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Evaluation of adverse drug reactions associated with the psychotropic drugs in the management of patients with schizophrenia

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ABSTRACT

Adverse drug reactions (ADRs) to psychotropic agents are common and maydirect to noncompliance or even termination of therapy. We considered it worthwhile to assess the suspected ADR profile of psychotropic drugs administered for schizophrenic patients in the psychiatric unit of a tertiary care teaching hospital in south India.A prospective observational study was carried out in the in-patient department of the concerned psychiatric unit. Adverse event history, medication history and other relevant details were recorded in a specially designed format.The collected ADRs were assessed for causality, probability, severity, predictability and preventability. 200 schizophrenic patients were recruited in the study. We have recorded 352 suspected ADRs. The most commonly reported ADRs are dizziness (14.20%) followed by drowsiness (6.81%), constipation (6.53%) hypersalivation (6.53%), tremor (6.25%), insomnia (5.68%),orthostatic hypotension(5.11%), sedation (4.82%) and blurred vision (4.82%).Causality assessment byNaranjo's scale shows that out of 352 reported ADRs, 49.14% are possible. Probability assessment byWHO scale shows that 45.2% of ADRs are possible. Severity assessment by Hartwig and Siegel scaleshows that 73.3% of ADRs are mild. Predictability assessment reveals that 96.5% of ADRs are predictable. Preventabilityassessment by Modified Schumock and Thornton's Scale shows that91.5% of ADRs are not preventable. Among the psychotropic drugs, antipsychotics represented the majority, with olanzapine topping the list (30.96%) followed by risperidone (29.26%). This study presents a representative profile of ADRs to be expected in schizophrenic in-patients in asouth Indian tertiary care hospital.

Key words: schizophrenia, psychotropic drugs, adverse drug reactions.

INTRODUCTION

Schizophrenia is a persistent debilitating psychotic disorder that involves disconnection in thinking process. It affects a person's thought, feelings, perceptions and overall behaviour while interfering with filtering of stimuli from the environment [1].Antipsychotic agents are the cornerstone of acute and maintenance treatment of schizophrenia and are effective in the treatment of hallucinations, delusions and thought disorders. The mechanism of action involves, at least in part, binding to dopamine D_2/D_3 receptors in the ventral striatum [2]. For more than a decade after the invention of chlorpromazine's antipsychotic effect, there were few evidencesconcerning its mode of action. The neurotransmitter dopamine was identified [3] but few correlated it to the antipsychotics effect. Early assessments of chlorpromazine had shown its tendency to produce extrapyramidal adverse effects similar in many ways to the signs of parkinson's disease [4]. The detection that extrapyramidal effects need not be inevitablyrelated to remedial effects led eventually to the introduction of newer antipsychotics, the atypical. Amongst these arethe drugs that have the pharmacological similarity to clozapine, the thienobenzodiazepine olanzapine, and other structurally differentmolecules such as risperidone, sertindole and aripiprazole [5]. Patient wellbeing has become a leading topic at the national level. ADRs related with psychotropic drugs can direct to non-compliance, and at times discontinuation of therapy [6]. An ADR can lead to significant morbidity, mortality and financial costs. ADRs that may be preventable might be considered a form of medical error [7].Our study defines the possible adverse drug

events reported during the antipsychotic drug therapy in the patients with schizophrenia in the psychiatric unit of a tertiary care hospital.

MATERIALS AND METHODS

The study was conducted at a 1200-bed private tertiary care hospital located in Dakshina Kannada district.All the in-patients aged above 18 years with schizophrenia admitted to the psychiatrydepartment during the study period were enrolled after getting approval from Institutional Ethics Committee. The patient's case records were reviewed daily. Information's regarding demography details, antipsychotic drug therapy and adverse drug events were documented in the suitably designed data collection form.The collected ADRs were assessed for causality, probability, severity, predictability and preventability.

The causality was determined by Naranjo's causality assessment scale, probability by WHO probability scale, severity by Hartwig and Siegel scale, predictability by classifying the ADRs [8]and preventability by Modified Schumock and Thornton's Scale.The data collection form designed for use in the study was computerized using Microsoft access 2007 for easy accessibility, retrieval and analysis of collected data. The collected data were analyzed using SPSS software version 16.0.

RESULTS AND DISCUSSION

A total of 200 patients who met the study criteria were enrolled in the study. Patients were grouped gender wise into male and female and their respective percentage proportion was calculated. Schizophrenic admissions constitute 125(62.5%) males and 75(37.5%) females. (Table 1). The male preponderance identified in this study was similar to studies conducted by Padmini et al [9].

Table 1. Sex wise distribution of enrolled patients under study

Sex	N=200	%
Male	125	62.5
Female	75	37.5

Patient's age was sub classified into different age groups with a class interval of ten years.Higher numbers of patients were identified in the age group of 21-30 years(Table 2). Similar studies have also quoted the mean age of patients with ADRs within the same range [10,11,12].

Table 2. Age wise distribution of patients under study

Sl. No	Age groups	N=200	Percentage
1	18-20	10	05.0
2	21-30	69	34.5
3	31-40	64	32.0
4	41-50	38	19.0
5	51-60	19	09.5

Diagnosis of all the enrolled patients was classified according to WHO ICD 10th Revision.Number of patients with diagnosis of schizophrenia as categorized under different chapters of ICD and their respective percentage proportions with different diseases of specific chapters was calculated.Six different types of schizophrenia were noticed in the study population, which includes paranoid, unspecified, undifferentiated, residual, hebephrenic and catatonic schizophrenia. It was observed that majority of the patients fall in the category of paranoid schizophrenia 62% (n=124) followed by unspecified schizophrenia 16% (n=32).(Table 3). A related study also tells that paranoid schizophrenia is more common when compared to other types of schizophrenia [13].

Table 3. Types of schizophrenia in the study population

Sl. No	Schizophrenia types		
	Type	N= 200	%
1	Paranoid	124	62.0
2	Unspecified	32	16.0
3	Undifferentiated	26	13.0
4	Residual	8	04.0
5	Hebephrenic	7	03.5
6	Catatonic	3	01.5

During the study period we have identified 352 adverse drug reactions reported during the management of schizophrenia. The most commonly reported ADRs aredizziness (14.20%) followed by drowsiness (6.81%), constipation (6.53%) hypersalivation (6.53%), tremor (6.25%), insomnia (5.68%),orthostatic hypotension(5.11%), sedation (4.82%) and blurred vision (4.82%).Another study on ADRs due to psychotropic drugsshows that weight gain, dizziness, sleep disturbance and appetite disturbance accounted for nearly 78% of the events. Rest ofreported ADRs includes constipation, nausea, vomiting, insomnia, mouth ulcer, somnolence, hypersalivation and EPS [14]. The nature of ADRs observed in our study was similar to those reported in previous studies [15,11].The other ADRs reported in our study were scheduled in the Table 4.

Table 4. Adverse Drug Events Reported during the study period

Sl. No	Adverse Drug Events	N= 352	Percentage
1	Dizziness	50	14.20
2	Drowsiness	24	6.81
3	Constipation	23	6.53
4	Hypersalivation	23	6.53
5	Tremor	22	6.25
6	Insomnia	20	5.68
7	Orthostatic hypotension	18	5.11
8	Sedation	17	4.82
9	Blurred vision	17	4.82
10	Nausea	14	3.97
11	Headache	14	3.97
12	Increased appetite	13	3.69
13	Akathesia	11	3.12
14	Dystonia	9	2.55
15	Fatigue	9	2.55
16	Vomiting	9	2.55
17	Fever	8	2.27
18	Anxiety	7	1.98
19	Diarrhoea	7	1.98
20	Hypotension	6	1.70
21	Tachycardia	6	1.70
22	Dry mouth	5	1.42
23	Weight gain	5	1.42
24	Agitation	4	1.13
25	Tardive dyskinesia	4	1.13
26	Seizures	3	0.85
27	Pseudoparkinsonism	3	0.85
28	Gynecomastia	1	0.28
Total		352	100

All the ADRs reported during the study period were assessed by different scales for causality, probablity, severity, predictability andpreventability.

Naranjo's Causality assessment of ADRs shows that out of 352 reported ADRs, 19.60% of ADRs falls in the definite criteria, 31.81% as probable, 49.14% as possible and 0% as unlikely. (Table 5). In contrast, another study shows no case falls under 'definite" since the suspected ADRs were mostly of mild to moderately severe [11].

Using WHO probability scale, the ADRs were categorized as certain, probable, possible, unlikely, unassessible/unclassifiable and unclassified/conditional. Number of ADRs in each of these categories and their respective proportions of all ADRs were calculated. Probablity assessment shows that out of 352 reported ADRs, 20.45% of ADRs are certain, 34.1% are probable, 45.2% as possible, 0% as unlikely and 0% as unassessible. (Table 6). A study conducted by Hemalatha, et al shows that 57.6% of reported ADRs are probable, 11.53% are possible and 30.75% are certain [16].

Severity assessment by Hartwig and Siegel scaleshows that out of 352 reported ADRs, 73.3% are mild, 26.4% are moderate, 0.3% is severe, and 0% is lethal. (Table 7). Similarly, assessment of ADR by Solanke et al reports that maximum patients were in the mild category (84.89%), 12.5% are moderate and 2.60% are severe. None of the ADR falls in the lethal category [17].

We have also assessed the predictability of the reported ADR by predictable scale. The findings revealed that 96.5% are predictable and 3.40% are not-predictable. (Table 8)

Preventabilityassessment by Modified Schumock and Thornton's Scale shows that out of 352 reported ADRs, 91.5% are not preventable, 8.5% are probably preventable and none of theADRs was definitively preventable. (Table 9)

Table. 5 Naranjo's causality assessment of ADRs (N= 352)

Sl. No	Types of Causality	No. of ADRs	(%)
1	Definite	69	19.60
2	Probable	112	31.81
3	Possible	173	49.14
4	Unlikely	0	0

Table. 6 WHO probability assessment of ADRs (N= 352)

Sl. No	Types of reaction	No. of ADRs	(%)
1	Certain	72	20.45
2	Probable/likely	120	34.1
3	Possible	159	45.2
4	Unlikely	0	0
5	Unassessible/Unclassifiable	0	0

Table. 7 Hartwig and Siegel severity assessment of reported ADRs (N= 352)

Sl. No	Types	No. of ADRs	(%)
1	Mild	258	73.3
2	Moderate	93	26.4
3	Severe	1	0.3
4	Lethal	0	0

Table.8 Predictable Scale (N= 352)

Sl. No	Types	No. of ADRs	(%)
1	Predictable	340	96.5
2	Non-predictable	12	3.40

Table.9 Preventability (Modified Schumock and Thornton's Scale) (N= 352)

Sl. No	Types	No. of ADRs	(%)
1	Definitely Preventable	0	0
2	Probably Preventable	30	08.5
3	Not Preventable	322	91.5

We have identified the suspected ADR and categorized it depending on the suspected drugs which caused the ADR and number of times of its occurrence. We have noticed that dizziness was the most common ADR that was caused by few atypical agents(olanzapine, risperidon, clozapine and quetiapine) and typical antipsychotic agent chlorpromazine. Drowsiness was observed in six different drugs which includes olanzapine, risperidone, clozapine, quetiapine, fluphenazine, lorazepam and escitalopram. Incidence of constipation was noticed with olanzapine. Observation also shows that clozapine records the highest frequency of hypersalivation. Evidence of tremor is also observed during the management of the disease with olanzapine and risperidone. Olanzapine, risperidone and amisulpride show the prevalence of insomnia in schizophrenic patients. A report on orthostatic hypotension was observed to be high with olanzapine. Sedation was accounted with commonly used atypical antipsychotics which include olanzapine, risperidone and clozapine. Similarly large number of cases was reported with blurred vision and nausea due to risperidone, clozapine and olanzapine induced headache, olanzapine and risperidone induced increased appetite. Akathesia was recognized in patients administered with both typical and atypical antipsychotics. Fatigue was noticed only in patients who were on atypical antipsychotic therapy. Just as, antipsychotics induced dystonia, vomiting, fever, anxiety, diarrhoea, hypotension, tachycardia, dry mouth, weight gain, agitation, tardive dyskinesia, seizures and pseudoparkinsonism was also reported during the study period. One patient suffered from gynecomastia who was on olanzapine for a prolonged period of time was also detected. Distribution of the nature of ADRs and the group of psychopharmacological agents responsible for the ADRs are depicted in detail (Table 10).

Drug wise categorization was made to identify the highest number of ADRs reported by each drugs during the study period. We observed that olanzapine caused the highest number of ADRs (30.96%) followed by risperidone (29.26%), clozapine (20.45%), amisulpride (4.26%). The particulars of other drugs which caused the number of ADRs and its percentage are presented in the (table 11). Similarly a study reports by Solanke et al, also shows that maximum percentage of ADRs was observed with olanzapine (18.75%), followed by amitriptyline (13.02%) and clozapine (12.5%). The study also tells that atypical antipsychotics caused the most frequent ADRs in 40.10% of patients [17].

Table. 10Spectrum of suspected adverse drug reactions seen during the study period

Drug-related events	Number of incidences (%) (n= 352)	Individual drug (number of incidences)
Dizziness	50 (14.20)	Olanzapine (24). Risperidone (10), Clozapine (11), Quetiapine (3), Chlorpromazine (2)
Drowsiness	24 (6.81)	Olanzapine (7). Risperidone (5), Clozapine (7), Quetiapine (1), Fluphenazine (1), Lorazepam (2), Escitalopram (1)
Constipation	23 (6.53)	Olanzapine (10). Risperidone (6), Clozapine (7),
Hypersalivation	23 (6.53)	Clozapine (20), Risperidone (1), Olanzapine (1). Chlorpromazine (1)
Tremor	22 (6.25)	Olanzapine (13). Risperidone (5), Clozapine (2), Aripiprazole (1), Asenapine (1)
Insomnia	20 (5.68)	Olanzapine(4), Risperidone(7), Clozapine (1), Amisulpride(5), Quetiapine (1), Aripiprazole(1), Escitalopram (1)
Orthostatic hypotension	18 (5.11)	Olanzapine (11). Risperidone (5), Clozapine (1), Chlorpromazine (1)
Sedation	17 (4.82)	Olanzapine (4). Risperidone (9), Clozapine (4),
Blurred vision	17 (4.82)	Risperidone (8), Clozapine (2), Aripiprazole (1), Haloperidol (3), Trihexyphenidyl (2), Divalproex sodium (1)
Nausea	14 (3.97)	Olanzapine (3). Risperidone (7), Clozapine (2), Amisulpride(2),
Headache	14 (3.97)	Olanzapine (3), Clozapine (5), Amisulpride(1), Aripiprazole (3), Fluphenazine (1), Escitalopram (1)
Increased appetite	13 (3.6)	Olanzapine (7). Risperidone (6)
Akathesia	11 (3.12)	Olanzapine (4). Risperidone (2), Haloperidol (1), Zuclopenthixol (1), Chlorpromazine (2), Fluphenazine (1)
Fatigue	9 (2.55)	Olanzapine (1). Risperidone (5), Clozapine (2), Aripiprazole (1)
Dystonia	9 (2.55)	Risperidone (7), Haloperidol (1), Zuclopenthixol (1),
Vomiting	9 (2.55)	Olanzapine (4). Risperidone (2), Clozapine (1), Amisulpride(1), Quetiapine (1),
Fever	8 (2.27)	Olanzapine (2), Clozapine (6),
Anxiety	7 (1.98)	Risperidone (2), Amisulpride(3), Aripiprazole (1), Chlorpromazine (1),
Diarrhoea	7 (1.98)	Olanzapine (1). Risperidone (5), Escitalopram (1)
Hypotension	6 (1.70)	Olanzapine (2) Risperidone(2), Quetiapine (1), Chlorpromazine (1)
Tachycardia	6 (1.70)	Olanzapine (1), Risperidone (2), Clozapine (1), Haloperidol (1) Imipramine (1)
Dry mouth	5 (1.42)	Olanzapine (1), Quetiapine (1), Aripiprazole (3)
Weightgain	5 (1.42)	Olanzapine (4). Risperidone (1),
Agitation	4 (1.13)	Risperidone (2), Amisulpride(1), Fluphenazine (1)
Tardive dyskinesia	4 (1.13)	Risperidone (2), Haloperidol (1), Trifluoperazine (1)
Seizures	3 (0.85)	Olanzapine (1), Amisulpride(2)
Pseudoparkinsonism	3 (0.85)	Risperidone (2), Trifluoperazine (1)
Gynecomastia	1 (0.28)	Olanzapine (1)

Table. 11Drugs responsible for the adverse drug reactions noted among the study population

Sl. No	Drugs	No of ADRs	%
1	Olanzapine	109	30.96
2	Risperidone	103	29.26
3	Clozapine	72	20.45
4	Amisulpride	15	4.26
5	Aripiprazole	11	3.12
6	Quetiapine	8	2.27
7	Chlorpromazine	8	2.27
8	Haloperidol	7	1.98
9	Fluphenazine	4	1.13
10	Escitalopram	4	1.13
11	Lorazepam	2	0.56
12	Trihexyphenidyl	2	0.56
13	Trifluoperazine	2	0.56
14	Zuclopenthixol	2	0.56
15	Divalproex sodium	1	0.28
16	Asenapine	1	0.28
17	Imipramine	1	0.28
Total		352	100

CONCLUSION

The present study has reported the incidence of suspected ADRs to psychotropic drugs in the psychiatric in-patient department in the Indian context. This post-marketing surveillance study may not provide the true incidence or prevalence figures, but offers a representative proposal of the ADR profile of psychotropic drugs thatcan be expected tocome across in the in-patients of anIndian private psychiatric unit. Non-compliance with drug therapy due to ADRs is a major concern in psychiatric patients. Continuous monitoringin detecting ADRs followed by dose adjustments will be considered safer and more effective. Thus compliance towards medication can also be improved.

Active collaboration of psychiatrists and clinical pharmacists can make difference in the management of drug therapy and by reporting the possible ADRs. Such records can be a ready reckoner in identifying unwanted drug reactions.

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