

AN OBSERVATIONAL STUDY OF DRUG UTILISATION PATTERN AND PHARMACOVIGILANCE OF ANTIPSYCHOTICS

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Received: 20 Aug 2017, Revised and Accepted: 13 Oct 2017

ABSTRACT

Objective: Drug Utilization Research (DUR) 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". The main aim of conducting drug utilisation research is to facilitate rational use of drugs i.e the prescription of a well documented drug together with correct information at an affordable cost. Psychiatric disorders form an important public health priority among which psychotic disorders are the chief contributors to disability-adjusted life years [DALYs] and are associated with high levels of health service utilization and treatment cost. Without the knowledge of how drugs are being prescribed and used it is difficult to initiate a discussion on rational drug use or to suggest measures to improve prescribing patterns. To analyse the drug utilization pattern by using standard parameters.

Methods: After getting approval from the institutional human ethics committee and consent from the patients willing to participate in this study, a total of 79 prescriptions containing at least one antipsychotic drug was collected in one year period from patients attending psychiatric OPD. The patients were given a one month follow up and the adverse effects which arise out of therapy are noted and analysed.

Results: Out of the 79 participants, 59.49% were males and 40.51% were females. Regarding the morbidity distribution, Schizophrenia contributes to 50.63% and bipolar disorder contributes to 29.11% of diagnosis. Based on the analysis by WHO/INRUD standard guidelines, the average number of drugs and antipsychotic drugs per prescription were 3.32 and 1.38 respectively. The utilisation of antipsychotic drugs assessed by PDD/DDD ratio is equal to one for haloperidol and aripiprazole while it is less than one for other antipsychotic drugs. The adverse effects commonly encountered while treating psychotic cases are sedation, extrapyramidal symptoms, weight gain and anticholinergic side effects like constipation and urinary retention.

Conclusion: The age and morbidity distribution of the participants are similar to the outcomes of many studies. The antipsychotic drugs haloperidol and aripiprazole are utilised appropriately while there is under utilisation of other antipsychotics. The volume of use of haloperidol, olanzapine benzodiazepines should be judicious considering their adverse effects.

Keywords: Schizophrenia (SCHZ), Bipolar disorder (BPAD), Persistent delusional disorder (PDD), Mental Retardation with significant impairment of behaviour (MR/SIB), International network for rational use of drugs (INRUD).

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DOI: <http://dx.doi.org/10.22159/ijcpr.2017v9i6.23430>

INTRODUCTION

Though the evidence provided by pre-marketing clinical trials serves as the basis for therapeutic practice, complementary data obtained from post-marketing surveillance are of paramount importance for improving the clinical practice with drug therapy. Drug Utilization Research (DUR) 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". DUR serves as an important part of pharmacoepidemiology since it describes the extent, nature and determinants of drug exposure [1]. Pharmacoepidemiology is drug oriented emphasizing the safety and effectiveness of individual drugs or groups and utilization aims at improving the quality of drug therapy through educational intervention [1]. The main aim of DUR is to facilitate rational use of drugs i.e the prescription of a well-documented drug together with correct information at an affordable cost. Rational drug prescribing is the use of the least number of drugs to obtain the best possible effect in the shortest period and at a reasonable cost [2]. Without the knowledge of how drugs are being prescribed and used it is difficult to initiate a discussion on rational drug use or to suggest measures to improve prescribing patterns [1]. Irrational prescribing and disparity between the prescription and the consumption of medicines may offset the benefits which are demonstrated by randomized controlled trials on drug efficacy [3]. The recent proliferation of new drugs, the increasing recognition of delayed adverse effects and the focus on pharmaco-economic considerations have stimulated interest in the prescribing patterns of physicians. Psychiatric disorders form an important public health priority among which psychotic disorders are the chief contributors to disability-adjusted life years [DALYs] and are

associated with high levels of health service utilization and treatment cost. In developing countries like India, these costs are mostly paid by the patients [4]. Antipsychotics are primarily used to manage psychosis in conditions such as schizophrenia and mania associated with bipolar disorders. During the past two decades, the development of atypical antipsychotics has drastically changed the treatment protocols. The recognition of the virtual explosion in the marketing of newer drugs, the wide variations in the patterns of drug prescribing and consumption, and the increasing concern about the cost of drugs being prescribed has increased the interest in drug utilization studies in recent years.

This study was conducted to analyse the drug utilization pattern of antipsychotics with the following objectives,

1. To analyse the drug utilization pattern by using standard parameters
2. To delineate the various drugs used in psychotic disorders
3. Documenting adverse drug reactions reported or experienced by the patient.

Since drug utilization data of antipsychotics are scarce, we conducted a study to describe the observed pattern of antipsychotic drug use.

MATERIALS AND METHODS

Methodology

Study site: This study was conducted in psychiatric OPD of Rajah Muthiah medical college and hospital, a tertiary care teaching

hospital under Annamalai University, Chidambaram, Tamilnadu, India.

Study design: A prospective observational study

Study period: One year from March 2016-Feb 2017.

Sample size: Seventy-nine prescriptions were analysed on the basis of standard guidelines.

Selection criteria: Inclusion criteria: Patients attending psychiatric OPD, RMMCH irrespective of age and sex with prescription having at least one antipsychotic drug.

Exclusion criteria: 1. Patients who are not willing to participate in the study. 2. Patients who could not comply with the study such as severe mental retardation and unconsciousness.

Study procedure: The proposal for this drug utilization study has been submitted to The Institutional Human Ethics Committee, Rajah Muthiah Medical College, Annamalai University and the approval was obtained before the commencement of the study. The data of the patients attending psychiatric OPD during the period 1st march 2016 to 28th February 2017 were collected and recorded in a structured case record form after getting consent from the patient. The patients are given a one month follow up and at the end, the adverse reactions which develops out of the drugs are noted.

Data collection: The following data were collected.

- Patients details like name, age, gender, OPD no and educational status
- Patient diagnosis
- Prescription details like a number of drugs, the name of the individual drugs, dosages, dosing schedule and duration of drugs.
- On the follow-up, history of adverse events if any are noted

Data analysis: The data analysis was done as follows:

a) Assessment of prescription pattern as per the WHO/INRUD drug use indicators.

b) Classification of prescribed drugs according to the anatomical therapeutic chemical (ATC)-defined daily dose (DDD) [5]

c) The prescribed daily dose (PDD) and its ratio to DDD was calculated.

RESULTS

Morbidity distribution pattern

Out of the 79 prescriptions containing antipsychotic drugs analysed, 40 prescriptions were of the diagnosis schizophrenia, 23 were of Bipolar affective disorder, 7 were of Mental retardation with significant impairment of behaviour, 6 belongs to others and 3 were of the persistent delusional disorder.

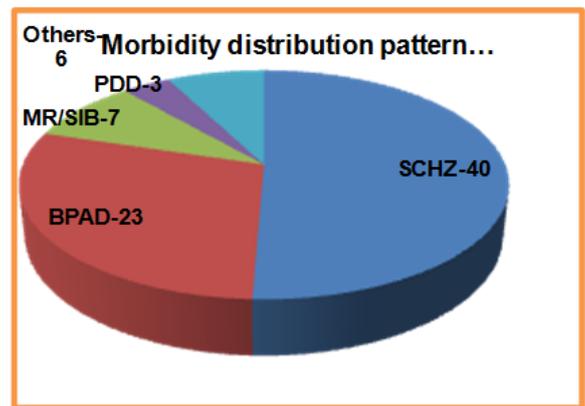


Fig. 1: Morbidity distribution pattern

Table 1: Gender and age distribution of patients

Psychotic illness	Age groups (y)				Total	Sex		Total
	<20	20-40	41-60	>60		Male	Female	
Schizophrenia	4	24	12	-	40	24	16	40
BPAD	1	12	10	-	23	12	11	23
MR/SIB	3	2	2	-	7	6	1	7
PDD	-	2	-	1	3	2	1	3
Others	1	4	1	-	6	3	3	6
Total	9 (11.39%)	44 (55.69%)	25 (31.65%)	1 (1.27%)	79	47 (59.49%)	32 (40.51%)	79

Characteristics of study participants

Among the study participants, the percentage of a male was 59.49% and the female was 40.51%. The relative distribution of

patients prescribed with antipsychotic medications, with respect to their to their age and sex are shown in fig. 2.

The age range was 12-65 y

Table 2: Assessment of prescription pattern as per WHO/INRUD drug use indicators [12]

S. No.	Drug use indicators	Result
1	Average number of drugs per prescription	3.32
2	Average number of antipsychotics per prescription	1.38
3	Percentage of drugs prescribed by generic names	76.34%
4	Percentage of prescriptions containing FDCs	7.6%
5	Percentage of antipsychotics prescribed from the Tamilnadu essential drug list	50%
6	Percentage of antipsychotics dispensed from hospital drug store at free of cost	40.36%
7	Percentage of antipsychotics purchased by patients at cost	59.64%

A total of 262 drugs were contained in 79 prescriptions. Out of 262 drugs, 109 were antipsychotics. Various other features observed are 1. The average number of antipsychotics per prescription was 1.38 in which the typical and atypical contributes 0.56 and 0.82 respectively. 2. Prescriptions containing more than five drugs was

3.8%. 3. A large proportion of drugs were prescribed with generic names and these drugs are available at free of cost. 4. The drugs which were prescribed for cost are prescribed with proprietary names. 5. The only FDC which was used in the prescriptions was Risperidone and trihexyphenidyl in different dose combinations.

Table 3: ATC/DDD pattern analysis

Drug	ATC	PDD	DDD	PDD/DDD
Haloperidol	N05AD01	8.84	8	1.105
Chlorpromazine	N04AA01	146.43	300	0.488
Trifluoperazine	N05AB06	100	20	5
Risperidone	N05AX08	2.294	5	0.459
Olanzapine	N05AH03	8.036	10	0.803
Quetiapine	N05AH04	97.5	400	0.244
Aripiprazole	N05AX12	15	15	1
Amisulpride	N05AL05	200	400	0.5
Escitalopram	N06AB10	6.25	10	0.625
Diazepam	N05BA01	6.58	10	0.658
Clonazepam	N03AE01	1.444	8	0.18
Lorazepam	N05BA06	2	2.5	0.8
valproate	N03AG01	1500	1500	1
Lithium	N05AN01	13 m mol	24 m mol	0.54
Carbamazepine	N03AF01	445	1000	0.445
Phenytoin	N03AB02	175	300	0.583

1. The PDD/DDD ratio for trifluoperazine is high ranging to 5 while for haloperidol and aripiprazole, it is almost equal to one, 2. For other antipsychotic drugs used the ratio was less than one ranging from 0.244 for quetiapine to 0.823 for Olanzapine., 3. The PDD/DDD ratio for other drugs used along with antipsychotics are less than one ranging from 0.18 for clonazepam to 0.8 for lorazepam with the exception being valproate for which the ratio is one.

Table 4: Details of drugs co-prescribed with antipsychotics

Co prescribed	Drugs	Percentage of prescription
Class of drugs		
Anticholinergics	Trihexyphenidyl	45.57%
Vitamin supplements	B Complex tablet	32.9%
Anti anxiety-Benzodiazepines	Diazepam	25.32%
	Clonazepam	20.25%
	Lorazepam	7.6%
Mood stabilisers	Divalproate sodium	24.05%
	Carbamazepine	12.66%
H2 receptor blocker	Ranitidine	10.12%
Antidepressants	Escitalopram	7.6%

The other drugs commonly co-prescribed with antipsychotics were antidepressants, anticholinergics, Benzodiazepines, vitamin B complex, Multivitamins, Proton pump inhibitors, H2 receptor blockers, etc. Among the antidepressants, SSRIs especially escitalopram is the most commonly prescribed drug. Trihexyphenidyl is the commonly prescribed anticholinergic found in 45.57% of prescriptions. Among the anti-anxiety drugs diazepam, clonazepam and lorazepam are the commonly prescribed drugs found in 25.32%, 20.25% and 7.6% of prescriptions. Divalproate sodium is the mood stabilisers widely prescribed found in 24.05% of prescriptions. Among the anti-ulcer drugs, Ranitidine, a H2 receptor blocker and pantoprazole, a proton pump inhibitor are the commonly prescribed drugs found in 10.12% and 3.79% of prescriptions. The tablet B-complex is found in 32.9% of prescriptions, almost one in every three prescriptions.

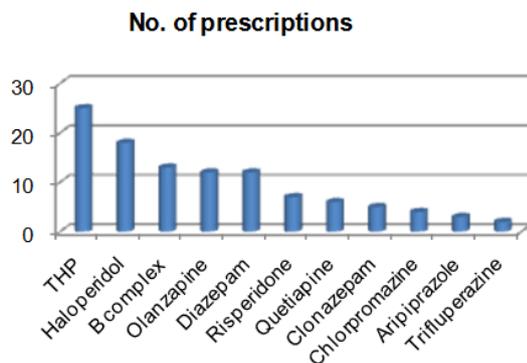


Fig. 2: Observed prescription pattern in schizophrenia

Trihexyphenidyl is a centrally acting anticholinergic commonly prescribed along with antipsychotic medications in Schizophrenia in about 62.5% of prescriptions. The most commonly prescribed antipsychotic in schizophrenia is haloperidol and the least commonly prescribed is trifluoperazine

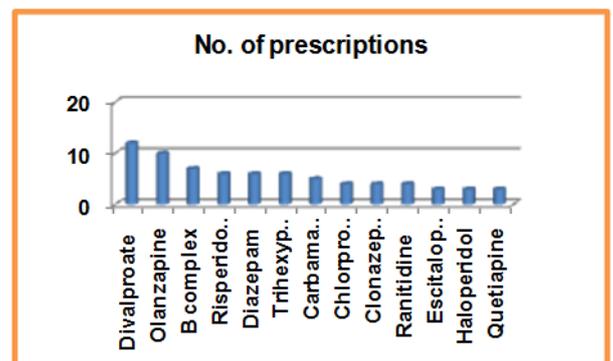


Fig. 3: Observed prescription pattern in BPAD

Divalproate is the most commonly prescribed drug found in 52.17% of prescriptions for BPAD. Among the antipsychotics used in the treatment for BPAD, olanzapine and quetiapine are the most and least commonly prescribed drugs.

In cases of MR/SIB, the typical antipsychotics are used in which chlorpromazine is most prescribed while haloperidol is least.

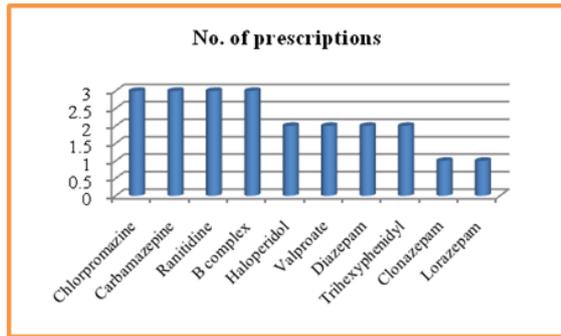


Fig. 4: Observed prescription pattern in MR/SIB

In Persistent delusional disorder, the anticholinergic trihexyphenidyl is the most commonly prescribed drug almost in all prescriptions (100%). Risperidone is the most commonly prescribed

antipsychotic while haloperidol is the least. Escitalopram is the preferred antidepressant in the prescription for the persistent delusional disorder.

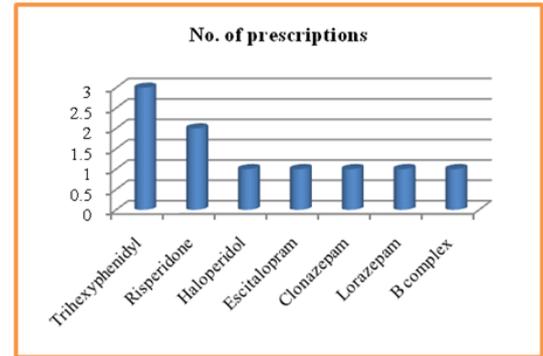


Fig. 5: Observed prescription pattern in PDD

Table 5: Adverse events encountered by the patients during follow up

ADR reported	No of cases	Drug responsible	% of patients
Sedation	6	Chlorpromazine	46.15%
	3	Clonazepam	18.75%
EPS Tremors	12	Haloperidol	42.85%
Sialorrhea	9	Haloperidol	32.14%
Constipation	5	THP	13.89%
	5	Risperidone	29.41%
Urinary retention	2	THP	5.5%
Weight gain	2	Risperidone	11.76%
	3	Olanzapine	11.54%

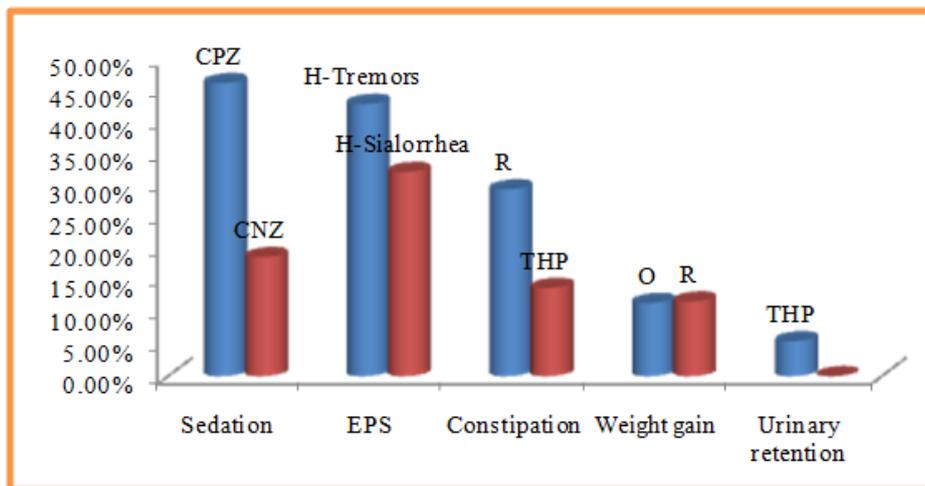


Fig. 6: Adverse effects experienced by proportion of patients among exposed, CPZ= Chlorpromazine, R= Risperidone, THP = Trihexyphenidyl, CNZ= Clonazepam, O= Olanzapine

H=Haloperidol The adverse effects encountered by the patients during the one month follow up period are sedation, extrapyramidal symptoms, constipation, weight gain and urinary retention. The total number and the percentage of patients who experience the symptoms are given in Fig.10. Among the patient's prescribed haloperidol, 42.85% of cases complaints of tremors and 32.14% of cases complaints of sialorrhea. Sedation is complained by 46.15% of patients prescribed chlorpromazine and 18.75% of patients with clonazepam. Constipation and urinary retention are found in 13.89% and 5.5% of patients prescribed with the anticholinergic drug trihexyphenidyl. Risperidone produces constipation in 29.41% and weight gain in 11.76% of cases prescribed with the drug. Olanzapine produces weight gain in 11.54% of cases.

DISCUSSION

Morbidity distribution pattern

Schizophrenia contributes to 50.63% of patients taking antipsychotics followed by BPAD which contributes about 29.11%. A finding almost similar to it has been found in many studies [6].

Profile of study participants

Among the patients taking antipsychotics, males outnumbered the females in a 3:2 ratio and a similar finding is noted [6] but when the whole of the patients attending psychiatric OPD is concerned it is the females who are predominant [7]. The prevalence of psychotic disorder was significantly high in the age group of 20-60 y

contributing 87.34% in which 20-40 y and 41-60 y contribute to 55.69% and 31.65% respectively. The prevalence in the 20-40years age group is also reflected in a study by Pradeep Bodke *et al.* [6] and also in many other studies [8]. The Prevalence of schizophrenia and Mental retardation with significant impairment of behaviour is significantly high in males when compared to females in the ratio of 3:2 and 6:1 respectively, while the study says there is no difference in prevalence though the incidence seems to be higher in males [9]. The prevalence pattern of BPAD shows almost no difference in their distribution with respect to gender as shown in a number of studies [10]. Patients with mental impairments or developmental delays are usually prescribed with a number of psychotropic medications with the aim of managing aggression, agitation, mood, or behavioural or psychiatric disturbances; the failure of monitoring of these medications is recognized as the most frequent cause of preventable adverse drug events, particularly with antipsychotic medications. The standard guidelines of practice is to start with one medication and monitor for tolerability, side effects and determination of efficacy after an optimal duration of treatment. Once the initial antipsychotic medication trial fails to achieve a therapeutic response, then we can turn to the use of combination therapy, which is an increasingly common practice in the treatment of schizophrenia and other psychotic disorders.

Prescription pattern analysis as per WHO/INRUD

The average number of antipsychotics per prescription was 1.38 which was lower than that in similar studies ranging from 1.79 to 3 [11]. The percentage of prescriptions containing more than five drugs was 3.8%, a significantly lower percentage and it shows that the practice of polypharmacy has very well come down consciously to avoid pharmacokinetic drug interactions, adverse events, etc. In the analysis of prescription of antipsychotics, it is found that a large proportion of drugs are prescribed in their generic names. It is a known fact that substitution by generic drugs helps in decreasing the overall cost of therapy and is hence recommended. Generic substitution can be beneficial, provided, adequate quality control is assured [12]. The drugs which were prescribed with proprietary names are to be bought by the patient at its own cost. Thus the socio-economic status of a patient largely influences the selection of drugs for his diagnosis and here the role of pharmacoconomics becomes significant which is explained clearly in Ajay Bera *et al.* [13]. The only fixed drug combination noted in the analysis was Risperidone, an atypical antipsychotic along with Trihexyphenidyl, an anticholinergic in various dose combinations under the brand name Riscure LS (Risperidone 2 mg+Trihexyphenidyl 2 mg) and Riscure plus (Risperidone 3 mg+Trihexyphenidyl 2 mg) but the CDCSCO recommendations says that this combination is irrational [14]. The WHO has recommended that anticholinergics should not be used routinely for preventing extrapyramidal side effects in individuals with psychotic disorders. It can be used judiciously for a short term in patients taking antipsychotics.

ATC/DDD classification

When the PDD/DDD ratio is less than one it represents under utilisation and more than one represents over utilisation of drugs. Nevertheless, it is important to note that the PDD can vary according to patient and disease factors. The PDDs can also vary substantially between different countries, for example, PDDs are often lower in Asian than in Caucasian populations. In addition, the DDDs obtained from the WHO ATC/DDD website are applicable for management of conditions of moderate intensity and are based on international data. Thus, the WHO encourages countries to have their own DDD list based on indigenous data [5].

Observed drug use pattern in schizophrenia

The use of typical and atypical antipsychotics was almost the same and also their combinations in a few number of patients. For some years, it was believed that the newer/2nd generation drugs were more effective, but that belief is now fading. In addition, the high cost of the atypical/2nd generation antipsychotics is a matter of concern. There have been some important studies which brought to light the finding that 1st generation drugs are as useful as the 2nd generation drugs [15]. In 2009 the American Psychiatric Association (APA) acknowledged the fact that the distinction between first-and

second-generation antipsychotics appears to have limited clinical utility [16]. Also, the National Institute for Clinical Excellence (NICE) guidelines-2010, suggested that there it is no longer imperative to prescribe an "atypical" agent as first-line treatment [17]. Clozapine may be offered only after primary failure of two antipsychotic drugs. Anticholinergics use should be judicious to avoid adverse effects such as urinary retention, constipation, dry mouth, an attack of angle-closure glaucoma, etc. Many observers have noted that the addition of anticholinergic medication can exacerbate existing Tardive Dyskinesia (TD), and that discontinuing anticholinergic drugs may improve the condition [18]. Benzodiazepines are co-prescribed in about 52.5% of the schizophrenic cases. Among the benzodiazepines, Diazepam was the most commonly prescribed drug followed by clonazepam and lorazepam in almost equal percentages. Benzodiazepines are quite safe medications. Though their use reduces the requirement of anticholinergics, there is no significant improvement in the general mental state. They can lead to falls, particularly in the elderly. With long-term use, the adverse effects such as addiction potential, memory impairment, depression, tolerance, and dependence outweigh the benefits. Patients taking benzodiazepines shows an increased mortality has been shown in some studies [19]. These drugs are to be used for short-term, four weeks maximum or their minimum effective doses should be given in intermittent doses [20].

Observed drug use pattern in BPAD

In cases of BPAD, atypical antipsychotics are preferred over typical antipsychotics in use. The drug use ratio of atypical to typical is almost equal to 4:1. The combination of typical and atypical antipsychotics have also been used in fewer cases of BPAD. Antipsychotics are beneficial in the treatment of acute mania while their use in depressive episodes are doubtful except for quetiapine [21]. Mood stabilisers are the most commonly prescribed group of drugs along with antipsychotics in which Divalproate sodium contributes to about 52.17% Of the prescriptions. First-line mood stabilizers of manic episodes are lithium, sodium valproate, divalproex, carbamazepine and second-generation antipsychotics. Second-line treatment options are: clonazepam, lorazepam and some other benzodiazepines [22].

Observed drug use pattern in MR/SIB

Antipsychotics are prescribed in cases of mental retardation with significant impairment of behaviour. There was a six-fold increase in the use of antipsychotics in behavioural disorder among children and adolescents. The trend in the use of antipsychotics continues to increase in the recent years. Among the antipsychotics, second-generation drugs are preferred but the major concern about its use are the metabolic side effects [23] which may be the reason for the choice of typical or first-generation antipsychotics in this study.

Observed drug use pattern in PDD

The introduction of second-generation antipsychotics has changed the treatment trends of the persistent delusional disorder. The difference in efficacy between first and second generation stands to reason for this. In our study, we find that risperidone is the commonly prescribed antipsychotic. Now a days most patient's presents with coexisting depressive symptoms and hence antidepressants are also added to prescriptions which correlate with the use of escitalopram in our study findings [24]. The other group of drugs that are co-prescribed are the benzodiazepines (diazepam and clonazepam), anticholinergic (Trihexyphenidyl), carbamazepine and antidepressants (escitalopram) contributing to 43.47%, 26.08%, 21.74% and 13.04% respectively

Adverse events

The first-generation antipsychotics are more likely to be associated with movement disorders, because it binds tightly to D2 dopaminergic receptors, such as haloperidol, and less likely in drugs that bind weakly, such as chlorpromazine. Anticholinergic effects are especially prominent with weaker-binding first-generation antipsychotics, as well as with the second-generation antipsychotic clozapine. The newer second-generation antipsychotics, especially clozapine and olanzapine, generally tend to cause more problems

relating to metabolic syndromes, such as obesity and type 2 diabetes mellitus. All antipsychotic medications are associated with an increased likelihood of sedation, sexual dysfunction, postural hypotension, cardiac arrhythmia, and sudden cardiac death [25].

Weight gain

In recent years, it has come into light that the antipsychotic agents, particularly atypical antipsychotics induces weight gain and metabolic side effects. Although it is clear, it is not uniform. Different agents can cause it to a different extent and not in all cases. The proposed mechanisms being leptin desensitisation, 5HT_{2C} antagonism, H₁ antagonism and hyperprolactinemia [26]. Olanzapine and risperidone showed an increase in weight among patients which correlates exactly with the study conducted in south asian population, saddicha *et al.* [27] this has been extensively studied with similar reports in various studies.

Extrapyramidal symptoms

The extrapyramidal symptoms associated with the use of antipsychotics especially the older typical agents are parkinsonism, akathisia, tardive dyskinesia and acute dystonia [28]. In this study, haloperidol atypical antipsychotic agent produced tremors and sialorrhea which are features of parkinsonism. Similar results have been found in various studies [29].

Sedation through desired in acute psychosis is found to be reported in patients taking chlorpromazine and the benzodiazepine, clonazepam [30]. Trihexyphenidyl being an anticholinergic has found to produce constipation and urinary retention, especially in elderly patients [31]. Risperidone has been found to produce constipation in almost 29.41% of patients prescribed with the drug. Though, in general atypical antipsychotics are devoid of anticholinergic adverse effects, risperidone has been found to produce constipation and even paralytic ileus in many studies [32].

CONCLUSION

Among patients receiving antipsychotic medications, Schizophrenia was the most common diagnosis followed by bipolar disorder, mental retardation with significant impairment of behaviour, Persistent delusional disorder and others.

- A significant percentage of cases falls in the age group of 20-40 y followed by 41-60 y.
- A larger proportion of drugs has been prescribed in their generic names.
- The average number of antipsychotics per prescription was 1.38.
- In Schizophrenia, the most commonly prescribed single drug was haloperidol, two drug therapy was haloperidol and chlorpromazine while the least commonly prescribed drugs were Trifluoperazine, aripiprazole and amisulpride.
- In Bipolar disorders, the most commonly prescribed antipsychotic drug and mood stabiliser were olanzapine and divalproate sodium respectively while the antipsychotics trifluoperazine and aripiprazole are not at all used and the least commonly prescribed mood stabiliser was lithium.
- The most commonly co-prescribed antidepressant and anti-anxiety drugs are escitalopram and diazepam respectively.
- A major part of the total cost per prescription was borne by the patients and measures have to be initiated to reduce it.
- The principles of rationality in prescribing the drugs were followed according to the various drug use indicators given by WHO/INRUD. A few deviations were found from the guidelines (APA and NICE) due to socioeconomic reasons, financial constraints and technical difficulties.

The following recommendations are made out of the study:

- The Hospital Drug Schedule: Need to add atypical antipsychotics so that the drugs will be made available free of cost
- Anticholinergics should be used judiciously only in selected cases of patients on antipsychotics.

- The use of haloperidol should be considered for its adverse effects.
- The use of benzodiazepines has to be limited.
- The use of FDC Risperidone and Trihexyphenidyl has to be reconsidered.

ACKNOWLEDGEMENT

I would like to thank Prof. and HOD Dr. P. Nirmala and other faculties, Department of Pharmacology and Prof and HOD Dr. R. Gandhi Babu, faculties and postgraduates, Department of Psychiatry, RMMCH, Annamalai university, Chidambaram

CONFLICT OF INTERESTS

Declared none

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