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A STUDY ON POTENTIAL DRUG-DRUG INTERACTIONS AND ADVERSE DRUG REACTIONS ASSOCIATED WITH PSYCHOTROPIC MEDICATIONS

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ABSTRACT

Aim and Objectives: To study the potential drug-drug interactions and adverse drug reactions in psychotropic drug prescriptions. **Methodology:** A prospective observational study on in-patients of psychiatric unit was carried out. Patients were regularly followed and monitored for potential drug-drug interactions (pDDI) and adverse drug reactions (ADRs). The collected data was documented in suitable data collection form. The identified ADRs were assessed for causality, severity and preventability scales. **Results:** Most of the patients were diagnosed with alcohol dependence syndrome 52(34.7%) followed by schizophrenia 42(28%). Antipsychotics are the most commonly prescribed drugs. Out of 150 patients 366 potential drug-drug interactions were identified. Out of this 109 were considered major, 243 were moderate, and 14 were minor. During the study period 84 ADRs were identified. Most common ADR noticed in this study was sedation followed by tremor, akathisia, and hyper salivation. As per the WHO causality assessment 54(64.2%) of ADR`s were probable. Hart wig`s severity scale showed that 45.2% of the identified ADR`s were moderate. Majority of the ADRs were not preventable. Most of the ADRs were caused during antipsychotic drug therapy. Rispiridone was the suspected drug for most of the identified ADR`s. **Conclusion:** The study identified pDDI and ADRs associated with the psychotropic drugs. Analysis shows that antipsychotics are the major class of drugs that caused major drug interaction and adverse drug reactions. Frequent monitoring and early detection may enhance better management.

KEYWORDS

Psychotropic medications, Potential drug-drug interactions and Adverse drug reactions.

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INTRODUCTION

"Psychotropic drugs are the chemical substance that changes brain function and results in alterations in perception, mood, or consciousness". Mostly the psychotropic drugs are used in the treatment of mental disorders such as schizophrenia, mood disorder, bipolar disorder, mental retardation, psychosis, mania, depression, etc.

Whenever two or more drugs are taken concurrently there is a chance that there will be interaction between the drugs. An increase in the number of drugs enhances the risk of potential drug-drug interaction. Patients who are long term therapy with multiple drugs and comorbidities produce drug-drug interactions[1].

Psychotropic drugs are increasingly prescribed in clinical practice these drugs are notorious in causing ADRs and drug-drug interactions, due to this either non adherence or at times discontinuation of therapy. Pharmacovigilence in psychiatry plays an important role for therapeutic safety by detecting early alarming signals[2].

The patients with mental illnesses are significant users of health services; they will be having frequent or lengthy hospitalizations and require extensive medication therapy. Polypharmacy is common in patients with psychiatric illnesses; psychosocial problems and patient non-compliance potentially contribute for drug related problems in psychiatry. Many studies have proven that the clinical pharmacist in psychiatry can improve prescribing practices, enhances the treatment outcomes and reduces psychotropic drug related morbidity. The contribution of clinical pharmacists' results from the training and skills developed in practice is important therefore this study is aimed to describe the role of clinical pharmacist for the improvement of patient care in psychiatric practice[3].

MATERIAL AND METHODS

A prospective observational study on analysis of adverse drug reaction was carried in a psychiatry department at a private tertiary care teaching hospital centrally located in Dakshina Kannada, over a period of eight months. A total of 150 patients were enrolled in the study after obtaining the informed consent. All hospitalized patients of age 18 years and above and who were on psychotropic drugs were included in the study.

Institutional ethics committee approval was obtained before initiating the study. During the study period, the in patients of psychiatry ward who were prescribed with psychotropic medications were observed on daily basis. The potential drug-drug interactions were noted down and whenever an ADR is suspected, it was documented in specially designed data collection form and ADR reporting form. It was then discussed with the treating physician for further evaluation. Once the ADR was confirmed it was analyzed for causality for causality using WHO probability scale[4] and the severity is analyzed by using Hart wigs severity scale[5]. And the preventabilty was assessed by using Shomock and Thoronton preventability scale[6]. Potential drug-drug interactions were also identified and documented.

Data analysis was carried using statistical package for social sciences (SPSS) 16.0 for windows. Descriptive statistics was applied for analyzing the collected data.

RESULTS

Out of 150 patients enrolled, majority of the patients were males (77.3%) and 22.7% patients were females. Most of the patients were in the age group of 30-39 (30.7%), followed by 20-29 (28%) and then 40-49 (24.7%), 50-59 (8.7%) and 8% of patients were above 60 years of age. Among these 116(77.3%) male patients, 24.7% patients are smokers and 60% patients are alcoholics.

Out of 150 patients analyzed most of the patients were diagnosed to have alcohol dependence syndrome 52 (34.7%), schizophrenia 42 (28%), other bipolar affective disorder 36 (24%), other psychosis 13 (8.7%), depression 12 (8%), mental retardation 7 (4.7%), mood disorder 7 (4.7%), mania 1 (0.7%),

Anxiolytic drug lorazepam 98(22.1%) was mostly prescribed in this study then the antipsychotic drugs risperidone 46(10.4%), haloperidol 37(8.3%), valproic acid 33(7.4%), olanzapine 29(6.5%), trihexyphenydyl 26(5.8%), quetiapine and clonazepam 22(4.9%), lithium 20(4.5%) details are given in (Table No.1).

Potential drug-drug interaction

Out of 109 potential drug-drug interactions most of them caused QT interval prolongation. Haloperidol-

risperidone was noticed to be the most common interacting pair 12(11%), followed by haloperidol-quetiapine 8(7.3%), haloperidol-chlorpromazine 4(3.6%).

The second common effects of pDDIs are cardio-respiratory depression and increased CNS depression. Most common interacting pair was lorazepam-olanzapine 19(17.4%)

Further, patients were also observed with the chances of extrapyrimidal symptoms EPS and encephalopathy as a result of the interaction drugs. Here the combination of haloperidol-lithium had higher chances interactions 10(9.1%), followed by lithium-olanzapine 6(5.5%), lithium-rispiridone 2(1.8%), fluphenazine-lithium 1(0.9%), chlorpromazine-lithium1(0.9%) have each Other effects include low blood preasure, shallow breathing, weak pulse, drowsiness, confusion was also noticed from 8(7.3%) interactions. Lorazepam-clozapine, diazepam-olanzapine, chlorpromazine-clozapine, clonazepam-olanzapine are the interacting pairs. The comprehensive informationson the chances of interactions with the drug combinations and their possible outcomes are presented in (Table No.2).

Theanalysed drug-drug interaction was found to be major in 29.7% moderate in 66.3% and minor in 3.8% of the study population.

Adverse drug reaction

During the study period 84 ADRs were identified. The most frequently observed ADR was sedation 12(14.2%), followed by tremor 11(13%), akathisia 8(9.5%), hypersalivation 8(9.5%), insomnia 6(7.1%) and weight gain 6(7.1%) others include increased appetite, constipation, anxiety, vomiting, tardivi dyskinesia, etc were reported. The below mentioned table will give the detailed informations on type of ADRs identified in the study populations (Table No.3).

Out of 84 ADRs most of the reactions was caused by rispiridone 17(20.2%) followed by lorazepam 14(16.6%), haloperidol 11(13%), aripiprazole 9(10.7%), clozapine 8(9.5%), olanzapine 5(5.9%), clonazepam and escitalopram 4(4.7%) each. Details are given in Figure No.1.

The study evaluated the various types of ADRs that were found to be associated with the psychotropic drugs. Sedation was most frequently observed during the management with lorazepam and clonazepam, followed by tremor which was noticed to have associated with chlorpromazine, risperidone, haloperidol, and lithium, akathisia was developed in 8 patients with haloperidol, amisulpride, rispiridone, chlorpromazine, hypersalivationin patients undergoing treatment with clozapine, and rispiridone. The spectrum of identified ADRs and the drugs responsible for it are presented in (Table No.4).

Out of this 84 ADRs 30(35.7%) were possible, and 54(64.2%) were probable as per the WHO probability scale. Severity scale shows that most of the ADRs were mild 32(54.7%), and 46(45.2%) was of moderately severe. Reports on the probability scale tells that 43 ADRs fall in the category of probably preventable 38(45.8%), not preventable 46(54.7%).

DISCUSSION

In this study a total of 109(29.7%) interactions were categorized to have major clinical significance. 243(66.3%) interactions were categorized to have moderate clinical significance, and 14(3.8%) drug-drug interactions were minor. This result is in contrast with the study reports of Nieuwstraten C *et al*[7]. In their study they identified 439 potential drug-drug interactions out of which, 145(33%) interactions were found to have major clinical significance, 128(29%) interactions were of moderate clinical significance and 166(38%) interactions were of minor clinical significance.

In the current study out of 150 patients, 109 drug-drug interactions were identified, A similar study was conducted by Rafi M S *et al*[8] where the study results tells that out of 245 patients drug prescriptions they identified 181 drug-drug interactions.

In the present study, most of the potential drug-drug interactions were seen with haloperidol and most interacting pair is lorazepam-olanzapine 19(17.4%), followed by haloperidol-rispiridone 12 (11%), and

haloperidol-lithium 10(9.1%). The drugs which are having greater propensity to interact is haloperidol, risperidone, olanzapine, and lorazepam. When an antipsychotics with another antipsychotics is prescribed together the chances of QT interval prolongation is more. Here 13 types of drug interaction shows QT interval prolongation. When anxiolytics are taken with antipsychotics then the chances of cardiorespiratory depression or increased CNS depression can occur. When antipsychotics are taken with anxiolytics it can lead to the increased chances of EPS, weakness and dyskinesia. In this study there were no major potential drug-drug interaction that are found to be associated with trihexyphenydyl. The study is in contrast with the study outcomes of Jain T *et al*[9] where they reported that trihexyphenydyl is the drug that was found to be the cause of most drug-drug interactions.

In present study 84 ADRs were identified. Sedation is the most common of all the ADRs followed by tremor and akathisia. This result is in contrast with the study reports of Sarumathy S *et al*[10], Sandiya R *et al*[11], Lahon K *et al*[12].In present study antipsychotics were the common class of drug, which caused most of the identified ADRs. This result is learned to be similar with the study outcomes of Prajapati H K *et al*[13].

In the current study causality of the reported ADR according to WHO causality assessment scale showed that most of the reactions were probable (67.4%) followed by possible (32.6%). This report is almost similar with the study reports of Prajapati K H *et al*[13].

According to Hart wig severity scale 74.4% of ADRs was of mild in severity and 25.6% of ADRs were of moderately severe. The study reports of Prajapati K H *et al*[13] tells that 65.8% of ADRs was of moderately severe and 33.6% of the ADRs was of mild in severity.

Table No.1: Drugs prescribed of the enrolled patients

Class of drugs		Drugs	frequency	Percentage
Antipsychotics	1st Generation	Haloperidol	37	8.3
		Chlorpromazine	10	2.2
		Fluphenazine	6	1.3
		Flupenthixol	3	0.6
		Zuclopenthixol	5	1.1
	2nd Generation	Rispiridone	46	10.4
		Olanzapine	29	6.5
		Quetiapine	22	4.9
		Clozapine	12	2.7
		Aripiprazole	10	2.2
		Amisulpride	8	1.8
Anxiolytics		Lorazepam	98	22.1
		Clonazepam	22	4.9
		Diazepam	6	1.3
Antidepressants		Escitalopram	10	2.2
		Mirtazapine	8	1.8
		Desvenlafaxine	4	0.9
Mood Stabilizers		Valproic Acid	33	7.4
		Lithium	20	4.5
		Carbamazipine	15	3.3
Hypnotics		Zolpidem	12	2.7
Anticholinergic/ Antiparkinsonian		Trihexyphenydyl	26	5.8

Table No.2: Potential drug-drug interactions and their expected outcomes

Outcomes	Potential Drug-drug interaction	Frequency (n= 109)	Percentage
QT- interval prolongation	Haloperidol-risperidone	12	11
	Haloperidol-quetiapine	8	7.3
	Haloperidol-chlorpromazine	4	3.6
	Risperidone-escitalopram	3	2.7
	Olanzapine- quetipine	3	2.7
	Quetiapine-rispiridone	2	1.8
	Chlorpromazine-quetiapine	1	0.9
	Clozapine-quetiapine	1	0.9
	Aripiprazole-promethiazine	1	0.9
	Rispiridone-trifluperazine	1	0.9
	Aripiprazole-olanzapine	1	0.9
	Aripiprazole-haloperidol	1	0.9
	Clozapine-escitalopram	1	0.9
Cardiorespiratory depression Increased CNS depression	Lorazepam- olanzapine	19	17.4
	Haloperidol-clozapine	2	1.8
	Lorazepam-mirtazapine	2	1.8
Weakness, dyskinesia, EPS, encephalopathy	Haloperidol-lithium	10	9.1
	Lithium-olanzapine	6	5.5
	Fluphenazine-lithium	1	0.9
	Chlorpromazine-lithium	1	0.9
	Lithium-rispiridone	2	1.8
Low BP, shallow breathing, weak pulse, drowsiness, confusion.	Lorazepam-clozapine	3	2.7
	Diazepam-olanzapine	2	1.8
	Chlorpromazine-clozapine	1	0.9
	Clonazepam-olanzapine	2	1.8
Respiratory depression	Clobazam-phenobarbital	1	0.9
	Diazepam-phenobarbital	1	0.9
Decreasesquetiapine efficacy	Carbamazepine-quetiapine	1	0.9
	Phenytoin-quetiapine	1	0.9
Serotonin syndrome	Escitalopram-mirtazapine	1	0.9
	Escitalopram-desvenlafaxine	1	0.9
Increased risk of bleeding	Clopidogrel-diclofenac	1	0.9
	Diclofenac-escitalopram	1	0.9
Antiplatelet and thrombotic events	Amlodipine-clopidogrel	1	0.9
Lower seizure threshold	Bupropion Hcl-desvenlafaxine	1	0.9
Hypotension and cardiac arrest	Haloperidol-propranolol	1	0.9
Myopathy or rabdomyolysis	Fenofibric acid- rosuvastatin	1	0.9
Reduced plasma level of clonazepam	Carbamazepine-clonazepam	1	0.9
Reduced clozapine exposure and decreased efficacy	Carbamazepine- clozapine	1	0.9
Increased rispiridone exposure	Rispiridone- sertraline	1	0.9
Decreased phenytoin exposure	Phenytoin-theophylline	1	0.9
Increased clozapine exposure	Clozapine- propranolol	1	0.9
Increased aripiprazole exposure	Aripiprazole - ranitidine	1	0.9
Alteration in serum phenytoin concentration	Diazepam-phenytoin	1	0.9

Table No.3: Adverse drug reaction identified in the study population

S.No	ADR	Frequency	Percentage
1	Sedation	12	14.2
2	Tremor	11	13
3	Akathisia	8	9.5
4	Hyper salivation	8	9.5
5	Insomnia	6	7.1
6	Weight Gain	6	7.1
7	Increased appetite	5	5.9
8	Constipation	5	5.9
9	Anxiety	4	4.7
10	Vomiting	4	4.7
11	Decreased appetite	4	4.7
12	Tardive dyskinesia	4	4.7
13	Dry mouth	3	3.5
14	Headache	2	2.3
15	Cogwheel rigidity	1	1.1
16	Fever	1	1.1
Total		84	100

Table No.4: Incidence of ADR associated with psychotropic drugs

S.No	Type of ADR	Frequency	Drugs responsible for the ADRs
1	Sedation	12	Lorazepam-8, clonazepam-4
2	Tremor	11	Chlorpromazine-2, risperidone-2, haloperidol-5, lithium-2
3	Akathisia	8	Haloperidol-4, amisulpride-1, rispiridone-2, chlorpromazine-1
4	Hypersalivation	8	Clozapine-5, rispiridone-3
5	Insomnia	6	Escitalopram-2, aripiprazole-4
6	Weight Gain	6	Olanzapine-4, clozapine-2
7	Increased Appetite	5	Lorazepam-2, mirtazapine-2, rispiridone-1
8	Constipation	5	Rispiridone-3, escialopram-2
9	Anxiety	4	Rispiridone-1, aripiprazole-3
10	Vomiting	4	Risperidone-3, quetiapine-1,
11	Decreased Appetite	4	Lorazepam-4
12	Tardative Dyskinesia	4	Risperidone-2,haloperidol-2
13	Dry Mouth	3	Aripiprazole-2, olanzapine-1
14	Headache	2	Quetiapine-2
15	Cogwheel Rigidity	1	Flupenthixol-1
16	Fever	1	Clozapine-1
Total		84	84

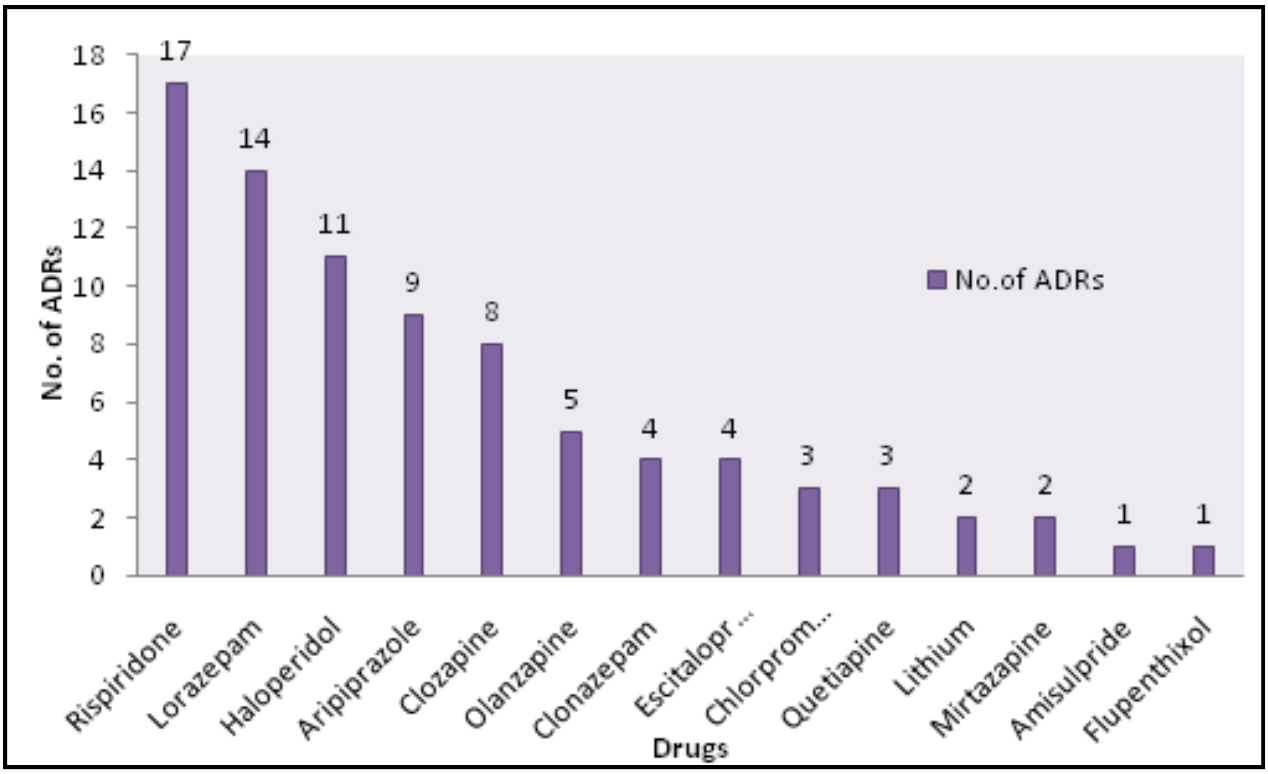

Figure No.1: Drugs which caused adverse drug reaction in the study population

CONCLUSION

The study provides the essential information regarding the characteristics of Drug-drug interaction and Adverse Drug Reactions associated with psychotropic drugs. Antipsychotics are the major class of drugs that caused major drug interactions. QT interval prolongation or cardio toxicity is one of the common interactions identified during antipsychotic therapy. Patients with cardiovascular disorders should be strictly monitored while they are prescribed with psychotropic medications. The current study also shows that antipsychotics are more prone to cause ADRs and it is also observed that the use of second generation antipsychotics minimize the incidence on the severity of ADRs. Drug-drug interactions and Adverse Drug Reactions are found to be more common in psychotropic prescriptions. Frequently monitoring the drug therapy can identify and prevent the unwanted effects of these psychotropic drugs. Thus, early detection may enhance the better management.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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