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Drug Interactions and Adverse Drug Reactions in Hospitalized Psychiatric Patients
A Critical Element in Providing Safe Medication Use

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Abstract

Background: Schizophrenia represents a major burden on mental health services globally, and there are nearby 15 million cases in India. The treatment of schizophrenia promises improvement only with long-term medication, but non-compliance, adverse reactions and interactions are a major hurdle in the pathway.
Methods: A six-month prospective study was conducted at the MDM Hospital, Jodhpur. Schizophrenic patients (n=205) aged 18-70 years and prescribed with antipsychotics were evaluated for drug interactions (DI) and adverse drug reactions (ADR). Extrapyramidal symptoms (EPS) were evaluated at baseline and endpoint; weight gain and lipid profile were evaluated at variable time points.
Results: In the present study, 463 interactions occurred; 70 were of major severity. Antipsychotics were involved in 42% of the total interactions, amongst which haloperidol (21.5%), and olanzapine (10.3%) were involved in most, while aripiprazole (3.48%) was involved in least interactions. A total of 194 ADRs including 19 severe (5, arrhythmia, 4, tremor, and 10, EPS) were reported. Other frequently reported ADRs were insomnia, anxiety, dry mouth and EPS. Weight gain in the aripiprazole vs. olanzapine group was 0.23 kg vs. 2.74 kg (p <0.001). Patients on olanzapine vs. aripiprazole experienced elevated total cholesterol (6.7 mg/dl vs. -11.2 mg/dl), low density lipoprotein (4.3 mg/dl vs. -13.2 mg/dl), and triglyceride levels (12.7 mg/dl vs. -22.13 mg/dl).
Conclusion: Reasons of non-compliance and inadequate clinical improvement in schizophrenia are long-term medication, ADRs and drug interactions. ADRs and interactions were least in aripiprazole prescriptions. Further long-term studies are required (German J Psychiatry 2011; 14: 26-34).

Keywords: antipsychotics, adverse drug reactions, interactions, metabolic syndrome

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Introduction

Schizophrenia is one of the most complex and challenging psychiatric disorders. It represents a heterogeneous syndrome of disorganized and bizarre thoughts, delusions, hallucinations, inappropriate affect, and impaired psychosocial functioning (American Psychiatry Association, 2000).

Antipsychotics are the mainstay of treatment for psychotic disorders. Newer atypical antipsychotics and their more traditional counterparts are subject to drug-drug interactions amongst themselves and with agents used in the treatment of various physical ailments. Furthermore, drug interactions

have been documented to occur with many agents commonly used in conjunction with antipsychotics such as anticholinergics, anticonvulsants, antidepressants, anxiolytics and lithium. Most data on antipsychotic interactions come from case reports and limited specific studies making assessment of the interactions difficult (Troy & Jann, 1998).

Most of the first generation and to a lesser degree, second generation antipsychotic agents are associated with adverse events and adverse drug reactions like extrapyramidal symptoms (EPS), sedation, anticholinergic side effects and metabolic disorders. A general approach to monitor and assess side effects requires prospective monitoring by clinicians and clinical pharmacists, preferably using a thorough review of systems approach. Patient-oriented self-rated side-effect scales may also be helpful, as many patients with schizophrenia do not readily complain of side effects due to lack of volition, perception, poor understanding or because of the actual interference of side effects themselves (e.g. sedation). In the recent years, suggestions of an increased occurrence of diabetes and other metabolic disturbances with some atypical antipsychotics agents, such as clozapine (CLZ) and olanzapine (OLZ), have raised significant concerns. A number of prior studies have documented abnormal glucose metabolism during treatment with CLZ, OLZ, risperidone (RSP) and quetiapine (QTP) (Dipiro et al., 2005).

Although prospective controlled comparisons of multiple agents are limited in number, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study showed that OLZ was associated with greater increases in weight gain and measures of glucose and lipids (Schneider et al., 2003). Growing evidence indicates a lower likelihood of metabolic and diabetes-related adverse events with the newer atypical agents ziprasidone and aripiprazole (APZ). In addition, both agents have shown a potential to reverse abnormal glucose metabolism related to treatment with other antipsychotics (Nasrallah, 2008).

With the variety of antipsychotics currently available, using an alternative drug should be considered in patients who complain of poorly tolerated side effects. Because medication side effects are one of the primary predictors of patient non-adherence, clinicians should take advantage of the treatment options currently available in an attempt to improve patient outcomes. As new antipsychotics become available, side effects and risks associated with different drugs should be re-evaluated. Attention of clinicians and health care professionals can reduce the frequency of interactions and preventable adverse drug reactions (Nasrallah, 2008).

Methods

Operational Modality

A six-months open label prospective study was carried out at the Mathura Das Mathur Hospital, Jodhpur. Prior to the initiation of the study, ethical approval was obtained from the local ethics committee. The study was conducted according to the Declaration of Helsinki and Good Clinical Practice. After complete explanation of the study procedures, consent was obtained from the patients, who were further screened and enrolled in the study based on certain inclusion-exclusion criteria.

Inclusion and Exclusion Criteria

Inclusions were made on following basis: the patient was willing to participate in study, between 18 and 70 years of age, diagnosed as schizophrenic according to ICD-10 or DSM-IV-TR, not on any depot preparation for the last two months, and had at least one follow-up visit. Patients with pregnancy or lactation, renal or hepatic failure, on a drug regimen known to alter the metabolism of the studied drugs, suffering from other chronic diseases and medico-legal cases were excluded from study. Total of 205 patients were included in the current study and 22 were excluded.

Study Materials

In order to record the necessary data for the current study, a separate case record form (CRF) was designed based on the data required for the study. The CRF contained patient demographics, medical history, complains on admission, medication history, diagnosis, course of treatment in the hospital, daily drug treatment chart for inpatients, discharge medications and condition on discharge. The data were collected for personal and clinical characteristics, diagnosis of subtype of schizophrenia, duration of illness, medical history, past medication history of antipsychotics use, antipsychotics medication change, current antipsychotics treatment, use of depot preparations, adjuvant medications to the main drug and adverse events to the past as well as present treatment for each patients.

Adverse drug reactions (ADR) were reported on specially designed forms containing patient demography, date of commencement of therapy, date of onset of ADR and brief description of ADR with a note by pharmacist. EPS-related adverse events were evaluated using the Simpson-Angus Scale (SAS), the Barnes Akathisia Rating Scale (BARS) and the Abnormal Involuntary Movement Scale (AIMS) scales.

Adverse events and their relationship with treatment and vital signs were recorded by investigators throughout the study.

From a list of medications prescribed to the patients, all probable and severe drug interactions were evaluated, notified and documented. Drug interactions were evaluated using MICROMEDEX® 2.0 Healthcare Series, (THOMSON REUTERS) accessed in association with Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, India (Micromedex-Drug Reax System, 2006).

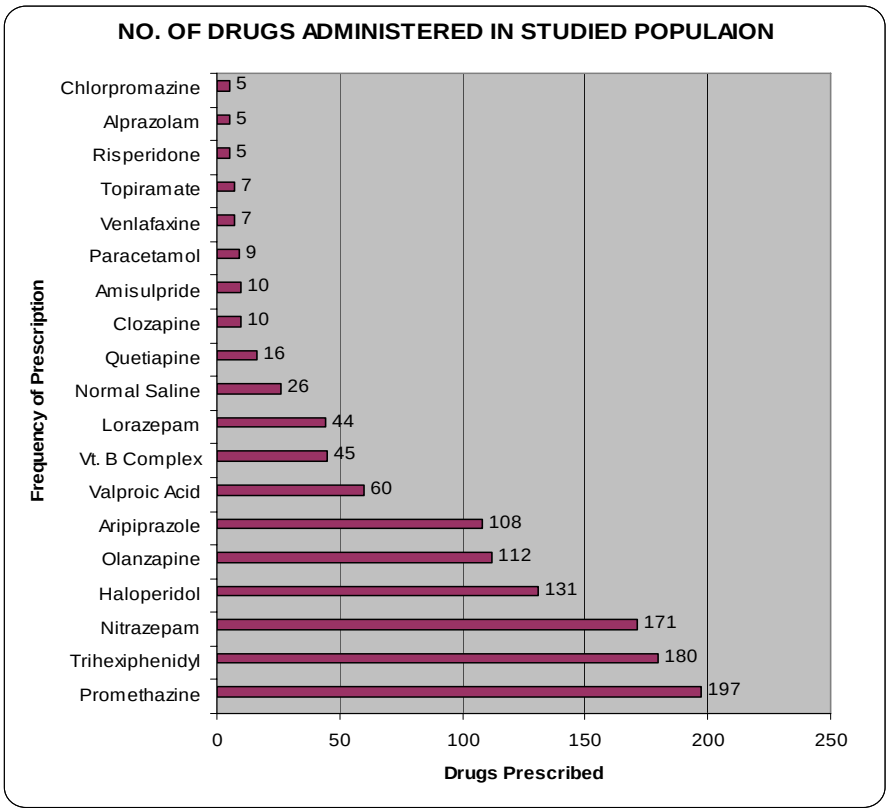

Fig. 1: Prescription Pattern of Study (n=205). **Other Drugs with *Frequency 4 were Ceftrixone, Olfloxacin, Propranolol, Diclofenac and Cefixime; with *Frequency 3 were Diazepam, Amoxcillin+ Clavulinic Acid; with *Frequency 2 was Serratipeptidase and with *Frequency 1 were Clonazepam and Lithium

Each potential drug-drug interaction was categorized according to its level of significance. The level of significance relates to the type and magnitude of the effect and subsequently to the necessity of monitoring the patients or altering therapy to avoid potentially adverse consequences. Primary factors that define level of clinical significance include time of onset of the interactions, and the severity with which an interaction occur clinically.

The potential severity of an interaction is important in assessing the risk-benefit ratio of treatments.

ADRs were evaluated during ward rounds based on the observations made by unit doctors and the clinical pharmacist (investigator), complaints of patients, abnormal laboratory data, previous history and other possibilities. ADRs were evaluated mainly on the basis of causality assessment, using Narnanjo's scale and the World Health Organization (WHO) probability scale. Extrapyramidal symptoms were evaluated in patients on HPL, OLZ, APZ (frequently prescribed antipsychotics) and other medicines, using the SAS, the BARS and the AIMS at different time points.

Outcome measures for weight gain were evaluated and compared between the groups of patients taking OLZ vs. APZ. The mean change from baseline was compared with week 2, 4, 6, and 8; an increase of ≥ 7% was considered significant. The lipid profile was evaluated at baseline and after week 8, when a patient came for a follow up visit. Blood pressure, pulse rate, body weight, ECG changes and other vitals were evaluated initially and at the end of study.

Analysis of the change from baseline in EPS, lipid profile and body weight were performed using descriptive statistics including analysis of variance (ANOVA) and paired t-tests.

Results

Demographics and diagnosis of the studied population

The mean age of the studied population (n =205) was 35.94±16.78, in which 158 (77%) were male and 47 (23%) were female. The average initial weight of the patients was 71.22±39.12, with a range of 31–139 kg. The mean duration of illness was 10.41±6.67 years (range of 1-24 years), while the onset of disease was found to be 23.54±09.11 years (range of 14-62 years). All patients enrolled in study were suffering from one or other types of schizophrenia. The paranoid (n=76; 36.90%) and undifferentiated form (n=68; 32.70%) were most prominent; 25% of the population was suffering from the disorganized (n=29; 14.14%) and residual form (n=21; 11.12%) while the catatonic type was least observed (n=9 ; 4.35%) in the studied population.

Drug Interactions

Prescribed antipsychotic drugs and co-medicines were evaluated for severity and significance of drug-drug interactions. Amongst the studied population, 71 percent were on polytherapy with 6 to 10 medicines prescribed at a given time point. Most frequently prescribed agents were promethazine (PMZ) (197), trihexyphenidin (THP) (180), nitrazepam (NTZ) (171), haloperidol (HPL) (131), OLZ (112) and APZ (108). The prescription pattern and frequency of prescription is presented in Figure 1.

Interactions were evaluated on the basis of severity, time of onset, category of drugs involved in interactions, individual drugs involved in various interactions, and the pharmacological consequences of drug interactions. Results of collected data were analysed using descriptive statistics.

In the 205 patients, out of 463 interactions, 70 interactions (15.2%) were of major severity, requiring urgent clinical interventions. 392 interactions were of moderate severity and only one interaction was of minor severity.

Out of 463 interactions, 28 occurred with rapid onset (6%), 373 with delayed onset (81%) and in 63 (13%) interactions; the time frame was not specified. The drugs involved in rapid onset of drug interactions were CLZ with lorazepam, fluroquinolines with phenothiazines (PTZ), HPL with propranolol and venlafaxine (VFL), and lorazepam with valproic acid (VA).

It can be seen from Figure 2 that most cases of drug-drug interactions were associated with anticholinergics, first and second generation antipsychotics and antihistaminic agents. Anticholinergics accounted for 30%, while first and second generation antipsychotics were involved in 42% and antihistaminic in 23% of total interactions.

Drugs most frequently involved in interactions were THP (24.77%), HPL (21.54%), PMZ (18.58%) and OLZ (10.26%). Amongst the drugs prescribed, least interaction was seen with APZ (3.48%) when compared with frequency of drug prescriptions (42.92%).

The observed drug interactions amongst the studied population were mostly of major and moderate severity, with rapid, delayed and non-significant onset of interaction. Pairs of drugs involved in interaction of clinical significance were HPL with amisulpride, propranolol, quetiapine (QTP), risperidone, and venlafaxine; PTZ with antipsychotics and gatifloxacin; lithium and antipsychotics, lorazepam and valproate. In such cases, either the drug administration should be adjusted by a gap of 4 to 5 hours if the interaction is of pharmacokinetic type; or a safer alternative should be prescribed, if the interaction is of the pharmacodynamic type, especially between drugs having a longer elimination half-time. Interactions along with the pharmacological inferences, severity type and onset are tabulated below in Table 1.

Adverse Drug Reactions

ADRs and their relationship to treatment and vital signs were recorded by the investigator throughout the study. Blood pressure, pulse rate, body weight and other vital signs

Table 1: Drug–Drug Interactions (DDI) with Pharmacological Consequences, Severity and Onset

S. No	DDI	Pharmacological Consequences	Severity	Onset
1.	Amisulpride–HPL	Cardio toxicity and Q_T prolongation	Major	Non Sign
2.	Antipsychotics–PTZ	Cardio toxicity and Q_T prolongation	Major	Non Sign
3.	CPZ–THP	Decreased PTZ serum concentrations, effectiveness, enhanced anticholinergic effects	Moderate	Delay
4.	Clozapine–LZP	CNS depression.	Minor	Rapid
5.	Gatifloxacin–PTZ	Cardiotoxicity. Q_T prolongation, torsades de pointes.	Major	Rapid
6.	HPL–Propranolol	Hypotension and cardiac arrest.	Major	Rapid
7.	HPL–Risperidone	Cardiotoxicity and Q_T prolongation	Major	Non Sign
8.	HPL–THP	Excessive anticholinergic effects	Moderate	Delay
9.	HPL–Venlafaxine	Increased HPL serum concentrations and cardiotoxicity	Major	Rapid
10.	Lithium–Antipsychotics	Weakness, dyskinesias, EPS, encephalopathy and brain damage.	Major	Delay
11.	Lorazepam–VA	Increased lorazepam concentrations.	Moderate	Rapid
12.	OLZ –HPL	An increased risk of parkinsonism	Moderate	Delay
13.	PMZ–THP	Decreased phenothiazine serum concentrations and effectiveness, enhanced anticholinergic effects	Moderate	Delay
14.	Quetiapine–HPL	Cardio toxicity and Q_T prolongation	Major	Non Sign
15.	Quetiapine–RSP	Cardio toxicity and Q_T prolongation	Major	Non Sign
16.	Risperidone–VA	Increased plasma VA concentrations.	Moderate	Non Sign
17.	Topiramate–VA	Decreased topiramate or VA concentrations, encephalopathy	Moderate	Delay

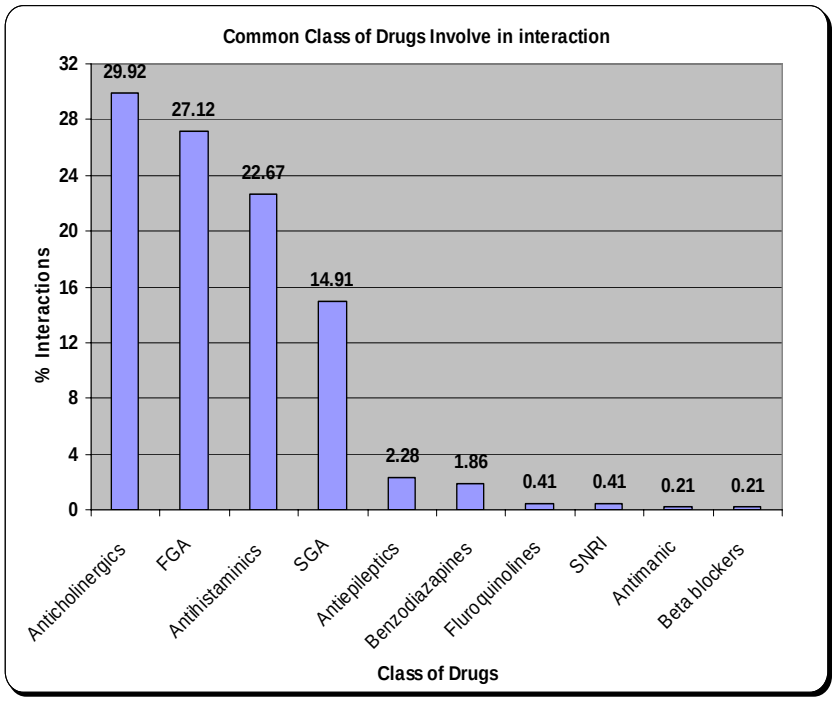

Figure 2. Common drug classes involved with drug-drug interactions

were evaluated initially and at end of study. The ADRs observed and evaluated in the current study were further separated into two segments, for evaluation of safety and efficacy of APZ vs. OLZ and overall ADR in the study population. In a comparison between APZ and OLZ, the incidence of adverse events was similar in both groups, with the majority of events being mild to moderate in intensity as given in Table 2.

Weight gain (APZ 2%; OLZ 10%) and EPS (APZ 2%; OLZ 8%) showed a difference of ≥ 5% between groups. Serious adverse events were reported in four patients prescribed with APZ and six patients prescribed with OLZ. Arrhythmia was reported in two patients taking OLZ (based on the QT_c interval). Insomnia and anxiety were reported by more than one patient in either group. Overall, a total of 194 ADRs were reported. Amongst them, 19 serious ADRs were documented from 205 schizophrenic patients. Frequently reported ADR were insomnia, anxiety, dry mouth and EPS. Serious adverse effects included arrhythmia (5), tremors (4) and EPS (10). The EPS were mainly observed in HPL and OLZ regimens, either together or individually prescribed, though the possibility of other drugs causing EPS cannot be ignored except APZ.

The mean change from baseline at week 8 did not differ between groups for the SAS (APZ -0.13; OLZ -0.35 and HPL -0.31; p=0.58), AIMS (APZ -0.27; OLZ -0.25 and HPL -0.11; p=0.12) or BARS (APZ -0.08; OLZ -0.14 and HPL -0.22; p=0.19) scores. Extrapyramidal side effects were observed more often in the OLZ group than in the APZ group (11% vs. 15%).

At week 8, the mean weight gain in the APZ group was 0.23 kg vs. 2.74 kg in the OLZ group (p <0.001). More patients showed significant weight gain (≥ 7 % increase from baseline) with OLZ (10%) than with APZ (2%), as given in Figure 3. Significantly more patients in the OLZ group than in the APZ group experienced increased total cholesterol (6.7 mg/dl vs. -11.2 mg/dl), LDL (4.3 mg/dl vs. -13.2 mg/dl), and TG levels (12.7 mg/dl vs. -22.13 mg/dl), which was statically significant (p<0.001). In addition, more patients developed new onset lipid elevations (except HDL) with OLZ than with APZ (p<0.001).

The incidence of vital sign abnormalities was similar in both studied groups. However, the incidence of arrhythmias was higher in patients treated with OLZ (n=2, 2.5%) when compared with APZ (n=0, 0%), based on a significant change in mean QT_c interval in the OLZ group (9.18 ms) compared with the APZ (1.87 ms) group, using the Food and Drug Administration Neuropharmacology Division formula ($QT/RR^{0.37}$) (Food and Drug Administration, 2000).

The overall incidence of arrhythmia was 5 (2.58%) of 205 patients enrolled in the study. A comparison of the various adverse drug reactions (individually for APZ or OLZ and overall comparison) is presented in Table 2 and Figure 4.

Discussion

In the current study, 70 interactions out of 463 were of major severity, while 28 occurred with rapid onset, requiring urgent clinical considerations to prevent adverse consequences. A previous study by Brown et al. (1999) had already shown that clinically relevant drug interactions may occur with many couples of drugs prescribed together like clozapine-lorazepam, clozapine-fluvoxamine, and sertindole-quinidine.

The newer psychotropic agents are extensively metabolized in the liver by cytochrome P450 (CYP) enzymes and are therefore susceptible to metabolically based drug interactions with other psychotropic medications or with compounds used for the treatment of concomitant somatic illnesses. The co-administration of inhibitors or inducers of the CYP isoenzymes involved in metabolism of various antipsychotic compounds may alter their plasma concentrations, possibly leading to clinically significant effects (Spina et al., 2003).

A clinical study by Ferslew et al. (1998) showed that concomitant administration of fluoxetine and clozapine produces increased plasma concentrations of clozapine and enhances

Table 2. ADRs evaluated in Psychiatric Patients

ADRs	ADR due to APZ		ADR due to OLZ		Total ADR Observed	
	No	%	No	%	No	%
Wt Gain	1	1.89	6	9.84	9	4.64
Insomnia	11	20.75	10	16.39	29	14.95
Anxiety	7	13.21	9	14.75	23	11.86
Somnolence	4	7.55	4	6.56	13	6.70
Headache	6	11.32	5	8.20	18	9.28
Reaction Schizophrenic	6	11.32	5	8.20	17	8.76
Akasthisia	5	9.43	4	6.56	12	6.19
Dry Mouth	4	7.55	5	8.20	22	11.34
Nausea	4	7.55	2	3.28	14	7.22
Tremor	2	3.77	2	3.28	7	3.61
CNS Stimulation	2	3.77	2	3.28	8	4.12
EPS	1	1.89	5	8.20	17	8.76
Arrhythmia	0	0.00	2	3.28	5	2.58
Total ADRs	**53**		**61**		**194**	

clozapine's pharmacological effects due to suspected inhibition of clozapine metabolism by fluoxetine.

Aripiprazole and haloperidol are metabolized primarily by hepatic enzyme systems such as CYP 3A4 and 2D6; the addition of APZ on HPL has the potential to alter plasma concentrations and metabolism of HPL and its metabolite (Shim et al., 2002).

In the current study, various pharmacokinetic drug interactions have occurred between groups of drugs prescribed together, such as increased HPL serum concentrations and cardiotoxicity with venlafaxine. This interaction is of major severity and has a rapid onset of action. Similarly, co-administration of lorazepam with valproic acid causes an increase in lorazepam concentration. Risperidone and valproic acid when prescribed together, may lead to increased valproic acid concentrations, while the concentration of topiramate decreases with valproic acid co-administration, which further increases the risk of encephalopathy.

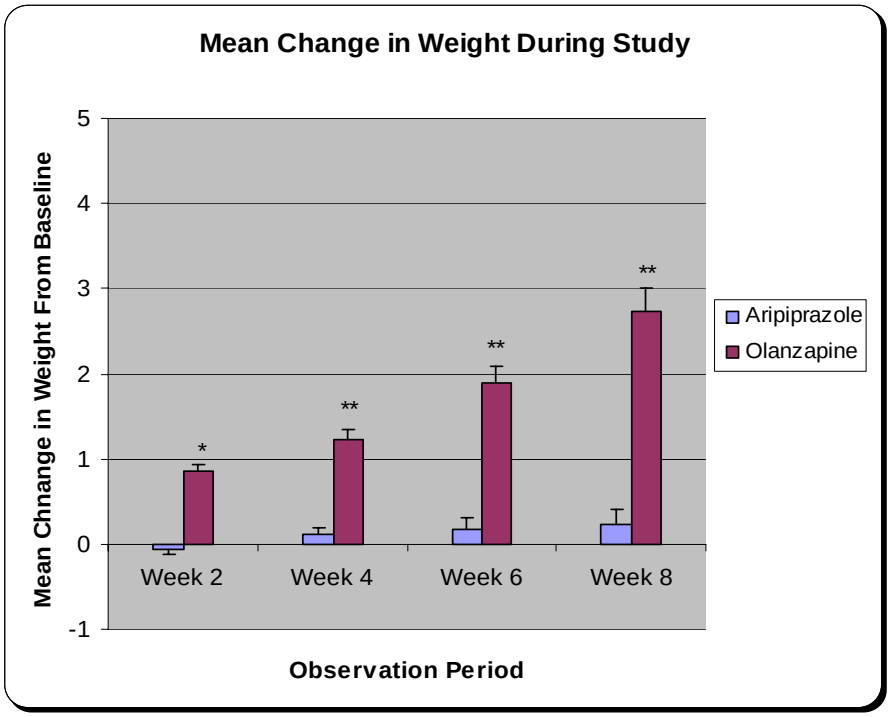

Figure 3: Mean change in body weight (Kg) from baseline. *p<0.01; **p<0.001 OLZ vs. APZ. Mean ± SEM baseline weight: APZ (n=81), 73.40 ± 0.48 Kg; OLZ (n=80), 74.80 ± 0.52 Kg.

The potential for metabolically-based drug interactions of any new psychotropic agent may be anticipated on the basis of knowledge about the CYP enzymes responsible for its metabolism and about its effect on the activity of these enzymes. This information is essential for rational prescribing and may guide selection of an appropriate compound which is less likely to interact with already taken medications.

It is well known that users of typical antipsychotic drugs have an increased risk of serious ventricular arrhythmias and sudden cardiac death. However, less is known regarding the cardiac safety of the atypical antipsychotic drugs, which have largely replaced the older agents in clinical practice (Ray et al., 2009).

Various antipsychotic agents when prescribed together may cause cardiotoxicity, either by synergism of side effects or by other mechanisms, thus needing clinical consideration. The finding from the current study suggests that the concomitant use of

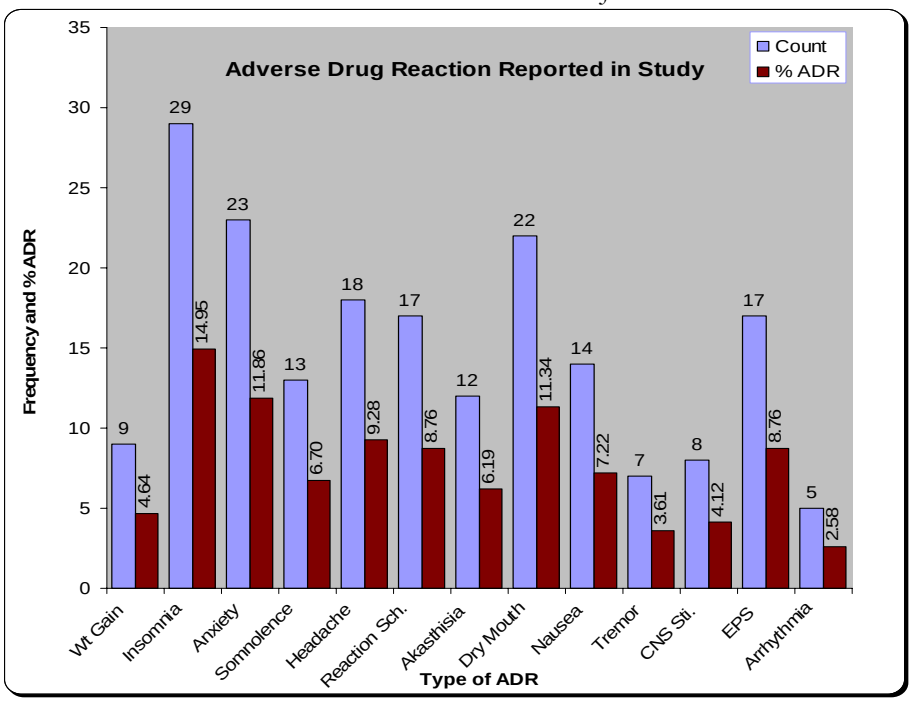

Figure 4: Frequency and percentage of individual ADRs reported in study

haloperidol with propranolol may cause hypotension and cardiac arrest, and the onset is rapid in nature. Cardiotoxicity, Q_T prolongation, and *torsades de pointes* could be precipitated by combining various drugs like haloperidol with risperidone, amisulpride and quetiapine, risperidone with quetiapine, or antipsychotics and gatifloxacin with phenothiazines.

Besides the pharmacokinetic and cardiotoxicity type of drug interactions, various other interactions are of clinical interest, like CNS depression by clozapine with lorazepam, rigidity and unstable gait by olanzapine and haloperidol, weakness, dyskinesias, increased EPS, encephalopathy and brain damage by lithium with other antipsychotics which were found in the current study when evaluating by the drug information database system (Micromedex-Drug Reax System, 2006).

The most significant adverse effects associated with antipsychotics are agranulocytosis with clozapine, dose-dependent extrapyramidal side effects (EPS) with risperidone, and neuroleptic malignant syndrome with clozapine and risperidone. The most common adverse drug reactions observed in current study were weight gain, insomnia, anxiety, somnolence, headache, reaction schizophrenic, akathisia, dry mouth, nausea, tremors, CNS stimulation, EPS and arrhythmia (Brown et al., 1999).

In a study by Ray et al. (2009), current users of typical and of atypical antipsychotic drugs had higher rates of sudden cardiac death than did nonusers of antipsychotic drugs, with adjusted incidence-rate ratios of 1.99 (95% confidence interval (CI), 1.68 to 2.34) and 2.26 (95% CI, 1.88 to 2.72), respectively. The incidence-rate ratio for users of atypical antipsychotic drugs as compared with users of typical antipsychotic drugs was 1.14 (95% CI, 0.93 to 1.39). In the present study, though no causality occurred, a total of 5 cases with cardiac arrhythmia due to the prescribed drugs were observed. Amongst them two patients were on olanzapine and three patients on other antipsychotics (except aripiprazole). Thus, the findings strengthen the risk relationship between olanzapine and cardiac arrhythmia in psychotic patients.

In a study by Koller & Doraiswamy (2002), a total of 237 patients with olanzapine-associated diabetes or hyperglycemia were observed, amongst which 196 cases were identified with the USFDA-MedWatch Drug Surveillance System, and 41 cases were identified with MEDLINE or through meeting abstracts. Of the 237 cases, 188 were new-onset diabetes, 44 were exacerbations of pre-existent disease, and 5 could not be classified. Hyperglycemia recurred in 8 of 10 cases with re-challenge. The number of reports, temporal relationship to start of olanzapine therapy, relatively young age, and improvement on drug withdrawal suggested that olanzapine may precipitate or unmask diabetes in susceptible patients.

Previous studies have suggested that the atypical antipsychotics clozapine and olanzapine may be associated with an increased risk of glucose intolerance and diabetes mellitus. Early studies have also suggested an association between use of conventional antipsychotics and the development of glucose intolerance. Treatment with clozapine, olanzapine or risperidone appears to be associated with an increased risk of glucose intolerance (Hedenmalm et al., 2002).

Though blood glucose levels at different time points were not monitored in the current study, but changes in lipid profile and body weight mainly in patients on olanzapine strongly suggested a definite correlation between olanzapine treatment and the onset of diabetes. In the current study, 9 patients were observed with significant weight gain, amongst them 6 were on olanzapine. The mean change in body weight of olanzapine patients when compared with aripiprazole (0.23 kg) patients was found to be 2.74 kg. Similarly, the lipid levels (except HDL) were also elevated in the olanzapine group. Both parameters were increased significantly ($p<0.0001$) in week 8 when compared with baseline.

EPS evaluated using SAS, AIMS and BARS showed no significant changes over time course of study, but the overall percentage incidence of EPS was higher with typical antipsychotics (67%) when compared with atypicals (33%). The safest drug in terms of severe EPS was found to be aripiprazole, and also other atypical antipsychotics could be better alternatives. Other severe adverse drug reactions, which resulted in prescription changes and withdrawal of suspected drugs, were a schizophrenic reaction in 17, tremors in 7 and CNS stimulation in 8 cases.

Conclusion

The major reasons of non-compliance and inadequate clinical improvement in psychiatric patients, especially in schizophrenia, are the need of long-term medication, adverse drug reactions and interactions between prescribed agents, although the patients' clinical conditions, mental alertness levels and understanding of the disease can be other secondary prime factors.

Drug interactions of major severity and rapid onset must be clinically endorsed. Various groups of drugs on co-administration leading to cardiotoxicity, like haloperidol with risperidone and quetiapine should be assessed prior administration, especially in patients carrying risk factors such as cardiac arrhythmia or other cardiovascular disorders. The pharmacokinetics type of drug interactions may occur in prescriptions containing enzyme inducer or inhibitors and can be avoided by rational prescribing and selection of an appropriate compound, which is less likely to interact with co-administered agents.

It is a well established fact that antipsychotics (mainly typical) are associated with various types of ADR. ADRs, which may be potentially fatal, are arrhythmias, EPS and metabolic disorders. Cardiotoxicity, particularly arrhythmia, can be minimized by selection of safer agents like aripiprazole and by keeping a note on possible drug interactions. Cases of EPS have been drastically reduced by the discovery of newer second generation antipsychotics. Therefore, patients with EPS should be switched to second generation antipsychotics. In the current study, patients on aripiprazole showed non-significant changes in parameters concerning the metabolic syndrome, while olanzapine was associated with metabolic changes in many cases, and the possibility of new-onset diabetes should not be ignored. The overall incidence of arrhythmias and EPS were least in aripiprazole amongst prescribed agents with comparable improvements in clinical conditions of the patients, giving a clue for safer and more efficacious future medicines for management of schizophrenia. However, it is too early to certain this statement, as data are still lacking for future promises. Further long term studies are required for strong and affirmative confirmation.

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References

American Psychiatric Association (APA). Schizophrenia and other psychotic disorders. In: APA. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Text Revision. Washington, DC: American Psychiatric Association; 2000: 297-319.

Brown S, Markowitz JS, Moore TR, Parker NG. Atypical antipsychotics: Adverse effects, drug interactions, and costs. The Annals of Pharmacotherapy 1999; 33(2): 210-217.

Dipiro JT, Talbert RL, Yees GC. Schizophrenia In: Pharmacotherapy - A Pathophysiologic approach. 6th ed. McGraw-Hill Publication Ltd. 2005: 1209-1233.

Ferslew KE, Hagardorn AN, Harlan GC, McCormick WF. A fatal drug interaction between clozapine and fluoxetine. J Forensic Sci 1998; 43(5): 1082-1085.

Food and Drug Administration: Recommendations for QT Interval Correction (FDA Guidance in Response to Pre-NDA Meeting). Rockville Pike, Maryland: FDA Division of Neuropharmacological Drug Products, 2000.

Hedenmalm K, Hagg S, Stahl M, Mortimer O, Spigset O. Glucose Intolerance with Atypical Antipsychotics. Drug Safety - Adis International 2002; 25(15): 1107-1016.

Koller EA, Doraiswamy PM. Olanzapine-Associated Diabetes Mellitus. Pharmacotherapy 2002; 22(7): 841-852.

Micromedex-Drug Reax System. Thomson Micromedix, USA, 2006.

Nasrallah HA. Atypical antipsychotic-induced metabolic side effects: insights from receptor-binding profiles. Molecular Psychiatry 2008; 13: 27–35.

Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical Antipsychotic Drugs and the Risk of Sudden Cardiac Death. N Engl J Med 2009; 360: 225-235.

Schneider LS, Ismail MS, Dagerman K et al., Clinical Antip sychotic Trials of Intervention Effectiveness (CA-TIE): Alzheimer's disease trial. Schizophr Bull 2003; 29(1): 57-72.

Shim JC, Jae YM, Shin JG et. al. Drug interactions between APZ and HPL: double blind placebo controlled study. Psychotic disorders and antipsychotics – Antipsychotics (clinical) 2002; S438.

Spina E, Scordo MG, D'Arrigo C. Metabolic drug interactions with new psychotropic agents. Fundamental & Clinical Pharmacology 2003; 17(5); 517-538.

Troy LZ, Jann MW. Drug Interactions with Antipsychotic Agents: Incidence and Therapeutic Implications. CNS Drugs 1998; 9(5): 381-401.