



Pharmacotherapy and Pharmacovigilance In Bipolar Affective Disorder During The Covid Pandemic: A Prospective Study

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Abstract

Background: The deleterious impact of Covid 19 in the form of social distancing and lockdown had affected the lives of people with mental illness especially bipolar disorders. Hypothetical association between the bipolar disorder and Covid 19 was the cause for initiation of this study. It was done to evaluate the safety and efficacy of drugs prescribed for this condition during this Covid pandemic.

Materials and Method: This prospective observational study was conducted for a period of 12 months in the Department of Psychiatry at Rajah Muthiah Medical College. A total of 105 bipolar disorder patients of both sexes were evaluated and their treatment was analyzed for efficacy and safety, i.e. Pharmacotherapy of drugs prescribed, drug utilization pattern and Pharmacovigilance to monitor compliance and adverse effects of drug.

Results: Majority of bipolar patients of both manic and depressive phase received Valproate sodium instead of Lithium as mood stabilizer. Among antipsychotic drugs, Risperidone was preferred to Quetiapine and Olanzapine. Clonazepam was the Benzodiazepine most commonly used in the treatment of this condition. Sedation and weight gain were adverse drug reactions frequently reported.

Conclusion: Though lithium is widely used in bipolar patients, in this study Valproate sodium, used as mood stabilizer had a greater efficacy and safety profile. Polypharmacy yielded the best results in the treatment of Bipolar affective disorder when compared to monotherapy.

Keywords: Bipolar disorder, Mood stabilizer, Pandemic, Polypharmacy

Introduction

Covid 19, a global phenomenon and an unforeseen pandemic has shattered the world much to the jeopardy of mankind. Every country in the world was forced to take stringent measures like lock down and social isolation in order to control the pandemic. The life style of the human beings was considerably altered, endangering the normal daily routine and social rhythm of the people. The resultant quarantine precipitated various problems like feelings of fear, anger, anxiety, loneliness and panic about the worst possible outcomes. Particularly individuals who were

already afflicted with mental illness worsened following the covid pandemic. People with Bipolar disorder affective disorder (BPAD) were especially vulnerable to circadian dysregulation in the face of chrono-disruptive events that led to circadian rhythm instability, precipitating mood episodes.^[1] BPAD affected about 2% of world's population in which prevalence in India was about 0.3%. Most of the patients 37% patients relapsed into depression or mania within 1 year and 60% within the second year, which implies its chronicity.^[2]

A number of the measures that have been advocated to curtail the spread of Covid-19, such as home confinement, social distancing, lockdowns and quarantine, can potentially disrupt both habitual patterns of sleep and wakefulness as well as the number and quality of social contacts and activities. This could have a deleterious influence on the risk of both manic and depressive relapses.^[3] Patients with bipolar disorders were likely to have relapses due to alterations in both availability of regular medication and medication compliance.^[4] For substance use disorder patients, this period was almost lethal as non-availability of substance or medicine could precipitate severe withdrawal symptoms or medical emergencies like delirium and seizures, which can be life threatening due to inadequate accessibility to dwindling emergency services.^[5] Substance abuse and bipolar disorder were most often linked with each other sharing a common diathesis. The comorbidity of Alcohol abuse and BPAD in a larger segment of the population, although probably hidden, produced a significant increased risk of associated psychopathology including longer duration of withdrawal from alcohol, increased severity of manic and depressive symptoms.^[6]

Hence the covid pandemic lockdown increased the vulnerability of symptoms in bipolar patients with an increased incidence of an association between seropositivity for coronaviruses and the risk of mood disorders and suicide. Though the significance of this association was unclear, it may be related to the neurotropic potential of respiratory coronaviruses, or to their ability to provoke a systemic inflammatory reaction, both of which may be associated with mood dysregulation.^[7] Therefore it was of vital importance to assess the treatment of bipolar disorder during this pandemic time.

The pharmacotherapy of bipolar disorder included mood stabilizers like lithium, valproate, and carbamazepine along with second generation atypical Typical Antipsychotics with or without benzodiazepines. Lithium the agent of “first hour” in the treatment of BD and has been used over decades in all phases of the disease. Lithium treatment aims at the prevention of relapses and is used in the treatment of acute episodes, such as mania, depression, and specific subtypes, such as mood episodes with mixed features or rapid cycling.^[8] Though lithium was found to be the best in bipolar disorder, it was not

used in this study as it required continuous monitoring of serum levels, which was not possible during this covid pandemic time, the patients were not able to come for regular follow up due to several reasons. Monitoring the drug intake and pharmacovigilance were done mainly through the phone calls. World Health Organization (WHO) defines Pharmacovigilance as “the science and activities relating to the detection, assessment, understanding and prevention of adverse drug reactions, or any other medicine-related problems”.^[9]

The main objective of this study is to assess the safety and efficacy of drug treatment and Pharmacovigilance of bipolar disorder during the covid pandemic.

Materials & Methods

Study Design: The present study was a prospective, observational study done in 105 Bipolar patients for a period of one year.

Study Setting: Study approval with proposal number IHEC/762 /2021, was obtained from Institutional Human Ethics Committee before initiating the study. Informed consent was obtained from all the subjects prior to their enrolment in the study. The study was carried out in Psychiatry department of Rajah Muthiah Medical College Hospital, Chidambaram, a tertiary care hospital.

Study Period: Study was carried out from July 2021 to June 2022.

Study Participants

Inclusion Criteria: Patients of both sexes, in the age group of 20-60 years, who were diagnosed with Bipolar Disorder were included in the study. Patients with mild to moderate comorbidities in the age group of 40-60 were also included in the study.

Exclusion Criteria: Patients who were not willing to include themselves and patients less than 20 years or above 60 years of age were excluded. Patients with severe comorbidities were also excluded from the study.

Data Sources: Sources of collecting data were Patient interview and Patient case sheet. Data sheets were prepared for 105 patients with consent forms. The details of age, sex, socio economic status, history of substance abuse, history of comorbidities,

diagnosis and prescription data were obtained from the case records as well as by interviewing patients.

Outcomes

The follow up was done at the end of one month, 6 months and at the end of the study. Telephone calls were made to assess the compliance of the patients after every month. From the observed data, efficacy of drugs, compliance of medication was assessed and Pharmacovigilance evaluation using WHO causality assessment scale was used to quantify the nature and percentage of adverse drug reactions.

Sample Size

As per the reference no.10, Single mood stabilizer prescription was 79% and keeping this prior information, the required sample size was calculated using ‘n’ master sample size software. One proportion test procedure was used. Relative precision as 10%, level of confidence as 95%, the required sample size was 102. Hence a sample of 105 was taken into consideration.

Statistical Analysis

The data were entered in excel and analyzed in SPSS 18. Data’s were expressed in frequencies and percentage.

Results

Socio-demographic status of the patients. [Vide table 1]

Among 105 patients, there were 56 male patients and 49 female patients. The sociodemographic status of the patients as summarized in Table 1. Individuals that were in the age group 41-50 years (32.3%), followed by (27.6%) in the age group 51-60 years, (22.8%) in 31-40 years and (17.1%) were in 20-30 years. Males who were alcoholics (43.8%) and smokers (8.7%) constituted the majority gender wise. Percentage of patients in Lower middle class (42.9%), Upper lower class (35.3%) and Upper middle class (21.9%). The comorbidities were minimal including mild Diabetes mellitus, Hypertension and hypothyroidism.

TABLE 1: Socio-demographic status of the patients

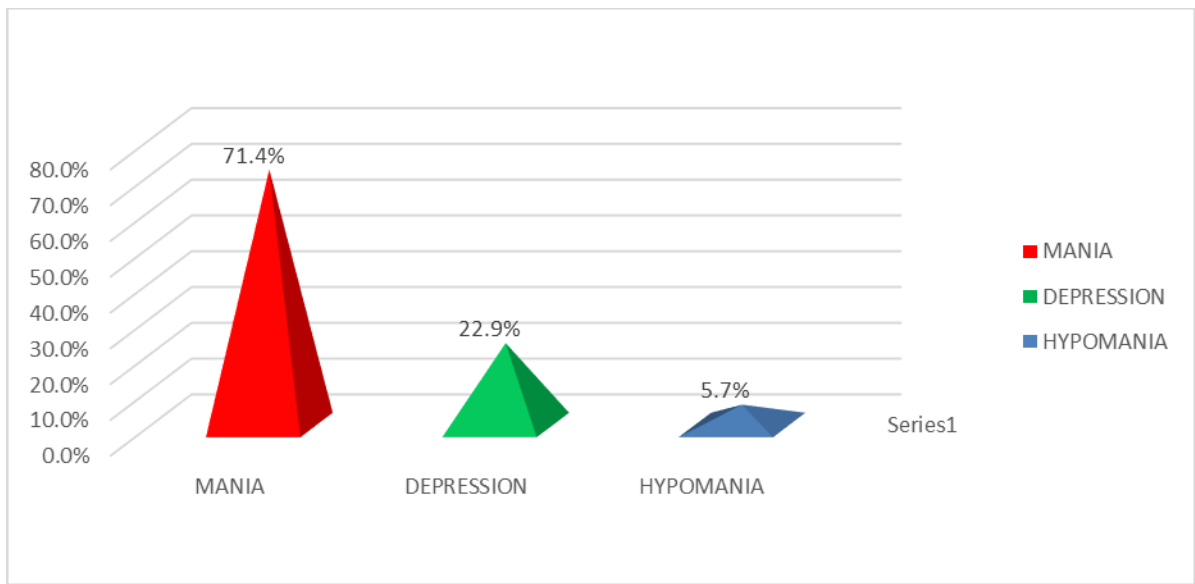
SOCIODEMOGRAPHIC STATUS	NUMBER & PERCENTAGE (N=105)
GENDER	
Male	56 (53.3%)
Female	49 (46.7 %)
AGE	
20-30	18 (17.1%)
31- 40	24 (22.8 %)
41- 50	34 (32.3%)
51 – 60	29 (27.6 %)
SUBSTANCE ABUSE	
Alcoholic	43.8%
Smoking	8.7%
SOCIOECONOMIC STATUS	
LM	45(42.9%)
UL	37 (35.3%)

UM	23 (21.9%)
COMORBIDITY DISTRIBUTION	
Patients with diabetics	13(11.4%)
Patients with hypertension	11(9.52%)
Patients with hypothyroidism	2(1.6%)

Morbidity distribution pattern. (Vide Fig 1)

Out of the 105 prescriptions analyzed, 75(71.4%) were diagnosed with the Mania, 24(22.9%) were in the depression, 6(5.7%) were in the hypomania.

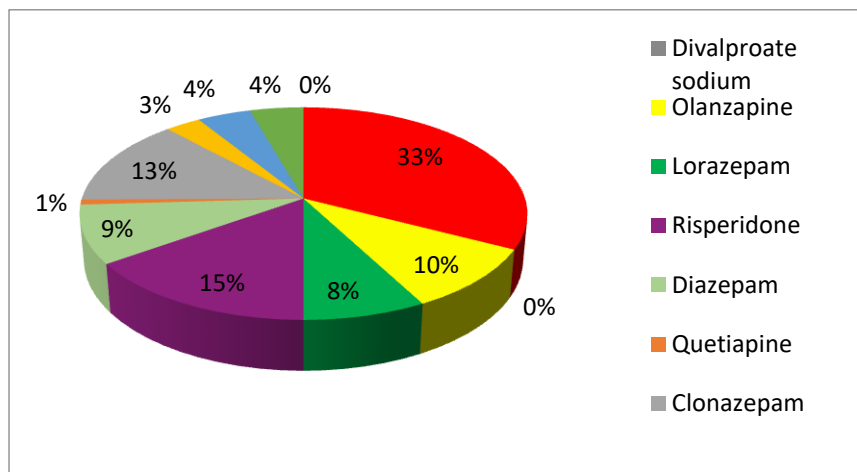
Fig 1: Morbidity distribution pattern



Drugs Prescribed in Mania: (Vide fig 2)

Among the drugs prescribed, the mood stabilizer, Valproate sodium was the most common drug prescribed for (88%), the reason being that, Lithium has lot of adverse effects and requires constant monitoring. Since this was not possible in Covid Pandemic we resorted to use of other mood stabilizers. The atypical antipsychotic Risperidone accounted for (41%) and the benzodiazepine Clonazepam (36%). The other atypical antipsychotic Olanzapine was prescribed for (26%), diazepam for (24%) and lorazepam for (21%). Only (2%) of patients were received Quetiapine.

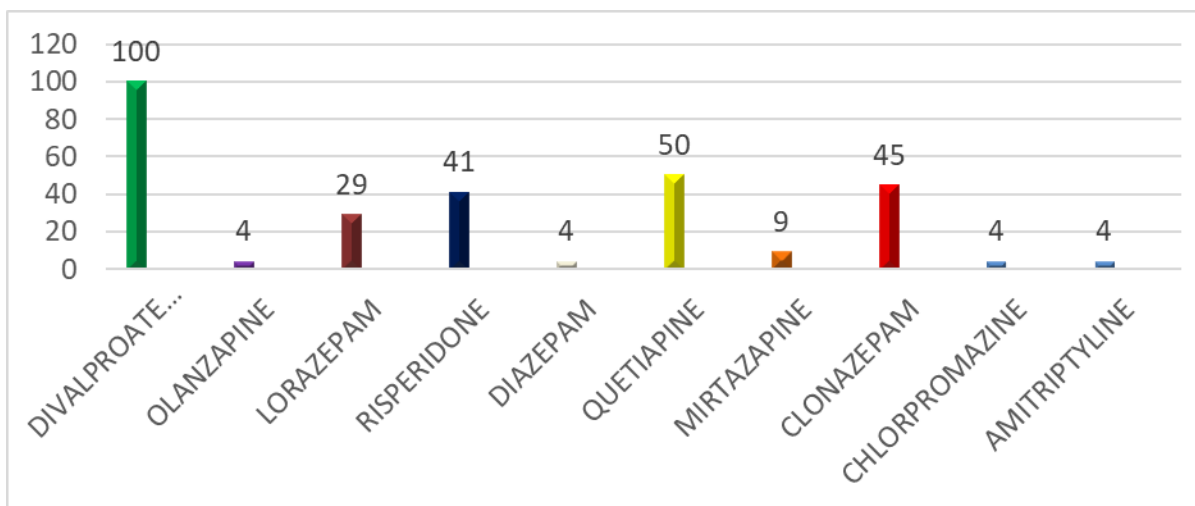
Fig 2: Drugs Prescribed in Mania



Drugs prescribed in Depression: (vide Fig 3)

Valproate sodium as mood stabilizer, was prescribed for all of patients diagnosed with depression, 100%. Quetiapine was given for (50%) followed by Clonazepam (45%). Of the atypical Typical Antipsychotics, Risperidone accounted for (41%) and the antidepressant, Mirtazapine was prescribed for (37%). Only 4% of patient had received Amitriptyline and chlorpromazine.

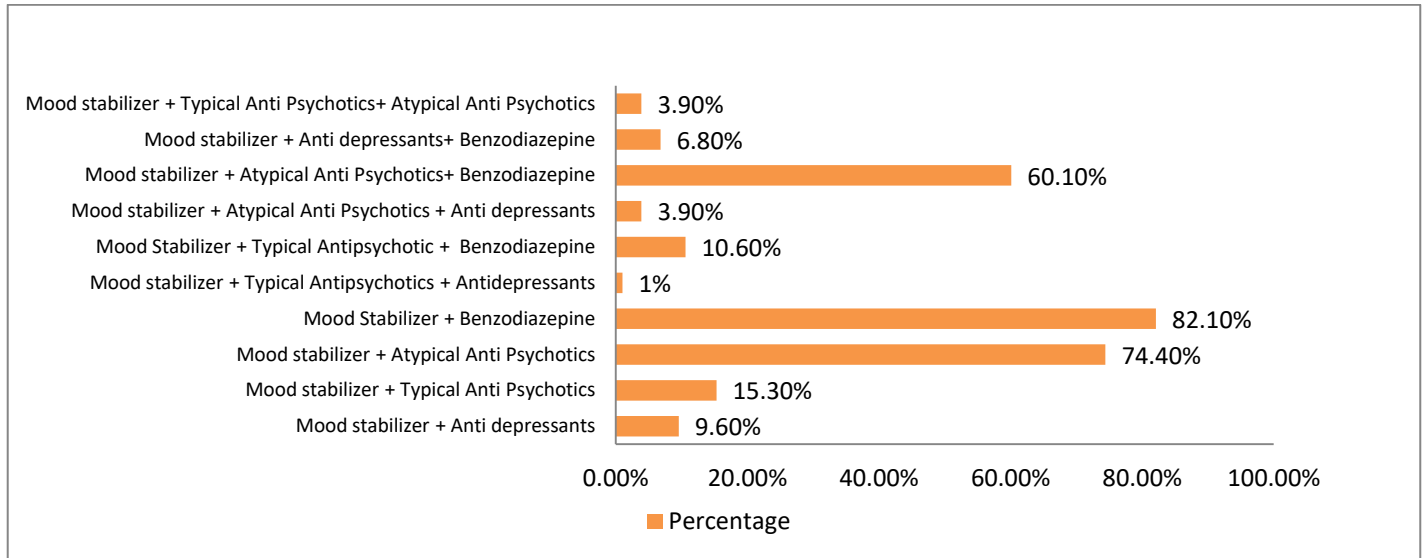
Fig 3: Drugs prescribed in Depression



Drug combinations prescribed: (Vide Fig 4)

Polypharmacy was the mainstay of therapy in this condition. Drug combination of Mood stabilizers along with benzodiazepines (82.1%) and with atypical Typical Antipsychotics (74.4%), followed by a combination of all three (60.1%). The least commonly preferred combination was Mood stabilizers and Typical Antipsychotics with Antidepressants (1%), Mood stabilizers and Atypical Typical Antipsychotics with Antidepressants 3.9%. These drugs were prescribed as individual drugs. Fixed drug combination was used only for high doses of risperidone combined along with trihexyphenidyl.

Fig 4: Drug combinations prescribed



Pharmacovigilance

Among the adverse effects observed, Sedation was most commonly reported by the patients (24.8%) followed by Weight gain (13.3%) and Asthenia (7.6%). Only (2.9%) patients reported Tremors. Hair loss with sedation was minimal (0.9%). Based on the WHO UMC causality categories 41% of cases were under Probable category, whereas 33% were under Possible category. (Vide Fig 5, Table 2)

Fig 5: Pharmacovigilance

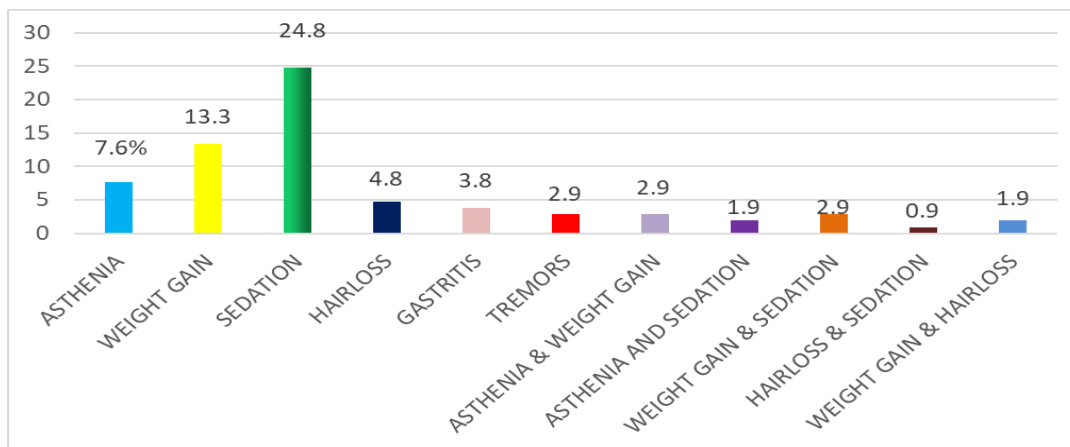


Table 2: WHO UMC Scale

Causality term	Number of ADRs	Percentage of ADRs
Certain	0	0%
Probable	41	50.6%
Possible	33	17.1%
Unlikely	0	0%
Conditional	0	0%
Un assessable	0	0%

Discussion

There was an outburst of bipolar disorder symptoms impacting Covid-19 Pandemic. Bipolar patients had more pandemic related stress, sleep difficulties and anxiety compared to normal individuals. Work related and financial difficulties due to lockdown caused great psychological stress as reported by Uvais et al who stated that onset of mania even in non- infected females occurred with or without previous psychiatric disorder.^[11] Globally 46 million people had reported bipolar disorder. The average age onset being 25 years old.^[12] The prevalence of bipolar disorder in the present study was high in the age group of 41-50 years of age, contributing to 32.3%. Such a correlation was observed in similar study in African population, by Holzapfel ME et al in which a greater number of bipolar cases were observed in age group between 36-50 years of age, which was (36.78%).^[13] This was contrast in a study by Ajitabh soni et al in which he mentioned that earlier age of onset of BPAD was common.^[14] But in the present study most of the people were above 40 years and the disease probably would have been induced by the covid-19 pandemic. Bipolar Disorders (BD) are disabling and severe psychiatric disorders, commonly perceived equally affected both men and women.^[15] Alcohol abuse with BD produced a significant increased risk like longer duration of withdrawal from alcohol, increased severity of manic and depressive symptoms increased suicide risk, poorer prognosis, higher cost, increased morbidity and overall decreased degree of function. Valproate sodium in addition to antimanic efficacy has been proven to alleviate alcohol withdrawal symptoms. The study by Conor K Farren et al reported patients of alcohol abuse to benefit from Valproate therapy.^[6] According to Laeticia et al,^[16] the correlation was more in individuals of higher socioeconomic status. In our study majority of patients in lower middle class bore the brunt of covid crisis during lockdown. Unemployment was the sole reason for such individuals. We encountered minor comorbid conditions like diabetes mellitus, hypertension, and hypothyroidism among bipolar patients which was similar to studies by Calkin et al.^[17]

Predominant polarity in Bipolar characterizes patients in whom recurrences of depression or mania/hypomania was reported. A depressive

polarity was found to prevail in studies including mainly BD type II and studies including only BD type I patients exhibited manic polarity.^[18] In our study, out of 105 patients around 75 patients were in mania polarity similar to the observation of Sandeep Grover et al.^[19]

According to a study by Arash Mowla et al, Valproate sodium was as effective as lithium in preventing mood episode recurrence in bipolar patient. Though lithium was a very effective mood stabilizer especially in all phases of bipolar disorder, it was not used in the present study because of the need for regular monitoring of blood levels which was not possible during covid pandemic. Lithium also accounted for progressive renal insufficiency and thyroid toxicity which should be ascertained prior to administration.^[20] The mood stabilizers and anti-psychotics were combined in the management of mania along with Benzodiazepines which still remains the mainstay of treatment. Atypical Typical Antipsychotics like olanzapine, quetiapine and risperidone showed better efficacy in mania compared to other drugs. Typical Typical Antipsychotics like chlorpromazine also had good efficacy in mania but was used in a small percent of patients in our study as also quoted by ninoslav mimica et al.^[21]

The diagnosis and treatment of bipolar depression poses a challenge with around 15% of people manifesting a suicidal tendency. Statistics reflected the severity and frequency of depressive episodes. Bipolar depression indicated a greater socio-economic burden than either mania or unipolar major depression and comprised majority of symptomatic illness in this condition with respect to time. Antidepressants, still widely used in bipolar depression, helped to minimize breakthrough episodes occurring in those on mood stabilizers. Risk of cycle acceleration and/or switching needed for further evaluation.^[22] Combination of valproate and antidepressants or mood stabilizers/Typical Antipsychotics and anti-depressants still remains the main stay of treatment of BPAD – Depression which coincided with Shah et al.^[23] Antidepressants as monotherapy were rarely used in this study as they had a tendency to cause switching to mania phase. Antidepressants were minimally used only when mood stabilizer and Typical Antipsychotics did not improve the patient depressive symptomology.^[24] The

symptomology was validated by Hamilton depression rating scale and Young mania's rating scale. Here Quetiapine was preferred as it was prescribed in other studies mentioned by Jann MW *et al.*^[25] In this study the patients who used the antidepressant Mirtazapine were benefited from therapy. Wichiniak A *et al.* suggested that use of sleep promoting antidepressants like mirtazapine decreased the risk of switching, because of effective treatment of insomnia. In bipolar patient it improves the course of disorder, hence mirtazapine was a safer alternative.^[26]

Polypharmacy was often observed in the therapy of BPAD and in general was an add on strategy to accelerate the therapeutic effect. In BPAD it was given with minimum doses of mood stabilizer and Typical Antipsychotics. In our present study, combinations were preferred, because the beneficial effect of the combination at therapeutic dose was more than the adverse effect caused by increasing the dose of single drug. So this combination of mood stabilizer and atypical antipsychotic was highly preferred in this present study and they produced a very good response when given in combination. Jain A *et al.*^[27]

Pharmacovigilance

All the effective drugs used for the treatment of bipolar disorder, no matter how competently used, may cause adverse reactions. Thus, a continuous monitoring of ADRs during post marketing phase was essential. Early detection of drug toxicity helped in timely treatment of the patient, improves compliance and decreases cost of therapy. In BPAD, adverse drug reactions occurred because of use of mood stabilizers and Typical Antipsychotics. Of the adverse drug reactions observed during follow up sedation was predominantly found followed by weight gain, asthenia and hair loss.

In a similar study Aashal Shah *et al.* stated that mood stabilizers were responsible for 90% of most of the Adverse drug reactions (ADR) followed by Typical Antipsychotics.^[28] Weight gain was observed in many of the patients on this regimen. Although not preventable, we can motivate the patients for life style modifications like doing exercises regularly, balanced diet as evidenced by the studies of Calkin CV *et al.* and Jann MW *et al.*^[17, 25]

The extrapyramidal symptoms like tremors reported by the patients was due to antipsychotic therapy. This could be prevented by taking anticholinergic like trihexyphenidyl which was given as FDC. Hair loss was also reported by few patients in the study with Valproate sodium. Thinning of hair by Valproate sodium was in line with the study by Druschly.K *et al.*^[29] The present study categorized according to WHO-UMC causality scale, reported most of cases under 'probable' followed by 'possible' category. None of the cases was reported as "certain" since no rechallenge was done. Aashal Shah *et al.* made same observations, the ADRs likely to be encountered in bipolar patients were often mild in nature. Regarding causality assessment, maximum cases were classified as 'probable' based on WHO-UMC scale.^[28]

Conclusion

By and large it can be presumed that more number of people were affected by bipolar disorder during the covid-19 pandemic. This implies that there was a significant underlying relationship between bipolar disorder and covid-19 pandemics noticeable in the age group of 41-50 years of age, observed mainly in the male patients who were alcoholics. Polarity indicates Mania phase predominantly. From the prescription analysis, mood stabilizer along with Typical Antipsychotics showed maximum efficacy in accordance with Hamilton depression rating scale and Young mania rating scale. Among the mood stabilizers, Valproate sodium was preferred to Lithium, because it showed better tolerability profile, better patient compliance and required less need for Therapeutic drug monitoring. Risperidone and Quetiapine was often prescribed when the patients reported in depressive phase. Antidepressants were minimally used in the treatment of BPAD. Among the Benzodiazepines, Clonazepam was preferred in the pharmacotherapy of BPAD.

During the follow up period, adverse effects commonly noted was Sedation and weight gain. These adverse effects based upon the WHO UMC assessment scale were reported to be 'probable' and 'possible' events. Most of the drugs were available as free of cost and patients had to bear only partial cost of other drugs. Polypharmacy yielded the best results in the treatment of bipolar disorder when compared to monotherapy. Majority of the drugs were

prescribed in generic names. Drugs prescribed were according to the WHO/INURD indicators.

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