ORIGINAL ARTICLE

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) activity.[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 Scale[55]; MMSE, Mini-Mental State Examination; SCID-IV, Structured Clinical Interview for *DSM-IV* Axis I Disorders.[44,56]

[a] Calculated 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 action[27] 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 Scale[46] 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 inactive[58] (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 variance (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 Scale[45] 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 function[72] 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). 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.

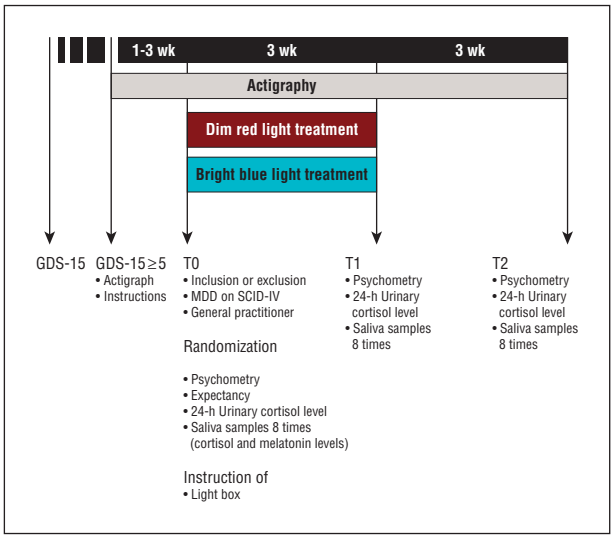

Figure 1. Diagram of the study protocol. Assessments of psychometry and hypothalamic-pituitary axis function and parameters of sleep and circadian rhythmicity were conducted before the start of 3 weeks of light treatment (T0), after 3 weeks of treatment (T1), and 3 weeks after discontinuation of treatment (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.

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).

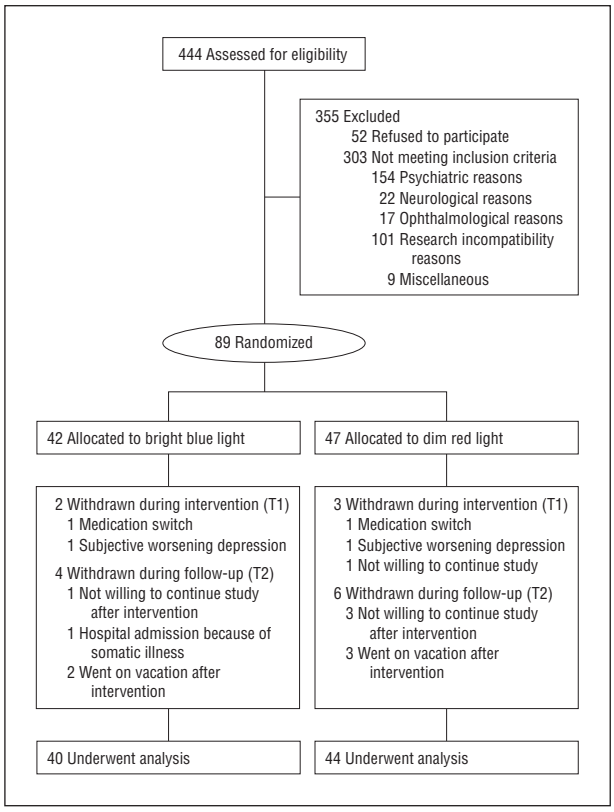

Figure 2. Flow of study patients. Every randomized patient started treatment. Five patients discontinued the intervention and refused follow-up. Analyses fulfill intention-to-treat characteristics because none of the patients assigned to a condition switched to another condition and because analyses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

Table 2. Outcomes in Depression Ratings[a]

	Placebo Group, Mean (SD)			BLT Group, Mean (SD)			Change From T0 to T1[b]			Change From T0 to T2[b]		
Outcome	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 Depression[47]; T0, baseline; T1, after 3 weeks of treatment; T2, 3 weeks after discontinuation of treatment.

[a] Outcome descriptions are given in the "Outcome Measures" subsection of the "Methods" section.

[b] Indicates differences between BLT and placebo in the change from T0 to each patient's own end point for the change in depression rating.

[c] Calculated 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.

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

[e] The intention-to-treat analysis used the last observation carried forward.

[f] With repeated-measures ANCOVA, using the T0 rating as a covariate was significant.

[g] Performed 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 placebo 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).

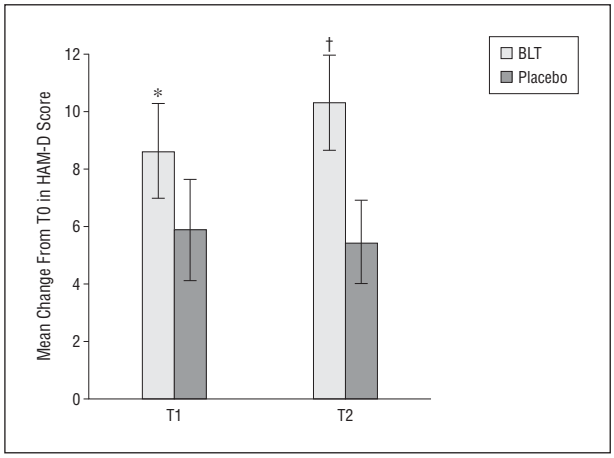

Figure 3. Changes in the Hamilton Scale for Depression (HAM-D) from baseline (T0) in groups receiving bright light treatment (BLT) and placebo for nonseasonal major depressive disorder in elderly individuals. Bars indicate standard deviations. T1 indicates after 3 weeks of treatment; T2, 3 weeks after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

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 ($\chi^2_1 = 0.70$; $P = .20$) (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%) ($\chi^2_1 = 3.76$; $P = .05$). The number needed to treat for HAM-D score improvement at T2 was 5 (95% CI, 1-151) (eTable 3).

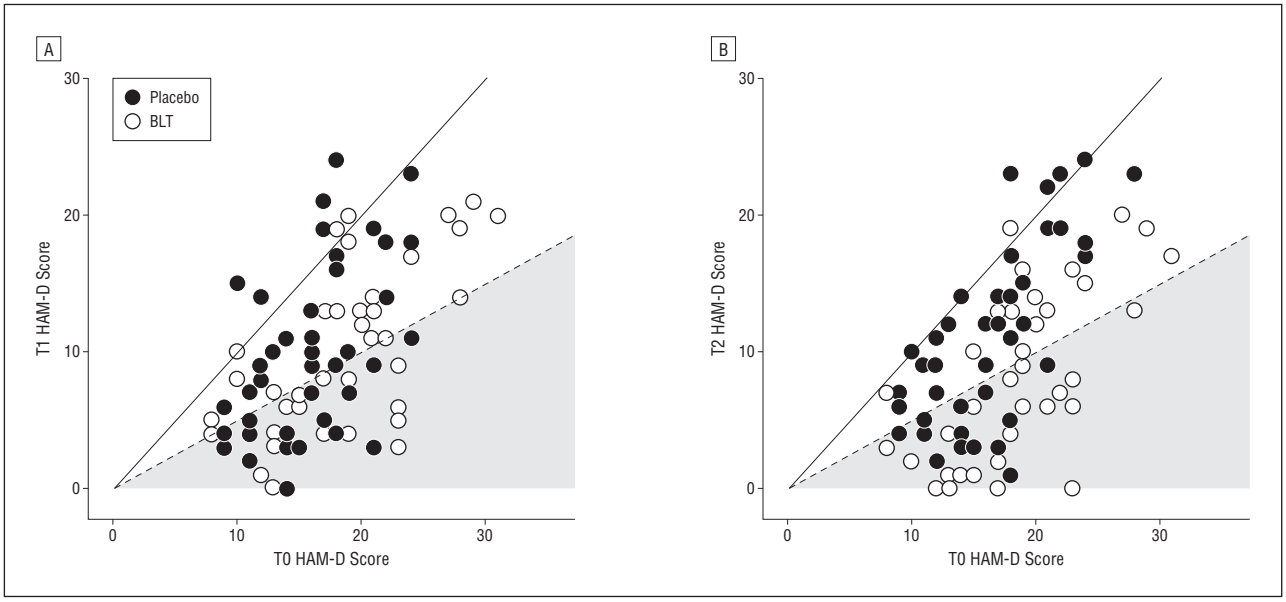

Figure 4. Scatterplots of individual patients' Hamilton Scale for Depression (HAM-D) scores at baseline (T0), after 3 weeks of treatment (T1) (A), and 3 weeks after discontinuation of treatment (T2) (B). Treatment consisted of bright light treatment (BLT) or placebo. Points that fall below the solid 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 significance (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] µg/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] µg/dL per minute to T2 at 0.05 [0.04-0.09] µg/dL per minute; placebo, 7% increase from T0 at 0.08 [0.05-0.11] µg/dL per minute to T2 at 0.10 [0.04-0.15] µg/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)**	0.26	3.3 (–0.5 to 6.9)	**$F_{1,81}$=4.32 (.04)**	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 Scale[46]; 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.

[a] Outcome descriptions are given in the "Outcome Measures" subsection of the "Methods" section.

[b] Indicates differences between BLT and placebo in the change from T0 to each patient's own end point for the change in depression rating.

[c] Calculated 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.

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

[e] With 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%; χ^2=3.95; P=.05) and fatigue (34% vs 19%; χ^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),

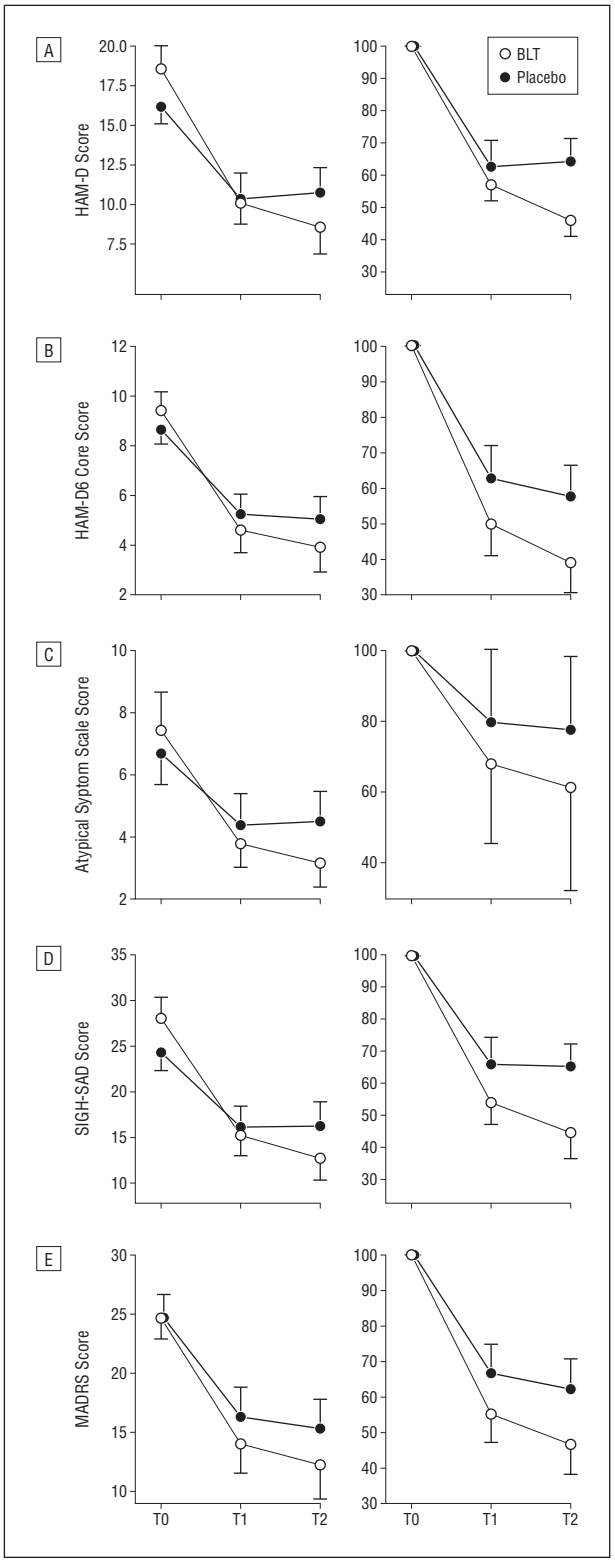

Figure 5. Effects of bright light treatment (BLT) and placebo in elderly patients with nonseasonal major depressive disorder. Data are depicted as means; error bars show the 95% confidence intervals. Absolute values are given on the left side, and the percentage of change from baseline (T0) is shown 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.

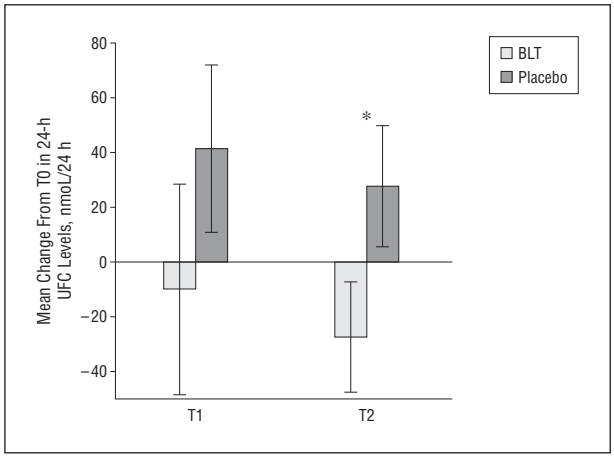

Figure 6. Mean change from baseline (T0) in patients receiving bright light treatment (BLT) and placebo by effects on 24-hour urinary free cortisol (UFC) levels. Data are depicted as mean change from baseline UFC levels; error bars show the 95% confidence intervals. T1 indicates after 3 weeks of treatment; 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, ≥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 al[78] 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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REFERENCES

1. Bunney WE, Bunney BG. Molecular clock genes in man and lower animals: possible implications for circadian abnormalities in depression. *Neuropsychopharmacology.* 2000;22(4):335-345.
2. Boivin DB. Influence of sleep-wake and circadian rhythm disturbances in psychiatric disorders. *J Psychiatry Neurosci.* 2000;25(5):446-458.
3. Grandin LD, Alloy LB, Abramson LY. The social zeitgeber theory, circadian rhythms, and mood disorders: review and evaluation. *Clin Psychol Rev.* 2006;26(6):679-694.
4. Rusting CL, Larsen RJ. Diurnal patterns of unpleasant mood: associations with neuroticism, depression, and anxiety. *J Pers.* 1998;66(1):85-103.
5. Deuschle M, Schweiger U, Weber B, Gotthardt U, Körner A, Schmider J, Standhardt H, Lammers CH, Heuser I. Diurnal activity and pulsatility of the hypothalamus-pituitary-adrenal system in male depressed patients and healthy controls. *J Clin Endocrinol Metab.* 1997;82(1):234-238.
6. Hoogendijk WJ, van Someren EJ, Mirmiran M, Hofman MA, Lucassen PJ, Zhou JN, Swaab DF. Circadian rhythm–related behavioral disturbances and structural hypothalamic changes in Alzheimer's disease. *Int Psychogeriatr.* 1996;8(suppl 3):245-252, 269-272.
7. Zhou JN, Riemersma RF, Unmehopa UA, Hoogendijk WJ, van Heerikhuize JJ, Hofman MA, Swaab DF. Alterations in arginine vasopressin neurons in the suprachiasmatic nucleus in depression. *Arch Gen Psychiatry.* 2001;58(7):655-662.
8. Gold PW, Chrousos GP. Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states. *Mol Psychiatry.* 2002;7(3):254-275.
9. Terman M, Terman JS. Light therapy for seasonal and nonseasonal depression: efficacy, protocol, safety, and side effects. *CNS Spectr.* 2005;10(8):647-663, 672.
10. Wirz-Justice A, Benedetti F, Berger M, Lam RW, Martiny K, Terman M, Wu JC. Chronotherapeutics (light and wake therapy) in affective disorders. *Psychol Med.* 2005;35(7):939-944.
11. Riemersma-van der Lek RF, Swaab DF, Twisk J, Hol EM, Hoogendijk WJ, Van Someren EJ. Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities: a randomized controlled trial. *JAMA.* 2008;299(22):2642-2655.
12. McEnany GW, Lee KA. Effects of light therapy on sleep, mood, and temperature in women with nonseasonal major depression. *Issues Ment Health Nurs.* 2005;26(7):781-794.
13. Thalén BE, Mørkrid L, Kjellman BF, Wetterberg L. Cortisol in light treatment of

seasonal and non-seasonal depression: relationship between melatonin and cortisol. *Acta Psychiatr Scand*. 1997;96(5):385-394.
14. Scheer FA, Buijs RM. Light affects morning salivary cortisol in humans. *J Clin Endocrinol Metab*. 1999;84(9):3395-3398.
15. Berson DM, Dunn FA, Takao M. Phototransduction by retinal ganglion cells that set the circadian clock. *Science*. 2002;295(5557):1070-1073.
16. Hannibal J, Fahrenkrug J. Melanopsin: a novel photopigment involved in the photoentrainment of the brain's biological clock? *Ann Med*. 2002;34(5):401-407.
17. Hattar S, Liao HW, Takao M, Berson DM, Yau KW. Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity. *Science*. 2002;295(5557):1065-1070.
18. Benedetti F, Barbini B, Colombo C, Smeraldi E. Chronotherapeutics in a psychiatric ward. *Sleep Med Rev*. 2007;11(6):509-522.
19. Wirz-Justice A. From the basic neuroscience of circadian clock function to light therapy for depression: on the emergence of chronotherapeutics. *J Affect Disord*. 2009;116(3):159-160.
20. Frazão R, Pinato L, da Silva AV, Britto LR, Oliveira JA, Nogueira MI. Evidence of reciprocal connections between the dorsal raphe nucleus and the retina in the monkey *Cebus apella*. *Neurosci Lett*. 2008;430(2):119-123.
21. Kawano H, Decker K, Reuss S. Is there a direct retina-raphe-suprachiasmatic nucleus pathway in the rat? *Neurosci Lett*. 1996;212(2):143-146.
22. Campbell SS, Kripke DF, Gillin JC, Hrubovcak JC. Exposure to light in healthy elderly subjects and Alzheimer's patients. *Physiol Behav*. 1988;42(2):141-144.
23. Espiritu RC, Kripke DF, Ancoli-Israel S, Mowen MA, Mason WJ, Fell RL, Klauber MR, Kaplan OJ. Low illumination experienced by San Diego adults: association with atypical depressive symptoms. *Biol Psychiatry*. 1994;35(6):403-407.
24. Turner PL, Mainster MA. Circadian photoreception: ageing and the eye's important role in systemic health. *Br J Ophthalmol*. 2008;92(11):1439-1444.
25. Van Someren EJ, Riemersma-Van Der Lek RF. Live to the rhythm, slave to the rhythm. *Sleep Med Rev*. 2007;11(6):465-484.
26. Golden RN, Gaynes BN, Ekstrom RD, Hamer RM, Jacobsen FM, Suppes T, Wisner KL, Nemeroff CB. The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. *Am J Psychiatry*. 2005; 162(4):656-662.
27. Martiny K, Lunde M, Simonsen C, Clemmensen L, Poulsen DL, Solstad K, Bech P. Relapse prevention by citalopram in SAD patients responding to 1 week of light therapy: a placebo-controlled study. *Acta Psychiatr Scand*. 2004;109(3):230-234.
28. Labbate LA, Lafer B, Thibault A, Sachs GS. Side effects induced by bright light treatment for seasonal affective disorder. *J Clin Psychiatry*. 1994;55(5):189-191.
29. Kripke DF, Tuunainen A, Endo T. Benefits of light treatment for depression. *Am J Psychiatry*. 2006;163(1):162-163.
30. Even C, Schröder CM, Friedman S, Rouillon F. Efficacy of light therapy in nonseasonal depression: a systematic review. *J Affect Disord*. 2008;108(1-2):11-23.
31. Tuunainen A, Kripke DF, Endo T. Light therapy for non-seasonal depression. *Cochrane Database Syst Rev*. 2004;(2):CD004050.
32. Forbes D, Morgan DG, Bangma J, Peacock S, Pelletier N, Adamson J. Light therapy for managing sleep, behaviour, and mood disturbances in dementia. *Cochrane Database Syst Rev*. 2004;(2):CD003946.
33. Kim S, Song HH, Yoo SJ. The effect of bright light on sleep and behavior in dementia: an analytic review. *Geriatr Nurs*. 2003;24(4):239-243.
34. Loving RT, Kripke DF, Elliott JA, Knickerbocker NC, Grandner MA. Bright light treatment of depression for older adults [ISRCTN55452501]. *BMC Psychiatry*. November 9, 2005;5:41. doi:10.1186/1471-244X-5-41.
35. Loving RT, Kripke DF, Knickerbocker NC, Grandner MA. Bright green light treatment of depression for older adults [ISRCTN69400161]. *BMC Psychiatry*. November 9, 2005;5:42. doi:10.1186/1471-244X-5-42.
36. Terman M. Evolving applications of light therapy. *Sleep Med Rev*. 2007;11(6):497-507.
37. Sumaya IC, Rienzi BM, Deegan JF II, Moss DE. Bright light treatment decreases depression in institutionalized older adults: a placebo-controlled crossover study. *J Gerontol A Biol Sci Med Sci*. 2001;56(6):M356-M360.
38. Tsai YF, Wong TK, Juang YY, Tsai HH. The effects of light therapy on depressed elders. *Int J Geriatr Psychiatry*. 2004;19(6):545-548.
39. World Medical Association. *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*. 5th rev. Edinburgh, Scotland: World Medical Association; 2000.
40. Volz HP, Mackert A, Stieglitz RD. Side-effects of phototherapy in nonseasonal depressive disorder. *Pharmacopsychiatry*. 1991;24(4):141-143.
41. Kripke DF, Mullaney DJ, Klauber MR, Risch SC, Gillin JC. Controlled trial of bright light for nonseasonal major depressive disorders. *Biol Psychiatry*. 1992;31 (2):119-134.
42. Baumgartner A, Volz HP, Campos-Barros A, Stieglitz RD, Mansmann U, Mackert A. Serum concentrations of thyroid hormones in patients with nonseasonal affective disorders during treatment with bright and dim light. *Biol Psychiatry*. 1996;40(9):899-907.
43. Cohen J, ed. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates Inc; 1998.
44. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 4th ed, text revision (*DSM-IV-TR*)*. Washington, DC: American Psychiatric Press; 2000.
45. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, Leirer VO. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res*. 1982-1983;17(1):37-49.
46. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. April 1979;134:382-389.
47. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol*. 1967;6(4):278-296.
48. Terman M, Williams JBW. SAD assessment tools revisited. *Light Treat Biol Rhythms*. 1994;7:23.
49. Williams JBW, Link MJ, Rosenthal NE, Amira L, Terman M. *Structured Interview Guide for the Hamilton Depression Rating Scale–Seasonal Affective Disorder Version (SIGH-SAD)*. New York: New York State Psychiatric Institute; 1992.
50. O'Sullivan RL, Fava M, Agustin C, Baer L, Rosenbaum JF. Sensitivity of the six-item Hamilton Depression Rating Scale. *Acta Psychiatr Scand*. 1997;95(5):379-384.
51. Martiny K. Adjunctive bright light in non-seasonal major depression. *Acta Psychiatr Scand Suppl*. 2004;(425):7-28.
52. Terman M, Amira L, Terman JS, Ross DC. Predictors of response and nonresponse to light treatment for winter depression. *Am J Psychiatry*. 1996;153 (11):1423-1429.
53. Rosenthal NE, Genhart M, Sack DA, Skwerer RG, Wehr TA. Seasonal affective disorder: relevance for treatment and research of bulimia. In: Hudson JL, Pope HG, eds. *Psychobiology of Bulimia*. Washington, DC: American Psychiatric Press; 1987.
54. Lieverse R, Nielen MM, Veltman DJ, Uitdehaag BM, van Someren EJ, Smit JH, Hoogendijk WJ. Bright light in elderly subjects with nonseasonal major depressive disorder: a double blind randomised clinical trial using early morning bright blue light comparing dim red light treatment. *Trials*. July 31, 2008;9:48. doi:10.1186/1745-6215-9-48.
55. Parmelee PA, Thuras PD, Katz IR, Lawton MP. Validation of the Cumulative Illness Rating Scale in a geriatric residential population. *J Am Geriatr Soc*. 1995; 43(2):130-137.
56. First MB, Spitzer RL, Gibbon M, Williams JB. *Structured Clinical Interview for* DSM-IV *Axis I Disorders–Patient Edition. SCID-I/P, Version 2.0*. New York: New York Psychiatric Institute, Biometric Research Dept; 1996.
57. Martiny K, Lunde M, Undén M, Dam H, Bech P. Adjunctive bright light in nonseasonal major depression: results from clinician-rated depression scales. *Acta Psychiatr Scand*. 2005;112(2):117-125.
58. Brainard GC, Sliney D, Hanifin JP, Glickman G, Byrne B, Greeson JM, Jasser S, Gerner E, Rollag MD. Sensitivity of the human circadian system to short-wavelength (420-nm) light. *J Biol Rhythms*. 2008;23(5):379-386.
59. Beauchemin KM, Hays P. Sunny hospital rooms expedite recovery from severe and refractory depressions. *J Affect Disord*. 1996;40(1-2):49-51.
60. Deltito JA, Moline M, Pollak C, Martin LY, Maremmani I. Effects of phototherapy on non-seasonal unipolar and bipolar depressive spectrum disorders. *J Affect Disord*. 1991;23(4):231-237.
61. Kripke DF. Therapeutic effects of bright light in depressed patients. *Ann N Y Acad Sci*. 1985;453:270-281.
62. Kripke DF. Light treatment for nonseasonal depression: speed, efficacy, and combined treatment. *J Affect Disord*. 1998;49(2):109-117.
63. Kripke DF, Risch SC, Janowsky D. Bright white light alleviates depression. *Psychiatry Res*. 1983;10(2):105-112.
64. Loving RT, Kripke DF, Shuchter SR. Bright light augments antidepressant effects of medication and wake therapy. *Depress Anxiety*. 2002;16(1):1-3.
65. Mackert A, Volz HP, Stieglitz RD, Müller-Oerlinghausen B. Phototherapy in nonseasonal depression. *Biol Psychiatry*. 1991;30(3):257-268.
66. Neumeister A, Goessler R, Lucht M, Kapitany T, Bamas C, Kasper S. Bright light therapy stabilizes the antidepressant effect of partial sleep deprivation. *Biol Psychiatry*. 1996;39(1):16-21.
67. Yamada N, Martin-Iverson MT, Daimon K, Tsujimoto T, Takahashi S. Clinical and chronobiological effects of light therapy on nonseasonal affective disorders. *Biol Psychiatry*. 1995;37(12):866-873.
68. Colombo C, Lucca A, Benedetti F, Barbini B, Campori E, Smeraldi E. Total sleep deprivation combined with lithium and light therapy in the treatment of bipolar depression: replication of main effects and interaction. *Psychiatry Res*. 2000; 95(1):43-53.
69. Bloching B, Dechêne C, Täschner KL. Outlasting antidepressant effect of late partial sleep deprivation by bright light therapy. *J Sleep Res*. 2000;9(suppl 1):21.
70. Newell-Price J, Trainer P, Besser M, Grossman A. The diagnosis and differential diagnosis of Cushing's syndrome and pseudo-Cushing's states. *Endocr Rev*. 1998; 19(5):647-672.
71. Schatzberg AF, Samson JA, Bloomingdale KL, Orsulak PJ, Gerson B, Kizuka PP, Cole JO, Schildkraut JJ. Toward a biochemical classification of depressive disorders, X: urinary catecholamines, their metabolites, and D-type scores in subgroups of depressive disorders. *Arch Gen Psychiatry*. 1989;46(3):260-268.
72. Van Someren EJ, Nagtegaal E. Improving melatonin circadian phase estimates. *Sleep Med*. 2007;8(6):590-601.
73. Ancoli-Israel S, Clopton P, Klauber MR, Fell R, Mason W. Use of wrist activity for monitoring sleep/wake in demented nursing-home patients. *Sleep*. 1997; 20(1):24-27.
74. Kushida CA, Chang A, Gadkary C, Guilleminault C, Carrillo O, Dement WC. Comparison of actigraphic, polysomnographic, and subjective assessment of sleep parameters in sleep-disordered patients. *Sleep Med*. 2001;2(5):389-396.
75. Sacket DL, Straus SE, Richardson WS, Rosenberg W, Haynes RB. *Evidence-Based Medicine: How to Practice and Teach EBM*. 2nd ed. New York, NY: Churchill Livingstone; 2000.
76. Altman DG. Confidence intervals for the number needed to treat. *BMJ*. 1998;317 (7168):1309-1312.
77. Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. *N Engl J Med*. 1988;318(26):1728-1733.
78. Martiny K, Lunde M, Undén M, Dam H, Bech P. The lack of sustained effect of bright light, after discontinuation, in non-seasonal major depression. *Psychol Med*. 2006;36(9):1247-1252.