cates that bright light is a potent zeitgeber for human circadian rhythms, and suggests that natural daylight may act as a zeitgeber for humans. Successful entrainment of human circadian rhythm by bright lights and the failure of entrainment by lights of a lower intensity are comparable with effective suppression of nocturnal melatonin level by bright lights and the failure of suppression by dim lights[7]. As suggested previously, the sensitivity of the human circadian system may be lower than that of other mammals. Recently, Czeisler and his coworkers[8] reported a phase-setting effect of bright lights on body temperature rhythm.

We assume that phase-dependent responsiveness of human circadian rhythm to bright light underlies entrainment. This kind of responsiveness is conventionally expressed as a phase response curve (PRC), which explains the entrainment of a circadian rhythm to a zeitgeber with a different period[10]. When the intrinsic period of the circadian rhythm is longer than the period of the zeitgeber, the circadian rhythm entrains to it by advancing the phase in each cycle, and when the intrinsic period is shorter than the zeitgeber period, the rhythm entrains to it by delaying the phase. Considering the phase relationship between sleep and bright lights in the present results, bright lights during the late sleep period or soon after waking-up may phase-advance the circadian rhythm in an amount equal to the difference between the free-running period and the period of the zeitgeber. In the PRC of a diurnally active mammal, the phase advance portion is located from the late subjective night to the early subjective day[11]; however, a human PRC for light has not yet been established. But the present result as well as Czeisler's finding[8] suggest the existence of a similar phase response curve, or at least of the phase advance portion. Preliminary results from our laboratory indicate that free-running human circadian rhythms are able to phase-advance in response to a single bright light pulse[12].

In conclusion, bright light cycles alone are capable of entraining human circadian rhythms in sleep-wakefulness and rectal temperature under temporal isolation.

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Dose relationships of morning bright white light in seasonal affective disorders (SAD)

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Summary. Bright white full spectrum light (> 2500 lux) can improve depressive symptomatology in a selected group of patients with recurrent autumn and winter depression. This crossover study demonstrates that 0.5-h morning white light is not an effective treatment, whereas 2-h is.
Key words. Bright white light; seasonal affective disorder; dose relationships.

Since the finding that high intensity white light (WL, > 2500 lux) can modify human circadian rhythms[1], enormous interest has been generated in the potential of a 'natural' therapy for certain disturbances where circadian pathophysiology is thought to be involved: sleep disorders[2,3], jet lag[4], and seasonal affective disorders (SAD)[5,6].

SAD is characterised by recurrent depressions in autumn and winter alternating with euthymia or hypomania in spring and summer, and atypical symptoms of hypersomnia, fatigue, increased appetite (particularly carbohydrate craving) and weight gain[5,6]. It was the attribute of seasonality in this illness that led to comparison with mechanisms of seasonality in animal behaviour–hibernation, migration, reproduction. These seasonal behaviours are initiated by changes in daylength (photoperiod) throughout the year, and can be simulated with artificial light[7]. Although humans are not overtly seasonal in their behaviour, many studies have documented changes throughout the year in population statistics such as birth and death, depressive illness and suicide, and in neurotransmitter and neuroendocrine function[8–10]. Thus the initial rationale for treatment of a winter depression was to simulate a summer day by extending the photoperiod with bright white light[5]. Since the first treatment of a SAD patient with light at dawn and dusk in 1980[11], light therapy has been shown to be remarkably and rapidly effective[12–24].

We have replicated the therapeutic efficacy of WL in a group of SAD patients in Switzerland[16]. In such outpatient studies it was of practical importance to establish a minimal effective dose of equivalent intensity WL. The methods used were essentially the same as in the previous study[16], patients being seen weekly by the same psychiatrist (A.C.S.) and given a set of lights (Vitalites®) to use in their own homes. The time of day for treatment was held constant: morning was chosen for theoretical reasons as being perhaps the most sensitive circadian phase[17,24].

During the winter of 1985/86, depressive patients (N = 33) who fulfilled both the diagnostic criteria for major affective disorder (DSMIII) and for SAD[5,6], and whose depression scores were of sufficient gravity to warrant treatment (Hamilton Rating Scale HRS $\geqslant$ 15)[5,6], entered the study (table). They were treated with 0.5-h or 2-h WL for 1 week between 06.00 and 08.00 h, and after 1 week withdrawal with the other duration of WL: 15 patients had complete psychometric data for the crossover study of 2-h vs 0.5-h WL. In addition, 9 patients had complete psychometric data for 1-h WL.

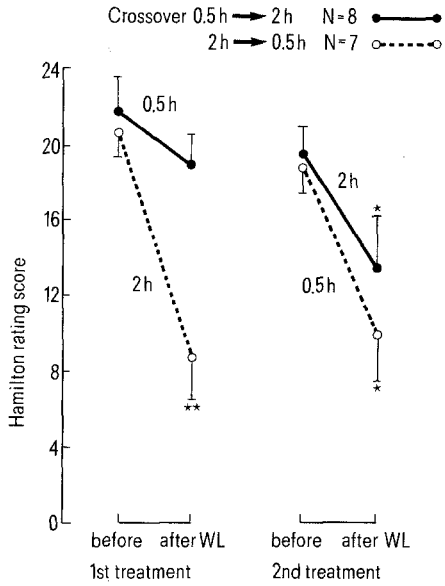
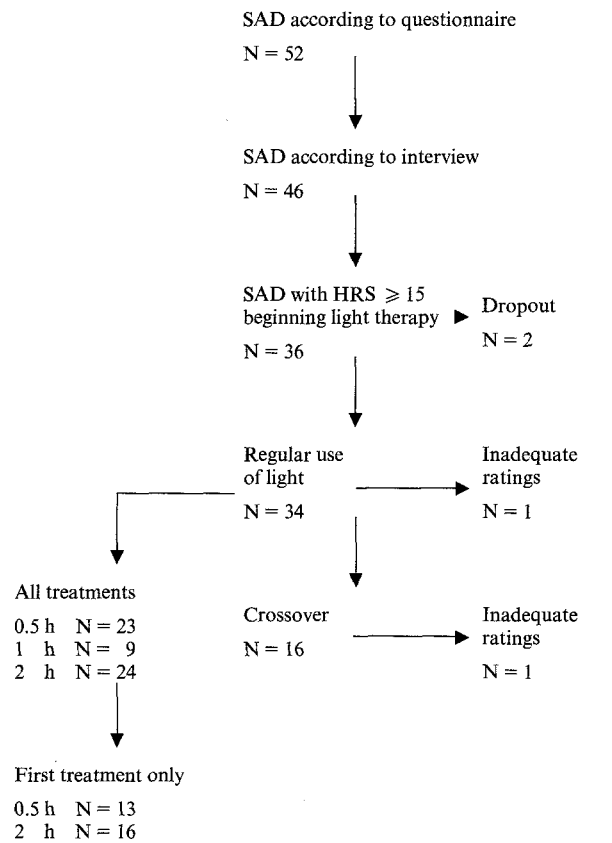


Figure 1. Hamilton rating scores (21 item scale, mean ± SEM) for SAD patients with completed crossover: either beginning with 0.5-h bright white light from 06.00 to 06.30 h (black lines) or beginning with 2-h bright white light from 06.00 to 08.00 (dotted lines). The values before and after treatment for one week are shown in order of application.
2-way ANOVA for first treatment: effect of light duration, $F(1,13) = 8.2$, $p = 0.01$; effect of treatment, $F(1,13) = 24.1$, $p < 0.01$; light × treatment, $F(1,13) = 9.36$, $p < 0.01$.
2-way ANOVA for second treatment: effect of light duration, $F(1,13) = 1.0$, n.s.; effect of treatment, $F(1,13) = 13.9$, $p < 0.01$; light × treatment, $F(1,13) = 0.5$, n.s.
Separate 1-way ANOVA for treatment effects: *$p < 0.05$; **$p < 0.01$.

Course of light therapy protocol in SAD patients 1985/86



A significant order effect was found: 0.5-h WL given first was not antidepressant, whereas 0.5- WL given after 2-h WL was. 2-h WL improved depressive symptoms independent of order (fig. 1). Therefore all first treatments only were considered using stringent criteria for clinical remission: a > 50% reduction of the baseline depression rating as well as a post-treatment HRS score of ≤ 8[18]. Of the 13 SAD patients who received 0.5-h WL as first treatment, only 4 were thus considered responders; of the 16 SAD patients who received 2-h WL as first treatment, 11 fulfilled the criteria as responders ($\chi^2 = 4.14$, $p < 0.05$). Seven of the 9 patients using 1-h WL also responded (for a case study of dose-response relationships, see Wirz-Justice et al.[19]).
Many patients tried different light exposures without necessarily being interviewed by the psychiatrist (missing HRS scores). However all were asked before they began a given light duration to rate their expectations; at the end of the study to give their global subjective impression of the efficacy of each duration. This was important to make sure there was no bias towards any one treatment protocol. For the group as a whole, positive 'expectation' ratings (Visual Analogue Scale) did not differ for any duration of WL (fig. 2A). In contrast, 'retrospective judgement' ratings showed that 2-h and 1-h WL were considered to have been efficacious and 0.5-h was not (fig. 2B).
These results add to the growing body of evidence that bright WL is indeed an adequate treatment for seasonal depression[5,6,11-24], and establish a minimal duration for morning WL of 1–2 h. This finding provides a practical treatment paradigm h as

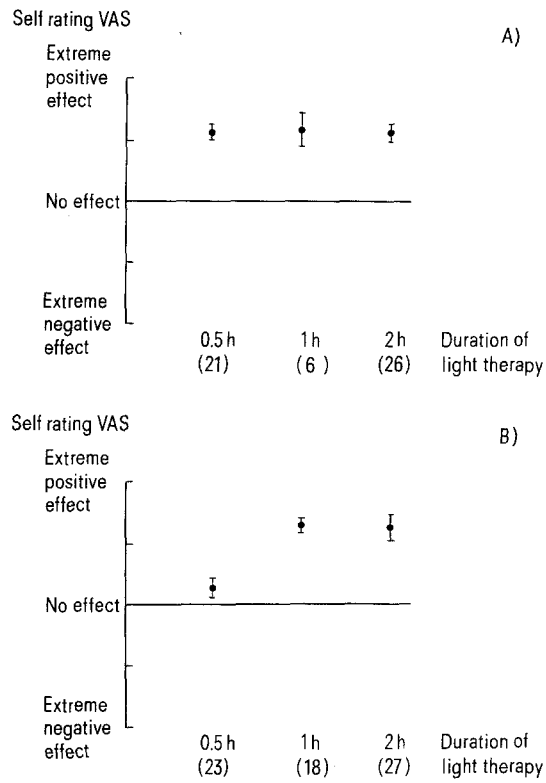


Figure 2. All patients were asked, but not all completed, a 100-mm VAS scale of their 'expectation' ratings for each duration of light treatment (A). No differences were seen in these predictions. At the end of the study, all patients were again asked to complete a 'retrospective judgement' rating of the therapeutic effect of each light duration that they had experienced (B). This time 0.5-h treatment was judged as having no effect, in contrast to the positive results with 1-h or 2-h. Statistical analysis was carried out with the small group of patients that completed the crossover design. It should be noted that the number of ratings exceed the number of HRS ratings (Table). 1-way ANOVA for prediction rating 0.5-h vs 2-h (N = 10): n.s.; for retrospective judgement rating 0.5-h vs 2-h (N = 15): $p < 0.01$.

well as a tool to investigate mechanisms underlying the antidepressant response.

Treatment of SAD with bright WL first used photoperiod extension (3-, 2-, or 1-h WL at dawn and dusk); these were all effective[5,6,11–16]. Later studies found that giving WL only in the morning, evening, or at midday also appeared to be effective[12–15,17,19–24]. However most studies have been carried out with a relatively small number of patients. A recent global analysis[18] of all studies of WL treatment of SAD patients until now (N = 185) has indicated that clinical remission obtained with photoperiod extension or morning WL is of the order of 50%, whereas all evening WL averaged a response rate of 35%. The latter corresponds to the average placebo response rate found in atypical depression[18].

Thus although the pathogenesis of SAD and the mechanism of action of WL in improving the symptoms of SAD is not known, the findings that photoperiod extension is not necessary for light to exert beneficial effects indicate that the seasonal model invoked in its inception may no longer be valid. Morning light appears more efficacious than evening light[18,24]; further studies with low duration of WL exposure are needed to establish whether early morning is indeed the most sensitive circadian phase.

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Continuous light abolishes the maternal entrainment of the circadian activity rhythm of the pups in the field mouse

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Summary. 12:12-h cycles of presence and absence of mother mouse act as a 'zeitgeber' and entrain the circadian rhythm of locomotor activity in the pups of *Mus booduga* under continuous darkness or continuous dim light. Continuous higher illumination of 15–25 lx abolishes this impressive maternal entrainment.

Keywords. Maternal entrainment; freerun; period; circadian pacemakers; *Mus booduga.*

Most studies on circadian behaviors in mammals have been restricted to adult animals in which the pathway of entrainment by environmental light and darkness (LD) is exclusively through the eyes[2,3]. In the infants of mice and rats the mother further acts as a transducer and coordinates the timing (phase) of the developing biological clock to her own clock time which, in turn, is entrained by ambient lighting[4–6]. We reported previously for *Mus booduga* that cycles of presence and absence of the mother mouse (PA cycles) entrain the circadian locomotor activity rhythm of pups both in continuous darkness (DD) and in continuous dim light (LL)[7]. However, some of our experiments (unpublished data) revealed that entrainment to PA cycles in LL of 3-10 lx was somewhat wobbly. LL is known to bring about radical alterations in circadian features[8] and even induce arrhythmia, split rhythms, etc.[9–11]. It has also been reported from this laboratory that social cues which synchronized the circadian flight activity rhythm of members of a colony of *Hipposideros speoris* bats in DD failed to do so in LL of 10–20 lx[12]. We therefore performed experiments to investigate whether LL of appropriately high intensities would in any manner impair the maternal entrainment of the circadian activity rhythm of pups.

Materials and methods. Pregnant mice *M. booduga* (17 in number) were captured from the fields around the University campus. Seven of them were maintained in DD and the other 10