

# INCIDENCE OF ADVERSE REACTIONS TO COMMONLY PRESCRIBED PSYCHOPHARMACOLOGICAL AGENTS DURING EARLY PHASE OF THERAPY

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*Five hundred and ninety two patients attending a psychiatric department as outpatients or as inpatients were included in this study. Details regarding age, sex, diagnosis and drugs prescribed were entered in a proforma. The information regarding drugs prescribed, dosage and the types of reactions were noted. All patients were followed up for a period of 3 to 4 weeks. Incidence of adverse reactions was calculated as percentage of the total number of prescriptions of the same group of drugs. The incidence of reactions to antipsychotic and antidepressants ranged from 35 to 46.9%. The incidence of reactions to haloperidol was higher than the reactions to other drugs. Antianxiety drugs were found to produce only minimal reactions. Two or more drugs prescribed together was associated with a higher incidence of reactions. Among the 193 patients who were reported to have reactions, 65.8% had extrapyramidal symptoms. The frequency of these reactions were highest with antipsychotic drugs haloperidol, chlorpromazine, trifluoperazine and thioridazine in that order. Dystonic reactions were reported within one to two days after the initiation of therapy in a large group of patients. Anticholinergic side effects were associated with prescription of tricyclic antidepressants and phenothiazines. Drowsiness, giddiness and postural hypotension were the other reactions associated with tricyclics.*

*Key words: adverse reactions, psychopharmacological agents.*

## INTRODUCTION

Many psychiatric patients are required to be on long term therapy with drugs and many of them develop adverse effects. Adverse reactions are one of the main factors which prompt patients to discontinue the medications. These also frighten the relatives who at times actively encourage patients to discontinue the medication. Awareness of these reactions and measures to combat them are important for the practicing physician. This study highlights the incidence and profile of common reactions developing during early phase of treatment and factors influencing these reactions.

## MATERIALS AND METHODS

Patients attending the outpatient clinic and those admitted in the wards of a psychiatry unit were included in this study. All patients were followed up for a minimum period of 3 to 4 weeks. The study period involves two six months periods. Details regarding age, sex, diagnosis and drugs prescribed were entered in a proforma prepared for this study. Reactions which were disturbing to the patients were reported by them. In addition, the reactions which were observed by the investigator were also recorded. These observations were guided by a check-list which included all the known side effects

of psychopharmacological agents as reported in literature. Patients attending outpatient clinic were followed up during their subsequent visits.

Incidence of adverse reactions were calculated as percentage of the total number of prescriptions of the same group of drugs. In each group, age and sex of patients who were receiving these drugs were noted. Reactions were grouped into various categories such as acute dystonia, other extrapyramidal symptoms and anticholinergic effects. Number of occurrence of each reaction was noted and the total frequency of each group of reactions were calculated. Proportion test was done to compare two group to determine significance.

## RESULTS

### Incidence of reactions:

Of the 592 patients included in this study, 322 were males and 270 were females. Diagnostic details of this group of patients are presented in Table 1; 193 patients in this group of 592 developed adverse reactions. The overall incidence of adverse reactions in this group is 32.6%.

The pattern of prescriptions show that the main group of drugs prescribed were antipsychotics and antidepressants. The major group of antipsychotics prescribed were haloperidol and phenothiazine. Among the phenothiazine the most frequently

**Table 1**  
Morbidity pattern of patients included in this study

| Disease group   | Sex        |            | Total      |             |
|---|------------|------------|------------|-------------|
|   | Male       | Female     | No.        | %           |
| <b>Affective disorders</b>                                      | 182        | 174        | 356        | 60.1        |
| MDP mania and<br>MDP circular currently<br>manic                | 74         | 66         | 140        | 23.6        |
| MDP depression<br>and MDP currently<br>depressed                | 108        | 108        | 216        | 36.5        |
| Schizophrenia   | 24         | 16         | 40         | 6.8         |
| Reactive psychoses  | 10         | 13         | 23         | 3.9         |
| Paranoid state  | 9          | 7          | 16         | 2.7         |
| Neurotic depression   | 44         | 31         | 75         | 12.7        |
| Obsessive compulsive<br>neurosis                                | 11         | 4          | 15         | 2.5         |
| Anxiety, panic disorder   | 8          | 4          | 12         | 2.0         |
| Neuroses (Not otherwise<br>specified)                           | 11         | 11         | 22         | 3.7         |
| Alcohol dependence  | 12         | -          | 12         | 2.0         |
| Neurological disorders<br>associated with<br>behavioral changes | 11         | 10         | 21         | 3.5         |
| <b>Total</b>  | <b>322</b> | <b>270</b> | <b>592</b> | <b>99.9</b> |

Age group of patients: 20-39 yrs 61.4%; 49-59 yrs 22.6%; below 20 yrs 11.4%; above 60 yrs 4.6%.

prescribed drug was chlorpromazine (75%). Trifluoperazine, thioridazine and fluphenazine decanoate were the other members of the phenothiazine group which were prescribed. The major group of antidepressants prescribed were tricyclics of which amitriptyline and imipramine were the most frequently prescribed drugs. Dothepin, doxepin and clomipramine were the other tricyclic drugs prescribed. The major anti-anxiety drugs were benzodiazepines (chlordiazepoxide and diazepam). The antimanic drugs used were lithium and carbamazepine. The details regarding age and sex of patients developing reactions are presented in Table 2.

The incidence of reactions to various groups of drugs are presented in Fig 1. The overall incidence to the most commonly prescribed drugs viz antipsychotics and antidepressants ranged from 35 to 46.9%. The incidence of reactions of haloperidol was significantly higher ( $p < 0.001$ ) than the reactions associated with phenothiazine. Patients who were prescribed chlorpromazine reported an in-

**Table 2**  
Age and sex distribution of patients with drug reactions

| Age in years | Male |           | Female |           | Total |            |
|--------------|------|-----------|--------|-----------|-------|------------|
|              | N    | R         | N      | R         | N     | R          |
| Upto 20      | 37   | 8 (21.6)  | 30     | 16 (53.3) | 67    | 21 (35.8)  |
| 20-39        | 218  | 73 (33.4) | 146    | 52 (35.6) | 364   | 125 (34.3) |
| 40-59        | 65   | 16 (24.6) | 69     | 20 (28.9) | 134   | 36 (26.8)  |
| Above 60     | 15   | 6 (40)    | 12     | 2 (16.7)  | 27    | 8 (29.6)   |

N indicates the number of patients observed and R indicates the number of reactions present. Incidence is expressed as a percentage of total number of patients receiving drugs belonging to the same age and sex group. Incidence in the male patients 32% and female patients 33%. Incidence in the age group below 40 yrs 34.6% and in the group above 40 yrs is 27.3%. The incidence in the younger age is higher than the older age groups, but this does not reach the level of significance.

**Table 3**  
Incidence of reactions and number of drugs

| Drugs                             | Total | One drug |      | Two or more |      | p value |
|-----------------------------------|-------|----------|------|-------------|------|---------|
|                                   |       | No.      | %    | No.         | %    |         |
| <b>All drugs</b><br>(whole group) | 592   | 100      | 23.8 | 93          | 53.7 | 0.001   |
| Haloperidol                       | 162   | 12       | 27.2 | 77          | 65.2 | 0.001   |
| Chlorpromazine                    | 158   | 19       | 21.5 | 39          | 55.7 | 0.001   |
| Tricyclic anti-depressants        | 322   | 60       | 25.0 | 50          | 62.0 | 0.002   |

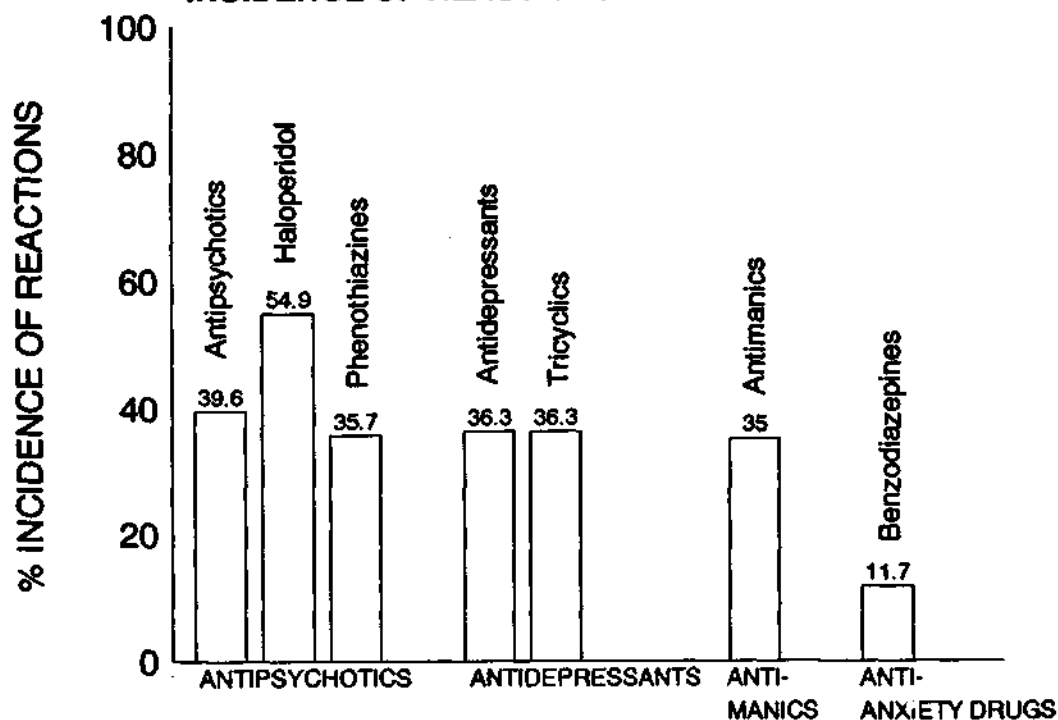
Total number of patients receiving drugs for each group are indicated. Number of patients developing or not developing reactions in each group were calculated (Reactions + or -). Incidence of reactions in each group is calculated as a percentage of the number of patients prescribed the same drug either alone or in combination.

incidence of 37% while those who were prescribed thioridazine and trifluoperazine had incidence of 21.7% and 23% respectively. The number of drugs prescribed and the incidence of reactions are presented in Table 3. Two or more drugs prescribed together is associated with a higher incidence of reactions.

#### Nature of reactions and their relation to drug groups:

Extrapyramidal symptoms (EPS) were observed in many patients during early phase of therapy. These reactions included tremors, slurred speech, rigidity, akinesia, loss of associated movements, fixed posture of limbs, excessive salivation, lip smacking, protrusion of tongue, paucity of expres-

## INCIDENCE OF REACTIONS TO MAJOR DRUG GROUPS



## Legend to Figure 1

This figure is based on the following number of prescriptions, Antipsychotics 381 (Haloperidol 162, Phenothiazines 210, Pimozide 9); Antidepressants 325 (Tricyclics 322); Anxiolytics 34; Antimanics 37 (Lithium 29, Carbamazepine 8). Incidence is expressed as a percentage on the basis of number of patients developing reactions among these who were prescribed the same drugs.

sion, slopping gait and difficult in swallowing. Among the 193 patients who were reported to have adverse reactions, 65.8% had extrapyramidal symptoms. Male to female ratio in this group was 1:1.08. The age distribution of this group of patients show that there was a higher incidence in patients below 40 yrs (84%). The frequency of these reactions were highest with haloperidol, chlorpromazine, trifluoperazine and thioridazine in that order. Some patients on tricyclics and antimanics also developed EPS - but such patients were invariably on antipsychotics also at the same time. Tremors were reported as a reaction by 7% of patients who were prescribed imipramine. Half of these had imipramine as the only drug while the remaining 50% had combination of imipramine and phenothiazine.

Extrapyramidal symptoms were reported as a disturbing side-effect by the patients during initial

phase of therapy. In 65% of those reported, onset of these reactions were noted after one week, while 35% had noted these symptoms within one week (2-5 days). The dose of chlorpromazine in the group of patients with EPS ranged from 200-600 mg; and that of haloperidol 5-10 mg. Most of these patients responded to treatment with anticholinergic drugs like trihexiphenidyl or kemaprine. Very few patients only required reduction of dose of antipsychotic.

Among the various extrapyramidal symptoms, dystonia was the most disturbing one to the patient. Dystonic reactions reported by patients include turning of the neck to one side, inability to protrude tongue, pulling sensation in the neck and oculogyric crisis. Analysis was done to determine various factors associated with this reaction. Acute dystonia was frequently observed as a reaction during early phase of therapy. Onset of this reaction in 80% of the patients was within one to two days after the

Table 4  
Nature of reactions and drug groups

| Reaction                      | Drug group      | Incidence % |
|-------------------------------|-----------------|-------------|
| Extrapyramidal symptoms (EPS) | all drugs       | 21.5        |
|                               | antipsychotics  | 30.0        |
|                               | antidepressants | 25.0        |
|                               | antimanic       | 7.0         |
| Dystonia* (alone)             | all drugs       | 6.7         |
|                               | antipsychotics  | 6.7         |
| Anticholinergic reactions     | all drugs       | 17.0        |
|                               | tricyclics      | 36.3        |
| Dry mouth                     | tricyclics      | 15.2        |
| Constipation                  | tricyclics      | 9.0         |
| Blurring of vision            | tricyclics      | 2.1         |
| Retention of urine            | tricyclics      | 0.9         |
| Giddiness                     | all drugs       | 5.4         |
|                               | tricyclics      | 9.0         |
| Postural hypotension          | all drugs       | 1.7         |
| Tremors                       | all drugs       | 7.6         |
|                               | antipsychotics  | 6.8         |
|                               | tricyclics      | 7.4         |

The most common type of reactions are presented. In patients who developed EPS, one drug alone was prescribed for 44%, more than one drug was prescribed for 56% of these patients.

\* All patients who developed dystonia had combinations of antipsychotics with antimanics or tricyclics.

initiation of therapy. The male to female ratio was 2:1 in this group. Age distribution of these patients showed that 27 out of 40 patients were below the age of 30 yrs. 66% of these patients had two or more drugs while 33% had single drug. The most frequently used combination was haloperidol and phenothiazine (66%). Injection haloperidol in combination with oral haloperidol and/or phenothiazine appeared to enhance the onset of acute dystonic reaction. The duration of acute dystonic reaction ranged from 10 to 30 minutes. These patients responded well to treatment with injection phenergan (IM or IV). In most patients the improvement was dramatic. Anticholinergic side effects were associated with prescription of tricyclic antidepressants and phenothiazine. None of the patients with these reactions required any specific treatment.

Skin reactions like rashes, were reported by two patients who were prescribed chlorpromazine. These reactions subsided on withdrawal of the drug. Polyuria and polydipsia was reported by one patient who was given (1050 mg) of lithium (single drug). Erectile dysfunction was reported by two

patients who were on clomipramine. An episode of seizure occurred in one patient who was on treatment for delusional depression, with imipramine, chlorpromazine, and oral haloperidol (40 mg). Seizures responded to treatment with phenytoin. Detailed analysis of these reactions could not be carried out since the number of patients reporting these reactions were very few.

## DISCUSSION

The incidence of adverse reactions to most group of drugs is 35% or more with the exception of anxiolytics. This incidence is lower than the incidence reported in some other studies (Schmidt et al, 1984). This study includes report of reactions from 462 outpatients and 130 inpatients. It is likely that some of the reactions were not observed or reported by outpatients. Differences in rates of incidence have been reported by Grohmann et al (1984) when system of monitoring involves intensive drug monitoring (IDM) and organized spontaneous reporting system (OSR). The relative frequency of Grade III ADR was similar for neuroleptic and antidepressants (54% and 53% in OSR) in the study reported by Grohmann et al (1984). Inpatients monitored by IDM had a high incidence rate in their study, although life threatening ADR were of equal intensity by both system of monitoring.

In the present study, inpatients are noticed to have a higher incidence (39%) of reactions as compared to outpatients (24%). This may be attributed to a better opportunity for observations by staff in addition to the report by relatives who also were required to stay with the patients in this hospital. The period of follow up is 3 to 4 weeks. It is likely that some of the reactions such as weight gain are not noticed by patients during this period. Similarly polyuria and polydipsia which are usually delayed reactions to lithium therapy was reported by one patient only in the early phase of treatment.

Number of drugs prescribed concomitantly increases the incidence of adverse reactions (Table 3). The pharmacological effects of two antipsychotics like haloperidol and phenothiazine may produce additive effects of dopaminergic blockade and lead to high incidence of extra pyramidal symptoms. Addonizio et al (1988) have suggested that the addition of lithium to neuroleptic alters the pharmacokinetics. This may contribute to the increased incidence of extrapyramidal symptoms. There is no evidence to suggest that such combinations may add

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to the therapeutic efficacy. Therefore the advisability of such combinations which would result in increased EPS becomes highly questionable. Murphy and Hartman (1988) have hypothesized that the pathological changes produced by underlying disease state may contribute to EPS. These authors have suggested that the patients with affective disorder may be more vulnerable than schizophrenic patients to the development of EPS with the combination of lithium and neuroleptic.

Among the antipsychotics prescribed haloperidol is associated with the highest incidence of reactions which indicate that the potency of the drug is also another factor which influence the incidence of reactions. The most disturbing symptoms reported by patients who were prescribed antipsychotic drugs were the extrapyramidal symptoms. Parkinsonism and inconvenient sedation are mentioned as the severe reactions responsible for drug withdrawal (Schmidt et al, 1984). It is important to recognize these reactions early and also to provide sufficient information to the patients and relatives when drug therapy is initiated (Hermesh et al, 1985). The aim of therapy should be to keep the incidence and severity of these reactions as low as possible. Acute dystonic reactions are known to be frightening to the patient although the incidence of this reaction is low (Barach et al, 1989). Young male patients are likely to develop this reaction. Prophylactic anticholinergic treatment during early phase of therapy is justified in such patients, particularly those receiving high-potency drugs (Jack & Robert, 1989).

Akathisia described as a subjective sense of restlessness has been observed in some patients. Akathisia associated with increased doses of neuroleptics has been attributed to worsening of Tourette's disorder by Weiden and Brunn (1987). Akathisia has been viewed as a forerunner of tardive dyskinesia by some authors (Goswami & Channabasavanna, 1984). This reaction is reported to be less likely to respond to anticholinergic treatment. The anticholinergic side effects most frequently associated with tricyclics and antipsychotics are less disturbing to the patient although the incidence of these reactions is high.

In summary this study presents the incidence and profile of reactions to commonly prescribed psychopharmacological agents. Pharmacoepidemiological methods for identifying and quantifying adverse reactions can assist therapeutic decisions in patients with special risk of side effects to psychotropic drugs and also help in the education

of patients and relatives (Leber, 1983; Chaturvedi, 1985; Zito & Craig, 1988). Such information may help to decrease the noncompliance with regular medication which is one of the most troublesome problems in the treatment of psychiatric patients.

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