Total sleep deprivation combined with lithium and light therapy in the treatment of bipolar depression: replication of main effects and interaction

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Abstract

The clinical usefulness of total sleep deprivation (TSD) in the treatment of bipolar depression is hampered by a high-rate short-term relapse. Previous literature has suggested that both long-term lithium treatment and light therapy could successfully prevent relapse. We randomized 115 bipolar depressed inpatients to receive three cycles of TSD, alone or in combination with morning light exposure, given at an intensity of 150 or 2500 lux. Forty-nine patients were undergoing long-term treatment with lithium salts (at least 6 months), while 66 patients were taking no psychotropic medication. Mood was self-rated by the Visual Analogue Scale three times a day during treatment. The results showed that both light therapy and ongoing lithium treatment significantly enhanced the effects of TSD on the perceived mood, with no additional benefit when the two treatments were combined. Subjective sleepiness during TSD, as rated by the self-administered Stanford Sleepiness Scale, was significantly reduced by light exposure, and was correlated with the outcome. This study confirms the possibility of obtaining a sustained antidepressant response to TSD in bipolar patients. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Total sleep deprivation; Light therapy; Lithium salts; Bipolar disorder; Depression

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1. Introduction

The American Psychiatric Association (1995) practice guidelines for the treatment of bipolar depression suggest the possible usefulness of non-pharmacological treatments, because of latency of action, side effects, and the risk of manic switches associated with antidepressant drug treatments. Total sleep deprivation (TSD) can induce rapid and marked mood improvements in 60% of depressed patients with a low associated risk of switches into mania (Colombo et al., 1999) and no reported side effects, but the mood amelioration is usually followed by a high-rate short-term symptomatological relapse in the first few days after treatment (Wu and Bunney, 1990). Despite TSD's rapid efficacy in bipolar depression, the clinical usefulness of this technique has thus long been a matter for debate (Leibenluft and Wehr, 1992).

In an attempt to prevent a short-term relapse, TSD was combined with other non-pharmacological treatments, with promising results. Sleep phase advance, but not sleep phase delay, was shown to prevent a short-term relapse after TSD in roughly 75% of TSD responders (Berger et al., 1997; Riemann et al., 1999). A recent study showed a favorable interaction between partial sleep deprivation and bright light therapy: exposure to 2500 lux light in the morning and in the evening, for 2 h each, was shown to prevent relapse after sleep deprivation for at least 12 days (Neumeister et al., 1996).

A recent study by our group showed that ongoing lithium treatment can successfully enhance the effect of TSD and prevent relapse after treatment (Benedetti et al., 1999a). In a sample group of 20 bipolar depressed patients who had been treated with lithium for at least 6 months before the onset of the depressive episode, we observed a 65% sustained (3 months) antidepressant response after three cycles of TSD without combined antidepressant drugs other than lithium salts. Since lithium salts are the first-choice treatment for bipolar patients, we proposed this combined treatment as a possible first-choice therapy for bipolar depression.

The combination of lithium, light, and TSD has never been studied. Moreover, few data are available on the interaction between lithium and light in bipolar depression. Long-term lithium treatment has been shown to decrease retinal sensitivity to light (Carney et al., 1988; Wirz-Justice et al., 1997; Duncan et al., 1998), and a preliminary clinical trial showed a reduced response to light therapy in lithium-treated patients in comparison with lithium-free depressed inpatients (Heim and Morgner, 1997). Lithium could, therefore, modify the effect of light when combined with TSD.

The purpose of our study was to define the effect of lithium salts and light therapy in sustaining the acute antidepressant effect of sleep deprivation in bipolar depression. We evaluated, in open conditions, the effects of three cycles of TSD alone or in combination with ongoing lithium salts and/or light therapy.

2. Method

2.1. Subjects

One-hundred and fifteen bipolar depressed (DSM IV criteria) inpatients were studied. Forty-nine had been taking lithium salts for at least 6 months before the onset of the current depressive episode, while 66 had not been placed on a long-term medication by previous psychiatrists in charge.

The inclusion criteria were: Axis I diagnosis of bipolar disorder; a depressive episode according to DSM-IV criteria; absence of other diagnoses on Axis I; absence of mental retardation on Axis II; absence of pregnancy, history of epilepsy, major medical and neurological disorders; and absence of a history of drug or alcohol dependency or abuse within the last 6 months. Excluded from the study were patients who assumed treatments with long-acting neuroleptic drugs in the last 6 months before admission, or who had been treated with neuroleptics or irreversible MAOIs in the previous month before admission. For lithium-treated patients, we requested that they have had no period off lithium during the last 6 months.

Physical examinations, laboratory tests and electrocardiograms were performed on admission. After a complete description of the study to the subjects, written informed consent was obtained.

2.2. Treatment

If patients were undergoing long-term lithium salts treatment, they continued to receive lithium carbonate at the same dose throughout the study period. If patients were not taking lithium, they were not administered any psychotropic drug treatment. If patients were treated with benzodiazepines, we made a progressive dose reduction before the run-in period.

All patients underwent a 7-day run-in period, during which semi-structured interviews based on DSM-IV for Axis I diagnoses were completed. After the run-in period, all patients had a 21-item Hamilton Depression Rating Scale (HDRS; Hamilton, 1960) score of > 18, and no improvement was observed.

All patients were administered three consecutive TSD cycles (day 1−6), and each cycle was composed of a period of 36 h awake. On days 1, 3, and 5, the patients were totally sleep deprived from 07:00 h until 19.00 h of the following day. They were then allowed to sleep during the night of days 2, 4, and 6 (Barbini et al., 1998).

TSD was carried out in a room with 80 lux ambient light. Patients were randomized to receive: (1) no additional exposure to bright light ($n = 35$); (2) exposure for 30 min to a 150-lux red light ($n = 38$), given at 03:00 h during the TSD night, in the morning after the recovery sleep, and half an hour after awakening, between approximately 08.00 h and 09.00 h; (3) exposure for 30 min to a 2500-lux white light ($n = 42$), given at the same times.

2.3. Data collection

During the TSD treatment, subjective mood levels were assessed with a self-administered 10-cm Visual Analogue Scale (VAS; Aitken, 1969) three times during the day (08.00, 13.00, and 18.00 h), from day 1 (i.e. before the first TSD) to day 7 (i.e. after the last recovery night). Patients were instructed to rate their mood between 'very sad' (on the left) and 'very happy' (on the right), with a median 'normal' point in the center. Scores of 0, 50, and 100 denoted extreme depression, euthyrnia, and euphoria, respectively. Each patient's perceived mood level on each day was calculated as the mean of the three scores for that day.

Sleepiness during the night of TSD was evaluated hourly with a self-administered Italian version of the Stanford Sleepiness Scale (Scarone and Colombo, 1991) from 21.00 until 08.00 h the following morning. We then calculated the sum of the hourly scores as an index of total sleepiness during TSD procedure.

2.4. Data analysis

Clinical and demographic characteristics between the groups were compared using the Chi-square test (with Yates' correction) and a one-way analysis of variance (ANOVA) as appropriate.

To evaluate the effect of the treatment, we analyzed changes in VAS scores over time with respect to the baseline. The data were analyzed with repeated measures ANOVA, with a post hoc Newman−Keuls critical ranges test.

Computerized analyses were performed with a commercially available statistical package.

3. Results

Seven patients switched polarity during the TSD treatment and were excluded from further study. Three of these had been taking lithium salts and were treated with red 150 lux light, and four were without lithium and were treated with red ($n = 2$) and bright white light ($n = 2$).

Clinical and demographic characteristics of study completers ($n = 108$), divided according to treatment groups, are shown in Table 1. No difference was statistically significant.

In the whole sample, a three-way repeated measures ANOVA with time, lithium and light as independent factors showed a highly significant effect of time ($F = 27.03$; d.f. $= 6,612$; $P <$

Table 1
Clinical and demographic characteristics of study completers ($n = 108$) divided according to treatment group

|	150 lux red light		2500 lux white light		80 lux ambient light		F (d.f. = 5,102)	P
	TSD + lithium ($n = 14$)	TSD alone ($n = 19$)	TSD + lithium ($n = 17$)	TSD alone ($n = 23$)	TSD + lithium ($n = 15$)	TSD alone ($n = 20$)		
Sex (m/f)	5:9	6:13	7:10	4:19	5:10	9:11		
Age	45.6 ± 14.6	41.6 ± 12.9	42.6 ± 12.1	45.1 ± 12.8	51.0 ± 13.2	49.5 ± 10.5	1.51	0.19
Age at onset	28.3 ± 10.2	27.9 ± 7.7	25.8 ± 8.5	29.9 ± 13.6	35.0 ± 13.2	31.0 ± 10.9	1.52	0.19
Number of previous illness episodes	9.21 ± 12.2	6.2 ± 8.3	8.4 ± 6.7	6.9 ± 4.2	5.2 ± 1.7	7.3 ± 4.8	0.7	0.62
Duration of current episode (weeks)	9.9 ± 13.5	8.6 ± 6.9	7.4 ± 4.3	10.8 ± 9.3	6.3 ± 6.3	12.5 ± 13.0	1.04	0.40
Plasma lithium levels (mmol/l)	0.66 ± 0.11	–	0.63 ± 0.10	–	0.64 ± 0.09	–	0.21	0.81
HDRS score at outset	20.9 ± 3.9	20.4 ± 3.6	22.0 ± 3.4	20.6 ± 3.8	21.5 ± 3.9	20.7 ± 3.9	0.49	0.79
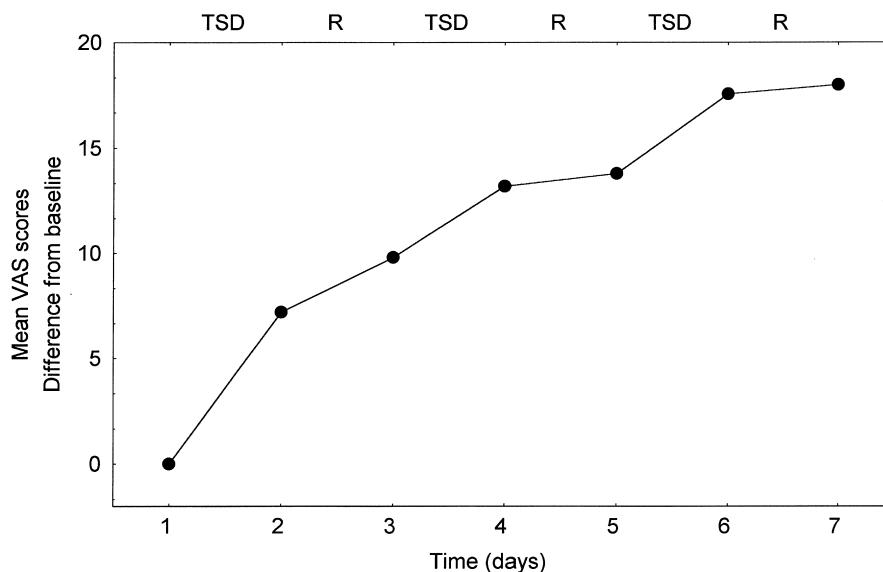
Fig. 1. Overall change in perceived mood during treatment. All patients are pooled together.

0.00001) (see Fig. 1), meaning that VAS scores showed an overall change during treatment; a significant lithium × light interaction ($F = 4.37$; d.f. = 2,102; $P = 0.0150$), meaning that the effect of one treatment is different depending on whether the other is present or absent; and a highly significant time × lithium × light interaction ($F = 2.31$; d.f. = 12,612; $P = 0.0068$), meaning that both treatments influenced the time-lagged change in VAS scores (see Fig. 2). The effects of lithium, light, time × lithium and time × light were not significant. This is because lithium-free/light-treated patients showed patterns of VAS change similar to lithium-treated/ambient light patients, and because the effects of light and lithium treatments were not additive (see Fig. 2). The similar effect of the two treatments is readily apparent by inspecting Fig. 3, where lithium-free/light-treated patients (both red and white light plotted together) are compared with lithium-treated/ambient light patients.

Newman−Keuls post hoc comparisons showed, among lithium-treated patients (see Fig. 2, left), a significant difference only at day 3 (i.e. after the first recovery night), when patients treated with red light showed significantly worse VAS scores

than ambient light patients ($P = 0.029$). Among the lithium-free patients (see Fig. 2, right), ambient light patients showed significantly worse VAS scores than white light patients after the second and third recovery nights ($P = 0.0029$ at day 5 and $P = 0.0027$ at day 7, respectively), with a marginal significant difference after the first recovery night ($P = 0.09$ at day 3). Ambient light patients showed worse VAS scores than red light patients after the first and third recovery nights ($P = 0.015$ at day 3 and $P = 0.014$ at day 7, respectively). No significant difference was detectable between the groups after the three TSD nights (day 2, day 4, and day 6); white light and red light treated patients did not differ at any point.

To better characterize the main effects of lithium and light, we performed additional two-way repeated measures ANOVAs. In patients who were sleep deprived with ambient light only (see Fig. 4), a two-way repeated measures ANOVA with time and ongoing lithium treatment as independent factors showed significant effects of time ($F = 5.68$; d.f. = 6,198; $P = 0.00002$), lithium ($F = 7.32$; d.f. = 1,33; $P = 0.0107$), and a significant time × lithium interaction ($F = 2.34$; d.f. = 6,198;
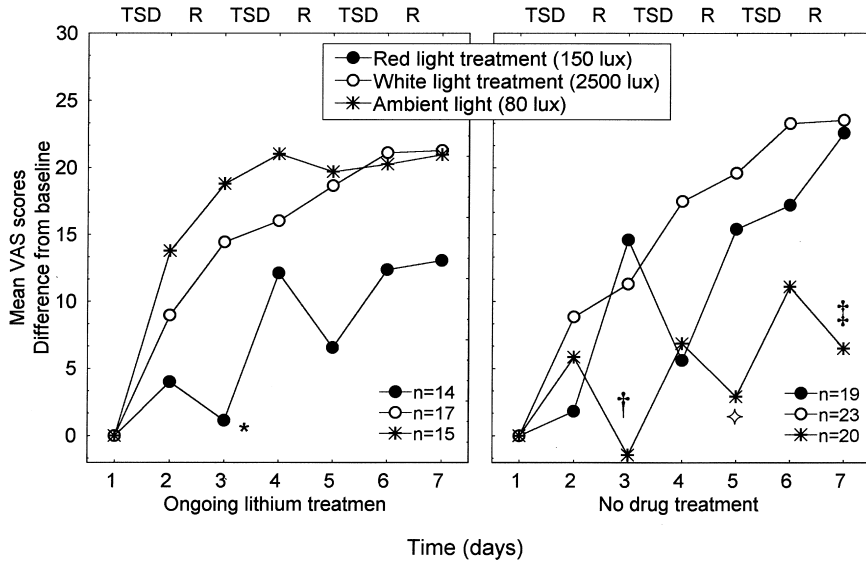
Fig. 2. Changes in perceived mood during TSD treatment. Significant differences (Newman–Keuls post hoc test) are marked as follows: * = ambient light vs. red light, $P = 0.029$; † = red light vs. ambient light, $P = 0.015$, white light vs. ambient light, $P = 0.09$; ☆ = white light vs. ambient light, $P = 0.029$; ‡ = red light vs. ambient light, $P = 0.014$, white light vs. ambient light, $P = 0.027$

$P = 0.0335$). Newman–Keuls post hoc comparisons showed non-significant differences at days 2 and 6 (i.e. after the first TSD and the third TSD; $P = 0.367$ and $P = 0.224$, respectively), and significant differences at days 3, 4, 5, and 7 (i.e. after the three recovery nights and after the second
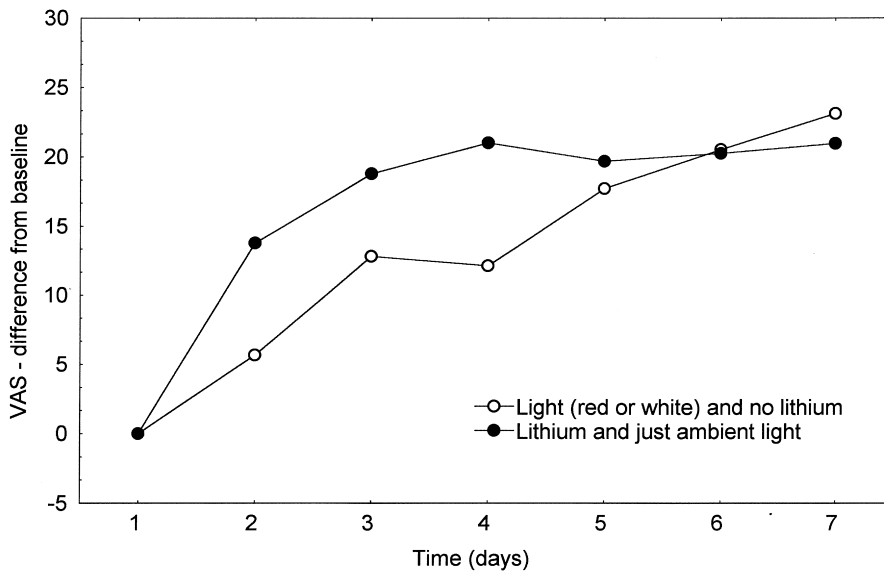

Fig. 3. Changes in perceived mood in patients treated with lithium and sleep deprived with ambient light only, and in patients without lithium and treated with light therapy (red light and white light pooled together).
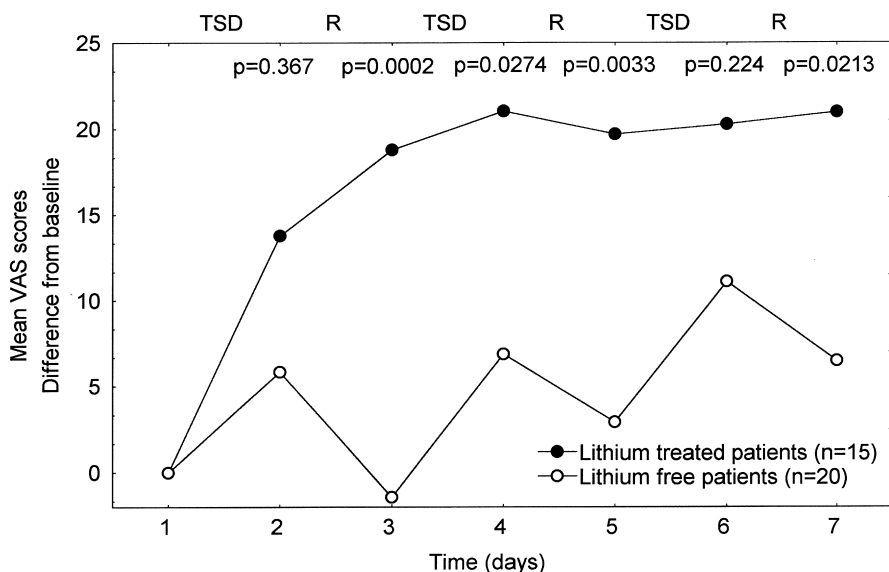
Fig. 4. Changes in perceived mood of patients with or without lithium treatment and sleep deprived with ambient light only. Newman–Keuls post hoc results are reported on the upper *x*-axis.

TSD; $P = 0.0002$, $P = 0.0274$, $P = 0.0033$, and $P = 0.0213$, respectively), thus confirming the significant effect of lithium in preventing the rapid relapse of depressive symptoms after recovery sleep.

In patients without long-term lithium treatment (see Fig. 2, right), a two-way repeated measures ANOVA with time and light treatment as independent factors showed significant effects of time ($F = 14.79$; d.f. = 6,354; $P < 0.00001$), light ($F = 4.39$; d.f. = 2,59; $P = 0.0166$), and a significant time × light interaction ($F = 2.83$; d.f. = 12,354; $P = 0.0010$). Newman–Keuls post hoc comparisons yielded results similar to the three-way analysis: white and red light did not differ at any point, red light was superior to ambient light after the second and third recovery nights ($P = 0.0079$ and $P = 0.0043$, respectively), and white light was superior to ambient light after the second and third recovery nights ($P = 0.0017$ and $P = 0.0011$, respectively). This means that light treatment did not significantly enhance the effect of TSD, but significantly prevented relapse after recovery sleep.

When pooling together patients treated with red or with white light, without lithium salts, and comparing them with patients treated with lithium salts and sleep deprived with ambient light only (see Fig. 3), a two-way repeated measures ANOVA showed a significant effect of time only ($F = 15.89$; d.f. = 6,330; $P < 0.00001$), with no significant effects of treatment or time × treatment interactions ($F = 0.72$; d.f. = 1,55; $P = 0.399$, and $F = 1.33$; d.f. = 6,330; $P = 0.241$). This means that both treatments have similar efficacy in sustaining the acute effects of TSD.

The Stanford Sleepiness Scale scores in the morning after TSD (08:00 h) are plotted in Fig. 5. Patients exposed to light showed a lower sleepiness than patients who were not. A two-way repeated measures ANOVA showed a significant effect of light ($F = 4.50$; d.f. = 2,105; $P = 0.0133$), with neither a significant effect of time nor a time × treatment interaction. Newman–Keuls post hoc comparisons showed a significant difference between white light and ambient light after the first and second TSD ($P = 0.041$ and $P = 0.0022$, respectively), and a significant difference between red light and ambient light after the first TSD ($P = 0.031$).
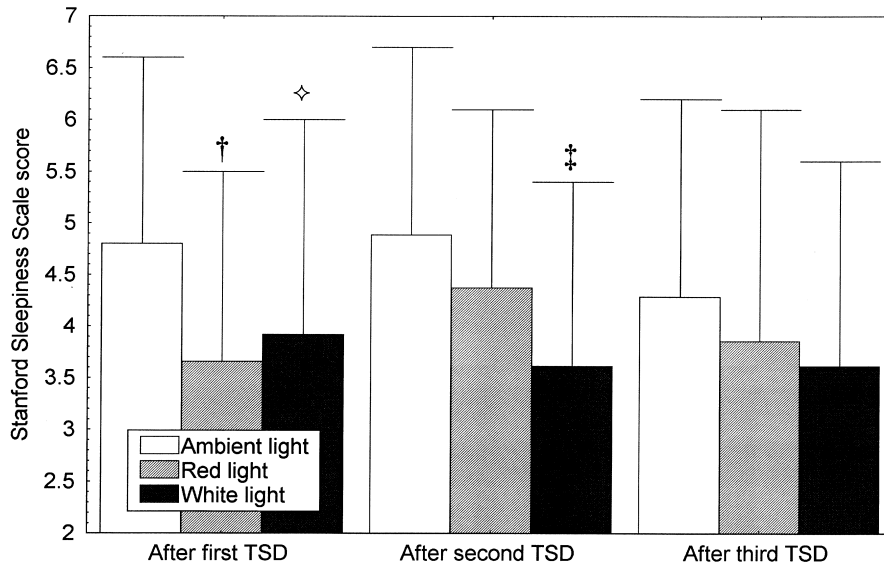
Fig. 5. Subjective sleepiness in the morning after TSD. Values are means ± S.D. Significant differences (Newman−Keuls post hoc test) are marked as follows: † = red light vs. ambient light, $P = 0.031$; ☆ = white light vs. ambient light, $P = 0.041$; ‡ = white light vs. ambient light, $P = 0.002$

Pearson's product−moment test (Table 2) showed that total sleepiness during TSD was significantly correlated with the VAS scores on the days before and after treatment.

4. Discussion

In agreement with the previous literature (see Section 1), the results of the present study con-

firmed that both long-term lithium treatment and light therapy sustained the acute antidepressant effect of repeated TSD on the perceived mood of bipolar depressed patients. No additional benefit was observed, however, when both lithium and light were combined with TSD.

The rate of switch into the manic phase during repeated TSD treatments (7/115, 6.1%) was the same as observed in previous studies by our group (Colombo et al., 1999), and was comparable with

Table 2

Correlations between total sleepiness during TSD (sum of hourly Stanford Sleepiness Scale scores from 21.00 h. to 08.00 h) and VAS scores before and after TSD

		VAS scores					
		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Total sleepiness	First TSD	$r = -0.2252$ $P = 0.0191$	$r = -0.0197$ $P = 0.8396$	–	–	–	–
	Second TSD	–	–	$r = -0.3539$ $P = 0.0002$	$r = -0.2564$ $P = 0.0073$	–	–
	Third TSD	–	–	–	–	$r = -0.3531$ $P = 0.0002$	$r = -0.3898$ $P < 0.0001$

that observed with patients taking antidepressant drug medication (Peet, 1994).

A dim 150-lux red light and a bright 2500-lux white light were equally effective in preventing a relapse after TSD. Patients affected by bipolar disorder have been shown to be supersensitive to the biological effects of light (Lewy et al., 1981, 1985; Nathan et al. 1999), and a positive interaction between TSD and light in bipolar depression has been reported with light intensities as low as 80 lux (Wehr et al., 1985), with few differences in respect to bright light. Moreover, a recent finding suggests that in normal humans, entrainment or synchronization of the circadian system can be attained with less than 100 lux (Kenneth et al., 1999).

A possible explanation of our finding could then be a kind of 'ceiling effect': all the possible benefits of light therapy in bipolar depression could be obtained with a low-intensity light. However, due to the absence of a placebo condition for light therapy in our study, we cannot rule out the possibility of a placebo effect to explain the positive interaction of the red 150-lux light and TSD. In this respect, it should, however, be noted that recent studies using new devices as a placebo condition (e.g. negative ion generators) showed that light therapy had a specific antidepressant effect beyond its placebo effect (Eastman et al., 1998; Terman et al., 1998).

Morning light therapy has been shown to increase blood serotonin throughout the day in both healthy subjects and in patients affected by non-seasonal depression (Lam and Levitt, 1999); the effect was already apparent with light intensities as low as 50 lux (Rao et al., 1990, 1992). Acute tryptophan depletion, which reduces brain serotonin content, could induce a transient depressive relapse in drug-free patients with seasonal depression who responded to bright light therapy (Neumeister et al., 1997, 1998). These data lead to the hypothesis that an increased activity of the serotonin system might play a major role in the mechanism of the action of light therapy.

Serotonergic drug treatments have been shown to positively interact with sleep deprivation: the selective serotonergic drug fluoxetine (Benedetti et al., 1997), the mixed serotonergic-noradrenergic drug amitriptyline (Kuhs et al., 1996), and the 5-HT1A-beta adrenoreceptor blocker pindolol (Smeraldi et al., 1999) can enhance and sustain the antidepressant effect of sleep deprivation. Moreover, recent findings showed that a functional polymorphism within the promoter of the serotonin transporter gene could influence the antidepressant response to both the serotonergic drug treatments (fluvoxamine and paroxetine; Smeraldi et al., 1998; Zanardi et al., 1999) and TSD (Benedetti et al., 1999b), thus supporting the role of serotonin in the mechanism of action of TSD.

Preclinical and clinical evidence suggests that an enhancement in 5-HT function may be a common denominator in the therapeutic action of most antidepressant treatments (Charney et al., 1984; Blier et al., 1990). Light therapy and TSD seem to share this mechanism of action, which could provide a tentative neurobiological explanation of the positive interaction of the two treatments.

A different, but not alternative, explanation of the positive interaction between light and TSD takes into account the possible occurrence of microsleep during the TSD night. Continuous electroencephalographic recording showed that during sleep deprivation in depressed patients, the amount of subjectively unrecognized microsleep is increased in the early morning, and that a high amount of microsleep could hamper the antidepressant effect of sleep deprivation (Hemmeter et al., 1998). Moreover, short naps during the day after TSD are known to cause a relapse of depressive symptoms (Riemann et al., 1993; Reist et al., 1994). Exposure to light is known to reduce the sleepiness induced by sleep deprivation in humans (Clodore et al., 1990; Wright et al., 1997), and the reduction in subjective sleepiness after bright light was more pronounced in patients with seasonal affective disorder than in healthy control subjects (Partonen et al., 1997). In agreement with these studies, we observed a significant effect of light in reducing subjective sleepiness as measured by the Stanford Sleepiness Scale. It is then possible that, in our study, light therapy could have enhanced

the effect of TSD by reducing microsleep. The presence of a significant correlation between subjective sleepiness and VAS scores during treatment is in agreement with this hypothesis. Since the main effect of light observed in our study was the prevention of relapse after recovery sleep (see Fig. 2, right), the possible reduction in microsleep during TSD cannot completely explain the positive interaction of the two treatments.

No additional benefit was observed when combining light and lithium together with TSD, in comparison with single combinations (light plus TSD and lithium plus TSD). A consistent body of evidence shows that lithium reduces sensitivity to light in bipolar patients (Carney et al., 1988; Wirz-Justice et al., 1997; Duncan et al., 1998), and this could explain our observation, which is in agreement with a previous preliminary study on the association of lithium and light in depressed patients (Heim and Morgner, 1997). Since no other studies are available on the effect of light plus TSD in lithium-treated bipolar depressives, further research is needed to clarify this point.

From a clinical point of view, the positive response to TSD in bipolar depressives and the replication of the main effect of lithium in sustaining the effect of repeated TSD confirms the usefulness of TSD as a first-choice therapy in long-term lithium-treated bipolar depressed patients; in lithium-free patients, light therapy can be a useful method to prevent a short-term relapse after TSD.

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