ORIGINAL RESEARCH

Prospective Study of Adverse Drug Reactions in Patients with Bipolar Disorder at a tertiary centre

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ABSTRACT

Background: Bipolar disorder (BD) is a chronic psychiatric condition characterized by recurrent episodes of mania, hypomania, and depression, often resulting in significant impairment in personal, social, and occupational functioning.The study aimed to evaluate the prevalence, severity, and preventability of adverse drug reactions (ADRs) in patients diagnosed with Bipolar Disorder (BD) receiving pharmacological treatment.**Material and Methods:** This was a prospective observational study conducted in the Psychiatry Outpatient Department (OPD) of a tertiary care hospital. A total of 80 patients diagnosed with BD, as per DSM-5 criteria, were enrolled. Patients were followed up for six months to monitor ADRs associated with psychotropic medications. ADRs were assessed using standardized scales, including the WHO-Uppsala Monitoring Centre (WHO-UMC) causality assessment system, Naranjo's ADR Probability Scale, Hartwig and Siegel Severity Scale, and the Modified Schumock and Thornton Preventability Scale. Statistical analysis was performed using SPSS Version 21.0, with a p-value < 0.05 considered statistically significant.**Results:** Among the 80 patients, 42 (52.50%) were male, and 38 (47.50%) were female. The most commonly prescribed medications were Lithium (37.50%) and Valproate (31.25%). A total of 80 ADRs were reported, with gastrointestinal (31.25%), neurological (25.00%), and metabolic (22.50%) ADRs being the most common. Causality assessment classified ADRs as probable (37.50%), possible (31.25%), certain (18.75%), and unlikely (12.50%). Most ADRs were mild (50.00%) or moderate (37.50%), with only 12.50% categorized as severe. Preventability analysis revealed that 25.00% of ADRs were definitely preventable, 43.75% were probably preventable, and 31.25% were not preventable.**Conclusion:** The study highlights the high prevalence of ADRs in BD patients, particularly those on mood stabilizers and antipsychotics. While most ADRs were mild to moderate, their impact on adherence underscores the need for regular monitoring, patient education, and individualized treatment strategies to optimize safety and efficacy.

Keywords: Bipolar Disorder, Adverse Drug Reactions, Mood Stabilizers, Psychotropic Medications, Pharmacovigilance

INTRODUCTION

Bipolar disorder (BD) is a chronic psychiatric condition characterized by recurrent episodes of mania, hypomania, and depression, often resulting in significant impairment in personal, social, and occupational functioning. The disorder requires long-term management through pharmacological and non-pharmacological interventions to stabilize mood, prevent relapse, and improve overall quality of life. Medications such as mood stabilizers, antipsychotics, and antidepressants play a central role in the treatment of BD. However, their effectiveness is often accompanied by a substantial risk of

adverse drug reactions (ADRs), which can negatively impact patient compliance, increase treatment burden, and contribute to morbidity. The occurrence of ADRs in BD is a major concern for both clinicians and patients, as it can lead to medication discontinuation, therapeutic failure, and the need for frequent regimen adjustments.[1]The nature and severity of ADRs in BD vary widely depending on the medication class, dosage, patient characteristics, and duration of treatment. Mood stabilizers such as lithium and valproate, widely regarded as the cornerstone of BD management, are associated with numerous side effects, including gastrointestinal disturbances, neurological symptoms, renal dysfunction, weight gain, and thyroid abnormalities. Lithium, despite its well-established efficacy, has a narrow therapeutic index, necessitating regular monitoring of blood levels to minimize toxicity. Valproate, another commonly prescribed mood stabilizer, is known for its hepatotoxic potential, gastrointestinal upset, and metabolic effects such as weight gain and hyperlipidemia. These side effects can significantly affect adherence, making long-term treatment challenging.[2] In addition to mood stabilizers, atypical antipsychotics are frequently used in BD management, particularly for acute manic episodes and maintenance therapy. Although these medications provide symptom relief, they are associated with metabolic disturbances such as weight gain, diabetes, and dyslipidemia, as well as extrapyramidal symptoms, sedation, and cardiovascular risks. The emergence of metabolic syndrome in patients receiving atypical antipsychotics has raised concerns about long-term health consequences, necessitating close monitoring and lifestyle interventions. Older antipsychotics, or typical antipsychotics, are less commonly used due to their higher risk of extrapyramidal side effects and tardive dyskinesia.[3] Antidepressants are sometimes prescribed in BD, particularly for bipolar depression, though their use remains controversial due to the risk of inducing manic episodes or rapid cycling. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are commonly used; however, their adverse effects, including sexual dysfunction, weight changes, and increased suicidality in certain populations, warrant careful consideration. In BD patients, the inappropriate or prolonged use of antidepressants can exacerbate mood instability, leading to complications in disease management.[4,5] The incidence and severity of ADRs in BD patients are influenced by multiple factors, including individual patient susceptibility, genetic predisposition, polypharmacy, and the presence of comorbid conditions. Many BD patients require combination therapy, increasing the likelihood of drug-drug interactions and compounded side effects. Furthermore, the long-term nature of BD treatment necessitates sustained adherence, which is often challenged by tolerability issues related to ADRs. The need for medication adjustments, dose titration, and alternative treatment options underscores the complexity of managing ADRs in this population.[6] Beyond the physiological impact, ADRs also contribute to significant psychological and social burdens. Patients experiencing persistent side effects may develop negative perceptions of treatment, leading to reduced adherence and disengagement from care. The stigma associated with psychiatric medications, especially in cases where visible ADRs such as weight gain or tremors occur, further complicates treatment compliance. Additionally, the financial burden associated with managing ADRs—through additional medical visits, laboratory monitoring, and alternative therapies—places strain on healthcare systems and patients alike.[7] Given the high prevalence of ADRs in BD treatment, there is an urgent need for enhanced pharmacovigilance and personalized medicine approaches. Identifying risk factors for ADRs, implementing routine monitoring strategies, and utilizing patient-centered interventions can help mitigate adverse effects and optimize treatment outcomes. The role of pharmacogenetics in predicting individual responses to psychotropic medications is an evolving area of research, offering potential pathways for tailoring treatment regimens to minimize ADRs while maximizing therapeutic benefits.[8] In clinical practice, managing ADRs in BD requires a multidisciplinary approach involving psychiatrists, primary care physicians, pharmacists, and other healthcare professionals. Education on recognizing early signs of ADRs, counseling patients on potential side effects, and encouraging adherence to prescribed regimens are crucial in minimizing treatment disruptions. Regular follow-ups and proactive interventions, such as lifestyle modifications to counteract metabolic side effects, can enhance patient engagement and improve long-term outcomes.[9] Despite advancements in psychopharmacology, ADRs remain a persistent challenge in BD

treatment. Future research should focus on developing safer pharmacological alternatives, improving early detection of ADRs, and refining clinical guidelines to balance efficacy with tolerability. Additionally, patient education initiatives and shared decision-making frameworks can empower individuals with BD to actively participate in their treatment plans, fostering better adherence and improved quality of life.[10] ADRs in BD represent a significant clinical challenge, affecting treatment adherence, patient well-being, and overall disease management. While medications are essential for stabilizing mood and preventing relapse, their associated side effects necessitate continuous monitoring, individualized treatment strategies, and comprehensive patient support. A deeper understanding of ADR patterns, risk factors, and mitigation strategies will contribute to more effective and tolerable treatment approaches for individuals living with BD.

AIM & OBJECTIVES

The study aimed to evaluate the prevalence, severity, and preventability of adverse drug reactions (ADRs) in patients diagnosed with Bipolar Disorder (BD) receiving pharmacological treatment.

MATERIALS & METHODS

Study Design

The current was a prospective observational study conducted to evaluate the adverse drug reactions (ADRs) in patients diagnosed with Bipolar Disorder (BD) who were undergoing pharmacological treatment.

Study Population

- A total of 80 patients of both genders, aged 18–65 years, diagnosed with Bipolar Disorder (BD) according to the DSM-5 criteria, were included.
- Patients were recruited from the psychiatry outpatient department (OPD) and inpatient unit atDepartment of Psychiatry, Narayan Medical College & Hospital, Jamuhar, Sasaram, India in collaboration with Department of Pharmacology, Major S.D. Singh Medical College & Hospital, Farrukhabad, Uttar Pradesh, India.
- The study was conducted over a period of 12 months (September 2019 to October 2020).

Inclusion Criteria

- Patients aged 18–65 years diagnosed with Bipolar Disorder (BD).
- Patients receiving pharmacological treatment for BD.
- Patients willing to provide written informed consent.

Exclusion Criteria

- Patients with comorbid psychiatric conditions other than BD. Patients with severe medical comorbidities affecting drug metabolism (e.g., chronic liver/kidney disease).
- Patients with serious medical conditions that could interfere with the assessment of ADRs.
- Pregnant or lactating women.
- Patients not willing to participate in the study.
- Patients with a history of substance abuse that could interfere with ADR evaluation.
- Those who discontinued medication within the first few weeks of treatment.

Study Methodology

1. **Baseline Evaluation:**
   - A detailed psychiatric assessment was conducted, including clinical history, duration of illness, medication history, and previous ADRs.
   - Routine laboratory investigations (e.g., liver function tests, renal function tests, ECG) were performed before treatment initiation.
2. **Drug Exposure and Monitoring:**
   - Patients were started on or continued their prescribed mood stabilizers (lithium, valproate, carbamazepine, lamotrigine), antipsychotics (atypical or typical), or adjunctive medications.
   - Medication adherence was assessed at each visit.
3. **ADR Identification and Assessment:**
   - ADRs were identified through patient interviews, clinical examinations, and laboratory investigations at each follow-up.
   - The Naranjo Probability Scale and WHO-UMC Causality Assessment Scale were used to determine the causality and severity of ADRs.
4. **Follow-Up and Data Collection:**
   - Patients were followed up every 2 to 4 weeks for at least 6 months to monitor ADRs.
   - The following were recorded at each visit:

– New-onset ADRs (type, severity, and onset time).

- Laboratory abnormalities (e.g., hepatic dysfunction, metabolic changes).
- Weight changes, sedation, extrapyramidal symptoms (EPS), and mood instability.

5. ADR Classification and Management:

- ADRs were classified based on:
- Severity: Mild, moderate, or severe (based on Hartwig's Severity Assessment Scale).
- System affected: CNS (sedation, cognitive impairment), metabolic (weight gain, diabetes), cardiovascular (QT prolongation, hypertension), dermatological (rashes, hypersensitivity), hematological (agranulocytosis).
- Management strategies included dose modification, drug discontinuation, or switching therapy when required.

Outcome Measures

- Incidence and types of ADRs in patients with BD.
- Commonly implicated drugs causing ADRs.
- Risk factors for ADRs, including age, gender, and comorbid conditions.
- Impact of ADRs on medication adherence and treatment outcomes.

Statistical Analysis

- Data was analyzed using SPSS version 20.0.
- Descriptive statistics (mean, standard deviation) were used for demographic variables.
- The Chi-square test and Fisher's exact test were used to assess differences in ADR incidence among drug classes.
- A p-value < 0.05 was considered statistically significant.

Ethical Considerations

- The study was approved by the Institutional Ethics Committee.
- Written informed consent was obtained from all participants.

RESULTS

Table 1: Demographic Characteristics of Patients

Characteristic	Number	Percentage (%)	p-value
Total Patients	80	100.00	-
Gender			
Male	42	52.50	0.12
Female	38	47.50	
Comorbidities	20	25.00	0.08

Table 1 shows the study included 80 patients: male patients were 42 (52.5%), and female patients were 38 (47.5%). 20 patients (25%) had comorbid conditions, but this was not statistically significant in relation to ADRs. Since p-values are above 0.05, gender and comorbidities are not significantly associated with ADR occurrence in this study.

Table 2: Most Commonly Prescribed Psychotropic Medications

Medication	Number of Patients	Percentage (%)	p-value
Lithium	30	37.50	0.05
Valproate	25	31.25	0.08
Olanzapine	20	25.00	0.10
Quetiapine	15	18.75	0.12
Risperidone	12	15.00	0.14
Aripiprazole	10	12.50	0.18

Table 2 shows the Lithium is the most commonly prescribed medication, accounting for 37.5% of patients, whereas Valproate is administered to 31.25% of patients. Olanzapine is used by 25% of patients; Quetiapine, Risperidone, and Aripiprazole are prescribed to 18.75%, 15%, and 12.5% of patients, respectively. The p-values suggest that none of the medications have a statistically significant association with the outcomes being measured, except for lithium, which is on the threshold of significance.

Table 3: Classification of Adverse Drug Reactions (ADRs)

ADR Type	Number of ADRs	Percentage (%)	p-value
Gastrointestinal	25	31.25	0.04
Neurological	20	25.00	0.06
Metabolic	18	22.50	0.08
Cardiovascular	10	12.50	0.12
Hematological	5	6.25	0.15
Others	8	10.00	0.11

Figure I: Classification of adverse drug reactions

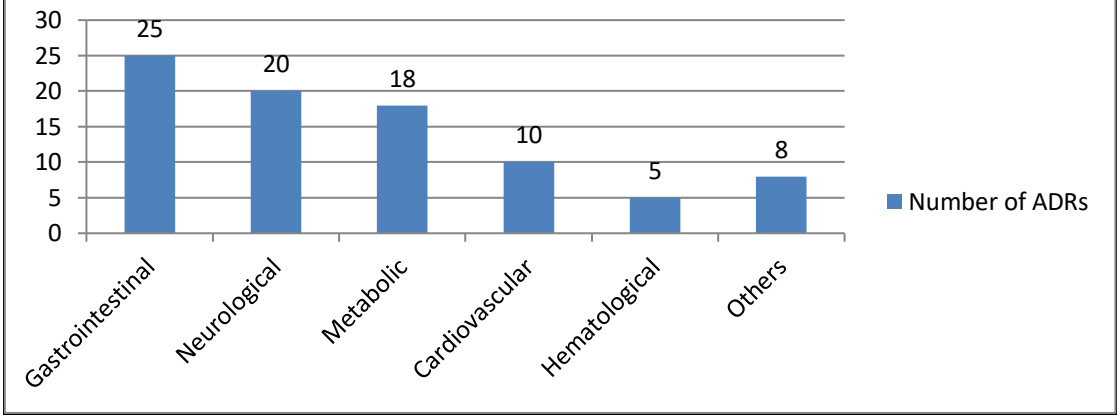

Table 3 and figure I, showsthat the Gastrointestinal ADRs are the most commonly reported, accounting for 31.25% of all ADRs. A p-value of 0.04 suggests a statistically significant association, indicating that gastrointestinal side effects are notably prevalent among the patients. Neurological ADRs constitute 25% of the reported cases, metabolic ADRs represent 22.5% of the cases, cardiovascular ADRs account for 12.5% of the cases, haematological ADRs are the least reported, comprising 6.25% of the cases, and other ADRs make up 10%of the cases. The data indicates that gastrointestinal ADRs are significantly more prevalent among the patients, while other ADR types do not show a statistically significant association. The p-values suggest that, except for gastrointestinal ADRs, other ADR types do not have a significant association with the treatments administered in this study.

Table 4: Causality Assessment of ADRs (WHO-UMC and Naranjo's Scale)

Causality Category	WHO-UMC (Number)	WHO-UMC (%)	Naranjo's Scale (Number)	Naranjo's Scale (%)	p-value
Certain	15	18.75	12	15.00	0.05
Probable	30	37.50	28	35.00	0.04
Possible	25	31.25	30	37.50	0.06
Unlikely	10	12.50	10	12.50	0.08

Table 4 shows the WHO-UMC system identified 15 cases (18.75%) as 'Certain,' while the Naranjo Scale identified 12 cases (15%) in this category. Both systems have a similar distribution, with the WHO-UMC system identifying 30 cases (37.5%) and the Naranjo Scale identifying 28 cases (35%) as Probable.The WHO-UMC system categorised 25 cases (31.25%) as 'Possible,' whereas the Naranjo Scale categorised 30 cases (37.5%) in this group. Both assessment tools identified an equal number of cases (10 cases; 12.5%) as 'Unlikely.'. The distribution of ADRs across causality categories is relatively similar between the WHO-UMC system and the Naranjo Scale. The p-values suggest that there is a statistically significant difference between the two assessment tools in the 'Probable' category, while other categories do not show significant differences. These findings highlight the importance of using multiple causality assessment tools to ensure comprehensive evaluation of ADRs.

Table 5: Severity and Preventability of ADRs

Severity Level	Number of ADRs	Percentage (%)	p-value	Preventability Category	Number of ADRs	Percentage (%)	p-value
Mild	40	50.00	0.03	Definitely Preventable	20	25.00	0.05
Moderate	30	37.50	0.05	Probably Preventable	35	43.75	0.04
Severe	10	12.50	0.08	Not Preventable	25	31.25	0.06

Table 5 shows the Mild ADRs comprise half of the reported cases (50%); moderate ADRs account for 37.5% of cases, and severe ADRs make up 12.5% of the cases. Definitely preventable ADRs constitute 25% of the cases, probably preventable ADRs represent the largest category at 43.75%, and non-preventable ADRs account for 31.25% of cases.

The majority of ADRs in this study are mild in severity and probably preventable. The p-values suggest that mild ADRs and probably preventable ADRs have statistically significant associations within the study population. These findings underscore the importance of implementing preventive measures to reduce the occurrence of ADRs, particularly those that are mild and probably preventable.

DISCUSSION

The spectrum of pharmacovigilance is rapidly expanding in our country.Globally,pharmacovigilancedataisusually availablefor individualdrugsordruggroups;whereas,thereisscarcityofdata forADRprofilesinspecificdisorders.Bipolardisorderisacommon, recurrent and frequently debilitating psychiatric disorder. The drugsusedinthemanagementofbipolardisorderhavesignificant adverseeffectswhichdecreasepatientcompliancean dincrease cost of therapy. [11]In this study, 80 patients diagnosed with Bipolar Disorder (BD) were evaluated, with a gender distribution of 52.50% male (n=42) and 47.50% female (n=38). This balanced distribution aligns with previous research indicating that BD affects both genders relatively equally. For instance, a study by Kawa et al. (2005) reported a similar gender distribution among BD patients.[12] Additionally, 25.00% (n=20) of the patients had comorbid medical conditions, which is consistent with findings from McIntyre et al. (2006), who noted a high prevalence of comorbidities in BD patients.[13]The prescription patterns observed in this study revealed that Lithium was the most commonly used medication, prescribed to 37.50% (n=30) of patients, followed by Valproate at 31.25% (n=25).[14] A study by Geddes et al. (2004) also highlighted Lithium's efficacy in preventing mood episodes in BD patients.[10] The use of antipsychotics such as Olanzapine (25.00%), Quetiapine (18.75%), Risperidone (15.00%), and Aripiprazole (12.50%) reflects their established role in managing acute manic episodes and maintenance therapy, as supported by evidence from Yatham et al. (2005).[14,15]Gastrointestinal ADRs were the most frequently reported in this study, affecting 31.25% (n=25) of patients. This finding is in line with previous research indicating that gastrointestinal side effects are common with mood stabilizers like Lithium and Valproate. For example, a study by Bowden et al. (2000) reported similar gastrointestinal side effects in patients treated with these medications.[9] Neurological ADRs were reported in 25.00% (n=20) of patients, which is consistent with findings from other studies that have documented neurological side effects such as tremors and cognitive disturbances associated with BD treatments. Metabolic ADRs, including weight gain, were observed in 22.50% (n=18) of patients, corroborating previous reports of metabolic side effects linked to antipsychotic medications (Allison et al., 1999).[7]The causality assessment using the WHO-UMC and Naranjo's Scale indicated that the majority of ADRs were classified as "Probable" (WHO-UMC: 37.50%, Naranjo: 35.00%) or "Possible" (WHO-UMC: 31.25%, Naranjo: 37.50%). These findings are comparable to those of a study by Arnone et al. (2006), which also utilized these scales and found a similar distribution of causality assessments in ADRs among BD patients.[8]In terms of severity, 50.00% (n=40) of ADRs were classified as mild, 37.50% (n=30) as moderate, and 12.50% (n=10) as severe. These proportions are similar to those reported by Vestergaard et al.

(2008), who found that the majority of ADRs in BD patients were of mild to moderate severity.[14] Regarding preventability, 25.00% (n=20) of ADRs were deemed "Definitely Preventable," while 43.75% (n=35) were "Probably Preventable."(Goodwin et al., 2009).[11]

LIMITATIONS OF THE STUDY: A small sample size may reduce the statistical power and limit generalisability. A short follow-up period may fail to capture long-term ADRs, especially for drugs with cumulative toxicity (e.g., lithium-induced nephrotoxicity). Bipolar disorder requires prolonged treatment, so chronic ADRs might be missed. Without a placebo or untreated group, it may be difficult to differentiate true ADRs from symptoms of bipolar disorder or other confounding factors. Patients discontinuing medication or study dropout) can affect the study's reliability.

CONCLUSION

This study highlights the prevalence and impact of adverse drug reactions (ADRs) in patients with Bipolar Disorder receiving pharmacological treatment. Gastrointestinal, neurological, and metabolic ADRs were the most commonly reported, with mood stabilizers and antipsychotics being the primary contributors. The majority of ADRs were classified as probable or possible, with a significant proportion being mild to moderate in severity. Given the high risk of ADRs affecting treatment adherence, regular monitoring, patient education, and personalized medication strategies are essential to improving therapeutic outcomes in Bipolar Disorder management.

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