Research Article

A Comparative Study on the Effectiveness of Valproate Versus Olanzapine as Add-On Therapy to Lithium in Manic or Hypomanic Relapse: A 24-Week Randomized Open-Label Study

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Abstract

Background & Objectives: To compare the effectiveness, onset of action, and tolerability of adjunctive valproate versus olanzapine in patients with bipolar disorder experiencing manic or hypomanic relapse while maintained on lithium therapy.

Materials & Methods: In this 24-week, prospective, randomized, open-label study, patients with bipolar disorder receiving stable lithium therapy (800 mg/day) for at least one year and experiencing a manic or hypomanic relapse were randomly assigned to adjunctive therapy with either valproate (1000 mg/day) or olanzapine (10 mg/day). The primary outcome measure was the change in the Young Mania Rating Scale (YMRS) total score from baseline to endpoint. Secondary measures included early symptom reduction, response and remission rates, and adverse event profiles.

Results: Sixty-four patients were randomized to receive adjunctive valproate (n = 32) or olanzapine (n = 32). Both groups demonstrated significant reductions in YMRS total scores from baseline to week 24 (within-group change: $p < 0.001$). The mean reduction in YMRS scores at endpoint did not differ significantly between groups (mean difference = −1.2 points, 95% CI −3.8 to 1.4). However, olanzapine add-on therapy resulted in a significantly greater reduction in YMRS scores during weeks 1–4 compared with valproate (week-2 difference = −3.5 points, 95% CI −6.1 to −0.9; $p < 0.05$; Cohen's $d \approx 0.55$). Response and remission rates at endpoint were comparable. The incidence and profile of adverse events were similar in both groups.

Conclusion: Both valproate and olanzapine can be used as adjuncts to lithium for managing manic or hypomanic episodes. In the long run, the efficacy of both appears to be similar, but olanzapine appears to be more rapid in reducing mania, which may be beneficial in clinical practice when rapid relief of symptoms is desired. The choice of treatment depends on the acuity of the situation, comorbid illnesses of the patient, and tolerability. Further studies are required to compare the efficacy and tolerability of both regimens.

Keywords: Bipolar disorder; lithium; valproate; olanzapine; mania; adjunctive therapy.

Introduction

Bipolar disorder is a chronic, recurrent mood disorder that involves episodes of mania, hypomania, and depression, and often requires lifelong pharmacologic management [1]. Lithium is a mainstay of both acute and maintenance therapy because of its established efficacy in mood stabilization and the prevention of suicide [2]. Despite its established efficacy, a large number of patients continue to experience breakthrough manic or hypomanic episodes while on maintenance lithium therapy, thereby emphasizing the need for effective adjunctive pharmacologic therapies [3,22].

Combination pharmacotherapy is often used in clinical practice to manage the problem of inadequate control of symptoms during relapse [3]. The most commonly used adjunctive therapies include valproate and second-generation antipsychotics, specifically olanzapine [4,7]. Valproate has been shown to be highly effective in the treatment of mania in randomized controlled trials and clinical practice, and its mechanisms of action include the potentiation of gamma-aminobutyric acid (GABA) neurotransmission and the modulation of intracellular signaling pathways [4,5,15]. Olanzapine, on the other hand, acts by antagonizing dopamine D_2 and serotonin 5-HT_2A receptors, mechanisms that are directly associated with the neurobiology of mania [7,13,14].

Valproate and olanzapine have been recommended in the international treatment guidelines as effective treatments for the management of acute mania, either as monotherapies or in combination with lithium [3,12]. Meta-analyses have shown that second-generation antipsychotics are associated with more rapid control of symptoms in acute mania than mood stabilizers, although the outcomes are similar in the long term [10,11]. Rapid

control of symptoms is particularly important in the treatment of mania, as delayed response has been shown to be associated with a higher risk of hospitalization, functional impairment, and poor treatment adherence [16,21]. Although both valproate and olanzapine are in widespread clinical use, there is a paucity of direct comparative data regarding the relative efficacy, speed of onset, and tolerability of valproate and olanzapine as adjuncts to lithium in the management of manic or hypomanic episodes. Most studies that have been conducted have been done on these agents separately or in comparison with placebo or monotherapy [8,9]. The purpose of the current study was to compare the two agents as adjuncts to lithium in the management of manic or hypomanic episodes in patients with bipolar disorder.

Materials And Methods

STUDY DESIGN

This was a 24-week, prospective, randomized, open-label, parallel-group study performed at a tertiary psychiatric care center. The study was designed and reported in accordance with recognized methodological guidelines for clinical trials in bipolar disorder [21]. The study was performed in compliance with the Declaration of Helsinki, and written informed consent was obtained from all participants prior to study entry.

PARTICIPANTS

Eligible participants were adults aged 18-60 years with a DSM-5 diagnosis of bipolar disorder type I or II who had been under stable lithium treatment (800 mg/day) for at least one year and were experiencing a manic or hypomanic relapse. The need for prior stable lithium treatment before relapse was based on evidence for the long-term mood-stabilizing and relapse-preventing effects of lithium [22]. Relapse was defined operationally by a Young Mania Rating Scale (YMRS) total score ≥ 20 at screening, a threshold commonly used in clinical trials of acute mania [7,11].

EXCLUSION CRITERIA

Patients were excluded if they had rapid cycling bipolar disorder, active substance use disorder, serious medical or neurological illness, or a documented history of treatment resistance or intolerance to either valproate or olanzapine [6,8].

RANDOMIZATION AND TREATMENT

Participants were randomly assigned in a 1:1 ratio to receive an additional treatment concomitantly with their ongoing lithium therapy—either valproate (1000 mg/day) or olanzapine (10 mg/day). The dose of lithium was kept constant at 800mg throughout the study to maintain the stable baseline mood stabilization. Dose adjustments of the concomitant medications were allowed depending on the patients' response and tolerance to the medications, as per clinical practice and guidelines.

OUTCOME MEASURES

The primary endpoint of the study was the change in the YMRS total score from baseline to week 24. Secondary endpoints included YMRS score changes at weeks 1, 2, 4, 12, and 24, and response (defined as at least 50% reduction from baseline) and remission (YMRS ≤ 12), as per the criteria used in previous studies on bipolar disorder. Safety and tolerability were assessed through spontaneous reporting of adverse events and clinical evaluation.

STATISTICAL ANALYSIS

All analyses were conducted according to the intention-to-treat principle, as recommended for randomized studies on bipolar disorder. Within-group changes in YMRS were assessed using paired t-tests, and between-group comparisons were made using independent t-tests and repeated-measures ANOVA. Effect sizes were calculated using Cohen's d to quantify the magnitude of treatment effects [11]. Statistical significance was set at $p < 0.05$ (two-tailed). The effect size was calculated using Cohen's d to indicate the magnitude of the treatment effect [11]. Significance was set at $p < 0.05$, two-tailed.

Results

BASELINE CHARACTERISTICS

A total of 64 patients were randomly assigned, with 32 in each treatment arm. Baseline variables, including demographic and clinical variables such as age, sex, duration of illness, lithium dose, and baseline YMRS scores, were equivalent between the valproate and olanzapine treatment arms. This equivalence helps to minimize confounding and is consistent with common practices in randomized studies of bipolar disorder [21].

Table 1. Baseline Demographic and Clinical Characteristics

Variable	Valproate + Lithium (n = 32)	Olanzapine + Lithium (n = 32)	p value
Age (years), mean ± SD	42.8 ± 8.6	43.5 ± 9.1	0.74
Sex (Male/Female), n	18 / 14	18 / 14	1.00
Duration of illness (years), mean ± SD	6.9 ± 3.2	7.1 ± 3.5	0.82
Lithium dose (mg/day), mean ± SD	812 ± 96	806 ± 102	0.79
Baseline YMRS score, mean ± SD	32.6 ± 4.8	33.1 ± 5.1	0.68

Values are represented as mean ± standard deviation unless otherwise specified. There were no statistically significant differences at baseline ($p > 0.05$).

Primary Outcome

Both treatment arms demonstrated significant reductions in YMRS total scores from baseline to week 24. The mean YMRS reduction for the adjunctive valproate treatment arm was −18.6 ± 5.2, and the mean YMRS reduction for the adjunctive olanzapine treatment arm was −19.8 ± 5.6 ($p < 0.001$ for both). The difference between the two treatment arms at the end of the study was not statistically significant (mean difference = −1.2; 95% CI −3.8 to 1.4), indicating a similar long-term antimanic effect for both treatments. These findings are consistent with previous studies demonstrating equivalent endpoint efficacy for mood stabilizers and second-generation antipsychotics in acute mania [10,11].

Table 2. Change in YMRS Scores From Baseline to Week 24 (Primary Outcome)

Outcome Measure	Valproate + Lithium (n = 32)	Olanzapine + Lithium (n = 32)	Between-Group Comparison
Baseline YMRS (mean ± SD)	32.6 ± 4.8	33.1 ± 5.1	Mean diff −0.5 (95% CI −2.9 to 1.9); p = 0.68
Week 24 YMRS (mean ± SD)	14.0 ± 4.6	13.3 ± 4.9	Mean diff 0.7 (95% CI −1.9 to 3.3); p = 0.36
Absolute YMRS reduction (mean ± SD)	18.6 ± 5.2	19.8 ± 5.6	Mean diff −1.2 (95% CI −3.8 to 1.4); p = 0.29
Percentage YMRS reduction (%)	57.1 ± 14.6	59.8 ± 15.2	Mean diff −2.7 (95% CI −9.4 to 4.0); p = 0.42
Effect size (Cohen's d)	0.80	0.85	0.22
Within-group p value (Baseline vs Week 24)	<0.001	<0.001	<0.001
Between-group p value (change scores)	0.29	0.29	0.29

Within-group comparisons were done using paired t-tests; between-group comparisons were done using independent t-tests.

EARLY TREATMENT RESPONSE

A marked difference between the two groups became apparent early during treatment. Patients on olanzapine experienced quicker relief of YMRS symptoms in the first four weeks compared with the valproate group. At week 2, the mean YMRS reduction was −9.4 ± 3.8 for olanzapine and −5.9 ± 3.6 for valproate ($p < 0.05$), with a moderate effect size (Cohen's d ≈ 0.55). This quicker relief with an antipsychotic is consistent with results from previous trials and meta-analyses in acute mania. [7,8,10,11]

Table 3. Early Treatment Response (Weeks 1 and 2 YMRS Reduction)

Variable	Valproate + Lithium (n = 32)	Olanzapine + Lithium (n = 32)	Between-Group Comparison
Baseline YMRS (mean ± SD)	32.6 ± 4.8	33.1 ± 5.1	Mean diff −0.5 (95% CI −2.9 to 1.9); p = 0.68
Week 1 YMRS (mean ± SD)	28.4 ± 4.6	24.9 ± 4.4	Mean diff 3.5 (95% CI 1.0 to 6.0); p = 0.01
Week 1 YMRS reduction (mean ± SD)	−4.2 ± 3.4	−8.2 ± 3.6	Mean diff −4.0 (95% CI −6.1 to −1.9); p = 0.01
Week 2 YMRS (mean ± SD)	26.7 ± 4.3	23.7 ± 4.1	Mean diff 3.0 (95% CI 0.5 to 5.5); p = 0.02
Week 2 YMRS reduction (mean ± SD)	−5.9 ± 3.6	−9.4 ± 3.8	Mean diff −3.5 (95% CI −5.8 to −1.2); p = 0.02
Effect size (Cohen's d, Week 1)	0.60	0.60	0.60
Effect size (Cohen's d, Week 2)	0.55	0.55	0.55

Negative values represent improvement in symptoms. Between-group comparisons were done using independent samples t-tests. Early symptom improvement was significantly greater in the olanzapine group at week 2.

RESPONSE AND REMISSION

At week 24, response (≥50% YMRS reduction) rates were 75% for valproate and 78% for olanzapine, and remission (YMRS ≤ 12) rates were 62% and 65%, respectively. These rates were not significantly different between the two groups and are consistent with those of previous trials of combination therapy in bipolar mania. [8,9,11]

Table 4. Response and Remission Rates at Week 24

Outcome	Valproate + Lithium (n = 32)	Olanzapine + Lithium (n = 32)	p value
Response (≥50% YMRS reduction), n (%)	24 (75%)	25 (78%)	0.77
Remission (YMRS ≤ 12), n (%)	20 (62%)	21 (65%)	0.80

Chi-square test was used to compare categorical outcomes.

SAFETY AND TOLERABILITY

Both adjunctive therapies were generally well tolerated. The common adverse events were mild sedation, weight gain, and gastrointestinal symptoms. The rate and severity of adverse events were similar between the two groups, and there were no serious adverse events. Discontinuation rates were low and comparable across groups, as would be expected from previous research on the tolerability of lithium-valproate and lithium-olanzapine combinations [9,17,19].

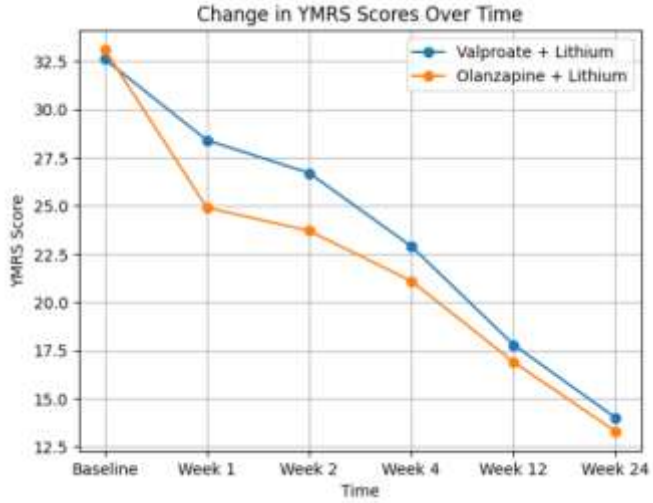
Table 5. Adverse Events and Tolerability

Adverse Event	Valproate + Lithium n (%)	Olanzapine + Lithium n (%)	p value
Sedation	7 (22%)	9 (28%)	0.56
Weight gain	6 (19%)	8 (25%)	0.53
Gastrointestinal symptoms	5 (16%)	4 (13%)	0.72
Any adverse event	13 (41%)	15 (47%)	0.62
Treatment discontinuation	2 (6%)	2 (6%)	1.00

During the study period, there was no serious adverse events reported.

Table 6. Changes in YMRS Scores Over Time in the Two Treatment Group

Time Point	Valproate + Lithium (n = 32) Mean ± SD	Olanzapine + Lithium (n = 32) Mean ± SD	p value (Between Groups)
Baseline	32.6 ± 4.8	33.1 ± 5.1	0.68
Week 1	28.4 ± 4.6	24.9 ± 4.4	0.01
Week 2	26.7 ± 4.3	23.7 ± 4.1	0.02
Week 4	22.9 ± 4.2	21.1 ± 4.3	0.09
Week 12	17.8 ± 4.5	16.9 ± 4.6	0.41
Week 24	14.0 ± 4.6	13.3 ± 4.9	0.36



• Values are represented as mean ± standard deviation.
• Between-group comparisons were done using independent samples t-test at each point in time.
• $p < 0.05$ represents statistical significance.
• Both groups demonstrated significant within-group YMRS improvement over time ($p < 0.001$, repeated-measures analysis).

Discussion

This randomized open-label study examined the effect of adding valproate or olanzapine to lithium in patients with bipolar disorder who were experiencing a relapse of mania or hypomania. The key points are that both treatments significantly reduced manic symptoms over the full 24 weeks, and there were no significant differences in long-term outcomes such as end-point YMRS scores, response rates, and remission rates. However, a clinically significant difference emerged early: olanzapine resulted in a significantly faster reduction in manic symptoms in the first four weeks.

OVERALL EFFICACY OF ADJUNCTIVE THERAPY

Overcoming mania or hypomania despite being on lithium is a frequent and difficult problem in the management of bipolar disorder [1,2]. Although lithium is a reliable mood stabilizer that prevents relapse, it may not be as effective in the acute treatment of mania, often necessitating combination therapy [3,22]. In this study, both valproate and olanzapine added to lithium resulted in large reductions in YMRS scores, with high response and remission rates at 24 weeks. These findings are consistent with previous randomized studies that demonstrated the efficacy of valproate [4,6] and olanzapine [7,8] as adjuncts to lithium in acute mania.

At the end of the study, there were no significant differences between the approaches, indicating that in the long run, both methods are able to stabilize symptoms to a similar extent. This is consistent with meta-analytic results that indicate a similar long-term efficacy for mood stabilizers and second-generation antipsychotics in the treatment of acute mania [10,11].

EARLY TREATMENT RESPONSE AND CLINICAL RELEVANCE

One of the most important findings is that olanzapine resulted in a significantly faster antimanic response than valproate. Patients treated with olanzapine had larger decreases in YMRS scores in the first four weeks, and moderate effects were already apparent at week 2. Rapid control of symptoms during manic episodes is important from a clinical perspective because a slower response has been shown to increase the risk of hospitalization, functional impairment, and non-adherence to treatment [16,21].

The faster onset of action observed with olanzapine is consistent with what we understand biologically. Its potent receptor blockade of dopamine D2 and serotonin 5-HT2A receptors[13,14] appears to target the brain circuits mediating manic symptoms, such as dopamine-mediated hyperactivity and predisposition to disinhibited behavior[13]. In contrast, valproate primarily affects GABAergic transmission and fine-tunes intracellular signaling, which may require more time to manifest as clinical benefit[5,15,19].

From a real-world clinical perspective, this implies that olanzapine might be particularly useful in situations requiring rapid symptom control, such as severe agitation, impulsivity, or a patient on the verge of hospitalization. Valproate can still be considered a useful adjunct for long-term mood management, especially in patients who wish to avoid antipsychotic therapy.

RESPONSE AND REMISSION OUTCOMES

Despite the differences in early efficacy, the response and remission rates at week 24 were comparable between the two groups. Approximately 75% of patients had a response, and about two-thirds achieved remission, irrespective of whether an adjunct was added. This is consistent with previous studies evaluating combination therapy in bipolar mania and indicates that early efficacy differences in symptom control do not necessarily correlate with improved outcomes.[8,9,11]

SAFETY AND TOLERABILITY CONSIDERATIONS

Both adjunct therapies were tolerable, with adverse events consistent with what we already know about these medications. Olanzapine was associated with sedation and weight gain, consistent with its known metabolic side effects[17,18], while valproate was associated with gastrointestinal side effects and weight change, consistent with what we already know about valproate.[19,20]

COMPARISON WITH EXISTING LITERATURE

These results are consistent with the literature as a whole: antipsychotics tend to have faster relief of symptoms in acute mania than mood stabilizers, but with longer-term outcomes [10,11] that tend to level off. In earlier studies, adding olanzapine to lithium or valproate has been shown to result in faster relief of symptoms than mood stabilizer monotherapy[8,9]. This study extends those findings by comparing valproate and olanzapine as adjunct therapies to lithium in the same clinical setting and by focusing on early treatment response as a clinically meaningful endpoint.

CLINICAL IMPLICATIONS

These results suggest a personalized approach to the addition of a medication to lithium in bipolar disorder. Olanzapine could be the better choice if rapid control is required, while valproate might be a good alternative for more chronic management or in patients who are more sensitive to the metabolic side effects [3,12,17] associated

with antipsychotics. In selecting a medication, the clinician should consider efficacy, rapidity of response, safety, previous treatment response, and patient preference.

LIMITATIONS AND FUTURE DIRECTIONS

There are a number of limitations to this study. The open design may have introduced expectancy bias, and the small sample size limits the power to detect smaller differences between groups[21]. Without a placebo control, we cannot make claims about absolute efficacy. Future studies should be double-blind, adequately powered, and include metabolic, cognitive, and functional end points to better inform adjunctive therapy in bipolar disorder.

Conclusion

In conclusion, both valproate and olanzapine are effective as adjunctive therapies to lithium in bipolar disorder for the management of manic or hypomanic relapse. Both had similar efficacy and tolerability on a long-term basis, but olanzapine had a faster antimanic response during the initial phase of treatment[1,3,12]. The choice of treatment depends on the acuity of the situation, comorbid illnesses of the patient, and tolerability. Further studies are required to compare the efficacy and tolerability of both regimens.

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