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Short communication

Chronotherapy shortens hospitalization for bipolar depression: a single-center replication across three decades (1994-2024)

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ABSTRACT

Background: Chronotherapeutic interventions have been proposed as non-pharmacological strategies for the rapid modulation of depressive symptoms in bipolar disorder. Total sleep deprivation (TSD) may induce short-term mood improvements, and morning bright light therapy (BLT) has been suggested to help stabilize these effects. However, the impact of these interventions on service-level outcomes, including length of hospital stay (LOS), has not been systematically evaluated.

Methods: We analyzed two non-overlapping retrospective cohorts (1994–1998 and 2015–2024) from the same Mood Disorders Unit, including adults hospitalized for a bipolar depressive episode. Within each cohort, patients received either treatment as usual (TAU) or TAU with chronotherapy, consisting of TSD in the earlier cohort and TSD with morning BLT in the later one. LOS was examined with general linear models adjusted for age and sex.

Results: The combined sample included 1241 admissions (706 from 1994–1998; 535 from 2015–2024). In both cohorts, LOS was shorter with TSD than with TAU (1994–1998: 20.99±11.09 days vs 23.23±13.34, $F = 5.31$, $p = 0.02$; 2015–2024: 24.00±8.24 vs 27.62±8.67, $F = 15.46$, $p < 0.01$), with a small effect size in the earlier cohort ($d = 0.176$) and a small-to-moderate effect in the later one ($d = 0.425$). Treatment × Cohort interaction was not significant ($F = 0.55$, $p = 0.46$).

Conclusions: Across three decades, the use of chronotherapy was consistently associated with shorter LOS in bipolar depression, despite major changes in clinical practice, organizational structure, and environmental circadian stressors. While causality cannot be inferred due to the observational design, these findings suggest that TSD-based chronotherapeutic interventions may represent a promising approach within acute inpatient care pathways, potentially contributing to improved hospitalization trajectories and discharge readiness in bipolar depression.

1. Introduction

Bipolar Disorder (BD) is a chronic disorder consistently linked to diminished quality of life, impaired psychosocial functioning, and disability stemming from the illness (Grande et al., 2016; Murru et al., 2019). The vast majority of patients require hospitalization during both depressive and manic illness episodes. Extended periods of hospitalization exert a considerable negative influence, not only diminishing a patient's trust in therapeutic regimen and hindering vocational reintegration, but also instigating increased financial burdens and leading to an inefficient allocation of healthcare resources (Fornaro et al., 2018; Wolff et al., 2015).

Chronotherapeutics, interventions targeting the sleep–wake cycle and circadian systems, have been proposed as rapid-acting strategies for depressive episodes, potentially bypassing the pharmacokinetic latency of standard treatments. Among these, total sleep deprivation (TSD) has been reported to induce rapid mood improvements, and its effects may be sustained when combined with repeated schedules and bright light therapy (BLT) as an adjunct to mood stabilizers (Benedetti et al., 2005, 2014; Dallaspezia and Benedetti, 2015; Wirz-Justice et al., 2004).

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However, the current evidence base remains inconsistent. A recent systematic review and meta-analysis of randomized controlled trials by Mitter et al. (2022) found no clear evidence that the addition of sleep deprivation to treatment strategies improves depressive outcomes, reflecting the limited number of robust positive RCTs and the heterogeneity of available studies. Other meta-analytic work found however consistent positive effects of TSD, even when considering its effect without adjunctive potentiation interventions (such as light therapy or sleep phase advance) (Boland et al. 2017). Moreover, most controlled studies have primarily focused on short-term changes in depressive symptom severity, with limited attention to broader clinically meaningful outcomes. In this context, real-world observational data may provide complementary insights by capturing the impact of chronotherapeutic interventions in routine clinical settings and on pragmatic outcomes, such as hospitalization trajectories.

Here, we studied two naturally separated retrospective cohorts (1994–1998 and 2015–2024) from the same mood disorders unit, to assess the association between chronotherapy augmentation and length of stay (LOS) across markedly different organizational eras. We hypothesized that, in both timeframes, chronotherapy augmentation would be associated with shorter LOS relative to treatment as usual (TAU) alone.

2. Methods

We conducted two retrospective analyses of inpatient data from the Mood Disorders Unit, IRCCS San Raffaele Hospital, Milan, Italy. All patients had been consecutively referred for hospitalization by their psychiatrists in charge, for a major depressive episode without psychotic features, in course of bipolar disorder. The cohorts, sharing similar inclusion and exclusion criteria, were non-overlapping in time and spanned two distinct organizational eras: 1994–1998 and 2015–2024.

Electronic medical records of all admissions were reviewed. Eligible participants were adults aged 18–65 years with a DSM-based diagnosis of BD in a current non-psychotic depressive episode, admitted for at least six days.

Exclusion criteria included major psychiatric comorbidities with predominant symptomatology, intellectual disability, medical conditions or non-clinical factors dictating discharge timing.

In the 1994–1998 cohort, 706 inpatients met inclusion criteria. Patients received TAU (supportive psychotherapy and pharmacotherapy with mood stabilizers and antidepressant drugs) or TAU augmented with chronotherapy, consisting of three consecutive cycles of TSD followed by one recovery night, as described in earlier publications (Dallaspezia and Benedetti, 2015).

In the 2015–2024 cohort, 535 inpatients met inclusion criteria. Patients received TAU (supportive psychotherapy, mood stabilizers, and antidepressants), or TAU augmented with the same TSD protocol, updated per ward practice to include scheduled morning BLT exposure (Benedetti et al., 2005).

2.1. Outcomes and analysis

The primary outcome was the LOS, measured in days. For each cohort, LOS differences between TAU and TSD were examined using a general linear model with Treatment and Sex as fixed factors and Age as a covariate. In the combined dataset, a two-way general linear model including Treatment and Cohort as fixed factors, with Age and Sex as covariates, was used to test for main effects and their interaction. Standardized mean differences (Cohen's d) were calculated from group means.

3. Results

The combined sample included 1241 admissions, with 706 from the 1994–1998 cohort and 535 from the 2015–2024 cohort.

Sociodemographic characteristics for each treatment group are presented in Table 1 and mean LOS values for each Treatment by Cohort combination are presented in Table 2 and Fig. 1.

3.1. 1994–1998 cohort

Among 706 admissions (TAU $n = 492$, 69.7 %; TSD $n = 214$, 30.3 %), mean LOS was 23.23 ± 13.34 days for TAU and 20.99 ± 11.09 days for TSD, corresponding to a difference of 2.24 days. The standardized mean difference was small (Cohen's $d = 0.176$. Treatment had a significant main effect on LOS ($F = 5.31$, $p = 0.02$). Sex ($p = 0.52$) and age was positively associated with LOS ($F = 25.21$, $p < 0.01$) with higher age meaning longer LOS. Gender did not influence hospital stay.

3.2. 2015–2024 cohort

Across 535 admissions (TAU $n = 336$, 62.8 %; TSD $n = 199$, 37.2 %), mean LOS was 27.62 ± 8.67 days for TAU and 24.00 ± 8.24 days for TSD, corresponding to a difference of 3.62 days. The standardized mean difference was small-to-moderate (Cohen's $d = 0.425$). The analogous general linear model showed a significant main effect of Treatment ($F = 15.46$, $p < 0.01$)and age on LOS ($F = 8.34$, $p < 0.01$). Gender did not influence hospital stay in the second cohort too.

3.3. Combined analysis across cohorts

A two-way general linear model including Treatment and Cohort as fixed factors, with Age and Sex as covariates, showed a significant main effect of Treatment ($F = 15.97$, $p < 0.01$)and a significant main effect of Cohort ($F = 20.18$, $p < 0.01$). The Treatment by Cohort interaction was not significant ($F = 0.55$, $p = 0.46$). Age remained positively associated with LOS ($F = 35.40$, $p < 0.01$).

4. Discussion

In two independent inpatient cohorts separated by two decades, chronotherapy augmentation was consistently associated with shorter LOS in BD depression. This finding complements the rapid antidepressant action of TSD documented in clinical trials and naturalistic studies, extending its relevance to service-level outcomes. (Benedetti et al., 2005; Dallaspezia and Benedetti, 2015) Several considerations support the robustness and clinical utility of these observations.

In our inpatient unit, augmentation with sleep deprivation has remained a stable component of care over time, showing a relative increase of approximately one-third between the two study cohorts (1994–1998, 30.3 % Vs 2015–2024, 37.2 %). This reflects the persistence and progressive integration of chronotherapy into the clinical workflow of the unit.

These cohorts, however, were embedded in different organizational and financing contexts. The earlier cohort corresponds to an earlier phase of Italian psychiatric services, when hospital reimbursement was primarily based on Diagnosis-Related Group (DRG) per-patient model, preceding the national transition toward a per-day reimbursement system, which had become fully consolidated by the time of the second

Table 1
Sociodemographic and clinical characteristics of the sample by cohort and treatment group (SD = standard deviation).

	1994–1998 cohort		2015–2024 cohort	
	Treatment as usual (n = 492)	Chronotherapy (n = 214)	Treatment as usual (n = 336)	Chronotherapy (n = 199)
Female, n	349	135	231	104
Age, mean ± SD (years)	47.51 ± 12.54	47.56 ± 12.17	52.92 ± 9.67	50.96 ± 10.35

Table 2
Length of stay (LOS) by cohort and treatment group (SD = standard deviation).

	1994–1998 cohort		2015–2024 cohort	
	Treatment as usual (n = 492)	Chronotherapy (n = 214)	Treatment as usual (n = 336)	Chronotherapy (n = 199)
LOS, mean ± SD (days)	23.23 ± 13.34	20.99 ± 11.09	27.62 ± 8.64	23.99 ± 8.24

cohort (Fattore and Torbica, 2006). These two different National Health Service (NHS) reimbursement models have a moderate impact on the length of hospital stays and can account for the mean difference in duration observed between the two cohorts. Moreover, over the decades, the composition and structure of hospital clinical teams have undergone significant changes, alongside the evolution of TAU and established clinical routines. All these modifications can potentially impact the duration of hospitalization. Temporal robustness across different systems suggests a true and reproducible clinical effect of chronotherapeutics on depression and LOS, rather than an artifact of contemporaneous practice patterns.

The more recent cohort (2015–2024) reflects an era marked by increasing evening exposure to light-emitting screens and by widespread social jetlag, factors known to disrupt circadian alignment and worsen sleep quality in the general population, as well as to exacerbate clinical outcomes in individuals with mood disorders (Burns et al., 2023; Chang et al., 2015; Esaki et al., 2022; Wright et al., 2013). Despite these modern stressors, TAU plus TSD remained associated with a comparable reduction in LOS to that observed in the mid-1990s, demonstrating the restorative power of this intervention in reestablishing circadian alignment even under the more complex environmental conditions.

By accelerating symptomatic improvement without adding sedative pharmacological load, TSD-based chronotherapy may help limit polypharmacy escalation, streamline discharge planning, and reduce hospitalization length. These findings are consistent with extensive clinical research (Benedetti et al., 2005; Colombo et al., 2000; Wirz-Justice et al., 2005), demonstrating the rapid efficacy, good tolerability, and logistical feasibility of chronotherapeutic protocols in inpatient settings, implementable through standardized procedures, nursing-led supervision, and integration with mood stabilizers (Keramatian et al., 2023).

The larger effect size observed in the 2015–2024 cohort may reflect the progressive refinement of the sleep-deprivation protocol, including the structured integration of morning BLT, which is known to stabilize and prolong the antidepressant response to wake therapy (Benedetti et al., 2005). Enhanced procedural standardization and optimized patient selection over time may also have contributed to the greater consistency of outcomes.

In light of these results, TSD-based chronotherapy with adjunctive BLT may represent a promising approach within inpatient care pathways for BD depression. While evidence from randomized controlled trials (Mitter et al. 2022), primarily focused on changes in depressive symptom severity under controlled conditions, has not consistently supported its role as a first-line intervention, the present findings suggest a potential impact on clinically relevant outcomes in routine practice. In this context, chronotherapeutic interventions, even in the absence of a clearly established antidepressant effect in controlled trials, may influence broader aspects of clinical management, including LOS.

4.1. Limitations

This study has limitations that should be considered when interpreting the results.

This study is retrospective and single-center. As a real-world observational investigation, patient allocation to treatment conditions was not randomized, introducing the possibility of selection bias and confounding by indication. In routine clinical practice, the decision to propose TSD is likely influenced by specific clinical criteria, including the absence of cardiovascular contraindications, the absence of psychotic symptoms, and the patient's ability to adhere to a demanding intervention.

Finally, over the decades, the chronotherapeutic protocol has been progressively optimized, and in the 2015–2024 cohort the ward routinely adopted combined TSD with structured morning BLT. Further studies are warranted to investigate the effect of this new combined protocol on patient outcomes, specifically focusing on rates of relapse

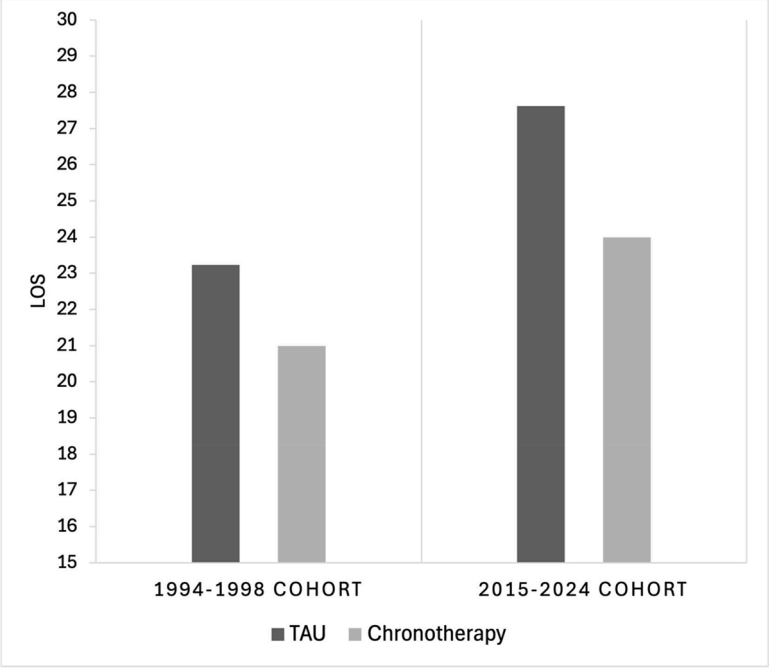

Fig. 1. Mean length of stay by Treatment and Cohort (LOS = length of stay, days; TAU = Treatment as usual, p-value 1994–1998 = 0.02, 2015–2024 < 0.01).

and the incidence of new hospital admissions

5. Conclusions

Across nearly three decades, the addition of chronotherapy to TAU was consistently associated with a reduction in LOS among patients with BD depression. While causality cannot be inferred due to the observational design, these findings suggest that TSD-based chronotherapeutic interventions may represent a promising approach within acute inpatient care pathways, potentially contributing to improved hospitalization trajectories and discharge readiness in BD depression.

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CRediT authorship contribution statement

Sara Dallaspezia: Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Francesco Attanasio:** Writing – original draft, Methodology, Investigation. **Simone Maruca:** Investigation. **Francesco Benedetti:** Writing – review & editing, Project administration, Conceptualization. **Cristina Colombo:** Supervision, Project administration.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

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