Brit. J. Psychiat. (1969), 115, 1383–5

The Response to Treatment of Individual Patients in a Drug Trial

By SINCLAIR S. SUTHERLAND, ALISTAIR E. PHILIP
and MACKENZIE S. SUTHERLAND

It has been suggested by Philip (1969) that more information could be gleaned from conventional drug trials if it were possible to assess the efficacy of treatment for each patient in the trial. A method for the statistical analysis of individual response to treatment has been put forward by Philip using a modification of Ferguson's nonparametric trend analysis of correlated observations (Ferguson, 1965). Sutherland, Sutherland and Philip (1967) have described the details of a double-blind drug trial in which the efficacy of Prondol, an imipramine derivative, was compared with a standard imipramine preparation. The patients in their trial were rated on the Hamilton scale for depression (Hamilton, 1960) on admission, after two weeks' treatment and after four weeks' treatment. Since the data were not amenable to analysis by parametic methods, Mann-Whitney U tests (Siegel, 1956) were calculated to ascertain whether the change scores between rating occasions were different for the two groups of patients. This cumbersome procedure showed that there was no difference in change scores between the trial drug group and their controls for the 0–2 week and 0–4 week comparisons; there was, however, a significant tendency for the control drug group to show significantly greater change between the two week and four week assessments.

Method

Patients were admitted to the drug trial of Sutherland *et al.*, if (a) a significant degree of depression was noted by the referring agent, admitting doctor or ward sister and (b) a diagnosis of depression was made by one or both psychiatrists following interview. A standard double-blind procedure was used to allocate patients to the trial or control groups. Each patient was given one tablet (15 mgm. Prondol or 25 mgm. imipramine) thrice daily for seven days, then two such tablets thrice daily for the remaining three weeks of the trial. The present study is concerned with the fifty women in the trial who completed their course of treatment in the trial and were assessed on all three rating occasions.

Philip (1969) has described in detail the method of analysing ratings using a trend analysis approach. When symptom ratings given on three occasions are reduced to ranks and tested for significant differences in the distribution of ranks over these occasions, two trends can be observed. The first trend is of the monotonic, or straight line, order, while the second follows a bitonic, or U-shaped, path. In some cases both these trends are present to a significant degree.

Using Philip's procedure, significant changes in the ratings of symptoms in the present study fall into eight categories or types. Type 1 shows a monotonic, straight-line reduction in symptomatology. Type 2 has both monotonic and bitonic features, with most of the improvement occurring between the second and third assessments. Type 3 also has monotonic and bitonic features, but in this case most of the improvement occurs early, between the first and second assessments. Types 4, 5 and 6 are the reversed counterparts of the first three types, showing worsening instead of improvement. In type 4 the worsening follows a monotonic trend, in type 5 the worsening is more pronounced late in the trial, while in type 6 early worsening is the main characteristic. Types 7 and 8 indicate bitonic trends, the former showing early

improvement which then falls off, the latter showing early worsening which then recovers to the initial level of symptomatology. The cases which show no significant change form a further category, type 9.

Results

For each patient the ratings of symptoms on the Hamilton scale were ranked over the three assessment occasions, and tests for significant trends were carried out using the method of Philip (1969). Table I shows the types of response shown by patients. Of those patients on the trial drug, ten showed a significant, monotonic improvement in symptom rating, two showed a significant, monotonic worsening of symptoms, three had a pattern of response marked by early improvement and later deterioration, and ten showed no significant change in their condition.

Thirteen of the patients on the standard preparation had a significant monotonic type of improvement. One patient showed significant improvement which was more marked in the early phase of the trial, while the remaining eleven patients showed no significant change in their condition.

Considering response types 1 and 3 as good results and all other response types as poor results, the frequency of good and bad results in each group did not differ significantly ($\chi^2 = 0{\cdot}71$, d.f. $= 1$, n.s.).

Discussion

Sutherland *et al.*, (1967) found no overall significant differences between their trial and control groups, although the control group was found to show more symptom reduction towards the end of the trial. The present re-analysis of their data showed that the groups differed in several respects in response to treatment, although an overall test of differences between the groups was not significant. While 40 per cent of the patients on the trial drug manifested significant type 1 improvement, 8 per cent showed significant type 4 worsening. Three patients (12 per cent) improved at first only to deteriorate later on in the trial, and it seems likely that the bitonic trend reflected response to being admitted to hospital or some other undetermined factor. The remaining 40 per cent of patients in the trial drug group showed no significant change.

The control group, given a standard imipramine preparation, contained eleven patients (44 per cent) who showed no significant change, and thirteen (52 per cent) who improved in a monotonic fashion. In addition, the single patient with a type 3 response showed a predominantly monotonic improvement, so that a total of 56 per cent of this group could be said to have shown significant improvement.

In the light of these results it can be seen that the two groups of patients differ in ways which are of great interest to the clinician who is concerned with individual rather than aggregate response to treatment. Not only did fewer patients given the trial preparation show a significant improvement, but two of them actually got much worse. This is a finding which is of great importance to any clinician, but one which did not come to light in the original analysis. A further finding is that more patients in the control group than in the trial group had

Table I

Type of response to treatment

Trial drug		Standard preparation	
	n		n
Type 1	10 (2 at $p<{\cdot}001$; 5 at $p<{\cdot}01$; 3 at $p<{\cdot}05$)	Type 1	13 (5 at $p<{\cdot}001$; 5 at $p<{\cdot}01$; 3 at $p<{\cdot}05$)
Type 4	2	Type 3	1
Type 7	3	Type 9	11
Type 9	10		

https://doi.org/10.1192/bjp.115.529.1383 Published online by Cambridge University Press

type I responses which reached a very high level of significance. Such marked improvement in a relatively short period of time is a feature of some interest to the clinician, but again did not come to light using conventional methods of analysis.

Nonparametric trend analysis has here shown itself to be superior to the more conventional statistical method used by Sutherland *et al.*, (1967) in their drug trial report. When individual responses are lumped together and the aggregate performances of the two groups compared, no statistically significant difference is found between them. However, by considering each individual pattern of response it is possible to obtain interesting, important information regarding the effects of the drugs used. The presence of two instances of significant *worsening* of condition in the trial group has little effect on the group results, but is nonetheless important in the assessment of treatment. Some items of information are qualitatively more important than others and should not be ignored for the sake of statistical orderliness.

Summary

The results of a drug trial have been re-analysed using a method of nonparametric trend analysis. This method has been modified by Philip (1969) to deal with the assessment of the individual case. It has been demonstrated that information which customarily does not appear when conventional methods of statistical analysis are used can be presented in a quantitative manner. The importance of such information in the evaluation of treatment is briefly discussed.

Acknowledgements

Thanks are due to Dr. D. J. Richards who provided much help in the planning and execution of the parent drug trial and to John Wyeth and Brother Ltd. who supplied matching tablets.

References

Ferguson, G. A. (1965). *Nonparametric Trend Analysis*. Montreal: McGill University Press.

Hamilton, M. (1960). 'A rating scale for depression.' *J. Neurol. Neurosurg. Psychiat.*, **23**, 56–62.

Philip, A. E. (1969). 'A method for analysing assessments of symptom change.' *Brit. J. Psychiat.*,

Siegel, S. (1956). *Nonparametric Statistics for the Behavioral Sciences*. New York: McGraw Hill.

Sutherland, M. S., Sutherland, S. S., and Philip, A. E. (1967). 'Depressive illness—comparison of effects of Prondol (WY 3263) and imipramine.' *Clin. trials J.*, **4**, 857–60.

Sinclair S. Sutherland, M.B., Ch.B., D.P.M., *Consultant Psychiatrist, Woodilee Hospital, Lenzie, Near Glasgow*

Alistair E. Philip, M.A., Ph.D., Dip. Clin. Psychol., *Scientific Staff, Medical Research Council, Unit for Research on the Epidemiology of Psychiatric Illness, Edinburgh University Department of Psychiatry, Edinburgh, 10*

Mackenzie S. Sutherland, M.B., Ch.B., D.P.M., *Senior Registrar, The Ross Clinic, Cornhill Road, Aberdeen*

All formerly members of staff at Kingseat Hospital, Newmachar, Aberdeenshire

(*Received 20 September 1968*)