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Original Research Article

Drug Utilization Pattern and Adverse Drug Profile of Psychotropic Drugs in Outpatient Department of Psychiatry of Tertiary Care Teaching Hospital

Ankur F Chaudhari[1], Dinesh M Parmar[2], Pooja J Patel[3], Hiren R Trivedi[4]

[1]MD Pharmacology, Tutor in Pharmacology Department, NAMO Medical Education and Research Institute, Silvassa. Dadra and Nagar Haveli and Daman and Diu

[2]Associate Professor, Pharmacology Department, Shri M P Shah Government Medical College, Jamnagar, Gujarat

[3]Assistant Professor, Department of Anaesthesia, NAMO Medical Education and Research Institute, Silvassa, Dadra and Nagar Haveli and Daman and Diu

[4]Professor and Head, Department of Pharmacology, Shri M P Shah Government Medical College, Jamnagar

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Corresponding author: Dr Ankur F Chaudhari

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Abstract

Background: Psychiatric illnesses are one of the major causes of morbidity nowadays. Mental and behavioral disorders are universal across all regions, societies and countries not exclusively limited to any special group. Prescription of psychotropic drugs are increasing day by day which results increase health care cost of person and country, occurrence of number of adverse drug reactions (ADRs), noncompliance, discontinuation of therapy and prolong hospitalization. In developing countries like India, various factors like cost and availability of drugs, local paradigms, decision of physician, and social and culture-specific barriers play important role in prescription of psychotropic drugs.

Material and Methods: A prospective cross sectional drug utilization study was carried out in 600 patients visiting psychiatric outpatient department after approval from institutional ethics committee. Drug use indicators and adverse drug reactions (ADRs) due to psychotropic drugs were analyzed as per study criteria.

Results: Major depressive disorder (34.66%) and schizophrenia (30%) accounts highest morbidity among observed psychiatric illnesses. Most of the psychiatric illnesses were found in the age group of 35-44 years in both sexes.Out of the 600 patients surveyed, 299(49.83%) and 301(50.16%) belonged to male and female respectively. Around 93.33% drugs are prescribed by generic name among the prescribed drugs. 42.85% drugs are prescribed from WHO Essential drug list (2017) and National Essential drug list (2015). Atypical antipsychotics were more prescribed than typical antipsychotics in schizophrenia. Anticholinergic drug was co-prescribed in schizophrenic encounters parallel to antipsychotic drugs suggest its overuse and irrational use. Prescribing frequency of selective serotonin reuptake inhibitors (SSRI) was found greater than tricyclic antidepressant in major depression. Lithium (36.73%) and sodium valproate (35.71%) were prescribed in bipolar mood disorders in decreasing order. Average cost for psychotropic drugs per encounter was 60.54 INR per month. 64 patients (10.66%) from the total of 600 patients developed ADR. ADRs were observed most commonly in age group of 25-34 years according to preferred

term (PT), tremor (21.87%) followed by salivation (12.5%) and rigidity (9.375%) were most commonly reported reactions. Risperidone was responsible for most of the ADR (37.5%) followed by lithium (14.06%) and fluoxetine (12.5%).

Conclusion: Major depressive disorder was the most common psychiatric illness followed by schizophrenia, bipolar mood disorder and schizoaffective disorder. Females were more affected with depressive disorder while males with schizophrenia, bipolar mood disorder. Most of the psychiatric illnesses were found in the age group of 35-44 years in both sexes. Atypical antipsychotics were more prescribed than typical antipsychotics in schizophrenia. Prescribing frequency of selective serotonin reuptake inhibitors (SSRI) was found greater than tricyclic antidepressant in major depression. Lithium and sodium valproate were prescribed in bipolar mood disorders in decreasing order.

Keywords: Schizophrenic, National Essential Drug List, Anticholinergic Drugs, ADR

Introduction

Drug Utilization was defined by the 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 implications" [1]. Drug utilization forms the basis for implementation of drug dispensing policies at national as well as local level [2]. It describes the extent, nature and determinants of drug exposures as a fundamental and essential part of pharmacoepidemiology [3].

Mental and behavioral disorders are universal across all regions, societies and countries not exclusively limited to any special group. Neuropsychiatry disorders analysed between 1990 and 2016 were the leading cause of DALYs and second leading cause of deaths. The absolute number of deaths and DALYs from all neurological disorders combined increased (deaths by 39% and DALYs by 15%) whereas their age-standardized rates decreased (deaths by 28% and DALYs by 27%) [4]. Disorders of mood, thinking, and behavior may be due to a primary psychiatric diagnosis (DSM-IV Axis I major psychiatric disorders) or a personality disorder (DSM-IV Axis II disorders) or may be secondary to metabolic abnormalities, drug toxicities, focal cerebral lesions, seizure disorders, or degenerative neurologic disease [5]

Prescription of psychotropic drugs are increasing day by day which results occurrence of number of adverse drug reactions (ADR), sometime may be fatal [6]. These ADRs can lead to noncompliance, discontinuation of therapy and prolong hospitalization [7]. In developing countries like India, ADRs due to psychotropic drugs are still underreported and limited numbers of reports are available on the ADR profile of pharmacological agents.

The objective of present study was to focus on the trends in the drug utilization study of psychotropic drugs and to evaluate the clinical spectrum of all adverse drug reactions of antipsychotic drugs in the department of psychiatric.

Methodology

A cross sectional, prospective drug utilization study was carried out in outdoor patient of psychiatry department in a tertiary care teaching hospital attached to medical college, Jamnagar. Prior to initiation of study, approval from Institutional Ethical Committee was obtained for conducting the study. Patients of all age groups of either sex including pregnancy and lactating mothers attending the

psychiatry outpatient department were included in this study. Exclusion criteria for the study participants were referred indoor cases from other departments, patients with epilepsy, autism patients and patients with uncertain diagnosis. As per the WHO recommendations for conduction of drug utilization study, six hundred prescriptions were collected. Data of patients matching inclusion criteria were recorded in case record form.The diagnosis of the adverse drug reaction (ADR) was done by a consultant physician based on clinical and laboratory investigation data. All the information of ADR was recorded in CDSCO suspected ADR reporting form.

Results

Out of 600 encounters, most frequent morbidity found was major depressive disorders (37.6%), next to that were schizophrenia (34.8%), bipolar mood disorder (16.3%) and schizoaffective disorder (3.8%). Obsessive compulsive disorder, brief psychotic disorder, mental retardation, anxiety disorders and social phobia cases were reported in less frequent numbers among total encounters surveyed. (Table 1)

Table 1: Morbidity pattern of psychiatric illness observed in out-patients

S. N.	Diagnosis	Male (%)	Female (%)	Total (%)
1	Major depressive disorder	91(15.1)	135(22.5)	226(37.6)
2	Schizophrenic disorder	108(18)	101(16.8)	209(34.8)
3	Bipolar mood disorder	62(10.3)	36(6)	98(16.3)
4	Schizoaffective disorder	14(2.3)	9(1.5)	23(3.8)
5	Anxiety disorders	6(1)	14(2.3)	20(3.3)
6	Other psychiatric illnesses	18(3)	6(1)	24(4)
Total		299(49.8)	301(50.2)	600(100)

In our study, mean ± SD of age of male and female patients of schizophrenia is 40.82 ± 13.931 years and 40.75 ± 13.95 years respectively in 209 patients. While in major depressive disease out of 226 patients, mean ± SD of age of male and female patients were 40.71 ± 13.91 years and 40.72 ± 13.90 respectively. Among bipolar mood disorders, 40.72 ± 13.97 years and 41.03 ± 13.89 years were mean ± SD of age of male and female patients respectively. (Table 2)

Table 2: Sex wise distribution of various psychiatric illnesses

Psychiatric Illness	Male (mean±SD)	Female (mean±SD)	Total (%)
Schizophrenia	108 (40.82 ± 13.9)	101 (40.75 ± 13.9)	209(34.8)
Major depressive disease	91 (40.71 ± 13.9)	135 (40.72 ± 13.9)	226(37.6)
Bipolar mood disorder	62 (40.72 ± 13.9)	36 (41.03 ± 13.9)	98(16.3)

The total number of psychotropic drugs prescribed was 1499 in 600 encounters surveyed. The average number of drugs per encounter was 2.50 in our study with prescribing range of 1-6.

In our study 42.8% drugs were prescribed from WHO Essential Drug List (EDL) and National list of Essential Medicine (NLEM), 2015 while 57.1% drugs were not prescribed from WHO EDL or NLEM. In present study majority of the drugs (93.33%) were prescribed by its generic names while 6.66% drugs were prescribed by brand names. The drugs prescribed other than antipsychotic agents were vitamin B complex (26.7%), folic acid (5%), antacid (2%), and analgesic (1%).

In schizophrenia, most commonly prescribed drugs are were diazepam (65%) followed by risperidone (51.7%), trihexyphenidyl (49.3%) olanzapine (37.3%), clozapine (11.5%), trifluoperazine (8.1%) (figure1)

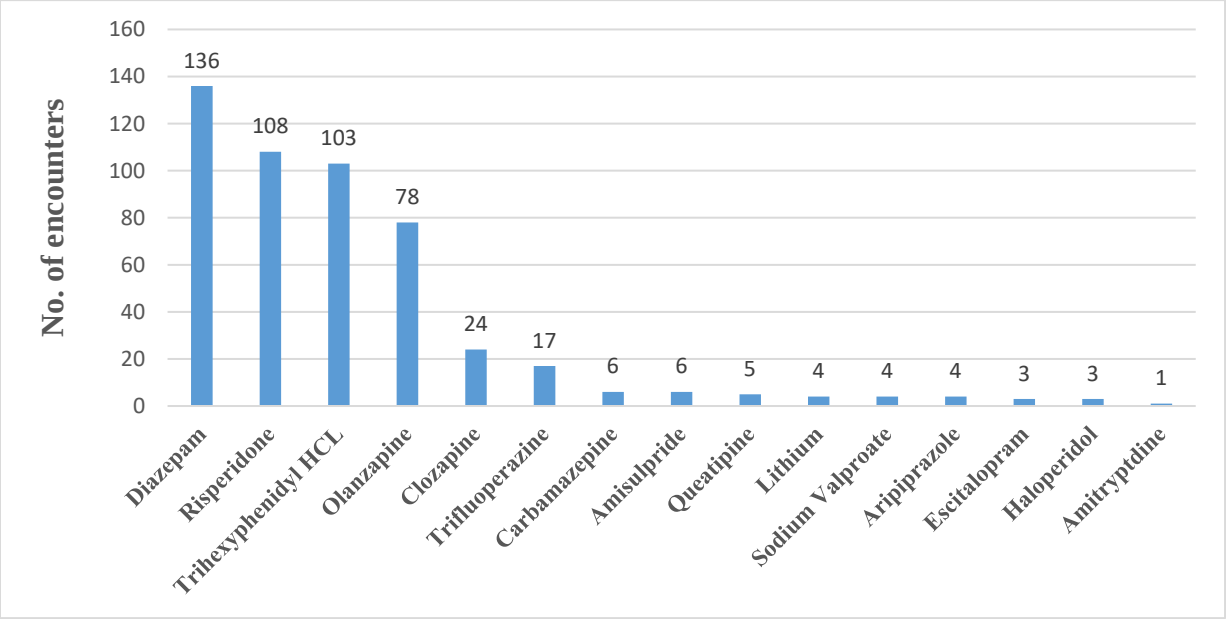

Figure 1: Frequency of psychotropic drug usage in schizophrenia

In major depressive disorder, majority of the patients were prescribed clonazepam (63.7%) and escitalopram (46%) followed by imipramine (36.3%), diazepam (28.8%) and fluoxetine (23.9%). (Figure-2)

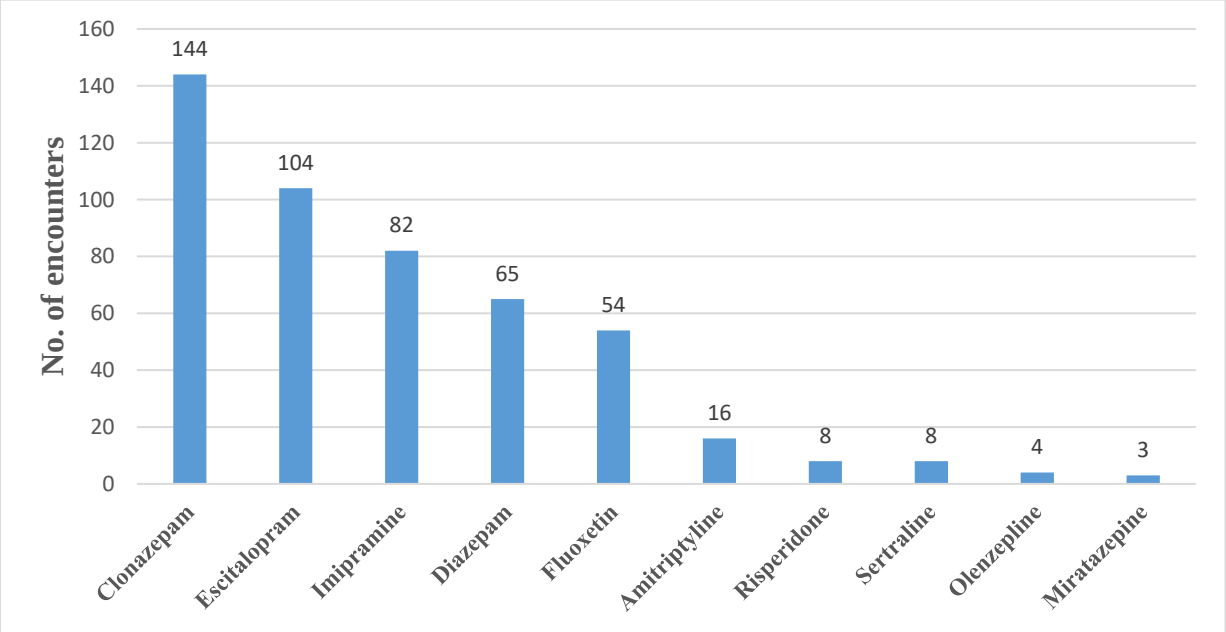

Figure 2: Frequency of psychotropic drug usage in major depression

In bipolar mood disorder, most commonly prescribed antipsychotic agent was olanzapine in 44.89% patient followed by diazepam (39.79%), lithium (36.73%), sodium valproate (35.71%), and clonazepam (28.57%) (Figure-3)

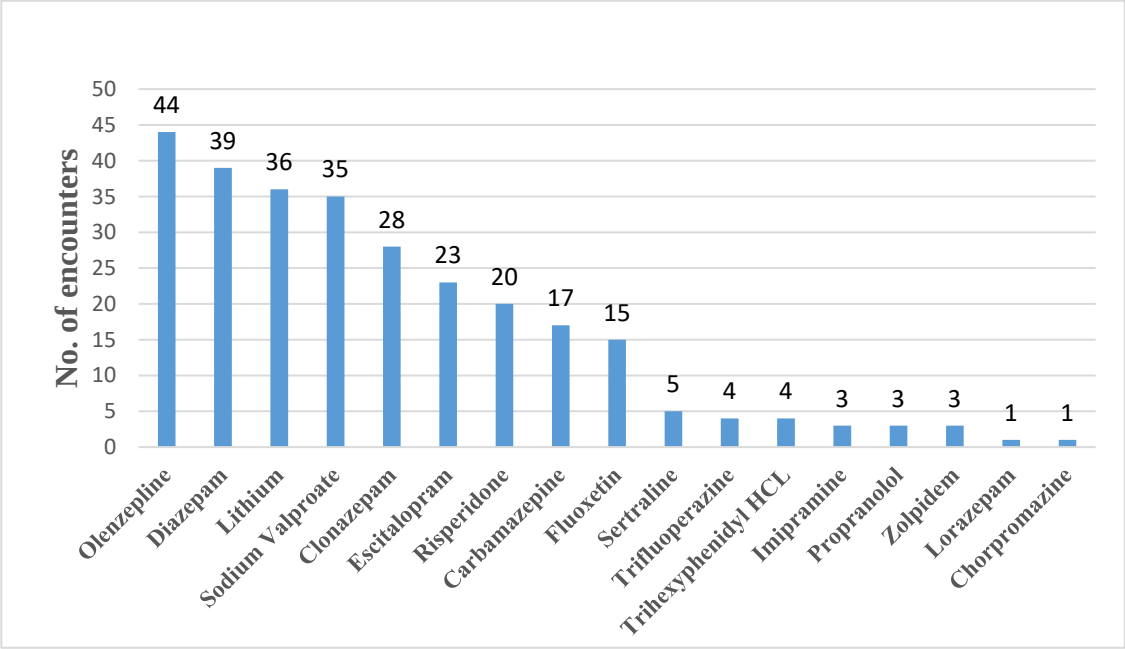

Figure 3: Drugs prescribed in bipolar mood disorder

The average cost per prescription was 2.018 INR, out of 600 prescriptions. ATC/DDD classification, PDD values and PDD/DDD ratio of psychotropic drugs prescribed in our study on 600 patients attending the psychiatry outpatient department mentioned in table 3.

** For conversion of dose of lithium from mg to mmol the formula used was (16): mg/l × 0.144 = mmol/l × 6.94

Table 3: Prescribed Daily dose (PDD), Defined Daily Dose (DDD) and PDD/DDD ratio of most frequently prescribed psychotropic drugs

Drug	ATC Code	DDD (mg)	PDD (mg)	PDD/DDD
Sodium valproate	N03AG01	1500	804.65	0.53
Carbamazepine	N03AF01	1000	589.28	0.58
Lithium**	N05AN01	24 mmol	694.44	0.74
Clozapine	N05AH02	300	106.62	0.35
Amitriptyline	N06AA09	75	77.94	1.02
Imipramine	N06AA02	100	64.56	0.64
Fluoxetine	N06AB03	20	33.17	1.65
Trifluoperazine	N05AB06	20	21.30	1.05
Escitalopram	N06AB10	10	14.89	1.4
Olanzapine	N05AH03	10	12.24	1.2
Diazepam	N05BA01	10	5.04	0.5
Risperidone	N05AX08	5	4.15	0.82
Trihexyphenidyl HCL	N04AA01	10	2.88	0.28
Tab. Clonazepam	N03AE01	8	0.59	0.07

In our study, risperidone was responsible for about 37.5% of the adverse drug reactions followed by lithium (14.06%), fluoxetine (12.5%) and imipramine (9.37%). (Table 4)

Table 4: Adverse drug reactions causing antipsychotic drugs

Drug class	Drug	No of adverse drug reaction (%)
Antipsychotic	Risperidone	24(37.5%)
	Olanzapine	5(7.81%)
	Trifluoperazine	5(7.81%)
	Clozapine	4(6.25%)
	Haloperidol	3(4.68%)
Antidepressant	Fluoxetine	8(12.5%)
	Imipramine	6(9.375%)
Mood stabilizer	Lithium	9(14.06%)

Discussion

Magnitude of clinical problem of major depressive disorder 37.6% has consistently attracted the attention of major figures in total encounters surveyed, next to that schizophrenia accounts 34.8%, bipolar mood disorder 16.3%. Study conducted in Madhya Pradesh by Rode *et al* showed that among 520 psychiatric patients most common Psychiatric illness was depression 42.9% followed by schizophrenia 23% and bipolar mood disorders 17.9% which is comparable to our study. In India survey of mental morbidity was carried out in specialized hospitals for mental disorder in 2004. Total numbers of outdoor cases treated were 896425, among those, numbers of cases were 0.75% of psychotic substance users, 6% of schizophrenia, 3.5% of mood disorder, 4.2% of neurotic and stress related, 0.1% disorders occurring in childhood found [8]. Epidemiological Catchment Areas (AEC) sponsored by the National Institute of Mental Health reported a life time prevalence of schizophrenia 0.6 to 1.9 percent, roughly equal worldwide [9].

In this study, female accounts high frequency as compared to male to be having major depression. Among the female patients high frequency 19.9% is noted in age group 35- 44 years while in male most frequency in patients 8.84% in age group of 25-34 years. Study conducted in ahmedabad by Memon *et al.* showed that among 489 patients depression was reported in 41.53% of male and 58.57% of female which is comparable to our study [10]. Study conducted in Madhya Pradesh by Rode *et al.* showed that among 520 psychiatric patients depression was found in 42.9% [11]. Among 520 patient number of female patients observed is 53.8% and number of male patient observed was 46.2%. It also accounts depression high frequency in female patients. The mean age of onset of major depression is 40 years while 50% of patients having an onset between the age group of 20-50 years. Recent epidemiological data suggest that the incidence of major depressive disorder may increase among people less than 20 years old. This may be related to the increased use of alcohol and drugs of abuse in this age group [9]. An almost universal observation independent of country or culture is the twofold greater prevalence of major depressive disorder in women than in men. The reasons for the difference have been hypothesized to involve hormonal differences, the effects of childbirth, differing psychosocial stress for women and for men. Manic episodes are more common in men, and depressive episodes are more common in women. When manic episodes occur in women, they are more likely than men to present a mixed picture (mania and depression) [9].

Among 209 of encounters of schizophrenia, male patients 51.67% accounts more than half of total encounters, while female patients were 48.32%. Study conducted by Thakkar *et al.* in mumbai showed that 30% of the patients were schizophrenia which is comparable to our study. Total numbers of male were 112(62.22%) and female were 78(37.78%). As this is a cross sectional study includes both old

and new case, age of onset of disease can't be detected.

Among 98 encounters of bipolar mood disorder, number of male patients and female patients are 62 (63.26%) and 36(36.73%) respectively**.** Among both sex more affected age group is 35-44 years in female and 25-34 years in male. Study conducted in Madhya Pradesh by Rode *et al.* showed that among 520 psychiatric patients bipolar disorder found in male patients was 53(56.98%) and female was 40 (46.02%) which is comparable to our study.

In our study the total number of different psychotropic drugs prescribed was 1499 in 600 encounters surveyed. The average number of psychotropic drugs per encounter prescribed was 2.50 with prescribed range of 1 to 6. Pharmaco-epidemiological study done by Rode *et al*. observed average number of psychotropic drugs per encounter was 2.1 among 520 patients with total 1092 psychotropic drugs [11]. Similar study conducted at Jamnagar by Piparva *et al*. showed that among 600 patients total 1756 psychotropic drugs are prescribed and average number of psychotropic drugs per encounter prescribed is 2.96 with total range of drug 1-6 [3].

Apart from psychotropic drugs, few encounters also prescribed drugs like co-prescribing of drugs other then psychotropic drugs like vitamin B complex, folic acid, antacid, analgesic, antipyretic and iron in 160 prescriptions with vitamin B complex prescribed most commonly. Study conducted by Thakkar *et al*. showed that commonly co-prescribed drugs were calcium lactate, vitamin B complex and multivitamins [12]. There are varieties of vitamin deficiencies that can contribute to depression symptoms like vitamin B3 (niacin), vitamin B5 (pantothenic acid), vitamin B6 (pyridoxine), vitamin B12 and folic acid. Harmful side effect of psychiatric drugs can be treated with vitamins E and vitamin B6 like neuroleptic malignant syndrome, a fairly rare but serious side effect of psychiatric drugs [13].

In our study, 42.85% drugs were prescribed from WHO Essential Drug List formulary, 2017 and National Essential Drug List. This was comparable to study conducted by Rode *et al.* in which total 28.57% drugs were prescribed from WHO Essential Drug List and National Essential drug list. In our study 98.33% drugs were prescribed by generic name and 6.66% drugs were prescribed by brand name which was comparable to study conducted by Thakkar *et al.* in which 76.01% drugs were prescribed from generic name [12]. Drugs with Generic name were prescribed more than Brand name in our study. Increasing generic prescribing would rationalize the use and reduce the cost of drugs [14].

In present study, most commonly prescribed drugs in schizophrenia were diazepam (65.07%) followed by risperidone (51.67%), olanzapine (37.32%), trihexyphenidyl (12%), and clozapine (11.48%). Atypical antipsychotic risperidone and olanzapine were more frequently prescribed than typical antipsychotic drugs during this study. It was comparable with study done at Pondicherry by Lahon *et al.* observed most commonly antipsychotic drug were olanzapine in 65.66% and risperidone in 19.19% of patients [15]. Antipsychotic are the keystone in schizophrenia treatment and now rated as first-line agents for adjunctive treatment of mania because their low propensity to cause EPS, efficacy against refractory cases and better control over negative symptoms; better tolerance and low relapse rate and safer adverse effect profile. Atypical antipsychotic are also rated as first-line agents for combined treatment of psychotic depression and they are strongly preferred when an antipsychotic is required for long-term maintenance [16].

One observation found in our study was that the prescribing frequency of central anticholinergics drug trihexyphenydyl was 49.28%. As it is accounting higher prescribing frequency means that it was prescribed with all antipsychotics whether these were typical or atypical. The prescribing frequency was lower

compare to study by Thakkar *et al*. with prescribing frequency of 64% in schizophrenia patients [12].

In major depression patients, clonazepam (63.71%) and escitalopram (46.01%) were prescribed more commonly. Next in line were imipramine (36.28%), diazepam (28.76%) and fluoxetine (23.89%). This result is comparable to Rode *et al*. study observed most commonly prescribed drugs were escitalopram (39.21%) followed by amitriptyline (24.1%) and imipramine (16.55%).(11) With regard to antidepressants, selective serotonin reuptake inhibitors (SSRI) were the most commonly prescribed compared to tricyclic anti-depressants.

In bipolar mood disorder patients**,** most commonly prescribed drug were olanzapine (44.89%) and diazepam (39.79%) followed by lithium (36.73%), sodium valproate (35.71%) and clonazepam (28.57%). Study conducted by Rode *et al*. showed carbamazepine (49.1%), valproate (40.96%) and lithium (9.64%) were more frequently prescribed drugs. It shows there was increase used of second line anti manic drugs.

In our study average cost per encounter for psychotropic drugs is 2.018 INR per one day. Initially the drugs were prescribed for 3 days for new cases, then if no adverse effects found, duration of treatment was extended for 15 days to month. Changes in drug costs can result from changes in prescription volumes, quantity per prescription or in the average cost per prescription. Most countries have experienced a marked increase in the case of anti-psychotic drugs over the last 5-10 years [17].

In our study risperidone was responsible for about half of the ADR (37.5%) followed by lithium (14.06%), fluoxetin (12.5%) and imipramine (9.37%). Risperidone was mainly responsible for tremor, rigidity, salivation, slurring of speech, acute dystonia. Lithium was mainly responsible for polyuria, tremor and polydipsia while imipramine for constipation and dryness of mouth. A number of authors have reported nearly the same observations [18,19].

Conclusion

Major depressive disorder was the most common psychiatric illness followed by schizophrenia, bipolar mood disorder and schizoaffective disorder. Females were more affected with depressive disorder while males with schizophrenia, bipolar mood disorder. Most of the psychiatric illnesses were found in the age group of 35-44 years in both sexes. Atypical antipsychotics were more prescribed than typical antipsychotics in schizophrenia. Anticholinergic drug was co-prescribed in schizophrenic encounters parallel to antipsychotic drugs suggest its overuse and irrational use. Prescribing frequency of selective serotonin reuptake inhibitors (SSRI) was found greater than tricyclic antidepressant in major depression. Lithium and sodium valproate were prescribed in bipolar mood disorders in decreasing order. Adverse drug reactions were observed most commonly in age group of 25-34 years more frequently due to risperidone followed by lithium and fluoxetine.

Possible study limitations of the study: 1. As the study is cross sectional, includes both old and new cases at one time, we can't evaluate age of onset of any particular psychiatric illness e.g. schizophrenia. 2. In one point study, evaluation of duration of treatment, and effectiveness of treatment can't be studied. 3. Conclusions of single focal study can't be extrapolated because of relatively small sample size as well as shorter duration of the study.

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