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Original Research Article

Comparative Efficacy and Tolerability of Oxcarbazepine, Carbamazepine, and Lithium in the Treatment of Acute Mania

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Abstract

Background: Carbamazepine is an established mood stabilizer for the treatment of acute mania; however, its clinical use is often limited by adverse effects. Oxcarbazepine, a structural analogue of carbamazepine, has been suggested as a potentially better-tolerated alternative, though evidence regarding its efficacy in mania remains limited and inconsistent.

Objectives: To compare the efficacy and tolerability of oxcarbazepine with carbamazepine in patients with acute manic episodes, using lithium as an active control.

Methods: This randomized, open-label, lithium-controlled trial was conducted at a tertiary care government hospital. Ninety patients diagnosed with a manic episode as per DSM-IV-TR criteria and having a Young Mania Rating Scale (YMRS) score ≥20 were randomized in a 1:1:1 ratio to receive oxcarbazepine, carbamazepine, or lithium and were followed for six weeks. The primary outcome was adequate response, defined as a ≥50% reduction in YMRS score from baseline. Safety and tolerability were assessed using the Systematic Assessment for Treatment-Emergent Effects (SAFTEE) checklist along with clinical and laboratory monitoring. Statistical analysis was performed using SPSS version 16, with $p<0.05$ considered statistically significant.

Results: No patient in any treatment group achieved adequate response at one week. At two weeks, response rates remained low and were not significantly different among groups ($p=0.232$). At six weeks, carbamazepine (80.0%) and lithium (73.3%) demonstrated significantly higher response rates compared with oxcarbazepine (46.7%) ($p=0.015$). Oxcarbazepine was associated with fewer adverse effects, whereas carbamazepine showed significantly higher rates of blurred vision, benign leukopenia, and deranged liver function tests.

Conclusion: Oxcarbazepine was less effective than carbamazepine and lithium in the treatment of acute mania, although it demonstrated a more favorable tolerability profile.

Keywords: Acute mania; Oxcarbazepine; Carbamazepine; Lithium; Mood stabilizers.

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Introduction

Mania is a core clinical feature of bipolar I disorder and is frequently associated with significant functional impairment, behavioral dysregulation, and an increased risk of hospitalization. The lifetime prevalence of bipolar I disorder is approximately 1% in the general population, and manic episodes often constitute psychiatric emergencies requiring prompt pharmacological intervention [1].

The primary goals of treatment include rapid symptom control, prevention of complications, and minimization of adverse effects. Lithium remains one of the most extensively studied and effective agents for the treatment of acute mania as well as for maintenance therapy in bipolar disorder [2]. In addition to lithium, anticonvulsants such as valproate and carbamazepine have been widely used as mood stabilizers in the management of acute manic episodes [3]. Carbamazepine has demonstrated efficacy in acute mania and is approved for this indication; however, its clinical use is frequently limited by adverse effects including sedation, dizziness, hematological abnormalities, and hepatic dysfunction [4].

Oxcarbazepine, a keto analogue of carbamazepine, was developed to improve tolerability while retaining antimanic efficacy. Pharmacologically, oxcarbazepine has a mechanism of action similar to

carbamazepine, primarily involving voltage-gated sodium channel blockade, but it is associated with fewer drug–drug interactions and a lower risk of hematological toxicity [5]. Several studies and reviews have suggested that oxcarbazepine may be effective in mood disorders, including acute mania, and may offer a more favorable side-effect profile compared with carbamazepine [11]. However, findings across studies have been inconsistent, and oxcarbazepine is not currently approved for the treatment of mania.

Evidence from controlled clinical trials evaluating oxcarbazepine in acute mania remains limited, with some studies reporting comparable efficacy to established mood stabilizers, while others have demonstrated inferior response rates [9–12]. Given these conflicting findings and the clinical need for better-tolerated alternatives to carbamazepine, further evaluation of oxcarbazepine in acute mania is warranted.

The present study was designed to compare the efficacy and tolerability of oxcarbazepine with carbamazepine in patients with acute manic episodes, using lithium as an active control, in a real-world tertiary care setting and reported in accordance with established randomized trial reporting guidelines [6]. Symptom severity and treatment response were assessed using the Young Mania Rating Scale, a validated and reliable instrument for the assessment of manic symptoms [7], while adverse effects were systematically evaluated using the SAFTEE checklist [8].

Methods

Study Design and Setting: This randomized, open-label, lithium-controlled clinical trial was conducted in the Department of Psychiatry of a tertiary care government hospital in Kolkata over an 18-month period (2010–2011).

The study was approved by the Institutional Ethics Committee, and all procedures were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Participants: Ninety consecutive inpatients and outpatients aged ≥18 years diagnosed with a manic episode as per DSM-IV-TR criteria were enrolled. Written informed consent was obtained from patients or their legal guardians prior to inclusion.

Inclusion Criteria:

- Diagnosis of manic episode (DSM-IV-TR)
- YMRS score ≥20
- Availability of a reliable informant
- Willingness to participate in the study

Exclusion Criteria:

- Age <18 years
- Pregnancy or lactation
- Substance abuse
- Severe renal disease, thyroid disorder, dehydration, or hyponatremia
- Pre-existing blood dyscrasias or obesity (BMI ≥30 kg/m²)
- Current use of psychotropic medications within two weeks prior to evaluation
- Suicidality or homicidal risk

Randomization and Interventions: Eligible patients were randomized on a 1:1:1 basis to receive oxcarbazepine, carbamazepine, or lithium. Randomization was performed using a systematic alternate allocation method.

- **Oxcarbazepine:** Initiated at a low dose and titrated upward by 300 mg every two days during a two-week titration period to a maximum tolerated dose (1200–2400 mg/day).
- **Carbamazepine:** Titrated upward by 100 mg/day during the titration period to a maximum tolerated dose (600–1200 mg/day).
- **Lithium:** Administered as slow-release lithium carbonate (900–1800 mg/day), with dose adjustments guided by serum lithium levels (target range: 0.8–1.2 mEq/L).

Lorazepam was permitted on an as-needed basis in all groups to control severe agitation or disruptive behavior.

Outcome Measures: Severity of manic symptoms was assessed using the Young Mania Rating Scale (YMRS) at baseline, 1 week, 2 weeks, and 6 weeks. The primary efficacy outcome was adequate response, defined as a ≥50% reduction in YMRS score from baseline.

Safety Assessment: Safety and tolerability were assessed through clinical evaluation, vital signs, laboratory investigations (hematological and biochemical parameters), ECG, and the SAFTEE checklist administered at baseline and follow-up visits. Adverse events were categorized by severity and relationship to treatment.

Statistical Analysis: Categorical variables were expressed as frequencies and percentages and compared using the Chi-square test. Continuous variables were expressed as mean ± standard deviation and compared using the Kruskal–Wallis test. Statistical analysis was performed using SPSS version 16, with $p<0.05$ considered statistically significant.

Results

Baseline Characteristics: All three treatment groups were comparable at baseline with respect to age, sex distribution, socio-demographic variables, duration of illness, and baseline YMRS scores. The only statistically significant difference observed was age at onset of first affective episode ($p=0.037$).

Treatment Response: No patient in any group achieved adequate response at one week. At two weeks, adequate response was observed in 3.3% of patients in the oxcarbazepine group, 16.7% in the carbamazepine group, and 13.3% in the lithium group, with no statistically significant difference among groups (p=0.232).At six weeks, adequate response rates were significantly higher in the carbamazepine (80.0%) and lithium (73.3%) groups compared with the oxcarbazepine group (46.7%) (p=0.015). Carbamazepine demonstrated the highest response rate among the three groups.

Lorazepam Requirement: Requirement of lorazepam for behavioral control was higher in the oxcarbazepine group compared with carbamazepine and lithium groups; however, this difference did not reach statistical significance (p=0.180).

Adverse Effects: Oxcarbazepine was associated with fewer adverse effects overall. Carbamazepine showed significantly higher rates of blurred vision (p=0.008), benign leukopenia (p=0.045), and deranged liver function tests (p=0.015). Hyponatremia was more frequently observed in the oxcarbazepine group but was not statistically significant.

Table 1: Baseline Demographic and Clinical Characteristics of Patients

Variable	Oxcarbazepine (n=30)	Carbamazepine (n=30)	Lithium (n=30)	P value
Age (years), mean ± SD	35.8 ± 9.56	38.0 ± 10.16	33.7 ± 10.15	0.202
Male, n (%)	19 (63.3)	20 (66.7)	22 (73.3)	0.700
Age at first affective episode (years), mean ± SD	31.9 ± 6.92	34.0 ± 7.82	29.4 ± 6.52	**0.037**
Baseline YMRS score, mean ± SD	35.2 ± 9.46	36.5 ± 10.18	35.2 ± 9.94	0.835
Duration of current episode (weeks), mean ± SD	1.83 ± 0.70	2.03 ± 0.61	1.93 ± 0.52	0.435

Table 2: Treatment Response at 2 and 6 Weeks (≥50% Reduction in YMRS Score)

Time point	Oxcarbazepine n (%)	Carbamazepine n (%)	Lithium n (%)	P value
2 weeks – Adequate response	1 (3.3)	5 (16.7)	4 (13.3)	0.232
6 weeks – Adequate response	14 (46.7)	24 (80.0)	22 (73.3)	**0.015**

Table 3: Requirement of Lorazepam for Behavioral Control

Lorazepam requirement	Oxcarbazepine n (%)	Carbamazepine n (%)	Lithium n (%)	P value
Required	12 (40.0)	6 (20.0)	7 (23.3)	0.180
Not required	18 (60.0)	24 (80.0)	23 (76.7)	

Table 4: Common Adverse Effects Observed During Treatment

Adverse effect	Oxcarbazepine n (%)	Carbamazepine n (%)	Lithium n (%)	P value
Sedation	4 (13)	10 (33)	7 (23)	0.187
Blurred vision	1 (3)	6 (20)	0 (0)	**0.008**
Benign leukopenia	0 (0)	3 (10)	0 (0)	**0.045**
Deranged LFT	0 (0)	4 (13)	0 (0)	**0.015**
Hyponatremia	3 (10)	1 (3)	0 (0)	0.160

Discussion

The present study compared the efficacy and tolerability of oxcarbazepine with carbamazepine in the treatment of acute mania, using lithium as an active control. The findings demonstrate that oxcarbazepine was significantly less effective than carbamazepine and lithium in achieving adequate symptomatic response at six weeks, although it exhibited a more favorable tolerability profile.

The absence of an adequate treatment response at one week across all treatment groups highlights the delayed onset of action commonly observed with mood stabilizers when used as monotherapy. This finding differs from reports in which adjunctive antipsychotics were employed, resulting in earlier symptom improvement [9]. In the present study, antipsychotic augmentation was deliberately avoided, which may explain the slower onset of response observed across all groups. At six weeks, carbamazepine and lithium demonstrated superior efficacy compared with oxcarbazepine. These findings are consistent with previous controlled trials and meta-analyses that have established the robust antimanic efficacy of carbamazepine and lithium in acute manic episodes [10]. In contrast, studies reporting comparable efficacy of oxcarbazepine have often involved smaller sample sizes, heterogeneous populations, or different study designs [11,12], which may account for the variability in outcomes reported in the literature.

The tolerability findings of the present study are in line with existing evidence, indicating that

oxcarbazepine is associated with fewer hematological and hepatic adverse effects compared with carbamazepine [13].

Although hyponatremia was observed more frequently in the oxcarbazepine group, this did not reach statistical significance. The improved safety profile of oxcarbazepine may make it a clinically useful alternative in patients who are unable to tolerate carbamazepine, despite its relatively lower efficacy.

Conclusion

Oxcarbazepine demonstrated inferior efficacy compared with carbamazepine and lithium in the treatment of acute mania, although it was better tolerated. Carbamazepine and lithium remain more effective options for acute symptom control, while oxcarbazepine may be considered in patients with tolerability concerns.

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