

Morning Light Treatment Hastens the Antidepressant Effect of Citalopram: A Placebo-Controlled Trial

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Background: Selective serotonin reuptake inhibitors are effective in approximately 70% of patients with a major depressive episode, but therapeutic changes usually require 2 weeks of administration to become clinically relevant. Adjunct light therapy has been proposed to hasten the effects of drug treatment. The purpose of the present study was to evaluate the effect of morning light therapy or placebo combined with citalopram in the treatment of patients affected by a major depressive episode without psychotic features.

Method: Thirty inpatients (DSM-IV major depressive disorder [N = 21] and bipolar disorder [N = 9]) were treated with citalopram, 40 mg, and randomized in a 3:2 manner to receive 30 minutes of 400 lux green light treatment in the morning or placebo (exposure to a deactivated negative ion generator) during the first 2 weeks of drug treatment. Timing of light therapy was individually defined to obtain a 2-hour phase advance to morning light. Outcome was measured with the Hamilton Rating Scale for Depression and the Zung Self-Rating Depression Scale every week, and with a Visual Analogue Scale 3 times a day during the first week.

Results: All outcome measures showed significantly ($p < .05$) better mood improvement in light-treated patients, resulting in faster responses to antidepressant treatment.

Conclusion: The combination of citalopram and light treatment was more effective than citalopram and placebo in the treatment of major depression. With an optimized timing of administration, low-intensity light treatment significantly hastened and potentiated the effect of citalopram, thus providing the clinical psychiatrists with an augmenting strategy that was found effective and devoid of side effects.

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Although selective serotonin reuptake inhibitors (SSRIs) are effective in approximately 70% of patients with a major depressive episode, they have a delayed onset of action, and therapeutic changes usually require 2 weeks of administration to become clinically relevant. Nonpharmacologic chronobiological interventions, such as sleep deprivation, have been successfully associated with the SSRIs to enhance and accelerate their effects.^{1,2} In this perspective, the possible usefulness of combined morning light therapy has been suggested based on European studies,³ but the scarcity of controlled trials suggested the need of further study before routine clinical use of this technique.⁴ Moreover, the potential benefits of drug–light therapy combination seemed to depend on the kind of administered drug: adjunct light therapy was reported to trigger response in patients who had failed an adequate trial of tricyclic antidepressants or monoamine oxidase inhibitors (MAOIs)⁵ and to hasten response when combined with amitriptyline,⁶ but also to lack efficacy or even to decrease response when combined with trimipramine,^{7,8} and to lack efficacy when combined with imipramine.⁹

The efficacy of light therapy alone in the treatment of winter seasonal affective disorder (SAD) is well established,¹⁰ but literature data about non-SAD patients affected by a major depressive episode are less clear. Exposure to light therapy alone was reported to have antidepressant effects in patients with major depression in the course of bipolar or major depressive disorder with a seasonal pattern of depressive recurrence,^{11,12} but contrasting results were observed in patients with non-seasonal depression (i.e., positive effects¹³ and lack of efficacy¹⁴). Interestingly, a controlled trial reported a significant 18% net benefit with respect to placebo after a 1-week light therapy treatment in nonseasonal depressed patients,¹⁵ but with a partial symptomatologic relapse after treatment that resembled the short-term relapse observed after other nonpharmacologic treatments such as total sleep deprivation,¹ thus bringing into question the usefulness of this technique in clinical practice. In an open trial, a similar trend toward short-term relapse has been observed after successful light therapy treatment of

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antepartum depression.¹⁶ These latter observations further sustain the opportunity of combining light therapy with drug therapies to enhance and sustain its clinical effects in nonseasonal depression.

Finally, several issues regarding timing and intensity of light therapy are still under consideration. Morning light therapy, which phase advances circadian biological rhythms, was proven superior to evening light therapy in the treatment of winter depression¹²; recent studies defined a correlation between light therapy–linked phase advance and therapeutic response in patients with seasonal patterns of winter depression,¹⁷ thus leading to the definition of protocols for the individual assessment of best light therapy timing.¹⁸ Intensity of light in clinical trials is usually 5,000 to 10,000 lux, which may cause annoying side effects,^{8,19,20} but studies of SAD patients receiving light therapy administered in a manner to simulate dawn showed that intensity of 250 lux was clinically effective.^{21,22} These optimization strategies and low-intensity light therapy have not been tested in combination with drugs or in non-SAD patients with nonseasonal patterns of recurrence.

In the present study, we evaluated the effect of morning low-intensity light therapy or placebo combined with the SSRI citalopram in the treatment of patients affected by a major depressive episode.

METHOD

Patients

The study took place in winter (December 2001 through February 2002). Thirty consecutively admitted inpatients affected by a major depressive episode without psychotic features were studied. Diagnoses (DSM-IV criteria) were major depressive disorder (N = 21) and bipolar disorder (N = 9). None of the patients fulfilled DSM-IV criteria for seasonal pattern of illness recurrence, but 13/30 patients reported a seasonal worsening of depressive symptomatology.

Inclusion criteria were absence of other diagnoses on Axis I; absence of mental retardation on Axis II; absence of pregnancy, history of epilepsy, and major medical or neurologic disorders; no treatment with long-acting neuroleptic drugs in the last 3 months before admission; no treatment with neuroleptics or irreversible MAOIs in the last month before admission; and absence of a history of drug or alcohol dependency or abuse within the last 6 months. Physical examinations, laboratory tests, and electrocardiographs were performed at admission. After complete description of the study to the subjects, written informed consent was obtained. The study was approved by the hospital ethics committee.

Patients were assigned to treatment conditions based on a computer-generated randomization schedule with no stratification of the sample.

Treatment

At study outset all patients were free of psychotropic medications. All patients were treated with citalopram *per os*, started at 10 mg/day at day 1, then rapidly titrated to 40 mg/day at day 4. The same dose was continued until week 4. Citalopram was chosen because in a small (N = 8) sample of SAD patients, the combination of citalopram and light therapy was found to be superior to light therapy alone,²³ thus suggesting a synergistic effect between this SSRI and light therapy.

During the first 2 weeks of pharmacologic treatment, patients were randomized in a 3:2 manner to receive adjunct 30 minutes of morning light therapy or placebo.

Timing of morning light therapy administration was chosen on the basis of the observed correlation between the magnitude of phase advances to morning light therapy and improvement in depression ratings,¹⁷ with maximum effects at phase advances of 1.5 to 2.5 hours (about 7.5–9 hours after dim-light melatonin onset the evening before). Since scores on the Morningness-Eveningness Questionnaire (MEQ)²⁴ are strongly correlated with sleep midpoint and melatonin secretion, a predictive algorithm based on MEQ scores was developed to define the individual optimal timing of light therapy administration.¹⁸ In the present study, we optimized timing of morning light therapy for each subject on the basis of the results of this assessment tool.²⁵

The lighting device (Sunnex Biotechnologies, Winnipeg, Manitoba, Canada) provided 400 lux green light, with spectrum ranging from 485 to 515 nm and peak at 500–505 nm. Since light intensities as low as 150 lux are able to entrain the human circadian pacemaker,²⁶ low-intensity light in the green wavelength spectrum can phase-shift biological rhythms in SAD patients²⁷ with minimal risks of side effects.

The placebo condition was a 30-minute exposure to a deactivated negative ion generator. To avoid phase advance to ambient light, timing of placebo exposure was 1.5 hours after the optimal timing for light therapy, as calculated with MEQ. The average beginning time of treatment was 6:00 a.m. for the green light group and 7:45 a.m. for the placebo group.

We did not rate expectations toward the efficacy of the nonpharmacologic interventions with objective instruments, because previous trials using light therapy and the same placebo procedure showed no difference in expectations among treatments.¹⁰

Data Collection and Analysis

Study duration was 4 weeks. Changes of mood over time were rated using 3 outcome measures. The Hamilton Rating Scale for Depression (HAM-D)²⁸ was administered in the morning at baseline and every week thereafter by trained raters. Whenever possible the same rater conducted admission and follow-up ratings for each patient.

Table 1. Clinical and Demographic Characteristics of the Sample Divided According to Treatment Group^a

Characteristic	Morning Light (N = 18)	Placebo (N = 12)	t	p Value
Age, y	53.0 ± 10.3	56.2 ± 12.3	0.76	.45
Sex (M/F)	3/15	3/9	NA	.66 ^b
Diagnosis (MDD/BPD)	12/6	9/3	NA	.70 ^b
Age at onset, y	38.5 ± 13.7	44.4 ± 13.2	1.16	.25
Number of previous illness episodes	3.6 ± 2.3	6.0 ± 9.2	1.07	.29
Duration of current episode (wk)	17.3 ± 15.1	14.9 ± 20.6	0.37	.71
MEQ score at study outset	58.83 ± 8.81	56.83 ± 9.72	0.88	.39
HAM-D score				
Week 0	23.72 ± 6.90	22.58 ± 4.89
Week 1	16.33 ± 8.46	22.83 ± 8.57
Week 2	11.72 ± 9.25	18.75 ± 7.78
Week 3	8.61 ± 8.46	14.92 ± 8.62
Week 4	7.39 ± 7.72	13.08 ± 8.30

^aAll values are mean ± SD and student t test unless otherwise indicated.

^bFisher exact test.

Abbreviations: BPD = bipolar disorder, HAM-D = Hamilton Rating Scale for Depression, MDD = major depressive disorder, MEQ = Morningness-Eveningness Questionnaire, NA = not applicable, ... = no data available.

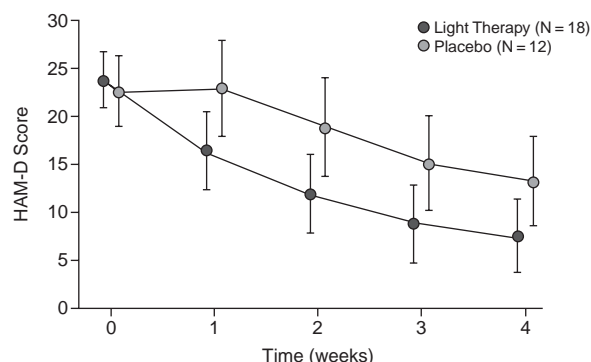
Questions by the patients to the raters during the clinical interviews made it impossible to keep the raters blinded to treatment options. At the same timepoints, patients self-rated their depressive symptoms on the Zung Self-Rating Depression Scale (SDS).²⁹

During the first week of treatment, patients self-assessed subjective mood levels with a 10-cm Visual Analogue Scale (VAS)³⁰ 3 times during the day (8 a.m., 1 p.m., and 6 p.m.). Patients were instructed to rate their mood between “very sad” (on the left) and “very happy” (on the right), with a median “normal” point. Scores of 0, 50, and 100 denoted extreme depression, euthymia, and euphoria, respectively.

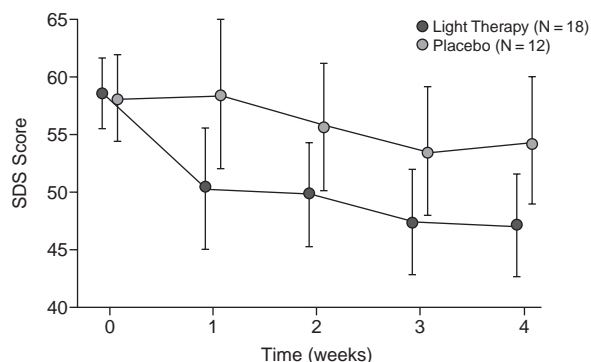
Between-group baseline demographic data, clinical history variables, and baseline values of the outcome measures were analyzed using the chi-square test for categorical variables and the Student t test for continuous variables. Changes in outcome measures over time were analyzed with a 2-way repeated-measures analysis of variance (ANOVA), with Newman-Keuls post hoc test. Homogeneity of variances at baseline was tested using the Levene test. Response to treatment was categorically defined as a 50% reduction in HAM-D scores, and rates of response over time were analyzed with the Cox F test for survival.

RESULTS

Clinical and demographic characteristics of the patients divided according to treatment group, HAM-D scores during treatment, and MEQ scores at outset are summarized in Table 1. No clinical difference was statistically significant.

Figure 1. Changes (mean ± SD) in HAM-D Scores During Treatment in the 2 Groups

Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

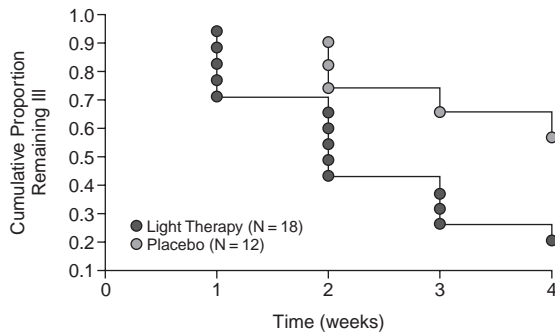
Figure 2. Changes (mean ± SD) in SDS Scores During Treatment in the 2 Groups

Abbreviation: SDS = Zung Self-Rating Depression Scale.

Homogeneity of variances at baseline was successfully tested for both HAM-D ($F = 1.70$, $df = 1,28$; $p = .20$) and SDS scores ($F = 0.024$, $df = 1,28$; $p = .88$). A 2-way repeated-measures ANOVA on HAM-D scores (Figure 1) showed a marginal effect of treatment ($F = 4.14$, $df = 1,28$; $p = .051$), a highly significant effect of time ($F = 28.88$, $df = 4,112$; $p < .00001$), and a significant time-per-treatment interaction ($F = 2.88$, $df = 4,112$; $p = .026$), meaning that changes in psychopathologic status did not follow parallel slopes of time course in the 2 groups. Post hoc comparisons showed no difference at baseline ($p = .837$) and significantly better scores for light therapy patients at every timepoint thereafter (week 1 $p = .0084$, week 2 $p = .0058$, week 3 $p = .0111$, and week 4 $p = .0269$).

Similar results were observed for SDS scores (Figure 2), where a 2-way repeated-measures ANOVA showed a marginal effect of treatment ($F = 3.39$, $df = 1,28$; $p = .076$), a highly significant effect of time ($F = 10.24$, $df = 4,112$; $p < .00001$), and a significant time-per-group

Figure 3. Patterns of Response (50% reduction in HAM-D scores) Over Time in the 2 Treatment Groups^a



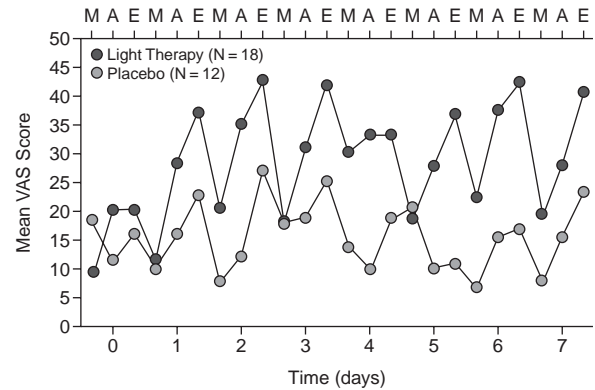
^aPoints are patients responding to treatment; lines are the cumulative proportions of patients remaining ill. Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

interaction ($F = 2.83$, $df = 4,112$; $p = .028$). Post hoc comparisons showed no difference at baseline ($p = .971$) and significantly better scores for light therapy patients at every timepoint thereafter (week 1 $p = .0015$, week 2 $p = .0304$, week 3 $p = .0155$, and week 4 $p = .0066$).

Rates of response over time (50% reduction in HAM-D score) significantly differed between the 2 groups (Figure 3). Survival analysis detected a significantly better pattern of response for light therapy patients (Cox $F = 2.94$, $p = .038$). At the end of treatment, responders (50% reduction of HAM-D scores) were 14/18 (77.8%) in the light therapy group and 5/12 (41.7%) in the placebo group ($\chi^2 = 4.04$, $df = 1$, $p = .044$). No patient switched polarity during treatment. Neither one of the diagnoses, nor any one of the baseline clinical and demographic characteristics, as reported in Table 1, was significantly different in responders versus nonresponders.

Changes in perceived mood during the first week of treatment, as rated by VAS scores, significantly differed between groups (Figure 4). A 2-way repeated-measures ANOVA showed a significant effect of treatment ($F = 4.48$, $df = 1,28$; $p = .043$), a highly significant effect of time ($F = 3.92$, $df = 23,644$; $p < .00001$), and a significant time-per-group interaction ($F = 1.71$, $df = 23,644$; $p = .021$). Inspection of Figure 4 shows that mean circadian mood fluctuations were typical (mood worse in the morning) and apparently different between groups (i.e., higher in the light therapy group after the first days of treatment). A repeated-measures ANOVA with mean daily circadian mood fluctuations (i.e., evening minus morning VAS scores) as dependent variable showed a significant effect of treatment condition ($F = 5.65$, $df = 1,28$; $p = .0246$) and of time ($F = 2.51$, $df = 7,196$; $p = .0170$) with nonsignificant interaction ($F = 0.98$, $df = 7,196$; $p = .446$), thus confirming the statistical significance of the observation.

Figure 4. Changes in VAS Scores During the First Week of Treatment in the 2 Groups



Abbreviations: A = afternoon, E = evening, M = morning, VAS = Visual Analogue Scale.

DISCUSSION

Morning light therapy was superior to placebo in augmenting the antidepressant effect of citalopram. This effect began during the first days of treatment, as shown by self-ratings of perceived mood, and continued throughout the 4 study weeks, resulting in different rates of response between groups.

After the first 2 weeks of treatment (i.e., when the treatment conditions differed), HAM-D scores decreased to 49.4% of baseline levels in light therapy patients and to 83.1% in placebo-treated patients, with a 33.7% net relative advantage of light therapy over placebo. The difference remained almost the same during the following weeks: at the end of treatment HAM-D scores decreased to 31.2% of baseline levels in light therapy patients and to 58.0% in placebo-treated patients, with a 26.8% net relative advantage of light therapy over placebo. Remarkably, these values are close to the 27% net benefit of bright light (as compared to dim-light placebo) observed in early European studies of antidepressant drug-treated patients,^{3,6,31} and to the 35.4% net benefit that was observed in 1 week with the combination of light therapy, partial sleep deprivation, and antidepressant drug treatment.³²

The mechanism of the antidepressant action of light therapy is still unknown and is likely to involve changes in phase of biological rhythms.^{17,33,34} Studies in animal models showed that SSRIs down-regulate the serotonin-7 (5-HT₇) receptor in the suprachiasmatic nucleus,³⁵ shorten the circadian period of activity,³⁶ and modulate phase-shift responses of circadian rhythms to light.³⁷ It is then possible to hypothesize that the light therapy-induced phase advance and the effect of citalopram on regulatory mechanisms of biological rhythms may produce a synergistic interaction; to date, however, the lack of basic data on this topic does not allow discussion of this hypothesis.

From a neurochemical point of view, studies of serotonin function in patients affected by SAD suggested a role for the 5-HT enhancement in the mechanism of action of light therapy. Challenge studies showed that light therapy tended to normalize the blunted growth hormone response to sumatriptan,³⁸ and cortisol and prolactin responses to *m*-chlorophenylpiperazine.³⁹ Both tryptophan and catecholamine depletion reversed the beneficial effects of light therapy,^{40,41} with tryptophan depletion showing no effects in patients in natural summer remission.⁴² Finally, B_{\max} for [³H]imipramine binding was found to increase,⁴³ and B_{\max} for platelet [³H]paroxetine binding was found both to decrease⁴⁴ and increase⁴⁵ during light treatment.

Citalopram, on the other hand, acts by enhancing 5-HT transmission by blocking the 5-HT transporter. In vivo microdialysis, however, showed that at the beginning of treatment with citalopram, the 5-HT-increasing action is limited by a negative feedback at somatodendritic level, due to the activation of 5-HT_{1A} somatodendritic autoreceptors, with a resulting acute reduction of 5-HT neuronal firing.⁴⁶ This effect could be responsible for the well-known delay in onset of action of SSRIs, and, consistent with this hypothesis, clinical trials showed that 5-HT_{1A} antagonists hasten the effect of these drugs.⁴⁷ The possible rapid enhancement of 5-HT transmission produced by light therapy could explain the synergistic effect of light therapy combined with citalopram during the drug action latency period.

Moreover, in our study we purposely timed active treatment and placebo differently to avoid the potential phase-advancing effect of ambient light in the placebo group. Early treatment in the active group could have led to some small late partial sleep deprivation (1–2 hours) during the first days of treatment, which could have contributed to the more rapid amelioration seen in the active versus the placebo group. The exact contribution of light exposure, sleep-wake cycle phase advance, and possible late partial sleep deprivation to the antidepressant effect observed in the active treatment group needs further studies and objective measurements (actigraphy, melatonin) to be defined.

In conclusion, our controlled study confirmed the synergy between light therapy and SSRI antidepressant treatment. With an optimized timing of administration, low-intensity light therapy significantly hastened and potentiated the effect of citalopram, thus providing the clinical psychiatrists with a new effective augmenting strategy. An early hope of research on biological rhythms and depression was that chronobiological interventions could become a benign alternative to more radical treatments of depression, such as long-term high-dosage drugs or electroconvulsive therapy, but on one side biological rhythm research failed to provide a sound biological basis for these treatments, and on the other clinical results remained uncertain.⁴⁸ Whatever the exact mechanism of the

synergistic effects of light and drugs, the results of our study should warrant interest for clinical application and replication in independent and larger samples.

Drug names: amitriptyline (Elavil and others), citalopram (Celexa), imipramine (Tofranil and others), sumatriptan (Imitrex), trimipramine (Surmontil).

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