Rapid Treatment Response of Suicidal Symptoms to Lithium, Sleep Deprivation, and Light Therapy (Chronotherapeutics) in Drug-Resistant Bipolar Depression

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ABSTRACT

Background: One third of patients with bipolar disorder attempt suicide. Depression in bipolar disorder is associated with drug resistance. The efficacy of antidepressants on suicidality has been questioned. Total sleep deprivation and light therapy prompt a rapid and stable antidepressant response in bipolar disorder.

Method: We studied 143 consecutively admitted inpatients (December 2006–August 2012) with a major depressive episode in the course of bipolar disorder (*DSM-IV* criteria). Among the 141 study completers, 23% had a positive history of attempted suicide and 83% had a positive history of drug resistance. During 1 week, patients were administered 3 consecutive total sleep deprivation cycles (each composed of a period of 36 hours awake followed by recovery sleep) combined with bright light therapy in the morning for 2 weeks. At admission, patients who had been taking lithium continued it, and those who had not been taking lithium started it. Severity of depression was rated according to the Hamilton Depression Rating Scale (HDRS) (primary outcome measure) and Beck Depression Inventory (BDI).

Results: Two patients switched polarity. Among the 141 who completed the treatment, 70% achieved a 50% reduction in HDRS score in 1 week, which persisted 1 month after in 55%. The amelioration involved an immediate and persistent decrease in suicide scores soon after the first total sleep deprivation cycle ($F_{3,411} = 42.78$, $P < .00001$). A positive history of suicide attempts was associated with worse early life stress and with worse suicide scores at baseline, but it did not influence response. Patients with current suicidal thinking or planning responded equally well ($F_{3,42} = 20.70$, $P < .000001$). Remarkably, however, nonresponders achieved a benefit, with significantly decreased final scores also including suicidality ratings ($F_{3,120} = 6.55$, $P = .0004$). Self-ratings showed the same pattern of change. Previous history of drug resistance did not hamper response. During the following month, 78 of 99 responders continued to stay well and were discharged from the hospital on lithium therapy alone.

Conclusions: The combination of total sleep deprivation, light therapy, and lithium is able to rapidly decrease depressive suicidality and prompt antidepressant response in drug-resistant major depression in the course of bipolar disorder.

J Clin Psychiatry

Submitted: *March 6, 2013; accepted June 24, 2013.*
Online ahead of print: *December 10, 2013 (doi:10.4088/JCP.13m08455).*
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Bipolar depression is a difficult-to-treat condition that has been associated with extremely low success rates of antidepressant drugs in naturalistic settings.[1] Patients with bipolar disorder spend a substantial proportion of their time ill,[2] with depression representing their predominant abnormal mood state,[3] and with the repeated use of antidepressant drugs being related to poor prospective response to naturalistic antidepressant treatment.[4] Possibly as a consequence of their disabling condition, about 30% of patients with bipolar disorder attempt suicide,[5,6] and about 20% eventually die of suicide.[7,8]

Treatment of suicidality is a major issue, but few options are available. Patients with suicidal thoughts or intent compared to those without suicidal thoughts or intent have a clearer lifetime history of recurrence of major depressive episodes but are usually excluded from trials,[9] thus limiting the generalizability of results.[10] Antidepressant interventions prompt remission and can then reduce the suicide risk associated with acute mood episodes, but a large-scale epidemiologic study[11] did not support the usefulness of antidepressant drugs in reducing lifetime completed and attempted suicide in mood disorders. Administration of antidepressants to acutely suicidal patients can even be risky because of an age-dependent risk of suicidal behavior and ideation associated with use of antidepressants, which led to a US Food and Drug Administration black box warning for patients under age 25 years.[12] When effective, antidepressants are slow, however, with literature trials showing that no difference can be expected during the first 2 weeks between active and placebo treatments[13] Additionally, the selective publication of positive trials boosted the apparent efficacy of active drugs.[14] Lithium is able to reduce the lifetime suicide risk of patients with bipolar disorder to the same levels of the general population,[15,16] but it shows a long latency of antidepressant action and is then of little help in the acute phase. Finally, the overall depression severity is moderately associated with suicidal ideation, which associates more with core mood symptoms and self-punitive thinking, and can remain high even when somatic and vegetative symptoms improve as a result of treatment response.[17,18]

The unmet clinical need for the rapid resolution of breakthrough life-threatening symptoms,[19] such as suicide, and the conundrum between the risks of treatment-emergent mania[20,21] and of relapse after treatment discontinuation[22] often lead to prolonged and highly complex medication regimens to achieve a stable response in bipolar disorder.[23] Hence, the interest in chronotherapeutics that might eliminate the long latencies of traditional antidepressant treatments yet offer

Clinical Points

- A rapid treatment of acute suicidality is an unmet need in severe drug-resistant bipolar depression because the efficacy of antidepressants on suicidality has been questioned and because clearly effective drugs, such as lithium, have a long latency of action.
- The combination of chronotherapeutic techniques (sleep deprivation, light therapy) with lithium can prompt treatment response in drug-resistant depression, with a clinical benefit that involves an immediate decrease in suicidality. These benefits partly extend to nonresponders.

comparable efficacy.[24–27] Previous studies[28–30] by our group showed that the combination of lithium, repeated total sleep deprivation, and light therapy caused a stable remission of bipolar depression in more than half of the treated patients. Despite suicidal thoughts or intent not having been an exclusion criterion in these trials, the specific issue of the efficacy of chronotherapeutics with regard to suicidality was never addressed. Thus, in the present study, we aimed to investigate a homogenous sample of patients affected by a major depressive episode in the course of bipolar disorder.

METHOD

Patients and Treatment

We studied 143 consecutively admitted inpatients affected by a major depressive episode without psychotic features in the course of bipolar disorder (*DSM-IV* criteria, SCID-I interview[31]). Among the 141 study completers, 32 patients (22.7%) had a positive history of suicidality. The criterion for suicidality was 1 or more documented suicide attempt (broadly defined as any behavior aimed at killing oneself) during the lifetime.[32] This sample does not overlap with those described in previous studies.[29,30] Patients were recruited between December 2006 and August 2012.

Inclusion criteria were a baseline Hamilton Depression Rating Scale (HDRS)[33] score of 18 or higher; absence of other Axis I diagnoses; absence of mental retardation in Axis II diagnoses; absence of pregnancy, history of epilepsy, and major medical and neurologic disorders; no treatment with long-acting neuroleptic drugs in the last 3 months before admission; and absence of a history of drug or alcohol dependency or abuse within the last 6 months. After complete description of the study to the subjects, written informed consent was obtained. The study was approved by the local ethics committee.

All patients were administered 3 consecutive total sleep deprivation cycles (day 0–7); each cycle was composed of a period of 36 hours awake. On days 0, 2, and 4, patients were totally sleep deprived from 0700 until 1900 of the following day. They were then allowed to sleep during the night in a sleep window 1900–0800 of days 1, 3, and 5. Patients were administered light therapy (exposure for 30 minutes to a 10,000 lux bright white light, color temperature 4,600 K) at 0300 during the total sleep deprivation night and in the morning after recovery sleep, half an hour after awakening, between 0800 and 0900. Light therapy in the morning was then continued for 2 weeks. At admission, patients who had been taking lithium continued it (n = 49), and those who had not been taking lithium started it together with the chronotherapeutic procedure to enhance its effect and prevent relapse (n = 92).[34–36] No other antidepressant was administered.

Patients were followed up for 1 month after the acute chronotherapeutic treatment. Nonresponders were treated by the psychiatrists in charge upon clinical need. Responders continued lithium alone.

Data Collection and Analysis

Severity of depression was rated (days 0, 1, 2, and 6) by the psychiatrists in charge of the patients according to a modified version of the 21-item HDRS (referred to as the HDRS-NOW,[37] the primary outcome measure), from which items that could not be meaningfully rated due to the total sleep deprivation procedure were excluded (ie, weight changes and insomnia: item numbers 4, 5, 6, and 16). Response was defined as a 50% reduction of HDRS scores. Perceived depression was self-rated on the 13-item Beck Depression Inventory (BDI).[38] Current suicidality was rated according to the HDRS suicide item, which correlates with number of suicide attempts, age at first attempt, and other ratings of suicidality[39,40] and on the BDI.

Given the negative relationship between response to total sleep deprivation and history of drug resistance,[29] the latter was assessed according to Thase and Rush criteria[41]: 24 patients (17.0%) had no history of drug resistance, 54 (38.3%) were resistant to 1 class of drugs, 42 (29.8%) were resistant to 2 classes, and 21 (14.9%) had higher stages of resistance.

Given the positive relationship between early life stress and suicidality in bipolar disorder,[6] early (age 5–15 years) and recent (last 3 years) stressful life events were scored according to the Social Readjustment Rating Scale (SRRS),[42] which focuses on occurrences that lead to readjustment-requiring changes in usual activities[43] and which was validated in similar settings.[32]

Repeated-measures analyses of variance were performed in the context of the general linear model.[44,45] The analysis was separately performed on the 3 outcome measures: HDRS, HDRS item 3 (suicide) score, and BDI. The main factors of interest were response to treatment and history of suicide attempts. Time and ongoing lithium treatment were also considered as factors. The significance of the effect of the single independent factors on the dependent variable was estimated (least squares method) by parametric estimates of predictor variables and following standard computational procedures.[46] Analyses were separately performed in the whole sample and in patients who presented current suicide thinking or planning.[9,10]

RESULTS

One hundred forty-one patients completed the treatment. Two patients switched polarity, showing moderate manic

Table 1. Clinical and Demographic Characteristics of the 141 Participants, Divided According to Their Lifetime History of Suicide Attempts and Response to Antidepressant Treatment[a]

	Positive History of Attempted Suicide		Negative History of Attempted Suicide			
Characteristic	Responders	Nonresponders	Responders	Nonresponders	F or χ^2	P
n	21	11	78	31	0.42	NS
Age, y	45.71 (11.90)	43.36 (8.61)	47.91 (10.97)	47.61 (13.44)	0.63	NS
Sex, n					2.41	NS
Male	6	5	29	15		
Female	15	6	49	16		
Education, y	11.38 (3.88)	12.73 (3.58)	10.8 (3.94)	11.87 (5.19)	0.91	NS
Age at onset, y	32.71 (10.77)	23.27 (5.73)	31.77 (10.59)	33.10 (9.16)	2.85	NS
Duration of illness, y	13.00 (8.36)	20.09 (9.59)	16.14 (9.22)	14.52 (12.95)	1.39	NS
Duration of current episode, wk	33.18 (40.49)	12.13 (7.43)	22.19 (21.31)	29.74 (31.20)	1.59	NS
No. of previous depressive episodes	5.00 (4.27)	3.82 (2.18)	5.99 (5.94)	6.55 (7.66)	0.71	NS
No. of previous manic episodes	3.10 (3.10)	1.91 (1.22)	3.88 (4.82)	3.10 (4.02)	0.85	NS
Total no. of previous recurrences	8.10 (6.56)	5.73 (3.23)	9.87 (10.03)	9.66 (10.76)	0.75	NS
Early stressors, no. of events[b]	15.54 (10.94)	20.30 (11.03)	12.78 (9.10)	11.09 (6.73)	2.70	<.05
SRRS score[b]	345.08 (249.46)	450.20 (272.06)	301.11 (195.42)	235.55 (125.64)	2.84	<.05
Recent stressors, no. of events	19.54 (8.13)	21.00 (9.30)	17.17 (11.53)	16.14 (10.03)	0.65	NS
SRRS score	506.85 (201.99)	537.90 (283.88)	462.13 (306.39)	393.09 (212.99)	0.83	NS
21-item HDRS baseline score	23.76 (3.95)	21.60 (3.20)	23.27 (4.80)	23.59 (4.12)	0.61	NS
HDRS-NOW day 1	20.71 (3.93)	18.45 (2.77)	20.01 (4.51)	20.45 (4.75)	0.73	NS
HDRS-NOW day 2[c]	10.24 (5.99)	16.18 (3.84)	11.68 (6.07)	16.29 (6.63)	6.71	<.001
HDRS-NOW day 3[c]	9.95 (5.47)	16.36 (3.56)	9.83 (5.90)	15.58 (5.29)	11.23	<.001
HDRS-NOW day 7[c]	4.33 (3.26)	15.00 (5.40)	4.37 (3.13)	16.19 (4.90)	90.59	<.001
BDI baseline score[c]	15.67 (7.86)	21.64 (8.76)	14.49 (7.34)	19.00 (7.63)	4.40	<.01

[a]Values shown are mean (SD) unless stated otherwise.
[b]Significantly higher values in patients with a positive history of suicide attempts.
[c]Significantly lower values in responders.
Abbreviations: BDI = Beck Depression Inventory, HDRS-NOW = modified version of Hamilton Depression Rating Scale, NS = nonsignificant, SRRS = Social Readjustment Rating Scale.

symptoms after the first total sleep deprivation, and were then treated with benzodiazepines and a second mood stabilizer, thus restoring euthymia.[47] Clinical and demographic characteristics of the 141 completers, divided according to history of suicide attempts and response to treatment, are summarized in Table 1.

Patients with a positive history of suicide attempts compared to those with a negative history showed higher levels of early life stress (mean [SD] number of events: 17.61 [10.99] vs 12.29 [8.47], $t = 2.91$, $P = .004$; SRRS score: 390.78 [258.97] vs 282.13 [179.73]; Student $t = 2.70$, $P = .008$) but not of recent stress. Responders showed a lower severity of current depression than nonresponders on baseline self-rated BDI score (14.71 [7.37] vs 19.59 [7.80]; $t = 3.25$, $P = .001$) but not on HDRS. No other effect of these variables, nor their interaction, was significant.

Effect of Chronotherapeutics

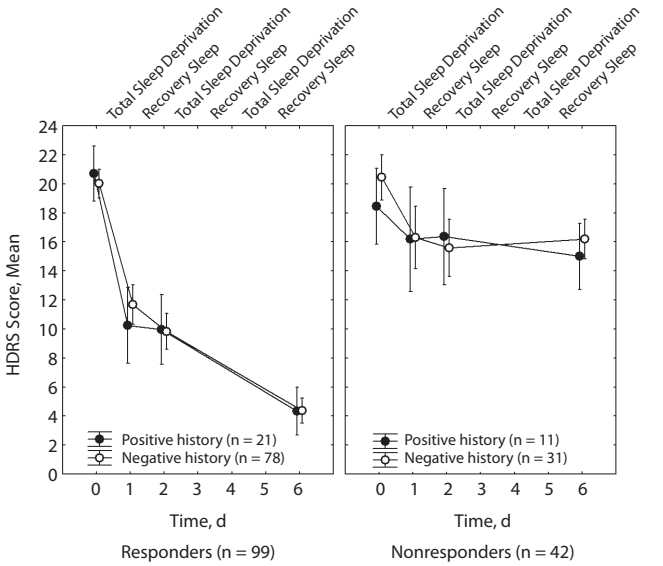
Ninety-nine patients (70.1%) responded to treatment. A positive history of suicide attempts was not associated with response (50% reduction in HDRS score; see Table 1).

HDRS scores significantly decreased after chronotherapeutics (Figure 1; main effect of time: $F_{3,411} = 119.04$, $P < .00001$).

This effect was not influenced by previous history of suicide attempts (2-way interaction of time and history: $F_{3,411} = 0.55$, $P = .647$; 3-way interaction of time, response to treatment, and history: $F_{3,411} = 1.42$, $P = .237$). Remarkably, however, nonresponders achieved a benefit from treatment and showed significantly decreased final HDRS scores in respect to baseline whether they did (post hoc Newman-Keuls test, $P = .024$) or did not have ($P = .001$) a positive history of suicide attempts.

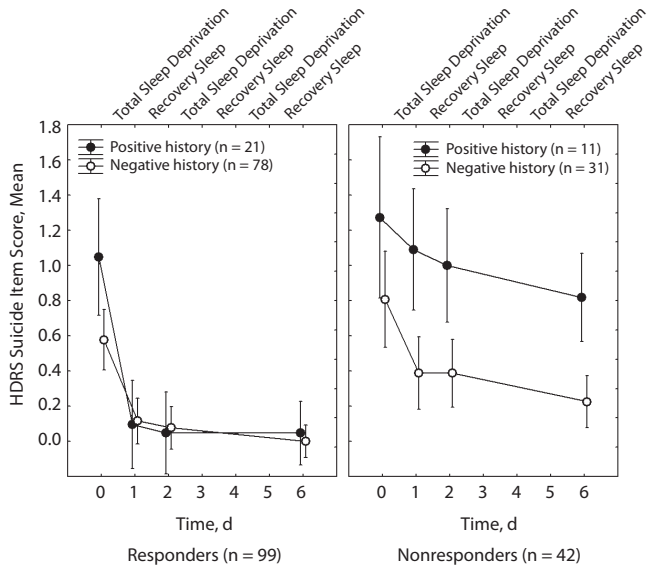
The significant HDRS decrease included the suicide item (Figure 2; main effect of time: $F_{3,411} = 42.78$, $P < .00001$).

Figure 1. Pattern of Change of Depression Severity (HDRS score) During Treatment in Patients Divided According to Chronotherapeutic Treatment Response and to Previous History of Suicide Attempts[a]



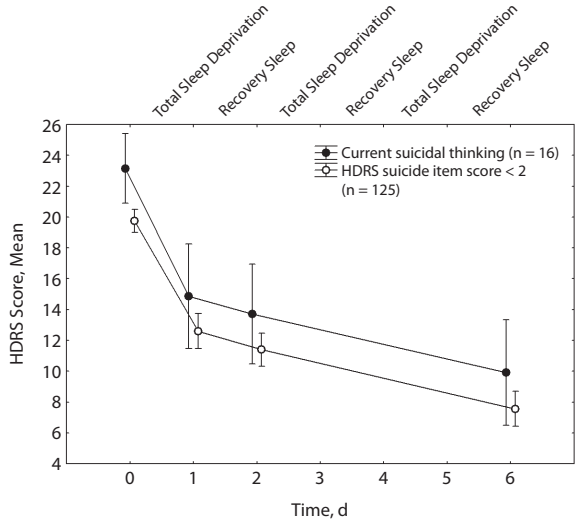
[a]Error bars indicate confidence limits.
Abbreviation: HDRS = Hamilton Depression Rating Scale.

Figure 2. Pattern of Change of the HDRS Suicide Item Scores During Treatment in Patients Divided According to Chronotherapeutic Treatment Response and to Previous History of Suicide Attempts



[a]Error bars indicate confidence limits.
Abbreviation: HDRS = Hamilton Depression Rating Scale.

Figure 3. Pattern of Change of Depression Severity (HDRS scores) During Chronotherapeutic Treatment in Patients Divided According to the Presence or Absence of Current Suicidal Thinking or Planning[a]



[a]Error bars indicate confidence limits.
Abbreviation: HDRS = Hamilton Depression Rating Scale.

Previous history of suicide attempts was associated with worse suicide scores at baseline ($\beta = .248$, $t = 2.84$, $P = .005$) and did not interact with time in influencing the decrease of HDRS suicide scores ($F_{3,411} = 0.77$, $P = .512$), but it significantly interacted with time and response ($F_{3,411} = 3.42$, $P = .017$). This differential result occurred because the interaction of time and history was significant among responders but not among nonresponders. Responders with a positive suicide history showed higher baseline levels and a bigger decrease after the first total sleep deprivation + light therapy treatment ($F_{3,291} = 6.31$, $P = .0004$). Nonresponders, however, who achieved a smaller, although significant benefit from treatment (effect of time: $F_{3,120} = 6.55$, $P = .0004$), showed a similar significant decrease in HDRS score independent of history of previous suicide attempts (post hoc Newman-Keuls test: positive history, $P = .039$; negative history, $P = .004$).

A subgroup of 16 patients (11.4%) reported current suicidal thinking or planning (HDRS suicide item score ≥ 2) and showed the same trend of decrease in HDRS suicide scores observed in the whole sample (effect of time: $F_{3,42} = 20.70$, $P < .000001$) (Figure 3), with a significant final benefit for nonresponders too (post hoc Newman-Keuls test: $P = .002$ in respect to baseline). None of the patients' scores on the suicide item decreased.

Compared with patients who lacked current suicidal planning, suicidal patients showed marginally worse overall HDRS scores ($F_{1,139} = 3.93$, $P = .049$) due to significantly worse scores at baseline (day 0: $\beta = .233$, $t = 2.82$, $P = .005$), but not during and after treatment (day 1: $t = 1.25$, $P = .21$; day 2: $t = 1.35$, $P = .18$; day 6: $t = 1.30$, $P = .20$).

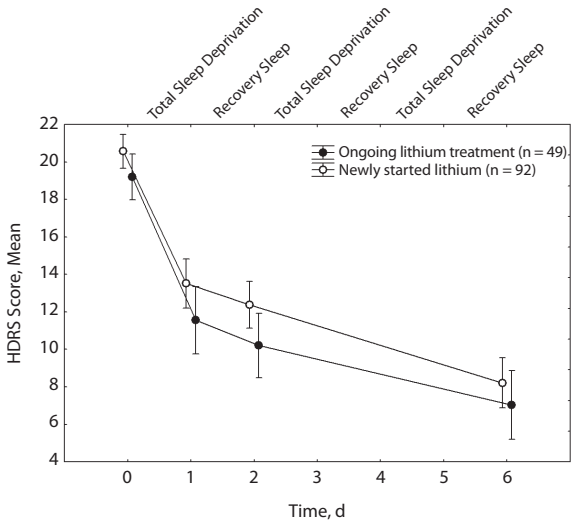
Self-ratings of depression (13-item BDI) confirmed these same effects. Correlations between BDI and the corresponding HDRS scores were all significant ($r = 0.23$, 0.48, 0.49, and 0.61, at days 1, 2, 3, and 7, respectively). A complete set of 4 daily ratings was obtained in 109 of 141 patients. Patterns of change over time were closely similar to those observed with HDRS: a highly significant decrease in depression severity after treatment ($F_{3,324} = 36.36$, $P < .000001$), with a significant amelioration of symptoms also found in nonresponders (post hoc Newman-Keuls, $P = .0007$); no influence of previous history of suicide attempts (interaction with time: $F_{3,321} = 0.85$, $P = .469$) nor of current suicidality ($F_{3,321} = 1.59$, $P = .192$); and, most important, a highly significant decrease of the suicide item ($F_{3,342} = 9.99$, $P = .000002$), again involving a significant decrease in nonresponders (post hoc Newman-Keuls, $P = .0006$).

Effect of Lithium

Ongoing lithium treatment conferred some advantage in respect to newly started lithium (Figure 4), with a significant main effect on global HDRS scores ($F_{1,139} = 4.18$, $P = .043$) due to a better improvement after the first total sleep deprivation + light therapy cycle (day 2: $\beta = .169$, $t = 2.03$, $P = .045$) but with similar final scores (day 7: $\beta = .087$, $t = 1.03$, $P = .303$).

History of drug resistance did not significantly influence the pattern of decrease of HDRS scores, either when comparing drug-resistant and non–drug-resistant patients ($F_{3,417} = 1.46$, $P = .223$) or when dividing the drug-resistant patients into 3 classes (stage 1, stage 2, stage 3 or higher: $F_{9,411} = 1.31$, $P = .232$).

Figure 4. Pattern of Change of Depression Severity (HDRS scores) During Chronotherapeutic Treatment in Patients Divided According to the Status of Lithium Medication (ongoing or newly started)[a]



[a]Error bars indicate confidence limits.
Abbreviation: HDRS = Hamilton Depression Rating Scale.

During the following month with lithium monotherapy, 21 of 99 responders showed signs of relapse and were administered an adjunctive antidepressant treatment by the psychiatrists in charge, while the other 78 of 99 responders continued to stay well and were discharged from the hospital with lithium therapy alone.

DISCUSSION

The 1-week combination of lithium and chronotherapeutics was followed by a 70% response rate in patients affected by bipolar depression. Considering the 21% relapse rate in the following weeks, this brings the success to 55.3% of patients achieving a sustained response. Consistent with previous studies,[47] the rate of switch into mania was very low (1.4%) and manic symptoms rapidly disappeared.

The rate of success is higher than that reported in previous studies of drug-resistant bipolar depressed patients (44% of acute response, with only 40% of responders staying well after 1 month).[29] The improvement in success rate from 17.6% to 55.3% could be due to 2 methodological innovations: starting lithium together with chronotherapeutics in patients not treated with lithium and prolonging light therapy for 1 week after the acute response. Lithium promotes response in nonresponders[48] and can overcome the detrimental effects of biological factors hampering response to antidepressants.[36,49] Light therapy promotes response in drug-resistant depression.[50,51] Both lithium and light therapy are synergistic with sleep deprivation,[30] and could then interact to sustain its effects. The decrease in suicide scores was immediate, soon after the first total sleep deprivation + light therapy, thus suggesting a direct therapeutic effect of total sleep deprivation (and not of recovery sleep) on this symptom (Figures 2–3).

Confirming the literature, our results showed that a positive history compared to a negative history of suicidal acts was associated with more early stress[32,52] and with worse current suicidality.[53] Nevertheless, 66% of patients with a positive history responded with a rapid drop in suicidal symptoms. Remarkably, suicidality also decreased in nonresponders, who then obtained a substantial benefit despite not achieving final response.

These effects on suicidal thinking confirm previous studies showing that sleep deprivation rapidly reverts the baseline mood-congruent cognitive biases toward negative stimuli in depression.[54,55] Cognitive distortions include pessimism and self-deprecatory and self-accusatory thoughts. We showed that effective antidepressant chronotherapeutics normalized the reactivity of corticolimbic circuitries to emotional and moral stimuli, thus restoring an efficient top-down control on response to negative stimuli by cortical regions involved in the generation and control of depressed mood.[56]

Mechanisms of these rapid effects involve multitarget actions on several neurobiological pathways.[57] Total sleep deprivation acts on brain serotonin, dopamine, norepinephrine, glutamate, and adenosine, and changes in these signaling cascades are proportional to the observed behavioral effects.[58] These factors influence both behavior[59] and brain metabolism and reactivity[56,60,61] as well as a steady increase of excitability of cortical circuits.[62,63] Remarkably, a comparable rapid effect on suicidality had been reported for the glutamatergic *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine.[64–66] sleep deprivation itself alters the circadian cyclicity of glutamatergic neurotransmission,[63] with changes of glutamate/glutamine concentrations being proportional to mood improvement,[67] and has been shown to modify the expression of NMDA receptor subunits[68] and reduce NMDA sensitivity in model organisms.[69] Treatment response in this study was significant on day 1, but it continued to drop after treatment repetition, while, in contrast, the suicidal ideation dropped to a very low level on day 1 and remained low thereafter (Table 1). This is directly compatible with the effects reported after extremely low doses of ketamine.[64–66] Changes of glutamatergic neurotransmission could then be a core component of these effects uniquely common to the 2 treatments.

Lithium could potentiate these mechanisms by acting on signaling cascades downstream the monoaminergic pathways,[70,71] by promoting synaptic plasticity,[72] and by overcoming the detrimental effects of genetic factors associated with treatment failure and suicide.[32,36] Lithium protects against both the reduction of gray matter volumes associated with suicidal behavior in bipolar disorder[32] and the disruption of white matter connecting corticolimbic circuitries.[73,74] Bipolar disorder,[75] drug-resistant depression,[76] and suicide[77] have been associated with a proinflammatory state and with an abnormal activation of brain microglia and of circulating monocytes,[78] and again both sleep manipulations[79] and lithium[80] target inflammatory mechanisms associated with depression.[81,82]

The clinical relevance of the above is remarkable in light of the debated issue of how to treat suicidality in depression. In other psychiatric conditions, such as schizophrenia, a protective effect of adequate and effective antipsychotic medication against suicide has been repeatedly confirmed.[83] The analysis of proprietary data submitted to the US Food and Drug Administration suggests instead that the net effect of antidepressant drugs, compared with placebo, could be negative among adults aged under 25 years, neutral on suicidal behavior but possibly protective for suicidal ideation in adults aged 25–64 years, and protective against both suicidality and suicidal behavior in those aged more than 65 years.[12] In the present study, we observed no suicidal behavior (completed suicide, attempted suicide, or preparatory acts), and no worsening of suicidal ideation among participants, who were aged a mean (SD) of 47.16 (11.50) years (range, 19–71). Only 3 participants were aged < 26 years, thus preventing conclusions on the effects of chronotherapeutics on suicide in younger adults, but our observation of protective effects in the overall sample confirms its central role as a rapid first-line option in bipolar depression.[27] Again, lithium could favorably interact with chronotherapeutics in limiting the suicide symptoms because it has a clear protective effect on suicide behaviors in bipolar disorder[15,16] and it can sustain and enhance the antidepressant effect of sleep deprivation. It has been proposed that lithium can act on suicide by decreasing impulsivity, aggression, or decision-making deficits, which are endophenotypes intermediate between suicidal thoughts and behaviors[84,85]; our data suggest that, at least when sustaining effective chronotherapeutics, lithium could also help to decrease suicidal thoughts as rated on the BDI and HDRS.

A major caveat when using chronotherapeutics in clinical settings comes from the possibility of depressive relapse in the first month after chronotherapeutics. This is all but unexpected in patients with bipolar disorder, who present depression and depressive cycling as a substantial problem in some two-thirds of intensively treated bipolar outpatients[86] and who remain well on antidepressants for more than 2 months at a very low rate,[86] with further discontinuation being associated with a further substantially increased risk of depressive relapse.[22] A careful monitoring of mood in the weeks after acute response to chronotherapeutics is then advised[24] in order to promptly start that complex pattern of medication trials, which chronotherapeutics could not avoid in these cases.[23]

Limitations of the present study include lack of placebo control for the chronotherapeutic procedure, lack of assessment of lifetime medications and of their possible effects on the current status, absence of drug-naive patients, absence of evaluation for lifetime compliance, absence of testing of interrater reliability, and the low number of patients who reported current suicidal thinking or planning, which prevented the study of interactions (eg, the possible potentiating effect of lithium salts) in this subgroup.

In conclusion, the combination of total sleep deprivation, light therapy, and lithium was able to rapidly decrease depressive suicidality and prompt antidepressant response in drug-resistant major depression in the course of bipolar disorder. This study adds new evidence to warrant a role for chronotherapeutics as a first-line treatment for bipolar depression.

Drug names: ketamine (Ketalar and others), lithium (Lithobid and others).
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Potential conflicts of interest: The authors have no financial conflicts of interest to disclose.
Funding/support: The study was partly funded by the European Union (FP7 grant 222963-MOODINFLAME).
Role of the sponsor: The study sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

REFERENCES

1. Post RM, Leverich GS, Altshuler LL, et al. Differential clinical characteristics, medication usage, and treatment response of bipolar disorder in the US versus The Netherlands and Germany. *Int Clin Psychopharmacol*. 2011;26(2):96–106.
2. Altshuler LL, Kupka RW, Hellemann G, et al. Gender and depressive symptoms in 711 patients with bipolar disorder evaluated prospectively in the Stanley Foundation bipolar treatment outcome network. *Am J Psychiatry*. 2010;167(6):708–715.
3. Kupka RW, Altshuler LL, Nolen WA, et al. Three times more days depressed than manic or hypomanic in both bipolar I and bipolar II disorder. *Bipolar Disord*. 2007;9(5):531–535.
4. Post RM, Leverich GS, Altshuler LL, et al. Relationship of prior antidepressant exposure to long-term prospective outcome in bipolar I disorder outpatients. *J Clin Psychiatry*. 2012;73(7):924–930.
5. Chen YW, Dilsaver SC. Lifetime rates of suicide attempts among subjects with bipolar and unipolar disorders relative to subjects with other Axis I disorders. *Biol Psychiatry*. 1996;39(10):896–899.
6. Leverich GS, Altshuler LL, Frye MA, et al. Factors associated with suicide attempts in 648 patients with bipolar disorder in the Stanley Foundation Bipolar Network. *J Clin Psychiatry*. 2003;64(5):506–515.
7. Osby U, Brandt L, Correia N, et al. Excess mortality in bipolar and unipolar disorder in Sweden. *Arch Gen Psychiatry*. 2001;58(9):844–850.
8. Jamison KR. Suicide and bipolar disorders. *Ann N Y Acad Sci*. 1986;487 (1 Psychobiology):301–315.
9. Partonen T, Sihvo S, Lönnqvist JK. Patients excluded from an antidepressant efficacy trial. *J Clin Psychiatry*. 1996;57(12):572–575.
10. Zimmerman M, Mattia JI, Posternak MA. Are subjects in pharmacological treatment trials of depression representative of patients in routine clinical practice? *Am J Psychiatry*. 2002;159(3):469–473.
11. Tiihonen J, Lönnqvist J, Wahlbeck K, et al. Antidepressants and the risk of suicide, attempted suicide, and overall mortality in a nationwide cohort. *Arch Gen Psychiatry*. 2006;63(12):1358–1367.
12. Stone M, Laughren T, Jones ML, et al. Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. *BMJ*. 2009;339:b2880.
13. Walsh BT, Seidman SN, Sysko R, et al. Placebo response in studies of major depression: variable, substantial, and growing. *JAMA*. 2002;287(14):1840–1847.
14. Turner EH, Matthews AM, Linardatos E, et al. Selective publication of antidepressant trials and its influence on apparent efficacy. *N Engl J Med*. 2008;358(3):252–260.
15. Baldessarini RJ, Tondo L, Hennen J. Lithium treatment and suicide risk in major affective disorders: update and new findings. *J Clin Psychiatry*. 2003;64(suppl 5):44–52.
16. Goodwin FK, Fireman B, Simon GE, et al. Suicide risk in bipolar disorder during treatment with lithium and divalproex. *JAMA*. 2003;290(11):1467–1473.
17. Keilp JG, Grunebaum MF, Gorlyn M, et al. Suicidal ideation and the subjective aspects of depression. *J Affect Disord*. 2012;140(1):75–81.
18. Grunebaum MF, Keilp J, Li S, et al. Symptom components of standard depression scales and past suicidal behavior. *J Affect Disord*. 2005;87(1):73–82.
19. Thase ME. Antidepressant combinations: widely used, but far from empirically validated. *Can J Psychiatry*. 2011;56(6):317–323.
20. Frye MA, Helleman G, McElroy SL, et al. Correlates of treatment-emergent mania associated with antidepressant treatment in bipolar depression. *Am J*

Psychiatry. 2009;166(2):164–172.
21. Gao K, Kemp DE, Ganocy SJ, et al. Treatment-emergent mania/hypomania during antidepressant monotherapy in patients with rapid cycling bipolar disorder. *Bipolar Disord*. 2008;10(8):907–915.
22. Altshuler L, Suppes T, Black D, et al. Impact of antidepressant discontinuation after acute bipolar depression remission on rates of depressive relapse at 1-year follow-up. *Am J Psychiatry*. 2003;160(7):1252–1262.
23. Post RM, Altshuler LL, Frye MA, et al. Complexity of pharmacologic treatment required for sustained improvement in outpatients with bipolar disorder. *J Clin Psychiatry*. 2010;71(9):1176–1186, quiz 1252–1253.
24. Benedetti F, Colombo C. Sleep deprivation in mood disorders. *Neuropsychobiology*. 2011;64(3):141–151.
25. Benedetti F, Barbini B, Colombo C, et al. Chronotherapeutics in a psychiatric ward. *Sleep Med Rev*. 2007;11(6):509–522.
26. Wirz-Justice A, Benedetti F, Berger M, et al. Chronotherapeutics (light and wake therapy) in affective disorders. *Psychol Med*. 2005;35(7):939–944.
27. Wirz-Justice A, Benedetti F, Terman M. *Chronotherapeutics for Affective Disorders. A Clinician's Manual for Light and Wake Therapy*. Basel, Switzerland: Karger; 2009.
28. Benedetti F, Dallaspezia S, Fulgosi MC, et al. Phase advance is an actimetric correlate of antidepressant response to sleep deprivation and light therapy in bipolar depression. *Chronobiol Int*. 2007;24(5):921–937.
29. Benedetti F, Barbini B, Fulgosi MC, et al. Combined total sleep deprivation and light therapy in the treatment of drug-resistant bipolar depression: acute response and long-term remission rates. *J Clin Psychiatry*. 2005;66(12):1535–1540.
30. Colombo C, Lucca A, Benedetti F, et al. Total sleep deprivation combined with lithium and light therapy in the treatment of bipolar depression: replication of main effects and interaction. *Psychiatry Res*. 2000;95(1):43–53.
31. First MB, Spitzer RL, Gibbon M, et al. *Structured Clinical Interview for DSM-IV Axis I Disorders, Research Version, Patient Edition*. New York, NY: Biometric Research, New York State Psychiatric Institute; 1997.
32. Benedetti F, Radaelli D, Poletti S, et al. Opposite effects of suicidality and lithium on gray matter volumes in bipolar depression. *J Affect Disord*. 2011;135(1–3):139–147.
33. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol*. 1967;6(4):278–296.
34. Benedetti F, Colombo C, Barbini B, et al. Ongoing lithium treatment prevents relapse after total sleep deprivation. *J Clin Psychopharmacol*. 1999;19(3):240–245.
35. Baxter LR Jr. Can lithium carbonate prolong the antidepressant effect of sleep deprivation? *Arch Gen Psychiatry*. 1985;42(6):635.
36. Benedetti F, Barbini B, Bernasconi A, et al. Lithium overcomes the influence of 5-HTTLPR gene polymorphism on antidepressant response to sleep deprivation. *J Clin Psychopharmacol*. 2008;28(2):249–251.
37. Leibenluft E, Moul DE, Schwartz PJ, et al. A clinical trial of sleep deprivation in combination with antidepressant medication. *Psychiatry Res*. 1993;46(3):213–227.
38. Beck AT, Beck RW. Screening depressed patients in family practice: a rapid technic. *Postgrad Med*. 1972;52(6):81–85.
39. Desseilles M, Perroud N, Guillaume S, et al. Is it valid to measure suicidal ideation by depression rating scales? *J Affect Disord*. 2012;136(3):398–404.
40. Valtonen HM, Suominen K, Sokero P, et al. How suicidal bipolar patients are depends on how suicidal ideation is defined. *J Affect Disord*. 2009;118(1–3):48–54.
41. Thase ME, Rush AJ. When at first you don't succeed: sequential strategies for antidepressant nonresponders. *J Clin Psychiatry*. 1997;58(suppl 13):23–29.
42. Holmes TH, Rahe RH. The Social Readjustment Rating Scale. *J Psychosom Res*. 1967;11(2):213–218.
43. Dohrenwend BP. Inventorying stressful life events as risk factors for psychopathology: toward resolution of the problem of intracategory variability. *Psychol Bull*. 2006;132(3):477–495.
44. McCulloch CE, Searle SR, Neuhaus JM. *Generalized, Linear, and Mixed Models*. 2nd ed. New York, NY: John Wiley & Sons; 2008.
45. Timm N, Kim K. *Univariate and Multivariate General Linear Models: Theory and Applications With SAS*. 2nd ed. Berlin, Heidelberg, Germany: Springer; 2006.
46. Hill T, Lewicki P. *Statistics: Methods And Applications. A Comprehensive Reference For Science, Industry, And Data Mining*, Chapter 18. Tulsa, OK: General Linear Models, StatSoft; 2006:245–276.
47. Colombo C, Benedetti F, Barbini B, et al. Rate of switch from depression into mania after therapeutic sleep deprivation in bipolar depression. *Psychiatry Res*. 1999;86(3):267–270.
48. Bschor T, Bauer M. Efficacy and mechanisms of action of lithium augmentation in refractory major depression. *Curr Pharm Des*. 2006;12(23):2985–2992.
49. Benedetti F, Colombo C, Serretti A, et al. Antidepressant effects of light therapy combined with sleep deprivation are influenced by a functional polymorphism within the promoter of the serotonin transporter gene. *Biol Psychiatry*. 2003;54(7):687–692.
50. Prasko J, Brunovsky M, Latalova K, et al. Augmentation of antidepressants with bright light therapy in patients with comorbid depression and borderline personality disorder. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2010;154(4):355–361.
51. Goel N, Terman M, Terman JS, et al. Controlled trial of bright light and negative air ions for chronic depression. *Psychol Med*. 2005;35(7):945–955.
52. Labonte B, Turecki G. Epigenetic Effects of Childhood Adversity in the Brain and Suicide Risk. In: Dwivedi Y, ed. *The Neurobiological Basis of Suicide*. Boca Raton, FL: CRC Press; 2012.
53. Oquendo MA, Galfalvy H, Russo S, et al. Prospective study of clinical predictors of suicidal acts after a major depressive episode in patients with major depressive disorder or bipolar disorder. *Am J Psychiatry*. 2004;161(8):1433–1441.
54. Baving L, Maes H, Bohus M, et al. Can negative self-schemes in depressives be altered through sleep deprivation? *J Affect Disord*. 1997;42(2–3):93–101.
55. Benedetti F, Barbini B, Florita M, et al. Rapid improvement in information processing after sleep deprivation and sleep phase-advance in bipolar depression. *Clinical Neuropsychiatry*. 2005;2(3):180–182.
56. Benedetti F, Bernasconi A, Blasi V, et al. Neural and genetic correlates of antidepressant response to sleep deprivation: a functional magnetic resonance imaging study of moral valence decision in bipolar depression. *Arch Gen Psychiatry*. 2007;64(2):179–187.
57. Millan MJ. Multi-target strategies for the improved treatment of depressive states: conceptual foundations and neuronal substrates, drug discovery and therapeutic application. *Pharmacol Ther*. 2006;110(2):135–370.
58. Benedetti F, Smeraldi E. Neuroimaging and genetics of antidepressant response to sleep deprivation: implications for drug development. *Curr Pharm Des*. 2009;15(22):2637–2649.
59. Benedetti F, Dallaspezia S, Lorenzi C, et al. Gene-gene interaction of glycogen synthase kinase 3-β and serotonin transporter on human antidepressant response to sleep deprivation. *J Affect Disord*. 2012;136(3):514–519.
60. Ebert D, Berger M. Neurobiological similarities in antidepressant sleep deprivation and psychostimulant use: a psychostimulant theory of antidepressant sleep deprivation. *Psychopharmacology (Berl)*. 1998;140(1):1–10.
61. Wu JC, Buchsbaum M, Bunney WE Jr. Clinical neurochemical implications of sleep deprivation's effects on the anterior cingulate of depressed responders. *Neuropsychopharmacology*. 2001;25(suppl):S74–S78.
62. Huber R, Mäki H, Rosanova M, et al. Human cortical excitability increases with time awake. *Cereb Cortex*. 2013;23(2):332–338.
63. Vyazovskiy VV, Cirelli C, Pfister-Genskow M, et al. Molecular and electrophysiological evidence for net synaptic potentiation in wake and depression in sleep. *Nat Neurosci*. 2008;11(2):200–208.
64. Larkin GL, Beautrais AL. A preliminary naturalistic study of low-dose ketamine for depression and suicide ideation in the emergency department. *Int J Neuropsychopharmacol*. 2011;14(8):1127–1131.
65. DiazGranados N, Ibrahim LA, Brutsche NE, et al. Rapid resolution of suicidal ideation after a single infusion of an *N*-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. *J Clin Psychiatry*. 2010;71(12):1605–1611.
66. Price RB, Nock MK, Charney DS, et al. Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. *Biol Psychiatry*. 2009;66(5):522–526.
67. Benedetti F, Calabrese G, Bernasconi A, et al. Spectroscopic correlates of antidepressant response to sleep deprivation and light therapy: a 3.0 Tesla study of bipolar depression. *Psychiatry Res*. 2009;173(3):238–242.
68. Park HJ, Kang WS, Paik JW, et al. Effect of valproic acid through regulation of NMDA receptor-ERK signaling in sleep deprivation rats. *J Mol Neurosci*. 2012;47(3):554–558.
69. Novati A, Hulshof HJ, Granic I, et al. Chronic partial sleep deprivation reduces brain sensitivity to glutamate N-methyl-D-aspartate receptor-mediated neurotoxicity. *J Sleep Res*. 2012;21(1):3–9.
70. Beaulieu JM, Caron MG. Looking at lithium: molecular moods and complex behaviour. *Mol Interv*. 2008;8(5):230–241.
71. Beaulieu JM, Gainetdinov RR, Caron MG. Akt/GSK3 signaling in the action of psychotropic drugs. *Annu Rev Pharmacol Toxicol*. 2009;49(1):327–347.
72. Schloesser RJ, Martinowich K, Manji HK. Mood-stabilizing drugs: mechanisms of action. *Trends Neurosci*. 2012;35(1):36–46.
73. Benedetti F, Absinta M, Rocca MA, et al. Tract-specific white matter structural disruption in patients with bipolar disorder. *Bipolar Disord*. 2011;13(4):414–424.
74. Benedetti F, Bollettini I, Barberi I, et al. Lithium and GSK3-β promoter gene

variants influence white matter microstructure in bipolar disorder. *Neuropsychopharmacology*. 2013;38(2):313–327.
75. Padmos RC, Hillegers MH, Knijff EM, et al. A discriminating messenger RNA signature for bipolar disorder formed by an aberrant expression of inflammatory genes in monocytes. *Arch Gen Psychiatry*. 2008;65(4):395–407.
76. Lanquillon S, Krieg JC, Bening-Abu-Shach U, et al. Cytokine production and treatment response in major depressive disorder. *Neuropsychopharmacology*. 2000;22(4):370–379.
77. Steiner J, Bielau H, Brisch R, et al. Immunological aspects in the neurobiology of suicide: elevated microglial density in schizophrenia and depression is associated with suicide. *J Psychiatr Res*. 2008;42(2):151–157.
78. Drexhage RC, Knijff EM, Padmos RC, et al. The mononuclear phagocyte system and its cytokine inflammatory networks in schizophrenia and bipolar disorder. *Expert Rev Neurother*. 2010;10(1):59–76.
79. Imeri L, Opp MR. How (and why) the immune system makes us sleep. *Nat Rev Neurosci*. 2009;10(3):199–210.
80. Jope RS, Yuskaitis CJ, Beurel E. Glycogen synthase kinase-3 (GSK3): inflammation, diseases, and therapeutics. *Neurochem Res*. 2007;32(4–5):577–595.
81. Voderholzer U, Fiebich BL, Dersch R, et al. Effects of sleep deprivation on nocturnal cytokine concentrations in depressed patients and healthy control subjects. *J Neuropsychiatry Clin Neurosci*. 2012;24(3):354–366.
82. Voderholzer U, Hohagen F, Klein T, et al. Impact of sleep deprivation and subsequent recovery sleep on cortisol in unmedicated depressed patients. *Am J Psychiatry*. 2004;161(8):1404–1410.
83. Heilä H, Isometsä ET, Henriksson MM, et al. Suicide victims with schizophrenia in different treatment phases and adequacy of antipsychotic medication. *J Clin Psychiatry*. 1999;60(3):200–208.
84. Gould TD, Can A, Gottesman II, et al. Differential lithium efficacy in reducing suicidal behaviors compared with suicidal thoughts. *Am J Psychiatry*. 2012;169(1):98–99, author reply 99.
85. Kovacsics CE, Gottesman II, Gould TD. Lithium's antisuicidal efficacy: elucidation of neurobiological targets using endophenotype strategies. *Annu Rev Pharmacol Toxicol*. 2009;49(1):175–198.
86. Post RM, Leverich GS, Nolen WA, et al; Stanley Foundation Bipolar Network. A re-evaluation of the role of antidepressants in the treatment of bipolar depression: data from the Stanley Foundation Bipolar Network. *Bipolar Disord*. 2003;5(6):396–406.