, but not sitting right in front of a TV, or a computer display, nor keeping all lights on.”
- (3) Third, and finally, to verify dim light conditions, we analyzed light exposure during the 4 hours of saliva sampling as recorded on the wrist with a light sensor integrated in the actigraph. During the dim light melatonin onset (DLMO) period, mean wrist-measured light intensity was loglux of 0.52 (SD, 0.50) if averaged over logtransformed light intensity, corresponding to about 3.3 lux, or 25 (SD, 57) lux if averaged over untransformed light intensity.

Statistics

Using mixed effects linear regression using the 4 successive evening saliva samples, referenced to habitual bedtime, at T0, T1 and T2, the effects of treatment on the slope (upslope gradient, steepness of melatonin rise) and intercept (timing of the melatonin rise) of the regression lines can be compared. When the slope of the regression line increases, the increasing steepness of the melatonin rise indicates increasing amplitude, and when the slope decreases the melatonin rise is blunted. An increasing intercept indicates that the melatonin onset curve phase-advances, whereas decreasing intercept indicates phase-delay.

The mixed effect linear regression analysis model consisted of 3 levels (e.g. participants grouped in their randomization condition, time of samplings on the evening, and time of samples relative to treatment [T0, T1 or T2]). The model that fitted to the data was: $\text{Melatonin}_{ijk} = b_{0ijk} \text{cons} + 0.366 (0.087) \text{timePP}_{ijk} + 0.048 (0.168) \text{BLT} \times \text{timePP}_{ijk} + 0.483 (0.208) \text{BLT}_{\text{now}} \times \text{timePP}_{ijk} + 0.293 (0.192) \text{after BLT} \times \text{timePP}_{ijk} + 1.317 (1.271) \text{BLT}_k + -0.252 (0.536) \text{BLT}_{\text{now}ijk}$, where melatonin is the variable of interest and each observation in time is denoted as *i*, each participant as *j*, and sample-time relative to treatment (T0, T1 or T2) as *k*. The *b* provide the intercept (*b*₀) and the effect estimates (*b*_{*ijk*}).

Dim Light Melatonin Onset was defined as the first time-point at which the melatonin level was above baseline, with the further requirements that the next point was even higher.

Result: Mean evening saliva melatonin levels were 1.0 (95% confidence interval [CI], 0.7-1.3) ng/L at T0, 2.2 (95% CI, 0.5-3.8) ng/L at T1, and 1.4 (95%CI 0.6-2.2) ng/L at T2. At T1 relative to T0, the major effect of BLT was to increase the steepness of the evening increase in melatonin level by 81% (95% CI, 7% - 155%, *P*=.03), without altering the onset phase. At T2 relative to T0, the BLT and placebo groups did not differ significantly with respect to the steepness or phase of melatonin onset (mean effect, 57%; 95% CI, 7 – 51; *P*=.13).

For DLMO establishment we excluded 20 incomplete series. Out of 171 complete series we established a DLMO in 63 (37%). In 108 complete series (63%), no DLMO was observed. At baseline there were no statistically significant group differences in DLMO (mean, 8:42 PM [95% CI, 8:13-9:11]). No effect of time or time by treatment was found. Thus, between T0 and T1 DLMO did not change in the BLT group (T0: 8:41 PM [95%CI, 7:43-9:39 and T1:8:13 PM [95%CI, 7:34-8:52], or in the placebo group (T0: 20:43 PM [95%CI, 8:13-9:11] and T1: 20:45 PM [95%CI, 8:15-9:32], repeated measures ANOVA ($F_{1,9}=2,661$; $P=.137$). At T2 relative to T0, DLMO in the BLT group (T2: 8:50 PM [95%CI, 8:15-9:25]) and in the placebo group (T2: 8:46 PM [95%CI, 8:15-9:17]) did not differ either.

Comment: BLT elevated the upslope gradient of the melatonin rise.

C. SUPPLEMENTAL INFORMATION ON URINARY AND SALIVARY CORTISOL

Method: For case-control comparison of baseline values 24-hour urinary free cortisol (UFC) levels, we recruited 22 healthy age- and sex matched non-depressed (Geriatric Depression rating Scale [GDS] scores, 0) control subjects consecutively volunteered for participating the study.

Results: At T0 (MDD+; n=40) patients showed significantly higher mean (SD) UFC levels (5.65 (3.73) $\mu\text{g}/24\text{-hour}$) than a healthy non-depressed age and sex matched control group (MDD-; n=22) (4.31 (2.07) $\mu\text{g}/24\text{-hour}$) (Mean difference 1.34 μg (95% CI, 0.10 – 2.60); $P=.01$).

At T2 BLT 24-hour UFC was 4.82 (2.65) $\mu\text{g}/24\text{-hour}$ (compared with T0 mean difference 0.98 μg (95% CI 0.15 to 1.49; $P=.02$). 24-hour UFC from T2 BLT-treated subjects did not differ from healthy controls ($P=.47$)

Conclusion: The pre-treatment data (T0) in depressed patients showed elevated UFC levels in reference to healthy controls, and that BLT at T2 had lowered UFC levels, which did not differ from healthy control values.