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Research Article

Impact of Clinical Pharmacist Driven Adverse Drug Reaction Profile in Schizophrenia Patients on Atypical Antipsychotics at A Tertiary Care Setting

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ABSTRACT

Introduction: Schizophrenia is one of the most serious and frightening of all mental illnesses. Atypical antipsychotics are first line drugs for schizophrenia. They have significant adverse drug events. Aim: The study was conducted with an aim to evaluate the pattern of occurrence of Adverse Drug Reactions (ADRs) in the patients with schizophrenia and to assess their causality and severity. Materials and Methods: A prospective study was carried out in the psychiatry inpatient and outpatient department of KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi, Karnataka for 3 months. All patients diagnosed with schizophrenia and stable on atypical antipsychotics and receiving pharmacotherapy was included. Assessment of causality and severity of recorded ADRs was done using Naranjo's scale and Hartwig Scale respectively. Results: A total 32 ADRs were recorded from 25 patients out of 60 patients. The most common ADRs were weight gain (28.13%) and insomnia (18.75%). Majority of ADRs were Probable (53.13%)on Naranjo's causality assessment scale and Level 4b (40.63%) on Hartwig's severity assessment scale. The drug Aripriprazole showed maximum ADRs (34.38%). Conclusion: ADRs are frequent occurrence in patients with schizophrenia which are probable in most cases. Incidence of ADRs can be decreased and compliance as well as quality of patient can be improved by early detection and management.

Keywords: Adverse Drug Reaction, Atypical Antipsychotics, Schizophrenia, Naranjo's scale, Hartwig's scale.

INTRODUCTION

The significant component of powerful drug regulation systems, clinical practice and public health programs and also describes the process for monitoring and evaluating ADRs is Pharmacovigilance it is the pharmacological science related to the collection, detection, assessment, monitoring and prevention of adverse effects or any other drug-related problem[1].

World Health Organization (WHO) defines an ADR as "A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the moderations of physiological function"[2]. ADRs are recognized to be one of the significant cause of hospital admissions and the incidence varied from 0.2% to 41.3%.[3] According to the Centre for Health Policy Research, more than 50% of the approved drugs were associated with some type of adverse reactions not detected prior to approval.[4,5]

Schizophrenia referred by the fifth Diagnostic Manual of Mental Disorders (DSM-V) as Individuals suffering from characteristic psychotic symptoms and a noted impairment in adaptive functioning. Two or more from a list of symptoms must be present, with at least one them being delusion, hallucinations, or disorganised speech. The time frame is an active phase of the disorder lasting approximately one month and these symptoms, with possibly of less intensity, continue for duration of at least six months.[6] The first goal of treatment for patients with mental disorders focused on schizophrenia is to control symptoms to allow return to normal levels of psychological functioning and rapid control of symptoms such as agitation, aggregation, delirium, visual hallucinations, etc. The commonly prescribed Atypical Antipsychotics drugs are; Amisulpride, Aripiprazole, Clozapine, Olanzapine, Quetiapine, Risperidone, Zotepine.[7]The common adverse events of Atypical Antipsycotics: Hyperglycemia, Weight gain, Dyslipidemia, Dry mouth.[8] All the effective drugs used for the treatment of schizophrenia, no matter how competently used, may cause adverse reactions. Thus, a continuous monitoring of ADRs is essential.[9] Early detection of drug toxicity helps in timely treatment of the patient, improve compliance and decrease cost of therapy. In India, there is a scarcity of information related to ADRs occurring due to psychotropic drugs.

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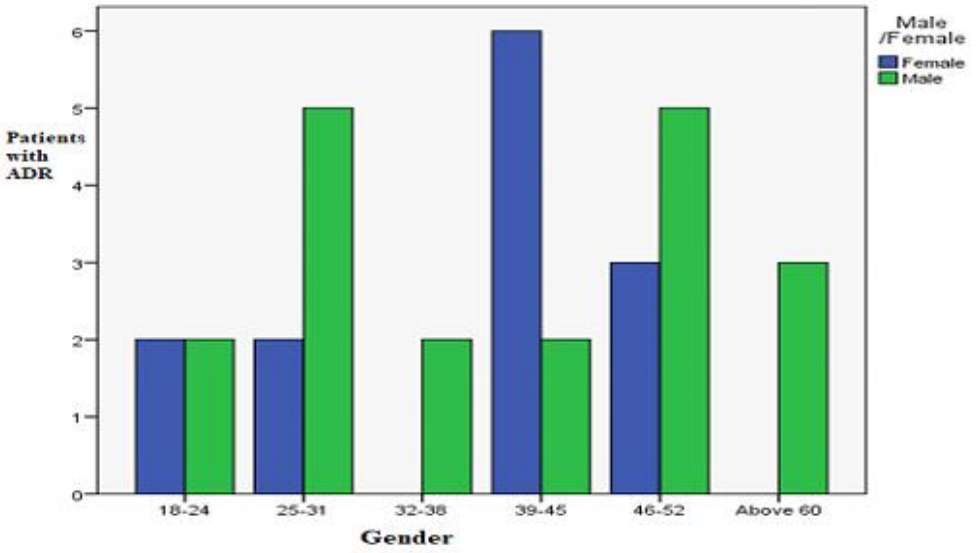

Figure 1: Demographic Details of ADR Patients

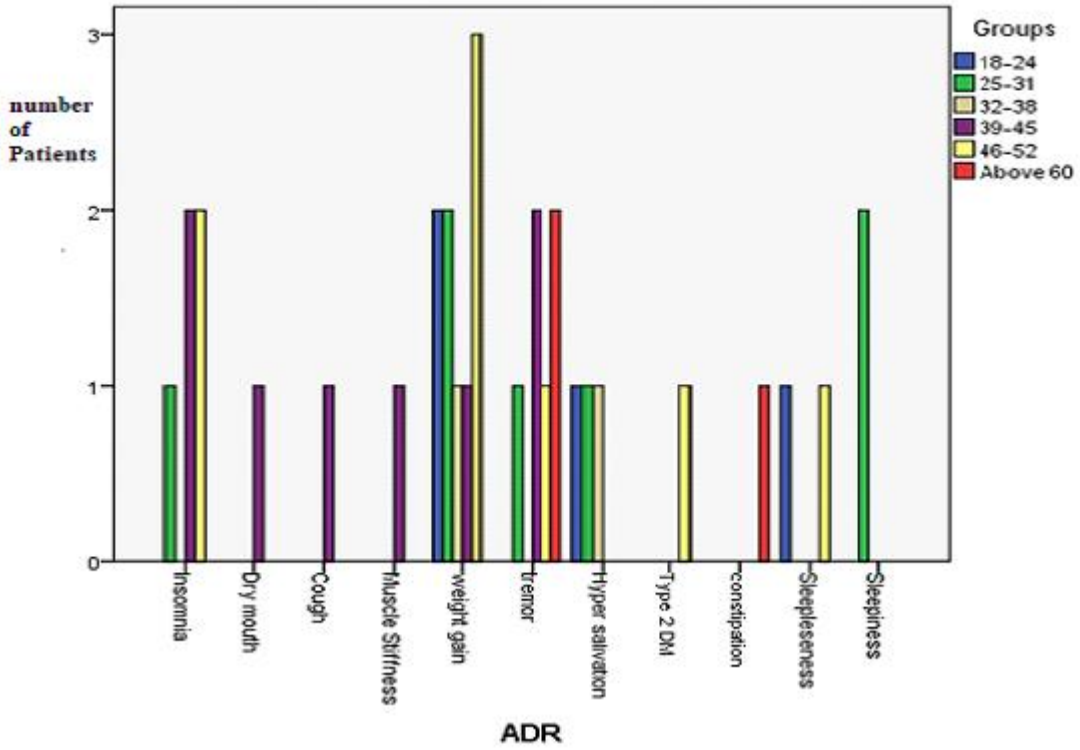

Figure 2: Types of ADR in Patients

So, with this background, the principal aim of this prospective study was to determine the pattern of ADRs occurring in the patients of schizophrenia those stable on atypical antipsychotics coming to Psychiatry Department on Inpatient and Outpatient Department of Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi, Karnataka. The ADRs were also assessed for their causality and severity.

MATERIALS AND METHODS

Ethical Issue: Institutional Ethical Committee Clearance was obtained from the Human Ethics Committee of KLE College of Pharmacy, Belagavi. The study protocol was the explained and all the study documents such as patient information sheet, Inform consent form (Kannada, English, Marathi) were validated by ethical committee members. Upon willingness to participate the written consent was obtained from the patients in the initiation stage of the study.

Study design and patient recruitment: A prospective study was conducted to assess and evaluate the Adverse Drug Reactions in the Inpatient and Outpatient department of Psychiatry for a period of 3 months. Total 60 patients were enrolled in study those were aged 18 to 65 years of

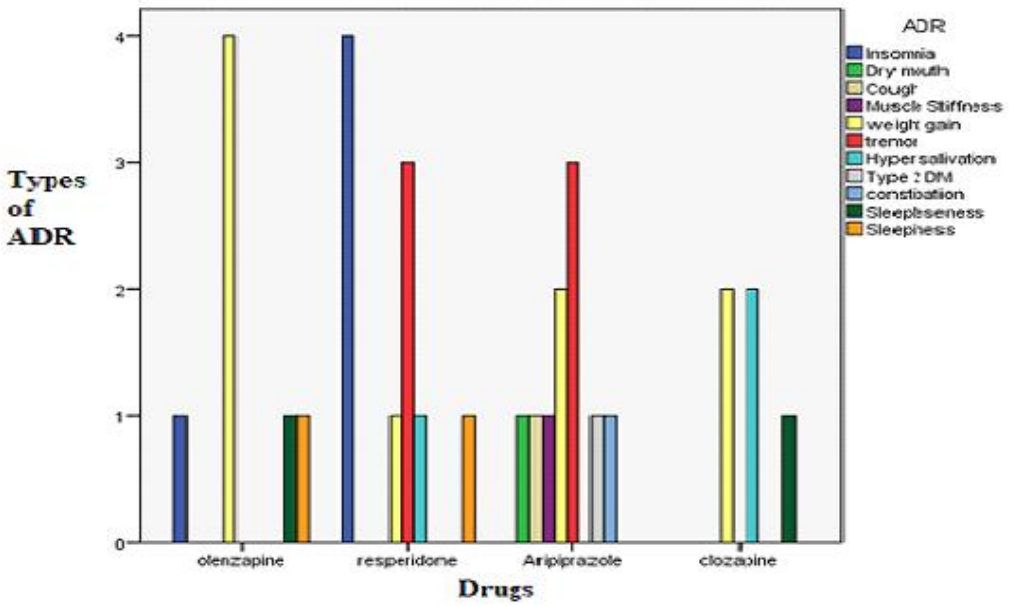

Figure 3: ADRs with respect to drugs

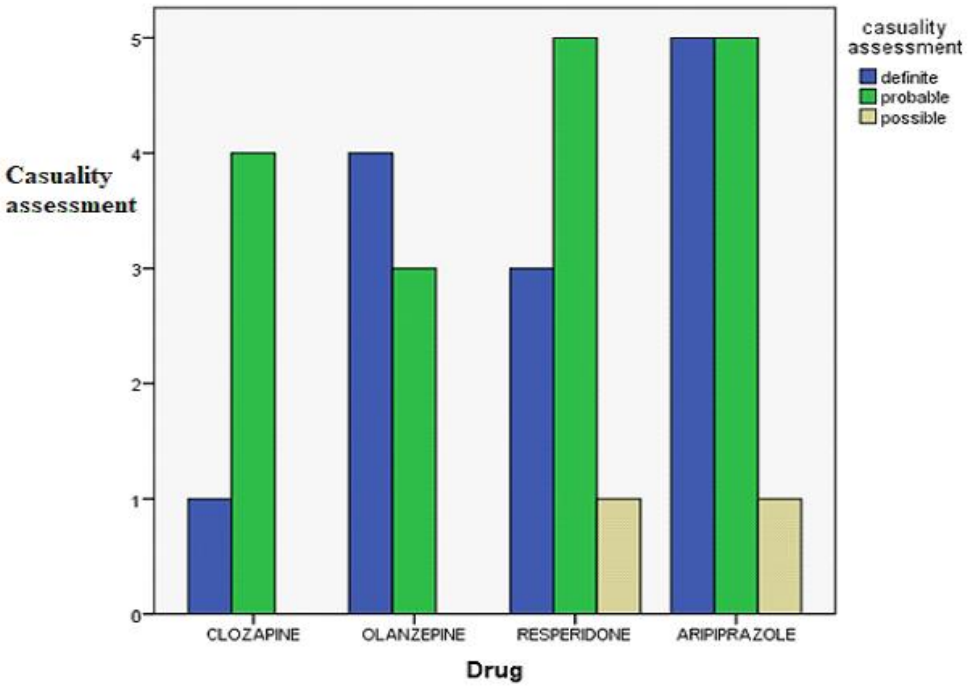

Figure 4: Casuality Assessment by Naranjo's Scale

either gender. Patients with schizophrenia stable on Atypical Antipsychotic drugs were enrolled in the study. Patients with cardiovascular diseases specifically Coronary Artery Disease, Cardiac Arrest, Congestive cardiac failure, Congenital Heart disease, stroke, history of seizures, head injury or brain tumour, liver or kidney disease and mentally retarded were excluded from the study.

Study Protocol: The enrolled patients' details accounted for patient's demographics, medical history, medication history, complaints on admission, provisional diagnosis, current therapy, drug treatment chart, discharge medication and advice. Diagnosis of ADRs due to atypical antipsychotic drugs was done by Consultant Psychiatrist. On suspicion of an ADR the patient was evaluated and reported to Department of Pharmacology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre. ADRs were documented on ADR reporting forms and Alert Card were provided to the suspected patients. The reactions were further assessed with the scientific tools like Naranjo Scale and Hartwig Scale into Casual, Probable, Preventable and Severe ADRs.

RESULTS

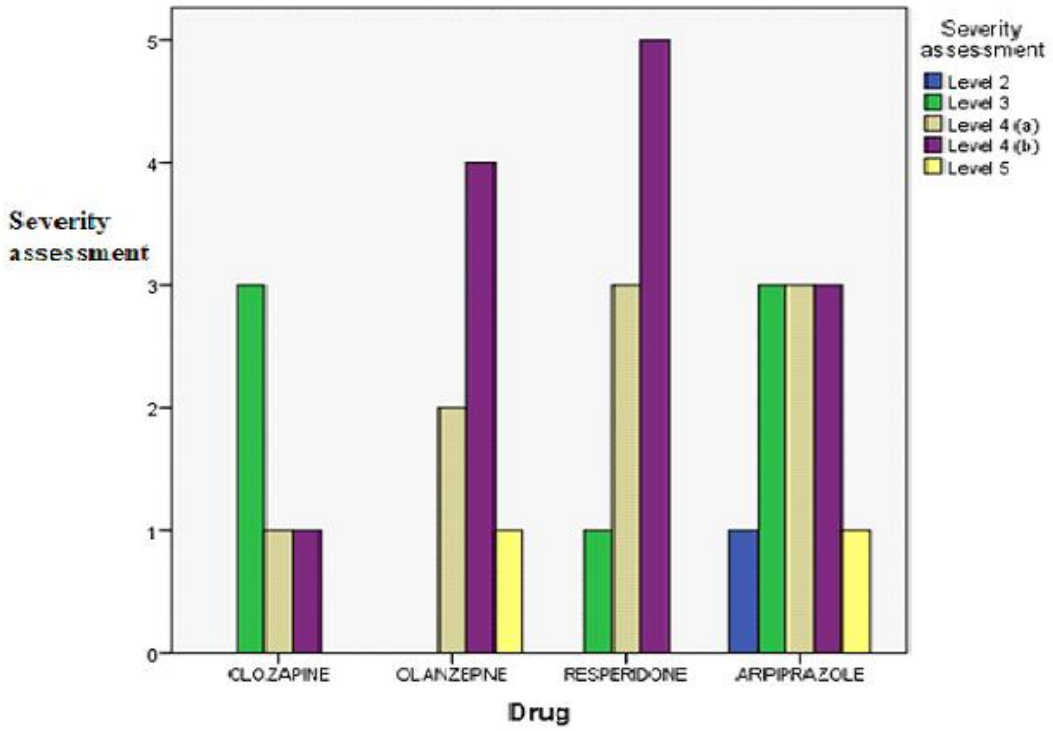

Figure 5: Severity assesment by Hartwig's scale

A total number of 60 patients were screened during the study period , out of which 25 patients developed a total of 32 ADRs, a maximum of 8 (25%) were in the age group of 39-45 and 46-52, followed by 7 (21.87%) in 25-31, 4 (12.5%) in 18-24 , 3 (9.37%) in 60-65 and 2 (6.25%) in 32-38 group. Male predominance was observed 59.37%, the drug history was noted very cautiously before attributing them to face ADRs (Table No.:01) (Figure No.:01).

A sum of 32(100%) ADRs were observed, major were weight gain 9(28.13%), followed by tremor 6(18.75%), hyper-salivation 3(9.38%), sleeplessness 2(6.25%), sleepiness 2(6.25%), dry mouth 1(3.13%) , cough 1(3.13%), muscle stiffness 1(3.13%), type 2 DM 1(3.13%), constipation 1 (3.13%). (Table No.: 02) (Figure No.:02).

The drug that accounted for maximum ADRs in the study included atypical antipsychotics such as Resperidone (31.25%) and Aripirazole (31.25%), 97 lanzapine (21.85%) and Clozapine (15.63%) can be observed in Table no.:03 .Many patients were deprived of appetite on correlation it was observed most of it were due to the disease progression. Weight gain in patients varied from 2kg to 10kg with respect to patient mainly observed in olanzepine 28.13% (Table No.:03) (Figure No.:03).

The atypical antipsychotic drugs were segregated according to Anatomical Therapeutic Chemical Classification system. The other antipsychotics (n05ax) Resperidone (N05AX08), Aripirazole (N05AX12) were the highest drugs to cause ADRs (Table No.:04).

The causality assessment was done by using Naranjio's scale wherein ADRs categorised as definite (n=13), possible (n=02) and probable (n=17) (Table no.:05)(Figure no.: 04). The severity assessment was done by using Hartwig's scale wherein ADRs categorised as Level 2 (n=1),Level 3 (n=7), Level 4a (n=9), Level 4b (n=13), Level 5 (n=2) (Table no.:05) (Figure no.:05).

The Table no.:07 represents the management with respect to the ADR occurred. In the worst cases the drug was withdrawn or else the dose was altered, continued with same dose. The antidote was given in certain condition where patient had suffered severe ADR. Rechallange was not attempted in any patient. Dechallanged drugs were Respiredone and Olanzepine for 3 (12%) of the patients. In one patient ADR was observed to be metabolic syndrome of having Type 2 diabetes mellitus (Table No.:07).

Table 1 Demographic details of ADR patients

Age (years)	Gender		Total
	Male	Female	
18-24	2 (6.25%)	2 (6.25%)	4 (12.5%)
25-31	5 (15.63)	2 (6.25%)	7 (21.87%)
32-38	2 (6.25%)	0(0%)	2 (6.25%)
39-45	2 (6.25%)	6 (18.75)	8 (25%)
46-52	5 (15.63%)	3 (9.37%)	8 (25%)
53-59	0(0%)	0(0%)	0(0%)
Above 60	3 (9.37%)	0(0%)	3 (9.37%)
Total	19 (59.37%)	13 (40.63%)	32 (100%)

DISCUSSION

The manufacturing of medicinal products is a heavily regulated process to ensure those products are safe, efficacious and effective is important. Collecting data on

Table 2 Types of ADR in patients

ADR	Groups						Total
	18-24	25-31	32-38	39-45	46-52	Above 60	
Insomnia	0(0%)	1(3.13%)	0(0%)	2(6.25%)	2(6.25%)	0(0%)	5(15.63%)
Dry mouth	0(0%)	0(0%)	0(0%)	1(3.13%)	0(0%)	0(0%)	1(3.13%)
Cough	0(0%)	0(0%)	0(0%)	1(3.13%)	0(0%)	0(0%)	1(3.13%)
Muscle Stiffness	0(0%)	0(0%)	0(0%)	1(3.13%)	0(0%)	0(0%)	1(3.13%)
weight gain	2(6.25%)	2(6.25%)	1(3.13%)	1(3.13%)	3(9.38%)	0(0%)	9(28.13%)
Tremor	0(0%)	1(3.13%)	0(0%)	2(6.25%)	1(3.13%)	2(6.25%)	6(18.75%)
Hyper salivation	1(3.13%)	1(3.13%)	1(3.13%)	0(0%)	0(0%)	0(0%)	3(9.38%)
Type 2 DM	0(0%)	0(0%)	0(0%)	0(0%)	1(3.13%)	0(0%)	1(3.13%)
Constipation	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	1(3.13%)	1(3.13%)
Sleeplessness	1(3.13%)	0(0%)	0(0%)	0(0%)	1(3.13%)	0(0%)	2(6.25%)
Sleepiness	0(0%)	2(6.25%)	0(0%)	0(0%)	0(0%)	0(0%)	2(6.25%)
Total	4(12.5%)	7(21.85%)	2(6.25%)	8(25%)	8(25%)	3(9.38%)	32(100%)

Table 3: ADRs with respect to the drugs

ADR	Type of a drug				Total
	Olenzapine (N05AH03)	Resperidone (N05AX08)	Aripiprazole (N05AX12)	Clozapine (N05AH02)	
Insomnia	1 (3.13%)	4(12.5%)	0(0%)	0(0%)	5(15.63%)
Dry mouth	0(0%)	0(0%)	1(3.13%)	0(0%)	1(3.13%)
Cough	0(0%)	0(0%)	1(3.13%)	0(0%)	1(3.13%)
Muscle Stiffness	0(0%)	0(0%)	1(3.13%)	0(0%)	1(3.13%)
weight gain	4 (12.5%)	1(3.13%)	2(6.25%)	2(6.25%)	9(28.13%)
Tremor	0(0%)	3(9.38%)	3(9.38%)	0(0%)	6(18.75%)
Hyper salivation	0(0%)	1(3.13%)	0(0%)	2(6.25%)	3(9.38%)
Type 2 DM	0(0%)	0(0%)	1(3.13%)	0(0%)	1(3.13%)
constipation	0(0%)	0(0%)	1(3.13%)	0(0%)	1(3.13%)
Sleeplessness	1(3.13%)	0(0%)	0(0%)	1(3.13%)	2(6.25%)
Sleepiness	1(3.13%)	1(3.13%)	0(0%)	0(0%)	2(6.25%)
Total	7(21.85%)	10(31.25%)	10(31.25%)	5(15.63%)	32(100%)

Table 4: ATC Classification

Name of Drug	Organ System affected	Drug Class (ATC code)
Olenzapine (N05AH03)	Nervous System(N)	Antipsychotics (n05a)
Resperidone (N05AX08)	Nervous System(N)	Other antipsychotics (n05ax)
Aripiprazole (N05AX12)	Nervous System(N)	Other antipsychotics (n05ax)
Clozapine (N05AH02)	Nervous System(N)	Antipsychotics (n05a)

safety continues throughout the life of a drug in the clinical research as well in routine clinical practises. Hence, comprehensive compilation adverse drug reaction is significant to increase quality of life of the patients. This study was conducted to emphasis the pattern of ADR among the patients stable on atypical antipsychotics in schizophrenia from psychiatric department.

The present study showed the impact of clinical pharmacist in assessing and evaluating ADRs from IDP and OPD. A total of atypical anti-psychotics were prescribed which were olanzapine, respiridone, aripirprazole and Clozapine majorly for 25 subjects resulting into 32 ADRs from total sample size of 60 Schizophrenia patients. Male prepondance was observed 59.37%, the drug history was noted significantly to assess the ADRs.

The weight gain (28.13%) ADRs were exclusively reported for olanzapine drug followed by extrapyramidal side effect tremor (18.75%). It is suggested that switching the medication or psychotherapy, education and health lifestyle will be beneficial in treating the drug induced weight gain.[10]

Among atypical anti-psychotics respiridone (31.25%) and aripiprazole (31.25%) were commonly prescribed drugs. We also observed one metabolic syndrome side effect i.e type 2 diabetes mellitus due to aripiprazole.

The drugs were segregated according Anatomical Therapeutic Chemical Classification System (ATC). This study adds on to recognition of side effects and their management to execute strategies and optimize patient care. Such initiatives would increase the specialty and collaborative care services in the country.

The study limitations were seen were routine haematological, clinical chemistry or ECG screening of patients or blood samples for sugar, lipid and prolactine estimation was not possible routinely. Short duration of study is another demerit . Another drawback was

Table No.:05 Casuality Assessment by Naranjo's Scale

Drugs	Casuality Assessment			Total
	Definite	Probable	Possible	
Clozapine	1(3.13%)	4(12.5%)	0 (0.0%)	5(15.63%)
Olanzepine	4(12.5%)	3(9.38%)	0 (0.0%)	7(21.88%)
Resperidone	3(9.38%)	5(15.63%)	1(3.13%)	9(28.13%)
Aripiprazole	5(15.63%)	5(15.63%)	1(3.13%)	11(34.38%)
Total	13(40.63%)	17(53.13%)	2(6.25%)	32 (100.0%)

Table No.:06 Severity assessment by Hartwig's scale

Drugs	Severity levels						Total
	Level 1	Level 2	Level 3	Level 4(a)	Level 4 (b)	Level 5	
Clozapine	0(0.0%)	0(0.0%)	3 (9.38%)	1(3.13%)	1(3.13%)	0 (0.0%)	5 (15.63%)
Olanzepine	0(0.0%)	0(0.0%)	0(0.0%)	2 (6.25%)	4 (12.5%)	1(3.13%)	7 (21.88%)
Resperidone	0(0.0%)	0(0.0%)	1(3.13%)	3 (9.38%)	5 (15.63%)	0(0.0%)	9 (28.13%)
Aripiprazole	0(0.0%)	1(3.13%)	3 (9.38%)	3 (9.38%)	3 (9.38%)	1(3.13%)	11(35.38%)
Total	0(0.0%)	1(3.13%)	7 (21.88%)	9 (28.13%)	13 (40.63%)	2 (6.25%)	32

Table No.: 07 Management of ADRs

Management of ADR	Reaction	IP No. of subject	OP No. of subject	Total
Drug withdrawn	Insomnia	-	1	1
	Weight gain	-	1	1
	Tremor	-	1	1
	Total	-	3	3
Dose alter	Tremor	-	1	1
	Constipation	-	1	1
	Total	-	2	2
No change	Dry mouth	-	1	1
	Cough	-	1	1
	Weight gain	1	7	8
	Hyper salivation	1	2	3
	Type 2 DM	-	1	1
	Sleeplessness	-	1	1
	Sleepiness	-	2	2
	Total	2	15	17
Antidote	Insomnia	1	3	4
	Muscle Stiffness	1	-	1
	Tremor	1	3	4
	Sleeplessness	-	1	1
	Total	3	7	10
Grand Total		5	27	32

spontaneous reporting due to lack of awareness both at healthcare professionals and patient level. The severity of ADR can be even explained by comorbidities and concomitant medication but we did not consider the correlation in the study.

The study elucidates the pattern of ADR in atypical anti-psychotics for schizophrenia patients. The increasing use of atypical anti-psychotics correlates with various patterns of ADRs. It is evident that ADRs are well established in psychiatric arena. The collaborative approach of clinical pharmacists with psychiatrist would create extensive impact on assessment and evaluation of ADR profile achieves compliance of drug therapies.

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