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PRESCRIPTION TREND OF ANTIPSYCHOTIC DRUGS IN PATIENTS WITH EXTRA-PYRAMIDAL SIDE EFFECTS IN A TERTIARY CARE HOSPITAL IN INDIA

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ABSTRACT

Antipsychotic drugs form the cornerstone of the management of psychosis but are associated with extrapyramidal side effects (EPS). Conflicting studies regarding the incidence of EPS with either class of antipsychotic drugs, viz., typical and atypical, exist. The present study was therefore undertaken to determine the prescription pattern of antipsychotic drugs in patients experiences EPS. A total of 100 prescriptions were analyzed over a period of 1 year. The EPS were more common in women than in men, 54 versus 46. Tremor (n=59) was the most frequent EPS observed. Akathisia was observed in 34 and acute muscle dystonia in 7 patients. Tardive dyskinesia was not observed in any patient. Olanzapine (n=61) and Risperidone (n=53) were the most commonly prescribed antipsychotic drugs, followed by Haloperidol (n=44) and Trifluoperazine (n=31). Trihexyphenidyl was noted to 73 prescriptions. Risperidone monotherapy was implicated in the development of EPS in 14 patients. It was thus concluded that both classes of antipsychotic drugs lead to EPS. A higher incidence of EPS was observed with those prescribed with Olanzapine and Risperidone in the present study.

KEYWORDS: Akathisia, Dystonia, Tardive dyskinesia, Trihexyphenidyl, Risperidone, Olanzapine.

INTRODUCTION

Antipsychotic drugs are the cornerstone in the management of psychosis. Although they do not cure the illness, the symptoms are greatly reduced, allowing the patient to lead a better quality of life. The typical antipsychotic drugs, chlorpromazine and others, successfully control the positive symptoms of psychosis but fail to afford relief from the negative symptoms as well as cause various side effects, including those affecting the neurologic (nervous) system i.e. extrapyramidal side effects (EPS).

Extrapyramidal side effects (EPS) include Acute Muscle Dystonia (AMD), Akathisia, Parkinsonism and Tardive Dyskinesia (TD). These are serious, sometimes debilitating and stigmatizing adverse effects, and require additional pharmacotherapy.[1] EPS develops in two phases. Early, acute EPS, most often develops during the beginning of antipsychotic therapy or when the dose of the antipsychotic drug is increased. This is the main cause behind poor adherence to antipsychotic treatment. The late onset EPS usually occurs after prolonged treatment and presents as tardive dyskinesia which is known to have a serious impact on patients and caregivers with respect to quality of life.[2,4]

The atypical antipsychotic drugs were introduced to overcome these drawbacks. However, all the atypical drugs (except clozapine) have failed to live up to the expectation and lead to extrapyramidal side effects to a certain degree.[5,8]

Multiple contradictory studies exist with respect to the incidence of EPS with either class of antipsychotic drugs. The present study was thus undertaken to understand the pattern of antipsychotic drug prescription specifically in patients experiencing EPS.

MATERIALS AND METHODS

The study was undertaken after obtaining the permission of the institutional ethics committee in the department of psychiatry of a tertiary care hospital for a period of 1 year, from June 2016 to May 2017. The participants were enrolled as per the selection criteria after obtaining a written informed consent from them or the Legally Acceptable Representative, wherever applicable. Sample size was calculated with a 95% confidence level and a 5% confidence interval considering the number of patients suffering from psychosis and experiencing EPS due to antipsychotic drugs visiting the psychiatry unit of the hospital over a duration of 12 months i.e. 9 to 12 patients in a month which comes to 120 patients a year. Accordingly, a total of 100 prescriptions were analyzed using descriptive statistics.[9] The data obtained was filled on a case record form which included the

demographic details, details of the EPS and the prescribed antipsychotic drugs.

Inclusion criteria

1. Patients who had received antipsychotic drugs (typical or atypical) and developed extrapyramidal side effects.
2. Patients aged 18 years or above.

Exclusion criteria

1. Patients who had received antipsychotic drugs (typical or atypical) and had not developed extrapyramidal side effects.
2. Patients who had developed extrapyramidal side effects due to drugs other than antipsychotics.
3. Pregnant and nursing women.

RESULTS AND DISCUSSION

The youngest patient to experience EPS was 18 years old while the oldest was 74. The highest frequency of EPS was seen in patients aged 40-60 years (n=50). A small incidence of EPS was seen in patients aged more than 60 years (n=10) while EPS was seen in 40 patients aged between 18 to 40 years. A similar observation was made in a study by Patel et al., wherein the maximum psychiatric ADRs (adverse drugs reactions) were noted within the age group of 20 to 59 years (54 of 67) while in patients above 60 years of age only 8 (of 67) developed psychiatric ADRs.[10]

A slight female preponderance was observed in our study such that out of 100 patients, 46 were males and 54 were females. Similarly, Lucca et al., reported a total of 217 psychiatric ADRs, with a greater incidence in women (119 [57.21%]) as compared to men (98 [42. 25%]).[11] The increased risk of psychiatric ADRs in women may be due to the gender-related differences in pharmacokinetic, immunological, hormonal factors and differences in the use of medications as women usually have a lower lean body mass, a reduced hepatic clearance, differences in the activity of CYP450 enzymes and different drug metabolism rates as compared to men. [12] Another hypothesis is that estrogen blunts dopamine overproduction, a pathophysiological feature of psychosis, by reducing dopamine receptor sensitivity and increasing the threshold for vulnerability.[13]

Tremor was the most frequent extrapyramidal side effect which was observed in 59 patients. Akathisia and acute muscle dystonia was experience by 34 and 7 patients respectively. Tardive dyskinesia was not complained of by any patient as shown in Figure 1. It was also observed that tremors were more frequent in men (32 men versus 27 women) while akathisia and acute muscle dystonia were more frequent in women. Table 1 demonstrates the gender-wise distribution of EPS. The patients experienced EPS within 1 month of onset of antipsychotic drug therapy with AMD occurring with 24 hours of onset of therapy.

The most common antipsychotic drugs prescribed to the patients included, in the descending order, Olanzapine (n=61), Risperidone (n=53), Haloperidol (n=44), Trifluoperazine (n=30) and Aripiprazole (n=3). Figure 2 described the number of antipsychotics drugs prescribed in a total of 100 prescriptions. 36 of 100 prescriptions comprised of only 1 antipsychotic drug while the remaining 64 prescriptions had either 2 (37 of 64) or 3 (27 of 64) antipsychotic drugs (Table 5). Not more than 3 antipsychotics were prescribed to any patient.

Along with the antipsychotic drugs trihexyphenidyl (an anticholinergic drug) was prescribed to 73 patients. A potentially lower incidence of EPS may thus be noted as anticholinergic drugs are used in the management of EPS. This can be hypothesized on the basis of a study by Piparva et al., which states that when risperidone was used alone on 25 occasions, ADRs occurred in 11 cases, whereas if risperidone was combined with central anticholinergic drug, incidence of ADRs was 4 out of 13.[14]

Amongst the patients receiving a single antipsychotic drug, tremors were seen most commonly with trifluoperazine (n=8), olanzapine (n=8) and haloperidol (6 patients). In patients receiving risperidone monotherapy, 5 patients experienced tremors. Akathisia (n=6) and acute muscle dystonia (n=3) were exclusively seen with risperidone.

Amongst the 64 patients who were prescribed more than one antipsychotic drug, 37 patients received 2 while 27 patients were prescribed 3 antipsychotic drugs. More than 3 antipsychotic drugs were not prescribed to any patient. In patients receiving antipsychotic polytherapy, 32 patients experienced tremors, 28 had akathisia and 4 developed AMD. Table 2 summarizes the distribution of EPS with respect to the number of antipsychotic drugs prescribed.

The most frequent multiple antipsychotic drug combination employed was haloperidol – olanzapine - risperidone (HOR) (n=23), followed by haloperidol – olanzapine (HO) (n=14). Figure 3 summarizes the most frequently prescribed multiple antipsychotic drug combinations.

It was 10 mg of Haloperidol (n=35), 25 mg of Trifluoperazine (n=14), 15 mg of Olanzapine (n=36), 4 mg of Risperidone (n=27) and 3 mg of Aripiprazole (n=3) which was observed to be prescribed most frequently to patients who had experienced EPS. Table 3 summarizes the doses at which the EPS was most frequently observed.

Patel et al., in a study of psychiatric drug related ADRs in 67 patients wherein a total of 55 antipsychotic drugs were prescribed which were associated with 22 incidences of EPS.[10] Parkinsonism was reported in 18 of these patients. Most common antipsychotic drugs

responsible for causing EPS were haloperidol (10 of 22 patients), risperidone (6 of 22 patients), clozapine (3 of 22 patients), and aripiprazole (3 of 22 patients).

In contrast to the present study in which aripiprazole was prescribed only in those who developed AMD, other studies have reported EPS other than AMD with aripiprazole. In a case series of 14 patients treated with aripiprazole (dose range: 2 to 20 mg per day, alone or in combination therapy) reported by Selfani et al., 4 cases of TD, 4 cases of Parkinsonism, and 1 case of akathisia were observed.[15]

In a review on randomized controlled trials conducted by Edwards and Smith, it was observed that risperidone was most likely and quetiapine least likely to be associated with EPS.[16] In a meta-analysis by Klemp et al., comparing 4 atypical antipsychotic drugs with Haloperidol and placebo, it was found that there was a lower risk of experiencing extrapyramidal side effects with olanzapine compared with placebo in contrast to aripiprazole and risperidone. No significant increase in the EPS risk was associated with clozapine compared with the placebo groups.[17] In contrast, a data mining study from Japan carried out by Kose et al., reported the risk of EPS was similar with atypical and typical antipsychotics while a review by Crossley et al., concluded a higher incidence of EPS with typical antipsychotics.[18,19]

Table 1: Gender-wise distribution of EPS.

	Extrapyramidal Side effect			
n=100	**Tremor**	**Akathisia**	**AMD**	**Total**
Male	32	13	1	46
Female	27	21	6	54
Total	59	34	7	100

Table 2: Patients experiencing EPS, monotherapy versus polytherapy.

n=100	**Tremor**	**Akathisia**	**AMD**	**Total**
Monotherapy				
Haloperidol	6	-	-	6
Trifluoperazine	8	-	-	8
Olanzapine	8	-	-	8
Risperidone	5	6	3	14
Aripiprazole	-	-	-	-
Polytherapy				
2 drugs	15	18	4	37
3 drugs	17	10	-	27
Total	**59**	**34**	**7**	**100**

Table 3: EPS and antipsychotic drug doses.

n=100	**Tremors**	**Akathisia**	**AMD**	**Total**
Haloperidol				
10 mg	22	13	-	**35**
3 mg	6	3	-	**9**
Trifluoperazine				
25 mg	8	6	-	**14**
15 mg	4	5	-	**9**
5 mg	3	1	-	**4**
1.5 mg	3	-	-	**3**
Olanzapine				
15 mg	19	17	-	**36**
10 mg	8	8	2	**18**
5 mg	7	-	-	**7**
Risperidone				
6 mg	2	15	5	**22**
4 mg	22	4	1	**27**
2 mg	4	-	-	**4**
Aripiprazole				
3 mg	-	-	3	**3**

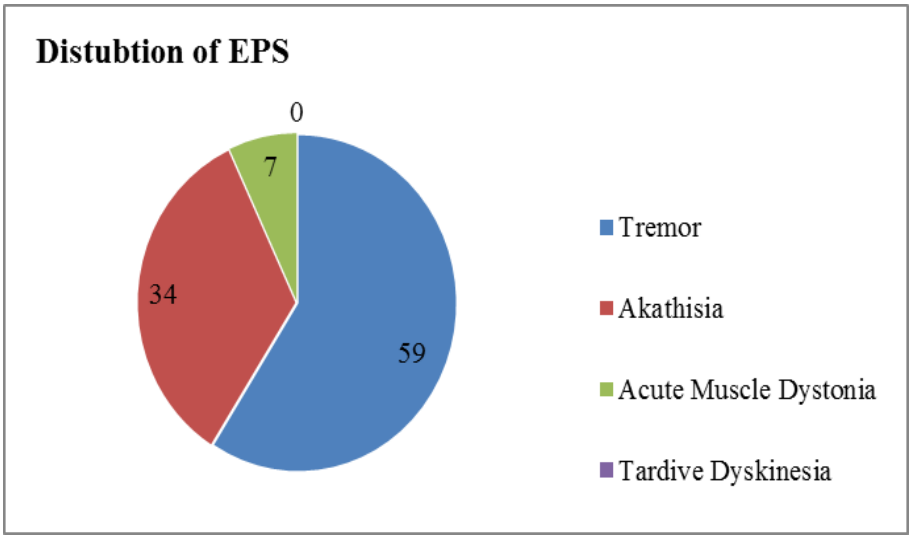

Figure 1: Distribution of EPS (n=100).

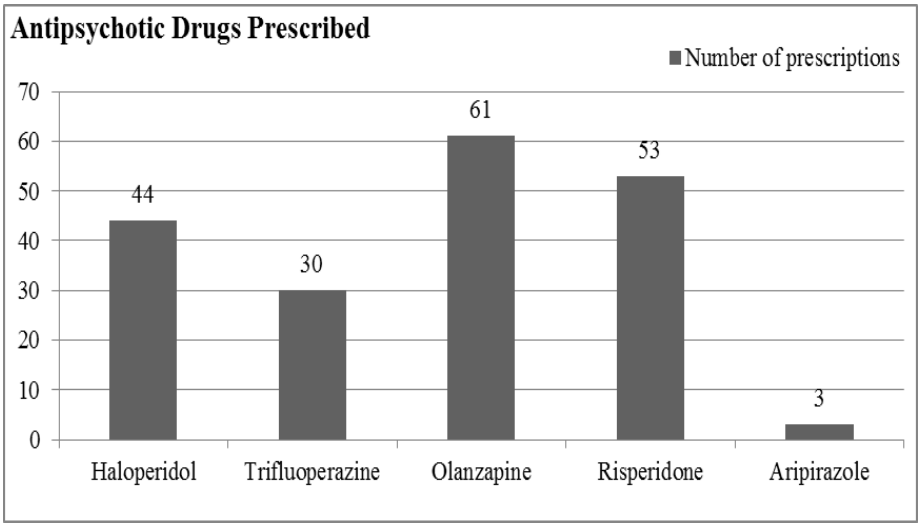

Figure 2: Number of antipsychotic drugs prescribed (n=100).

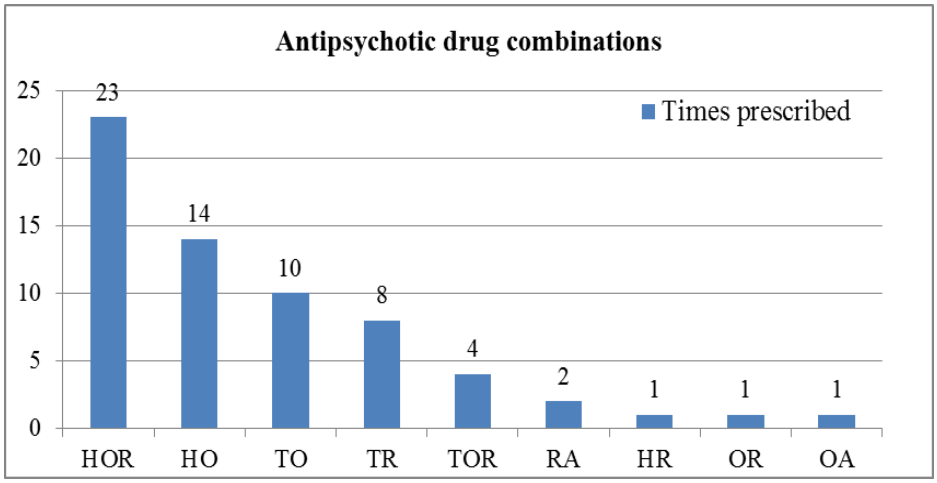

Figure 3: Antipsychotic drug combinations prescribed.

CONCLUSION

Irrespective of being prescribed alone or in combinations, EPS was seen more with atypical antipsychotic drugs than with typical antipsychotic drugs with a practice of initiating therapy with a concomitant anticholinergic drug. However, this may be due to the trend towards greater prescription of atypical antipsychotic drugs. As compared to the other antipsychotics, risperidone monotherapy lead to a higher number of extrapyramidal side effects whereas

aripiprazole when used in combination with olanzapine or risperidone lead to AMD. A reduction in the dose of the antipsychotic drug caused a reduction in the severity of the EPS. Initiating antipsychotic therapy with lower doses of drugs may thus be helpful. However, a study involving a larger number of patients and a longer duration may help shed more light in this regard.

Limitations

The present study did have a few limitations. A short duration limits the possibility of discovering a greater number of individuals with extrapyramidal side effects, especially tardive dyskinesia as it occurs late in therapy. The present study conducted only in adult patients. Only 5 antipsychotic drugs were prescribed which may be due to the hospital policies. Similarly, none of the patients were prescribed a parenteral preparation of any antipsychotic drug. Causality assessment was not included in the study design. 73% of the individuals who developed these side effects were also prescribed an anticholinergic drug from the very beginning which may have affected the occurrence and severity of EPS.

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Conflict of Interest: None.

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