Sleep deprivation in bright and dim light: antidepressant effects on major depressive disorder

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Summary

Twenty-three patients with a major depressive disorder were deprived of a night’s sleep twice weekly, one week staying up in the dimly lit living room of the ward (< 60 lux), and one week in a brightly lit room (> 2000 lux). Immediate, but transient beneficial effects of sleep deprivation were observed primarily in eight patients (the ‘responders’). The immediate effects did not differ greatly for the two conditions, indicating that exposure to light at night is an implausible explanation for the antidepressant effects of total sleep deprivation. There was some evidence that the bright light condition led to a more prolonged improvement of the responders.

Key words: Depression; Sleep deprivation; Light therapy

Introduction

One night of total sleep deprivation (TSD) is known to lead to improvement in many depressed patients (for a review, see Gillin, 1983). However, the antidepressant effect is nearly always transient, the typical pattern being a relapse after subsequent sleep. Ways are sought, therefore, to prevent this relapse, for example by using special time schedules of sleep deprivation (total or partial) and/or by combining sleep deprivation with other treatment. Some of these attempts may develop into practical therapy, but it is still much too early to speak of a major breakthrough. Parallel to these investigations, research is being devoted to the clarification of the still unknown mechanism of the antidepressant response. Van den Hoofdakker and Beersma (1988) and Wehr et al. (1988) review a large number of recent studies.

Another successful intervention, also of a biological but non-pharmacological nature, consists of the administration of artificial bright light. The efficacy of this treatment has been demonstrated particularly with regard to seasonal affective disorders (Yerevanian et al., 1986; Terman et al., 1989), but reports have also appeared indicating a beneficial effect in more classical types of depres-
sion (Fleischhauer et al., 1988; Kripke, 1989). Regarding the effectiveness in treating seasonal affective disorders, Terman et al. (1989) reviewed the studies to date and summarized some of the findings as follows: ‘In most studies, patients were exposed to light for 2 to 6 hours per day, although some patients have apparently benefited from durations of 30 minutes to 1 hour. The antidepressant response usually occurs within 3 to 4 days of treatment, with a similar time course for relapse during withdrawal. A few studies, however, have suggested protracted post-treatment benefit of up to several weeks’ (p. 2). In their meta-analysis, Terman et al. (1989) established that, in the treatment of disorders of low severity, light therapy was most effective when applied in the early morning. No time dependence of the antidepressant response was, however, found in moderate to severe cases. Although it is unclear how long the remission would typically be sustained in this group after discontinuation of light therapy, the data in general suggest that it would be longer than the usual single-day response produced by TSD.

In the present investigation, we compared the efficacy of TSD in dimly lit and brightly lit surroundings. Since both TSD and bright light appear to have antidepressant potential, the simultaneous application of these two modes of treatment may lead to more substantial effects. We attempted to obtain a more lasting antidepressant response by applying TSD twice, using the schedule: sleep - TSD - sleep - TSD - sleep. Our reasoning was that the usual relapse subsequent to the first night of sleep following TSD might be (partially) offset by a more protracted response due to the addition of bright light. A second TSD might then give a further ‘push’ towards recovery. The subjects were seriously depressed patients with the symptoms of a non-seasonal, major depressive disorder.

A second rationale for conducting this study was based on the idea that the exposure to light that normally accompanies TSD could be the crucial mediating factor in producing the antidepressant response. If this is the case, one might expect the combination of TSD and exposure to very bright light to have an antidepressant effect which occurs earlier and more frequently and which is greater and possibly less transient. Kripke (1981) put forward the hypothesis that, in particular, exposure to light in the very early morning is the effective stimulus. In agreement with this supposition, Kripke et al. (1983a,b) reported that waking up (non-seasonally) depressed patients at 5 a.m. and administering very bright light for 1 h had a greater antidepressant effect than dim light exposure at the same time or early in the night. An alternative explanation of these results, however, is that the light per se is not the crucial factor, but that phase shifts of circadian rhythms caused by the light exposure are responsible for these effects (Lewy et al., 1985). It has recently been shown that bright light exposure in the early morning does indeed cause a phase shift of the human circadian pacemaker (Dijk et al., 1988). Bright light exposure in the evening, on the other hand, also causes a phase shift, but in the opposite direction (Czeisler et al., 1986). It can therefore be expected that all-night exposure to bright light will induce both types of phase shift within one night, leading probably to virtually no change. Hence, the present investigation will allow a less confounded study of the role of light in producing the antidepressant response to TSD.

Our study can be regarded as a sequel to a small-scale investigation by Wehr and his colleagues (1985), which also addressed Kripke’s hypothesis. These investigators applied TSD once in nearly complete darkness and once in very bright light, with an interval of approximately a week. The subjects were two non-seasonal and three seasonal depressives. The results partly confirmed that the addition of bright light affects the antidepressive response to TSD in the direction presumed. During the TSD night, the patients improved more, relative to pretreatment levels, when bright light was administered. This suggests that exposure to bright light triggers an earlier response. Comparing the state of the patients on the days before and after TSD, however, no additional beneficial effect of the bright light condition could be assessed (perhaps due to the small sample size). Particularly interesting was the observation that for three patients the ‘improvement persisted for nearly one week after the bright light sleep deprivation but for only a day or so after the dim light sleep deprivation’. As the authors noted,
however, these were anecdotal observations not supported by objective ratings, and the three patients concerned were those diagnosed as seasonal depressives. All patients eventually relapsed.

The patients in Wehr et al.'s study were all drug-free and additional medication might conceivably have prevented the eventual relapse. For this reason, and also because of more general considerations concerning practical relevance, feasibility and ethics, the patients in our study received appropriate medication. This medication, however, was kept constant during the trial.

In summary, four questions were addressed in the present investigation.

- Does the combination of bright light and TSD ('bright light TSD') lead to an antidepressive response more often than TSD without this addition ('dim light TSD')?
- Comparing the state of the patients on the days before and after TSD, are the immediate responses to bright light TSD greater than those to dim light TSD?
- Does any antidepressant effect appear earlier with bright light TSD than with dim light TSD?
- Does the antidepressant response following bright light TSD last longer than that following dim light TSD?

The patients concerned in the study were potentially on pharmacological treatment for depression.

Patients and methods

The investigation was carried out in the Biological Psychiatry Unit of the University of Groningen, The Netherlands. Consecutively admitted patients were considered for participation if their self-ratings on the Beck Depression Inventory (Beck et al., 1961), as assessed on the first Monday morning of the (possible) trial, exceeded 16; this was regarded as indicative of a moderate to severe depression. Such patients were given an extensive interview in order to make a precise diagnosis and to assess the patient's status with regard to the Hamilton Depression Rating Scale (Hamilton, 1967). If a serious depression dominated the clinical picture, the patients were asked to participate after our procedures had been fully explained. Written consent was obtained from all subjects. Twenty-eight patients entered the study, but two left half-way through, having decided that they did not want to participate any longer. The data of three further patients were excluded from the analysis. One patient spontaneously remitted before the first TSD and remained stable during the rest of the trial. The self-ratings of the second patient were clearly unreliable. The third patient suddenly worsened during the study to such a degree that a large additional dose of neuroleptics was required. The medication of the remaining 23 patients, upon whose data our analysis is based, was left unchanged during the study, except that occasionally a benzodiazepine in low dosage was given upon request (but not during the TSD nights or on the days immediately following). Five patients were medication-free. The medication consisted mainly of the neuroleptics triflupromazine and haloperidol (seven patients), the tricyclic antidepressants clomipramine and amitriptyline (11 patients), and lithium (two patients). Five patients received only neuroleptics. These were psychotic depressive patients who entered the study shortly after admission to our ward. Before admission they had already been treated with neuroleptics for some time, and we were reluctant to introduce (additional) antidepressant medication in these cases in order to avoid contamination of the effects of major pharmacological changes and of TSD. Table 1, to be discussed further in the Results section and the Discussion, contains more detailed information on the medication. All but two patients met the DSM-III criteria for major depression (296.2 and 296.3). The classifications of the two remaining patients were atypical bipolar disorder, depressive phase (296.7) and atypical depression (296.8). The patients did not display the typical symptoms of a seasonal affective disorder (Rosenthal et al., 1984), nor did they mention any seasonality of their depression. Close or systematic inquiries after a possible seasonal dependence were not made, however. The group consisted of 11 women and 12 men with a mean age of 47.2 years (SD = 13.6; range 24–68 years). The mean Hamilton score was 23.9, with a range of 15–38 (SD = 6.4). For the computation of the Hamilton score, only the first 17 items in the scale were considered (Hamilton, 1986).
The trial lasted 2 weeks and always began on a Monday. The patients were deprived of sleep during the nights of Tuesday to Wednesday and of Thursday to Friday. In one week they stayed up in the dimly lit living room of the ward (< 60 lux), and in the other week they stayed in a separate, brightly lit room, from 11 p.m. to 7 a.m. The order of the two weeks was randomly arranged in this cross-over design. During sleep deprivation under bright light conditions, patients sat at a table in front of a plexiglass screen, behind which eight white fluorescent tubes (Vita light tubes) were vertically placed. The screen, positioned at a maximum distance of 1 m from the patient, served to spread the light and reduce UV content. The patients read, did some manual work or did nothing at all, whatever they pleased. They were asked to look at the screen at least once every minute. At eye level, the light intensity was > 2000 lux. A member of the nursing staff was always present. During all TSD nights and on the subsequent days, the patients were closely monitored in order to check tendencies to take a nap. Of the 23 patients, 11 received bright light TSD and 12 received dim light TSD during the first week.

On the two Monday mornings of the trial and on the Monday morning immediately following it, the patients rated their condition using the Beck Depression Inventory. From Tuesday to Saturday, daily at 9 a.m., 5 p.m. and 10 p.m., and during the TSD nights at 1 a.m. and 5 a.m., the patients rated themselves using von Zerssen’s ‘Adjective Mood Scale’ (von Zerssen, 1976, 1986). The ‘Adjective Mood Scale’ is a 28-item scale for self-rated depression with scores ranging from 0 (not depressed) to 56, and is particularly suited for frequent use at short intervals. A specially assigned research assistant, together with the nursing staff, ensured that the forms were completed conscientiously and on time. The Dutch versions of both the Beck inventory (Bouman et al., 1985) and the von Zerssen scale (Elsenga, 1988) have been shown to be psychometrically reliable.

Because the research design had a ‘cross-over’ structure, within-subject differences could be used for assessing treatment effects. The statistical tests based on these differences, however, were always preceded by preliminary checks for possible interaction effects between period and treatment, the presence of which might make the results difficult to interpret. The procedures described by Hills and Armitage (1979) were followed. No interaction effects were clearly demonstrable. Unless otherwise noted, the Mann–Whitney test was used for statistical analysis.

Results

Fig. 1 shows the mean self-ratings on the von Zerssen scale during the two treatments. Under both conditions the typical effect of TSD on depression is apparent, i.e., improvement on the day immediately following TSD and relapse after subsequent sleep. When a comparison is made across conditions between the overall mean scores on the days after TSD (Wednesday and Friday) and the mean scores on the other days (Tuesday, Thursday and Saturday), the difference is significant (Wilcoxon signed ranks test, \( P < 0.025 \)). However, inspection of the data showed that this difference was primarily produced by a minority of the patients who clearly responded to TSD. Using criteria corresponding to those previously applied in our clinic (Elsenga and van den Hoofdakker, 1987), ‘responders’ were defined as patients who, for at least two of the four TSDs, had a mean von Zerssen score on the day after TSD that was 6 or more points lower than the mean score on the day before. Using this definition, eight responders were
Fig. 2. Mean response to sleep deprivation, responders (n = 8).
- - - - Sleep deprivation in dim light, — — — sleep deprivation in bright light. The von Zerssen ‘Adjective Mood Scale’ was used for the self-ratings.

identified. The data for the responders are shown in Fig. 2. There were no significant differences between responders and non-responders with respect to age, gender or pretreatment depressive-ness (self-ratings on the Beck scale on the first Monday of the trial and mean self-ratings on the von Zerssen scale on the first Tuesday of the trial). However, responders and non-responders differed conspicuously with regard to the medication received (Table 1). The curious distribution shown in Table 1 will be further commented upon in the Discussion. Regarding the question whether the response to bright light TSD is different from the response to dim light TSD, however, it is relevant to note here that the responders who received the light treatments in the order dim–bright: the first subgroup consisted of three patients of whom one was medication-free, and the second subgroup consisted of five patients of whom two were medication-free. Results pertaining to the four questions posed at the end of the Introduction will be presented below separately for the total group of 23 patients and for the subgroup of eight responders. Within the subgroup of non-responders (n = 15), none of the analyses to be discussed yielded statistically significant results.

Using the criterion of a mean improvement of 6 points on the von Zerssen scale for assessing a response or non-response to TSD, the frequencies of response under the two TSD conditions were as follows. Of the total group of 23 subjects, nine responded to the first bright light TSD and five to the second. These results were six and seven, respectively, following the dim light TSD. In the subgroup of eight responders, all eight responded to the first bright light TSD and five responded to the second, while the corresponding results under dim light conditions were six and six. No formal statistical test was deemed necessary to determine the non-significance of these differences. Other criteria, applied to maximal rather than mean differences between pre- and post-TSD scores, also failed to suggest a differential effect between the two conditions.

In comparing the mean magnitudes of the immediate responses, we considered the differences between the mean self-ratings on the days before and after the TSD nights, as well as the differences between the mean scores on the days before TSD and the minimal (‘least depressive’)

### TABLE 1
**MEDICATION OF RESPONDERS AND NON-RESPONDERS: FREQUENCIES**

<table>
<thead>
<tr>
<th></th>
<th>AD &gt; 10 d.</th>
<th>AD &lt; 10 d.</th>
<th>Neuroleptics only</th>
<th>Lithium only</th>
<th>Medication-free</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td>5 (1)</td>
<td>3 (1)</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Non-responders</td>
<td>3 (2)</td>
<td>3 (1)</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>3</td>
<td>5</td>
<td>2</td>
<td>5</td>
<td>23</td>
</tr>
</tbody>
</table>

AD > 10 d., tricyclic antidepressants used for more than 10 days before the trial started; AD < 10 d., tricyclic antidepressants used for less than 10 days before the trial started. The frequencies in parentheses indicate the numbers of patients who received neuroleptics in addition to the antidepressant medication.
TABLE 2
SELF-RATINGS ON THE BECK DEPRESSION INVENTORY: MEANS (SD)

<table>
<thead>
<tr>
<th></th>
<th>Monday 1</th>
<th>Monday 2</th>
<th>Monday 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total group (n = 23)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BD (n = 11)</td>
<td>33.2</td>
<td>-B-</td>
<td>29.0</td>
</tr>
<tr>
<td>(n = 10)</td>
<td>(10.5)</td>
<td>(12.7)</td>
<td>(11.0)</td>
</tr>
<tr>
<td>DB (n = 12)</td>
<td>28.4</td>
<td>-D-</td>
<td>27.8</td>
</tr>
<tr>
<td>(n = 9)</td>
<td>(9.5)</td>
<td>(10.5)</td>
<td>(11.0)</td>
</tr>
<tr>
<td><strong>Responders (n = 8)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BD (n = 3)</td>
<td>29.7</td>
<td>-B-</td>
<td>16.0</td>
</tr>
<tr>
<td>(n = 3)</td>
<td>(7.8)</td>
<td>(5.2)</td>
<td>(3.9)</td>
</tr>
<tr>
<td>DB (n = 5)</td>
<td>29.2</td>
<td>-D-</td>
<td>32.6</td>
</tr>
<tr>
<td>(n = 5)</td>
<td>(9.0)</td>
<td>(14.0)</td>
<td>(16.2)</td>
</tr>
</tbody>
</table>

-B-, week of bright light TSD; -D-, week of dim light TSD; BD and DB indicate the subgroups who received the TSD treatments in the order bright-dim and dim-bright, respectively.

The earlier antidepressant response, the differences between the mean self-ratings on the days before TSD and the mean self-ratings during TSD (at 1 and 5 a.m.) were considered. For both the total group and the subgroup of responders, more improvement was observed during the first bright light TSD than during the first dim light TSD (P < 0.05). However, this earlier response could not be established during the second TSD. Using scores averaged across the two TSDs, the comparison did not yield treatment effects at a statistically significant level.

In order to evaluate whether bright light TSD had a more lasting effect than dim light TSD, the Monday to Monday differences on the Beck Depression Inventory were considered, as were the Tuesday to Saturday and Tuesday to Tuesday differences on the von Zerssen scale. Tables 2 and 3 show the data, separately for the total group and for the group of responders, and separately for the subgroups who received the treatments in the order bright-dim (BD) and for the subgroups who received the treatments in the order dim-bright (DB). The two tables do indeed show a trend in favor of bright light TSD. In the group of responders, significance was reached for the Beck data (at P = 0.05) but (just) not for the von Zerssen data. For the total group these trends were not significant. Apparently, the more lasting effect of bright light TSD was restricted to the subgroup of responders.

Table 2 also suggests that, within the subgroup of responders, the more lasting effect of bright light TSD was further restricted primarily to the three patients who received bright light TSD in the first week of the experimental period. However, the test for a possible period × treatment interaction effect was (only just) not significant, while the von Zerssen data of the responders

TABLE 3
SELF-RATINGS ON THE VON ZERSSEN SCALE: MEANS (SD)

<table>
<thead>
<tr>
<th></th>
<th>Tuesday 1</th>
<th>Saturday 1</th>
<th>Tuesday 2</th>
<th>Saturday 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total group (n = 23)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BD (n = 11)</td>
<td>45.4</td>
<td>-B-</td>
<td>39.1</td>
<td>~</td>
</tr>
<tr>
<td>(n = 10)</td>
<td>(5.6)</td>
<td>(10.3)</td>
<td>(9.7)</td>
<td>(9.7)</td>
</tr>
<tr>
<td>DB (n = 12)</td>
<td>40.9</td>
<td>-D-</td>
<td>35.7</td>
<td>~</td>
</tr>
<tr>
<td>(n = 11)</td>
<td>(9.8)</td>
<td>(12.3)</td>
<td>(9.9)</td>
<td>(13.4)</td>
</tr>
<tr>
<td><strong>Responders (n = 8)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BD (n = 3)</td>
<td>44.2</td>
<td>-B-</td>
<td>31.6</td>
<td>~</td>
</tr>
<tr>
<td>(n = 3)</td>
<td>(2.1)</td>
<td>(7.9)</td>
<td>(8.2)</td>
<td>(7.2)</td>
</tr>
<tr>
<td>DB (n = 5)</td>
<td>48.2</td>
<td>-D-</td>
<td>39.7</td>
<td>~</td>
</tr>
<tr>
<td>(n = 5)</td>
<td>(4.2)</td>
<td>(10.4)</td>
<td>(5.6)</td>
<td>(19.5)</td>
</tr>
</tbody>
</table>

-B-, week of bright light TSD; -D-, week of dim light TSD; BD and DB indicate the subgroups who received the TSD treatments in the order bright-dim and dim-bright, respectively.
(Table 3) do not carry the suggestion of such an interaction effect. All in all, it can be concluded that the data of the responders show some evidence of a more lasting antidepressive effect after bright light TSD.

Discussion

The findings of Wehr et al. (1985) were all reproduced in the present study, but our results clearly call for some amendments. Comparing the self-ratings during the TSD nights with those of the preceding day, we found evidence that, as in the study by Wehr et al., a first night of bright light TSD leads to a faster antidepressant response than a first night of dim light TSD. For the second TSD, however, this difference appeared to vanish. This suggests that the difference for the first night can at least partly be attributed to the novelty of the experience of treatment with bright light. Also, because the comparison of the self-ratings on the days before and after TSD did not yield better results for bright light TSD, the conclusion seems warranted that the immediate antidepressive effect caused by TSD is not dependent on the amount of light received during the TSD night. While, as Wehr et al. note, it is theoretically possible that a minimal supply of light at night is necessary for the antidepressant response to take place, perhaps in combination with the light experienced after sunrise, the data strongly suggest that other mechanisms to explain the immediate response to TSD must be sought. Furthermore, if the time of sunrise and the amount of light experienced thereafter are influential factors, one would expect comparatively less responsiveness to TSD during the dark and cloudy Dutch winters. Elsenga and van den Hoofdakker (1987), however, have found no evidence for a seasonal influence.

To what extent the medication might have affected the immediate response to TSD is difficult to decide within the confines of the present study. Table 1 shows that the responders either were subjects who had already used antidepressants for more than 10 days when entering the trial or were medication-free. There is some evidence that clomipramine, the antidepressant used most often in the present study, favorably affects the immediate response to repeated sleep deprivations (Elsenga and van den Hoofdakker, 1989). The data in Table 1 do not contradict this. More remarkable, however, is that eight of the 15 non-responders were treated with neuroleptics, against one of the eight responders ($\chi^2 (1) = 3.65, P < 0.03$, assuming we had such a hypothesis in advance). If this is not merely a chance result, it might mean either that patients eligible for treatment with neuroleptics are less responsive to TSD or that neuroleptics have an adverse effect on the response to TSD. The first possibility is less probable, in view of the evidence that depressives with psychotic features tend to react more favorably to TSD than non-psychotic depressives (Elsenga and van den Hoofdakker, 1987). We are unaware of any studies corroborating or contradicting the second possibility. If other investigations would confirm an adverse effect of neuroleptics on the antidepressant response to sleep deprivation, this might shed an interesting light on the mechanism by which it takes place.

The frequent use of neuroleptics in the present sample of patients might also explain the comparatively small number of responders — 35%. This contrasts with the average response rate of 58% estimated on the basis of some 30 studies (Gillin, 1983). Other possible explanations for the small number of responders, however, include random fluctuation, the fact that responses in the present study were defined on the basis of self-ratings (observers often note an improvement when the patient himself does not), and the trend, according to our impression, that depressed patients referred to University Hospitals (at least ours) over the years are increasingly therapy-resistant.

Despite the fact that the immediate antidepressant response to bright light TSD was not greater than that to dim light TSD, there was some evidence that, in the subgroup of responders, the response was more protracted after bright light TSD. As explained above, the design of our study was directed toward the possibility that the exposure to bright light, perhaps in combination with the medication administered, might counteract the usual relapse after the first night of sleep following TSD. Fig. 2 suggests this effect only for the second bright light TSD. To what extent the antidepressant medication might have been a con-
tributing factor is also difficult to assess here. Antidepressant medication per se has been found to prolong the response to sleep deprivation (Loosen et al., 1976; Philip, 1978; Baxter et al., 1986), and a relapse-suppressing effect due to an interaction with exposure to bright light is possible. We have tried to derive an indication in this direction from the individual data of the patients, but these efforts were unrewarding. Whatever the cause, however, the general trend in the self-ratings suggests that a continuation of the bright light TSD regimen might have shown a further improvement. A new study will be required to investigate this possibility. It should be noted, however, that overall there is not much evidence to suggest that the procedures applied in the present study would lead to a substantial long-term improvement, either for the non-responders to TSD or for the responders. From Table 1 it can be gathered that from Monday 1 to Monday 3 the total group improved by 4.0 points on the Beck Depression Inventory, which does not seem particularly impressive considering that time, medication, and possibly also a placebo effect may all have contributed to this change. The improvement after 2 weeks was even greater in the group of non-responders (3.4 points) than in the group of responders (4.4 points). Thus, perhaps, another kind of design in which some form of sleep deprivation is combined with the administration of bright light may be considered for use in future studies. Partial sleep deprivation late in the night (Sack et al., 1988), followed by exposure to bright light in the early morning, may be a promising alternative.

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References


