Indian J. Psychiat. (1983), **25**(3), 206—211

A STUDY OF PROPHYLACTIC VALUE OF ANTIPARKINSONIAN DRUG

P.B. BEHERE[1], M.D., D.Ac., Dip. Yoga.
P. RAMAKRISHNA[2], M.D.

SUMMARY

The present prospective study is conducted to determine the prophylactic value of antiparkinsonian drug (A.P.) at the time of initiation of antipsychotic therapy. Seventy patients were selected who fulfilled the selection criteria. Thirty five patients received antipsychotic drugs alone (Group A), while another thirty five patients received A. P. drugs concurrently with antipsychotic drugs (Group B.) These patients were assessed weekly for 4 weeks for any extra pyramidal symptoms (E. P. S.) There was no statistically significant difference between E. P. S. scores of the two groups in different weeks. The difference in percentage of patients who developed E. P. S. in different weeks in both the groups was statistically non-significant ($p<0.05$). None of the female subjects developed E. P. S. in either group.

Phenothiazines and other neuroleptics which are commonly used in psychiatry, are known to cause extrapyramidal symptoms (E. P. S.). The incidence of E. P. S. is 38.9% in patients treated with phenothiazines (Ayd, 1961; Laverne, 1961). Ayd (1961) reported 35% E. P.S. with chlorpromazine, 43% with prochlorpromazine, 44% with thioproperazate, 36% with perphenazine, 60% with trifluoperazine and 52% with fluphenazine. Parkinsonism like syndrome following antipsychotic medication can be patient related or dose related (Danial & Freedman, 1973).

Ayd (1961) has reported that 90% dyskinesias appear within first 4½ days and time and dosage are less important than individual susceptibility. Now-a-days, a high percentage of psychiatric patients treated by antipsychotic drugs receive concurrently one or the other antiparkinsonian (A. P.) medication, though antiparkinsonian medication has known toxic properties. Furthermore it has not been established that widespread use of A. P. medication as a preventive measure is necessary or desirable. It is a hypothesis that such use of these drugs is occasionaly required. Klett and Caffey (1972) and Dismascio & Demirgian (1970) concluded that the hazards of polypharmacy outweigh the advantage of prophylaxis and that A. P. drugs are overused.

It is also significant that some patients treated with phenothiazines do not seem to develop E. P. S., although they benefit by the antipsychotic properties of the phenothiazines (Davis & Casper, 1978). A. P. prophylaxis as a routine, for all patients, given with neuroleptic drugs doesn't always prevent E. P. S. and may even increase the frequency of rigidity and akathisia in some patients (Dismascio and Demirgian, 1970; Coleman and Hayes, 1975).

Previous researches conducted were in the area of evaluating long term need for A. P. drugs for chronic Schizophrenics (Orlov *et al.*, 1971; Klett & Caffey, 1972; McClelland, 1974, Rifkin, 1978). It has been reported that discontinuance of A.P. drugs did not increase the rate of E. P. S. among receipients of antipyschotic drugs (Dismascio and Demirgian, 1970).

LIMITATIONS OF PREVIOUS RESEARCHES:

The limitations are that Klett (1972), Mc Clelland (1974), Rifkin (1978), Orlov *et al.* (1971) have studied those patients who were already on phenothiazines and A. P. medication for more than 3 to 6 months

1 Lecturer, Deptt. of Psychiatry, Institute of Medical Sciences, B. H. U., Varanasi-221 005.
2 Psychiatrist, Mental Hospital, Hyderabad.

and in some studies even 4 to 5 years; were selected and in few patients A. P. drugs withdrawal were with placebo substitution. None of the authors indeed studied prophylactic role of A. P. drugs at the initiation of antipsychotic therapy, because if A. P. drugs are given in conjunction with phenothiazines for more than 3-6 month the requirement of A. P. drugs are practically nil. Mc Clelland (1974) reported that great majority of patients who have been on A. P. drugs for over 3 months these drugs are unnecessary and can be withdrawn without disadvantage.

The A. P. medications if administered in conjunction with antipsychotic drugs, have following disadvantages: 1. Many patients never manifest E. P. S. (Davis and Casper, 1978). 2. There are side effects associated with high doses of antiparkinsonian medication including dry mouth, blurred vision and very rarely paralytic ileus and urinary retention. 3. The expense of treatment is increased. 4. There is no absolutely convincing evidence that prophylactic routine use of A. P. medication prevents the occurence of E. P. S. Goodman and Gilman (1975) reported that A. P. medication is valid only for their rapid control and not to prevent their possible occurence or to mask their actual occurence. 5. Patients can, rarely develop behavioural toxicity and toxic psychosis (Kazamatsuri *et al.*, 1972; Johnson, 1972; Gerlach *et al.*, 1974; Marsden, 1975) 6. The chief neurological side effect i. e. parkinsonism is often (but not always) to some degree a necessary accompaniment of therapeutic benefit in the treatment of psychosis (Goldman, 1958). Positive relations between E. P. S. and therapeutic effects also were reported (Freyhan, 1957; Denham, 1961; Brunn, 1962). 7. A. P. medication added to phenothiazines lower the plasma levels of chlorpromazine (Chan *et al.*, 1973; Loga *et al.*, 1975; Rivera—Calimlim *et al.*, 1976) and possibly reduce the therapeutic effects (Ayd, 1961; Singh and Smith, 1973). A. P. drugs have also been reported to influence the absorption of drugs from the gut (Rivera Calimlim, 1976). Recently it has been proved to be a controversial issue (Simpson *et al.*, 1980). 8. Poor drug compliance many patients only continue A. P. medicine and stop antipsychotic drugs in follow up, as A. P. medicines are cheaper than antipsychotic drugs (Behere and Ramakrishna, 1980).

AIM

The present study was conducted to determine whether there is any prophylactic role of A. P. drugs at the time of initiation of antipsychotic therapy.

METHODS

Seventy patients were selected from Psychiatry Department of Institute of Medical Sciences, B. H. U., Varanasi. Following were the selection criteria.

SELECTION CRITERIA

1. Only newly registered cases were included in study from May 79 on-wards.
2. Only those patients coming from Varanasi city proper and neighbouring villages of Varanasi District were included in the study so as to ensure weekly regular follow up.
3. The age range was between 15 to 45 years.
4. The clinical diagnosis was that of functional psychosis.
5. Only those patients who were not on any antipsychotic drugs or any A. P. drugs at the time of inclusion in the study.
6. There should be no evidence of brain damage or neurological disorder such as primary parkinsonism.
7. Patients who were on thioridazine alone were excluded, as this drug has extremely low incidence of E. P. S.

DESIGN

A total of seventy patients who fulfilled the above criteria were included in the study, they were divided into two comparison groups of 35 each. Group A which consisted of 35 patients was given only antipsychotic drugs. The medication was adjusted according to the needs of the individual patients. Combination of antipsychotic drugs was avoided as far as possible. Group B consisted of 35 patients who were given A. P. drugs (Trihexyphenidyl Hcl) at the time of initiating antipsychotic therapy. In this group too, dose of antipsychotic drug was adjusted according to the needs of the individual patients. The trial was blind in that the clinical assessors were unaware which patients had received A. P. for prophylaxis at the initiation of antipsychotic medications.

Patients were assessed for any E.P.S. weekly on semistructured proforma (can be had from authors on request) which included various sub-items viz. tremors, autonomic symptoms (sialorrhoea etc.) general symptoms (gait, facies, posture, speech, swallowing difficulty, lost arm swing), rigidity, akathisia dystonic reaction, dyskinesias. For training purposes assessors had assessed few patients before start of trial, and after discussion, reached a consensus.

All the patients were assessed before the start of the study for any E.P..S. Patients of both groups were weekly assessed for individual symptoms for 4 weeks. If any patient in Group A developed E. P. S. of such severity that A. P. medication had to be started were given A. P. drugs but then for subsequent weeks he was not included for further assessment.

RESULTS

Table 1 shows the age distribution of both groups. The mean age in Group A was 21.91 years and 24.82 years in Group B. There was no statistically significant difference between the two groups (t=1.79, d.f.=68, N. S.). 24(68.6%) patients were male and 11(31.4%) were female in Group A, while in group B male to female ratio was 8 to 7 respectively. Patients included in study were 8(22.8%) from O. P. D. and 27(77.1%) from indoor in group A; while in group B distribution was 15(42.8%) and 20(57.1%) respectively, Disease wise break up was 32(91.4%) schizophrenics and 3(8.67%) MDP (Mania), in both the groups. The mean daily chlorpromazine equivalent dose of 35 patients who received antipsychotic alone was 711.52 mg; while of 35 patients who also received A. P. drug prophylaxis was 951.42 mg.

TABLE 1. *Age Distribution*

Years	Groups A (N=35) N	%	B (N=35) N	%
15—19	13	37.1	15	42.9
20—24	12	34.3	6	17.1
25—29	6	17.1	3	8.6
30—34	2	5.7	3	8.6
35—39	1	2.9	4	11.4
40—44	1	2.9	4	11.4
Mean		21.91		24.82
S. D.		5.85		8.48

In group A all 35 patients were assessed in the first week, 21 patients were assessed in second week (because 14 patients developed E.P.S. of such severity that patients had to be switched on to A.P. medication, and then not included for subsequent weeks), similarly 15 patients were assessed in third week (6 more patients were switched on to A.P. drugs). 15 patients were assessed in the fourth week. All 35 patients were asessed for four weeks in Group B (Table 2). There were no drop

TABLE 2. *Number of patients assessed in different weeks*

Weeks	Group A (%)	Group B (%)
I	35 (100)	35 (100)
II	21* (60)	35 (100)
III	15** (42.85)	35 (100)
IV	15 (42.85)	35 (100)

*14 patients developed severe E. P. S. for which A. P. drugs were added and discontinued from study from 2nd week onwards.

**6 more patients developed EPS and put on A.P. drugs and discontinued from study from 3rd week onwards.

outs in both group, all were available for follow up.

Total scores of E. P. S. in both the groups in different weeks are shown in table 3. There is no statistically significant difference between the E. P. S. scores in both groups in different weeks.

TABLE 3. *Total scores of E. P. S. in both Groups*

Groups	A		B		t	d. f.
Weeks	No. of Pts	Scores	No. of Pts.	Scores		
I	35	65	35	31	1.32	68
II	21	13	35	33	0.625	54
III	15	6	35	40	0.98	48
IV	15	3	35	26	0.89	48

All t values are not significant

Percentage of patients who developed E. P. S. in both the groups in different weeks are shown in table-4.

After applying analysis of variance the difference between two groups are statistically nonsignificant ($p>0.05$). These are neither dependent on weeks nor on drugs.

TABLE 4. *Percentage of patients, developed E.P.S. in both groups*

Weeks	A	B
I	31.42	22.85
II	23.80	22.85
III	26.66	25.71
IV	20.00	17.14

Analysis of Variance—$p.<0.05$

The rates of E. P. S. among antipsychotic recipients according to receipt and nonreceipt of A. P. medication prophylaxis at the end of four weeks are shown in table-5. 14.3% patients developed E.P.S.

TABLE 5. *Rates of E. P. S. among antipsychotic recipients according to receipt and nonreceipt of A. P. drug prophylaxis at the end of 4 weeks*

	No (A)	Yes (B)	Total
No. (%) with E. P. S.	3(20)	6 (17.14)	9 (18)
Total	15	35	56

among patients below 25 yrs. of age and 25% developed among above 25 yrs. of age in group A, while it was 19% and 14.3% in group B respectively. E. P. S. was commonly seen in male subjects in both groups, while none of the female patients developed E.P.S. in either group. However, the rates for those who did not and those who did receive A. P. drug as prophylaxis were 30% and 21.4% respectively (table-6). Patients were categorized; according to the presence of tremors autonomic symptoms, akathisia, and dystonic reactions (General symptoms). Among 35 patients in group A tremors were observed in 10 (28.69%), autonomic symptoms in 3 (8.6%), akathisia in 2 (5.7%), dysto-

TABLE 6. *Rates of E. P. S. among antipsychotic recipients according to receipt or non receipt of A. P. drug as prophylaxis according to age and sex at the end of 4 weeks*

	A. P. Medication Prophylaxis			
	No		Yes	
	No. of PTS	No. with EPS	No. of PTS	No. with E. P. S.
Age (in yr.)				
25	7	1(14.3%)	21	4(19.0%)
25	8	2(25.0%)	14	2(14.3%)
Sex				
M	10	3(30.0%)	28	6(21.4%)
F	5	0	7	0

nic reactions in 5(14.3%) and general symptoms in 5 (14.3%). The corresponding frequancies in 35 patients of Group B were 10 (28.6%), 1 (2.8%), 1 (2.8%), 2 (5.7%), none developed dystonic reaction, 7 (20%).

DISCUSSION

The treatment of E. P. S. is a subject of dispute, some psychiatrists advocating the use of prophylactic A. P. medication while others reserve such drugs for the treatment of emergenty symptoms. Centrally acting anticholinergic-antiparkinsonian drugs successfully relieve emergent E. P. S. but A. P. prophylaxis as a routine for all patients, given neuroleptic drugs, doesn't always prevent E. P. S.

From this study it is evident that A.P. medication (Trihexyphenidyl Hcl) has no prophylactic value in occurrence of E.P.S. age and sex, as well as many other factors, were evaluated to determine whether they could have obscured the prophylactic effect due to A. P. medication. None of these factors materially affected the results.

E. P. S. commonly seen in males in both the groups while none of the female patients developed E. P. S. in the two groups. This is in conformity with that of Chester *et al.* (1977). The dystonic reaction which was seen only in Group A (14.3%) and not in group B is an important observation. It is also possible that certain types of E. P. S. may be prevented by A. P. drugs (Trihexyphenidyl Hcl), while others are not. The authors suggest that there is no prophylactic use of A. P. medication concurrently with initiation of antipsychotic therapy.

ACKNOWLEDGEMENT

The authors would like to acknowledge the able assistance of Mr. B. P. Singh, Lecturer, Deptt. of Statistics, B.H. U. in data analysis. We further thank, Dr. V. K. Bhat, M. D., Head, Deptt. of Psychiatry, I. M. S. for encouragement to carry out this study. .

REFERENCES

AYD, F. J. (1961). A survey of drug induced Extrapyramidal Reactions. J. A. M. A., 175, 1054.

BEHERE, P. B.; RAMAKRISHNA, P. (1980). Drug compliance of mentally ill patients during follow up period. unpublished.

BRUNN, G. G. (1962). Relevance of drug induced extrapyramidal reactions to behavioural changes during neuroleptic and in combination with trihexy-phenidyl. Compreh. Psychiat., 3, 227.

CHAN, T. L., SAKALIS, G.; GERSHAN, S. (1973). Some aspects of Chlorpromazine metabolism in humans. Clin. Pharma. Thera., 14, 133.

CHESTER SWETT JR.; COLE, J. O; SHAPIRO, S. SLONE, D. (1977). Extrapyramidal side effects in chlorpromazine recipients emergence according to Benztropine Prophylaxis. Arch. Gen. Psychiat., 34, 942.

COLEMAN, J. H. AND HAYES, P. E. (1975). Drug induced extrapyramidal effects a review. Dis. Nerv. Sys., 36, 591.

DANIEL AND FREEDMAN (1973). Neurological syndromes associated with antipsychotic drug use (editorial). Arch. Gen. Psychiat., 28, 463.

DAVIS, J. M.; AND CASPER, R. C. (1978). Side effects of Psychotropic drugs and their management. In: Principles of Psychopharmacology, second edition, Clark, W. G. and Giudice, J. D. Academic Press.

DENHAM, J. (1961). The implications of Extrapyramidal symptoms in treatment of Schizophrenia. Revene Canadienne de Biologie, 20, 545.

DISMASCIO, A., DEMIRGIAN, E. (1970). Antiparkinsonian drug overuse. Psychosom., 11, 596.

FRYHAN, F. A. (1957). Psychomotility and parkinsonism in treatment with neuroleptic drugs. Arch. Neurol. Psychiat., 78, 465.

GERLACH, J; REISBY, N. AND RANDRUP, A. (1974). Dopaminergic hypersenstivity and cholinergic hypofunction in the pathophysiology of trardive dyskinesia. Psychopharmacologia Berlin, 34, 21.

GOLDMAN, D. (1958). The results of treatment of psychotic states with newer phenothiazine compounds effective in small doses. Amer. J. Med. Sci., 235, 67.

GOODMAN, L. S. AND GILMAN, A. (1975). The pharmacological basis of Therapeutics, Fifth Ed. Mac Millan Publishing Co. Inc. p. 238.

JOHNSON, D. A. W. (1972). The psychiatric side effects of drugs. Practitioner, 209, 320.

KAZAMATSURI, H; CHIEN, C. P. AND COLE J. O. (1972). Therapeutic approaches to tardive dyskinesia. Arch. Gen. Psychiat., 27, 491.

KLETT, C. J; GAFFEY, E. (1972). Evaluating the long term need for Antiparkinsonian drugs by chronic schizophrenics. Arch. Gen. Psychiat., 20, 374.

LAVERNE, A. (1961). Compendium of Neuropsychopharmacology. J. Neuropsychiat., 2, 280.

LOGA, S., CURRY, S. AND LADER, M. (1975). Interaction of or-phenadrine and phenobarbitone with chlorp romazine: plasma concentrations and effects in man. Brit. J. Clini. Pharma. 2, 197.

MARSDEN, C. D. (1975). The neuropharmacology of abnormal involuntary movement disorders. In : Modern trends in neurology, p. 141, London : Butter Worths.

MC CLELLAND, H. A;. BLESSAD, G.; BHATE, S.; ALI, N. AND CLARKE, P. A. (1974). The abrupt withdrawal of antiparkinsonian drugs in schizophrenic. Br. J. Psychiat., 124, 151.

ORLOV, P; KASPARIAN, G; DIMASCIO, A; COLE, J. O. (1971). Withdrawal of antiparkinson drugs. Arch. Gen. Psychiat., 25, 410.

RIVERA-CALSMLIM, L. (1976). Impaired absorption of chlorpromazine in rats given trihexyphenidyl. Brit. J. Pharm., 56, 301.

RIVERA-CALIMLIM, NARALLAH, H.; STRAUSS, J. AND LASAGNA, L. (1976). Clinical response and plasma levels: effect of dose, dosage schedules and drug interaction on plasma chlorpromazine levels. Am. J. Psychiat., 133, 646.

RIFKIN, A; QUITKIN, F; KANE, J. Stuve F and Klein D. F. (1978). Are prophylactic antiparkinsonian drugs necessary. Arch. Gen. Psychiat., 35, 483.

SIMPSON, G. M; COOPER, T. B; BARK, N; SUD, I. AND LEE, J. H. (1980). Effect of Antiparkinsonian medication on plasma levels of Chlorpromazine.Arch. Gen. Psychiat., 37, 205.

SINGH, N. M. AND SMITH, J. (1973). Reversal of some therapeutic effects of an antipsychotic agent by an Antiparkinson drug. J. Nerv. Ment. Dis., 157, 50.