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Pharmacological Treatments for Mood Disorders with Comorbid Substance Use Disorders: Systematic Review and Meta-Analysis

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Abstract

Background: The relationship between vividness of Visual Mental Imagery (VMI) and factors such as age and gender is poorly understood. We developed a Chinese version of the Visual Vividness Imagery Questionnaire (VVIQ), labelled VVIQ-C, and assessed its reliability.

Methods: VVIQ-C was developed, and its reliability was assessed. Using the VVIQ-C, we investigated individual vividness differences in 1,015 Chinese participants and explored the proportions of low and high vividness scorers in teenager (< 18 years old), younger (18-29 years old) and middle-aged adults (30-60 years old) of different gender.

Results: The reliability of VVIQ-C is high. Also, there were no significant differences in VVIQ-C median scores across different age groups and genders. However, the distribution of low vividness and high vividness group varied across different age groups, and this variation differed between women and men.

Conclusions: There might be a potential impact of age and gender on VMI abilities in Chinese population.

Keywords: Pharmacological Treatments; Mood Disorders; Substance Use Disorders (SUDs); Comorbidity; Meta-analysis.

Introduction

Depressive disorders presented a significant public health issue due to increasing prevalence rates, and worse clinical course [1]. Over 280 million people are affected by depressive disorders (e.g., bipolar disorders and mood disorders) that lead to disability, poor quality of life, high suicide risk and functional impairments [2]. The incidence rate of bipolar disorders is reported to be 40-50 million all over the world [3]. Affected individuals suffer psychologically and emotionally from these mood disorders, and because these are recurrent and require long-term care, they also impose a heavy cost on healthcare systems [4]. The presence of comorbid substance use disorders (SUDs) presents a significant challenge to the clinical management of mood disorders [5]. Substance use disorders (SUDs) comorbid with mood disorders occur frequently. The global incidence rates of SUDs (using substance for at least three months) are reported to be 45% among adult population suffering from mood disorder [4, 5]. This comorbidity of psychological issues presents a complex interplay as the SUDs can worsen the symptoms (e.g., higher suicide risks) of mood disorders among adult population [6]. To self-medicate emotional discomfort, people with depression sometimes utilize substances like alcohol or illegal narcotics. Substance abuse, on the

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Chaudhry R, et al., J Psychiatry Psychiatric Disord 2025
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other hand, can cause or exacerbate mood disorders because of changes in neurochemistry or social repercussions [7]. Additionally, substance use can prolong or exacerbate manic or depressive episodes in bipolar disorder [8].

The pharmacological treatment of individuals with mood disorders comorbid with substance use disorders (SUDs) posed several clinical challenges [9, 10]. Among these pharmacological treatments, psychotropic drugs such as mood stabilizers (Lithium, Lamotrigine, valproic acid, and carbamazepine) [11, 12], atypical antipsychotics (Olanzapine and Risperidone) [13, 14], and antidepressants (sertraline and venlafaxine) [15] are frequently used to treatment patients of mood disorders comorbid SUDs. The dual effectiveness of other drugs, such as bupropion, naltrexone, acamprosate, topiramate, and atypical antipsychotics like quetiapine and aripiprazole, has been assessed, either by themselves or in conjunction with psychosocial therapies [16, 17]. Additionally, the addiction to substance may affect the adherence to treatment, pharmacokinetics and the potential for drug-drug interactions among patients with mood disorders [17]. Following these complications, pharmaceutical methods that concurrently target mood symptoms and substance use behaviors are being studied by several studies [18]. However, there is still disparity in the data and disagreement over the best pharmacological interventions for these people with dual diagnoses. Previous studies have reported the effectiveness of various pharmacological interventions for treatment of patients of mood disorders with co-occurring SUDs [19, 20]. Many of these review, although, are now out of date, have a narrow emphasis, or are only applicable to particular substance types or mental disorders [21]. Furthermore, a wider range of drugs and combination treatments have been assessed in more recent years by observational studies and more current randomized controlled trials (RCTs). By updating and expanding upon earlier syntheses, these new studies present a chance to give researchers and physicians more thorough, evidence-based recommendations. Thus, this systematic review and meta-analysis aims to evaluate the efficacy of pharmacological treatments in patients diagnosed with mood disorders and comorbid substance use disorders (SUDs).

Methods

Search Design

The "Reporting Items for Systematic Review and Meta-Analysis (PRISMA)" guidelines were used to perform this systematic review and meta- [22] according to research aims. This study analyzed previously published studies, so there is no need for an additional ethical review.

PICO Framework

This study used the Population Intervention Control Outcome (PICO) framework to design research question.

P (Population): Adults or adolescents diagnosed with mood disorders (e.g., major depressive disorder, bipolar disorder) with comorbid substance use disorders (SUDs), such as alcohol use disorder or drug dependence from last three months at least.

I (Intervention): Pharmacological treatments, such as antidepressants, mood stabilizers, antipsychotics, or medications for addiction (e.g., naltrexone, buprenorphine, acamprosate).

C (Comparison): Placebo, no treatment, treatment as usual or alternative pharmacologic interventions (e.g., SSRI vs. mood stabilizers).

O (Outcomes): Improvement in mood symptoms (e.g., depression, mania), Reduction in substance use/relapse, treatment retention, adverse effects and quality of life

Search Strategy

The PRISMA guidelines assisted in the selection of research articles related to the study aims. Three Electronic databases, PubMed, EMBASE, APA PsychNet and the Cochrane Library, were searched from inception to February 2025. The MeSH keywords used for search of research articles from PubMed ("Mood Disorders"[MeSH] OR "Depressive Disorder"[MeSH] OR "Bipolar Disorder"[MeSH]) AND ("Substance-Related Disorders"[MeSH] OR "Substance Abuse"[MeSH]) AND ("Drug Therapy"[MeSH] OR "Psychotropic Drugs"[MeSH] OR "Antidepressants"[MeSH] OR "Mood Stabilizers"[MeSH]) AND ("Comorbidity"[MeSH] OR "Dual Diagnosis"). Similar search strategy was used for other databases. The databases were searched from 2010 to April 2025. The search was restricted to English language. We carefully examined the reference lists of all previous systematic reviews and meta-analysis-based articles to search for further research articles.

Eligibility Criteria

The eligibility criteria were used to select and screen research articles after searching for research articles from electronic databases.

Inclusion Criteria:

Studies analyzed the patient population (>18 years) diagnosed of mood disorder comorbid with substance use (last three months)

Studies evaluated the effects of different pharmacological therapies such as naltrexone, buprenorphine, acamprosate, valproic acid and lithium

Studies tracking patient outcomes related to the improvement in mood symptoms

Primary research studies such as randomized controlled trials (RCTs)

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Chaudhry R, et al., J Psychiatry Psychiatric Disord 2025
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Studies with full text available and published in English language

Exclusion Criteria

Those studies were excluded:

Studies analyzing the patient population with other psychological disorders

Studies analyzing the patient population without substance use disorders (SUDs)

Studies analyzing patient receiving other therapies such as behavioral and psychological therapies

Studies based on systematic review, meta-analysis, comprehensive reviews, narrative reviews, case-control studies, and editorials

Studies published in other languages rather than English and non-full text papers.

Data Extraction

Two independent reviewers extracted the data to be placed in a pre-specified table. The studies obtained by the database search were entered into the EndNote library. Duplicates were excluded in the next step. The eligibility criteria were applied by reviewers in a blinded manner to all individual studies. Discrepancies were sorted by mutual agreement. Data related to demographic information, such as authors, year, country, study population, study design, study follow up and primary outcomes, such as improvement in mood symptoms were extracted (Table 1). Discrepancies were resolved by consulting with a third reviewer.

Risk of Bias Assessment

The risk bias of included RCTs' was evaluated using the Cochrane risk of bias tool. The six areas of selection bias, allocation concealment, blinding of participants, blinding of outcome assessment, selective reporting, and additional bias were used to assess the risk bias of the included research. The included studies were grouped into three categories based on their score or level: low risk, unclear, and high risk [23].

Statistical Analysis

The statistical analyses have been performed using the Review Manager Software (Cochrane Collaboration, version 5.4.0). Here, the whole collection of studies was thought of as a random sample from the set of all possible studies which is an assumption of the analysis and then the analysis was used to generalize to that population. Also, employing a random effects model, data from studies with the possibility of being heterogeneous was pooled, respectively. It was defined as statistically significant if P-value was less than 0.05. The level of heterogeneity was tested for by means of the I2 statistic, whereby I2 values in excess of 50% indicated that the observed heterogeneity was significant [24].

Results

Study Selection

The selection and screening of research articles related to the study aim "Pharmacological Treatments for Mood Disorders with Comorbid Substance Use Disorders (SUDs): An updated Systematic Review & Meta-analysis" was performed by following the PRISMA guidelines in this meta-analysis. Total of 18,300 records were generated after database searches and 5413 remained after removal of duplicates as well as non-full text. Total 2108 research articles were initially screened and 1854 papers were sought for retrieval. Only 454 papers were assessed for eligibility criteria, and the final number of research articles was 11. In total, this meta-analysis is based on 11 RCTs studies, as mentioned in Figure 1.

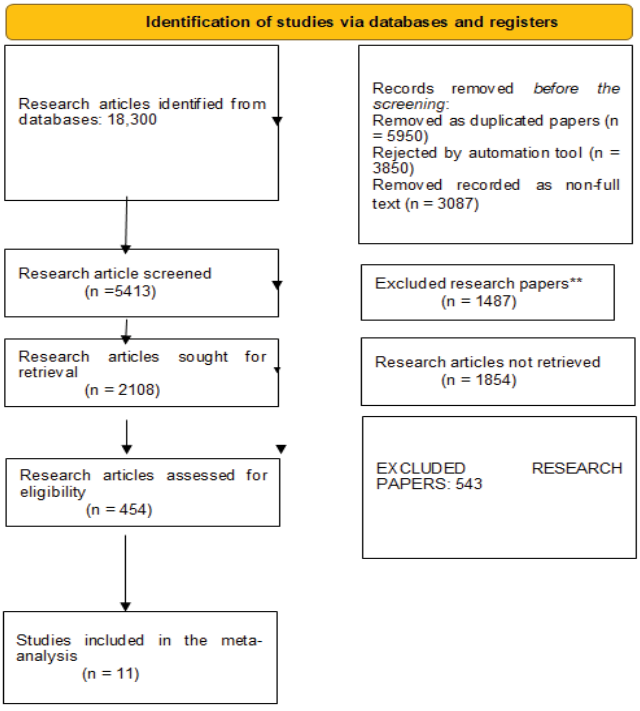

Figure 1: PRISMA Flow chart for screening and selection of included studies

Characteristics of Included Studies

Our study analyzed eleven randomized controlled trials (RCTs) and 1218 adult patients with mood disorder comorbid with substance use disorders (SUDs) (>18 years old) to evaluate the Pharmacological Treatments for Mood Disorders with Comorbid Substance Use Disorders (SUDs) through adopting meta-analysis research approach. The main characteristics of selected studies for pooled analysis have been presented in Table 1. All included studies have analyzed the patients with mood disorders comorbid SUDs having age ranged from 35.4 to 49 years. The number of patients with mood disorders comorbid SUDs ranged from 12 to 362

Chaudhry R, et al., J Psychiatry Psychiatric Disord 2025
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across eleven included studies. The study time period varied from 10 to 14 weeks. Among these studies, 4 RCTs reported the effects of pharmacological drugs among patients with bipolar disorder I & II and using cocaine as SUDs. One study reported the effects of pharmacological drugs among patients with mood disorders using cannabis. Other 6 RCTs reported the effects of pharmacological drugs patients among bipolar disorder I & II and using alcohol as SUDs, as mentioned in Table 1.

Table 1: Characteristic of Included Studies

Author, Year	Country	Study population (mean age)	Study Design	Study Follow up	Mood disorder & addiction disorder	Treatment	Mood scales used	Depression (HAM-D)	Manic Symptoms (YMRS)
Sylvia et al., 2016 [25]	USA	12 patients (43.6 years)	randomized, placebo-controlled trial	12 weeks	Bipolar I or II (*DSM-IV*) & Alcohol	topiramate	HAM-D and YMRS	T: 2.00 [−2.21, 6.21]	T: 2.80 [.41, 5.19]
		T: 5				150 mg		P: 0.72 [−7.54, 8.96]	P: .72 [−2.78, 4.20]
		P: 7							
Brown et al., 2015 [26]	Singapore	130 outpatients (42.6 years)	randomized, placebo-controlled trial	12 weeks	Bipolar I (*DSM-IV*) & Cocaine	Citicoline 2,000 mg/day	HAM-D and YMRS	T: 1.09 [0.11-2.09]	T: 1.80 [0.41-5.19]
		T: 61						P: 0.86 [-5.6-2.3]	P: 0.12 [−1.78, 3.20]
		P: 61							
Brown et al., 2012 [27]	Singapore	120 outpatients (45.1 years)	randomized, placebo-controlled trial	10 weeks	Bipolar II (*DSM-IV*) & Cocaine	**Lamotrigine**	HAM-D and YMRS		T: 1.50
		T: 55				400 mg/day			P: 0.19
		P: 57							
Tolliver et al., 2012 [28]	USA	33 adults (40.8 years)	randomized, placebo-controlled trial	14 weeks	bipolar I or bipolar II disorder & alcohol	Acamprosate 1998 mg/day	MADRS and YMRS	T: -3.8 [-3.4-6.5]	T: -1.7 [-2.9-4.5]
		T: 14						P: -1.1 [-3.2-2.89]	P: -0.6 [-2.3-1.8]
		P: 16							
Brown et al., 2010 [29]	Singapore	12 outpatients (43 years)	randomized, placebo-controlled trial	12 weeks	bipolar disorder & cocaine	Quetiapine	HAM-D and YMRS	T: -6.42 [-8.90-11.76]	T: -3.56 [-4.5-6.7]
		T: 7				400mg/day		P: -1.4 [-4.5-2.9]	P: -4.9 [-4.5-2.6]
		P: 5							
Pettinati et al., 2010 [30]	USA	170 outpatients (43.4 years)	Randomized, placebo-controlled trial	14 weeks	*DSM-IV* Alcohol dependence	sertraline (200 mg/day) plus naltrexone (100 mg/day)	HAM-D	T: -16	
		T: 42						P: -12	
		P: 39							
Raby et al., 2014 [31]	USA	140 outpatients (38 years)	Randomized, placebo-controlled trial	12 weeks	DSM-IIIR & cocaine	Venlafaxine 300 mg/day	HAM-D	T: -7.8 [-10.9-9.7]	
		T: 64						P: -4.5 [-5.6-7.8]	
		P: 66							

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Chaudhry R, et al., J Psychiatry Psychiatric Disord 2025
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Stedman et al., 2010 [32]	USA	362 outpatients (38.6 years)	Randomized, placebo-controlled trial	12 weeks	Bipolar I & Alcohol dependence	Quetiapine 300-800mg/d	HAM-D and YMRS	T: -4.39 (0.63)	T: -4.89 (0.44)
		T: 175						P: -4.17 (0.64)	P: -4.00 (0.43)
		P: 186							
Levin et al., 2013 [33]	USA	103 outpatients	Randomized, placebo-controlled trial	12-week,	DSM-IV & cannabis dependence	Venlafaxine	HAM-D	T: -7.42 (0.38)	
		T: 51						P: -1.17 (0.16)	
		P: 52							
Witte et al., 2012 [34]	USA	38 outpatients (49 years)	Randomized, placebo-controlled trial	12 weeks	DSM-IV & Alcohol dependence	Acamprosate 2000mg/d + escitalopram 10-30 mg/d	HAM-D	T: −5.6 ± 8.5 P: −7.8 ± 9.9	
		T: 12							
		P: 11							
Wang et al., 2010 [35]	China	98 patients (35.4 years)	Randomized, placebo-controlled trial	12 Weeks	Bipolar I & II	Lithium	MADRS & YMRS	T: –9.72 (11.16)	T: 2.17 (8.49)
		T: 18			alcohol	600 mg/d		P: –4.50 (13.08)	P: 2.11 (6.13)
		P: 18							

HAM-D: Hamilton Depression Rating Scale, **YMRS:** Young Mania Rating Scale, **MADRS:** Montgomery–Åsberg Depression Rating Scale

Risk of Bias Assessment

All included studies were randomized controlled trials (RCTs) in this analysis. The Cochrane tool was used for risk bias assessment of all included RCTs. The purpose of using this Cochrane tool was the evaluations of whole study's risk bias rather than methodological quality of each study. All included studies were low to moderate risk and no study was high risk, as mentioned in Figure 2 and Figure 3.

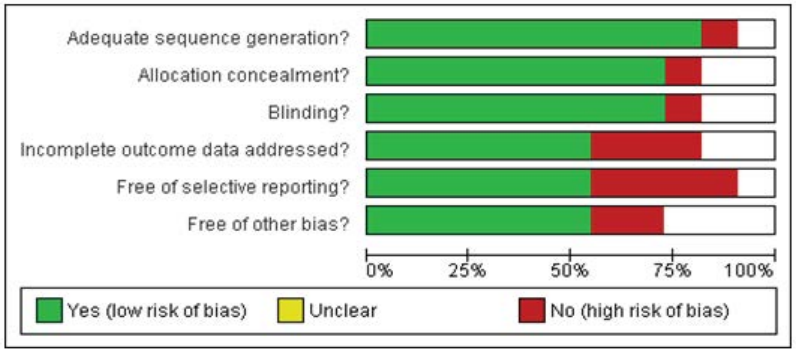

Figure 2: Risk of bias graph of included studies [26-35]

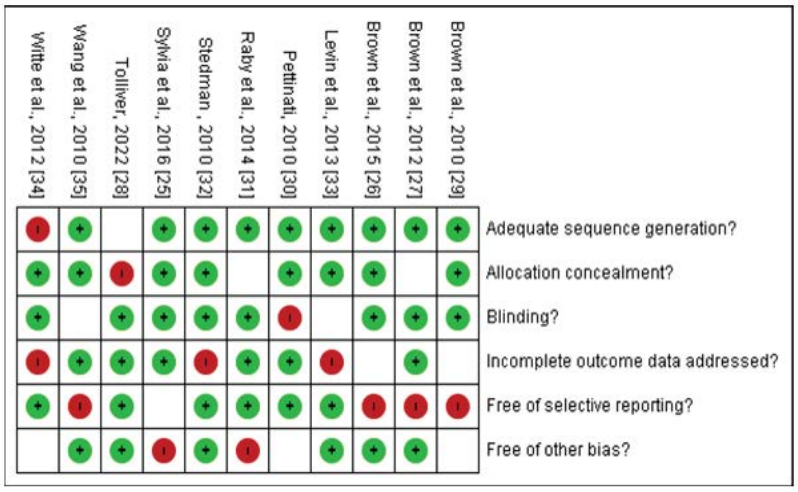

Figure 3: Risk of bias summary of included studies [26-35]

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Chaudhry R, et al., J Psychiatry Psychiatric Disord 2025
DOI:10.26502/jppd.2572-519X0247

PRIMARY OUTCOMES

Depression (HAM-D)

Among 11 included studies, 7 RCTs reported the mood symptoms through YMRS score as an outcome among patients with mood disorders comorbid with substance use disorder (SUDc) as compared to placebo. The bipolar + cocaine (MD = -2.39; 95% CI: -5.44 to 0.66; P = 0.13) and bipolar + alcohol (MD = -1.44; 95% CI: -3.51 to 0.62; P = 0.17) subgroups showed no statistically significant benefit, both with high heterogeneity (I^2 = 93%). In contrast, bipolar + cannabis showed a strong and significant effect favoring treatment (MD = -6.25; 95% CI: -6.36 to -6.14; P < 0.00001). The overall effect was non-significant (MD = -2.34; 95% CI: -5.07 to 0.39), with extreme heterogeneity (I^2 = 100%), as shown in Figure 4. The symmetrical distribution of studies on funnel plot showed low publication bias among included studies, as shown in Figure 5.

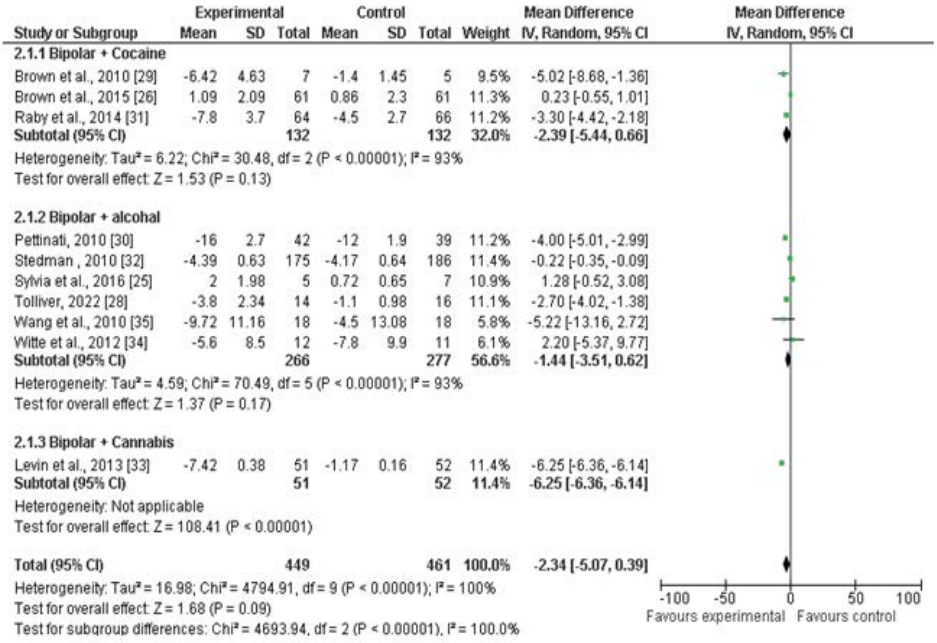

Figure 4: Forest plot of mean difference of depression (HAM-D) scores among patients receiving pharmacological drugs as compared to placebo [25,26,28-32,34,35]

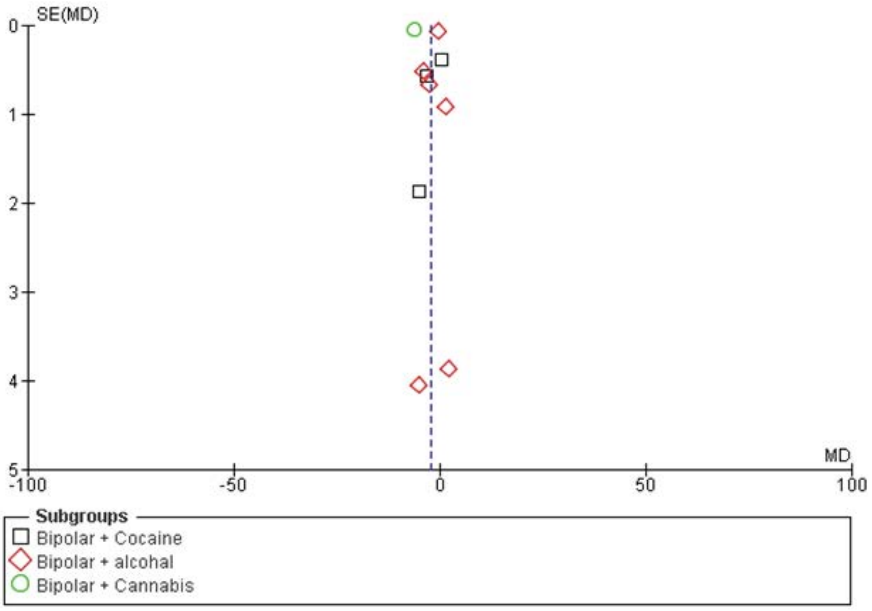

Figure 5: Funnel plot of mean difference of depression (HAM-D) scores among patients receiving pharmacological drugs as compared to placebo

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Chaudhry R, et al., J Psychiatry Psychiatric Disord 2025
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Mood or Mania Symptoms (YMRS)

Among 11 included studies, 7 RCTs reported the mood symptoms through YMRS score as an outcome among patients with mood disorders comorbid with substance use disorder (SUDc) as compared to placebo. In the bipolar + cocaine subgroup, treatment showed significant improvement over control (MD = 1.33; 95% CI: 1.08 to 1.58; P < 0.00001) and heterogeneity was zero (I^2 = 0%). Conversely, the bipolar + alcohol subgroup showed a negative mean difference favoring control (MD = -0.89; 95% CI: -0.98 to -0.80; P < 0.00001). However, the overall effect was non-significant (MD = 0.45; 95% CI: -0.89 to 1.79; P = 0.51) with high heterogeneity (I^2 = 98%), as shown in Figure 6. The symmetrical distribution of studies on funnel plot showed low publication bias among included studies, as shown in Figure 7.

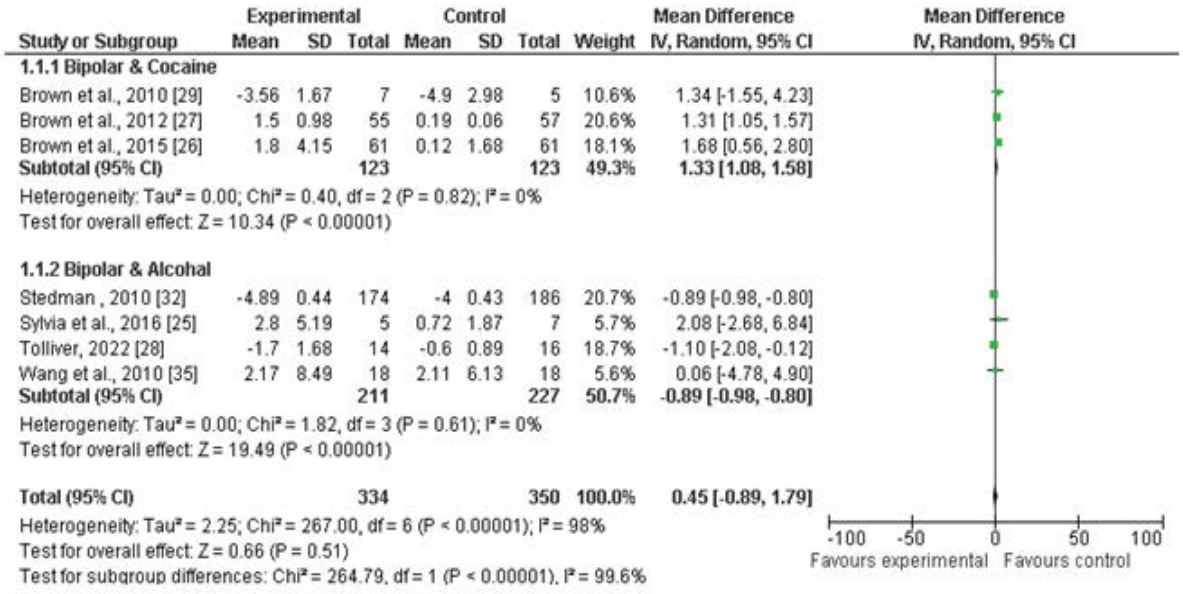

Figure 6: Forest plot of mean difference of depression (HAM-D) scores among patients receiving pharmacological drugs as compared to placebo [25-27,29,32,35]

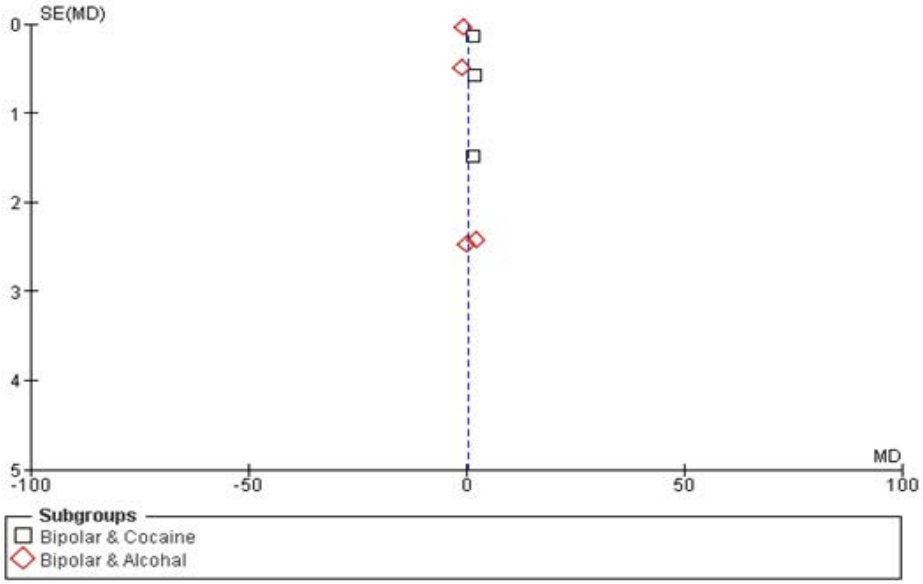

Figure 7: Funnel plot of mean difference of depression (HAM-D) scores among patients receiving pharmacological drugs as compared to placebo

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Chaudhry R, et al., J Psychiatry Psychiatric Disord 2025
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Discussion

This updated meta-analysis synthesized data from 11 randomized controlled trials (RCTs) involving 1,218 adult patients diagnosed with mood disorders comorbid with substance use disorders (SUDs), aiming to evaluate the effectiveness of pharmacological interventions in managing depressive and manic symptoms in this complex dual-diagnosis population. The findings provided a comprehensive understanding of effectiveness of pharmacological treatments across subtypes of mood disorders and substance addictions. The findings of this study reported that pharmacological treatments have mixed efficacy for both mood and depression symptoms. While the subgroup of patients with bipolar disorder and cannabis use disorder demonstrated a strong and statistically significant decrease in depression scores (MD = -6.25; 95% CI: -6.36 to -6.14; P < 0.00001), patients with bipolar disorder comorbid with either cocaine or alcohol use did not exhibit statistically significant improvements compared to placebo. This heterogeneity in results suggests that the type of comorbid substance plays a critical role in treatment response. However, high heterogeneity (I^2 = 100%) in the overall pooled effect of depression outcomes indicates considerable variability among studies in terms of interventions, populations, and methodologies. Similarly, the bipolar + cocaine subgroup showed a statistically significant improvement in mania symptoms, favoring the intervention (MD = 1.33; 95% CI: 1.08 to 1.58; P < 0.00001) with no heterogeneity (I^2 = 0%), indicating robust and consistent results across the included studies. However, the bipolar + alcohol subgroup showed a statistically significant difference in favor of the control (MD = -0.89; 95% CI: -0.98 to -0.80; P < 0.00001), again pointing toward the limited efficacy of pharmacological interventions in these patients. The overall mean difference in YMRS was statistically non-significant (MD = 0.45; 95% CI: -0.89 to 1.79). Another key observation from our meta-analysis is the low to moderate risk of bias across included studies, as assessed using the Cochrane risk of bias tool. Furthermore, the symmetrical funnel plot for HAM-D outcomes suggests low publication bias, increasing confidence in the reliability of the depression-related findings.

The findings of this meta-analysis are consistent with previous studies that reported the improvements in mood symptoms and depression after selective serotonin reuptake inhibitors (SSRI) in the treatment of depression, anxiety, and post-traumatic stress disorder among patients with substance use disorder [36]. Another study reported that pharmacologic treatments improved the alcohol use severity and depression symptoms among patients with SUDs [37]. Clinical practice of patients with mood disorder is significantly impacted by these findings. These emphasized the need of precision medicine in the care of patients with multiple diagnoses. Pharmacologic approaches that work for one subgroup (such as bipolar + cannabis) might not work as well for another (such as bipolar + alcohol or cocaine), hence tailored treatment programmes depending on the kind of SUD are required. Second, the data emphasize how crucial it is to combine behavioral and psychosocial therapy with pharmaceutical treatments, especially for subgroups that exhibit little to no pharmacologic effect. However, a number of limitations need to be noted. The HAM-D results' severe heterogeneity (I2 = 100%) suggests possible methodological variability, such as variations in dosage schedules, follow-up times, and evaluation instruments amongst trials. Some studies had modest sample sizes, which would have made it more difficult to identify meaningful effects. Additionally, adherence, relapse rates, and concomitant psychosocial therapies were not consistently evaluated in the included studies, which may have an impact on treatment results.

Conclusion

Overall, the findings of this study reported the effectiveness of pharmacological treatments in managing mood disorders comorbid with SUDs, with outcomes heavily influenced by the type of substance involved. The findings support a substance-specific approach to treatment planning and urge further excellent research to close current gaps. To achieve the best results in this difficult patient population, pharmacological and behavioural therapies must continue to be integrated.

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Chaudhry R, et al., J Psychiatry Psychiatric Disord 2025
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