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Original Research Article

Assessment of Drug Use Pattern and Adverse Drug Reactions in Patients with Bipolar Mood Disorder in Tertiary Care Teaching Hospital

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Abstract

Background: Prescription pattern of drugs plays an important role in helping the health care system to understand, interpret and improve the prescribing administration and using medications. Bipolar Mood Disorder is a chronic or episodic (which means occurring occasionally and at irregular intervals) mental disorder. It is characterized by recurrent episodes of mania, hypomania, depression, and mixed states separated by periods of relative euthymia. In past for bipolar mood disorder most of the drug utilization study was done in OPD bases. Present study is undertaken to evaluate the drug usage pattern and its safety profile in indoor patient at tertiary care teaching hospital.

Aims and Objectives: Assessment of drug use pattern and adverse drug reaction in patients with Bipolar Mood Disorder in tertiary care teaching hospital.

Methodology: This was a prospective, observational, single center study conducted at Psychiatry department of tertiary care teaching hospital in Gujarat from January 2019 to December 2019. Prescriptions of patients attending inpatients department were collected prospectively. Before collection of the data informed written consent of the patients was taken. The particulars of the participants were collected at the time of enrolment comprised of baseline demographics data, clinical data and therapeutic data. All data were recorded on case record forms and analyzed using descriptive statistics.

Results: A total of 1134 prescriptions were collected from 100 patients over a period of 12 months. More than half of the sample size comprised of patients between the age group of 21-40 years, out of 100 patients 70:30 being male female ratio, 73 were literate, 73 were married and 82 were unemployed. An average no. of hospital stay admitted in tertiary care teaching hospital was 11 days with ± 7.66 SD. 98 patients were prescribed mood stabilizer (Lithium turned out to be the most frequently prescribed mood stabilizer and sodium valproate ranked second). 98 patients were prescribed anti-psychotics, 2 patients were prescribed antidepressants, 99 patients were prescribed benzodiazepines. 29 different types of ADRs were noted in our study. Most of the reactions were classified as 'possible' according to WHO-UMC causality assessment scale, mild severity and found to be preventable.

Conclusion: In the present study, most frequently prescribed drugs were mood stabilizers (Lithium & Sodium Valproate). Most concomitantly prescribed drugs were Sedatives and Antipsychotic. ADR can be minimized by Therapeutic Drug Monitoring.

Introduction

Bipolar Mood Disorder is a persistent and recurrent mental illness characterized by episodes of abnormal and unstable mood, energy, activity, and cognitive function. These episodes can manifest as extreme fluctuations in mood and behavior, occurring sporadically and at irregular intervals. Bipolar disorder sometimes is called manic-depressive disorder or manic depression, which are older terms. [1] It is characterized by recurrent episodes of mania, hypomania, depression and mixed states separated by periods of relative euthymia. [2] The lifetime prevalence rates of bipolar disorder vary depending on the subtype, with Bipolar I disorder having a prevalence rate of 0-2.4%, Bipolar II disorder having a prevalence rate of 0.3-4.8%, Cyclothymia having a prevalence rate of 0.5-6.3%, and Hypomania having a prevalence rate of 2.6-7.8%. The annual incidence of bipolar disorder is generally believed to be less than 1%, although estimating this figure accurately can be challenging due to the under-diagnosis of milder forms of the disorder. [3]

The preferred initial pharmacological interventions for the treatment of bipolar disorder are mood stabilizers and atypical antipsychotics. Mood stabilizers are medications that are primarily utilized to regulate and balance mood. They are employed for the management of acute bipolar symptoms and for prophylactic treatment to prevent the recurrence of mood episodes. Additionally, adjunctive medications such as anxiolytics and antidepressants are often incorporated into the treatment plan. [4]

According to the World Health Organization (WHO), an adverse drug reaction (ADR) refers to an unintended and harmful response to a medication that occurs at doses commonly utilized in the prevention, diagnosis, or treatment of diseases, or in the alteration of normal physiological function. Monitoring adverse drug reactions (ADRs) involves the continuous surveillance of potential harmful effects that may arise from the use of medicinal products. While medications are designed to treat illnesses, they are not completely devoid of risk and may cause ADRs even when used appropriately. Therefore, it is crucial to implement ongoing ADR monitoring during the post-marketing phase of a drug's life cycle. Timely identification of drug toxicity can facilitate prompt treatment, improve patient compliance, and reduce the overall cost of therapy. [5]

Regularly reviewing patterns of drug utilization is also essential to prevent inappropriate medication use and safeguard patient safety. Every prescription must contain information such as the prescriber's name, address, and specialty, as well as the patient's name, sex, age, medication strength, quantity, dose, frequency, dosage form, and instructions for use. [6]

Drug utilization research was defined by WHO in 1977 as the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social, and economic consequences. The principal aim of drug utilization research is to facilitate the rational use of drugs in populations. [7]

In the past, most drug utilization studies for bipolar mood disorder were conducted on an outpatient basis. However, the present study aims to evaluate the pattern of drug usage and its safety profile in indoor patients at the Psychiatry department of a tertiary care teaching hospital in Gujarat.

Material and Methods

This is a prospective, observational study that was conducted at the Psychiatry department of a tertiary care teaching hospital in Gujarat from January to December 2019. The study was approved by the Departmental Screening Committee and Institutional Ethics

Committee and conducted in accordance with the guidelines of the Indian Good Clinical Practice (GCP) harmonized with the ICH-GCP guidelines. The treatment protocol of the patients remained unaffected by their participation in the study.

The inclusion criteria were patients of all ages and both sexes who were diagnosed with Bipolar Mood Disorder and attending the psychiatric inpatient department for general follow-up visits during the study period. Patients diagnosed with other psychotic disorders, such as Schizophrenia, those who were not willing to participate in the study, or those refusing to sign the Informed Consent Form were excluded from the study. Before collecting the data, informed and signed consent forms were obtained, and patients were provided with a patient information sheet to understand the study procedure and details.

A suitable case record form was designed to collect all the necessary and relevant information. The participants' particulars were collected at the time of enrollment, including baseline demographics data, clinical data, and therapeutic data collected during the study. All data were recorded on hardcopy and subsequently entered into an electronic platform. The recorded data were analyzed using descriptive statistics in Microsoft Office Excel-2013.

Results

A total of 1134 prescriptions were collected from 100 psychiatric patients of both sexes who were included in the study. As shown in Figure 1, 28% of the patients were in the 31-40 age group, followed by 24% of patients in the 21-30 age group. The patients enrolled in the study ranged in age from 16 to 68 years old, with a mean age of 37 years and a standard deviation of +/-13.42. [Figure 1] Out of the 100 patients, 70 were male and 30 were female, among whom 73 were literate, 73 were married, and 82 were unemployed, as shown in Figure 2.

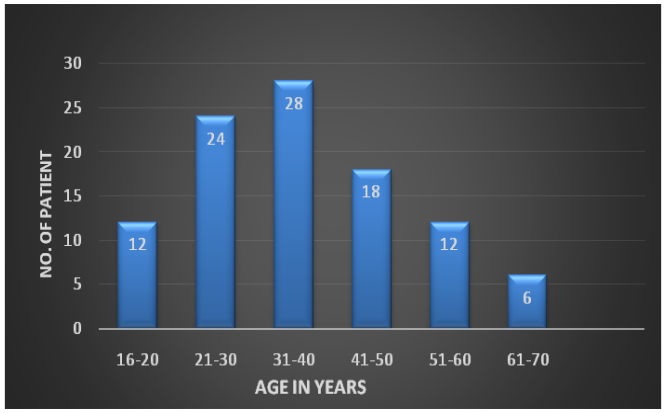

Figure 1: Age wise Distribution

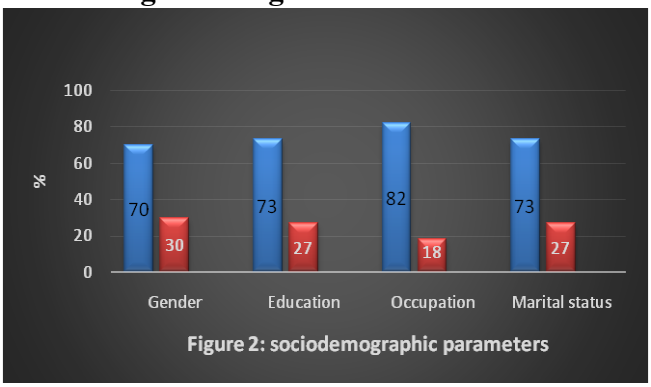

Figure 2: Socio-demographic data

The average length of hospital stay for patients admitted to the tertiary care teaching hospital was 11 days, as shown in Figure 3.

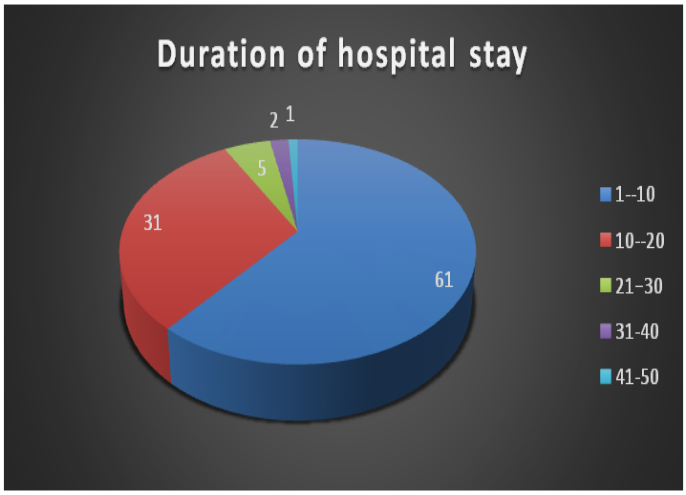

Figure 3: average length of hospital stay

The study observed that 91% of patients were prescribed a single mood stabilizer, while 7% were prescribed a combination of two mood stabilizers, as shown in Figure 4.

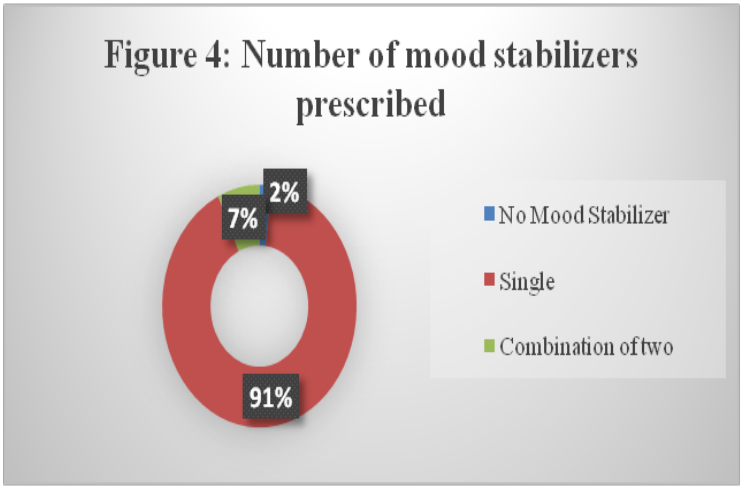

Figure 4: Number of mood stabilizers prescribed

The results of the study showed that 98 patients were prescribed anti-psychotics, 2 patients were prescribed antidepressants, and 99 patients were prescribed benzodiazepines, as presented in Table 1.

Table 1: Other medications prescribed with mood stabilizers.

Name of the medication	Number of patients
Benzodiazepines	99
Antipsychotic	98
Antidepressant	2

In the study, lithium was found to be the most frequently prescribed mood stabilizer, followed by sodium valproate, as shown in Figure 5.

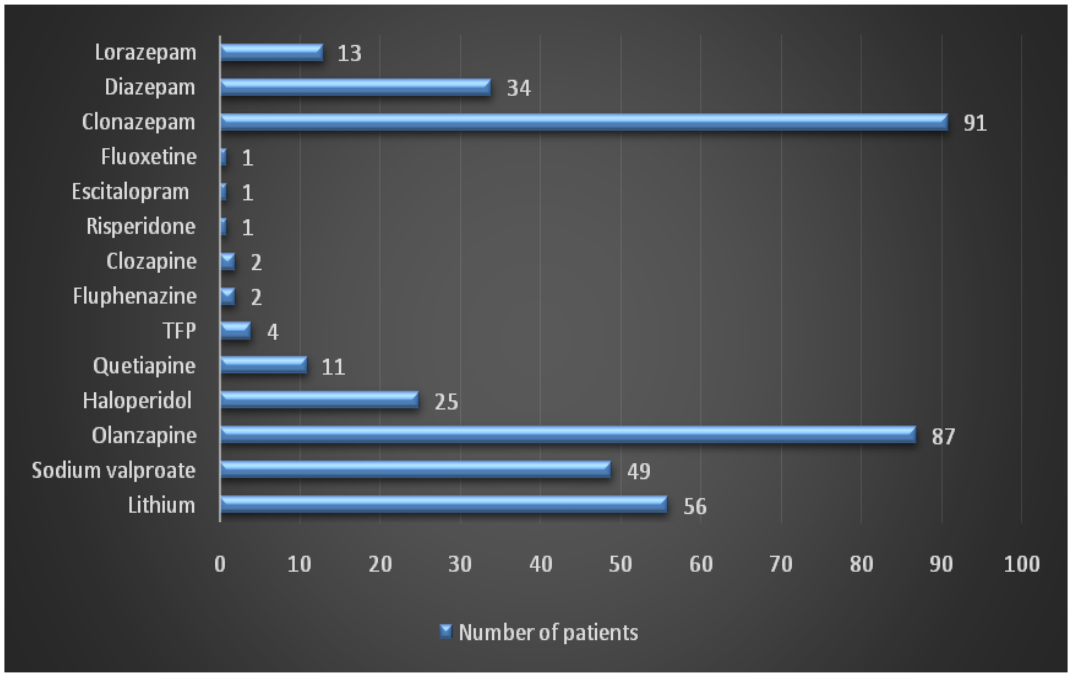

Figure 5: Most common drugs taken by medication class (N = 100)

The most frequently prescribed combinations were (Lithium + Olanzapine + Clonazepam) and (Sodium Valproate + Olanzapine + Clonazepam), as presented in Table 2. It is evident from the table that the highest number of patients received a combination of mood stabilizers with antipsychotics and benzodiazepines.

Table 2: Most frequent stable combinations by medication class (N = 100)

Sr no.	Combinations by class	Patients N (%)
1	1 Mood stabilizer + 1 Antipsychotic + 1 Benzodiazepine	49
2	1 Mood stabilizer + 2 Antipsychotics + 2 Benzodiazepines	16
3	1 Mood stabilizer + 1 Antipsychotic + 2 Benzodiazepines	10
4	1 Mood stabilizer + 2 Antipsychotics + 1 Benzodiazepine	10
5	2 Mood stabilizers + 1 Antipsychotic + 1 Benzodiazepine	4
6	1 Mood stabilizer + 1 Antipsychotic + 3 Benzodiazepines	2
7	1 Mood stabilizer + 3 Antipsychotics + 2 Benzodiazepines	2
8	2 Mood stabilizers + 2 Antipsychotics + 2 Benzodiazepines	2
9	1 Mood stabilizer + 2 Antipsychotics + 3 Benzodiazepines	1
10	1 Mood stabilizer + 1 Antipsychotic + 1 Benzodiazepine + 1 Antidepressant	1
11	2 Antipsychotics + 1 Antidepressant	1
12	1 Antipsychotic + 3 Benzodiazepines	1
13	2 Antipsychotics + 2 Benzodiazepines	1
Total		100

As presented in Table 3, the most common dose of lithium prescribed to patients was 1200 mg/day. Sodium valproate was most commonly prescribed at a dose of 800 mg/day for 15 patients, followed by 1500 mg/day for 12 patients.

Table 3: Number of patients with different dose (in mg/day) of mood stabilizers

Mood Stabilizers	600	800	900	1000	1200	1500	1600	1800	2000
Lithium	1	1	24	0	28	2	0	0	0
Sodium valproate	0	15	0	6	3	12	2	5	6

The study found that 92.28% of the drugs were prescribed using their generic name. Additionally, out of the total 3991 drugs used, 1749 (43.82%) of them were from the WHO Model List of Essential Medicines (2019). The average number of drugs prescribed per encounter was 3.51, as indicated in Table 4.

Table 4: Prescribing indicators

Prescribing Indicators	Finding
Average number of drugs per prescription	3.51
Percentage of drugs prescribed by generic name	92.28%
Percentage of drugs prescribed from WHO essential drug list	43.82%
Percentage of encounters prescribed antibiotics	0.26%
Percentage of encounters prescribed injections	18.87%

Table 5 summarizes the adverse drug reactions (ADRs) caused by different drugs used in the treatment of bipolar mood disorder.

Table 5: Evaluation of Adverse drug reactions

Sr no.	Adverse drug Reaction	No of pt	Suspected drug (WHO causality scale)	Hartwig and Siegel severity scale level	Preventability & Modified Schumock & Thornton scale
1	Tremor	15	Lithium, Sod. Valproate, Olanzapine, Quetiapine, Risperidone (Possible)	Mild	Preventable
2	Acneiform Eruption	1	Lithium (Probable)	Mild	Preventable
3	Ankle edema	1	Sod. Valproate (Probable)	Mild	Preventable
4	Constipation	3	Olanzapine (Probable)	Mild	Preventable
5	Diarrhoea	2	Lithium (Probable)	Mild	Preventable
6	Itching	1	Lithium, Fluoxetine, Quetiapine, Bexol (Possible)	Mild	Preventable
7	Nocturnal enuresis	1	Clozapine, Amlodipine (Possible)	Mild	Preventable
8	Sialorrhoea	1	Clonazepam (Probable)	Mild	Preventable
9	Tachycardia	2	Lithium (Probable)	Mild	Preventable
10	Vomiting	2	Lithium (Probable)	Mild	Preventable

The present study revealed an average of 3.5 drugs per encounter and 0.29 adverse drug reactions per patient. To investigate the correlation between the average number of drugs prescribed per day and adverse drug reactions, Pearson correlation coefficient score was used. The analysis showed a significant moderate degree of direct correlation between the average number of drugs prescribed per day and adverse drug reactions with a correlation coefficient (r) value of 0.3729. The p-value was found to be 0.0001 (Figure 6)

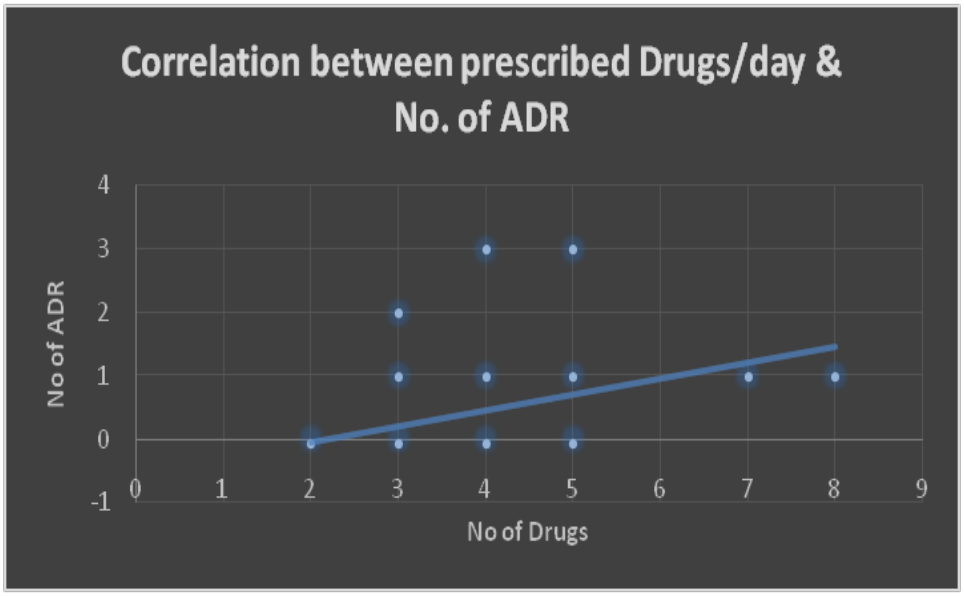

Figure 6: Correlation between prescribed drugs/day and number of ADR

In our study, we performed therapeutic drug monitoring (TDM) of Lithium in 15 patients, and a total of 10 adverse drug reactions were observed in these patients. To evaluate the correlation between TDM of Lithium and adverse drug reaction, we used Pearson correlation coefficient score. The analysis revealed a strong and statistically significant positive correlation between TDM and adverse drug reaction, with a correlation (r) value of 0.6855 and a p-value of 0.004. (Figure 7)

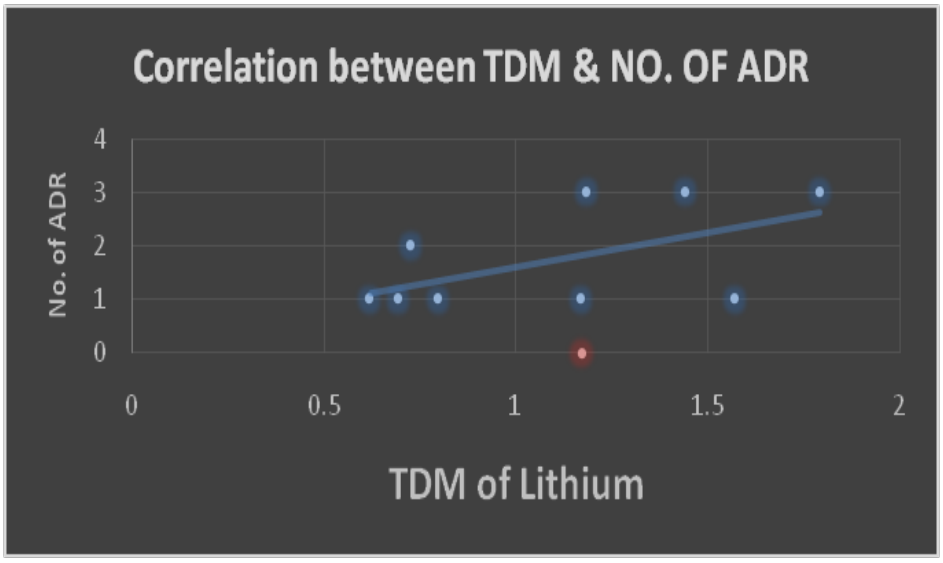

Figure 7: Correlation between TDM of Lithium and number of ADR

Table 6: Most frequently prescribed drugs and their ATC codes & Prescribed Daily Dose (PDD)

Name of Drug	ATC Code	PDD
Lithium	N05AN01	1129.35 mg
Sodium Valproate	N03AG01	1177.95 mg
Olanzapine	N05AH04	11.28 mg
Clonazepam	N03AE01	1.74 mg

Discussion

Our study was conducted in a unique setting compared to previous research. While most studies on bipolar mood disorder (BMD) have focused on outpatient care, our study specifically targeted inpatients at a tertiary care teaching hospital in Gujarat, India. This is important because patient profiles in mental hospitals in developing countries like India can vary considerably due to factors such as stigma, referral patterns, and physician expertise. While many of our findings were consistent with existing literature, our study also provided some new insights into the use of mood stabilizers and other medications in this specific setting.

In our study, more than half of the patients belonged to the age group of 21-40 years, which highlights the fact that bipolar disorder tends to affect the economically productive sections of our society. Therefore, our study highlights the need for developing better treatment regimens for bipolar disorder and making greater efforts to ensure regular and long-term compliance with medications. Similar findings have been reported by Trivedi J. K. et al. [4] and Ramdurg and Santosh [8].

In our sample, the majority of the subjects were found to be married. This could be attributed to the strong family values and beliefs in Indian society, where marriage is often considered as a potential cure for mental illness. Additionally, India is a male-dominated society where men are usually the primary breadwinners of the family. As a result, if they become mentally ill, it not only affects them but also the entire family. This could be a reason for the higher prevalence of male patients seeking treatment compared to females, as observed in the present study. Similar findings have been reported by Trivedi J. K. et al. (2018) and Ramdurg Santosh (2020). [4,8]

Out of the 100 patients included in the study, the average length of hospital stay in a tertiary care teaching hospital was found to be 11 days with a standard deviation of ± 7.66. These findings are consistent with a study by Sajatovic M. et al. [9] (2003), in which an average hospital stay of 11.6 ± 5.6 SD days was reported for 153 patients. It is noteworthy that all of the patients in our study were diagnosed with bipolar disorder type I (100%), which corresponds with the higher incidence of bipolar disorder type I worldwide. [10]

The majority of patients were prescribed a single mood stabilizer, which aligns with most guidelines that recommend using a single mood stabilizer before switching or augmenting it with another agent. However, 7% of the patients in this study were prescribed a combination of two mood stabilizers, indicating that polypharmacy is being practiced in the treatment of bipolar disorder. It is essential to justify the prescription of medications more than one, as it might be necessary to manage symptoms and ensure compliance. More than half of the patients received lithium, which is considered the only true mood stabilizer according to a literature review by Mark Bauer, MD of Brown University. Lithium has been proven to be effective in all phases of bipolar treatment, including acute mania, mania prevention, acute depression, and depression prevention. However, other medications have become more popular, and sodium valproate ranked

second in the hierarchy of prescriptions. [11]

The study highlights the need for evidence-based polypharmacy and justifying the prescription of medications. Lithium should be considered as a first-choice option, and more efforts should be made to ensure regular and long-term compliance on medications.

The study found that Carbamazepine and Lamotrigine were not frequently prescribed for bipolar disorder treatment. This may be due to the slow dosage increment required to reach an effective dose or concerns about adverse drug reactions like drug rash and Steven Johnson Syndrome, which are more commonly associated with Lamotrigine. It would be interesting to compare our treatment patterns with those followed in other reputable institutes. Many patients with bipolar disorder are admitted to the psychiatric ward during the manic phase of their illness, as it is more disruptive to attendants and others in general, while depressive symptoms may be missed at times. [12-14]

In the study, it was found that 98 patients were prescribed anti-psychotics along with mood stabilizers, 2 patients were prescribed antidepressants, 99 patients were prescribed benzodiazepines, 4 patients were prescribed propranolol along with mood stabilizer, and 1 patient was given a combination of antipsychotic with antidepressants. The most common combination of drugs prescribed was a combination of mood stabilizers with an antipsychotic and benzodiazepines, which highlights the need for initial symptomatic management. This also indicates the common complaints of the patients such as aggression (antipsychotics), disturbed sleep (benzodiazepines) and co-morbid anxiety (benzodiazepines). The treatment of bipolar disorder is individualized in clinical practice and there were 13 unique stable drug combinations prescribed for 100 patients. The most commonly prescribed drugs in these combinations were mood stabilizers. While a large number of drug combinations may be prescribed, considering only the most taken drugs in this study (2 mood stabilizers, 2 antidepressants, 6 antipsychotics, and 3 benzodiazepines), there are 9 possible combinations of mood stabilizer and antipsychotic drugs, 1 possible combination of mood stabilizer and antidepressant drugs, and 1 possible combination of mood stabilizer, antidepressant, and antipsychotic drugs. Finally, benzodiazepines were prescribed in 99 patients. [15]

The authors of the study acknowledge that there cannot be clinical trials for all possible combination therapies for bipolar disorder. While controlled studies of polypharmacy are increasing, the evidence of effectiveness and safety is limited. Some drug regimens used in the study may appear inconsistent with current guidelines, but the authors assume that these are the best regimens for the individual patient's circumstances. However, the wide variation in drug regimens and possible combinations suggest that clinicians need more evidence to optimize treatment. Although neuroscience research offers hope for a future with specifically targeted drugs, the routine use of polypharmacy highlights the importance of clinical judgment in the current treatment of bipolar disorder. [16,17]

The study found that lithium was the most commonly prescribed medication for bipolar disorder, with a dosage of 1200mg/day. The authors note that many patients admitted to the psychiatry department achieve therapeutic levels at this dose. Sodium valproate was prescribed in a dosage regimen of 800mg/day for 15 patients and 1500mg/day for 12 patients, which is lower than the recommended doses. The authors suggest that the use of lower doses may be due to a higher incidence of side effects associated with higher doses.

The authors of this study highlight that pharmacovigilance, the monitoring and reporting of adverse drug reactions (ADRs), is an important aspect of healthcare. While there is a wealth of pharmacovigilance data available globally for individual drugs or drug groups, there is a lack of data for ADR profiles in specific disorders, such as bipolar disorder. Bipolar disorder is a common and frequently debilitating psychiatric disorder, and the drugs used to manage it often have significant adverse effects. This can lead to decreased patient compliance and increased cost of therapy. The study aims to report the pattern of ADRs in bipolar disorder patients who were being treated with one or more medications.

The study found that there were 29 different types of adverse drug reactions (ADRs) noted in patients with bipolar disorder who were being treated with one or more medications. Tremor, extrapyramidal side effects (EPS), constipation, diarrhea, vomiting, tachycardia, acneiform eruption, ankle edema, itching, nocturnal enuresis, and sialorrhea were the most common ADRs observed. Mood stabilizers were associated with the majority of ADRs, with lithium being the most common drug implicated in 21 patients. Valproate was the second most commonly implicated drug. Atypical antipsychotics were also frequently prescribed, with olanzapine being the most common drug associated with ADRs, followed by risperidone. These findings are similar to those reported in a previous study by Lucca et al [18].

The study found that most of the ADRs were classified as "possible" according to WHO-UMC causality assessment scales. There were no cases of moderate or severe ADRs, and most of the reactions were of mild severity. The reactions that were most commonly observed were tremor, extrapyramidal side effects (EPS), constipation, diarrhea, vomiting, tachycardia, acneiform eruption, ankle edema, itching, nocturnal enuresis, and sialorrhea. The study also found that some of the ADRs were preventable, with vomiting and constipation being "definitely preventable" and diarrhea and EPS being "probably preventable." The most common age group in which ADRs were observed was the 21-40 years group, and the percentage of male patients who developed ADRs was slightly higher than that of female patients. The study is similar to another study by Sengupta et al., which quoted a mean age of patients with ADRs within the range observed in the current study [19,20].

he study performed a correlation analysis to investigate the relationship between the average number of drugs per encounter and therapeutic drug monitoring (TDM) of lithium with adverse drug reactions. The Pearson correlation coefficient test showed a direct strong significant correlation between the two variables, with a correlation value (r) of -0.3729 and 0.6855, respectively [21].

The study also determined the Anatomical Therapeutic Chemical (ATC) coding and Prescribed Daily Dose (PDD) for the most frequently prescribed drugs in bipolar mood disorder. The PDD for lithium was found to be 1129.35mg, for sodium valproate it was 1177.95mg, for olanzapine it was 11.28mg, and for clonazepam it was 1.74mg. [22]

Most of the studies have analyzed the prescription pattern on OPD bases, but in our study, we analyzed the prescription pattern in indoor patients with Bipolar Mood Disorder. From this study, we gained an idea of the drug use pattern, local demographic pattern of disease, and related adverse events. These data can be used to plan other studies like outcome analysis or pharmacoeconomic analysis in the field.

Conclusion

Based on our study, the prescription pattern for Bipolar Mood Disorder patients showed that mood stabilizers, specifically Lithium and Sodium Valproate, were the most commonly prescribed drugs. Concomitant

prescriptions of sedatives and antipsychotics were also observed. The study also highlighted the occurrence of adverse drug reactions (ADRs) and the importance of Therapeutic Drug Monitoring (TDM) in minimizing their occurrence. These findings can be used to develop strategies to optimize drug therapy for Bipolar Mood Disorder patients and minimize the risk of ADRs.

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