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IMIPRAMINE IN SCHIZOPHRENIA WITH DEPRESSIVE SYMPTOMATOLOGY[1]

DINESH DUA[2]
A. K. AGARWAL[3]
P. K. DALAL[4]

SUMMARY

Depressive mood is a common accompaniment of schizophrenia. The present study was taken up with the aim to study the effect of imipramine on depressivse symptoms of schizophrenia. Eighteen patients of schizophrenia with depressive symptoms were studied under a double blind controlled design with a chlorpromazine-imipramine and a chlorpromazine-placebo group. Both the groups showed significant improvement ($p<.001$) after the 6 week trial and the addition of imipramine to chlorpromazine therapy did not have any advantageous or deleterious effect.

Depressive symptoms are a common accompaniment of schizophrenia (Knights and Hirsch, 1981; Roy et al., 1983; Elk et al., 1986). Postpsychotic depression has been extensively studied (Johnson, 1981; Knights and Hirsch, 1981; Moller and Zerssen, 1981) but not many researchers have specifically evaluated the treatment strategies for managing depressive symptomatology during the course of schizophrenia. There are a number of studies which have used phenothiazines in combination with antidepressants for the treatment of schizophrenia. These have been reviewed by Siris et al. (1978) who concluded that majority of the studies have unfavourable responses and many of them employed low doses of antidepressants.

It has been observed that a large number of psychiatrists do use combinations of phenothiazines and antidepressants during the treatment of schizophrenia, so it was thought worthwhile to study the role of addition of imipramine to phenothiazines in a group of schizophrinics who show marked depressive symptoms. The aim of the study was to evaluate the role of imipramine in treating the depressive symptoms in schizophrenia.

MATERIAL AND METHOD

The sample for the study was selected from the patients admitted to the inpatient facility of the Department of Psychiatry, K.G.'s Medical College, Lucknow.

The patients between 17 and 45 years of age fullfilling Research Diagnostic Criteria for schizophrenia (Spitzer et al., 1978) who had not received neuroleptics and/or ECT's for the present episode, were screened after 7 days of phenothiazine treatmest on Hamilton Rating Scale for Depression and those who scored 17 or more were included in the study. Any patient needing parenteral medication or ECT's, having any other psychiatric disorder, pregnancy or physical illness was excluded. Informed consent was obtained from all patients or their relatives for participation in the trial.

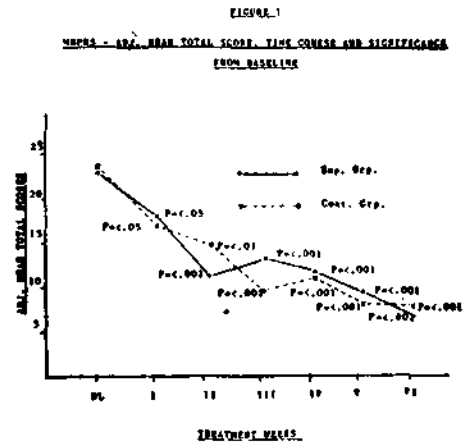
1. Paper presented in the 42nd Conference of Indian Psychiatric Society held at Chandigarh in 1990.

2. Senior Resident
3. Professor and Head
4. Lecturer
Department of Psychiatry
K. G.'s Medical College
Lucknow

On day 1, the patients fulfilling RDC for schizophrenia (Spitzer et al., 1978) were evaluated on Modified Brief Psychiatric Rating Scale "MBPRS" (Overall & Gorham, 1962) and Signs/Symptoms Scale for neuroleptics "SSS" (WHO, 1986). They were put on 800 mg Chlorpromazine in 2/3 divided doses alongwith trihexiphenidyl 2 mg thrice daily after evaluation. On day 7, patients who were found to be amenable for the administration of Hamilton Rating Scale for Depression "HRSD" (Hamilton, 1960) were evaluated on it. If they scored 17 or more on this scale, they were finally included in the study. They were also assessed on MBPRS, SSS, and Side effect rating scale for antidepressants "SERS" (Asberg et al., 1970). These patients were divided into 2 groups on a double blind basis, one group received imipramine 75 mg bed time and the other group a similar capsule of placebo material. Both the groups continued receiving chlorpromazine and Trihexiphenidyl. Weekly assessments were then made for both the groups on MBPRS, HRSD, SSS and SERS for 6 weeks. The dosage of CPZ was increased to 1200 mg/day and the dose of imipramine/placebo was doubled if scores on MBPRS or HRSD showed less than 50% improvement after 3 weeks of their respective treatments. The study was terminated on day 49.

OBSERVATIONS

Out of a total number of 89 patients who were assessed on HRSD on day 7, only 19 patients scored 17 or more and were included in the study. One patient absconded and could not complete the study. The experimental and control groups comprised of 9 patients each. The results were analysed statistically by using paired 't' test, Pearson's Product Moment Correlation Coefficient and Analysis of Covariance. Statistically significant improvemnt ($p<.001$) was observed in both the groups (Fig. 1 and 2). There was no statistically significant difference in improvement on MBPRS and HRSD in groups treated with imipramine or placebo. The effect of imipramine was also evaluated on individual items of HRSD but no significant difference from placebo treated group was observed.



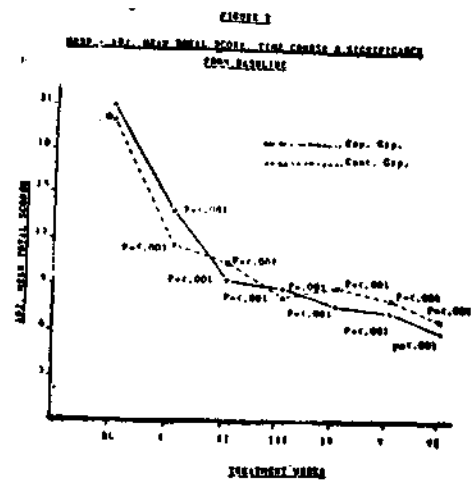


Table I shows weekly improvement on HRSD total scores and MBPRS-ANDP* subscores from the baseline with

*ANDP: Anxiety-Depression Category of MBPRS comprising of items No. 1, 2, 5, 9.

TABLE I—*Weekly correlation between improvements on total HRSD scores and MBPRS minus (ANDP) subscores*

Weeks	Exp. group Mean MBPRS *minus*-(ANDP)	Improvement From Baseline HRSD	r	Sig.	Cont. group Mean MBPRS *minus*-(ANDP)	Improvement from baseline HRSD	r	Sig.
After 1 WK.	1.77	7.33	0.02	NS	4.55	8.22	0.31	NS
After 2 WK.	7.77	11.88	0.47	NS	6.77	9.66	0.68	P<0.05
After 3 WK.	6.88	11.88	0.53	NS	11.11	12.22	0.26	NS
After 4 WK.	8.33	13.11	0.64	NS	10.44	11.22	0.45	NS
After 5 WK.	10.11	12.0	0.52	NS	11.77	12.0	0.13	NS
After 6 WK.	11.88	14.88	0.32	NS	12.33	13.66	0.58	NS

their coefficients of correlation. ANDP subscore was deducted from total MBPRS scores to minimize the overlap of symptoms between the 2 scales (MBPRS and HRSD) and to find out the relationship of improvements in psychotic and depressive symptoms after every week of treatment. The coefficiect of correlation was positive in both the groups. When these coefficients of correlation were compared between the two groups, they were found to be insignificant. The side-effects in both the groups were usually of mild to moderate degree and gradually reduced in severity during the course of treatment without any additional pharmacological intervention (Table II). Imipramine treated group did not exhibit more side-effects than the group receiving placebo.

DISCUSSION

Factors which often confound the issue of depression in schizophrenia are diagnostic laxity, use of illdefined criteria for identifying schizophrenia, imprecise techniques used for identifying and measuring depressive symptoms, inclusion of subjects already treated with neuroleptics and inadequate length of time for which patients are observed (Hirsch, 1982; Galdi, 1983). In the present study most of the above mentioned pitfalls were avoided by using Research Diagnostic Criteria, evaluating depression on a standardized depression rating scale, objectively measuring improvement and by employing adequate dosage and duration of antidepressant and neuroleptic.

This study may be criticized because of a small sample size. This sample size was mainly due to the fact that large number of patients were excluded as they scored less than 17 on HRSD but this high cut-off point was essential as there are 10 items in this scale which are common with the symptomatology of schizophrenia, so a number of cases who would not even be depressed could score atleast 10 on it. Therefore, a minimum score of 17 was considered necessary to identify depressive symptomatology in schizophrenia.

The scores on MBPRS and HRSD improved significantly in both the groups and continued to do so till the end of the study. This indicates that the addition of imipramine did not have adverse effect on the symptomatology of schizophrenia nor did it have any additional beneficial effect on the depressive symptoms of these

TABLE II—*Common side effects and their severity*

Side-effects	Exp. group			Cont. group		
	Mild	Mod.	Sev.	Mild	Mod.	Sev.
Drowsiness	2	7	0	3	6	0
Tremors	8	1	0	7	1	0
Blurring of vision	6	2	0	7	0	0
Orthostatic symp.	6	2	0	9	0	0
Dizziness	6	2	0	2	2	0
Constipation	3	4	0	3	2	0
Dryness of mouth	1	5	0	2	7	0
Weight gain	7	0	0	6	0	0
Phys. tiredness	3	2	1	3	2	0
Mict. disturbances	6	0	0	3	0	0
Palpitation	6	0	0	6	0	0
Headach	4	1	0	8	0	0
Akathesia	0	2	0	5	0	0

patients. This is in line with the findings of Becker (1983) who also failed to find any significant difference between the two groups although in his study, the two groups comprised of one receiving chlorpromazine-imipramine combination and the other thiothexene. Knights and Hirsch (1981) also stated that the depressive symptoms of schizophrenia decrease in severity with effective neuroleptic treatment alone. However, Prusoff et al. (1979) and Hanlon et al. (1970) reported that perphenazine-amitriptyline and fluphenazine-imipramine combinations respectively were better than either of the neuroleptics alone in the treatment of schizophrenia. These two studies are actually not comparable with the present one as the study by Prusoff et al. (1979) included only chronic schizophrenics after one month of perphenazine treatment where the possibility of pharmacogenic depression can not be ruled out and moreover the two compounds used were different. On the other hand Hanlon et al. (1970) included all newly admitted psychiatric patients without considering the presence or absence of depression as a part of their symptomatology.

In the present study, the addition of imipramine to chlorpromazine treatment also failed to show any advantage with regard to the individual items of HRSD nor did it have any beneficial effect on either MBPRS-ANDP subscores or HRSD total scores. This observation again substantiated the finding that chlorpromazine-imipramine and chlorpromazine-placebo combinations respectively have identical effects on psychotic as well as depressive symptoms of schizophrenia. Casey et al. (1961), Kurland et al. (1971), Hanlon et al. (1969) and Chuinard et al. (1975) also reported that the combination of neuroleptic and antidepressant is not superior to neuroleptic alone in cases of

schizophrenia. But all the above mentioned studies have tried the combination on acute or chronic schizophrenics with no regard to depressive symptomatology, thereby making these studies, in fact, incomparable with the present one. However, they do agree with the present observations that addition of antidepressants does not substantially improve the course of schizoprenia nor does it produce any deterioration, which is also evident from the present observation that the combination therapy did not lead to any additional side-effects especially central anticholinergic toxicity(Extein and Bowers, 1975) which could have been termed as alarming.

The overall results of the present study indicate that the depressive symptoms of schizophrenia abate by themselves with the improvement in psychosis and the addition of imipramine does not prove beneficial. This addition of antidepressant to neuroleptic treatment also does not deteriorate the course of schizophrenia nor does it produce any undesirable-side-effects. However, the use of imipramine in schizophrenia cannot be written off on the basis of the present study as it was carried out on a small group of patients. It will be worth-while to study different groups of schizophrenia i. e. acute and chronic, with or without depression for longer periods, to definitely establish the role of antidepressants in the treatment of schizophrenia.

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