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Original Article

Comparative Treatment Outcomes of Acute Manic Episodes with Antipsychotic Monotherapy Versus Combination Therapy with Mood Stabilizers: A Quasi-Experimental Study

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ABSTRACT

Objective: To study the comparison in effectiveness of monotherapy (Antipsychotic) versus combination therapy (antipsychotic with mood stabilizer) in acute mania.

Study Design: Quasi-Experimental study.

Place and Duration of Study: Department of Psychiatry, Armed Forces Institute of Mental Health, Rawalpindi, Pakistan, from Dec 2024 to Nov 2025.

Methodology: One hundred sixty patients aged 18-65 years, diagnosed with acute manic episode, having a baseline Young Mania Rating Scale (YMRS) score ≥ 20 at presentation, were included. The severity of mania was assessed using the Young Mania Rating Scale (YMRS) at baseline. Patients were allocated into two groups: Group-A (antipsychotic monotherapy) and Group-B (combination of antipsychotic plus mood stabilizer). At discharge, the YMRS score was reassessed to determine symptom improvement. Intergroup comparisons and logistic regression analysis were done.

Results: A total of 160 patients with acute manic episodes were enrolled in a 1:1 ratio. Baseline Median YMRS was 32.00 (15.00) in Group-A and 32.50 (12.00) in Group-B (p=0.91). Median YMRS decreased from 32.00 (15.00) to 22.00 (8.00) in Group-A and from 32.50 (12.00) to 19.00 (7.00) in Group-B. The reduction in YMRS (Δ) was greater with combination therapy 14.00 (5.00) vs 9.50 (6.00) with a significant between-group difference (both discharge scores and Δ: p<0.001). The proportion achieving ≥50% YMRS reduction was 0/80 (0.0%) in Group-A vs 15/80 (18.8%) in Group-B (p<0.001).

Conclusion: Combination therapy (antipsychotic with mood stabilizer) had a higher rate of acute manic episode control and reduction in YMRS score as compared to monotherapy (antipsychotics).

Keywords: Acute mania, Antipsychotics, Bipolar disorder, Mood stabilizer, Psychotherapy, Young Mania Rating Scale (YMRS).

How to Cite This Article: *Zia M, Shoaib A, Siab SR, Rabiya Adnan, Sana Zahra, Ishel Farid. Comparative Treatment Outcomes of Acute Manic Episodes with Antipsychotic Monotherapy Versus Combination Therapy with Mood Stabilizers: A Quasi-Experimental Study. Pak Armed Forces Med J 2026; 76(Suppl-5): S926-S931. DOI: https://doi.org/10.51253/pafmj.v76iSUPPL-5.14127*

INTRODUCTION

Mania is a psychiatric condition characterized by aberrantly elevated mood and activity levels along with inflated self-esteem, delusions, and feelings of grandiosity.[1] Usually, mania is associated with Type-I Bipolar Disorder (BD), whereby it is abrupt, severe, and can cause significant social or occupational functioning impairment.[2] The global prevalence of bipolar disorder is 0.5-6.1%, with a recurrence rate of 50%.[3] The incidence of manic episodes in BD is estimated at 1-2%, reaching up-to 2.4% in developing countries, occurring 0.65% in Type-I and 0.4% in type-II BD.[4] BD and mania usually show a bimodal distribution of onset, with early age at onset having longer episodes and requiring combination pharmacotherapy and psychotherapy.[5] In many cases, mania may go undiagnosed or misdiagnosed, due to overlapping symptoms with other psychiatric conditions, lack of awareness or delayed reporting due to social stigmata of psychiatric illness.[6]

In some cases, manic episodes subside within three to six months without treatment. However, in most cases, acute manic episodes require treatment typically involving a combination of pharmacological and psychotherapeutic approaches.[7] The most commonly used therapeutic agents are mood stabilizers such as Lithium, which remains a cornerstone of the treatment of mania, especially in early age onset mania.[8] However, patients on monotherapy with mood stabilizers usually have frequent relapses; therefore, combination therapy with mood stabilizers and antipsychotics like Olanzapine or Risperidone is recommended, especially during acute manic episodes.[9] Psychotherapy, including cognitive behavioral therapy (CBT) and psychoeducation, plays a crucial role in long-term management by helping individuals recognize early warning signs and improve medication adherence.[10]

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Received: 03 Jan 2026; revision received: 06 Mar 2026; accepted: 12 Mar 2026

Identifying the need for early treatment with mono- or combination pharmacotherapy and associated factors will guide clinicians in determining the best suitable treatment options early to control acute manic episodes and to prevent relapse. This study aims to compare the efficacy of mood stabilizers alone, with a combination of mood stabilizers plus anti-psychotics in the treatment of acute mania and for maintenance therapy, providing evidence to optimize treatment protocols and improve long-term management strategies for mania.

METHODOLOGY

This study was conducted as a Quasi-Experimental study at the Armed Forces Institute of Mental Health (AFIMH), Rawalpindi, Pakistan, a tertiary care psychiatry institute providing specialized mental health services to both military and civilian populations, from Dec 2024 to Nov 2025. The institute serves as an appropriate center for evaluating different treatment strategies in acute manic episodes due to its wide patient catchment and multidisciplinary clinical approach. The duration of the study was 12 months following approval from the ethical review board (ERC/2436/dated01Dec2024). All patients presenting with acute manic episodes during this period, who met the inclusion criteria, were enrolled and followed according to the study protocol.

The sample size was calculated using the OpenEpi online sample size calculator, taking confidence interval 95%, a margin of error 5%, 80% power of test, and a mean change in Young Mania Rating Scale (YMRS) score of -13.11±8.53 in olanzapine plus lithium/valproate and -9.10±9.36 in mood stabilizer monotherapy in acute mania, as concluded by Tohen *et al*.[11] The estimated sample size came out to be 160 patients (80 patients per group). A non-probability consecutive sampling technique was employed. All eligible patients presenting during the study period were approached for participation until the required sample size was achieved. All 204 patients with acute mania presenting to AFIMH during study period were evaluated and screened. A total of 172 patients fulfilling inclusion criteria were scrutinized and included in study, with 86 patients in each group. (Figure)

Inclusion Criteria: Patients aged 18 to 65 years, of either gender, diagnosed with an acute manic episode as per DSM-5 criteria, having a baseline Young Mania Rating Scale (YMRS) score ≥ 20 at presentation, and providing informed written consent were included.

Exclusion Criteria: Presence of mixed episodes or rapid cycling bipolar disorder, history of electroconvulsive therapy (ECT) for treatment-resistant mania, severe medical comorbidities (e.g., renal failure, cardiac arrhythmias), current substance-induced mania or active substance abuse, pregnancy or lactation rendered a patient excluded from the study.

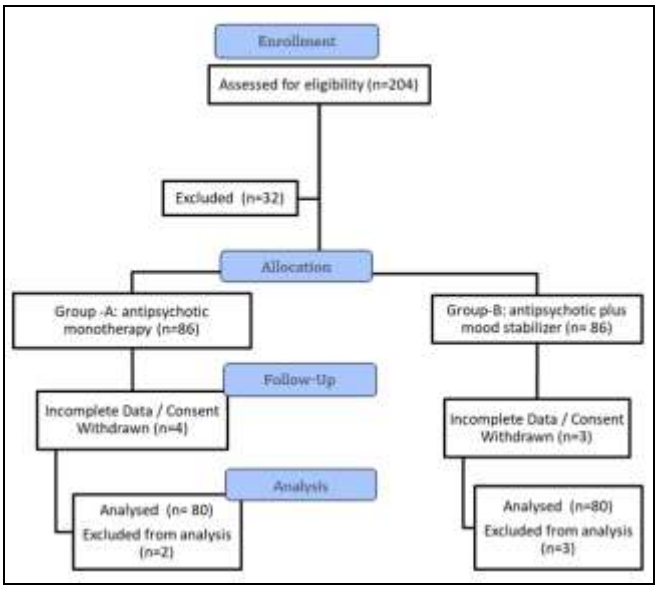

Figure: Patient Enrollment Flow Diagram

The data collection procedure involved recording detailed socio-demographic and clinical information at baseline. This included age, sex, marital status, education level, occupation, and employment status. Clinical details such as age at onset of bipolar disorder, duration of illness, number of previous manic episodes, number of prior hospitalizations, and the type of current episode (pure mania or mixed features) were documented. Comorbid medical or psychiatric conditions and any history of substance use were also recorded.

The severity of mania was assessed using the Young Mania Rating Scale (YMRS) at baseline. Patients were then allocated into two groups based on the treatment initiated by the attending psychiatrist: Group-A received antipsychotic monotherapy, while Group-B received a combination of antipsychotic plus mood stabilizer. The specific antipsychotic and mood stabilizer prescribed were documented. Previous exposure to the same medications was recorded, and treatment adherence during hospitalization was assessed, categorized as good, fair, or poor. At

discharge, the YMRS score was reassessed to determine symptom improvement. The need for electroconvulsive therapy (ECT), if any, was documented. All adverse events, treatment adherence, and medication tolerability were monitored throughout the hospital stay.

The data was analyzed, and the normality of the data was checked using Kolmogorov-Smirnov test. Continuous variables such as age, duration of illness, and YMRS scores were reported as median (interquartile range), based on data distribution. Categorical variables such as gender, marital status, treatment group, episode type, comorbidities, adherence, and ECT requirement were presented as frequencies and percentages. Intergroup comparisons were performed using Mann-Whitney U test for continuous variables, and Chi-square test or Fisher's exact test for categorical variables. A *p*-value of ≤0.05 was considered statistically significant.

RESULTS

One hundred sixty patients with acute manic episodes were enrolled in the study, divided in a 1:1 ratio with a median age of 39.50(18.00) years in Group-A and 36.00(18.00) years in Group-B (*p*=0.075). There were 36(45%) males and 44(55%) females in Group-A, while Group-B included 39(48.8%) males and 41(51.2%) females. Marital status, education level, occupation, and employment status of the two groups have been summarized in Table-I.

Table-I: Baseline Socio-demographic Characteristics of the Study Population (n=160)

Variable		Group-A (Monotherapy) (n=80)	Group-B (Combination) (n=80)	*p*-value
Age [years, Median(IQR)]		39.50(18.00)	36.00(18.00)	0.075
Gender, n(%)	Male	36(45.0%)	39(48.8%)	0.751
	Female	44(55.0%)	41(51.2%)	
Marital Status, n(%)		69(86.3%)	63(78.8%)	0.298
Education Level, n(%)	Illiterate	8(10.0%)	21(26.3%)	0.024
	Primary	31(38.8%)	33(41.3%)	
	Secondary	20(25.0%)	14(17.5%)	
	Graduate or Above	21(26.3%)	12(15.0%)	
Employment Status, n(%)	Employed	18(22.5%)	20(26.3%)	0.039
	Unemployed	26(32.5%)	39(41.3%)	
	Student	23(28.7%)	17(17.5%)	
	Retired	13(16.3%)	4(15.0%)	

There was no statistical difference in age at onset and duration of illness between both groups, as it was 33.00 (14.00) years in Group-A and 31.00 (10.00) years in Group-B (*p*=0.114), and duration was 5.00(5.00) years in Group-A and 4.50 (6.00) years in Group-B (*p*=0.39). Similarly, statistically insignificant differences in previous manic episodes (*p*=0.079) and previous hospitalizations were observed between both groups (*p*=0.997). The current episode was pure mania in 49(61.3%) patients in Group-A and 41(51.2%) in Group-B (*p*=0.265). Baseline YMRS was 32.00 (15.00) in Group-A and 32.50 (12.00) in Group-B (*p*=0.91). (Table-II).

Table-II: Clinical Profile of Patients in Both Treatment Groups (n=160)

Variable		Group-A (Monotherapy) (n=80)	Group-B (Combination) (n=80)	*p*-value
Age at Onset (years), median [IQR]		33.00(14.00)	31.00(10.00)	0.114
Duration of Illness (years), median [IQR]		5.00(5.00)	4.50(6.00)	0.39
Previous Manic Episodes, median [IQR]		3.00(4.00)	2.00(3.00)	0.079
Number of Previous Hospitalizations, median [IQR]		2.00(3.00)	2.00(3.00)	0.997
Current Episode Type, n(%)	Pure Mania	49(61.3%)	41(51.2%)	0.265
	Mixed Features	31(38.8%)	39(48.8%)	
Comorbid Medical Conditions, n(%)	None	37(46.3%)	48(60%)	0.165
	Diabetes	20(25.0%)	20(25.0%)	
	HTN / IHD*	2(27.5%)	11(13.8%)	
	Others	1(1.3%)	1(1.3%)	
Comorbid Psychiatric Conditions, n(%)	Yes	46(57.5%)	41(51.2%)	0.526
	No	34(42.5%)	39(48.8%)	
Substance Use History, n(%)	Yes	37(46.3%)	32(40.0%)	0.523
	No	43(53.8%)	48(60.0%)	

**HTN: Hypertension, IHD: Ischemic Heart Disease*

Regarding treatment characteristics, previous exposure to the same medications was reported in 38(47.5%) of Group-A and 49(61.3%) of Group-B (*p*=0.056). Treatment adherence was good in 62(77.5%) of Group-A and 58(72.5%) of Group-B, and inadequate in 18 (22.5%) vs 22 (27.5%), respectively (*p*=0.292). (Table-III)

For the primary outcome, YMRS decreased from 32.00 (15.00) to 22.00 (8.00) in Group-A and from 32.50 (12.00) to 19.00 (7.00) in Group-B. The reduction in YMRS (Δ) was greater with combination therapy—14.00 (5.00) vs 9.50 (6.00)—with a significant between-group difference (both discharge scores and Δ: *p*<0.001). The proportion achieving ≥50% YMRS reduction was 0/80 (0.0%) in Group-A vs 15/80 (18.8%) in Group-B (*p*<0.001). For secondary outcomes, the need for ECT was observed in 39 (48.8%) of Group-A and 22 (27.5%) of Group-B (*p*=0.009). (Table-IV)

In terms of secondary outcomes, the need for electroconvulsive therapy (ECT) was observed in 39(48.8%) of Group-A and 22(27.5%) of Group-B (p=0.009).

Table-III: Treatment Characteristics and Medication Details of Study Groups (n=160)

Variable		Group-A (Monotherapy) (n=80)	Group-B (Combination) (n=80)	*p*-value
Previous Exposure to Same Medications, n(%)		38(47.5%)	49(61.3%)	0.056
Treatment Adherence, n(%)	Good	62(77.5%)	58(72.5%)	0.292
	Inadequate	18(22.5%)	22(27.5%)	

Table-IV: Comparison of YMRS Scores at Baseline and Discharge (n=160)

YMRS* Score	Group-A (Monotherapy) (n=80)	Group-B (Combination) (n=80)	*p*-Value
Baseline, median [IQR]	32.00(15.00)	32.50(12.00)	0.91
At Discharge, median [IQR]	22.00(8.00)	19.00(7.00)	<0.001
Change (Δ), median [IQR]	9.50(6.00)	14.00(5.00)	<0.001
≥50% Reduction, n(%)	0	15(18.8%)	-

**YMRS: Young Mania Rating Scale*

DISCUSSION

In our comparative observational study from a tertiary psychiatric center, combination therapy with an antipsychotic plus a mood stabilizer was associated with greater short-term symptomatic improvement in acute mania than antipsychotic monotherapy. Ghaemi *et al*., showed that antipsychotic and MS combination therapy improved YMRS more than monotherapy (p=0.003), with >50% improvement on YMRS (67.7% vs 44.7%, p<0.001), respectively. It was also observed that combination therapy improved Hamilton Depression Rating Scale score more than monotherapy (4.98 vs 0.89 points, p<0.001).(11) Similarly. Richmond *et al*., observed that combination therapy of antipsychotics and mood stabilizers outperformed placebo and single agent in reducing maniac symptomology.[12]

Despite similar baseline YMRS (median 32.00 vs 32.50; p=0.91) and broadly comparable clinical profiles, patients in the combination arm showed a larger median reduction in YMRS (Δ 14.00 [5.00] vs 9.50 [6.00]; p<0.001) and lower discharge YMRS (19.00 [7.00] vs 22.00 [8.00]; p<0.001). Theodoratou *et al*., also found that atypical antipsychotics alone and in combination with mood stabilizers had greater clinical improvement as compared to a typical antipsychotic.[13]

Clinically, the absolute responder difference (≥50% YMRS reduction) favored combination therapy (18.8% vs 0%; p<0.001), corresponding to an approximate NNT of 6 for achieving a ≥50% reduction by discharge. Notably, the need for ECT was also lower in the combination group (27.5% vs 48.8%; p=0.009), suggesting that earlier co-prescription may reduce escalation to procedural interventions during the index admission. Goes *et al*., reported that ECT had a response rate of approximately 60-80% cases of severe depression and acute mania, which are observed more commonly in patients on monotherapy as compared to combination therapy.[14]

The multivariable responder analysis (excluding treatment group due to complete separation) identified higher baseline YMRS as independently associated with lower odds of achieving ≥50% reduction at discharge (OR 0.907; 95% CI 0.828–0.994; p=0.036). Adri *et al*., reported 61% decrease in YMRS on fifth day of admission in response to anti-psychotics in patients with acute mania.[15] Similar findings were reported by Simonetti *et al*., who noticed 82% remission rate in acute mania in response to combination therapy with a decline in YMRS and Clinical Global Impressions-Bipolar (CGI-BP) mania score within 4 weeks.[16]

In another study, Fengli et al., concluded that effective rate was higher in combination of antipsychotic and mood stabilizer Group-A, compared to the monotherapy group (49/65 vs 24/65, Z=4.05, p<0.001). Also, remission rate was higher in combination Group-A compared to monotherapy (45/100 vs 21/100, Z=3.62, OR=0.31, 95%CI: 0.17-0.59, p=0.003).[17] Tajika *et al*., observed a significant remission rate in augmentation therapy (combination drugs) as compared to monotherapy at both 3-week and 6-week follow-ups, with OR=1.43 (95%CI: 1.11-1.83) and OR=1.48 (95%CI 1.17-1.86), respectively. It was concluded that augmentation therapy was superior in terms of effectiveness and remission.[18]

It is noteworthy that education level and employment status differed between groups at baseline (p=0.024 and p=0.039, respectively). While most other demographic and clinical variables were balanced, these differences may reflect socioeconomic

or illness-related functioning disparities that could influence care pathways, help-seeking, or adherence outside the hospital. This aligns with clinical expectations that greater initial severity may be harder to halve over a brief inpatient course, even when absolute symptom reduction is substantial. Other covariates—age, gender, duration of illness, substance use, comorbidities, prior exposure, and adherence—were not significant predictors of responder status in this dataset. Together, these findings reinforce existing evidence that combination therapy confers an early advantage in acute mania management and may help curb downstream use of ECT within the same episode.

LIMITATIONS OF STUDY

Ours was an observational, clinician-allocated study from a single tertiary center, which used non-probability sampling, so selection bias, residual confounding, and limited generalizability are likely. Outcomes were short-term (to discharge) without follow-up on relapse, re-hospitalization, function, or maintenance tolerability. Zero responders in the monotherapy arm preclude treatment-effect modeling for the responder endpoint. Regimen heterogeneity (different antipsychotics/mood stabilizers and doses) and baseline imbalances (education, employment) may have influenced the results. Moreover, adverse effects were also not recorded in our study as most present at long term.

CONCLUSION

It was observed that the combination therapy of antipsychotics with mood stabilizers had better effectiveness and a higher rate of remission and reduction in YMRS score as compared to monotherapy with antipsychotics. Moreover, combination therapy provides better control of acute manic episodes, reducing the need for subsequent ECT for treatment of acute episodes as well as inducing remission.

ACKNOWLEDGEMENT

The authors are thankful to all colleagues for their assistance in data collection and analysis. We extend our gratitude to all patients and their attendants, colleague residents, psychologists and consultants, psychiatric OPD and ward staff for assistance in patient interviews, management and data collection.

Conflict of Interest: None.

Funding Source: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MZ & AS: Data acquisition, data analysis, critical review, approval of the final version to be published.

SRS & RA: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

SZ & IF: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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