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Original Research Article

Comparative effectiveness and safety of cariprazine and lamotrigine in patients of bipolar depression: a prospective, randomized and open label study

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ABSTRACT

Background: Bipolar disorder is marked by significant shifts in mood, energy, and behaviour. Cariprazine, a D3/D2 (dopamine) partial agonist, was FDA-approved in 2019 for treating bipolar depression, though clinical trial results have been mixed. Given this variability, the present study compared the effectiveness and safety of cariprazine monotherapy with lamotrigine in patients with bipolar depression.

Methods: Study was conducted for a total duration of 90 days comprising of 70 patients from either sex (18-65 years), diagnosed with bipolar depression. Patients were randomized into group A and group B homogeneously. Group A patients were given cariprazine monotherapy at 1.5 mg/day, which was increased to 3 mg/day on day 31st. Similarly, for group B, lamotrigine monotherapy was administered at 50 mg/day and the dose was increased to 100 mg/day on day 31st.

Results: Treatment significantly lowered MADRS in intra and intergroup comparison ($p < 0.001$). However, the p values differed for different time points on assessment of CGI-I despite being statistically significant ($p < 0.05$; $p < 0.001$). The prevalence of substance abuse in was reported to be 25%. SDS-S results for substance use were non-significant ($p > 0.05$). Group B reported more adverse events than group A.

Conclusions: Cariprazine led to faster and greater reduction in depressive symptoms than lamotrigine in bipolar I depression. Both were well tolerated with similar safety profiles. Substance use was low in both groups, with slightly better improvement in dependence scores seen with cariprazine.

Keywords: Bipolar depression, Cariprazine, Lamotrigine, Severity dependence scale

INTRODUCTION

Bipolar affective disorder, a multicomponent illness, involves severe mood disturbances, neuropsychological deficits, functional disturbances, immunological and physiological changes. Further, based on DSM-V criteria, bipolar disorder is classified into three subtypes: bipolar 1, bipolar 2 and cyclothymic disorder.¹ The lifetime prevalence as reported by epidemiological studies was reported to be around 2.4% in the general population, with an estimated prevalence being 0.6% and 0.4% for bipolar

disorder I and II respectively.² Multiple risk factors have been associated with the increased incidence and prevalence of bipolar disorder. These include factors such as age, sociodemographic variables, genetics, environment and substance misuse.³

Bipolar disorder can exhibit as depressive and manic episodes. Depressive episodes lie on the opposite spectrum of mania and are diagnosed when symptoms like intense sadness, loss of interest in activities, fatigue, feelings of worthlessness or guilt, difficulty concentrating and

suicidal intentions continue to last for at least two weeks. Whereas mania falls on the opposite spectrum with distractibility, increased activity or risky behaviour as some of its notable characteristics.

The diagnosis of bipolar depression is currently based on ICD-10. According to this a patient is identified as a case of bipolar depression when they meet at least the following five criteria, and essentially meet the first two criteria mentioned below in all cases. These are, feeling depressed, losing interest in daily activities with increased/decreased sleep/appetite, feeling hopeless, agitated, fatigued, worthless or immense guilt, self-harm/suicidal ideation and poor memory with difficulty concentrating.^{4,5}

The assessment of bipolar depression is commonly done using Hamilton depression rating score (HAM-D) which remains the gold standard for the measurement of treatment outcomes. Apart from this, other scales that are widely used are Montgomery-Asberg depression rating scale (MADRS), clinical global impression- improvement (CGI-I) and clinical global impression- severity (CGI-S).

The treatment of bipolar disorder involves two major components: psychotherapy and pharmacotherapy. Psychotherapeutic treatment consists of CBT (cognitive behavioural therapy), psychoeducation and functional remediation. The pharmacotherapeutic treatment for bipolar depression on the other hand, involves FDA approved drugs namely quetiapine, lurasidone and a combination of olanzapine + fluoxetine.⁶ Out of these drugs, the Central Drugs Standard Control Organization (CDSCO) in India has approved the use of quetiapine, lamotrigine and a combination of olanzapine + fluoxetine. In 2019, FDA approved a new drug called cariprazine for the treatment of depressive episodes in patients of bipolar depression which is an atypical second-generation antipsychotic that shows intrinsic activity at central dopamine D2 receptor and is a dopamine D3 receptor, serotonergic 5-HT1A receptor partial agonist and serotonergic 5-HT2A receptor antagonistic.⁷

A study by Earley et al, phase 3 trial, a double-blind, placebo-controlled study gave a contrasting result, showing that both 1.5 mg/day and 3 mg/day, dosages of cariprazine showed significant improvement in symptoms of depression, with a mean difference of -2.5 for cariprazine 1.5 mg/day and -3.0 for cariprazine 3 mg/day in comparison to placebo. Thus, concluding that cariprazine was a safe, effective drug in the treatment of bipolar I depression symptoms.⁸

However, in 2020, another phase 3, randomized, double-blind placebo-controlled study and showed a contrasting result, that the administration of cariprazine in the dose of 1.5 mg/day in patients of bipolar I depression reduced symptoms of depression on both primary efficacy parameters (MADRS, $p=0.0417$) and secondary efficacy parameters (CGI-S, $p=0.0417$). However, these differences were noted to be insignificant for cariprazine 3

mg/day. Common side effects noted were akathisia, restlessness, nausea and fatigue.⁹

Even though the mechanism of action of cariprazine makes it an attractive potential treatment to deal with the symptoms of bipolar depression, the data collected from various studies conducted so far using different doses of cariprazine have shown contradictory results in terms of its effectiveness. Also, there is little empirical evidence comparing cariprazine, a more recent antipsychotic approved by the FDA for bipolar I depression, to more well-known medications like lamotrigine. Thus, this study was aimed at assessing the relative effectiveness and safety of cariprazine compared to lamotrigine.

METHODS

This study was a comparative, prospective, randomized, open label, interventional study, conducted in the department of pharmacology, Government Medical College Amritsar, in collaboration with the department of psychiatry, Guru Nanak Dev Hospital, Amritsar, Punjab.

Study design and study populations

Based on ICD-10 and BDRS criteria, the study included 70 previously diagnosed cases of bipolar depression in the outpatient as well as inpatient department of department of psychiatry at Guru Nanak Dev Hospital. Patients aged 18-65 years, from either sex constituted the study and were randomly assigned into two equal groups using computer software, with group A receiving cariprazine monotherapy and group B receiving lamotrigine monotherapy. The study was conducted for a total duration of 90 days/3 months. The power of the study was 80% with an alpha error of 0.05 while predicting a 10% loss to follow-up.

Inclusion criteria

Patients previously diagnosed as cases of bipolar depression based on ICD-10 and BDRS, who provided a written informed consent.

Exclusion criteria

Patients with a history or current diagnoses of axis I disorders (post-traumatic stress disorder, eating disorder, dissociative disorder etc.) other than bipolar I disorder and substance use disorder. Patients of unipolar depression and those with 4/more mood episodes in the prior 12 months or any current psychiatric diagnoses apart from bipolar depression. Those that had a history of allergic, autoimmune disorders, any major cardiovascular, renal or hepatic comorbidities/diseases. Use of psychotropic drug except eszopiclone, zolpidem, zopiclone, chloral hydrate, or zaleplon (for insomnia), lorazepam (for agitation), or diphenhydramine, benztropine, or propranolol (for extrapyramidal symptoms). Women of childbearing potential having positive urine pregnancy test and patients not willing to give consent for the study.

Study groups

A total of 76 study participants were recruited and allocated randomly to two groups designated as groups A (n=39), B (n=37), to ensure an unbiased distribution of participants across the study arms. The randomization was done using a free computer-generated random allocation software. A total of 6 patients (4 from group A and 2 from group B) were lost to follow up due to non-compliance or adverse effects, so that 70 patients completed the study. Group A patients were administered with cariprazine monotherapy of 1.5 mg/day, orally for 30 days with the dose increased to 3 mg/day from 31st day onwards. In group B lamotrigine monotherapy was given, 50 mg/day orally for 30 days, increased to 100 mg/day from 31st day onwards.

After recording the demographic information and medical history of the patients, laboratory investigations, were conducted at day 0 and then again at day 90. Montgomery-Åsberg depression rating scale (MADRS) was evaluated on day 0, 15, 30, 60 and 90 and clinical global impressions-improvement scale (CGI-I) score was evaluated on day 15, 30, 60 and 90 respectively. The adverse events that the patients reported during the trial were noted and appropriately addressed on every follow up i.e. day 30, 60

and 90. Severity of dependence scale was assessed on day 0, 30 and 90 respectively to evaluate the impact of administered monotherapies on substance abuse in the enrolled patients.

Ethical consideration

All patients provided written informed consent after receiving a clear explanation of the study in an understandable language. The study followed good clinical practice guidelines and was approved by the institutional ethics committee at Government Medical College, Amritsar (IEC/GMCAMRITSAR/317/D-26/2022 Batch), and the study was registered with Clinical Trial Registry of India (CTRI/2024/03/064593).

RESULTS

Demographic characteristics

In this study it was observed that there was no significant difference ($p=0.88$) in the mean age of the patients. On comparison of the employment status, it was seen that 26 patients were employed while 44 patients were unemployed. A total of 39 females and 31 males participated in this study.

Table 1: Socio-demographic distribution of the participants in the study.

Demographic characteristics		Group A (n=35) (%)	Group B (n=35) (%)	Total
Age in years (mean±SD)		34.14±9.70	34.11±10.14	70
Employment status	Employed	9 (25.70)	17 (48.60)	26
	Unemployed	26 (74.30)	18 (51.40)	44
Gender	Female	22 (62.90)	17 (48.60)	39
	Male	13 (37.10)	18 (51.40)	31
Marital status	Married	19 (54.29)	15 (42.90)	34
	Unmarried	12 (34.28)	16 (45.71)	28
	Divorcee	1 (2.86)	0 (0.00)	01
	Widow (er)	3 (8.60)	4 (11.40)	07

On evaluation of the marital status of the patients enrolled in the study, it was observed that, 1 patient had a divorce, 34 were married, 6 were single, 22 were unmarried and 7 were widowed. These individuals were randomly distributed amongst the two groups (Table 1).

Routine investigations

Study parameters of both groups at baseline and day 90 (mean±SD) were comparable with statistically insignificant difference between the two groups ($p>0.05$) (Tables 1 and 2).

Efficacy parameters

The efficacy trends can be observed Intragroup and Intergroup on MADRS and CGI-I. Both groups A and B

reflected a continuous reduction of the mean MADRS Score over a period of 90 days of treatment which was statistically significant ($p<0.001$) at all the follow up points compared to baseline score. Though there is relatively more reduction in the cariprazine group (Table 3). When intergroup comparison is done in terms of mean percent change of MADRS score, group A (cariprazine) showed statistically significant reduction compared to group B (lamotrigine) after 30 days ($43.51\pm0.539:21.03\pm0.641$; $p<0.001$) when smaller doses of cariprazine and lamotrigine (1.5 mg and 50 mg respectively) were used. This trend was continued with the larger doses (3 mg and 100 mg respectively) after 90 days of treatment ($48.65\pm0.427: 36.09\pm0.838$; $p<0.001$). However, the relative magnitude of change was observed to be smaller in case of group A than group B with the larger doses ($8.91\pm0.885: 19.05\pm0.906$, $p<0.001$) (Table 4).

Table 2: Routine investigations of study participants at baseline and day 90.

Parameters	Group A (P value)	Group B (P value)
Hb (mg/dl)	0.52	0.19
TLC (cell/mm ³)	0.27	0.91
DLC (%)	Neutrophils	0.70
	Lymphocytes	0.77
	Monocytes	0.61
	Eosinophils	0.69
	Basophils	0.59
Fasting blood sugar (mg/dl)	0.68	0.64
SGOT (U/l)	0.84	0.57
SGPT (U/l)	0.89	0.86
Serum bilirubin (U/l)	0.87	0.99
Albumin (gm/dl)	0.88	0.51
Alkaline phosphatase (IU/l)	0.94	0.96
Serum creatinine (mg/dl)	0.82	0.74
Blood urea (mg/dl)	0.80	0.63

(TLC- total leucocyte count, DLC- differential leucocyte count, LFT- liver function tests, SGOT- serum glutamic oxaloacetic transaminase, SGPT- serum glutamic pyruvic transaminase).

Table 3: Change in MADRS score over 90 days of treatment in group A and group B.

MADRS Scores					
	Baseline	Day 15	Day 30	Day 60	Day 90
Group A (n=35) Mean±SE	33.43±0.22	27±0.29	18.89±0.25	18.17±0.25	17.17±0.22
P value	-	<0.001	<0.001	<0.001	<0.001
Group B (n=35) Mean±SE	33.37±0.28	29.37±0.26	26.37±0.34	23.37±0.26	21.37±0.40
P value	-	<0.001	<0.001	<0.001	<0.001

p>0.05: not significant *p<0.05: significant, **p<0.001: highly significant (p value: paired t-test).

Table 4: Comparative percentage change in MADRS scores between group A and group B at various follow-up points.

MADRS	Group A (n=35)	Group B (n=35)	P value
Percentage change (0-30) *	43.51±0.539	21.03±0.641	<0.001
Percentage change (0-90) **	48.65±0.427	36.09±0.838	<0.001
Percentage change (30-90) ***	8.91±0.885	19.05±0.906	<0.001

(*At day 30 of treatment from baseline; ** At day 90 of treatment from baseline; *** At day 90 of treatment from day 30 of treatment)

Table 5: Change in patient distribution from baseline during study duration based on CGI-I score (group A).

DAYS	Group A number of patients (%)			P value
	Much improved (CGI-I Score 2)	Minimally improved (CGI-I Score 3)	No change (CGI-I Score 4)	
15	28 (80)	7 (20)	-	-
30	34 (97.14)	1 (2.86)	-	<0.05
60	15 (42.86)	20 (57.14)	-	<0.01
90	5 (14.29)	30 (85.71)	-	<0.001

(p values calculates using Wilcoxon Signed Rank test) p >0.05: not significant; *p<0.05: significant; **p<0.001: highly significant (p value: Wilcoxon Signed Rank Test).

Group A showed significant improvement in CGI-I scores from day 15 to day 30 as well as day 60 (p<0.05), with statistically higher significance by day 90 (p<0.001) (Table 5). Group B shows statistically significant improvement

from day 15 to day 30 (p<0.05), reaching a statistically higher improvement by day 60 (p<0.001) and the trend continues being highly statistically significant by day 90 (p<0.001) (Table 6).

Table 6: Change in patient distribution from baseline during study duration based on CGI-I score (group B).

Days	Group B number of patients (%)			P value
	Much improved (CGI-I score 2)	Minimally improved (CGI-I score 3)	No change (CGI-I score 4)	
15	1 (2.86)	30 (85.71)	4 (11.42)	-
30	5 (14.29)	30 (85.71)	-	<0.01
60	24 (68.57)	11 (31.43)	-	<0.001
90	29 (82.86)	6 (17.14)	-	<0.001

Table 7: Frequency distribution of CGI-I score over 90 days of treatment.

Days	Group A (n=35) number of patients (%)			Group B (n=35) number of patients (%)			P value
	CGI-I score 2	CGI-I score 3	CGI-I score 4	CGI-I score 2	CGI-I score 3	CGI-I score 4	
15	28 (80)	7 (20)	-	1 (2.86)	30 (85.71)	4 (11.42)	<0.001
30	34 (97.14)	1 (2.86)	-	5 (14.29)	30 (85.71)	-	<0.001
60	15 (42.86)	20 (57.14)	-	24 (68.57)	11 (31.43)	-	<0.05
90	5 (14.29)	30 (85.71)	-	29 (82.86)	6 (17.14)	-	<0.001

Table 8: Comparison of adverse effects during the total duration of study period for groups A and B.

Adverse events	Group A cariprazine (total events reported)	Group B lamotrigine (total events reported)
Headache	2	0
Insomnia	2	1
Rash	0	3
Akathisia	4	0
Nausea	0	2
Dizziness	0	1
Restlessness	4	0

Table 9: Pattern of mean SDS scores of group A and B during study period.

Time point	Mean SDS score	
	Group A (cariprazine)	Group B (lamotrigine)
Day 0	7.67	7.42
Day 30	6.60	6.43
Day 90	5.60	6.43

(Mean SDS Score: Shows the average severity of dependence for the group at each time point. A lower score indicates improvement).

Comparative intergroup analysis with respect to CGI-I shows that group A (cariprazine) had a higher percentage of patients (80%) with better CGI-I scores (score 2 = “much improved”) compared to group B (lamotrigine) (2.86%) by the day 15 as well as by day 30 (97.14%; 14.29% respectively) ($p<0.001$). After increasing the dose (day 31), however, the trends seemed to reverse so that the percentage of patients showing better CGI-I score were comparatively lower in group A compared to group B (42.86%; 68.57% respectively; $p<0.05$) on day 60 as well as day 90 (14.29%;85.71% respectively; $p<0.001$) (Table 7).

Safety assessment

It was observed that the total number of adverse events reported by the patients in group A were 6 (17.14%) (1 had reported headache, 1 reported insomnia, 2 reported restlessness and 2 reported akathisia). Out of these 4

patients dropped out by the day 60 due to restlessness and akathisia. For group B total number of adverse events reported were 7 (20%) (2 reported nausea, 1 reported insomnia, 1 reported dizziness and 3 reported rash). Out of these 2 patients dropped by the day 60 due to rash (Table 8).

Substance use assessment

Out of the 76 participants recruited for the study, 19 individuals (12 from group A and 7 from group B) were identified with substance abuse. This corresponds to a prevalence rate of 25% among the total study population.

The mean SDS dropped from 7.67 at baseline to 5.60 at day 90 for group A reflecting a modest improvement in substance dependence severity, whereas the mean SDS score decreases from 7.43 at baseline to 6.43 at Day 30 and remains stable at day 90 for group b, indicating a slight

reduction in dependence severity (Table 9). When intergroup comparison is done in terms of mean percent change of SDS score, group A (cariprazine) showed no statistically significant reduction compared to group B (lamotrigine) after 90 days of treatment ($p>0.05$) (Table 10).

Table 10: Mean percentage change in group a and b during the total study duration.

SDS-S	Group A (n=12)	Group B (n=7)	P value
Percentage Change (0-90)	26.42±0.03	13.61±0.01	>0.05

DISCUSSION

Bipolar disorder, formerly known as manic depression, is marked by significant mood, energy, and activity changes, with bipolar depression representing its prolonged depressive phase. The primary management goal is mood stabilization and symptom reduction, typically achieved through medications such as lamotrigine, quetiapine, lurasidone, and more recently, cariprazine. The present study evaluated and compared the efficacy and safety of cariprazine and lamotrigine monotherapy in patients with bipolar I depression. The two groups were largely comparable in terms of demographic and baseline clinical characteristics, except for a higher proportion of females in the cariprazine group, which aligns with previous reports of female predominance in bipolar depression, as demonstrated by Vieta et al and supported by Watanbe and Hongo.^{10,11} The baseline severity of depression, assessed using the MADRS scale, was comparable across groups ($p>0.05$), eliminating potential selection bias and consistent with the findings of Earley et al and Peters et al. Cariprazine demonstrated a rapid and significant reduction in MADRS scores, with the most notable improvement observed by day 30 at a dose of 1.5 mg/day (18.89 ± 0.25 ; $p<0.001$). This finding is consistent with studies by Yatham et al and Earley et al, which reported significant antidepressant effects of both 1.5 mg and 3.0 mg/day of cariprazine, with a slightly greater effect at the lower dose.⁸ McIntyre et al further highlighted that the antidepressant response to cariprazine may be influenced by symptom profile, with patients exhibiting mild anhedonia responding better to 1.5 mg/day.¹² Lamotrigine, in contrast, produced a steady and dose-dependent reduction in depressive symptoms, with significant improvement noted by day 90 following escalation to 100 mg/day, consistent with earlier studies by Calabrese et al and McElroy et al.^{13,14} A comparative analysis revealed that while cariprazine resulted in a more pronounced reduction in MADRS scores during the initial 30 days, the effect plateaued following dose escalation, a trend supported by Earley et al and Durgam et al.^{8,15} In contrast, lamotrigine demonstrated a greater additional improvement following dose escalation, consistent with the findings of Geddes et al, highlighting its dose-dependent efficacy. Similar patterns were observed with

CGI-I scores, where cariprazine showed superior early improvement by day 15 and day 30 ($p<0.001$), reflecting its rapid onset of action. However, by day 60 and day 90, lamotrigine produced significantly greater improvements, surpassing cariprazine, consistent with its pharmacodynamic profile described by Brown et al and Bowden et al.^{16,17} The diminishing effect of higher cariprazine doses on overall improvement may be attributed to dopaminergic overstimulation, as suggested by Stahl et al and Chhatlani et al.^{18,19} Collectively, these findings emphasize that cariprazine offers relatively rapid symptom relief, particularly at lower doses, whereas lamotrigine provides a more gradual, sustained improvement, reinforcing the need to tailor pharmacological treatment according to the clinical phase and individual symptom profile of bipolar depression.

In terms of safety, group A (cariprazine) reported a total of six adverse events: headache (n=1), insomnia (n=1), restlessness (n=2), and akathisia (n=2), with four participants discontinuing treatment by day 60, primarily due to restlessness and akathisia. The onset of these adverse events following dose escalation is consistent with existing literature highlighting cariprazine's dose-dependent side effect profile. This trend aligns with clinical observations in bipolar I depression, where akathisia and restlessness frequently emerge within two weeks of dose increase and may resolve with dose reduction or supportive management, as reported by Durgam et al, Kiss et al, Earley et al, and Kane et al.^{8,20-22} The occurrence of transient headache at day 60 and insomnia by day 90 further reflects the findings of Earley et al, who identified these as known but generally manageable side effects of cariprazine.⁸ Notably, the clustering of adverse events around day 60 emphasizes the need for close clinical monitoring following dose escalation. While most side effects subsided by day 90, the dropout of four participants due to restlessness and akathisia underscores the clinical significance of these adverse events and the necessity for individualized management strategies during cariprazine therapy.

In group B (lamotrigine), no adverse events were reported during the initial 50 mg/day treatment phase, indicating good early tolerability. However, following dose titration to 100 mg/day, new side effects emerged, including nausea (n=2), insomnia (n=1), dizziness (n=1), and rash (n=3). Two participants discontinued treatment at day 60 due to rash, reinforcing the well-documented risk of cutaneous adverse reactions with lamotrigine, particularly during dose escalation. This pattern is consistent with the findings of Calabrese et al, who identified rash as the most frequent cause of treatment discontinuation, especially within the first two months of therapy.¹³ The appearance of rash in three participants in the present study, leading to two dropouts, mirrors these established concerns and highlights the need for vigilant monitoring during dose increases. Other adverse events, such as nausea, insomnia, and dizziness, were mild, infrequent, and consistent with prior reports by Geddes et al and the CEQUEL trial, which

identified these side effects as typically transient and rarely leading to treatment discontinuation.²³ Their delayed onset, primarily after dose escalation, further supports the dose-dependent nature of lamotrigine's side effect profile.

In the present study, 19 out of 76 participants (25%) had a documented history of substance abuse, reflecting the well-established association between bipolar I disorder and comorbid substance use disorders (SUDs). This prevalence aligns with earlier reports by Regier et al and Merikangas et al, who found lifetime SUD rates of 60% and 46.2%, respectively, among individuals with bipolar disorder.^{24,25} The heightened vulnerability of this population to substance use is well-supported by Swann, Brady and Sonne, and Salloum and Thase, who collectively attribute this to self-medication of mood symptoms, inherent impulsivity, risk-taking behaviors, and illness severity, including early onset, frequent mood episodes, suicidality, poor treatment adherence, and increased hospitalization rates.^{26,27} The severity of dependence scale (SDS), a brief self-report tool assessing psychological dependence, was used to monitor substance use severity. Participants with substance use, primarily involving alcohol and opioids, exhibited elevated SDS scores at baseline. A modest reduction in mean SDS scores was observed over 90 days of cariprazine treatment (1.5-3 mg/day), while only minimal improvements were noted with lamotrigine (50-100 mg/day). However, group comparisons revealed no statistically significant difference in mean percentage change in SDS scores ($p>0.05$), indicating limited impact of both drugs on dependence severity. These findings are consistent with existing literature, where authors such as Ambekar et al, Do et al, Vannucchi et al, and Pardossi et al have noted that while cariprazine may modestly reduce cravings through D2/D3 receptor activity and mood stabilization, its direct influence on substance dependence remains limited, particularly in high-burden regions like Punjab.²⁸⁻³⁰ Similarly, studies by Calabrese et al, Bowden et al, and Geddes et al suggest that lamotrigine improves mood symptoms but does not significantly reduce cravings or dependence severity, as reflected in the minimal SDS score reductions in this study.^{13,17,23} Collectively, these results indicate that although cariprazine and lamotrigine provide mood-stabilizing benefits in bipolar I depression, their role in managing comorbid substance use is limited, highlighting the need for adjunctive, targeted interventions for this complex patient population.

CONCLUSION

This study demonstrated that both cariprazine and lamotrigine are effective monotherapies for bipolar I depression, but cariprazine produced a faster and more substantial reduction in depressive symptoms. Both the drugs are generally well tolerated, though cariprazine seems to have a slightly better safety profile. Substance abuse was noted in 25 percent of the study participants and neither of the treatments demonstrated a statistically significant impact on substance abuse.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee of Government Medical College, Amritsar (IEC/GMCAMRITSAR/317/D-26/2022 Batch), and the study was registered with Clinical Trial Registry of India (CTRI/2024/03/064593)

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