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DRUG SURVEILLANCE PROGRAMME IN PSYCHIATRY-ADVERSE DURG REACTIONS

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SUMMARY

In a clinically monitored surveillance of adverse drug reactions in a sample of 186 indoor patients in a general hospital over an average hospital stay of about two weeks, the following points were noteworthy.

32.8% of the patients reported side-effects and of these 79.3% were of mild to moderate intensity.

Side-effects could be easily managed by specific antidotes and reassurance and permitted continuation of the same medication.

There was no association between side-effects and socio-demography or clinical characteristics of the patient. Side-effects fitted in with the pharmacological profiles of the drugs used. In only 7.3% of cases was major treatment change made after the occurence of the side effect. Improvement was independent of side-effects and no unusual or toxic reactions were seen.

Drug surveillance is defined as a systematic recording of drug administration and the experience of patients who have received specific drugs. The information deduced from such a surveillance would be of great value to the physician and his patients. Analysis of data would yield ample information about pharmacological agents in clinical practice (Michel and Kolakowska, 1981; Prien *et al.*, 1978; Clarks & delGuidice, 1970). It would also reveal patterns of prescribing, varying susceptibility of symptoms to pharmacotherapy and attitude of both patients and physician to drug treatment. It would reveal the incidence, type and intensity of adverse reactions, their acceptance by both doctors and patients and their treatment.

AIMS

A prospective total Drug Surveillance project in psychiatry in patients admitted at our unit in K. E. M. Hospital was undertaken as a joint project between the department of psychiatry and the clinical Pharmacology Unit in order to investigate the adverse reactions to psychotropic drugs. We followed, for the purpose of this study, the definition of an adverse reaction of a drug as one which is noxious, is unintended and occurs at dosages normally used in man. All side-effects come with-

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in the scope of this definition and for the purpose of this paper side-effects and adverse reactions have been used synonymously.

The aim of the present study was to evaluate the effects of psychotropic drugs in terms of side-effects and their association with 1) sociodemography 2) clinical characteristics of the patient 3) pharmacological profile of the drug and 4) the attitude of the patient and the physician towards the side effect.

MATERIAL AND METHODS

A randomised sample constituting 33% of the total indoor patient population of our unit was kept under surveillance for one year. The proforma for recording the data was evolved through joint consultations between the psychiatrists, the clinical pharmacologists and the statistician.

The details of the proforma was entered directly in code numbers which could be readily transferred to punchcards designed for computer analysis,

Each proforma represented a detailed record of all drugs administered, their dose, frequency, reasons for starting therapy, reasons for stopping or altering the dose, duration of drug administration, outcome of treatment and outcome of adverse reactions. Adverse drug reactions (ADR) were studied in detail to establish their relationship to drugs administered, their mechanisms, outcome, effect and antidote.

The International Classification of Diseases 9th revision (1975) was used. Provision was made for one principal and two additional diagnoses. A comprehensive 3 digit code was used for recording physical signs and symptoms. A social rating scale giving equal weightage to education, occupation and per capita income was used for determining the social status. The symptom check-list was administered every fifth day and on the day of discharge. A 3 digit code was used to record all possible ADRs. The day the reaction began, the day it subsided, its severity and any change in treatment were noted. Provision was made in the proforma to record 3 ADRs. occurring simultaneously.

A weekly meeting of the clinical pharmacologist, the psychiatrist and statistician was held to comment upon the nature of the ADR and to supervise the recording of the proformas by the house physicians.

The house physicians recorded the data daily with a periodic symptom assessment. It was found that patients did not report milder side-effects and so a list of thirteen questions was prepared pertaining to the known side-effects of dryness of mouth, constipation, difficulty in micturition, blurring of vision, giddiness, drowsiness, tremulousness, diplopia, nasal congestion, loss of appetite, restlessness, insomnia and muscle spasms.

186 patients were included in the study and then the data was subjected to statistical analysis. The chi-square test, the 't' test the 'z' test and correlation coefficient analyses were the statistical methods used to find out the relationships between the different variables. Computer-assisted tabulations were made by the statistician and interpretation was done by the clinicians. Laboratory investigations were not done routinely but only when indicated by the patient's clinical condition.

RESULTS AND DISCUSSION :

Socio-demographic variables :

The group of patients developing adverse reactions (SEG) (side effects group) comprising of 61 patients did not differ significantly from the total group (ALLG) of 186 patients in any socio-demographic variable. The average age of SEG was 34.8 years with standard deviation of 13.5 yrs and the average age of the ALLG

was 31.9 years with standard deviation of 12.7 yrs. The average SEG height was 166 cms with s. d. 8.2 and ALLG had an average height of 165 cms with s. d. of 8.30. 85.5% of the ALLG were urban based as against 84.1% of the SEG, which is in agreement with the drainage area of this city hospital. The mean weight of the ALLG was only 49 kg as against the mean weight of 56 kg. in the SEG but this too did not attain significance. 68.8% of the ALLG were male, as compared to 68.3% in the SEG. With respect to per capita income and educational achievements also the two groups did not show any significant differences.

Prescription pattern :

The most commonly employed psychotropic agents were Chlorpromazine (23.5%), Trifluperazine (9.8%), Imipramine, (23.2%), chlordiazepoxide (6.1%) and chloral hydrate (20.4%) which was used as a hypnotic. This prescription pattern is in tune with the drugs available on the hospital schedule. Such a restricted prescription pattern in a free public hospital does not allow comparison of various drugs but since several patients receive the same medication their responses can be compared and patient variables can be defined. This is in sharp contrast to Leckman et al's (1977) report where 10 different neuroleptics as against two in this study, 5 different antidepressants against one, four different anxiolytics against one in our study and 3 different anti-parkinsonian agents against one in our hospital, have been employed. As reported by Michel and Kolakowska (1981), Diamond et al (1976), Hemminki (1977) and Prien et al (1978), polypharmacy with psychotherapeutic agents is quite common but in our hospital, because of non-availability of different varieties of drugs the prescriptions are more concise. On an average each patient received only 3.4 drugs throughout his hospital stay and the side effect group received 3.8 drugs on an average. This marginal non-significant difference is attributable to the use of antiparkinsonian agents like Trihexiphenidyl 2 mg. tablets and Injectable Promethazine hydrochloride and Bitacodyl for the treatment of emergent symptoms.

The maximum dose received by each patient ranged from 400-1200mg daily of Chlorpromazine, 15-45 mg daily of Trifluperazine, 150-300 mg of Imipramine, 1 gm-2 gms of chloral hydrate and 60-90 mg of Chlordiazepoxide. In 68 out of 82 instances of side-effects, chlorpromazine (36), Imipramine (19), Trifluperazine (8) and chlordiazepoxide (5) were implicated.

Incidence of Adverse Drug Reaction

As shown in Table I 61 out of 186 patients under surveillance reported 82 instances of side effects. Thus 32.8% of patients developed on an average 1.34

TABLE 1. *Adverse Reactions*

Type	Frequency
1. Drowsiness	16
2. Constipation	15
3. Giddiness, Postural Hypotension	21
4. Dryness of mouth	11
5. Parkinsonian Reaction	6
6. Dystonia	2
7. Akathisia	1
8. Diarrhoea	2
9. Loss of Appetite	1
10. Difficulty in Micturition	4
11. Hyperpyrexia	1
12. Confusion—Disorientation	1
13. Drug Rash	1
Total	82

side effects each. In our study patients were interrogated daily regarding the commoner side effects using a side effects check list of 13 questions and so we were able to tap the milder side-effects. Leckman *et al.* (1977) report an incidence of 9.3% only in 5630 patients, but the methodology is totally different from what we have employed. Wade (1970) has calculated the incidence of adverse reactions per million prescriptions which yielded very low results of 20.7, 26.0 and 9.8 non-fatal adverse reactions per million prescriptions for phenothiazines, tricyclics and benzodiazepines respectively. Reports on outpatient populations suffer because of uncertain compliance. Mental hospital surveys include a disproportionate number of long stay patients chronically on medication and therefore yield results which are not comparable to ours.

In a general hospital with a mean hospital stay of 13.8 days, incidence of ADRS of 32.8% with the restricted drugs available for use, in our opinion, is acceptable.

Type of Adverse Drug Reaction

As seen in Table I all the side-effects were well known and common (Ban, 1969, Martin, 1971, Kelin & Davis, 1969; Jarvik, 1977; Shader and DiMascio, 1970) there were no toxic reactions or intoxication due to overdosage. No unusual reactions were seen. One case of confusion-disorientation was due to the additive anticholinergic effects of phenothiazines and antiparkinsonian drugs. Imipramine was responsible for the drug rash, this was confirmed and treated by withdrawing imipramine and starting antihistaminics.

TABLE II

No. of side-effects	No. of patients	Percentage
1	46	75.4
2	8	13.1
3	7	11.5
Total	61	100.0

Severity of side-effects	No. of side-effects	Percentage
Mild	30	36.6
Moderate	35	42.7
Severe	15	18.3
Extremely severe	2	2.4
Total	82	100.0

Number and Severity of Adverse Drug Reaction

As shown in Table II, 7 patients developed 3 ADRs. The common combination was constipation, dryness of mouth and giddiness in patients receiving between 150-225 mgm of Imipramine daily. 79% of side effects were mild or moderate in intensity. In only 2 instances of acute dystonia could the adverse reaction be labelled as extremely severe.

Attitude towards the adverse drug reactions (A D R)

As shown in Table III, 95.2% of the side effects were 'expected' being

TABLE III *Attitudes towards adverse reaction of drugs*

	N=82	%
A. Expected	78	95.2
Unexpected	2	2.4
Cannot Say	2	2.4
B. Accepted by Physician	70	85.4
Not Accepted by Physician	10	12.2
Cannot say whether Accepted or not	2	2.4
C. Accepted by Patient	39	47.6
Not Accepted by Patient	32	39.0
Cannot say whether Accepted by patient or not	11	13.4

known to be part of the pharmacological profile of the drug at the prescribed dosage. In two instances-drug rash and confusion-disorientation-the side effect was unexpected. In two instances of diarrhoea the symptom was treatment-emergent and since no cause could be found through laboratory investigations, it could not be said whether the reaction, was expected or other wise. In our opinion the symptom was not drug-related. In these same two cases it could not be decided whether the reaction was acceptable to the physician, but empirically, treatment with binding mixture was instituted.

In 84.4% the ADR was acceptable to the physician. In 10 instances the side effect was not accepted and treatment was modified accordingly.

The mild side effects as mentioned earlier were elicited on specific enquiry only and were accepted by the patient. In 11 instances it was not possible to judge the patient's acceptance because of their disturbed mental status at the time when the ADR occurred. Reassurances by the physician was sufficient in most patients to make them accept the side-effects and permit continuation of the same medication.

Treatment of adverse drug reaction (Table IV)

In 41.5% of ADRs no change was made because of acceptance by both physician and patient. In 18.3% the only change was reduction in drug dosage. Antidotes-Bisacodyl for constipation and trihexiphenidyl and injection Promethazine HCl for extra pyramidal symptoms were added in 32.9% of ADRs. Alternative treatment with ECT was begun in the patient developing drug rash with imipramine. The offending drug was stopped in only 5 out of 82 instances of ADRs. Thus in only 7.3% (6.1+1.2) of the ADRs was the treatment modified significantly.

TABLE IV *Treatment of adverse reactions* (N—82)

	N	%
Drug Stopped	5	6.1
Dose Decreased	15	18.3
Alternative Treatment	1	1.2
No Change	34	41.5
Antidote Added	27	32.9
	82	100.0

Certain clinical variables and adverse effects :

The side-effect group (SEG 61 patients) stayed slightly longer (mean 15 days with s.d. of 9.4 days) in the hospital as compared to those without side effects (125 patients, mean 13 days, s.d. 8.8 days). The 186 patients in our study initially reported 6.8 symptoms on an average as against 7.42 symptoms reported by SEG.

92.8% of 186 patients had improved markedly at the time of discharge and only 2.2% showed no improvement. The occurence or otherwise of ADRs made no difference in this respect. This also shows that short-term hospitalization and treatment are effective measures for this particular patient group.

The value of a study like the present one in leading to a drug audit and a minimum pharmacopoeia would be great but at our institution, as it is, perhaps out of necessity, we practice a minimum pharmacopoeia. To detect unusual ADRs a much larger sample consisting of patients from several different centres engaged in collaborative research will be required. ADR occuring after prolonged exposure to the drugs would require long term follow through studies. Facilities for monitoring drug treatment by routine instrumentation being lacking at our centre, it was not done, but future surveillance studies must aim at

correlating ADRs with biochemical investigations which will also serve as measures of patient compliance.

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