Rapid and Sustained Antidepressant Response with Sleep Deprivation and Chronotherapy in Bipolar Disorder

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Background: The development of a rapid-acting and sustainable treatment for bipolar disorder (BPD) depression has been a goal for decades. The most widely documented rapid-onset antidepressant therapy is sleep deprivation (SD), which acts within 24–48 hours in 40%–60% of depressed patients. Conventional antidepressants usually require 2–8 weeks to meet response criteria. The delay, which may prolong suffering and increase suicidal risk, underlines the urgency of alternative treatment strategies. This study evaluates the combined efficacy of three established circadian-related treatments (SD, bright light [BL]), sleep phase advance [SPA]) as adjunctive treatment to lithium and antidepressants.

Methods: Forty-nine BPD patients were randomly assigned to a chronotherapeutic augmentation (CAT; SD+ BL+ SPA) or to a medication-only (MED) group. Clinical outcome was assessed using the Hamilton Rating Scale for Depression.

Results: Significant decreases in depression in the CAT versus MED patients were seen within 48 hours of SD and were sustained over a 7-week period.

Conclusions: This is the first study to demonstrate the benefit of adding three noninvasive circadian-related interventions to SD in medicated patients to accelerate and sustain antidepressant responses and provides a strategy for the safe, fast-acting, and sustainable treatment of BPD.

Key Words: Bipolar disorder depression, chronotherapeutic augmentation, rapid-onset antidepressant response, sleep deprivation

The depressive phase of bipolar disorder (BPD) is a serious component of the illness with high rates of morbidity and mortality and a significant risk for suicide (1). The development of a rapid-acting and sustainable treatment for BPD depression has been a long-standing goal. Conventional medications typically require 2–8 weeks for response, prolonging suffering and suicidal risk (2,3). Sleep deprivation (SD) is the most widely documented chronotherapeutic intervention to reduce depressive symptoms robustly within 24–48 hours in 40%–60% of patients as documented in more than 1700 patients in over 60 studies worldwide (4,5). The benefit of adopting chronotherapeutic approaches to treat depression is the subject of several reviews (2,5–7), and although SD responses are transient, concomitant medications (e.g., selective serotonin reuptake inhibitors [SSRIs] and lithium) and circadian-related interventions of bright light (BL) and sleep phase advance (SPA) (5) sustain its effects. To our knowledge there are no studies that have combined one night of SD plus BL and SPA in medicated patients to reduce depression rapidly and to sustain responses over extended periods. In this study, we treated medicated BPD patients with all three interventions (SD, BL, SPA) and compared changes in depression ratings to medication-only (treatment-as-usual) patients. Previous studies demonstrated efficacy with repeated SD to expedite drug response (8,9); however, the current design employs only 1 night of SD to determine the benefit of using a short-term chronotherapeutic strategy to induce rapid and sustainable improvement.

Methods and Materials

Participants

Forty-nine BPD outpatients (29 men and 20 women) meeting DSM-IV (10) criteria for BPD major depressive episode based on the Structured Clinical Interview for DSM-IV (SCID) were entered into the study. All patients met the minimum intake inclusion score of 18 on the Hamilton Rating Scale for Depression—24 (HRSD-24) (Table 1). Exclusion criteria included a history of suicidal behavior, neurological disorders (e.g., epilepsy, dementia), current substance abuse (within the previous 6 months), sleep medication, sleep abnormalities (e.g., narcolepsy, apnea), pregnancy, adverse side effects to SSRIs, and comorbid medical disorders that could interfere with compliance. The study was conducted at the University of California Irvine (UCI) and San Diego (UCSD) sites. Written informed consents were obtained from each patient in accordance with UCI and UCSD Institutional Review Board (IRB) regulations.

Extensive training sessions by psychiatrists from both sites helped to ensure standardization and high interrater reliability (95%) between sites. Ratings were obtained twice daily during the first week and weekly thereafter by supervised trained staff using an abbreviated rating scale (HRSD-19) that eliminated nonmeaningful items (see Table 2 footnote for details). It was not possible to blind patients or raters to the SD procedure; interviews were videotaped to assess and maintain interrater reliability.

Following initial screening, patients were randomly assigned (JCW) using a random number generator program to a chronothera-

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Table 1. Statistical Analysis Comparing Chronotherapeutic (CAT) and Treatment-as-Usual (MED) Patients (Mean Values ± SD)

Characteristics	CAT ($n = 32$)	MED ($n = 17$)	Statistic	p Value
Age (Years)	39 ± 13.31	40 ± 14.1	$t = .32$, $df = 47$	.75
Gender (Male/Female)[a]	22 M/10 F	7 M/10 F	$\chi^2 = 3.49$, $df = 1$	.06
Age of Onset (Years)	19.9 ± 9.6	17.2 ± 9.1	$t = .96$, $df = 47$	.34
Initial Screening Rating (HRSD-24)	24.8 ± 9.0	21.9 ± 7.6	$t = 1.16$, $df = 47$	.25
Medication				
Sertraline/other Antidepressant	24/8	10/7	$\chi^2 = 1.36$, $df = 1$	.24
Lithium/other mood stabilizer	22/10	12/5	$\chi^2 = .02$, $df = 1$	.89
Mean daily dose (sertraline)	95.8 ± 14.1 mg	95 ± 15.8 mg	$t = .14$, $df = 32$	.89
Mean daily dose (lithium)	777 ± 256 mg	737 ± 174 mg	$t = .53$, $df = 32$	.60
Withdrawals				
Relocation	$n = 1$	$n = 0$	$\chi^2 = .54$, $df = 1$	.46
Unable to adhere to protocol during follow-up	$n = 2$	$n = 0$	$\chi^2 = 1.11$, $df = 1$	.29
Intolerance to medications	$n = 2$	$n = 0$	$\chi^2 = 1.11$, $df = 1$	.29

M, male; F, female; HRSD-24, 24-item Hamilton Rating Scale for Depression.

[a]Gender did not account for the intergroup differences in HRSD ratings ($F = 2.43$, $df = 44$, $p = .13$), nor were there significant gender × sleep deprivation ($F = 2.25$, $df = 43$, $p = .12$) or gender × sleep deprivation × time ($F = .95$, $df = 177$, $p = .51$) interaction effects.

peutic augmentation treatment (CAT) group (on a 3:2 ratio for follow-up studies; $n = 32$) or a medication-only (MED) group ($n = 17$).

Medications

All patients in the CAT and MED groups were maintained on mood stabilizers and antidepressants administered on the same time schedule. Lithium (or other mood stabilizers if intolerant) was initiated 1 week before the SD night to minimize the risk of switches into hypomania/mania. Sertraline was administered to all patients. However, patients intolerant to sertraline (i.e., failed to respond or had intolerable side effects such as severe nausea) were prescribed alternative antidepressants (Table 1; Table 1A and 1B in Supplement 1).

Procedures

CAT patients were studied as outpatients with the exception of four inpatient nights (SD night plus 3 days for BL and, SPA) at UCI or UCSD Medical Centers to ensure compliance with the CAT protocol.

Table 2. Statistical Differences for Daily (Week 1) and Weekly (Weeks 2–7) Ratings (HRSD-19)[a] in Chronotherapeutic (CAT) Patients Versus Treatment-as-Usual (MED) Patients

	CAT	MED	Statistic	p Value
Daily Ratings[b]				
Baseline (Day 0) versus	SD 19 ± 6.7	18.5 ± 7.1	$t = .22$, $df = 85$	$p = .83$
Day 1	BL, SPA 14.5 ± 6.2	16 ± 8.7	$t = 1.10$, $df = 272$	$p = .27$
Day 2	BL, SPA 11.2 ± 6.9	15.1 ± 7.1	$t = 2.24$, $df = 201$	$p = .03$
Day 3	BL, SPA 10.7 ± 7.4	14.8 ± 6.9	$t = 2.29$, $df = 175$	$p = .02$
Day 4	10.2 ± 7.2	14 ± 7.1	$t = 2.41$, $df = 150$	$p = .02$
Day 5	9.9 ± 7.9	13.5 ± 6.9	$t = 2.58$, $df = 126$	$p = .01$
Day 6	11.4 ± 8.2	12.8 ± 7.3	$t = 1.40$, $df = 82$	$p = .17$
Day 7	10.2 ± 7.3	14.4 ± 8	$t = 3.34$, $df = 270$	$p = .001$
Weekly Ratings				
Baseline (Day 0) versus				
Week 2	11.8 ± 8.8	15.1 ± 8.8	$t = 2.52$, $df = 220$	$p = .01$
Week 3	12.6 ± 9	16.9 ± 10.2	$t = 2.77$, $df = 174$	$p = .01$
Week 4	12.6 ± 9.8	17.4 ± 9.1	$t = 2.72$, $df = 140$	$p = .01$
Week 5	11.5 ± 10	14.3 ± 11	$t = 1.98$, $df = 104$	$p = .05$
Week 6	11.7 ± 9.9	14.3 ± 10.2	$t = 2.22$, $df = 73$	$p = .03$
Week 7	10.1 ± 9.6	15.2 ± 10.2	$t = 2.38$, $df = 64$	$p = .02$

Values are expressed as means ± SD; two-tailed t tests. Subjects were kept awake from 9 AM to 6 PM the day after sleep deprivation (33 hours of wakefulness).

BL, bright light therapy; HRSD-24, 24-item Hamilton Rating Scale for Depression; SPA, sleep phase advance.

[a]An abbreviated version of the HRSD-24 scale was used, excluding items that were not meaningful for frequent analysis (e.g., pertaining to sleep, weight loss, and diurnal variation).

[b]Differences between baseline Day 0 and subsequent time points.

Chronotherapeutic Augmentation Treatment

Sleep Deprivation. On the day of SD, patients were kept awake by psychiatric staff from 9 AM until 6 PM on the following day (33 hours). Patients were carefully monitored by trained staff including an overnight nurse (11:00 PM–7:00 AM) who was individually assigned to each patient to ensure that patients stayed awake for the entire SD procedure.

Bright Light Therapy. 5000 lux for 2 hours was administered for 3 consecutive days beginning on the morning following the SD night. The timing of bright light was calculated on an individual basis using the Morning-Eveningness Questionnaire, using an algorithm based on research by Terman (11) and Lewy (12), available online at http://www.cet.org.

Sleep Phase Advance. SPA (3 nights) was initiated on the first evening following SD. Sleep times were as follows: Night 1 (6:00 PM–1:00 AM), Night 2 (8.00 PM–3.00 AM), and Night 3 (10.00 PM–5.00 AM).

Statistical Analyses

A full factorial-by-time model was used in the data analyses using intention to treat." A Toeplitz covariance structure was selected by maximizing the Akaike's Information Criterion (AIC). Kenward-Roger's small-sample degrees of freedom correction was implemented for all inferences. Tests of model fixed-effects parameters were conducted using the Prasad-Rao-Jeske-Kackar-Harville method for obtaining fixed effects standard errors. This method has been shown to provide good performance for small samples in longitudinal analyses (13). The mixed-effects model repeated-measure analysis has been shown to have power comparable to or greater than the Kaplan-Meier survival analysis (14). This method offers several advantages over the more traditional analytic approaches such as repeated-measures of analysis of variance with the last observation carried forward (LOCF) method because it considers the duration of participation of patients with missing data or those who were terminated early in the study (15). Daily measurements were also analyzed using the same model, which included terms for treatment group, baseline HRSD, daily ratings for the first week, and treatment by ratings by time effects.

The criterion for response was a 50% decrease in HRSD ratings over baseline; remission criteria included the response criterion plus an HRSD rating ≤7 (at the end of 7 weeks).

Results

During follow-up, five patients in the CAT group terminated early because of relocation (n = 1), intolerance to medications (n = 2), or failure to adhere to protocol during follow-up (n = 2). None in the MED group terminated early. All CAT patients received chronotherapy. As seen in Table 1, the CAT and MED groups did not significantly differ in terms of age, sex, severity of depression, or medication use. Also, there were no significant differences between cohorts for drug-naive status, nonresponsiveness to drugs, or baseline medications.

The repeated-measures mixed effects model analysis showed a significant decrease in depression ratings (HRSD) in the CAT versus MED patients for all time points with the exception of Day 6. Significant decreases in depression ratings occurred as early as Day 2 and were sustained for 7 weeks (Figure 1, Table 2). At Day 7 and Week 7 the percentage of patients meeting response criteria was significantly higher in the CAT group (Day 7, χ^2 = 7.37, df = 1, p = .007; Week 7, χ^2 = 5.23, df = 1, p = .02). At the end of Week 7, 12 of 19 responders in the CAT group fulfilled the criteria for remission.

Adverse events were rare. A brief hypomanic switch in 2 of 32 CAT patients resolved within 24 hours without additional medication. None of the MED patients experienced adverse events.

Discussion

The adjunctive noninvasive interventions of SD, BL, and SPA produced robust decreases in depression as early as 48 hours post-SD that were sustainable for at least 7 weeks. A dramatic

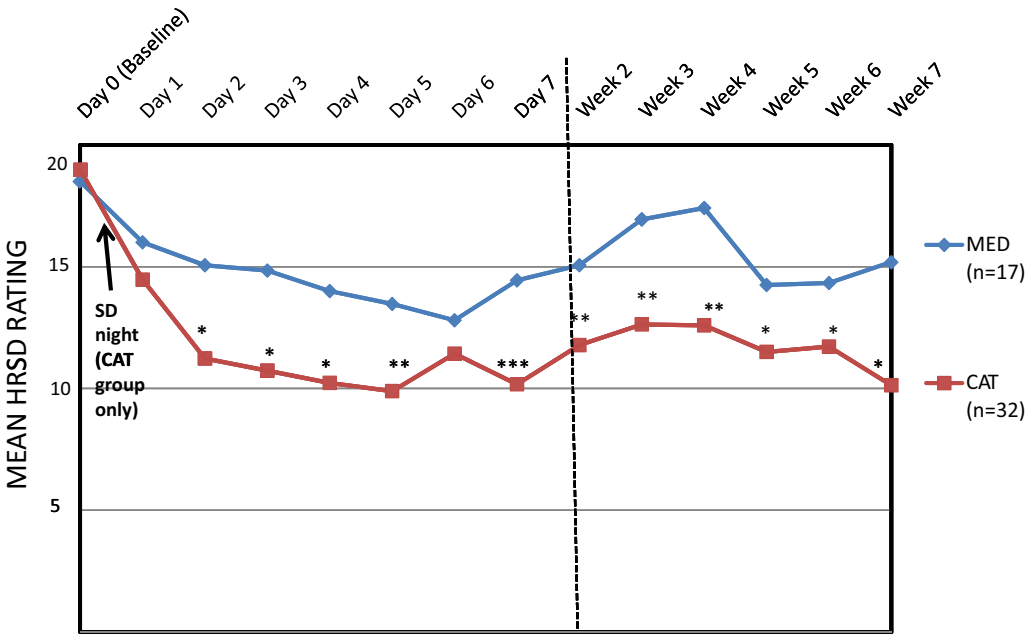

Figure 1. Significant reduction in mean depression (19-item Hamilton Rating Scale for Depression [HRSD]) ratings over baseline in subjects treated with chronotherapeutic augmentation treatment (CAT) within 48 hours of sleep deprivation (SD) compared with medication-only (MED) subjects. Significant improvement was maintained for Weeks 1–7 (with the exception of Day 6). *$p \leq .05$; **$p \leq .01$; ***$p \leq .001$.

improvement by Week 7 in the CAT over the MED patients provided further support for the long-term benefit of CAT interventions. These differences cannot be attributed to prior drug history or to responsiveness to medications because there were no significant differences between the groups at baseline. The relatively low response rate in the MED group (22%) is consistent with results from the Systematic Treatment Enhancement Program for BPD (STEP-BD) study (23%) (16).

To our knowledge, this is the first study to combine three established circadian interventions with medications compared with a treatment-as-usual cohort. A limitation to the study is the inherent difficulty in not being able to conduct blind investigations of SD, which is a long-standing challenge in the field. Future research might include a CAT plus placebo group, which would help delineate the role of antidepressants concomitant with mood stabilizers in therapeutic response of the CAT group. The hospitalization of CAT patients to ensure compliance with the protocol could have influenced the rapidity of response. However, the 48-hour response is consistent with a large number of inpatient SD studies over 4 decades (4,5,7). Robust and rapid responses to SD were also observed in an outpatient study (17). Improvement is unlikely to be a placebo effect because one would expect it to diminish significantly over 7 weeks. Our finding of sustained improvement is compatible with Benedetti's study (18), which used SD, BL, and mood stabilizers but no antidepressants.

The rapid response to CAT adjunctive therapy has important implications for the treatment of BPD. CAT offers a noninvasive and relatively safe method for accelerating, augmenting, and sustaining antidepressant responses.

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Clinical Trials (The Role of Dopamine Metabolism in the Antidepressant Effects of Sleep Deprivation and Sertraline in Depressed Patients; http://clinicaltrials.gov/ct2/results?term=sleep+deprivation+and+sertraline;NCT00581009).

Supplementary material cited in this article is available online.

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