A RESEARCH METHOD TO ASSESS A NEW TRANQUILLIZING DRUG

By

J. G. THORPE, Ph.D.

Research Psychologist

and

A. A. BAKER, M.D.

Deputy Physician Superintendent

Banstead Hospital, Sutton, Surrey

I. Introduction and Problem

A NUMBER of new tranquillizing drugs have recently become available. We report a method of assessment for one of these—"Pacatal". In this experiment the new drug was compared with (*i*) no treatment at all, (*ii*) treatment using dummy tablets of the same size and appearance as the Pacatal tablets, and (*iii*) Largactil. A group of patients suffering from schizophrenia were selected, all being deteriorated. These patients can be found in considerable numbers with a reasonably similar clinical picture which is relatively stationary without treatment.

Pacatal, which is N methyl piperidyl (3) methyl phenothiazine, is said to be similar in action to Largactil but to produce fewer side effects. The ward sisters were informed of this and that we intended to assess its effects. They were told we would use two forms of the drug and did not know one was a dummy. All results were analysed statistically by the use of Analysis of Covariance. One of the most efficient experimental designs used in the evaluation of methods of treatment is the one employing "matched" or "equated" groups. In this design, patients are given an initial score on whatever criterion is being employed in the experiment, and groups of patients are then formed so that they show as nearly as possible the same distribution of scores on this criterion. These groups are then assigned to one or other of the methods of treatment under investigation and the final mean criterion scores for the groups evaluated at the close of the experiment. The chief drawback of this design lies in equating the groups of patients on the criterion before the experiment can be started, and such designs invariably involve considerable administrative inconvenience. To avoid this difficulty the writers have resorted to the device of matching at the close of the experiment, by the use of Analysis of Covariance. Briefly, this analysis allows us to test the hypothesis that there are no real differences between the methods of treatment, and that any differences in the final mean scores of the methods groups, after allowances have been made for chance differences in initial mean scores, are due entirely to chance fluctuations in random sampling. In this way, by allowing for these chance differences in initial mean scores, we hope to attain the same precision had the groups been matched on the basis of initial measures.

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II. Method

(*a*) Patients and Treatments

All the patients in this experiment were female deteriorated schizophrenics under 50 years of age. Their length of hospitalization varied from three to twenty-nine years, with a mean stay of fifteen years. Three long-stay wards in the hospital were involved, two provided 12 patients, and a third provided 24 patients. Mean ages are given in Table I. For each ward separately the names of the selected patients were arranged in order of length of stay in hospital. The first person on the list was assigned to treatment group A, the second to B, the third to C, the fourth to D, the fifth to A and so on. In this way the first two wards both had three patients and the third six patients in each treatment group. There were thus, in all, four groups of twelve patients, each group having a different treatment, A, B, C, or D.

Treatments were allocated at random as follows:

Treatment Group A	Largactil
Treatment Group B	Pacatal
Treatment Group C	No treatment
Treatment Group D	"Dummy" Pacatal

The selected patients received no treatment whatever for two weeks and at the end of that time they were rated by one of the authors (A.A.B.) on the Behaviour Rating Scale (Baker and Thorpe, 1956a, 1956b). They were also interviewed and rated on a five point tension scale.

The treatments were then administered according to the above plan for two weeks in the following dosages:

Group A	50 mg. t.d.s.
Group B	50 mg. t.d.s.
Group C	No treatment
Group D	50 mg. t.d.s.

At the end of this period, ratings on the Behaviour Rating Scale, and on tension, were again carried out by the same author, who in addition noted any side effects, and the drug and placebo dosages were then increased to 100 mg. t.d.s.

After two more weeks all ratings and assessments of side effects were again completed in the same manner.

Ward sisters were asked, after the first two weeks and subsequently after four weeks of treatment to give their opinions as to whether each patient had improved, deteriorated, or not changed since treatment began. We wished to note whether the sisters' impressions were the same from ward to ward, and considered whether this influenced the results.

Extreme care was taken to ensure throughout the whole experiment that the doctor who carried out the ratings had no idea at all to which group any patient belonged.

(*b*) Criteria

The criteria according to which the different treatments were to be assessed were as follows:

(i) *Schizophrenic Deterioration*

This is adequately described in a previous paper (Baker and Thorpe, 1956b) and constitutes the first general factor in the Behaviour Rating Scale

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presented there. In the present study it is measured by the sum of the ratings on each of the ten Rating Scale items.

(ii) *Restlessness*

This constitutes the second factor of the Rating Scale which was also described in the same paper. In the present study it is measured by adding together the scores on the following items of the Rating Scale:

(A) Night restlessness
(C) Day restlessness
(I) Aggressiveness

Scores on this factor of restlessness were previously shown to be independent of the deterioration measures.

(iii) *Tension*

This was assessed by one of the authors (A.A.B.) after a short interview with each patient, and scores from +++ to − were given on the basis of the patient's immediate reaction to the interview, her position in a chair, facial expression, and gestures with hands.

(*c*) Statistical Analysis

As indicated earlier, Analysis of Covariance was employed in the analysis of scores. As more than one ward was involved in the experiment it was possible to test not only the main effects, i.e. the methods, but also whether the interaction effects (Methods × Wards) were significant. In other words we could test whether for all patients involved, one method was superior to another, and also whether this superiority obtained in all wards.

In the analysis the mean scores of the four groups on each of the above criteria were compared with one another after two weeks of treatment, and again after four weeks of treatment. First the methods differences were analysed and when these were statistically significant, or approaching significance, the analysis of the interaction variance (Methods × Wards) followed.

III. Results

The mean scores for each treatment group on each of the three criteria before and during the experiment, are given below (Table I). In all cases higher scores represent less adjusted behaviour, i.e. more deterioration, more restlessness, and more tension.

Analysis of covariance applied to these data gives the following results.

After two weeks of treatment with doses of 50 mg. t.d.s., and after a further two weeks at 100 mg. t.d.s., the F ratios (the reduced variance for Methods ÷ the adjusted Methods × Wards variance) worked out as in Table II. (In all cases, with 3 and 5 degrees of freedom respectively, an F ratio of 5·41 is required for 5 per cent. significance.)

Table II

Criterion	F ratio (2 weeks)	p	F ratio (4 weeks)	p
(i) Deterioration	<1·000	(NS)	2·269	(20%)
(ii) Restlessness	3·983	(10%)	3·877	(10%)
(iii) Tension	<1·000	(NS)	7·170	(5%)

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TABLE I

Mean Scores

	Deterioration				Restlessness				Tension			
	Treatment Groups				Treatment Groups				Treatment Groups			
	A	B	C	D	A	B	C	D	A	B	C	D
Initial	12·917	14·167	9·583	10·500	1·833	1·000	1·667	1·083	0·000	0·417	0·083	0·250
After 2 weeks treatment	12·000	14·000	11·000	11·250	0·917	1·167	2·000	1·833	−0·167	0·333	0·333	0·500
After 4 weeks treatment	11·000	14·083	11·333	11·583	0·750	0·833	2·083	1·750	−0·333	−0·167	0·333	0·500
N	12	12	12	12	12	12	12	12	12	12	12	12
Mean age (years)	42·083	43·667	41·166	43·083	As for Deterioration				As for Deterioration			

Higher scores represent more Deterioration, more Restlessness, and more Tension.

TABLE III

Adjusted Mean Scores

	Deterioration				Restlessness				Tension			
	A	B	C	D	A	B	C	D	A	B	C	D
After 2 weeks					·501	1·544	1·743	2·131				
After 4 weeks	10·130	12·247	13·041	12·582	·328	1·217	1·820	2·053	−·346	−·151	·326	·504
Difference between means required for 5 per cent. significance	2·75				1·237 (2 weeks) : 1·400 (4 weeks)				·546			

It will be seen from this Table that after 2 weeks of treatment at 50 mg. t.d.s., only restlessness has been affected to a degree approaching statistical significance. After 4 weeks, however, with increased dosages, all our criteria show changes which, if not completely acceptable statistically, are at least approaching statistical acceptability. It will, therefore, be instructive to determine which methods of treatment are responsible for these differences, even though some of them hardly reach the 5 per cent. level of confidence.

The following Table (Table III) gives the mean scores of the various treatment groups adjusted for initial chance differences on each of the three criteria. These adjustments are not given when the F is far from significant. In studying this table it may be assumed that all groups started out with the same average score. The amounts by which these adjusted means should differ in order to be significant are also given.

From this Table it will be seen that after two weeks the adjusted mean for group A (Largactil) in terms of restlessness is very much lower than the other adjusted group means. It is significantly lower than the means for both the no-treatment and placebo groups, and almost significantly lower than the mean for the Pacatal group. We may conclude from this analysis therefore, that Largactil and not Pacatal is responsible for the difference we saw earlier in Table II (a glance at Table I shows the Largactil group mean to be considerably reduced after two weeks and the Pacatal group mean to have increased), and therefore that in this experiment 50 mg. t.d.s., of Pacatal is not as effective as the same dose of Largactil in the treatment of restlessness.

We may now turn to the Deterioration scores after four weeks of treatment with increased doses. We saw earlier that the overall differences between the groups was significant at the 20 per cent. level. Table III suggests that again Largactil is mainly responsible for the difference between adjusted means, the Pacatal, the Pacatal Placebo, and the no-treatment group means being very close together, and there is an almost significant difference between the Largactil and Pacatal adjusted means in favour of Largactil. From Table I we see that Largactil has appreciably reduced the amount of deterioration, while Pacatal has left it unchanged. It is of passing interest to note from this Table that the no-treatment group appear to become slightly worse during the experiment.

The Restlessness scores after the same period of four weeks again suggest the same conclusion, and though, in this case, the difference between the adjusted means in Table III between Largactil and Pacatal is not significant, neither are the differences between Pacatal and Pacatal Placebo, and Pacatal and no-treatment, and once again Largactil is responsible for the biggest difference. Table I shows Largactil to reduce considerably the mean restlessness score.

Tension scores after four weeks of treatment show a slightly different picture. Here the Largactil and Pacatal adjusted means in Table III are very similar, and acceptable differences are shown by both these means when they are compared with the means for the Placebo and no-treatment groups. Table I shows that for both the Pacatal and Largactil groups tension is reduced appreciably, while for the two others an increase in tension is indicated.

As was pointed out earlier, the present design enables us to determine the degree to which these conclusions can be accepted as generalizations over the three wards in this study. This can be done by testing the significance of the interaction (Methods $\times$ Wards) variances, and it is considered to be extremely necessary here in view of notable differences in the attitudes of nursing personnel to the use of these drugs. It became obvious that the reports of Ward Sisters

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on whether the patients had improved or not during the experiment seemed to be determined by their attitudes to the use of tranquillizing drugs. The Ward Sisters on the first two wards approved of tranquillizing drugs, while on the third ward (having half the patients in the experiment) they believed that habit training was more valuable. Any significant effects that these attitudes may have had on the patients' behaviour can be taken account of by testing these variances.

In this experiment there is in no case a significant interaction variance—all in fact are less than unity. The above conclusions, as a direct consequence of this, can therefore be accepted as applying to all wards.

Finally a note about side effects. Of the twelve patients receiving Largactil, four showed side effects after the first two weeks of treatment. These appeared as drowsiness during the first day or so of treatment, and later, skin rashes. Of these four, only two still showed skin rashes which had not increased in severity after a further two weeks under increased dosage of Largactil, ten patients remaining free from side effects. In the case of Pacatal, whether after two weeks of 50 mg. t.d.s., or after a further two weeks of 100 mg. t.d.s., no side effects whatever were apparent.

IV. Conclusions

There seems little doubt that Pacatal in the dosages indicated above is generally less useful in the treatment of deteriorated psychotic female patients under fifty years of age than Largactil given in similar doses. With a dosage of 50 mg. t.d.s., all treatment groups fail to show significant differences in respect of either deterioration or tension, and the difference between the groups in terms of restlessness appears to be due to the superiority of Largactil rather than to anything else.

When dosages are increased to 100 mg. t.d.s., differences between the groups begin to emerge. In terms of deterioration, and restlessness, however, these differences are again due to the superiority of Largactil over the remainder of the treatments. At this dosage tension appears to be reduced appreciably both by Pacatal and by Largactil, and the difference between them is extremely small. This finding, coupled with the earlier one that Pacatal produced no side effects are the only positive findings emerging in the present evaluation of Pacatal. Further research is needed to assess the value of Pacatal in other conditions and with varying dosage. The apparent deterioration in the control group may reflect the relationship between nurse and patient when the latter feel others are being given preference.

V. Summary

The present study was designed to evaluate the usefulness of Pacatal in the treatment of deteriorated psychotic patients by comparing it with (*i*) a better known drug (Largactil), (*ii*) a placebo, and (*iii*) no treatment. The experiment was designed in such a way that the results could be analysed by Analysis of Covariance. The main experiment was duplicated in each of three wards in order to obtain as high a precision as possible. The results point to the general inferiority of Pacatal to Largactil except in the reduction of tension when the two drugs are equally efficient, and in the absence of the side effects so frequently found in patients receiving Largactil.

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