Combined Total Sleep Deprivation and Light Therapy in the Treatment of Drug-Resistant Bipolar Depression: Acute Response and Long-Term Remission Rates

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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 patients 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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At least 40% of patients treated for depression do not respond to the initial trial of antidepressant medication,[1] and at least one half of this percentage do not respond satisfactorily to several further treatment trials.[2] Treatment-resistant depression is, then, costly and associated with extensive use of depression-related and general medical services.[2]

The issue of drug resistance remains a persistent source of morbidity and mortality for patients with bipolar depression, who require careful clinical management that takes into account the life-threatening potential of their depression and the risk of iatrogenic mania or rapid cycling.[3,4] Recent long-term prospective trials in independent samples[5–7] showed that patients affected by bipolar I disorder are expected to spend, in the long term, roughly one third of follow-up weeks with depressive symptoms, which will present themselves in varying degrees of severity despite psychiatric care.[8,9] Effective acute antidepressant therapies for treatment-resistant bipolar depression are therefore strongly needed.

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 bipolar depression. These somatic treatments are nonpharmaceutical, safe, rapid, and effective

antidepressants, no less than common antidepressant medications.[10]

In recent years, LT, originally used in the treatment of seasonal affective disorder,[11] has been shown to be effective in the treatment of other depressive conditions such as premenstrual,[12] antepartum,[13,14] and postpartum depression[15,16]; bipolar depression[17]; and chronic depression,[18,19] alone or in combination with antidepressant drugs.[20,21] Antidepressant TSD is effective in about 60% of patients with major depression,[22,23] and its clinical effect is better in bipolar than in unipolar depressed patients.[24]

The clinical usefulness of these treatments has been questioned because of the short duration of their antidepressant effects, but recent trials have shown that the short-term depressive relapse can be prevented by combining chronotherapeutics with other nonpharmacologic treatments (such as sleep phase advance), with lithium salts, or with serotonergic or noradrenergic antidepressant drugs.[17]

Combined chronotherapeutic strategies have never been tested in the treatment of drug-resistant bipolar depression. These considerations prompted us to investigate the effect of repeated TSD and LT in treatment-resistant bipolar patients.

METHOD

Subjects

The sample included 60 consecutively admitted inpatients affected by a major depressive episode without psychotic features in the course of bipolar I disorder (DSM-IV criteria). The sample was divided into 3 groups following Thase and Rush criteria[25,26] for resistance to treatment. Group 1 (N = 33) was composed of patients who had no history of drug resistance. Group 2 (N = 10) was composed of patients belonging to Stage I (failure of at least 1 adequate trial of 1 major class of antidepressant). Group 3 (N = 17) was composed of patients belonging to Stage II or II+ (Stage I resistance plus failure of an adequate trial of at least 1 antidepressant in a distinctly different class from that used in Stage I).

The inclusion criterion was a baseline Hamilton Rating Scale for Depression (HAM-D)[27] score of 18 or higher. Exclusion criteria were other diagnoses on Axis I, mental retardation on Axis II, pregnancy, history of epilepsy, major medical or neurologic disorders, treatment with long-acting neuroleptic drugs in the last 3 months before admission, treatment with neuroleptics or irreversible monoamine oxidase inhibitors in the last month before admission, and history of drug or alcohol dependency or abuse within the last 6 months.

Physical examinations, laboratory tests, and electrocardiograms were performed on admission. After complete description of the study to the subjects, a written informed consent statement was obtained. The study was conducted according to Declaration of Helsinki guidelines. Data were gathered from September 2002 to July 2004.

Treatment

All patients were administered 3 consecutive TSD cycles (days 1–6); each cycle was composed of a period of 36 hours awake. On days 1, 3, and 5, patients were totally sleep deprived from 7 a.m. until 7 p.m. of the following day. They were then allowed to sleep during the nights of days 2, 4, and 6. TSD was carried out in a room with 80-lux ambient light; patients were administered LT (exposure for 30 minutes to a 400-lux green light) at 3 a.m. during the TSD night and in the morning after recovery sleep, half an hour after awakening, between 8 and 9 a.m. from day 1 to day 7.

At the beginning of the study, the patients, who had been referred for hospitalization by their psychiatrists in charge, were either drug-free (34/60, 56.6%) or taking antidepressant drugs (26/60, 43.3%) alone or in combination with lithium salts (16/60, 26.7%). Chronotherapeutic interventions were added to ongoing treatments: if patients were taking drugs, they continued to receive them at the same dose. If patients were not taking drugs, they were not administered any psychotropic drug treatment. Lithium was kept at therapeutic levels.

Data Collection

Perceived mood levels were assessed with a self-administered 10-cm visual analog scale (VAS) 3 times a day (8 a.m., 1 p.m., and 6 p.m.) (days 1–7). Patients were instructed to rate their mood between "very sad" (on the left) and "very happy" (on the right) with a median "normal" point. Raw data were converted to a 0-to-100 rating scale, with 0, 50, and 100 denoting extreme depression, euthymia, and euphoria, respectively. Each patient's perceived mood level on each day was calculated as the mean of the 3 scores for that day.

Objective mood ratings were obtained before and after the TSD + LT treatment (days 1 and 7) by administering in the morning a modified version of the 21-item HAM-D from which items that could not be meaningfully rated due to the TSD procedure and to the time frame were excluded (i.e., weight changes and insomnia: items 4, 5, 6, and 16).[28]

Measurement of Treatment Response and Follow-Up

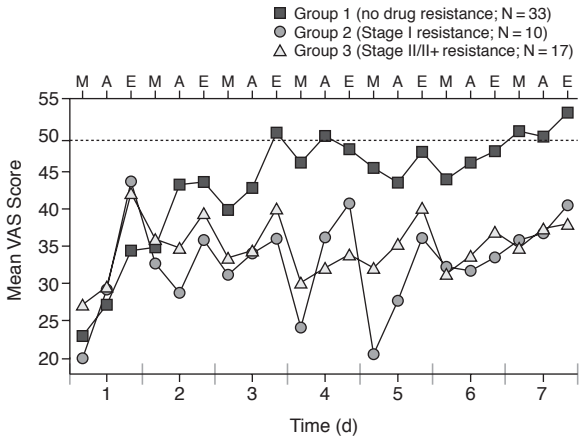
Response to treatment was defined as a 50% reduction in HAM-D scores between day 1 and day 7. Patients who responded to combined chronotherapeutic treatment continued or started treatment with lithium salts, and their clinical status was monitored during the following 9 months (once a week during the first month, and once a month during the following 8). Patients who did not respond or relapsed were treated with antidepressant drugs according to clinical need.

Table 1. Clinical and Demographic Characteristics of the Sample Divided Into 3 Groups According to History of Drug Resistance[a]

Characteristic	Group 1 (N = 33)	Group 2 (N = 10)	Group 3 (N = 17)	F	p
Age, y	43.3 ± 13.41	45.8 ± 7.39	53.7 ± 11.32	4.20	.012
Age at onset, y	30.30 ± 8.36	35.80 ± 9.29	33.47 ± 12.65	1.40	.253
No. of previous manic episodes	3.06 ± 3.25	2.70 ± 1.83	2.25 ± 1.29	0.50	.60
No. of previous depressive episodes	5.45 ± 5.20	5.20 ± 2.86	5.75 ± 3.21	0.05	.950
Duration of current episode, wk	14.51 ± 16.95	21.40 ± 18.54	30.88 ± 32.07	2.99	.058
HAM-D score at baseline	23.96 ± 4.82	24.30 ± 3.12	22.11 ± 2.89	1.36	.265

[a]Values are expressed as mean ± SD. Drug resistance groups were defined according to Thase and Rush criteria as follows: group 1, no drug resistance; group 2, stage I resistance; group 3, stage II/II+ resistance.
Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

Figure 1. Changes in Perceived Mood (VAS scores) During Treatment[a]



[a]0, 50 (dotted line), and 100 denote, respectively, extreme depression, euthymia, and euphoria. Visual analog scales were administered thrice per day in the morning (M), afternoon (A), and evening (E). All patients were sleep deprived after day 1, day 3, and day 5.
Abbreviation: VAS = visual analog scale.

Data Analysis

Clinical and demographic characteristics were compared with 1-way analyses of variance (ANOVAs). Changes of VAS scores over time with respect to the baseline were analyzed with a 2-way repeated-measures ANOVA with time and group (history of drug resistance) as independent factors. Frequencies of response (50% reduction in HAM-D score) and relapse, and time to relapse, were analyzed in the 3 groups by means of logistic regression and survival time analysis (Cox proportional hazards model). Calculations were performed with a commercially available software (STATISTICA 5.5; StatSoft, Inc.; Tulsa, Okla.).

RESULTS

Clinical and demographic characteristics of the sample divided according to treatment groups are summarized in Table 1. Age was significantly different and duration of current episode was marginally different between groups (more severe history of drug resistance was associated with older age and longer episodes).

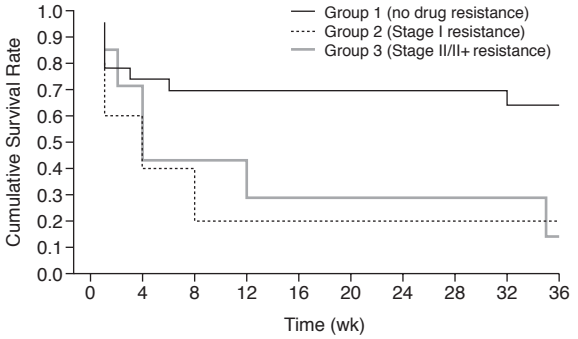
Logistic regression showed that response to treatment (50% reduction in HAM-D score) at day 7 was significantly influenced by the degree of history of drug resistance (group 1: 23/33, 69.7%; group 2: 5/10, 50.0%; group 3: 7/17, 41.2%; $\chi^2 = 4.006$, df = 1, p = .045).

Inspection of Figure 1 shows that changes in perceived mood did not follow parallel slopes of time course in the 3 groups. The major benefit occurred after the first night of TSD, with lesser additional benefit after the second night and without relapses after recovery sleep as expected from previous studies of the combination of TSD and LT.[29] A 2-way repeated-measures ANOVA with changes in VAS scores as dependent variable and with time and group (history of drug resistance) as independent factors confirmed significant effects of time (F = 2.73, df = 6,264; p = .0138), group (F = 8.15, df = 2,44; p = .00098), and time-by-group interaction (F = 1.91, df = 12,264; p = .0339).

All patients were taking lithium during the chronotherapeutic protocol. Twenty-six patients were taking combined antidepressant drugs at the beginning of the study and continued to take them. Drug status did not influence the effect of the TSD + LT treatment: a 3-way ANOVA on VAS scores with time (chronotherapeutics), degree of drug resistance, and drug status as independent variables confirmed that only time and the interaction of time and history of drug resistance had a significant effect on the pattern of mood change; drug status did not influence results either alone or in interaction with other factors. This was also true when 50% reduction in HAM-D scores was used as the response criterion ($\chi^2 = 0.580$, p = .447).

Inspection of Figure 2 shows that the majority of depressive relapses occurred within the first month after treatment, and the relapse rate during a 9-month follow-up was unevenly distributed between groups. A survival time analysis of the risk of experiencing a depressive relapse (Cox proportional hazards model) confirmed that history of drug resistance significantly influenced relapses and recurrences ($\beta = 0.54$, t = 2.11, p = .035). Two patients, both in group 1, had a manic episode.

Figure 2. Depressive Relapses/Recurrences in Responders to Treatment[a] During a 9-Month Follow-Up[b]



[a]Group 1, N = 23; group 2, N = 5; group 3, N = 7.
[b]Patients were interviewed first weekly (weeks 0–4) and then monthly (weeks 8–36) to assess their clinical status.

A logistic regression at the end of the observation period confirmed that the rate of euthymic patients among responders was still markedly influenced by the degree of lifetime drug resistance (group 1: 13/23, 56.5%; group 2: 1/5, 20.0%; group 3: 1/7, 14.3%; $\chi^2 = 5.308$, df = 1, p = .0212).

Gender and age did not significantly influence the acute response or long-term relapse pattern.

DISCUSSION

Lifetime history of drug resistance markedly influenced both the acute antidepressant response to the combination of repeated TSD and LT and the rate of relapse and time to relapse after having achieved an acute response. Among patients without a history of drug resistance, 70% achieved response and 39% (57% of responders) maintained it during the following 9 months, while among patients with a history of drug resistance, 44% achieved acute response and only 2/27 (7%) were still euthymic 9 months later. Most of the relapses were observed in the first 3 months after treatment, with the mean period of euthymia lasting 18.6 weeks in nonresistant and 9.1 weeks in treatment-resistant responders (Figure 2).

The response rate observed in patients without a history of drug resistance confirms previous studies by our group of the combination of TSD, lithium, and LT.[29,30] The main difference between groups was in maintaining a stable response over time. Adding repeated TSD and LT to existing antidepressant treatments in treatment-resistant patients was useful in triggering an acute response and giving a clinically relevant but transient relief to the patients, since it could not prevent a depressive relapse in the long term.

This observation suggests a relationship between drug resistance and time to relapse after response. There is little literature on this issue, since most of the trials of drug-resistant bipolar depressed patients focus on the achievement of acute response, and not on depressive relapse in the follow-up, and very few studies in nonresistant patients have provided a prolonged follow-up evaluation. A pivotal study on the long-term outcome of bipolar depressed patients who remitted with the combination of antidepressant drugs and mood stabilizers showed, however, that 70% of responders who discontinued antidepressants before 6 months and 53% who discontinued between 6 and 12 months experienced a depressive relapse.[31] Our 9-month survival rate for response in nonresistant bipolar I patients treated only with TSD plus LT for a week and then with lithium alone (56.5%) approaches is lower than the 1-year survival rate reported for patients who continued antidepressant medications for more than 6 months (64%).[31] Although many methodological issues hamper comparisons between different studies,[32] this observation confirms and extends our previous follow-up data about the long-term benefit of chronotherapeutic interventions in bipolar depression.[29,30,33]

Moreover, some prospective trials on chronic depression[34,35] suggest that even higher relapse rates should be expected when dealing with drug-resistant patients. The pattern of transient response and relapse observed in our study is similar to that described in drug-resistant patients who responded to electroconvulsive therapy,[36,37] in whom high relapse rates are expected during the first month after successful treatment.[38]

Our drug-resistant bipolar I depressed patients were treated with the addition of 1 week of TSD and LT to ongoing antidepressants, and with lithium in the follow-up. We can state that this treatment triggered response in bipolar depressed drug-resistant patients at a rate that is roughly similar to those reported for current treatment options for drug-resistant bipolar depression (e.g., lithium salts,[39,40] thyroid hormone,[40] buspirone hydrochloride[41]), but that continuing medications and adding lithium could not prevent a depressive relapse in the long term: the same drugs that could not trigger response were not able to maintain it. In this respect, it is possible that switching between or within classes of medications in patients who responded to our TSD + LT treatment, instead of continuing medications and just adding lithium, could prolong their well-being in the long term. It is also possible that repeating the TSD + LT treatment could give them more months of well-being. Following the same perspective, it is possible that TSD, LT, or even partial sleep deprivation or sleep phase advance could have prophylactic value in preventing relapses. These issues need further research to be tested.

Some concerns have been raised about the use of LT—with light intensities higher than that used in our study—in patients with ocular pathology,[42] and it has been suggested that patients with preexisting ocular abnormalities

and those using photosensitizing drugs undergo LT only with periodic ophthalmologic examination.[43] In rats, lithium has been shown to potentiate the light-induced arachidonic acid release in the retina,[44] affecting phospholipids membranes and then potentiating retinal light damages.[45] None of our patients experienced any side effect from LT, but it should be noted that we used lamps with light intensities much lower than those described in previous literature by other research groups (i.e., 400 lux vs. 5000–10,000 lux).

In conclusion, the treatment of drug-resistant bipolar depression is a major public health issue and is associated with significant personal, social, and economic burden. New strategies for its clinical management should be aimed not only at achieving acute response, but also at ensuring the persistence of a condition of euthymia in the long term. The addition of repeated TSD plus LT to continued antidepressant medication and lithium was useful for the former purpose, but could not completely achieve the latter. Further clinical research will focus on the development of combination treatments aimed at resolving this issue. Drugs such as pindolol[30] that are useful in both sustaining the effect of TSD in nonresistant patients and augmenting antidepressant effects in drug resistance will be good candidates for this purpose.

Drug names: buspirone (BuSpar and others), lithium (Lithobid, Eskalith, and others).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, buspirone is not approved by the U.S. Food and Drug Administration for the treatment of depression.

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