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

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Wu JC, Kelsoe JR, Schachat C, Bunney BG, DeModena A, Golshan S, Gillin JC, Potkin SG, Bunney WE.

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.

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Light Therapy for Bipolar Disorder: a Case Series in Women.

Bipolar Disord. 2007 Dec;9(8):918-27.

Sit D, Wisner KL, Hanusa BH, Stull S, Terman M.

OBJECTIVES: To perform a dose-ranging safety and efficacy study of bright light therapy for depression in women with bipolar disorder (BD). METHODS: Nine women with DSM-IV BD I or II in the depressed phase were exposed to 50 lux (illuminance at the receiving surface) red light for two weeks, after which they received 7,000 lux light therapy for two-week epochs of 15, 30 and 45 min daily. The Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement and the Mania Rating Scale were used to assess mood symptoms. Four patients received morning light and five patients received midday light. RESULTS: Three of the four subjects treated with morning light developed mixed states. The fourth subject achieved a full, sustained response. To decrease the risk of inducing mixed episodes, we changed the time of light exposure to midday. Of the five women who received midday light therapy, two achieved full response and two showed early improvement but required a dose increase to sustain response. One woman remained depressed with 45 min of midday light but responded fully to a switch to morning light, 30 min daily. CONCLUSIONS: Women with bipolar illness are highly sensitive to morning bright light treatment; the induction of mixed states is a substantial risk. Initiating treatment with a brief duration (15 min) of midday light for bipolar depression is advisable.
Combined Total Sleep Deprivation and Light Therapy in the Treatment of Drug-Resistant Bipolar Depression: Acute Response and Long-Term Remission Rates.


Benedetti F, Barbini B, Fulgosi MC, Colombo C, Dallaspezia S, Pontiggia A, Smeraldi E.

BACKGROUND: Drug resistance remains a persistent source of morbidity and mortality for patients with bipolar depression. A growing number of clinical studies support the usefulness of chronotherapeutic interventions, such as total sleep deprivation (TSD) and light therapy (LT), in the treatment of nonresistant bipolar depression. METHOD: To investigate the clinical usefulness of TSD plus LT in the treatment of drug-resistant bipolar depression, we treated 60 inpatients for 1 week with repeated TSD and LT combined with ongoing antidepressants and lithium salts. All patients had a DSM-IV diagnosis of bipolar I disorder. Drug resistance was rated according to Thase and Rush criteria. The pattern of relapses and recurrences was assessed during a prospective 9-month follow-up. Data were gathered from September 2002 to July 2004. RESULTS: A 2-way repeated-measures analysis of variance with changes in self-rated perceived mood scores as dependent variable and with time and group (history of drug resistance) as independent factors confirmed significant time-by-group interaction (p = .0339). A logistic regression on rates of achievement of response (50% reduction in Hamilton Rating Scale for Depression ratings) confirmed the significance of observed differences: overall, 70% (23/33) of nonresistant versus 44% (12/27) of drug-resistant patient s achieved response (p = .045). A survival time analysis (Cox proportional hazards model) showed that history of drug resistance significantly influenced the pattern of relapses and recurrences, with 57% (13/23) of nonresistant responders and 17% (2/12) of drug-resistant responders being euthymic after 9 months (p = .0212). DISCUSSION: The combination of repeated TSD and LT in drug-resistant patients was useful in triggering an acute response. Further clinical research is needed to optimize this treatment option for drug-resistant patients in the long term.

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Low Doses of Lithium Carbonate Reduce Melatonin Light Sensitivity in Healthy Volunteers


Hallam KT, Olver JS, Horgan JE, McGrath C, Norman TR.

Sensitivity of the pineal hormone melatonin to bright light at night has been posited as a putative marker of affective disorders. Research demonstrates melatonin supersensitivity to light in bipolar disorder, however the role that lithium carbonate plays in this response is unclear. This study assessed the effect of lithium on nocturnal melatonin secretion and sensitivity to light in healthy adults. Ten participants, tested on two nights, had blood samples drawn between 20:00 and 02:30 hours. On testing nights participants were exposed to 200 lux of light between 24:00 and 01:00 hours. Participants took 250 mg of lithium daily for 5 d between testing nights. The results indicated that lithium had a significant effect on sensitivity to light but not on overall melatonin synthesis. This finding has implications on the true magnitude of the melatonin light response in people with bipolar disorder and may elucidate possible mechanisms of action of lithium.
Treatment of Seasonal Affective Disorder: Unipolar Versus Bipolar Differences


Sohn CH, Lam RW.

Evidence-based treatments for seasonal affective disorder (SAD) include light therapy and pharmacotherapy. We briefly review the diagnosis and treatment of SAD, focusing on clinical and treatment differences between patients with unipolar and bipolar illness. Special considerations for the management of SAD in patients with bipolar disorder are discussed, including the need to monitor for emergence of manic and hypomanic mood switches, to use mood stabilizers in patients with bipolar I disorder, and to be aware of potential interactions between bright light and medications used in treating bipolar disorder. Chronobiological treatments such as bright light therapy may be combined with pharmacotherapy to enhance therapeutic effects, reduce adverse side effects, and optimize treatment in patients with seasonal and nonseasonal bipolar disorder.

Morning Sunlight Reduces Length of Hospitalization in Bipolar Depression

J Affect Disord. 2001 Feb;62(3):221-3

Benedetti F, Colombo C, Barbini B, Campori E, Smeraldi E.

BACKGROUND: Bright artificial light improves non-seasonal depression. Preliminary observations suggest that sunlight could share this effect. METHODS: Length of hospitalization was recorded for a sample of 415 unipolar and 187 bipolar depressed inpatients, assigned to rooms with eastern (E) or western (W) windows. RESULTS: Bipolar inpatients in E rooms (exposed to direct sunlight in the morning) had a mean 3.67-day shorter hospital stay than patients in W rooms. No effect was found in unipolar inpatients. CONCLUSIONS: Natural sunlight can be an underestimated and uncontrolled light therapy for bipolar depression. LIMITATIONS: This is a naturalistic retrospective observation, which needs to be confirmed by prospective studies.

Total Sleep Deprivation Combined with Lithium and Light Therapy in the Treatment of Bipolar Depression: Replication of Main Effects and Interaction.


Colombo C, Lucca A, Benedetti F, Barbini B, Campori E, Smeraldi E.

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.
**Effects of Chronic Lithium Treatment on Retinal Electrophysiologic Function**


**Lam RW, Allain S, Sullivan K, Beattie CW, Remick RA, Zis AP.**

Some hypotheses suggest that lithium produces its therapeutic effect by reducing sensitivity to light at the level of the retina. In humans, acute administration of lithium is associated with a reduction in retinal light sensitivity. To determine whether similar retinal light sensitivity changes occur with chronic use, we studied 24 euthymic bipolar patients on chronic lithium treatment and 21 age- and sex-matched normal comparison subjects using electroretinography (ERG) and electro-oculography (EOG). No significant differences were found in ERG b-wave amplitudes or implicit times, or in EOG ratios, between the two groups. We conclude that chronic lithium use is not associated with differences in retinal light sensitivity when bipolar patients are compared to normal comparison subjects, and that there is no evidence for retinal toxicity with long-term lithium treatment.

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**Light Therapy in Patients with Rapid Cycling Bipolar Disorder: Preliminary Results.**


**Leibenluft E, Turner EH, Feldman-Naim S, Schwartz PJ, Wehr TA, Rosenthal NE.**

Nine patients with rapid cycling bipolar disorder were treated with a total of 13 trials of bright light therapy in the morning (n = 5), evening (n = 3), or midday (n = 5). In each instance, the patient’s mood ratings during 3 months of light therapy (added to a stable medication regimen) were compared to his or her mood ratings during 3 months on the same medication but without light treatment. Of the 3 light therapy schedules, only midday lights appeared to have beneficial clinical effects, improving mood ratings in 3 patients. In contrast, the morning light therapy trial was terminated prematurely in 3 patients because of clinical instability. Light treatment was better tolerated if patients discontinued it on days when they were hypomanic. The clinical and theoretical implications of these preliminary findings are discussed.