



# Effects of Light Therapy on Mood and Insulin Sensitivity in Patients With Type 2 Diabetes and Depression: Results From a Randomized Placebo-Controlled Trial

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## OBJECTIVE

Depression is common in patients with type 2 diabetes and adversely affects quality of life and diabetes outcomes. We assessed whether light therapy, an antidepressant, improves mood and insulin sensitivity in patients with depression and type 2 diabetes.

## RESEARCH DESIGN AND METHODS

This randomized, double-blind, placebo-controlled trial included 83 patients with depression and type 2 diabetes. The intervention comprised 4 weeks of light therapy (10,000 lux) or placebo light therapy daily at home. Primary outcomes included depressive symptoms (Inventory of Depressive Symptomatology [IDS]) and insulin sensitivity (M-value derived from the results of a hyperinsulinemic-euglycemic clamp). Secondary outcomes were related psychological and glucometabolic measures.

## RESULTS

Intention-to-treat analysis showed that light therapy was not superior to placebo in reducing depressive symptoms (−3.9 IDS points [95% CI −9.0 to 1.2];  $P = 0.248$ ) and had no effect on insulin sensitivity (0.15 mg/kg\*min [95% CI −0.41 to 0.70];  $P = 0.608$ ). Analyses incorporating only those participants who accurately adhered to the light therapy protocol ( $n = 51$ ) provided similar results, but did suggest positive effects of light therapy on depression response rates ( $\geq 50\%$  reduction in IDS points) (26% more response;  $P = 0.031$ ). Prespecified analysis showed effect moderation by baseline insulin sensitivity ( $P = 0.009$ ) and use of glucose-lowering medication ( $P = 0.023$ ). Light therapy did not affect depressive symptoms in participants with higher insulin sensitivity or those who use only oral glucose-lowering medication or none at all, but it did produce a relevant effect in participants with lower insulin sensitivity (−12.9 IDS points [95% CI −21.6 to −4.2];  $P = 0.017$ ) and a trend toward effectiveness in those using insulin (−12.2 IDS points [95% CI −21.3 to −3.1];  $P = 0.094$ ). Light therapy was well tolerated.

## CONCLUSIONS

Although this trial is essentially inconclusive, secondary analyses indicate that light therapy might be a promising treatment for depression among a subgroup of highly insulin-resistant individuals with type 2 diabetes.

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One of five patients with type 2 diabetes suffers from clinical depression (1). The prevalence of depression among patients with type 2 diabetes is double that among the general population, and this comorbidity is recognized as a global public health challenge (2,3). Previous research suggests a bidirectional cause-and-effect relationship between type 2 diabetes and depression (4,5). In addition, shared underlying pathophysiological mechanisms, such as a disturbance of the sleep-wake cycle, have been described (4,5).

Unfortunately, depression in people with type 2 diabetes is associated with a poor prognosis and poor treatment results. The depression seems to be more persistent and recurrent (6), and some antidepressant drugs may even worsen glycemic control (7). Furthermore, patients with depression and type 2 diabetes exhibit a higher risk for diabetes complications and mortality (8). Clearly, more efficacious depression treatments are needed for patients with type 2 diabetes.

Light therapy, in which patients are exposed to bright light early in the morning for several days, is a patient-friendly and low-cost treatment, with early onset of action and low risk for adverse effects (9). It is a first-line treatment for seasonal depression and has recently been proven to be successful in treating nonseasonal depression as well, even in several difficult-to-treat patient groups (10–12). Light therapy is traditionally assumed to act by entraining the sleep-wake cycle via ocular stimulation of the brain's suprachiasmatic nucleus (the biological clock) (9), thereby improving sleep and circadian rhythmicity (13). Yet, recent findings also point to effects of light on mood via other cerebral pathways (14). The brain biological clock plays a main role in regulating glucose metabolism, and sleep disturbances have been associated with higher incidence rates of type 2 diabetes, hyperglycemia, and insulin resistance (15).

On the basis of these findings, we hypothesized that light therapy may be an effective antidepressant in people with depression and type 2 diabetes, and that it might concurrently improve insulin sensitivity. This hypothesis is supported by two case reports that describe an increase in insulin sensitivity and hypoglycemia, and less need for insulin, in two patients with diabetes who received light therapy to treat seasonal depression (16,17).

So far, no experimental evidence is available on the effects of light therapy on either mood or glycemic control in people with type 2 diabetes. To our knowledge, we are the first to conduct a randomized, placebo-controlled trial to test effects of light therapy on mood and insulin sensitivity in people with depression and type 2 diabetes.

## RESEARCH DESIGN AND METHODS

### Design

We performed a randomized, double-blind, placebo-controlled, parallel-arm trial to compare the effects of light therapy with those of a placebo. A description of the methods was published at the start of the trial (18), and the trial has been registered in the Netherlands Trial Register (NTR4942). Participants were assessed at baseline (week 0), after 4 weeks of receiving light therapy or placebo (week 4), and after 4 weeks of follow-up (week 8). Some measures were obtained at weekly intervals during the intervention (weeks 1, 2, and 3). Study procedures were performed at two locations. Participant enrollment started in 2014 and ended in 2017. Participants gave informed consent before participating. The study was executed in accordance with the Declaration of Helsinki and with approval from the medical ethics committee of Amsterdam University Medical Centers (Amsterdam UMC), location Vrije Universiteit.

### Participants

Participants were recruited through advertisements, referrals from clinicians, and databases of patients who consented to be informed about research studies open for participation. Eligibility was determined by a telephone screening and a screening visit. Included patients 1) were 18 years or older, 2) had a documented physician-based diagnosis of type 2 diabetes and used glucose-lowering medication or had HbA<sub>1c</sub> >42 mmol/mol (5.9%), and 3) had a major depressive episode according to DSM-IV criteria. Participants were excluded if they had a medical condition or recently experienced a medical event that could potentially compromise the effects or safety of light therapy (for specifics, see Supplementary Data, Information 1).

### Randomization and Masking

Participants were randomized to groups by using a computer-generated table, which

created blocks of six participants, with randomly varying sequences within blocks. Participants who agreed to participate in the hyperinsulinemic-euglycemic clamp (HEC) procedure were randomized separately. Upon approval by the ethics committee, participants were informed that the study investigated differences between white-yellow and green light therapy, but they were unaware that one of the conditions was a placebo. Participants were told that we could not ensure the effects of either intervention under study. The research assistants who delivered the lamps to the participants' homes were aware of the treatment allocation but were not involved in any other study activities; they received explicit instructions regarding their interactions with the participants in order to prevent disclosure of treatment allocation. All other study personnel, including the research assistants and physicians involved in obtaining measurements, were fully blinded to the conditions.

### Intervention

Participants were randomly assigned to receive active (broad-spectrum, white-yellow light, 10,000 lux) or placebo (monochromatic green light [545 nm], 470 lux) light therapy at home, scheduled for 30 min every morning over 4 weeks. CE-certified Diamond-5 SAD Lightbox light therapy lamps (SAD Lightbox Company, Berkshire, U.K.), adapted with light filters, were used. Estimates of irradiance are provided in Supplementary Table 1. Timing of light therapy was set in accordance with results from the Morningness-Eveningness Questionnaire (MEQ) (19), but each participant agreed to the time in order to ensure the therapy could be incorporated in the participant's daily life. Research assistants gave instructions on how to apply the therapy. Therapy compliance was monitored weekly by telephone and reinforced when necessary.

### Primary Outcome Measures

The prespecified primary outcome measures were changes in depressive symptoms and insulin sensitivity from baseline (week 0) to the end of the intervention period (week 4).

Depressive symptoms were assessed by using the self-report version of the Inventory of Depressive Symptomatology (IDS). A score  $\geq 14$  indicates clinically

significant symptoms of depression. Response to the intervention was defined as a reduction of IDS score by  $\geq 50\%$ . Depression remission was defined as an IDS score  $\leq 13$ . Relapse was defined as an IDS score  $\geq 26$ .

Insulin sensitivity was evaluated using an HEC, the gold standard for quantifying whole-body insulin sensitivity (20). This procedure quantifies the rate of exogenous glucose infusion required to maintain the blood glucose concentration at euglycemic levels (goal 5.0 mmol/L) in response to a fixed increase in blood insulin concentration through administration of insulin (i.e., NovoRapid 100 IU/mL; Novo Nordisk, Bagsvaerd, Denmark) at 40 mU/m<sup>2</sup>\*min. After 90 min, a steady state is reached, which allows the corrected M-value to be calculated; this value, expressed as the amount of glucose infusion (mg/kg\*min), reflects muscle insulin sensitivity. Lower M-values represent lower insulin sensitivity.

### Secondary Outcome Measures

Secondary outcome measures included anxiety symptoms (measured by using the Beck Anxiety Inventory [BAI]); diabetes distress (measured by using the Problem Areas in Diabetes [PAID] questionnaire; a score  $\geq 33$  indicates high diabetes distress); self-reported insomnia symptoms (based on the Insomnia Severity Index [ISI]; a score  $\geq 10$  indicates clinically relevant insomnia); and objective sleep duration, sleep efficiency, and mid-sleep time, derived from actigraphy data through the use of a validated algorithm. Glucometabolic secondary outcome measures included HbA<sub>1c</sub> concentration, fasting blood glucose (FBG) concentration (among the HEC subsample), self-reported hypoglycemic events, and body weight. Expectations regarding treatment were assessed by using a four-item questionnaire.

### Side Effects and Adverse Events

Side effects and adverse events were inventoried weekly using a side effect questionnaire and telephonic controls. Visual acuity, contrast sensitivity, and retinopathy grade were analyzed at the screening visit and at follow-up (week 8).

### Sample Size

On the basis of previous studies of light therapy (10–12,21) and of the effects of sleep restriction on insulin sensitivity

(22,23), we expected moderate effect sizes for depressive symptoms and large effect sizes for insulin sensitivity. The planned sample size of 84 yields 80% power for detecting a moderate effect size (Cohen's *d* of at least 0.50 throughout follow-up) for depressive symptoms, assuming four repeated measurements per participant and a maximum within-subject correlation of 0.6. The planned sample size of 54 for the HEC subsample yields 80% power to detect a large effect size (Cohen's *d* of at least 0.78) for a single follow-up measurement at 4 weeks.

### Statistical Analyses

The balance of randomization was tested with the independent samples *t* test and  $\chi^2$  test. Primary analyses of outcome measures included all participants (intention-to-treat); secondary analyses included analyses in which only those participants who accurately adhered to the light therapy protocol were incorporated (per-protocol). Differences between conditions are expressed as the mean absolute difference at week 4, with the 95% CI and the standardized difference or effect size (Cohen's *d* [the mean difference divided by the pooled SD] or relative risk). Linear mixed model (LMM) (continuous outcomes) and generalized estimating equation (GEE) (dichotomous outcomes) analyses included all measures from week 1 to week 4. To correct for differences at baseline, baseline values were incorporated into the model as covariates. Effects at follow-up (week 8) were evaluated in separate analyses. For HbA<sub>1c</sub>, an index of mean blood glucose concentrations within the past 2–3 months, primary analyses included data from week 4 and week 8.

Effect moderation was analyzed in order to identify subgroups that benefitted most from light therapy. For this purpose we used linear regression with depressive symptoms or the insulin sensitivity change score as dependent variables and the condition, the moderator, and their two-way interaction as predictors. A candidate moderator was declared an effect moderator when the two-way interaction was significant. Prespecified candidate effect-moderators included depressive symptoms at baseline, depression symptoms profile, insulin sensitivity, HbA<sub>1c</sub>, circadian rhythm type, insomnia severity, seasonality of depression, and time of year. Other

candidate effect moderators tested included age, sex, antidepressant medication, and glucose-lowering medication. In addition, we performed prespecified mediation analyses (the Sobel test) to evaluate whether the effects of light therapy on depressive symptoms and insulin sensitivity were mediated by changes in sleep (subjective insomnia symptoms, objective sleep duration, sleep efficiency, and mid-sleep time).

Significance was set at  $P=0.05$ . We did not power the study for post hoc per-protocol effect moderation analyses or mediation analysis, and therefore those should be regarded as exploratory. Statistics were analyzed by using IBM SPSS Statistics 22.

## RESULTS

### Sample Selection

In total, 155 participants were screened, of whom 43 did not meet inclusion criteria, 16 were excluded, and 13 declined to participate (Supplementary Data, Information 1). Thus we included 83 adults with depression and type 2 diabetes, of whom 43 were allocated to receive light therapy and 40 to receive placebo. A subgroup of 60 participants took part in the HEC procedure (Supplementary Data, Information 1).

One participant from the light therapy group was excluded from the analyses because their depression remitted (IDS score  $\leq 13$ ) between the screening and baseline measurements. Three patients discontinued the protocol after the baseline measurements: one for unknown reasons (placebo group) and two for medical reasons unrelated to the intervention (light therapy group). All participants who received the intervention completed the study protocol. Eight patients discontinued the HEC protocol: two because of difficult venous access, one because of discomfort during the procedure at baseline, three because of unforeseen absence of the HEC-supervising research-physician, and two due to discontinuation of the general protocol. Outcome measures were obtained from 79 participants (50 participants in the HEC subsample). A flowchart of the inclusion process is shown in Supplementary Fig. 1.

### Protocol Deviations

We did not foresee 13 participants changing their glucose-lowering medication during the protocol. One participant used an oral corticosteroid during the protocol. Glucometabolic measures that

could have been affected by medication changes were excluded from analyses before treatment allocation was disclosed. Exclusion was equally distributed over the light therapy and placebo conditions.

Per-protocol analyses included 51 of 82 participants (35 of 58 in the HEC subsample). Accurate treatment adherence was defined as  $\geq 21$  days of light therapy within 120 min of the time recommended by the MEQ.

### Sample Characteristics

Randomization was balanced regarding the demographic and clinical characteristics of the total sample and of the HEC subsample (Table 1 and Supplementary Table 2). As BMI was almost significantly different ( $P = 0.088$ ) for the HEC subgroup, we additionally analyzed the effects of light therapy on insulin sensitivity adjusted for BMI.

### Depression

After 4 weeks, light therapy had not statistically significantly reduced depressive symptoms (between-arm difference:  $-3.9$  IDS points, or  $-9.2\%$  [95% CI  $-9.0$  to  $1.2$  IDS points];  $P = 0.248$ , LMM; Cohen's  $d = 0.35$ ) (Fig. 1 and Table 2). When considering response and remission rates, light therapy did not result in more response or remission than that achieved with placebo at week 4 (between-arm difference: 16% more response [relative risk 1.55 [95% CI 0.84–2.86];  $P = 0.242$ , GEE], 0% more remission [relative risk 1.00 [95% CI 0.49–2.03];  $P = 0.430$ , GEE] (Table 2). Similar results were obtained 4 weeks after the intervention period was discontinued (week 8) (between-arm difference:  $-2.2$  IDS points, or  $-4.1\%$  [95% CI  $-7.3$  to  $2.8$  IDS points];  $P = 0.483$ , LMM), 8% more response [ $P = 0.492$ , GEE], 5% more remission [ $P = 0.624$ , GEE] (Fig. 1 and Supplementary Table 3).

Baseline characteristics did not differ between those who responded and those who did not respond to light therapy (Supplementary Table 4).

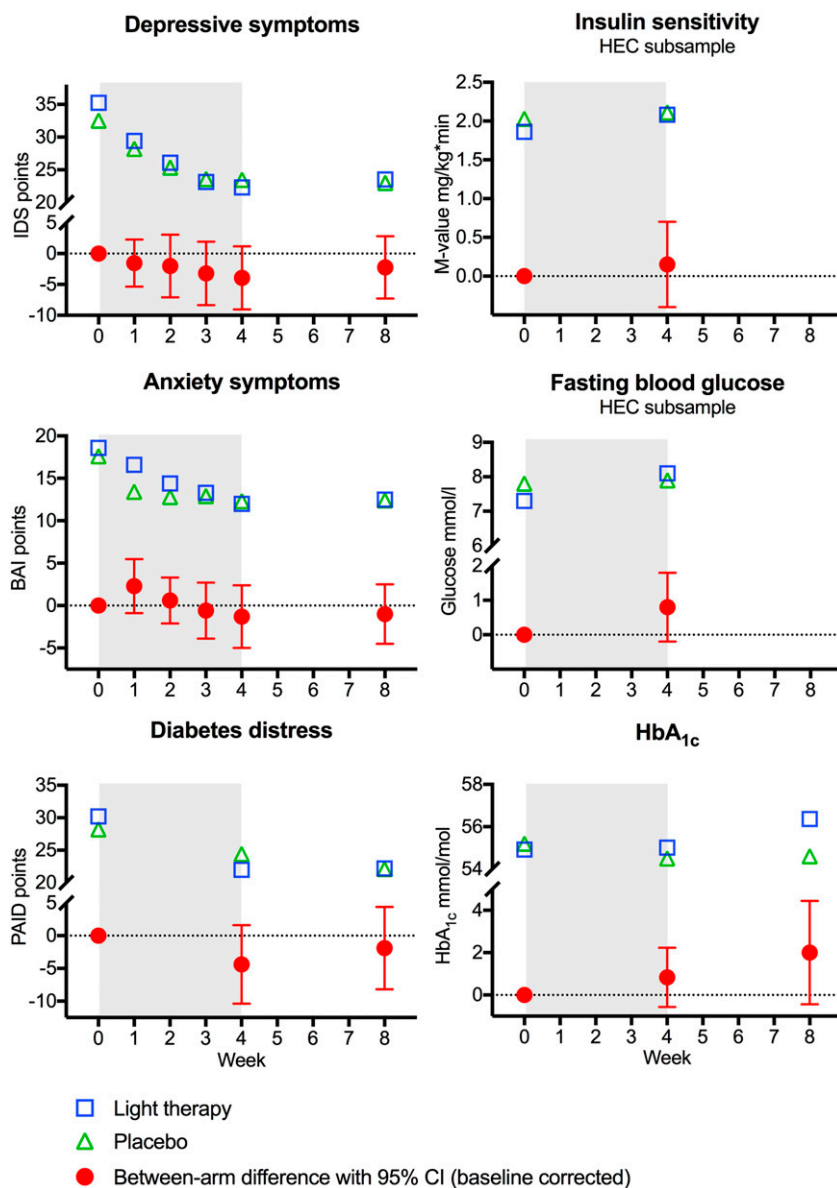
### Insulin Sensitivity

Light therapy had no effect on insulin sensitivity (between-arm difference in M-value at week 4:  $0.15$  mg/kg\*min [95% CI  $-0.41$  to  $0.70$ ];  $P = 0.608$ , LMM; Cohen's  $d = 0.16$ ) (Fig. 1 and Table 2). Analysis in which BMI was incorporated into the model as a covariate yielded

**Table 1—Baseline characteristics**

	Light therapy ( <i>n</i> = 42)	Placebo ( <i>n</i> = 40)
<b>General characteristics</b>		
Age, years (mean $\pm$ SD)	60.1 $\pm$ 9.8	62.9 $\pm$ 10.7
Sex, <i>n</i>		
Male	21	24
Female	21	16
Ethnicity, <i>n</i>		
European	38	36
Suriname or Dutch Antilles	2	2
South Asian	1	2
Unknown	1	0
Comorbid diseases in number of medications (mean $\pm$ SD)	9.0 $\pm$ 5.4	9.3 $\pm$ 4.4
Polypharmacy ( $\geq 5$ medications), %	74	83
BMI, kg/m <sup>2</sup> (mean $\pm$ SD)	33.1 $\pm$ 5.4	31.9 $\pm$ 5.7
<b>Depression-related characteristics</b>		
Major depressive disorder type		
Single episode	22	22
Recurrent	12	16
Unknown	8	2
Time since first episode of major depressive disorder, years (mean $\pm$ SD)	21.7 $\pm$ 14.6	23.7 $\pm$ 18.7
Depression severity by IDS score classification, <i>n</i>		
Mild	8	13
Moderate	21	17
Severe	9	5
Very severe	4	5
Antidepressant medication, <i>n</i>		
None	19	21
Selective serotonin reuptake inhibitor or similar	18	14
Tricyclic antidepressant	5	5
Comorbid anxiety disorder, <i>n</i>		
No	14	14
Yes	28	26
Benzodiazepine use, <i>n</i>		
No	33	32
Yes	9	8
<b>Diabetes-related characteristics</b>		
Diabetes distress, PAID score (mean $\pm$ SD)	31.4 $\pm$ 25.0	27.6 $\pm$ 23.0
Duration of diabetes, years (mean $\pm$ SD)	10.6 $\pm$ 6.4	12.7 $\pm$ 7.9
HbA <sub>1c</sub> , mmol/mol (mean $\pm$ SD)	54.9 $\pm$ 12.2	55.2 $\pm$ 14.2
HbA <sub>1c</sub> , % (mean $\pm$ SD)	7.2 $\pm$ 1.1	7.2 $\pm$ 1.3
FBG, mmol/L (mean $\pm$ SD)*	7.8 $\pm$ 1.9	7.3 $\pm$ 2.2
Insulin sensitivity, M-value as mg/kg*min (mean $\pm$ SD)*	2.03 $\pm$ 1.02	1.86 $\pm$ 1.22
Glucose-lowering medication, <i>n</i>		
None	3	3
Oral	26	23
Insulin	13	14
<b>Sleep, chronobiological, and seasonal characteristics</b>		
Obstructive sleep apnea risk per BQ, <i>n</i>		
Low	5	5
High	32	29
Unknown	5	6
Insomnia symptoms, ISI score (mean $\pm$ SD)	13.9 $\pm$ 6.3	13.6 $\pm$ 7.6
Sleep duration, h <sup>†</sup> (mean $\pm$ SD)	6.7 $\pm$ 1.7	6.8 $\pm$ 1.2
Sleep efficiency, % of time asleep while intending to sleep <sup>†</sup> (mean $\pm$ SD)	84 $\pm$ 9	86 $\pm$ 7
Mid-sleep time, time <sup>†</sup> (mean $\pm$ SD)	04:04 $\pm$ 1:27	04:19 $\pm$ 1:46
Circadian rhythm type, MEQ score (mean $\pm$ SD)	50.9 $\pm$ 12.2	51.5 $\pm$ 11.7
Seasonality of symptoms, GSS score (mean $\pm$ SD)	6.4 $\pm$ 5.4	7.4 $\pm$ 4.8
Time of year in protocol, <i>n</i>		
Autumn	7	10
Winter	8	12
Spring	18	13
Summer	9	5

BQ, Berlin questionnaire; GSS, Global Seasonality Scale. \*HEC subsample: light therapy,  $n = 31$ ; placebo,  $n = 27$ . PAID scores  $\geq 33$  indicate high diabetes distress. ISI scores  $\geq 10$  indicate clinically relevant insomnia. MEQ scores  $\leq 41$  indicate "evening types," scores 42–58 indicate "intermediate types," scores  $\geq 59$  indicate "morning types." GSS scores  $\geq 11$  indicate a seasonal pattern of symptoms. Test statistics/ $P$  values are shown in Supplementary Table 1. <sup>†</sup>Calculated from actigraphy-derived data.



**Figure 1**—Effects of light therapy on depression, insulin sensitivity, and secondary outcome measures. Data points represent the mean values for the light therapy (blue squares) and placebo (green triangles) arms and the mean difference between conditions (light therapy minus placebo; baseline corrected) (red circles). The error bars represent the 95% CI. Week 0 represents the baseline; week 4, the end of the intervention period; week 8, follow-up. The intervention period is marked in gray.

similar results ( $P = 0.546$ , LMM). Mean blood glucose concentration during the steady state was 5.0 mmol/L (SD 0.4 mmol/L); mean plasma insulin concentration was 434 pmol/L (SD 81 pmol/L) (subsample;  $n = 10$  HEC procedures).

**Secondary Outcome Measures**

Differences in anxiety symptoms and diabetes distress between conditions were not significant (between-arm difference at week 4:  $-1.3$  BAI points [95% CI  $-5.1$  to  $2.4$ ];  $P = 0.848$ , LMM; Cohen's  $d = 0.16$ ; and  $-4.4$  PAID points [95%

CI  $-10.5$  to  $1.6$ ];  $P = 0.142$ , LMM; Cohen's  $d = 0.33$ ; between-arm difference at week 8:  $-1.0$  BAI points [95% CI  $-4.5$  to  $2.6$ ];  $P = 0.503$ , LMM; and  $-1.9$  PAID points [95% CI  $-8.2$  to  $4.4$ ];  $P = 0.574$ , LMM) (Fig. 2, Table 1, and Supplementary Table 3).

Light therapy did not affect HbA<sub>1c</sub>, FBG concentration, or the number of self-reported hypoglycemic events (between-arm differences in HbA<sub>1c</sub>: 2.0 mmol/mol [95% CI  $-0.5$  to  $4.4$ ] at week 8 [ $P = 0.116$ , LMM; Cohen's  $d = 0.42$ ]; in FBG: 0.8 mmol/L [95% CI  $-0.2$  to  $1.8$ ] at week 4 [ $P = 0.181$ , LMM; Cohen's  $d =$

0.44]; in hypoglycemic events: 0.51 day/week [95% CI  $-0.00$  to  $1.02$ ] at week 4 [ $P = 0.506$ , GEE; Cohen's  $d = 0.42$ ] and 0.10 day/week [95% CI  $-0.25$  to  $0.46$ ] at week 8) (Fig. 1, Table 2, and Supplementary Table 3). Body weight did not change in response to light therapy (between-arm difference at week 4:  $-0.23$  kg [95% CI  $-0.73$  to  $0.27$ ] [ $P = 0.420$ , LMM; Cohen's  $d = 0.23$ ]; between-arm difference at week 8:  $-0.66$  kg [95% CI  $-1.40$  to  $0.07$ ] [ $P = 0.069$ , LMM]) (Table 2 and Supplementary Table 3).

Light therapy had no effect on subjective insomnia symptoms, objective sleep duration, sleep efficiency, or mid-sleep time at week 4 (between-arm differences in ISI points:  $-0.2$  points [95% CI  $-1.9$  to  $2.2$ ];  $P = 0.783$ , LMM; Cohen's  $d = 0.04$ ; in sleep duration:  $-13$  min [95% CI  $-53$  to  $27$ ];  $P = 0.329$ , LMM; Cohen's  $d = 0.16$ ); in sleep efficiency:  $-0.8\%$  [95% CI  $-4.3$  to  $2.8$ ];  $P = 0.130$ , LMM; Cohen's  $d = 0.38$ ; and in mid-sleep time:  $-2$  min [95% CI  $-27$  to  $24$ ];  $P = 0.580$ , LMM; Cohen's  $d = 0.03$ ) or at week 8 (ISI points:  $-0.2$  points [95% CI  $-2.1$  to  $2.5$ ];  $P = 0.951$ , LMM); sleep duration: 26 min [95% CI  $-7$  to  $59$ ];  $P = 0.266$ , LMM; sleep efficiency: 0.7% [95% CI  $-3.4$  to  $4.9$ ];  $P = 0.804$ , LMM; mid-sleep time: 8 min [95% CI  $13$ – $30$ ];  $P = 0.577$ , LMM) (Table 2 and Supplementary Table 3).

**Expectancy**

Expectancy scores did not differ between conditions or between responders (reduction of IDS score by  $\geq 50\%$ ) and nonresponders. Expectancy scores were not correlated with the percentage reduction in depressive symptoms (IDS points) (Supplementary Table 5).

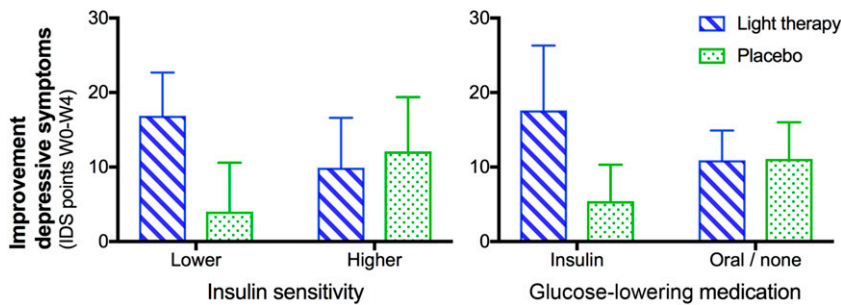
**Treatment Adherence**

Treatment adherence did not differ between patients receiving the light therapy and those receiving placebo (Supplementary Table 6). On average, participants were exposed to light therapy or placebo for 24 days, at a mean time of 7:56 A.M., which was, on average, 84 min later than the time recommended by the MEQ. Participants generally kept to the time that they agreed to during the screening visit; only one participant postponed the time of their therapy. One participant receiving light therapy decided to stop the intervention after 2 weeks because of headaches related to the intervention.

**Table 2—Effects of light therapy on depression, insulin sensitivity, and secondary outcome measures**

	Intention-to-treat analysis				Per-protocol analysis				
	Condition	ΔW0-W4	Difference at W4*	Cohen's d or relative risk (95% CI) at W4	Test statistic, LMM/GEE W1-W4 (P value)	ΔW0-W4	Difference at W4*	Cohen's d or relative risk (95% CI) at W4	Test statistic, LMM/GEE W1-W4 (P value)
<b>Primary outcomes</b>									
Depressive symptoms, IDS score	Light therapy Placebo	-12.9 -9.0	-3.9 (-9.0 to 1.2)	0.35	F = 1.357 (0.248)	-12.9 -7.0	-5.9 (-13.0 to 1.2)	0.47	F = 0.809 (0.373)
Insulin sensitivity, M-value as mg/kg*min	Light therapy Placebo	0.22 0.08	0.15 (-0.41 to 0.70)	0.16	F = 0.266 (0.608)	0.17 0.22	-0.05 (-0.86 to 0.76)	0.05	F = 0.004 (0.952)
<b>Secondary outcomes</b>									
Depression response, % of participants	Light therapy Placebo	44% 28%	16%	1.55 (0.84-2.86)	Wald $\chi^2$ = 1.366 (0.242)	43% 17%	26%	2.46 (0.92-6.62)	Wald $\chi^2$ = 4.643 (0.031)
Depression remission, % of participants	Light therapy Placebo	28% 28%	0%	1.00 (0.49-2.03)	Wald $\chi^2$ = 0.622 (0.430)	25% 26%	-1%	0.96 (0.37-2.46)	Wald $\chi^2$ = 0.195 (0.659)
Anxiety symptoms, BAI score	Light therapy Placebo	-6.6 -5.3	-1.3 (-5.1 to 2.4)	0.16	F = 0.037 (0.848)	-7.1 -5.0	-2.1 (-6.9 to 2.6)	0.25	F = 0.035 (0.853)
Diabetes distress, PAID score	Light therapy Placebo	-8.2 -3.8	-4.4 (-10.5 to 1.6)	0.33	F = 2.203 (0.142)	-8.8 -3.5	-5.3 (-12.8 to 2.2)	0.40	F = 2.619 (0.112)
FBG, mmol/L	Light therapy Placebo	0.8 0.1	0.8 (-0.2 to 1.8)	0.44	F = 1.842 (0.181)	0.4 0.1	0.3 (-0.7 to 1.3)	0.22	F = 1.092 (0.306)
HbA <sub>1c</sub> , mmol/mol	Light therapy Placebo	1.4 -0.5	2.0 (-0.5 to 4.4)	0.42	F = 2.534 (0.116)	2.1 -0.3	2.4 (-0.6 to 5.4)	0.53	F = 1.117 (0.297)
Hypoglycemic events, days/week	Light therapy Placebo	0.12 -0.39	0.51 (-0.00 to 1.02)	0.42	Wald $\chi^2$ = 0.443 (0.506)	0.08 -0.42	0.50 (-0.12 to 1.12)	0.55	Wald $\chi^2$ = 0.513 (0.474)
Body weight, kg	Light therapy Placebo	0.02 0.25	-0.23 (-0.73 to 0.27)	0.23	F = 0.658 (0.420)	0.09 0.33	-0.24 (-0.86 to 0.39)	0.24	F = 0.464 (0.500)
Insomnia, ISI score	Light therapy Placebo	-2.5 -2.6	-0.2 (-1.9 to 2.2)	0.04	F = 0.077 (0.783)	-2.9 -1.7	-1.2 (-1.0 to 3.4)	0.31	F = 1.746 (0.193)
Sleep duration, † min	Light therapy Placebo	-19 -7	-13 (-53 to 27)	0.16	F = 0.969 (0.329)	-9 -25	16 (-24 to 56)	0.28	F = 0.342 (0.563)
Sleep efficiency, ‡ %	Light therapy Placebo	-0.6 0.2	-0.8 (-4.3 to 2.8)	0.38	F = 2.354 (0.130)	0.8 1.5	-0.7 (-5.4 to 4.1)	0.10	F = 1.512 (0.228)
Mid-sleep time, † min	Light therapy Placebo	-15 -14	-2 (-27 to 24)	0.03	F = 0.309 (0.580)	-26 -15	-11 (-50 to 28)	0.19	F = 0.048 (0.827)

NA, not available; W, week. \*Data are the mean difference (95% CI) or the percentage difference. †HbA<sub>1c</sub>: Statistical testing included data from W4 and W8; Cohen's d was calculated on the basis of the mean difference between W0 and W8. ‡Calculated from actigraphy-derived data.



**Figure 2**—Effects of light therapy on depression according to insulin sensitivity (left) and glucose-lowering medication use (right) at baseline. The bar plots show the change in depressive symptoms from baseline (week 0 [W0]) to week 4 (W4) in the groups receiving light therapy (blue striped bars) or placebo (green dashed bars); error bars indicate the 95% CI. In the left panel, subgroups are sorted according to median value (lower  $\leq 1.75$ , higher  $> 1.75$  M-value mg/kg $\cdot$ min).

### Study Effects on Sleep and Circadian Rhythmicity

Analyses showed that in the 1st week of the intervention period all participants got out of bed earlier, both those receiving the light therapy ( $-36$  min [95% CI  $-49$  to  $-24$  min];  $P < 0.001$ ) and those receiving the placebo ( $-16$  min [95% CI  $-29$  to  $-2$ ];  $P = 0.025$ ), probably so they could follow the intervention at the agreed-upon time. The intervention period (irrespective of condition) did not result in significant changes in sleep duration, sleep efficiency, or mid-sleep time. Changes in these measures were not associated with changes in depressive symptoms (Supplementary Table 7).

### Per-Protocol Analyses

Per-protocol analyses provided results similar to those of the intention-to-treat analyses but suggest larger effects of light therapy on depressive symptoms ( $-5.9$  IDS points, or  $-14.3\%$  [95% CI  $-13.0$  to  $1.2$  IDS points]; Cohen's  $d = 0.47$ ) (Table 2). In this subgroup of participants, light therapy resulted in 26% more response ( $\geq 50\%$  reduction in depressive symptoms [IDS points]) (relative risk 2.46 [95% CI 0.92–6.62];  $P = 0.031$ , GEE) (Table 2).

### Effect Moderation Analyses

Glucose-lowering drugs (insulin vs. not insulin;  $P = 0.023$ ) and baseline insulin sensitivity ( $P = 0.009$ ) moderated the effect of light therapy on depressive symptoms (Supplementary Table 8). Subgroup analysis showed positive effects of light therapy on depressive symptoms in those with lower insulin sensitivity ( $-12.9$  IDS points [95% CI  $-21.6$  to  $-4.2$ ];  $P = 0.017$ , LMM; Cohen's

$d = 1.19$ ), whereas no effect was observed in those with higher insulin sensitivity (subgroups sorted according to median value) (Fig. 2 and Supplementary Table 9). Subgroup analysis based on glucose-lowering medication showed a trend toward positive effects of light therapy on depressive symptoms in those using insulin ( $-12.2$  IDS points [95% CI  $-21.3$  to  $-3.1$ ];  $P = 0.094$ , LMM; Cohen's  $d = 1.14$ ), whereas no effect was observed in those who did not use glucose-lowering medication or who used an oral form (Supplementary Table 9). Subgroups based on insulin sensitivity and glucose-lowering medication partially consisted of similar participants: 55% of the participants using insulin were also in the lower sensitivity subgroup. Combined modeling of both interaction effects suggests that the interaction effect of glucose-lowering medication ( $P = 0.094$ ) is partly explained by the effect of insulin sensitivity ( $P = 0.014$ ).

Other effect moderators we tested did not moderate the effect of light therapy on depressive symptoms or insulin sensitivity (Supplementary Table 8).

### Effect Mediation Analyses

Any effects of light therapy on depressive symptoms and insulin sensitivity were not mediated by changes in subjective insomnia symptoms, objective sleep duration, objective sleep efficiency, or mid-sleep time (depressive symptoms:  $P = 0.861$ ,  $P = 0.590$ ,  $P = 0.794$ ,  $P = 0.903$ , respectively; insulin sensitivity:  $P = 0.926$ ,  $P = 0.961$ ,  $P = 0.860$ ,  $P = 0.558$ , respectively [all values calculated with the Sobel test]).

### Adverse Effects

Four participants were hospitalized for several days because of serious adverse events not related to the study: non-specific chest pain ( $n = 2$ ), gastrointestinal bleeding from known esophageal varices ( $n = 1$ ), and renal colic ( $n = 1$ ). Adverse events that occurred in relation to the study protocol, such as headache and ocular complaints ( $n = 25$ ), seemed to be equally common among patients in both groups (Supplementary Table 10, with accompanying information). Self-reported adverse effects did not differ between those receiving light therapy and those receiving placebo (Supplementary Table 10, with accompanying information).

Light therapy did not affect best-corrected visual acuity (between-arm difference: right eye,  $-0.08$  [95% CI  $-0.10$  to  $0.02$ ];  $P = 0.122$ ; left eye,  $-0.08$  [95% CI  $-0.19$  to  $0.03$ ];  $P = 0.156$ ) or binocular contrast sensitivity (between-arm difference  $-0.03$  [95% CI  $-0.10$  to  $0.03$ ];  $P = 0.263$ ). One participant who received light therapy demonstrated progression of diabetic retinopathy (European Diabetes [EURODIAB] Prospective Complications Study stage 1–2) during the protocol.

### CONCLUSIONS

This is, to our knowledge, the first controlled experiment to investigate effects of light therapy on mood and insulin sensitivity in patients with type 2 diabetes and comorbid depression. The execution of the study seemed to be successful, given the balanced randomization and patient expectations, few dropouts, and acceptable treatment adherence. Intention-to-treat analysis showed no superiority of light therapy over placebo in reducing depression symptoms (IDS points). Nor did light therapy affect insulin sensitivity. Similar results were obtained for the secondary outcomes of anxiety symptoms, diabetes distress, insomnia symptoms, objective sleep duration, sleep efficiency, mid-sleep time, FBG, HbA<sub>1c</sub>, hypoglycemic events, and body weight. Per-protocol analysis, however, suggested positive effects of light therapy on depressive symptoms, underscoring the importance of adherence to light therapy. Moreover, baseline insulin sensitivity moderated the effect of light therapy on depressive symptoms, with clinically relevant effects in favor of light therapy in patients with highly insulin-resistant type 2 diabetes.

Although previous research has confirmed the effectiveness of light therapy for depression in a variety of patient groups, we could not establish such an effect in this sample of patients with type 2 diabetes. This may be due to a lack of power to affirm the observed small standardized effect size, as the study was designed to detect a moderate effect size. The absolute effect size, however—9.2% higher reduction of depressive symptoms with light therapy than with placebo—was comparable to effect sizes found in previous studies of the effects of light therapy and other antidepressant treatments (10–12,21). This discrepancy between the standardized and absolute effect sizes suggests more response variability in our study. Response variability may be due to variation in treatment adherence and the heterogeneity of our sample, which is supported by both the per-protocol and the effect moderation analyses. Yet, our negative findings might also represent the genuine effect of light therapy in this specific population, as depression in people with type 2 diabetes seems to be more persistent and recurrent than in those without type 2 diabetes (6). Also, improving depression and sleep in patients with sleep apnea, which is prevalent among those in our study sample, may be difficult.

Prespecified moderation analyses showed significant and clinically relevant effects of light therapy on depressive symptoms in patients with marked insulin resistance, whereas no effect of light therapy was observed in more insulin-sensitive patients—an intriguing finding, as this subgroup may represent patients with more advanced disease. Previous studies have demonstrated larger effects of light therapy in those with a stronger appetite and a higher BMI, factors that are associated with insulin resistance (24,25). A similar relationship between antidepressant effect and insulin resistance at baseline was demonstrated in a study that investigated the mood-altering effects of pioglitazone (26). Depressive symptoms are associated with insulin resistance, and insulin resistance seems to improve as depressive symptoms improve (26,27). This has led to the hypothesis that improvement of insulin resistance, or of related factors such as chronic low-grade inflammation, may be the underlying mechanism leading

to improvement in depressive symptoms (26–28). This is further supported by the antidepressant effects of medications that improve insulin sensitivity (28). This mechanism of antidepressant action could be more pronounced in patients with marked insulin-resistant type 2 diabetes (26).

Contrary to two case reports (16,17), our study showed no changes in insulin sensitivity in response to light therapy. These negative findings may be explained by a lack of an effect of light therapy on circadian and sleep measures, as we hypothesized that these would mediate improvements in insulin sensitivity. The majority of the participants in this study are at risk for sleep apnea, whereas improvements in sleep and thereby in insulin sensitivity as effects of light therapy may not be possible in these patients (29). Also, baseline circadian and sleep measures may have been disordered in different ways for different individuals, so that unidirectional effects of an intervention, such as demonstrated by a sleep-extension study in chronically sleep-restricted healthy volunteers, could not be expected (30). Last, effects of sleep restoration on insulin sensitivity may not be as big as effects of sleep restriction, or they may be small when sleep is only minimally disordered or chronically disturbed (31,32). Moderate to small effects on insulin sensitivity would have gone unnoticed in this study, as it was powered to detect large effects of light therapy on insulin sensitivity.

Light therapy did not affect anxiety symptoms and diabetes distress, two measures that to our knowledge have not been studied previously. Nor did light therapy affect glycemic control. On the basis of recent publications, we may have anticipated glycemic control to deteriorate as a result of the acute effects of light on both preprandial and postprandial glucose concentrations (33–35). Yet, 30 min of light daily may not be enough to change HbA<sub>1c</sub>. Although previous reports have suggested an increase in the number of hypoglycemic events (16,17) and a decrease in body weight (36–38) with light therapy, we could not replicate those findings.

Limitations of our study include the inability to obtain the required number of complete data sets and the selection of repeated measures a priori, which might have contributed to a further decrease in statistical power for the analyses regarding depressive symptoms, as

effects turned out to be most distinct after 4 weeks. Also, the exclusion of several glucometabolic measurements from analyses because of changes in glucose-lowering medication, albeit equally for both conditions, potentially biases the glucometabolic results. Furthermore, energy expenditure, caloric intake, timing of food intake and physical activity (in general or relative to the intervention), exposure to environmental light, and circadian timing of measurements were not taken into account, although these factors may have influenced findings. Last, we did not assess other factors that hypothetically might have mediated improvements in insulin sensitivity in response to light therapy, such as melatonin and cortisol concentrations, autonomic nervous system function (15), and changes in health behaviors. The observed placebo effect regarding depressive symptoms is probably attributable to general study-related factors, which is suggested by the magnitude of the placebo effect being comparable to that found in previous studies of light therapy and oral antidepressant drugs (21,39). It seems unlikely that general effects of our study design on sleep or circadian rhythmicity contributed to a placebo effect, as the study did not result in general changes in sleep duration, sleep efficiency, or mid-sleep time, and changes in these measures were not associated with changes in depressive symptoms.

Potential opportunities to increase the effectiveness of light therapy in future studies are related to the timing of the therapy, treatment adherence, and the specific light therapy protocol. For instance, the timing of light therapy, when based on the onset of melatonin concentration under dim light conditions—which is the most accurate marker for assessing an individual's circadian rhythm—may improve treatment results (19). Also, compliance can be optimized with, for example, daily monitoring by using wearable light-measuring devices. Furthermore, larger effects could be achieved with prolonged daily exposure to light, as the effect of light therapy seems to increase with the intensity and duration of daily exposure to light (9,40) and with increased duration of the therapy, as indicated by the increasing effect of light therapy over time in our study.

Although this is essentially an inconclusive trial, we did find evidence to



suggest that light therapy could be a promising treatment for depression in a subgroup of insulin-using and highly insulin-resistant individuals with type 2 diabetes. Light therapy is a well-tolerated intervention, also in patients with type 2 diabetes. The findings of this trial warrant further study of the antidepressant and glucometabolic effects of light therapy in people with highly insulin-resistant type 2 diabetes, and encourage research into the mechanisms by which insulin resistance moderates the antidepressant effect of light therapy.

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**Author Contributions.** A.B. performed statistical analyses, wrote the manuscript, set up and coordinated the trial, and performed study procedures. D.H.v.R. wrote the manuscript, designed and interpreted the diabetes-related outcome measures, and coordinated practical research assistance. H.-T.N. and A.C.M. wrote the manuscript, designed and interpreted the ophthalmological measures, and graded retinopathy. F.R. and P.J.M.E. wrote the manuscript, recruited participants, and coordinated practical research assistance. P.M.v.d.V. wrote the manuscript and designed statistical analyses. E.J.W.V.S. wrote the manuscript and designed and interpreted the trial conditions and sleep measures. F.J.S. and A.T.F.B. conceived of the study, designed the study, interpreted the results, and wrote the manuscript. M.A.B. conceived of the study, set up the study design, supervised the coordination of the trial, wrote the manuscript, and is the principal investigator of this study. A.B. and M.A.B. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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