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Research report

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

Masaru Echizenya*, Hideka Suda, Masahiro Takeshima, Yoshiyuki Inomata, Tetsuo Shimizu

Department of Neuropsychiatry, Bioregulatory Medicine, Akita University Graduate School of Medicine, 1-1-1, Hondo, Akita-City 010-8543, Japan

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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),

* Corresponding author: Tel.: +81 18 884 6122; fax: +81 18 884 6445.
E-mail address: echizenya@psy.med.akita-u.ac.jp (M. Echizenya).

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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

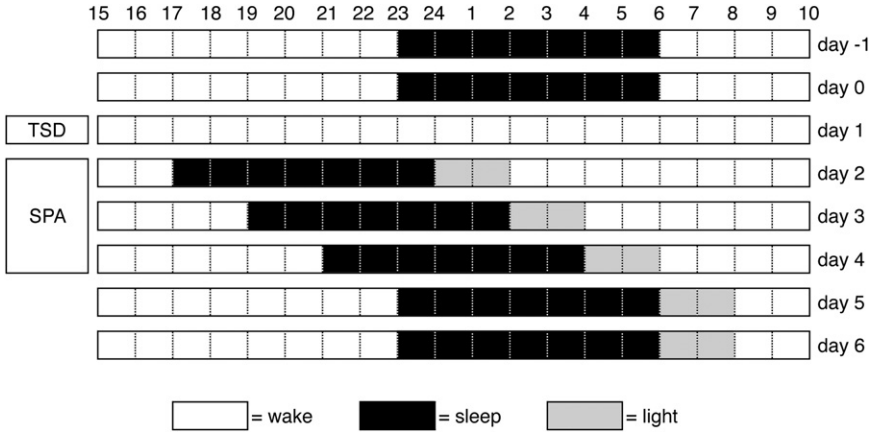

Fig. 1. The treatment protocol.