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Research report

Total sleep deprivation followed by sleep phase advance and bright light therapy in drug-resistant mood disorders

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ABSTRACT

Background: Drug-resistant depression is a major therapeutic issue in psychiatry and the development of non-drug therapies that treat drug-resistant depression is required. Sleep deprivation (SD) is a non-drug treatment classified as a form of chronotherapy in addition to bright light therapy (BLT) and sleep phase advance (SPA). Combined chronotherapy is hypothesized to improve drug-resistant depression. In this study, we investigated the benefits of total sleep deprivation (TSD) followed by SPA and BLT in drug-resistant depression alongside ongoing antidepressant medication and observed the added effectiveness of the combined chronotherapy.

Methods: Thirteen drug-resistant inpatients affected by a major depressive episode were studied. They were treated by TSD followed by SPA (three days) and BLT (five days) with ongoing drug treatment. Effectiveness was rated using the Hamilton Rating Scale for Depression (HAM-D), the Zung Self-Rating Depression Scale (SDS), and the Visual Analogue Scale (VAS) over 3 weeks.

Results: Significant improvements of depressive symptoms were observed in both objective mood ratings (HAM-D) and subjective mood ratings (SDS and VAS). Eight out of 13 patients maintained this responsiveness (50% or greater changes in HAM-D) across the study period. Moreover, no patients dropped out of the combined chronotherapy procedure.

Limitations: The study did not have a placebo group, and more subjects may be needed.

Conclusion: The trial of combined chronotherapy successfully induced rapid improvement in depressive symptoms in drug-resistant patients without early relapse or obvious side effects.

1. Introduction

Drug-resistant depression has recently become a major therapeutic concern in the field of psychiatry. Even though many antidepressants and augmentation therapies are available, many depressed patients who are treated with antidepressants show only a partial response if any (Fava and Davidson, 1996; Fawcett and Barkin, 1997). According to a recent meta-analysis of all published double-blind, placebo-controlled antidepressant trials, the average antidepressant response rate was reported to be 53.8% (Papakostas and Fava, 2009). Data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial demonstrated that approximately 33% of patients failed to achieve remission despite multiple treatment attempts, and relapse had occurred within 6–12 months in approximately 50% of those who remitted (Rush et al., 2006). Therefore, drug-resistant depression continues to be a major public health concern, and the development of alternative, non-drug therapeutic strategies that overcome drug-resistant depression is essential.

Sleep deprivation (SD) is a non-pharmacological treatment that is classified as a chronotherapeutic strategy along with bright-light therapy (BLT) and sleep-phase advance (SPA) (Benedetti et al., 2007; Wirz-Justice et al., 2009). As an alternative therapeutical intervention, SD in depressive patients is characterized by an early responsiveness, a relatively high efficacy rate (approximately 60% (Wu and Bunney, 1990)), and few if any side effects. Unfortunately, the clinical efficacy of SD alone seems to be hampered by early relapse after subsequent recovery sleep. That is, many of the patients who improve after SD will suffer from a relapse after the following night when they sleep again (Wu and Bunney, 1990). Fortunately, methods for increasing and sustaining the efficacy of sleep deprivation via combinatorial strategies have been reported in numerous studies. For example, it is possible to increase and sustain the efficacy of sleep deprivation by combining this treatment with medication (antidepressant drugs (Benedetti et al., 1997; Elsenga and van den Hoofdakker, 1982; Kuhs et al., 1996; Shelton and Loosen, 1993), lithium (Baxter et al., 1986; Benedetti et al., 1999; Szuba et al., 1994), etc.), BLT (Benedetti et al., 2005; Colombo et al., 2000; Loving et al., 2002; Neumeister et al., 1996),

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and/or SPA (Benedetti et al., 2001; Berger et al., 1997; Voderholzer et al., 2003; Wu et al., 2009). In summary, Wirz-Justice et al. (2005) concluded that relapse after SD can be prevented by concomitant medication, BLT, and/or SPA following SD, and combinations of these interventions can also prolong response duration. Early studies on SD and BLT showed that the effectiveness of SD became more significant when BLT was conducted in the morning (Wehr et al., 1985), and that BLT during SD could bring about a more prolonged improvement in responders (van den Burg et al., 1990). BLT during and after SD was then shown to stabilize the antidepressant effects of SD (Benedetti et al., 2005; Colombo et al., 2000; Loving et al., 2002; Neumeister et al., 1996). SPA has also been shown to prevent early relapse after SD. Early studies on SPA employed a one-week schedule: after SD, bedtime started at 5 PM on the first recovery night and was shifted (delayed) daily by 1 h until reaching a more conventional bedtime of 11 PM (Albert et al., 1998; Berger et al., 1997; Riemann et al., 1999, 1995; Vollmann and Berger, 1993). However, recent studies have implemented a three-day schedule in which the bedtime was shifted (delayed) daily by 2 h until the conventional bedtime, and it was found that this three-day schedule could successfully prevent relapse as well as the one-week schedule (Benedetti et al., 2001; Voderholzer et al., 2003; Wu et al., 2009).

Moreover, the clinical benefit of SD can be expected even in drug-resistant depression. Benedetti et al. (2005) investigated the clinical usefulness of the combination of total sleep deprivation and light therapy in drug-resistant bipolar depression. This study showed that combined chronotherapy was useful in triggering an acute beneficial response in drug-resistant patients, even though drug-resistant patients tended to relapse earlier relative to patients without a history of drug resistance.

The aim of the current study was to investigate the effect of combined chronotherapy on drug-resistant depression. We employed total sleep deprivation (TSD) followed by SPA (three days) and BLT (five days) along with ongoing antidepressant treatment in patients with drug-resistant depression and observed the effectiveness of this strategy over three weeks.

2. Methods

2.1. Patients

Thirteen consecutively admitted inpatients of Akita University Hospital affected by a major depressive episode without psychotic features were studied. Diagnoses (according to DSM-IV criteria) included major depressive disorder ($N=10$) and bipolar disorder ($N=3$). Inclusion criteria were a baseline Hamilton Rating Scale for Depression (HAM-D, 17 items) (Hamilton, 1960) score of 15 or higher, absence of other diagnoses on Axis I, absence of mental retardation on Axis II, absence of pregnancy, history of epilepsy, and major medical or neurological disorders, and absence of history of drug or alcohol dependency or abuse within the last year. Physical examinations, laboratory tests, and electrocardiographs were performed at admission. After a complete description of the study to the patients, a written informed consent to participate in the study was obtained from each patient. This study was approved by the Ethics Committee of Akita University Graduate School of Medicine.

The 13 patients (eight men and five women) had a mean age of 42.0 years (S.D. 10.8 years, range 29–62 years). The mean age of onset of symptoms was 35.8 years (S.D. 12.3 years, range 17–52 years). The mean duration of the current episode was 20.8 weeks (S.D. 17.6 weeks, range 5–71 weeks). The mean number of previous depressive episodes was 5.0 (S.D. 3.0, range 2–13). The mean total duration of illness was 78.6 months (S.D. 50.3 months, range 32–183 months). The mean HAM-D score (17 items) at baseline was 19.7 (S.D. 2.9, range 15–24). That is, all patients were refractory and drug-resistant. According to Thase and Rush criteria (Thase and Rush, 1997), no patients belonged to Stage I (representing a failure of at least one adequate trial of one major class of antidepressant drug), three patients belonged to Stage II (representing Stage I resistance plus failure of an adequate trial of an antidepressant drug in a distinctly different class from that used in Stage I), eight patients belonged to Stage III (representing Stage II resistance plus failure of an adequate trial of a TCA), one patient belonged to Stage IV (representing Stage III resistance plus failure of an adequate trial of an MAOI), and one patient belonged to Stage V (representing Stage IV resistance plus failure of a course of bilateral ECT).

2.2. Treatment design

The treatment protocol is illustrated in Fig. 1. All patients experienced one night of TSD followed by SPA (three days) and BLT (five days). On the day of the TSD (day 1), patients were kept awake from 6 AM until 5 PM on the following day. On the day after the TSD, they then underwent a consecutive three-day SPA, i.e., bed time was restricted to 5 PM until 12 AM on the first recovery night (day 2) after TSD, to 7 PM until 2 AM on the second night (day 3) after TSD, and to 9 PM until 4 AM on the third night (day 4) after TSD. Subsequently, patients were allowed to sleep between 11 PM and 6 AM. BLT using 5000 lux for 2 h that began upon waking, was administered for five consecutive days between day 2 and day 6. A portable light box, Bright Light ME (Solartone

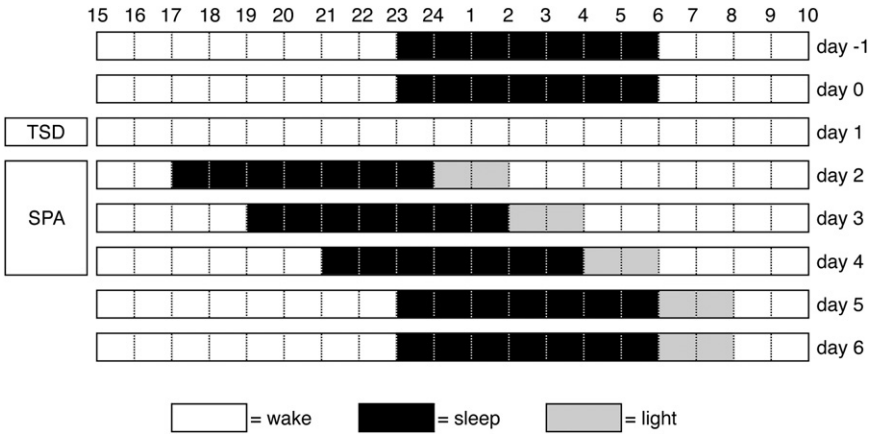

Fig. 1. The treatment protocol.

Incorporated, Tokyo, Japan), was used for BLT. This system generates a fluorescent full spectrum light with an intensity of 5000 lux at a distance of 50 cm at eye level.

It is important to note that chronotherapeutic interventions were added to ongoing medication therapy. The patients continued to receive medications at the same doses from at least four weeks before the TSD (day1) until day 20. All patients were taking one or more antidepressant drugs (paroxetine; 2, sertraline; 2, fluvoxamine; 1, milnacipran; 2, imipramine; 1, amitriptyline; 1, amoxapine; 4, mianserin; 1, trazodone; 3). In addition, four patients were taking lithium. All patients were also taking one or more benzodiazepine and/or non-benzodiazepine hypnotics (flunitrazepam; 6, brotizolam; 3, quazepam; 3, nitrazepam; 1, etizolam; 2, lormetazepam; 2, cloxazolam; 2, alprazolam; 1, zolpidem; 3, zopiclone; 2). Hypnotic agents that were usually taken before bedtime were not administered on the TSD night. Except for the TSD night, the patients took hypnotic agents 30 min before bedtime, including during SPA.

2.3. Data collection procedures

The treatment and observation period lasted from day −1 until day 20. Changes in depressive state over time were rated using the Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960), the Zung Self-Rating Depression Scale (SDS) (Zung, 1965), and the Visual Analogue Scale (VAS) (Aitken, 1969). From day −1 until day 6, HAM-D ratings using the 6-item version (depressed mood, feelings of guilt, work and activities, psychomotor retardation, anxiety and physical symptoms; maximum score 22) were performed every morning. On day −1, day 6, day 13, and day 20 (i.e., once a week), HAM-D ratings using the 17-item version (maximum score 52) were performed every morning. From day −1 until day 6, on day 13, and on day 20, patients self-rated their depressive symptoms every morning using SDS. From day −1 until day 6, patients self-assessed subjective mood levels with the 10-cm VAS 3 times during the day (8 AM, 1 PM, and 6 PM). Patients were instructed to rate their mood between "very sad" (on the far left) and "very happy" (on the far right), with a median "normal" point. Scores of 0, 50, and 100 represented extreme depression (very sad), euthymia (normal), and euphoria (very happy), respectively. Each patient's perceived mood level on each day was calculated as the mean of the three scores taken for that day.

2.4. Data analysis

For statistical analysis, means and standard deviations were calculated. General linear modeling with repeated measurements followed by Fisher's test of least significant difference (LSD) as the post-hoc range test was used to identify significant changes in HAM-D, SDS, and VAS values following chronotherapy. Huynh–Feldt adjustment was employed when a Mauchly Sphericity Test reached significance. All statistics were calculated with PASW statistics 18.0 (SPSS Japan Inc., Tokyo, Japan), and $p < 0.05$ was considered statistically significant. For individual HAM-D scores, the score at baseline was defined as 100%. A positive change of 50% or more relative to the baseline (100%) was defined as a response. For those who initially responded, going back to under a 50% change was defined as a relapse.

3. Results

A total of 13 patients completed the study. None of them reported obvious side effects, and none of them dropped out from this treatment protocol.

3.1. Objective mood ratings

The time course of the mean HAM-D scores (6 items) is shown in Fig. 2. General linear modeling with repeated measurements showed that the mean HAM-D scores on six items decreased significantly with the combined chronotherapy ($df=7$, $F=22.5$, $p < 0.0001$). The mean HAM-D scores on 6 items changed from 11.62 ± 1.76 to 11.62 ± 1.76, 10.50 ± 1.94, 7.75 ± 3.46, 6.75 ± 3.27, 6.33 ± 3.28, 6.42 ± 3.35, and 6.25 ± 3.13 (from day −1 to day 0, day 1, day 2, day 3, day 4, day 5, and day 6, respectively). In comparison with baseline (day −1), significant decreases were observed on day 2, day 3, day 4, day 5, and day 6.

The time course of mean HAM-D scores (17 items) is shown in Fig. 3. General linear modeling with repeated measurements showed that the mean HAM-D scores on 17 items decreased significantly with the combined chronotherapy ($df=2.26$, $F=47.3$, $p < 0.0001$). The mean HAM-D scores on 17 items changed from 19.77 ± 2.92 to 10.38 ± 5.77, 9.69 ± 5.72, and 8.46 ± 4.65 (from day −1 to day 6, day 13, and day 20, respectively). In comparison with

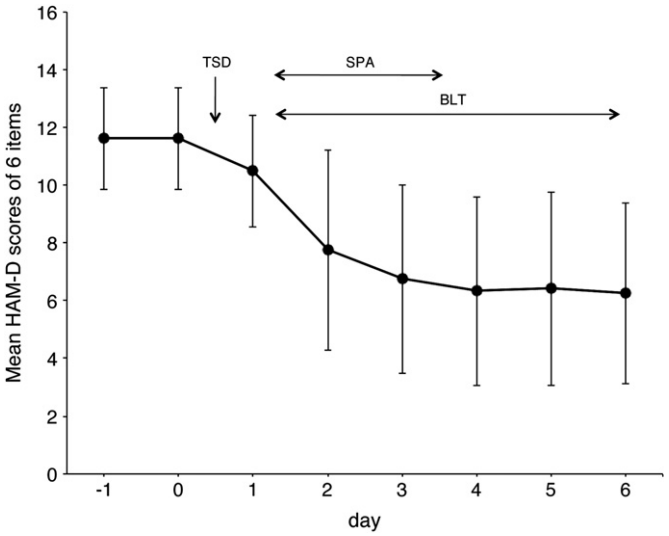

Fig. 2. The time course of mean HAM-D scores (six items). The data are expressed as means ± SD. Total sleep deprivation (TSD), sleep phase advance (SPA), and bright light therapy (BLT) time points and durations are indicated.

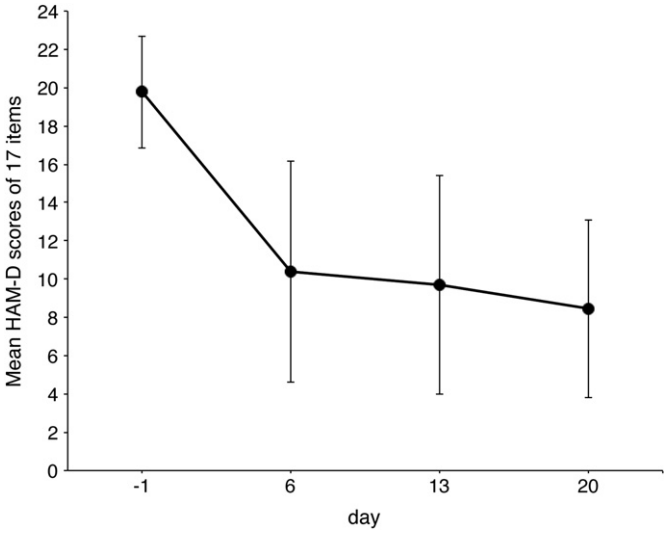

Fig. 3. The time course of mean HAM-D scores (17 items). The data are expressed as means ± SD.

baseline (day −1), significant decreases were observed on day 6, day 13, and day 20.

Individual changes in HAM-D scores on 17 items are shown in Table 1. Eight (Patients A, B, C, D, F, G, I, and L) out of 13 patients exhibited a response (50% or greater change) by day 6. One patient (Patient B) out of eight responders relapsed by day 13. One (Patient H) out of 13 patients exhibited a response by day 13. Four (Patients E, J, K, and M) out of 13 patients did not display a response until day 20. Finally, eight patients (Patients A, C, D, F, G, H, I, and L) maintained a response until day 20.

3.2. Subjective mood ratings

The time course of the mean SDS scores is shown in Fig. 4. General linear modeling with repeated measurements revealed that the mean SDS scores decreased significantly with the combined chronotherapy (df=2.82, F=9.66, po 0.0001). The mean SDS scores changed from 51.087 5.82 to 50.087 4.05, 51.087 7.63, 45.007 9.22, 43.777 9.61, 44.087 9.98, 43.777 9.63, 41.777 8.46, 41.467 10.29, and 39.857 8.87 (from day −1 to day 0, day 1, day 2, day 3, day 4, day 5, day 6, day 13, and day 20, respectively). In comparison with baseline (day −1), significant decreases were observed on day 2, day 3, day 4, day 5, day 6, day 13, and day 20.

Finally, the time course of the mean VAS scores is shown in Fig. 5. General linear modeling with repeated measurements showed that the mean VAS scores increased significantly with the combined chronotherapy (df=4.10, F=9.24, po 0.0001). The mean VAS scores changed from 32.287 10.91 to 31.817 10.49, 34.287 9.03, 39.447 10.51, 43.447 10.89, 44.567 11.40, 43.507 11.73, and 43.647 10.51 (from day −1 to day 0, day 1, day 2, day 3, day 4, day 5, and day 6, respectively). In comparison with baseline (day −1), significant increases were observed on day 3, day 4, day 5, and day 6.

Table 1
Individual changes in HAM-D scores (17 items).

Patient	Day −1	Day 6	Day 13	Day 20
A	15	2*	2*	2*
B	16	8*	9	11
C	18	7*	6*	6*
D	19	6*	5*	5*
E	22	16	16	12
F	23	11*	9*	7*
G	19	3*	2*	2*
H	23	14	11*	7*
I	19	9*	8*	8*
J	18	10	16	16
K	24	23	22	17
L	23	10*	9*	7*
M	18	16	11	10

HAM-D scores (17 items) of each patient. A positive change of 50% or more relative to the baseline score (day −1) was defined as a response.

* Response.

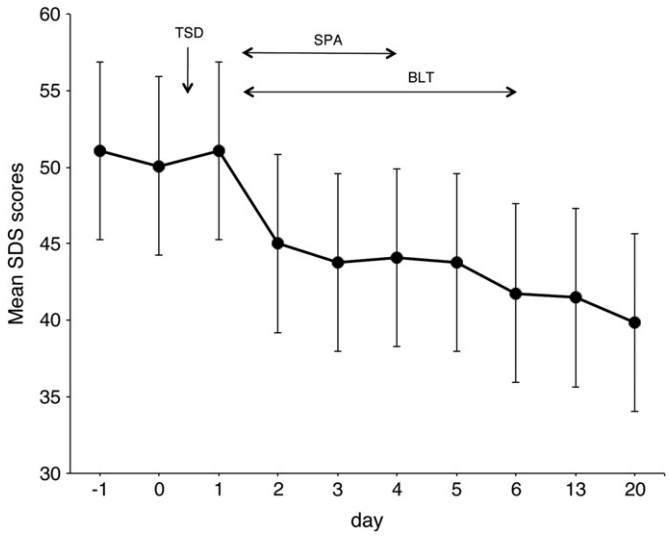

Fig. 4. The time course of mean SDS scores. The data are expressed as means 7 SD. Total sleep deprivation (TSD), sleep phase advance (SPA), and bright light therapy (BLT) time points and durations are indicated.

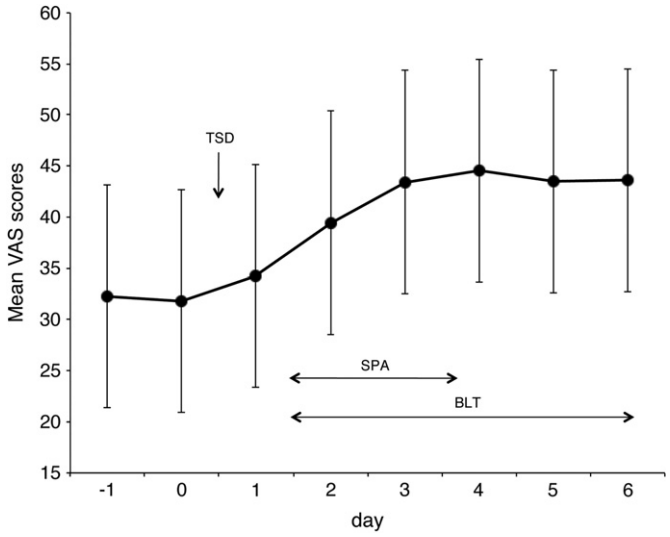

Fig. 5. The time course of mean VAS scores. The data are expressed as means 7 SD. Total sleep deprivation (TSD), sleep phase advance (SPA), and bright light therapy (BLT) time points and durations are indicated.

4. Discussion

The present study demonstrated a clinically significant improvement of depressive symptoms in terms of both objective and subjective mood ratings among drug-resistant depressive patients using the therapeutic intervention of combined chronotherapy. None of our patients experienced any obvious side effects from the combined chronotherapy. Importantly, early relapse could be prevented, at least during the observation period of three weeks.

All patients in this study were drug-resistant. Each of them had suffered from major depressive episodes multiple times, and for long periods, even though several antidepressant drugs had been tried. In spite of this, our trial of combined chronotherapy induced a rapid amelioration of symptoms in these refractory patients.

Although it is well documented in the literature that the beneficial effects of a single episode of single sleep deprivation on mood are generally reversed after a night of recovery sleep (Wu and Bunney, 1990), it is possible to increase and sustain the efficacy of sleep deprivation in combination with medication and certain chronotherapeutics (Benedetti et al., 2007; Wirz-Justice et al., 2005, 2009). It can be said that the more interventions that are combined, the longer the response duration lasts. The combined chronotherapy in this study was comprised of three chronobiological interventions, including total sleep deprivation (TSD), sleep phase advance (SPA) for three days, and bright light therapy (BLT) for five days. This combined chronotherapy successfully reduced HAM-D scores significantly, and in the end, 8/13 patients (61.5%) maintained this response (50% or greater changes in HAM-D scores) until the end of the observation period (day 20).

Recently, Wu et al. (2009) reported that chronotherapeutic augmentation (TSD, BLT, and SPA) in bipolar disorder patients also generated a sustainable antidepressant response. Their study protocol of combined chronotherapy was very similar to ours (TSD followed by SPA and BLT). Thus, two very similar chronotherapeutic interventions in different investigations producing successful antidepressant responses in addition to relapse prevention strongly support this therapeutic strategy.

Although the mechanism of action of SPA is still considered unknown, one explanation is based on the phase advance hypothesis of depression, which suggests that depression may be associated with an abnormal relationship between sleep phases and circadian rhythms. Phase advance of the sleep–wake cycle may synchronize sleep phases with other (already advanced) biological rhythms and by this mechanism improve depressive symptoms (Sack et al., 1985; Wehr et al., 1979). In addition, previous studies indicate that the mood of depressed patients is negatively affected by sleep, and that re-exposure to sleep may induce relapse after successful sleep deprivation. This is particularly true when patients sleep during a critical phase between early morning and noon (Riemann et al., 1993; Wiegand et al., 1987). The risk of relapse after successful sleep deprivation can be minimized by advancing the sleep period and thereby preventing sleep during this critical phase.

BLT during and after sleep deprivation has been shown to increase or stabilize the antidepressant effects of sleep deprivation (Benedetti et al., 2005; Colombo et al., 2000; Loving et al., 2002; Neumeister et al., 1996). In addition, BLT itself has antidepressant efficacy not only for seasonal affective disorder but also for non-seasonal depressive symptoms (Golden et al., 2005; Kripke, 1998; Martiny, 2004; Tuunainen et al., 2004; Yamada et al., 1995). Some previous studies of sleep deprivation combined with bright light therapy included administered light at night during sleep deprivation or in the morning after sleep deprivation. However, we intended to observe the effect of total sleep deprivation alone (day 1) and the sustaining effect of sleep phase advance and bright light therapy (day 2 and onward). Therefore, we did not administer bright light on day 1. Although it is unclear how BLT acts within the treatment protocol employed in our study, the usefulness of therapeutic combinations incorporating BLT is supported by a number of previous studies as mentioned above.

In the present study, the first significant changes were observed on day 2 in terms of HAM-D scores (6 items) and SDS scores, and on day 3 in terms of VAS scores. These responses are not very rapid relative to previous findings showing a marked decrease in depressive symptoms on the day after a night of TSD (Wu and Bunney, 1990). A slightly slower response to TSD may be due to the high rate of unipolar depressive patients in the present study. A previous study showed that unipolar patients improved after TSD but more slowly compared to bipolar patients (Barbini et al., 1998). In the present study, 10 out of 13 patients (77%) suffered from unipolar depression, and such a patient composition may be associated with a lack of rapid response. On the other hand, we speculate that SPA and BLT after TSD may cause TSD non-responders to improve later. Several previous studies that attempted SPA after SD conducted SPA only for SD responders in order to prevent relapse after successful SD therapy (Albert et al., 1998; Berger et al., 1997; Riemann et al., 1999; Voderholzer et al., 2003). However, we conducted SPA and BLT for all patients regardless of responsiveness after TSD. Furthermore, some patients might end up being non-responders if only a single TSD exposure is conducted. However, SPA and BLT after TSD might shift the non-responders in the present study to responders at later times. If this is the case, it may be expected that combined chronotherapy brings about not only rapid improvement on average but also delayed improvement in some individuals.

In the present study, although each patient received antidepressant drugs, they were resistant to the ongoing medications for at least four weeks before the TSD exposure. In this trial, significant improvements were observed in both objective ratings and subjective ratings within a few days after TSD. Such an improvement in such a relatively short period of time is obviously beyond the pharmacological effects of antidepressants alone. Therefore, the therapeutic responses of this trial cannot be explained by ongoing antidepressant exposure.

To our knowledge, this is the first report of a designed investigation of sleep deprivation affecting mood disorders in Japanese individuals. Chronotherapy is not a typical treatment for mood disorders in Japan or in most countries. However, chronotherapy is available in a wide variety of countries and hospitals. It should be noted that similar results are observed with chronotherapy in different countries and in different research groups and it is expected that more reports will be produced in many countries in the future.

Some limitations of the present study should be considered. First, a placebo effect cannot be excluded since there was no control group in this trial. It is difficult to design a control group in trials of TSD, SPA, and BLT that are blind to both researchers and patients. Thus, the HAM-D raters were not blind to the conditions. Second, our study includes a relatively small sample size ($N=13$). Third, the patients in the study consisted of both unipolar and bipolar depressives. Fourth, the therapeutic drug regimens that the patients took were not standardized. Despite these limitations, our study successfully detected an effect of combined chronotherapy against drug-resistant depression in a practical clinical situation.

In conclusion, this is the first trial reporting combined chronotherapy consisting of TSD, SPA, and BLT for drug-resistant depression. The findings in this study are very encouraging since they demonstrate a combination of high efficacy, rapid response, and no obvious side effects, and further support the advantages of additional/alternative treatments for drug-resistant depression. Since we often encounter patients who are resistant to typical antidepressant drug treatment, adding chronotherapy to the therapeutic choices may overcome drug-resistant depression and shorten treatment duration. However, our results need to be confirmed by additional studies using larger sample sizes and longer observation periods. Further, in order to gain better insight into the underlying mechanisms of chronotherapy, concomitant biological measurements will be required.

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Conflict of interest

All the authors declare that they have no conflicts of interest.

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