On the chronobiology of seasonal affective disorder
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Extraocular light therapy in winter depression

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ABSTRACT

Background
It has been hypothesized that the circadian pacemaker is phase-delayed in Seasonal Affective Disorder, winter type (SAD) and that the phase advance resulting from morning ocular light accounts for the efficacy of light therapy. Extra-ocular light has been reported to produce phase shifts of the human circadian pacemaker. This allows a double-blind placebo-controlled study of light therapy in SAD.

Methods
29 SAD patients participated. Clinical state was measured on day 1, 8 and 15 of the protocol. From day 4 - 8, 15 patients (4 M, 11 F) received extra-ocular light by fiber optic illumination and 14 (4 M, 10 F) placebo (no light) in the popliteal fossae, from 8 - 11AM. In the evening of day 3 and 8, the salivary dim light melatonin onset (DLMO) was assessed. Patients completed daily self-ratings on mood, alertness and sleep.

Results
Both conditions showed a progressive improvement of clinical state over time. Between conditions, no significant differences were observed in clinical scores, the self-ratings on mood and alertness, and in timing of the DLMO before and directly after treatment.

Conclusions
The response to extraocular light therapy in SAD patients did not exceed its placebo effect. Extraocular light did not induce a phase shift of the circadian pacemaker.
INTRODUCTION

Seasonal Affective Disorder, winter-type (SAD) is a depressive syndrome, the symptoms of which recur in autumn and/or winter. Besides symptoms of major depressive disorder, SAD patients often show ‘atypical’ symptoms, such as an increase of appetite, weight gain and hypersomnia (Rosenthal et al 1984). Because of the large response rate, bright light therapy is the treatment of first choice for SAD patients. It has been suggested that the circadian pacemaker is involved in the pathogenesis of SAD and in the mechanisms of action of light therapy. The definitive proof of this suggestion is still lacking due to the inherent problem that the perfect placebo treatment for light therapy does not exist. Recently, Campbell and Murphy reported that extraocular light pulses presented in the bend of the knees (the popliteal fossae) can produce phase shifts of the human circadian pacemaker (Campbell and Murphy 1998). This finding challenged the current knowledge about the (human) circadian system and provided a new perspective on the study of therapeutic effects of light in the treatment of SAD. While verification studies were started in various laboratories (Lindblom et al 2000a, 2000b; Eastman et al 2000), we simultaneously tried to utilize the possibility of a perfect placebo control and subjected SAD patients to extraocular light treatment.

In humans, the circadian pacemaker, or biological clock, is localized in the supra-chiasmatic nuclei (SCN) of the brain. The 24-hour variation in core body temperature and the secretion of melatonin by the pineal gland are under the control of the circadian pacemaker and are often used as a circadian phase marker. The circadian pacemaker is sensitive to light throughout the day (Jewett et al 1997) in a dose dependent manner (Boivin et al 1996). As in other species, light presented in the evening (i.e., prior to the circadian temperature minimum) stimulates the human circadian pacemaker to phase delay its rhythm (i.e., schedules it later in time), whereas a light stimulus given in the morning (after this minimum) produces a phase advance (Honma and Honma 1988; Minors et al 1991; Jewett et al 1997). The curve that describes the phase shifts as a function of the circadian phase of light application is called a phase response curve (PRC). Apart from phase-shifting effects, ocular light exposure at night also directly suppresses the production of melatonin by the pineal gland (Lewy et al 1980).

Surprisingly, light applied to the skin of the popliteal fossae has also been reported to induce phase shifts of the human circadian rhythm of core body temperature and of the dim light melatonin onset (DLMO) (Campbell and Murphy 1998). The PRC obtained in this extraocular light experiment seemed to resemble the PRC resulting from ocular light pulses. However, extraocular light has been demonstrated to be incapable of directly suppressing the secretion of melatonin at night (Lockley et al
1998; Hébert et al 1999; Jean-Louis et al 2000). Unfortunately, the findings of Campbell and Murphy (1998) could not be replicated in two recent studies (Lindblom et al 2000a, 2000b; Eastman et al 2000). While these studies raise doubts concerning the basic assumption underlying extraocular photoreception in humans, the results of the present study continue to be of interest in the context of placebo effects.

The phase-shifting effects of light are very relevant to SAD-research. The ‘phase-delay hypothesis’ is one of the major circadian hypotheses for SAD (Lewy et al 1987a). It postulates that SAD is caused by a phase delay of the circadian pacemaker and that the phase-advancing properties of bright light in the early morning hours account for the efficacy of light therapy in SAD. Constant routine studies (designed to study the human circadian pacemaker in subjects under prolonged wakefulness by experimentally controlling for masking influences such as posture and ambient light) in SAD patients have indeed revealed evidence for a phase delay of 24-hour rhythms in several physiological variables (Dahl et al 1993; Wirz-Justice et al 1995; Avery et al 1997). Moreover, recent large-scale studies report superiority of morning light over other therapy schedules (Eastman et al 1998; Lewy et al 1998; Terman et al 1998).

Although ocular light therapy has been shown to be very effective in the treatment of SAD (Terman et al 1989), the mechanism of action has remained unresolved. A major problem with ocular light therapy is that it is not easy to adequately control for placebo effects. Dim light is not an appropriate control since patients can see the difference with bright light. A negative ion generator or any other alternative is imperfect as well because placebo effects of one treatment modality cannot be used to estimate placebo effects of another treatment (Eastman 1990). Consequently, it is still questionable whether the actual response to light therapy exceeds its placebo effect. The aim of the present study, triggered by Campbell and Murphy’s (1998) finding of extraocular photoresponsiveness of the human circadian pacemaker, was to study the phase-shift hypothesis for SAD in a double-blind placebo-controlled protocol. It was hypothesized that in case of absence of induced phase shifts, the therapeutic response obtained in the current study, would still provide data of interest to the placebo discussion.

**METHODS AND MATERIALS**

Patients with SAD were recruited from the psychiatric outpatients clinic of the Groningen Academic Hospital and met the DSM-IV criteria for recurrent major depressive disorder with seasonal pattern (American Psychiatric Association 1994). Patients were physically healthy and free of psychoactive medication for at least 6 weeks. In the period before participation, patients weekly completed the Beck
Depression Inventory (BDI) (Beck et al 1979) and the Structured Interview Guide for the Hamilton Rating Scale of Depression, Seasonal Affective Disorder self-rating version (SIGH-SAD-SR) at home. The SIGH-SAD-SR consists of the 21-item Hamilton Rating Scale of Depression (HRSD) and an 8-item scale for atypical symptoms (Williams et al 1992). If a BDI score of greater than or equal to 13 was reached, patients were invited to participate in a 15-day double-blind placebo-controlled study.

All subjects were informed about (1) the possible involvement of the circadian pacemaker in the mechanism of action of regular ocular light therapy, (2) the recent finding of the phase-shifting effects of extraocular light on the circadian pacemaker, and (3) the double-blind nature of the study protocol. Subjects gave written informed consent to the protocol, which was approved by the Medical Ethics Committee of the Groningen Academic Hospital. Subjects were assigned to one of two treatment groups balanced for age, gender and baseline SIGH-SAD score. The experimental treatment took place at the clinic from 8:00 AM to 11:00 AM and consisted of 5 consecutive days of either extraocular light (13,000 lux, 455-540 nm), or placebo extraocular light (0 lux) in the bend of both knees. As in the study of Campbell and Murphy (1998), the extraocular light was provided by the Ohmeda Biliblanket Plus Phototherapy System. This light is emitted by a halogen lamp and transmitted through fibre-optic cables that end in a woven pad. The lighting devices were fitted in a wooden box and placed under an armchair. Independently of whether the phototherapy system would be activated or not, the box also included an additional light source and fan to obtain similar background light and noise leaks. The boxes were assigned by a staff member who was not involved in other experimental procedures. The light pad was fixed to the bend of each knee with an elastic bandage. A pair of black trousers and an opaque cover around each knee prevented leakage of light. During treatment, subjects remained seated in a dimly lit room (<10 lux). They were instructed not to sleep but were permitted to eat, drink, read, write and listen to music. If necessary, bathroom visits were made after being disconnected from the equipment while wearing dark sunglasses. Before (T1), directly following (T2), and 1 week after treatment (T3), on day 1, 8 and 15 of the protocol, respectively, the SIGH-SAD interview was applied. Interviewers were not involved in the administration of the experimental treatment and were blind to the treatment condition. During the experimental treatment days (day 4-8), subjects wore dark glacier sunglasses (CEBE2000 or CEBE3000 lenses; The transmission of these lenses in the visible wavelength range is below 7%) from 6:00 PM until bedtime to prevent ocular light exposure during the delaying phase of their PRC. Within the restrictions of the protocol, subjects adhered to their individual sleeping habits.

In the evenings prior to and directly following the experimental treatment, saliva samples were taken hourly from 7:00 PM to 1:00 AM to determine the dim light melatonin onset (DLMO). Saliva sampling was performed under dim light (<10 lux)
conditions, under staff member supervision. Eating and drinking (with the exception of coffee, tea, chocolate, and bananas) and smoking were permitted in the 15-minute interval following saliva collection. Subjects were seated during the last 15 minutes prior to saliva collection. During the entire sampling period, subjects could watch TV or perform leisure activities. Saliva was collected using Salivettes with cotton swab (Sarstedt, Nümbrecht, Germany) and centrifuged and frozen at less than or equal to -18°C immediately afterwards. Salivary melatonin concentrations were measured by a radioimmunoassay (RIA) (Bühlmann, Allschwil, Switzerland). Specifications: limit of detection 0.5 pg/mL; intra-assay variation of covariance 8.78% (mean melatonin concentration 8.65 pg/mL, n = 26; inter-assay variation of covariance at a low melatonin concentration 23.5% (mean 2.55 pg/mL, n = 22) and at a high concentration 13.4% (mean 16.70 pg/mL, n = 22).

Throughout the entire protocol, subjects completed several questionnaires concerning subjective mood, alertness and sleep. Three times daily, at 9:00 AM, 5:00 PM and 10:00 PM, the Adjective Mood Scale (AMS) (Von Zerssen 1986), the Activation Deactivation-Adjective Checklist (AD-ACL) (Thayer 1967), and Visual Analogue Scales for depressive mood (VAS-D) (Albersnagel 1987) and fatigue (VAS-F) (Lee et al 1991) were completed. At 9:00 AM, subjects also rated their subjective sleep quality (Mulder-Hajonides van der Meulen et al 1980) and completed a sleep log. For each type of questionnaire, less than 2% of the data was missing due to incomplete ratings. A third degree polynomial was used for the interpolation of missing data.

The efficacy of the experimental treatment was tested by performing a repeated measures analysis of variance (ANOVA) on the SIGH-SAD scores at T1, T2 and T3. Additionally, two remission criteria were defined. One remission criterion consisted of a decrease of greater than 50% on the 21-item HRSD and a final HRSD score less than 8. Taking into account the atypical symptoms of SAD, the other criterion was defined as a decrease of greater than 50% on the SIGH-SAD and a final SIGH-SAD score less than or equal to 8. A chi-square analysis was applied to compare the percentages of remission at T3 in both treatment groups. The clinical significance of the differences in SIGH-SAD scores at T1 and T3 were assessed by computing the effect size $d$ (Cohen 1988) for each group. The daily questionnaires on mood, alertness, and sleep and the data on melatonin were evaluated by means of ANOVAs and paired $t$ tests. Finally, the Spearman rank correlation coefficient was calculated to evaluate the association between treatment response and phase shifting of the DLMO. All statistical tests were two-tailed and statistical significance was accepted at $p$ less than .05.
RESULTS

During the winters of 1998 - 1999 and 1999 - 2000, 29 SAD patients entered the study in the months September through February. Fifteen (4 male, 11 female) patients, aged 39.6 ± 12.2 years (mean ± SD) were assigned to the active treatment condition and fourteen (4 male, 10 female) patients aged 43.4 ± 12.4 years were assigned to the placebo condition. In both treatment groups, 11 patients received regular ocular light therapy in the year(s) before the winter in which they participated. They were known as good responders.

SIGH-SAD Ratings

At baseline, patients in the active treatment group scored 27.6 ± 5.0 (mean ± SD) on the SIGH-SAD (HRSD 15.3 ± 3.6; ATYP 12.3 ± 2.7). In the placebo group, the SIGH-SAD score was 26.3 ± 6.6 (HRSD 15.7 ± 4.0; ATYP 10.6 ± 3.8). Compared to baseline (T1), a decline in the SIGH-SAD scores was observed in both groups at T2 and T3. Figure 3.1 depicts the SIGH-SAD, HRSD and ATYP ratings throughout the study. Statistical analysis revealed no significant differences in the SIGH-SAD ratings (F(2,26) = 0.148, p = .863), the HRSD scores (F(2,26) = 0.135, p = .875) or the scores on the ATYP (F(2,26) = 1.357, p = .275) between groups in the course of the experiment.

At T3, 40% (6 out of 15 patients) of the active treatment group and 36% (5 out of 14 patients) of the placebo group met the 21-item HRSD criteria for remission (a decrease of >50% on the 21-item HRSD and a final HRSD score <8). According to the SIGH-SAD criteria for remission (defined as a decrease of >50% on the SIGH-SAD and a final SIGH-SAD score ≤8) 4 out of 15 (27%) in the active and 3 out of 14 (21%) in the placebo treatment group were remitted at T3. For both criteria, these remission percentages are not significantly different (Pearson’s χ²₁ =0.056, p = .812 and Pearson’s χ²₁ = 0.109, p = .742). Comparing the SIGH-SAD scores at T1 and T3, the calculated effect size d was 1.52 in the active treatment condition and 0.97 in the placebo condition.

After the study, patients were asked to continue completing the BDI and SIGH SAD-SR on a weekly basis. During the remaining part of the winter season, 40% (6 out of 15) of the patients in the active treatment condition and 50% (7 out of 14) of the patients in the placebo condition, received additional ocular light therapy (Pearson’s χ²₁ = 0.293, p = .588).

Daily Questionnaires

The ratings on mood and alertness showed a similar course in both groups. Following the baseline days, mood and alertness improved gradually and remained at a lower level during the 5 days after finishing the experimental treatment (Figure 3.2).
Comparison of both conditions provided no statistical differences in mean values on the mood, alertness and sleep ratings, obtained during the subsequent baseline period, treatment period, and follow-up (AMS: $F(2,26) = 0.534, p = .592$; VAS-D: $F(2,26) = 0.101, p = .904$; VAS-F: $F(2,26) = 2.133, p = .139$; AD-ACL: $F(2,26) = 0.971, p = .392$; subjective sleep quality: $F(2,26) = 0.804, p = .458$).

Figure 3.3 shows the course of sleep and wake-up times. Pooled data of all subjects revealed an average total sleep duration (i.e., nocturnal sleep and day time naps combined) of $8.3 \pm 1.3$ hours (mean ± SD) during the 3 days prior to treatment, $7.0 \pm 0.9$ hours during treatment and $8.1 \pm 1.3$ hours during follow-up. Mean wake-up time was at $8.24 \pm 0.88$ AM before, $6.24 \pm 0.48$ AM during and $8.31 \pm 1.2$ AM after treatment. Finally, sleep onset took place at $00.38 \pm 1.20$ AM, $23.98 \pm 0.96$ PM and $00.69 \pm 1.08$ AM respectively. ANOVAs did not show significant differences between the two treatment conditions in total sleep duration ($F(2,26) = 0.711, p = .5$), time of awakening ($F(2,26) = 0.150, p = .862$) and sleep onset ($F(2,26) = 1.397, p = .265$). During the experimental treatment, subjects showed reduced total sleep duration by $1.32 \pm 0.93$ hours (mean ± SD; paired t test $p = .000$), an earlier timing of sleep onset by $0.39 \pm 0.69$ hours ($p = .005$) and a $2.0 \pm 0.86$ hours earlier timing of awakening ($p = .000$). The reduction of total sleep duration was induced by the regime of the experimental protocol and normalized after the treatment.

Figure 3.1 Effects of extraocular light and placebo (no light) illumination of the popliteal fossae in SAD. Mean (and SD) scores on the SIGH-SAD (A), the 21-item HRSD (B), and the Atypical symptom scale (C) in SAD patients at baseline (T1), immediately after 5 days of treatment (T2), and 1 week after treatment (T3). The SIGH-SAD (Structured Interview Guide for the Hamilton Rating Scale of Depression, Seasonal Affective Disorder) consists of the 21-item Hamilton Rating Scale for Depression and the 8-item Atypical symptom scale. The shaded box indicates the treatment period. HRSD = Hamilton Rating Scale for Depression; SAD = Seasonal Affective Disorder; SIGH-SAD = Structured Interview Guide for the Hamilton Rating Scale for Depression, Seasonal Affective Disorder.
Melatonin production differed largely between individuals. Therefore, the salivary melatonin concentrations of each subject were expressed as a percentage of the maximum value obtained in the first evening of sampling during the protocol. The obtained melatonin curves were judged by two raters who were blind to the treatment.
conditions. Two subjects treated with extraocular light and three subjects treated with placebo extraocular light were excluded from further analyses as data showed either large irregularities or large differences in maximum melatonin concentration prior to and following treatment. Figure 3.4 presents the normalized mean hourly melatonin concentrations of the evening before and directly following the experimental treatment for the remaining active \((n = 13)\) and placebo treatment group \((n = 11)\). Before and following the experimental treatment, the groups did not show significant differences in normalized melatonin concentrations \((F(6,17) = 0.389, p = .876)\) and in mean melatonin concentrations at all specific sampling times \((\text{ANOVA}s, p \geq .153)\). Nevertheless, visual inspection of the curves suggests a larger phase advance after extraocular light than after placebo. Hence, for each normalized melatonin curve the DLMO, defined as the crossing with the 25%-level, was determined to evaluate the phase-shifting effects of the experimental treatment. The DLMO could be assessed in

Figure 3.3  Timing of sleep onset and awakening during the protocol in SAD patients receiving extraocular light or placebo illumination in the popliteal fossae. Mean (and SD) timing of sleep onset and awakening did not differ between the two treatment groups. On day 4 and 9 of the protocol, sleep onset is delayed in both groups due to the assessment of the salivary dim light melatonin onset (DLMO). Contrary to day 4 (on which patients had to wake up early because of the start of the experimental treatment), the delayed sleep onset is followed by a later time of awakening on day 9. DLMO = dim light melatonin onset; SAD = Seasonal Affective Disorder.
all subjects in the placebo condition and in 12 of the active treatment condition. Comparing the two treatment conditions, we could not detect a significant difference in the DLMO before and directly following treatment ($F(1,21) = 1.956$, $p = .177$).

Finally, a significant correlation was observed between treatment response at T3, as measured with the 21-item HRSD, and phase shift of the DLMO (Spearman’s rho = $-0.440$, $p = .036$). This indicates that the larger the observed phase advance of the DLMO, the more pronounced the response to the experimental treatment, irrespective of whether extraocular light was administered or not.

**DISCUSSION**

Following the first description of SAD and the early empirical results on the efficacy of artificial ocular light exposure (Rosenthal et al 1984), light therapy has become the therapy of first choice for this disorder. Various attempts have been made to control for the placebo effects of ocular light therapy. One study compared morning or evening ocular light therapy with a morning placebo control (a deactivated negative ion generator). After 4 weeks of treatment, significantly different remission rates were

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**Figure 3.4** Melatonin concentrations (mean and SD) in SAD patients on the evening prior to and immediately following a 5-day treatment period with extraocular light or placebo (no light) illumination of the popliteal fossae. For each subject melatonin concentrations were expressed as a percentage of the maximum value obtained during the subject’s first sampling period. The DLMO was defined as the crossing with the 25%‐level (indicated by the dashed line). DLMO = dim light melatonin onset; SAD = Seasonal Affective Disorder.
reported between morning light (61%), evening light (50%) and placebo (32%) therapy (Eastman et al 1998). In another study, SAD patients were told that the aim of the study was to examine the effect of non-visible infrared light in a placebo-controlled protocol. Patients received therapy by means of a light box or a head-mounted device, which were either active or inactive. The response rates obtained from this study revealed no significant differences between the effects of the active and inactive devices after 2 weeks of treatment (light box 33% and 42%; head-mounted unit 58% and 40% respectively) (Levitt et al 1996). A last study compared 5 days of morning light treatment with morning imaginary light accomplished through suggestion. In both groups, a significant improvement in mood scores was reported. This improvement disappeared during the 10-day follow-up period in the imaginary light condition (Richter et al 1992).

The phase-shifting effects on the circadian pacemaker of extraocular light in healthy subjects (Campbell and Murphy 1998) led to the present genuine double-blind placebo-controlled study on the effects of light applied at the skin of the popliteal fossae in SAD patients. In an earlier (open) study which compared ocular with extraocular light therapy in SAD (Wehr et al 1987), patients received treatment for two 7-day periods in which light was applied for 4 consecutive hours to either the skin (while wearing dark sunglasses), or to the eyes (while the rest of the body was covered). In both conditions, full-spectrum light boxes with an intensity of 2500 lux were used. It was concluded that ocular light treatment was superior to extraocular light treatment. Obviously, a major difference with the present study is the fact that the patients were aware of the type of treatment. The study presented here applied extraocular light within the blue spectrum and with a much higher intensity and found similar therapeutic responses in the active and placebo group. A 5-day treatment period has proven to yield a large number of responders in our SAD outpatients clinic (Meesters et al 1995). Therefore, it is concluded that extraocular light has no specific anti-depressant effect. Strictly speaking, however, it might be possible that the 5-day treatment period is insufficient for revealing differences between extraocular light and placebo. Nevertheless, remission rates were far from zero in both groups (for the HRSD criterion 36 and 40%, and for the SIGH-SAD criterion 21 and 27%). It is known from psychiatric drug treatment studies in patients with major depression that the placebo response can be as high as 65% (Quitkin 1999). Hence, the therapeutic effects obtained in the present study might all be interpreted as placebo effects. The calculated effect size $d$ showed that both extraocular light and placebo appeared to be ‘powerful treatments’ for SAD ($d >0.8$). The effect sizes of 1.52 and 0.97, respectively, are in the range of effect sizes reported in previous ocular light therapy studies (Terman et al 1989). It is unlikely that this response is explained by the natural course of SAD symptoms because one study showed that the BDI scores of SAD patients who
received no treatment once their BDI score was greater than or equal to 13 were gradually rising during the subsequent month (Meesters et al 1993). Apart from placebo effects, we speculate that sleep curtailment played a significant role. Analysis of the sleep data revealed that the experimental treatment not only caused an earlier mean time of awakening, but also a shortening of total sleep duration. Like non-seasonal depressives (for a review, see Wirz-Justice and Van den Hoofdakker 1999), SAD patients also respond favorably to sleep deprivation (Graw et al 1998). Therefore sleep deprivation effects may have accounted for part of the response in both groups.

In addition to the studies by Lindblom et al (2000a, 2000b) and by Eastman et al (2000), the present study provides no support for extraocular light sensitivity of the human circadian pacemaker (Campbell and Murphy 1998). According to the PRC obtained by the exposure of humans to popliteal extraocular light, a slight phase advance would be expected to result from our experimental treatment. Although we did observe such a phase shift in DLMO, it was not significantly different from the placebo group. Possibly, the changes in sleep timing account for the phase shifts in both groups (Gordijn et al 1999).

It has often been suggested that a shift in the DLMO to an earlier time, is causally related to (part of) the response to morning light treatment (Lewy et al 1998). Recently, in SAD patients who adhered to a regular sleep-wake schedule, the magnitude of the phase advance resulting from morning ocular light therapy was reported to be positively related to the improvement on the SIGH-SAD (Terman et al 2001). Remarkably, after combining the data of all patients, a positive correlation between treatment response at T3 and the phase-advance shift of the DLMO was also observed in our study. Yet, we cannot exclude other possible explanations for the association between treatment response and the timing of the DLMO. For instance, it might be that the earlier subjects had to wake up to arrive at the hospital for the experimental treatment (resulting in a larger phase advance of the DLMO), the more they may have profited from the anti-depressant effects of sleep deprivation. Alternatively, it is possible that compliance with the protocol resulted in earlier wake-up times and that compliance is associated with susceptibility to placebo effects. Finally it might be that the placebo-induced improvement resulted in higher melatonin concentrations rather than an earlier timing of production. A reduction of melatonin secretion has been previously reported in non-seasonal depressed patients, while, compared to controls, no significant differences were observed in the mean melatonin levels after recovery (Souêtre et al 1989). In a constant routine study however, the salivary melatonin rhythm was similar in SAD patients and controls and did not change after light treatment (Wirz-Justice et al 1995b).

In summary, this double-blind placebo-controlled study shows that extraocular light and placebo extraocular light both yield a considerable reduction in symptoma-
tology. No significant differences in treatment response or DLMO before and directly following the experimental treatment could be detected between patients receiving the active or the placebo treatment. Thus, placebo effects and/or the effect of sleep deprivation induced by the experimental protocol may have been decisive for the response to treatment.

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