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Criteria for Measuring Change: Statistical Significance vs Clinical Significance

SIR: Eccleston *et al* (*Journal*, December 1985, **147**, 623–630), in their double-blind comparison of propranolol with thioridazine, conclude that propranolol resulted in a significant improvement on both the BPRS and the NOSIE, suggesting that it is useful in the treatment of chronic schizophrenia. Propranolol had a significant influence on both positive and negative symptoms of schizophrenia. In contrast, thioridazine had little to offer this group of patients. Their criteria for measuring the efficacy of propranolol does produce few statistically significant results. The central issue in a study such as this one is whether a statistically significant finding is also clinically significant or meaningful?

In using a maximum dose of 400 mg thioridazine per day, there seems to be an assumption that this is an adequate dose for treating schizophrenic patients. Davis & Garver (1978) have summarised the results of 207 double-blind comparisons of neuroleptics with placebo. There were 66 comparisons of chlorpromazine with placebo, and in 11 studies which did not show a significant treatment effect for chlorpromazine the dosage was inadequate. Chlorpromazine proved superior to placebo in all studies using daily doses of 500 mg or more. The relative potency of thioridazine is more or less equal to chlorpromazine (Davis, 1974). It may, therefore, be argued that the failure to get a treatment effect for thioridazine is because the investigators used a sub-optimal dose of the drug. Since all the patients recruited into the trial were already on neuroleptic medication and yet had florid psychotic symptoms, it would be of interest to document if the mean dose prior to commencing the trial was higher than 400 mg of thioridazine or its equivalent. For a sounder methodology, as well as to do justice to thioridazine, one should use a dose higher than that the patient was on prior to the trial. That is likely to alter the clinical effect of thioridazine as well as the statistical significance for the change in ratings, and perhaps also affect the between-group differences. Understandably, the investigators must have had good reasons for using this dose and drug (e.g. for blindness of the study). Theoretically, the inclusion of a placebo control group would have made it possible to conclude whether the patient population was treatment-responsive or not and thus account for the failure of response to thioridazine.

It is not clear if Eccleston *et al* found a between-group significant difference on the BPRS. The paper refers to propranolol resulting in a higher fall from base-line than thioridazine, but since the time period is not specified it perhaps refers to day 14 or 21 rather than to a significant effect throughout or at the end of the trial period. Patients in the propranolol group were also more severely ill at base-line, compared with the thioridazine group, and so there was greater room for change. The significant change in score reported in the propranolol group is, therefore, a weak effect. It is difficult to comprehend how a change from a mean base-line score of 24 to 16 on day 14 is significant at the level of $P<0.001$, whereas a reduction from a mean base-line level of 24 to approximately 15.5 on day 21 is significant at the level of $P<0.01$. What appears to be a marked improvement is an illusion (as can be seen if the Figure is redrawn by completing the broken line for mean BRPS score), since the maximum reduction in score is of the extent of only 33%. After day 21 the initial effect is dissipated. Thus a statistically significant result is probably not clinically significant, as considerable psychopathology is still evident at the end of the trial.

In our recent study (Manchanda & Hirsch, 1986) comparing d-propranolol with placebo with all the patients receiving haloperidol during the first week, we observed that d-propranolol had a better effect than placebo in sustaining the initial improvement with haloperidol. The overall magnitude of clinical

change from pre-treatment scores was small, the majority of the patients showing little or no overall improvement. We concluded that although d-propranolol has a detectable therapeutic effect on schizophrenic symptomatology, this effect is more of pharmacological interest than of major clinical significance, as the change on rating scales did not compare favourably with the changes observed with conventional neuroleptics in adequate doses.

Propranolol has been a subject of research for over a decade, and several studies conclude that it has a statistically significant effect in reducing psychotic symptomatology. Clinicians are far from convinced. A weak antipsychotic effect for propranolol is the best that can be concluded from experience so far. It remains to be seen whether or not the propranolol molecule can be modified to produce a more effective antipsychotic agent. The clinical investigator has done his work and this is now a challenge for the pharmaceutical industry.

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Professor Eccleston and Dr Hassanyeh Reply

SIR: Dr Manchanda asks if a statistically significant finding should also be seen as clinically significant. He concludes that with propranolol in schizophrenia (despite several studies which suggest a useful contribution) clinicians would regard such a finding, based on statistical significance, unconvincing. It is axiomatic that progress in research must be based on scientific methodology including statistics. If we revert to clinical opinion only, little progress in psychiatry can be hoped for. This, of course, does not mean that the findings of a study must be seen as clinically binding.

Dr Manchanda asks whether a dose of 400 mg thioridazine was therapeutically adequate. This is a relevant question, and further studies exploring this are obviously required. Our study, however, clearly suggests that propranolol at a dose of 640 mg a day was superior to thioridazine at a dose of 400 mg a day in patients with chronic schizophrenia. This superiority is based on the statistical findings in relation to measures on the BPRS (total score, positive and negative symptoms) and on the NOSIE. It should be noted also that although the improvement was not large there was a variation between the patients, some doing much better than others—but not in such a way that one could predict who was likely to show most benefit.

We do not suggest that propranolol radically changed or cured the illness—tables III and IV of our paper attest to that. What we do suggest is that it reduced the severity of some of the positive and negative symptoms; i.e. it made a quantitative and not a qualitative impact on the illness. Our conclusions were that propranolol at 640 mg/day may have a useful part to play in the treatment of chronic schizophrenia but that thioridazine at 400 mg/day does not. We also suggested that propranolol's effects on the negative symptoms warranted further investigation.

Would a higher dose of thioridazine have been more efficacious? As indicated earlier, this needs to be tested out in a clinical trial. Our impressions, however, are that it would not. Pre-trial, virtually all patients, whether in the propranolol or thioridazine group, were on *both* a depot and an oral neuroleptic at doses which clinicians would not have regarded as sub-optimal, yet despite which their illness had shown little or no change. If in this group of patients propranolol was shown to be beneficial, as was shown in our study (if only in a quantitative sense), what we suggested was that it ought at least to merit consideration in the drugs available to us which could be used in this condition.

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Is there a Right-hemisphere Dysfunction in Asperger's Syndrome?

SIR: We read with interest the report on a case of Asperger's syndrome (*Journal*, November 1985, **147**, 566–509), an entity unknown to us. We were surprised to see that one of the main features was non-verbal communication disorder (the inability to perceive the meaning of expressions and gestures of others and a poverty of non-verbal expressions), which has been named global aprosodia by Ross (1981) and is caused by right-hemisphere damage. The discrepancy between verbal and performance IQ in this patient also suggests right-hemisphere