ASSESSING A NEW PHENOTHIAZINE

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INTRODUCTION

7044 is a new phenothiazine derivative which can be regarded, pharmacologically, as resembling chlorpromazine much more closely than it does promethazine. It is said to have the characteristic central properties of chlorpromazine more highly developed, and in addition anti-adrenaline properties with anti-histamine properties comparable to those of promethazine. On a theoretical basis it might have the clinical indications of chlorpromazine.

The present report compares the efficiency of this new compound with that of chlorpromazine (Largactil) in the treatment of deteriorated female schizophrenic patients.

METHOD

(a) *Patients*

Twenty-eight deteriorated schizophrenic female patients, whose ages ranged from 35 to 55 years, who had relapsed following the termination of chlorpromazine therapy, were selected for the project. Of these, ten patients were from a ward where the nursing staff preferred habit training to drug therapy, ten from a ward where drug therapy was preferred, and the remaining eight from a third ward where no strong preference was apparent. These wards were chosen to exclude the effects of the nurses' attitudes which should otherwise be taken into account in evaluating the results (see Baker and Thorpe, 1957). Within each ward half the selected patients were treated with chlorpromazine, and half with 7044 R.P.

(b) *Treatments*

Whether each patient was to be treated with 7044 R.P., or chlorpromazine was decided by a random selection procedure and only the hospital pharmacist knew the identity of the tablets which were identical in size, colour, shape and smell, and similar in taste and texture.

With regard to dosage, for the purpose of this project, it was assumed that chlorpromazine was being prescribed for all the twenty-eight patients, and dosages were determined accordingly. Patients were under the constant supervision of the ward sisters and were seen weekly by one of the authors (A.A.B.) when dosages were adjusted according to the clinical picture presented by each patient.

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(c) *Behaviour Ratings*

The Behaviour Rating Scale (Baker and Thorpe, 1956), was used in this investigation. All patients were rated on this scale at the following times:

(i) During the previous course of chlorpromazine therapy.

(ii) During relapse after chlorpromazine was stopped.

(iii) After eight weeks therapy with 7044 R.P. or chlorpromazine.

(iv) After a further twelve weeks of therapy.

When ratings (iii) and (iv) were made, a note was kept of the drug dosage in use at the time.

Results

As was pointed out in our earlier article, the Behaviour Rating Scale can be regarded as having two components, first a general factor of schizophrenic deterioration and second a factor of restlessness.

During the investigation, two of the patients receiving 7044 R.P. had to be taken off the drug for reasons which will be discussed later. Among the chlorpromazine patients the drug had to be discontinued in only one case, so a second chlorpromazine patient was also omitted from the scheme, in order to even up the numbers and facilitate the statistical analysis. This patient was chosen on a random basis. Final figures are therefore based upon twelve patients receiving 7044 and twelve Largactil.

Statistical analysis revealed no significant differences between the mean ages or the mean duration of hospitalization for these two groups, which were 50 and 15 years respectively.

The mean ratings on the two factors obtained by the groups before and during the experiment are given in Table I.

Table I

Mean Scores During Experiment

	1		2		3		4	
	On Largactil		On Relapse		After 8 Weeks' Treatment		After a Further 12 Weeks' Treatment	
	D*	R†	D	R	D	R	D	R
Chlorpromazine Group	8·250	1·000	15·333	3·667	10·416	1·154	6·250	·750
7044 R.P. Group	8·750	·833	13·166	2·667	8·416	·500	7·250	·500

* D = Deterioration. (Sum of all the ten ratings.)
† R = Restlessness. (Sum of the A, C and I ratings.)

The significance of the differences between these means are given in Table II where differences which are significant at the 5 per cent. level are given one star, and those significant at the 1 per cent. level two stars.

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TABLE II

The Statistical Significance of the Changes in Mean Scores ("t" Test for Related Means)

		On Largactil		On Relapse		After 8 Weeks' Treatment		After a Further 12 Weeks' Treatment	
		D*	R*	D	R	D	R	D	R
On Largactil	Largactil ..	—	—	3·001†	2·540†	1·021	<1·000	1·329	<1·000
	7044 R.P. ..	—	—	3·025†	2·029†	<1·000	<1·000	1·102	<1·000
On relapse	Largactil ..					2·353†	2·293†	3·017†	2·472†
	7044 R.P. ..					2·811†	2·378†	3·163‡	2·434†
After 8 weeks' treatment	Largactil ..							2·239†	<1·000
	7044 R.P. ..							1·892	<1·000
After a further 12 weeks' treatment	Largactil ..							—	—
	7044 R.P. ..							—	—

* D = Deterioration R = Restlessness
† Significant at 5 per cent. level ‡ Significant at 1 per cent. level

Table III shows the adjusted means after eight weeks' therapy and those after a further twelve weeks' therapy. They have now been adjusted for chance differences which obtained immediately preceding the introduction of 7044/chlorpromazine therapy (Thorpe and Baker, 1956), i.e. the means appearing in columns 3 and 4 of Table I have now been adjusted to what they would have been if the corresponding means in Column 2 of the same Table had been identical. Table III also gives the statistical significance of the differences between these adjusted means.

TABLE III

Mean Scores in Columns Numbered 3 and 4 of Table I Adjusted for Chance Differences in Initial Means and Statistical Analysis

	3		4	
	After 8 Weeks' Treatment		After a Further 12 Weeks' Treatment	
	D*	R*	D	R
Largactil	9·995	1·068	5·498	·634
7044 R.P.	8·837	·586	8·002	·616
F ratio	1·279	·750	1·130	1·135
Statistical significance ..	NS	NS	NS	NS

* D = Deterioration R = Restlessness

The mean dosages of 7044 R.P. and chlorpromazine associated with the behaviour ratings in the above Tables are given in Table IV, together with the range of dosages. The figures in this Table refer to the number of milligrams given three times daily.

TABLE IV

Means and Ranges of Dosages in Milligrams T.D.S.

	Original Dose		After 8 Weeks' Treatment		After a Further 12 Weeks' Treatment	
	Mean	Range	Mean	Range	Mean	Range
Largactil ..	70·8	25–200	116·6	50–200	116·6	50–200
7044 R.P.	70·8	25–200	87·5	25–200	81·3	25–200

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Discussion

First with regard to schizophrenic deterioration. Tables I and II between them show for both groups marked changes in deterioration scores on relapse. These changes are statistically significant. After eight weeks' treatment with either drug, the deterioration scores show improvement which is again statistically acceptable. These scores are not significantly different from those obtained when the patients were previously taking chlorpromazine. After a further twelve weeks' treatment there is further improvement in the deterioration scores of both groups, and this improvement is either statistically acceptable (Largactil) or nearly so (7044). At no point in the experiment is there a significant difference between the two group means when allowances have been made for initial chance differences as is shown in Table III.

With regard to restlessness, the picture is very similar. Patients relapsing after being taken off chlorpromazine show significant increases in their scores on restlessness, but after eight weeks' treatment with 7044 or chlorpromazine they show statistically significant improvement again. Continuation of treatment for a further twelve weeks does not, in this case, however, produce further significant improvement. As with the deterioration scores, there is no evidence in these data to suggest that one or other of the two drugs is to be preferred.

It was mentioned earlier that two of the original fourteen patients being treated with 7044 had to be dropped from the project. The reason for this was that one developed a leucopenia, her white count dropping from 7,000 to 3,000 together with malaise, pallor and asthenia. The second developed a generalized erythematous rash. Only one of the chlorpromazine group had to be dropped as she was becoming increasingly lethargic and without initiative.

Although our results indicate that, in terms of deterioration and restlessness, our groups are equally responsive to 7044 or chlorpromazine, we must not lose sight of Table IV which shows that less 7044 than chlorpromazine was prescribed, although the difference was not marked. It is always possible, of course, that had we used different dosages, our results too would have been different, but it was felt that our knowledge of 7044 R.P. was too limited to allow us to predetermine the amounts which would be used.

Conclusion

In terms of our own Behaviour Rating Scale measuring schizophrenic deterioration and restlessness, 7044 and chlorpromazine are equally effective in the treatment of female deteriorated schizophrenic patients, although a slightly smaller dosage of 7044 was used. The appearance of leucopenia in one of the fourteen patients receiving 7044 suggests that additional evidence on this point is desirable.

Summary

Twenty-eight female deteriorated schizophrenic patients who had relapsed following chlorpromazine therapy were given further treatment with either chlorpromazine or 7044 R.P. Behaviour was assessed with the aid of the authors' Behaviour Rating Scale and no statistically acceptable evidence in favour of one or other of these two compounds in terms of this scale emerged. It was found, however, that slightly smaller doses of 7044 R.P. than chlorpromazine were required, and that one of the patients receiving 7044 R.P. developed leucopenia and another a skin rash.

No drug is likely to replace chlorpromazine unless it is more effective, safer or cheaper. 7044 does not appear to have any of these advantages in the case of deteriorated schizophrenic patients.

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