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Original Article

Alcohol misuse in bipolar depression: the effect of bright light therapy on irritability, agitation, and anger attacks

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SUMMARY

Objectives

This study aims to investigate the effectiveness of Bright Light Therapy (BLT) in reducing irritability, psychomotor agitation, and anger attacks in patients with bipolar depression comorbid with alcohol misuse. These symptoms, though commonly observed in clinical practice, have been under-researched, particularly in relation to treatment and prevention strategies.

Methods

A randomized trial was conducted with 60 inpatients diagnosed with bipolar disorder (BD), depressive episode, and comorbid alcohol misuse. Participants were divided into two groups: Group A received pharmacotherapy augmented with BLT, while Group B received pharmacotherapy alone. Assessments included qualitative evaluations of irritability, psychomotor agitation, and anger attacks, along with the Hamilton Depression Rating Scale for depressive symptoms and the Modified Overt Aggression Scale for aggression.

Results

After a four-week BLT regimen, Group A exhibited approximately half the cases of irritability and agitation, and a third fewer cases of anger attacks, compared to their counterparts in Group B. Notably, the positive effects of BLT on these symptoms were independent of depressive symptom remission.

Conclusions

BLT shows promise as a well-tolerated, adjunctive therapy for managing the symptom-complexes of irritability, psychomotor agitation, and anger attacks in patients with bipolar depression comorbid with alcohol misuse.
The therapeutic implications of these findings suggest that BLT could be a valuable addition to comprehensive treatment plans, offering a new approach to managing the challenges of BD.

Key words: irritability, psychomotor agitation, anger attacks, bipolar disorder, bipolar depression, bright light therapy, chronotherapy

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Introduction

Despite growing interest over recent decades in the intersection of psychiatry and violence, scientific research has predominantly focused on overt violent behaviors. This focus has left a significant gap in understanding symptoms like irritability, psychomotor agitation, and anger attacks, which are, nonetheless, a common occurrence in clinical practice across a wide spectrum of psychiatric conditions and have been consistently linked to violent behaviors in a small yet concordant body of literature [1-8]. These complex symptomatological presentations have not only been associated with violence but have also been described as a major source of distress among psychiatric patients and their caregivers. Studies have established their connection to social and familial dysfunction, treatment

non-adherence [9], suicide attempts [10], depressive recurrences, and a generally poor quality of life [11]. Given their significant impact, these symptoms represent a promising target for violence prevention strategies and for improving both clinical outcomes and quality of life.

Bipolar disorder (BD) is often characterized by the symptom-complexes of irritability, psychomotor agitation, and anger attacks, which, contrary to common belief, are particularly pronounced during its depressive phases [1-8]. This symptom profile has prompted various studies to propose that the presence of irritability may be a symptom distinguishing bipolar depression from Major Depressive Disorder [6,10,12].

Shifting to a broader concept of violence, it has been observed in BD that the polarity of episodes –whether manic, mixed, or depressive – does not significantly influence the severity and frequency of violence [13,14]. Studies have shown that an increased risk of violence is also present among individuals with depression [13,15] underscoring an association between the severity of depressive symptoms and aggression scores [16,17].

Alcohol misuse in addition to being an independent risk factor for violent behavior [18,19] and related aspects such as irritability, anger, and psychomotor agitation [20-23] is frequently identified as the most common comorbidity of BD. A substantial body of literature examines the association between BD and alcohol consumption, highlighting a comorbidity rate ranging from 45 to over 60% [24-28].

Current research indicates a bidirectional causal link between BD and alcohol misuse. Patients with BD experiencing depressive episodes often report heightened alcohol cravings [29]. Conversely, patterns and frequency of alcohol misuse can trigger BD episodes, including both manic and depressive states [30-32]. Moreover, escalating alcohol misuse correlates with a higher likelihood of subsequent depressive episodes in BD patients [33].

Although numerous studies have investigated the role of alcohol in moderating the relationship between BD and violent behaviors[13,24,34-38], there remains a significant gap in the literature regarding symptoms like irritability, psychomotor agitation, and anger attacks, particularly in terms of treatment and prevention strategies. This lack of targeted research underlines the need for more dedicated investigations into therapeutic approaches that specifically address these challenging aspects, providing a more comprehensive understanding and management of BD comorbid with alcohol misuse.

Bright Light Therapy (BLT), an established and well-tolerated intervention for depression, has demonstrated beneficial effects on depressive symptoms and sleep quality [39]. However, its impact on violent behavior, specifically irritability, psychomotor agitation, and anger attacks, has received limited attention. A recent pilot study conducted in our mood disorder unit revealed BLT's effectiveness in reducing irritability in bipolar depression, regardless of the remission of depressive symptoms [40]. This finding aligns with prior research that has examined BLT's efficacy in mitigating agitation in individuals with neurocognitive disorders [41].

Our study represents a first step to fill the large gap in the knowledge of irritability, psychomotor agitation, and anger attacks in BD. A better understanding of this symptom-complexes, from clinical assessment to possible therapeutic strategies, could provide an important improvement in the clinical management of depressive phases in BD when comorbid with alcohol misuse.

We conducted the first randomized trial with the aim of examine the effectiveness of BLT in a hospital setting in reducing irritability, psychomotor agitation, and anger attacks in individuals with bipolar depression and comorbid alcohol misuse.

Definitions

Irritability

The term irritability encompasses a range of definitions, all characterized by the negative valence of physical and psychological tension and heightened sensitivity to external stimuli. For our study, we have adopted a broad definition of irritability, enabling the inclusion of various interpretations of this largely subjective symptom [42-44].

Our definition, explicitly excluding components of aggression that imply an intent to cause harm, aligns with the American Psychiatric Association's conceptualization of irritability as an emotional state characterized by a short temper, easy annoyance, or anger, and an exaggerated sense of frustration over minor matters [45].

In bipolar depression, the prevalence of irritability varies from 26% to 68%, contingent upon the rigor of the criteria used, with a noted direct association with psychomotor agitation [6].

Psychomotor agitation

There is no single, universally accepted definition of psychomotor agitation, commonly described as a sensation of inner tension and restlessness [4,23].

Although violence is not inherent characteristics of agitation, a progression in the severity of agitation often precedes or leads to violent behaviors [46,47].

Anger attacks

Anger attacks have been extensively described by Fava in the context of unipolar depression, defined as sudden spells of anger accompanied by a surge of autonomic arousal, manifesting symptoms like tachycardia, sweating, flushing, and a feeling of being out of control. Individuals undergoing these episodes often perceive them as disproportionate and inappropriate responses

to the situations they encounter [48]. Recent literature has acknowledged that such occurrences may be more prevalent among bipolar depression [49].

Alcohol misuse

In line with many guidelines and recommendations [50-53], our study adopts the term "alcohol misuse" to encompass a broad spectrum of drinking behaviors. This includes risky or hazardous alcohol use, harmful alcohol use, alcohol abuse or dependence, and the DSM-5 alcohol use disorder diagnosis.

Materials and methods

We recruited 60 consecutively admitted inpatients diagnosed with BD according to the DSM-5-TR criteria [45], presenting with depressive episodes ranging from moderate to severe and comorbid with alcohol misuse.

Exclusion criteria included contraindications to BLT (retinal disease, photophobia, and medications inducing photosensitivity) [39], psychotic features, major psychiatric comorbidities (excluding alcohol use disorder), intellectual disabilities, cognitive decline, or severe neurological conditions.

All participants were admitted and followed a program spanning four weeks. We randomly assigned participants to groups in a 1:1 ratio using computer-generated randomization. Group A participants received pharmacotherapy and daily exposure to 10,000-Lux BLT from two CoeLux® 45 LC artificial windows for 30 minutes each morning at a time personalized based on the Morningness-Eveningness Questionnaire [39]; Group B participants received only pharmacotherapy.

All patients were on a stable and equivalent dose of antidepressants (fluoxetine equivalent dosage from 20 to 40mg/die). Low doses (equivalent diazepam dosage of 5-10mg) of short half-life benzodiazepines were permitted only as hypnotics to minimize their direct influence on the symptoms under study. Every patient was under a stable dosage of lithium or sodium valproate for at least 2 months.

Assessment was conducted by two trained psychiatrists, blinded to treatment conditions, ensuring high interrater reliability (Intra-Class Correlation Coefficient for HDRS = 0.95).

Raters and patients were blind to study structure and treatment assignment.

Depressive symptoms were assessed with the 21-item version of the Hamilton depression rating scale (HDRS) at both the beginning and the end of the hospitalization period. Response was defined as a ≥ 50% reduction of the HDRS score from the baseline, while remission was defined as achieving an HDRS score of ≤ 7 points [54].

Presence and severity of other-directed and self-directed aggressive behaviors during hospitalization were evaluated using the Modified Overt Aggression Scale (MOAS) [55]. The MOAS was divided into two main components: one assessing other-directed aggression, which includes the scores for 'Verbal Aggression', 'Aggression Against Property', and 'Physical Aggression'; and the other for self-directed aggression, comprising the 'Autoaggression' score.

Two trained psychiatrists performed a qualitative assessment of irritability. Data were collected using items derived from spontaneous descriptions of irritability (annoyance, anger, tension, hostility, sensitivity to noise and touch). Two clinicians asked patients a series of questions to globally evaluate their irritability at that moment as compared with their usual premorbid state, how severe the patient's irritability was at the presentation, and how much irritability may be considered normal for the patient [40].

Qualitative assessments of anger attacks and episodes of psychomotor agitation during hospitalization were conducted by two expert psychiatrists through the analysis of clinical diaries maintained daily by ward staff and through direct clinical evaluation of the patient. Both anger attacks and psychomotor agitation were also evaluated using the MOAS to examine any coexisting aggressive behaviors.

Information about previous lifetime violent behaviors was collected through clinical interviews.

Presence or absence of personality disorders (PD) was assessed by PD Structured Clinical Interview for DSM-5 once acute symptoms remitted [56].

We performed a preliminary sample size calculation based on data available in the previous literature. The Hospital's Ethical Committee approved the study, which complied with the most recent version of the Declaration of Helsinki. Written informed consent was acquired from all participants after thoroughly explaining the research procedures and aims.

Statistical analysis

To investigate clinical and demographic variables, upon normality distribution check, we performed Student T, Friedman, Mann-Whitney U tests and two-way repeated analysis of variance (RMANOVA) for continuous variables, Chi-square for categorical ones.

Power analyses based on the collected data were performed to evaluate the chances of detecting a statistically significant differences between groups for the variables of interest, with an alpha level set at 0.05 and a beta level at 0.20.

Results

No participants voluntarily withdrew from the study, and there were no reports of relevant side effects or significant withdrawal symptoms. 60 inpatients were enrolled

TABLE I. *Clinical and demographic characteristics of the sample according to Groups.*

	Group A (N = 30)	Group B (N = 28)	p-value
Age (y)	48.57 ± 10.79	50.29 ± 13.33	0.589[1]
Gender (F)	9 (30.00%)	10 (35.71%)	0.643[2]
Number of episodes lifetime (N)	7.37 ± 3.03	7.07 ± 5.59	0.271[3]
Diagnosis of personality disorder (N)	16 (53.33%)	10 (35.71%)	0.178[2]
HDRS T0	23.18 ± 5.19	22.30 ± 4.54	0.606[3]
HDRS T1	5.33 ± 2.72	7.75 ± 4.57	0.044[3]
Clinical remission (N)	25 (83.33%)	20 (71.43%)	0.277[2]
Depression severity distribution (%)	Moderate: 73.33% Severe: 26.67%	Moderate: 60.71% Severe: 39.29%	0.306[2]

[1] Student t-test, [2] Chi-squared test, [3] Mann-Whitney U test.

TABLE II. *Comparison of core symptom frequencies and MOAS scores between Groups.*

	Group A (N = 30)	Group B (N = 28)	p-value	Effect Size
Irritability (N)	6 (20%)	13 (46.3%)	0.032[1]	0.281*
Psychomotor agitation (N)	6 (20%)	13 (46.3%)	0.032[1]	0.281*
Anger attacks (N)	4 (13.33%)	11 (39.29%)	0.024[1]	0.296*
Total MOAS score	0.93 ± 2.18	2.11 ± 2.44	0.016[2]	0.319**
Other-directed MOAS score	0.43 ± 1.19	1.25 ± 1.78	0.030[2]	0.256**
Self-directed MOAS score	0.50 ± 1.59	0.86 ± 1.78	0.271[2]	0.107**

*[1]Chi-squared test, [2] Mann-Whitney U test. * Cramer's V, **rank-biserial correlation.*

and randomized. 3.33% of the original sample (0 patients in Group A and 2 patients in Group B) was excluded from the final analysis, due to a change in medication protocol (one patient) or discharge before the end of the trial (one patient).

The clinical and demographic characteristics of the sample are shown in Table I.

Improvements in depressive symptoms during the study, as assessed by the HDRS, were noted for both groups, as detailed in Table I (HDRS T0 and HDRS T1). A significant main effect of time was observed on HDRS scores ($p < 0.001$, RMANOVA). However, even if was noted a slight difference favoring Group A at the end of hospitalization (T1) as per Mann-Whitney U test (Tab. I), the interaction effect between time and BLT exposure was not significant ($p = 0.190$, RMANOVA) suggesting that the addition of BLT did not differentially affect the HDRS scores between the groups.

At the study's conclusion, a significant portion of the sample experienced core symptoms of interest: 32.76% (n = 19) reported episodes of irritability, an equal percentage (32.76%, n = 19) experienced psychomotor agitation, and 25.86% (n = 15) reported at least one anger attack.

A significant association was observed between the group variable, favoring Group A, and the incidence of irritability, psychomotor agitation, and anger attacks, respectively. For detailed data, refer to Table II.

The statistical analysis revealed significant associations among the core symptoms studied. Irritability was strongly associated with anger attacks ($\chi^2 = 15.122$, $p < 0.001$, Cramer's V = 0.511), indicating a robust association between these affective states. Similarly, a significant association was found between irritability and psychomotor agitation ($\chi^2 = 8.105$, $p = 0.004$, Cramer's V = 0.374). However, the association between psychomotor agitation and anger attacks was notably weaker ($\chi^2 = 3.888$, $p = 0.049$, Cramer's V = 0.259), suggesting that while these symptoms may occur concurrently, they do not exhibit a strong direct relationship within the context of this sample.

A difference between groups was observed for the total MOAS score and Other-directed MOAS score, favoring Group A; however, no difference was noted between the groups concerning the Self-directed MOAS score. See Table II for details.

In examining the association between age at the time of hospital admission and MOAS scores, a significant negative correlation was identified with both the total MOAS score (Spearman's rho = -0.410, $p = 0.001$) and the Other-directed MOAS score (Spearman's rho = -0.388, $p = 0.003$), as depicted in the respective analysis tables. These findings suggest that older age may be associated with lower levels of observed aggression in both categories. Conversely, the correlation between age and the Self-directed MOAS score did not reach statistical significance (Spearman's rho = -0.229, $p = 0.084$), indicating that self-directed aggressive behaviors may not be as closely associated with age in this sample.

In the analysis of associations between diagnosis of personality disorder and core symptoms of interest, chi-squared tests were conducted. For irritability, the association with personality disorder diagnosis was not statistically significant (χ^2 = 0.085, p = 0.771), indicating no clear relationship between the presence of personality disorders and levels of irritability in the sample. Similarly, psychomotor agitation did not show a significant association with diagnosis of personality disorder (χ^2 = 0.696, p = 0.404). However, a significant association was found between anger attacks and diagnosis of personality disorders (χ^2 = 3.902, p = 0.048. Cramer's V = 0.259).

In the statistical analysis of the association between previous violent behaviors and the core symptoms investigated, chi-squared tests revealed varying degrees of association. Both irritability and psychomotor agitation showed a similar and marginal degree of association with past violent behaviors (χ^2 = 3.888, p = 0.049) with a small effect size (Phi-coefficient = 0.259, Cramer's V = 0.259). For anger attacks, a significant association with past violent behaviors was noted (χ^2 = 17.570, p < 0.001), with a moderate effect size (Cramer's V = 0.550), indicating a robust link between historical violent incidents and current anger attacks.

Additional analyses were conducted to explore a wide range of potential associations and correlations, yet these did not yield statistically significant results. Specifically, no significant relationships were found between the core symptoms of interest and, HDRS scores at T0 and T1, the relative change in HDRS scores from baseline, number of lifetime episode, or sex.

Discussion

Despite limited attention to symptoms such as irritability, psychomotor agitation, and anger attacks in BD, their consistent presence across manic, mixed, and depressive phases suggests a fundamental role in the pathophysiology of BD. Deckersbach et al. (2004) emphasized the prevalence of irritability in bipolar depression, proposing its potential as a diagnostic marker distinguishing bipolar from unipolar depression. Recognizing these symptoms as integral to bipolar depression can inform both diagnostic accuracy and treatment planning. In fact, prompt recognition of these symptoms during depressive episodes is crucial for improved patient management. Their role as risk factors for violent behavior and their significant impact on patient outcomes, treatment efficacy, and the overall disease burden should not be underestimated.

In accordance with an expanding body of research, our study has adopted the term "alcohol misuse" to encompass a broad spectrum of behaviors related to alcohol consumption. This terminology more accurately characterizes the inconsistent alcohol use patterns seen in individuals with BD, notably during acute episodes of the illness. It is acknowledged that alcohol misuse among these patients may serve as self-medication during depressive states and as a manifestation of impulsivity and lack of restraint during manic periods [24,26].

Indeed, the complexity in managing BD is further amplified in cases involving alcohol misuse, a problem prevalent in over half of these patients. This co-occurrence exacerbates symptoms such as irritability, psychomotor agitation, and anger attacks, and complicates the treatment approaches, given the often intricate medication regimens that BD requires.

In this context, identifying potential treatment strategies like BLT that can effectively target these specific symptoms, without the complexities of additional pharmacotherapy, is particularly valuable.

In our study, approximately one-third of the participants displayed symptoms of irritability and psychomotor agitation, whereas around one-quarter reported anger attacks. These findings are congruent with the scant literature available [2-6,57-59].

The findings from this study highlight the substantial impact of BLT in attenuating irritability, psychomotor agitation, and anger attacks among patients with bipolar depression and concurrent alcohol misuse. Following a four-week regimen of BLT, the individuals in Group A demonstrated approximately half the cases of irritability and agitation, and a third fewer cases of anger attacks, compared to their counterparts in Group B. Notably, this reduction in core symptoms occurred independently of symptomatic remission, suggesting a direct and beneficial impact of BLT on these specific aspects of the disorder. The lower incidence of these specific symptoms in the BLT group, as compared to the control group, with effect sizes nearing the medium range (Cramer's V of 0.281 for irritability and agitation, 0.296 for anger attacks), is a noteworthy finding in the context of practical clinical application, particularly when considering the recurrent nature of BD and the complex challenges posed by comorbid alcohol misuse.

Due to a scarcity of precedent in the literature, the only viable comparison with previous studies pertains to the symptom of irritability. This symptom was previously examined by our team in a cohort of patients with bipolar depression [40], and the current study corroborates those earlier observations, demonstrating a positive effect of BLT in diminishing irritability, even in subjects with concurrent alcohol misuse.

The positive BLT effect observed on the total MOAS score and the Other-directed MOAS components both favoring Group A with a moderate effect size suggest a beneficial effect of BLT in reducing outwardly directed expressions of aggression in bipolar depression. Unex-

pectedly, no effect of BLT was observed on Self-directed aggression, highlighting an avenue for future research to explore targeted interventions for this aspect of aggression in BD when comorbid with alcohol misuse.

The notable association between anger attacks and the diagnosis of a personality disorder, but not with irritability or psychomotor agitation, despite their association with each other, suggests a more nuanced relationship between these symptoms and underlying personality characteristics.

It is conceivable that anger attacks may partly arise from a more enduring predisposition, which is exacerbated by the acute mood dysregulation seen in bipolar depression particularly when comorbid with alcohol misuse.

The observed association between previous violent behavior and current episodes of irritability, psychomotor agitation, and anger attacks represents a finding of considerable clinical interest. The strongest observed correlation between historical violence and present anger attacks, underscored by a moderate effect size, suggests a pattern where past behaviors potentiate the likelihood of future, similar responses to triggers.

The insight from these associations highlights the importance of historical behavior in informing current clinical assessments and pave the way for personalized treatment strategies that consider both past violent behaviors and personality configurations to mitigate the risk of aggression in BD.

In conclusion, our study underscores the complex nature of BD, identifying irritability, psychomotor agitation, and anger attacks as integral symptoms even during depressive phases. The observed effectiveness of BLT in alleviating these symptoms, including in cases with comorbid alcohol misuse, positions it as a promising and well-tolerated adjunctive therapy. The therapeutic implications of these findings suggest that BLT could be a valuable addition to comprehensive treatment plans, offering a new approach to managing the challenges of BD.

While the results of our study are encouraging, some limitations warrant consideration. The single inpatient setting of the study may affect the generalizability of our findings. Another limitation could be represented by the lack of a quantitative assessment specific for the symptoms of interest such as irritability, psychomotor agitation, and anger attacks. We opted against using placebo lights, considering the shared inpatient environment and the recognized influence of even dim lighting on circadian rhythms.

Conflict of interest statement

The Authors declare no conflict of interest.

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Author contributions

FA: conceptualization, methodology, investigation, original draft preparation, formal analysis; LF: methodology, investigation, reviewing and editing; VF: investigation, formal analysis, reviewing and editing; CC: project administration, supervision.

Ethical consideration

This study was approved by the Institutional Ethics Committee (IRCCS San Raffaele Hospital, Milan, Italy) (protocol number 10-06-SO).

The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki.

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