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DUAL PATHOLOGY: APPROACHES IN THE TREATMENT OF PATIENTS WITH BIPOLAR AFFECTIVE DISORDER AND ALCOHOL ADDICTION

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Abstract: Introduction: Bipolar Affective Disorder (BAD) and Alcohol Use Disorder (AUD) are common causes of psychopathology in today's society. In terms of treatment, low adherence is a major obstacle and can lead to high levels of residual symptoms, which are associated with frequent relapses, withdrawal symptoms, poorer quality of life, and increased suicide risk. **Objectives:** To explore treatment approaches for patients with BAD and alcohol addiction, analyzing their respective therapeutic interventions, as well as highlighting and discussing the interventions and effectiveness of these treatments in individuals. **Methodology:** The MedLine database was used to search for articles with the keywords "Alcohol," "bipolar disorder," and "treatment." Based on the inclusion criteria: text availability, review articles, systematic reviews, meta-analyses, publications within the last 14 years, and works in English, French, and Dutch, 8 articles were eligible for this review. **Results:** The effectiveness of medications such as valproate and lamotrigine was observed, especially when combined with psychosocial interventions, to reduce alcohol consumption and improve BAD symptoms. Quetiapine was noted as promising for treating psychiatric symptoms, while the lithium-valproate combination was effective in reducing alcohol use and preventing relapses. **Conclusions:** The association between BAD and AUD poses a significant challenge to clinical practice. The reviewed studies indicate that the combined use of valproate and lithium enables better outcome control.

Keywords: Bipolar affective disorder, alcohol use disorder, treatment, comorbidities.

INTRODUCTION

Bipolar Affective Disorder (BAD) and Alcohol Use Disorder (AUD) are individually common causes of psychopathology in today's society. The combination of BAD and AUD represents a significant portion of the population, although often underestimated. In the United States, nearly half of bipolar patients face alcohol abuse problems at some point in their lives. The coexistence of these disorders increases the risk of complications, such as longer withdrawal symptoms, intensified manic and depressive episodes, increased suicide risk, poorer prognosis, higher treatment costs, increased cognitive deficits, and reduced quality of life (Farren, et al., 2012) (Spijker, et al., 2018) (Azorin, et al., 2010).

The development of AUD and BAD can follow different patterns. In some cases, alcohol use may precede BAD, while in others, alcohol is used as a form of self-medication for bipolar symptoms. In genetic terms, both BAD and AUD have strong hereditary components. There are common neurochemical abnormalities between the two disorders, especially in the serotonin and dopamine pathways, suggesting similar pathology between BAD and AUD. Furthermore, the comorbidity between bipolar disorder and alcohol abuse is still underdiagnosed, which can lead to inappropriate medication use (Farren, et al., 2012) (Azorin, et al., 2010).

Factors such as the higher symptom burden of Substance Use Disorders (SUD) in adults with BAD, medical care costs, and the social costs generated by this population highlight the need and importance of identifying risk factors for dual diagnosis—psychiatric disorder with substance abuse—and effective approaches to managing these disorders (Secades-Álvarez, et al., 2017) (Messer, et al., 2017).

Challenges for effective therapeutic intervention include identifying and diagnosing bipolar disorder in patients with SUD, engagement in treatment, choosing appropriate pharmacotherapy and psychotherapy, and managing treatment phases (detoxification, control of acute bipolar episodes, and maintenance). These challenges underscore the need for an integrated treatment model, not focused solely on a single disease. (Salloum, et al., 2016) Genetic studies and molecular mechanism research have helped better understand the link between bipolar disorder and alcohol abuse. Subgroups of patients may respond better to certain treatments due to specific genetic characteristics, which may guide future studies (Azorin, et al., 2010).

In terms of treatment adherence, issues such as stigma and resistance to treatment by patients and their families can negatively impact outcomes. Low adherence is a major obstacle and can lead to high levels of residual symptoms, which are associated with frequent relapses (Salloum, et al., 2016).

OBJECTIVE

To explore various treatment approaches for patients with bipolar affective disorder and alcohol addiction, analyzing their respective therapeutic interventions, as well as highlighting and discussing the interventions and effectiveness of these treatments in individuals.

METHODOLOGY

A systematic review was conducted through searches in the MedLine database, using the MeSH (Medical Subject Headings) descriptors: "Alcohol," "bipolar disorder," and "treatment," applying the Boolean operator AND to combine the terms. On September 26, 2024, the search was conducted, initially resulting in 1,842 publications.

The selection process of the articles was carried out by the group members, who applied a filtering process based on the following inclusion criteria: text availability (full text),

article type (review, systematic review, meta-analysis), publication date (last 14 years), and language (English, French, and Dutch). After applying the criteria, 170 articles remained.

The titles and abstracts of the articles were analyzed and subjected to a thorough reading, resulting in the exclusion of reviews, systematic reviews, and meta-analyses, whose main focus did not align with the objective of this review. In the end, 8 articles were considered eligible and included in this review.

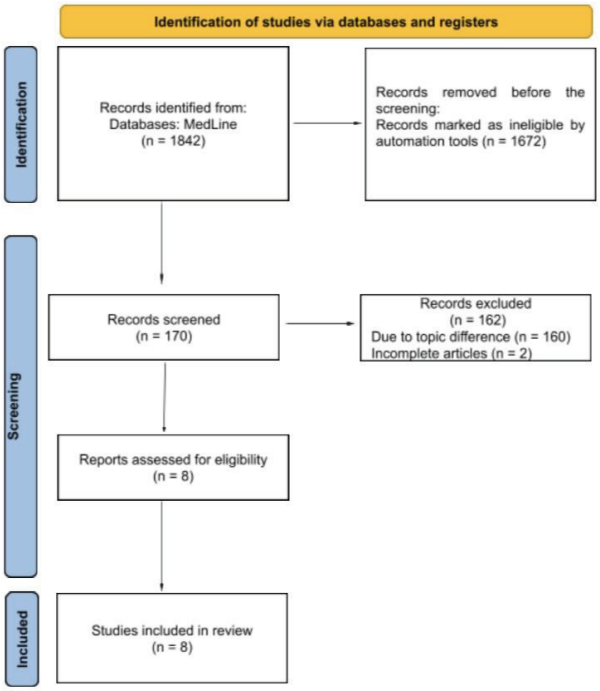

Figure 1: Study selection flowchart.

Source: Prepared by the authors, based on the articles read

RESULTS

This review was organized into three categories of studies: those addressing exclusively psychosocial treatment (Table 1), those focusing solely on medication treatment (Table 2), and finally, studies exploring combined approaches involving both psychosocial and pharmacological treatment (Table 3).

Gold et al. (2018) and colleagues analyzed 8 trials published in PubMed and PsycINFO, mainly randomized trials focusing on Integrated Group Therapy (IGT) as a therapeutic measure for Substance Use Disorders (SUD) and Bipolar Affective Disorder (BAD). IGT targets adults aged 18 to 65, with 20 weekly 60-minute sessions addressing topics such as identifying triggers that precede substance use, relationships with friends and family, refusing drugs and alcohol, coping with bipolar affective disorder (BAD) without abusing substances, among others. The program is structured so that individuals can join at any point in the treatment within a clinical setting. It was found that the efficacy of IGT in reducing substance use in the treatment of BAD was moderate. This was due to the ineffectiveness of all the reviewed trials that aimed to treat both symptoms, raising the hypothesis that the treatment should be staged. It is important to note that continuous research on psychosocial treatments is limited by the challenges associated with conducting intervention research in this population.

Gold et al. (2018) also assessed the effectiveness of two randomized studies on Cognitive Behavioral Therapy (CBT) for BAD and AUD: The first study was a 12-week program with an emphasis on relapse prevention, while the other was a 24-week value-based program that incorporated Acceptance and Commitment Therapy (ACT), combined with telephone monitoring. However, both treatments showed no advantage over control treatment in reducing substance use, although there were encouraging signs of beneficial effects on mood in the evaluated treatment.

It was found that psychosocial treatments validated for BAD can bring benefits in terms of mood and addiction, but only when correlated with psychiatric drug treatment (a feature of all the intervention trials reviewed). (Gold et al. 2018) .Psychiatric medications, such as valproate, citicoline, and naltrexone, were used in the randomized trials. Nevertheless,

Study (Author, Year)	Country	Study design	Reasearch tool	Nature
Alexandra K Gold, 2018	United States of America	Systematic review	PubMed e PsycINFO	No conflict of interest
Thomas Messer, 2017	Germany	Systematic review and meta analysis	PubMed, EMBASE, OVID, Cochrane, Scopus e Comprehensive Meta-analysis 2.0	No conflict of interest
Connor K Farren, 2012	Irland	Systematic review	Not reported	Not reported.
Study (Author, Year)	**Sample**	**Nature of trauma**	**Objective**	**Conclusions**
Alexandra K Gold, 2018	Patients with bipolar disorder and alcohol use disorder	Psychiatry pathology	Analysis of psychosocial interventions in patients with Bipolar Affective Disorder (BAD) and Alcohol Use Disorder (AUD)	None of the randomized clinical trials provided consistent evidence for managing both mood symptoms and substance use, although Integrated Group Therapy (IGT) demonstrated consistent beneficial effects on substance use outcomes. Other treatments showed benefits for mood symptoms, but without impact on alcohol or illicit substance use.
Thomas Messer, 2017	Patients with bipolar disorder and substance abuse disorder	Psychiatry pathology	Identify the main determining factors for Substance Use Disorders (SUD) in adults with Bipolar Affective Disorder (BAD)	SUD is not related to age, BAD subtype, hospitalization, or the coexistence of anxiety disorders or psychotic symptoms. It directly affects the clinical course, psychopathology, and prognosis in individuals with BAD.
Connor K Farren, 2012	Patients with bipolar disorder and alcohol use disorder	Psychiatry pathology	Examine the importance of BAD and AUD	There are few integrated treatment programs and therapeutic guidelines.

Table 1: Summary of studies on psychosocial interventions targeted at patients with Bipolar Affective Disorder (BAD) and Alcohol Use Disorder (AUD)

Source: Prepared by the authors, based on the articles read.

for a subsequent abstinence phase, additional psychosocial treatments may be necessary for BAD to improve mood and functionality in individuals. Lastly, it was observed that other treatments showed benefits for mood symptoms but did not impact alcohol or illicit substance use.

Messer et al. (2017), through a meta-analysis review using a random-effects model, did not confirm "age" as a significant risk factor for predicting substance use disorders (SUD) in patients with bipolar affective disorder. (P: 0.157, Z: -1.416, Variance: 0.013 [95% CI: -0.384–0.062], Standardized Mean Difference: -0.161). Nevertheless, his meta-analysis did not show a significant relationship between the BAD subtype and the risk of SUD among the affected individuals (Odds Ratio: 1.201 [95% CI: 0.703–2.053], Z: 0.669, P: 0.503). Additionally, male gender was a significant risk factor for SUD in patients diagnosed with BAD (Odds Ratio: 2.191 [95% CI: 1.121–4.281], Z: 2.294, P 0.022). However, the meta-analysis failed to demonstrate a significant relationship between the BAD subtype and the risk of SUD in affected individuals (Odds Ratio: 1.201 [95% CI: 0.703–2.053], Z: 0.669, P: 0.503).

The same meta-analysis searched for the coexistence of "any anxiety" as a risk factor for SUD in the selected studies. The findings do not support the significant predictive value of

comorbid anxiety in determining the risk of SUD in BAD patients (Odds Ratio: 1.195 [95% CI: 0.516-2.77], Z: 0.416, P: 0.678). Moreover, a higher number of manic episodes is significantly associated with an increased risk of substance use among patients with BAD (P: 0.001). Thus, the number of elevated phases (manic episodes) is an important risk factor for SUD (Standardized Mean Difference: 0.202 [95% CI: 0.078-0.327], Variance: 0.004, Z: 3.192) (Messer et al., 2017).

Additionally, the combined meta-analysis of the data extracted from the selected studies revealed a significant association between suicide attempts and the risk of SUD in BAD patients (P: 0.008), and this association can be interpreted as a mutual correlation. On the one hand, the presence of suicidal ideation may increase the risk of SUD; on the other hand, SUD may worsen suicidality in BAD patients. In conclusion, the analysis suggests a significant association between suicidality and the risk of SUD in BAD patients (Odds Ratio: 1.758 [95% CI: 1.156-2.674], Z: 2.637, P: 0.008) (Messer et al., 2017).

Azorin et al. (2010) reviewed clinical trials on the efficacy and tolerability of medications in bipolar disorder and comorbid alcoholism. Priority was given to randomized trials comparing medications with placebo or similar treatments.

Valproate is a drug used for the management of epilepsy, bipolar disorder, and migraine prevention. There was evidence of the efficacy of valproate in reducing excessive alcohol consumption in bipolar patients participating in a 24-week open-label study with 20 patients diagnosed with bipolar affective disorder with alcohol dependence (n = 10) or dependence on other stimulants (n = 10). As a result, participants halved the number of days of substance use (17.1 vs. 9.7 days) compared to the month prior to treatment with valproate, although the difference was borderline statistically significant (P = 0.07). It was found that valproate (extended-release sodium divalproate) promotes abstinence in newly abstinent alcoholics with comorbid mood and anxiety disorders. These authors conducted a 12-week double-blind, placebo-controlled clinical trial with valproate in 32 of these patients (Azorin et al. 2010). Patients with high anxiety scores were less likely to relapse into alcohol dependence if they were in the valproate treatment group (P = 0.017). In addition to promoting abstinence, valproate treatment improved psychiatric symptoms in alcohol-dependent individuals with more severe mood and anxiety symptoms.

Quetiapine is an atypical antipsychotic used to treat mood symptoms in bipolar disorder. The 2008 study analyzed by AZORIN J. et al. lasted 16 weeks with quetiapine in 28 alcohol-dependent subjects with high levels of mood and behavioral instability, including 16 patients with BAD. Quetiapine significantly reduced alcohol consumption (43% of patients remained completely alcohol-free during the study), alcohol cravings, and the intensity of psychiatric symptoms (HDRS and BPRS), while maintaining a good level of tolerability (Azorin, et al., 2010).

Risperidone: No significant differences were found between the use of extended-release valproate and risperidone in bipolar patients with substance use disorder.

Olanzapine: Valproate was superior to olanzapine in preventing relapses into alcoholism in women but not in men in the analyzed studies.

Gabapentin: No randomized studies on gabapentin in BAD and AUD were found in the literature.

Topiramate: No randomized studies on topiramate in BAD and AUD were found in the literature.

Naltrexone is effective in alcohol dependence; however, its safety and efficacy are not established in patients with BAD and AUD (Azorin, et al., 2010).

Study (Author, Year)	Country	Study design	Research tool	Nature
A.T. Spijiker, 2018	Germany	Systematic review	PubMed, Embase e Psychinfo	No conflict of interest
Jean-Michel Azorin, 2010	Canada	Systematic review	PubMed, Scirus, EMBASE, Cochrane Library, Science Direct	No conflict of interest

Study (Author, Year)	Sample	Nature of trauma	Objective	Population	Conclusions
A.T. Spijiker, 2018	Patients with bipolar disorder and alcohol use disorder	Psychiatry pathology	Provide an overview of recent literature on the diagnosis and treatment of BAD and AUD	Adults with both AUD and BAD	The combination of sodium valproate and lithium as the basis of treatment showed better outcomes.
Jean-Michel Azorin, 2010	Patients with bipolar disorder and substance abuse disorder	Psychiatry pathology	Analysis of pharmacotherapy in patients with BAD and AUD	Adults with both AUD and BAD	Therapeutic benefit of valproate for the prevention and reduction of excessive alcohol consumption. The efficacy of topiramate should be investigated.

Table 2: Summary of studies on pharmacological interventions targeted at patients with Bipolar Affective Disorder (BAD) and Alcohol Use Disorder (AUD).

Source: Prepared by the authors, based on the articles read.

Study (Author, Year)	Country	Study Design	Research tool	Nature
Ihsan M. Salloum, 2017	United States of America	Systematic review	MEDLINE, PubMed, WEB OF SCIENCES	No conflict of interest
Adrián Secades-Álvarez, 2015	Spain	Systematic review	Medline e PsycINFO	No conflict of interest
Glenn E Hunt, 2016	Australia	Systematic review and meta-analysis	Medline, EMBASE, psychINFO and CINAHL	No conflict of interest

Study (Author, Year)	Sample	Nature of trauma	Objective	Population	Conclusions
Ihsan M. Salloum, 2017	Patients with bipolar disorder and alcohol use disorder	Psychiatry pathology	Analysis of treatment studies for BAD and AUD	Adults with both AUD and BAD	There is a very limited number of pharmacotherapy interventions and an even smaller number of psychosocial interventions.
Adrián Secades-Álvarez, 2015	Patients with bipolar disorder and substance abuse disorder	Psychiatry pathology	Analysis of different psychological and pharmacological interventions	Adults with both AUD and BAD	Quetiapine and valproate showed the best outcomes in improving psychiatric symptoms. Psychoeducation and group therapies have yielded favorable results in reducing withdrawal symptoms.
Glenn E Hunt, 2016	Patients with bipolar disorder and substance abuse disorder	Psychiatry pathology	Estimate the prevalence rates of patients with AUD and BAD in both inpatient and outpatient settings	Adults with both AUD and BAD between 1990-2015	High prevalence of patients with AUD and BAD in hospital and community samples. The prevalence of SUD was similar in patients with bipolar I and bipolar II disorders.

Table 3: Summary of studies on psychosocial and pharmacological interventions targeted at patients with Bipolar Affective Disorder (BAD) and Alcohol Use Disorder (AUD).

Source: Prepares by the authors, based on the articles read

Secades-Álvarez et al. (2024) analyzed 30 experimental studies of various methodologies, in which 19 experimental studies met the required methodological criteria, with 19 referring to pharmacological treatments and 11 to psychological treatments. In these studies, a pre-post assessment was conducted with follow-ups ranging from 2 months to 5 years, with alcohol being the most frequently consumed drug, followed by cocaine, cannabis, and methamphetamine. Thus, the efficacy of valproate and lamotrigine in reducing alcohol consumption and other drugs in patients with BAD was observed. Still, for alleviating psychiatric craving symptoms, quetiapine, particularly, as well as risperidone or olanzapine

also showed good results. However, citicoline demonstrated an ability to address these symptoms while promoting greater treatment adherence, although the results are not confirmed by other literature. In studies involving patients with rapid cycling bipolar disorder, where lamotrigine was ineffective, classical treatment with lithium proved effective concerning psychiatric symptomatology.

In this way, Secades-Álvarez et al. (2024) stated that, based on the analyzed studies, quetiapine appeared to be the most promising medication for improving psychiatric symptomatology in bipolar affective disorder, while the lithium-valproate combination is the most effective for reducing alcohol consumption and preventing relapses. Furthermore, regarding psychological interventions, which are quantitatively more scarce than pharmacological ones, it is valid to assert that they are tested in more modest studies, with greater methodological limitations and high dropout rates. When comparing different psychological interventions, it was observed that Integrated Group Therapy (IGT) for the community is more effective than drug counseling IGT. However, both drug counseling and integrated group therapy show apparent efficacy in addressing bipolar affective disorder.

The study by Salloum et al. (2017) reviewed 16 treatments for Substance Use Disorders (SUD) in patients with associated bipolar disorder. Three psychotherapy trials and 13 pharmacotherapy trials were conducted. The medications evaluated included lithium carbonate, valproate, lamotrigine, topiramate, naltrexone, acamprosate, disulfiram, quetiapine, and citicoline. It was observed that valproate and naltrexone, in particular, are related to a decrease in alcohol consumption, while citicoline shows results related to a decrease in cocaine use and improvement in cognition.

Hunt et al. (2016) conducted a systematic review of 151 articles on the comorbidity rates of substance-related disorders in patients with bipolar disorder. The review indicates a higher risk of SUD in men compared to women. Furthermore, it was observed that the types of substance-related disorders most prevalent among patients with bipolar disorder were: alcohol use (42%); cannabis use (20%); and use of other illicit drugs (17%); Additionally, an earlier onset of bipolar disorder was reported in substance-using patients.

DISCUSSION

The association between BAD and SUD, particularly alcoholism, presents a significant challenge to clinical practice, requiring the integration of therapeutic approaches due to the complexity of this dual condition. The reviewed studies indicate that the concomitant use of valproate and lithium results in better outcomes, especially regarding psychiatric symptoms, but also as a viable option for the prevention and reduction of excessive alcohol consumption in patients with BAD. These findings support the need to utilize different combined approaches for managing both bipolar disorder and substance abuse (Azorin, et al., 2010).

Similarly, the use of quetiapine in combination with valproate has also proven effective in controlling psychiatric symptoms of BAD in cases of alcohol abuse. In parallel, other therapeutic interventions, such as group therapy and psychoeducation, have shown to be favorable in reducing withdrawal symptoms and supporting patient recovery. However, it is important to highlight the existence of few pharmacotherapeutic intervention studies and an even smaller number of adequately studied psychosocial approaches, which calls for the development of more robust research protocols (Azorin, et al., 2010).

Despite advances in pharmacological treatments, the studies still do not provide robust evidence for managing mood symptoms or substance use, although group therapy has shown positive results in relation to substance abuse. However, other treatments, while effective in improving mood symptoms, have not demonstrated significant impact on alcohol consumption, reaffirming the complexity of treating these comorbidities (Secades-Álvarez, et al., 2024)

It is evident that SUD is not directly related to age, the subtype of bipolar disorder, hospitalization, or the coexistence of anxiety disorders or psychotic symptoms, but it does directly affect the clinical course, psychopathology, and prognosis of patients. The high prevalence of patients with SUD and BAD in both hospital and community samples is alarming and reinforces the need for more effective and targeted interventions for this population. The similar prevalence of SUD among patients with bipolar I and II disorders also highlights the universality of this comorbidity, regardless of the subcategory of bipolar disorder (Mellick et al 2023).

Some study limitations were observed in the results of the reviewed studies. Firstly, there is difficulty in comparing types of interventions due to the divergence in the analyzed samples and different classifications of disorder severity. The studies suggest that the analysis of patients with BAD and SUD in association with other psychiatric disorders could alter the results related to symptom severity (Swann., et al., 2018). One of the studies describes greater impulsivity and obsessive--compulsive desire for alcohol in patients with bipolar disorder (BPD) and substance use disorder (SUD). According to the author, this is related to exacerbations of existing symptoms and the occurrence of other psychiatric disorders (Mellick et al 2023).

In spite of these limitations, the studies demonstrate the importance of combined treatment involving psychotherapeutic approaches and pharmacological interventions. These limitations, the studies demonstrate the importance of combined treatment involving psychotherapeutic approaches and pharmacological interventions. Of particular note is the benefit of cognitive-behavioral therapy (CBT) in mood stabilization and reducing alcohol consumption when complementary to medication therapy, as described in the article by Duncan et al. (2023).

The analysis of the reviewed articles led to the conclusion that, although the intervention combining medication and psychotherapy is indicated, there are currently no established treatment guidelines for this comorbidity, a fact that reveals the complexity of the treatment strategies currently used in patients with BAD and SUD.

CONCLUSION

It is evident that there remains a significant gap in the development of integrated treatment programs and specific therapeutic guidelines for patients with bipolar disorder and comorbid substance use disorders. Continued research focusing on combined and personalized therapeutic approaches is essential for advancing the management of these patients, aiming for better clinical outcomes and a substantial improvement in quality of life.

The development of more structured and evidence-based therapeutic protocols is crucial for the effective treatment of this population, which requires comprehensive and continuous clinical care.

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