CONTROLLED TRIAL OF PROCHLORPERAZINE ("STEMETIL") IN SCHIZOPHRENIA

SOUTH-EAST REGION (SCOTLAND) THERAPEUTIC TRIALS COMMITTEE*

Organization: The late Professor Alexander Kennedy initiated the suggestion that psychiatric drug trials should be on a Regional basis. A Therapeutic Trials Committee was accordingly established under the auspices of the Board of Studies and the Department of Psychological Medicine of the University of Edinburgh, with Professor Kennedy as Chairman. The following clinicians were responsible for the execution of this trial: Dr. G. Bell, Dr. J. K. Morrice, and Dr. R. Ratcliff, at Dingleton Hospital; Dr. A. K. Macrae, Dr. N. Imlah, and Dr. E. Howieson at Bangour Village Hospital; Dr. J. McPherson, Dr. W. W. Gordon, Dr. J. C. Holden and Dr. I. A. Gibson at Gartloch Hospital.

Introduction

Since Delay, Deniker and Harl (1952) first reported favourably on the use of chlorpromazine in disturbed psychotic patients the extended use of phenothiazines has contributed to the transformed atmosphere in mental hospital wards. There is still some doubt as to the precise mechanism of action of the phenothiazines. The blocking of arousal responses to afferent stimulation in animals following chlorpromazine has been fully demonstrated (Bradley and Hance, 1955, 1957). The production in man of a "parkinsonian syndrome" by chlorpromazine and later phenothiazines has been taken as evidence of drug activity as a basal ganglion level (Kruse, 1957). More recent work suggests that chlorpromazine may act by depressing the collateral inflow into the reticular formation from the afferent pathways rather than the brain stem activating system itself (Key and Bradley, 1958).

Clinical experience with the phenothiazines suggests that whereas chlorpromazine has what may be called a "sedative" component in its effect on schizophrenic behaviour the later derivatives seem to have an "activating effect". This is of some importance as the most appropriate treatment of long-stay and often anergic hospitalized schizophrenics is still in dispute. Whereas the phenothiazines have calmed the agitated, overactive and violent patients they have not materially affected the "hard core" of medium and long-stay schizophrenic patients. Many psychiatrists have emphasized approaches other than the pharmacological. Since the time of Conolly at Hanwell it has been recognized that psychological manipulation, including milieu therapy, work therapy and social rehabilitation, can result in significant improvements in behaviour, and to these has been added more recently the application of the principles of dynamic psychotherapy. Nevertheless the overall course of the illness is often not affected.

The efficacy of chlorpromazine in acute schizophrenic illness has been amply confirmed (Vaughan *et al.*, 1957; Kinross-Wright, 1957) and the drug is now often used in place of insulin coma therapy (Boardman *et al.*, 1956).

However, neither chlorpromazine nor some of the other phenothiazine derivatives such as promazine and acetyl promazine have been so effective in the less acute schizophrenic illnesses (Collard and Maggs, 1958). The reports that prochlorperazine was useful in just this group of patients (Milne and Berliner, 1958; Denham, 1958) suggested that the drug merited more extended

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trial. Our aim was to assess the value of prochlorperazine in the treatment of chronic schizophrenia and to compare its effect on the illness with that of chlorpromazine.

MATERIAL

The patients, all under the age of 60, were selected from three hospitals. One hundred and thirty-two patients were interviewed initially. The interviews were conducted by two psychiatrists working together and using a check list of symptoms to form the symptomatic basis for diagnosis. We took the following definition of schizophrenia given by Fish (1959): "A group of mental disorders in which there is no coarse brain disease and in which many different clinical pictures can occur. The form and content of the symptoms which occur in these different clinical states cannot be understood as arising rationally or emotionally from the affective state, the previous personality or the current situation, with the proviso that where a patient has a severe anxious depression with marked paranoid delusions the illness cannot be considered to be schizophrenia in the absence of clear-cut symptoms of the first rank as defined by Schneider (1955)". Using these criteria ten patients were excluded, some because of signs of organic mental disease. A further ten patients were excluded on administrative grounds, such as the reasonable possibility of the patient leaving hospital before the completion of the trial. Thus 112 patients were left for study. A list of factual data was prepared for each patient and then transferred to "Cope-Chat" punch cards. Using these cards two matching groups (A and B) were prepared. The main factors used in this matching were sex, age, diagnostic subgroup, physique, duration of illness, duration of stay in hospital, presence of delusions, hallucinations, affective disturbance, catatonic symptoms. Taking the 112 patients together there were 54 men and 58 women, the age range was from 20–58 years. Subsequent analysis of the groups A and B showed that the matching had been fairly effective (see Table I).

TABLE I

Factor	Group A	Group B	Difference
Male	29	25	4
Paranoid	11	13	2
Catatonic and hebephrenic	31	30	1
Other	14	15	1
Duration of illness under 1 year	0	1	1
1–5 years	9	10	1
+5 years	47	45	2
Age under 25	2	2	0
25–40	19	19	0
+40 years	35	35	0
Pyknic	17	18	1
Athletic	8	10	2
Asthenic and dysplastic	31	28	3
Hallucinations	40	43	3
Delusions	40	39	1
Abnormality of thought form	50	51	1
Abnormal affect	50	49	1
Catatonic inhibition	19	19	0
Treated E.C.T.	37	35	2
Hospital under 1 year	7	4	3
Hospital 1–5 years	14	18	4
Hospital +5 years	35	34	1

METHODS

1. *General Description*

We decided that whereas we wished to compare prochlorperazine with chlorpromazine, we also wished to make a comparison with placebo to establish whether the patients under trial did in fact benefit from chlorpromazine. Thus the baseline was chlorpromazine. After initial interviewing and allocation to Groups A and B all patients were placed on chlorpromazine and the dosage was adjusted to produce the maximal behavioural improvement with the minimum side-effects. This dosage adjustment was completed before the onset of the trial proper and determined the dosage throughout the other phases. The format (see Table II) was of the usual double-blind, cross-over variety with the addition of a first month on a stabilized dose of chlorpromazine.

TABLE II

Months	1	2	3
Group A	Cl.	X	Y
Group B	Cl.	Y	X

Cl.=Chlorpromazine. X=Prochlorperazine. Y=Placebo.

2. *Dosage*

As mentioned there was no standard dosage; the dosage was adjusted in the pre-trial period for each patient. In fact the dosage range was from chlorpromazine 25 mg. t.d.s., to 150 mg. t.d.s. This dosage, in terms of the number of 25 mg. chlorpromazine tablets per day, determined the dosage of prochlorperazine and placebo (number of tablets per day). The prochlorperazine tablets contained 6·25 mg. of active substance (dosage ratio of 1 : 4 to chlorpromazine) and, with the placebo tablets, were indistinguishable from the ordinary 25 mg. chlorpromazine tablets.

3. *Methods of Assessment*

(*a*) Weekly rating scales were completed for each patient by the doctor in charge of the ward in conjunction with the nursing staff. These scales were devised by members of the University Department of Psychological Medicine and comprised eighteen different items. Some items were of a simple behavioural type, such as eating, washing habits, level of activity, etc., while others were more specifically psychiatric such as hallucinatory experience, delusions, disturbance of speech form, etc. Each item was rated on a scale from 1 to 5, 1 representing "normal" or no comment and 5 representing "disturbed";

(*b*) Independently of the ward doctors and without discussion with the nursing staff, two members of the University Department interviewed the patients in the pre-trial period and the end of each drug period (i.e. monthly). The interviews were "structured" on the basis of a nine factor symptom scattergram. These factors were entitled hallucinations, delusions, interview attitude, speech form, affect, catatonic inhibition, anxiety, excitement, attention. These headings are evident except perhaps that of affect which was taken here to relate to affective blunting or incongruity of response. Each factor was rated on a three-point scale and on the basis of the completed scattergram a global rating on a five-point scale was made. This scale read in the same direction as that used by the ward doctors, i.e., 1 represented "no comment" and 5 represented "disturbed".

It should be emphasized that all the doctors making these assessments were ignorant of the key to Groups A and B, this information being held by other members of the University Department.

4. *Additional Treatments*

It was decided that any patient who required E.C.T. would have to be withdrawn from the trial. We decided that any additional medication should take the form of Sodium Amytal by day, pentobarbitone or Sodium Amytal at night. Such additional medication was noted on the weekly rating scales completed by the ward doctors. It was also decided that any severe parkinsonism should be treated with benzhexol hydrochloride (Artane).

Results

1. *Withdrawals*

Ten patients were withdrawn during the three-month period of the trial. Three patients became too disturbed. One was started on E.C.T., while the other two were started on specific pharmacological treatment. Three patients were discharged during the course of the trial at the request of their relatives. In two cases the diagnosis had to be revised during the course of the trial. One patient, not previously regarded as an epileptic, developed status epilepticus while the other showed, at successive interviews, emerging evidence of organic intellectual deterioration.

2. *Results*

These are shown in terms of the distribution of each drug group along the axis of the five-point rating scale.

Table III

Drug Group Distribution on 5-Point Rating Scale

	Rating Scale Positions					
Drug periods	1	2	3	4	5	Totals
Chlorpromazine	7	29	35	25	6	102
Prochlorperazine	14	13	39	29	7	102
Placebo	14	16	38	28	6	102
Totals	35	58	112	82	19	306

$p = <0{\cdot}3 > 0{\cdot}2$ if $n = 8$.

Table IV shows the same results expressed in the conventional terms; improved, unchanged and worse. These differences are not significant ($p = <0{\cdot}1 > 0{\cdot}05$ if $n = 2$).

Table IV

	Improved	Unchanged	Worse	Totals
Prochlorperazine	24	47	31	102
Placebo	27	48	27	102
Totals	51	95	58	204

As noted under methods the dosage for each patient was determined in the pre-trial phase on the basis of clinical response. We decided that it might be

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of interest to analyse the results of prochlorperazine in accordance with dosage, the threshold being set at 75 mg. daily (see Table V).

TABLE V

Results of Treatment in Relation to Dosage

	Improved	Unchanged	Worse	Totals
Prochlorperazine— less than 75 mg. per day	15	28	19	62
Prochlorperazine— 75 mg. per day or more	9	19	12	40
Totals	24	47	31	102

We had wondered whether amongst those patients receiving the higher doses of prochlorperazine the greatest number of deteriorations might not occur, owing to the distorting effects of unrecognized parkinsonism. In fact the percentage incidences of deterioration, 30·0 per cent. for the higher dosage and 30·6 per cent. for the lower dosage are not significantly different. Similarly the percentage improvements, 22·2 per cent. at the higher and 24·2 per cent. at the lower dosage, are not significantly different.

Next we considered whether the different order of drugs in Groups A and B might not affect the outcome. In Group A the order was chlorpromazine—prochlorperazine—placebo, while in Group B it was chlorpromazine—placebo —prochlorperazine.

TABLE VI

Results in Relation to Order of Drug Administration

		Improved	Unchanged	Worse	Totals
Group A	Prochlorperazine ..	10	22	19	51
	Placebo	15	22	14	51
Group B	Prochlorperazine ..	14	25	12	51
	Placebo	12	26	13	51
	Totals	51	95	58	204

The percentage deterioration for Group A and Group B on prochlorperazine, 37·3 per cent. and 23·5 per cent. respectively, are notably, though not significantly, different ($p = <0·3 > 0·2$).

The next table shows the results of treatment with prochlorperazine and placebo in relation to diagnostic group but irrespective of drug order.

TABLE VII

Results of Treatment in Relation to Diagnostic Groups

		Improved	Unchanged	Worse	Totals
Prochlorperazine	Paranoids ..	9	5	6	20
	Others ..	15	42	25	82
Placebo	Paranoids ..	7	9	4	20
	Others ..	20	39	23	82
Totals		51	95	58	204

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It is clear from Table VII that the treatment results are not closely linked with any diagnostic grouping.

In the next table (Table VIII) we have investigated the groups of patients who improved with prochlorperazine and with placebo in an attempt to elucidate what factors differentiated them from the patients who did not improve. The analysis suggests, in fact, that the patients who improved could not be differentiated on any of the factors studied from the trial group as a whole.

TABLE VIII

Analysis by Factors of Patients Improved on Prochlorperazine (24), Improved by Placebo (27), and the Entire Trial Group (112)

Factor	Placebo Improved (27 Patients)	Prochlorperazine Improved (24 Patients)	Total Trial Group (112 Patients)
Male	14 (51·8%)	14 (58·3%)	54 (48·2%)
Age under 40 years ..	15 (55·1%)	12 (50%)	42 (37·5%)
Paranoids	6 (22·2%)	7 (29·4%)	24 (21·4%)
Illness under 5 years ..	6 (22·2%)	5 (20·8%)	20 (17·9%)
Pyknic build	7 (25·9%)	7 (29·4%)	35 (31·2%)
Hostility	6 (22·2%)	4 (16·7%)	25 (22·4%)
Hallucinations	15 (55·1%)	17 (70·8%)	83 (74·1%)
Excitement	5 (18·5%)	4 (16·7%)	22 (19·7%)
Hospital under 5 years ..	10 (37·1%)	9 (37·5%)	44 (39·4%)

So far all the tables have been based on the five-point rating scale completed by the two psychiatrists and using the symptom scattergram. Analysis of the Behaviour Rating Scale used by the doctors in the three hospitals revealed a similar absence of significant shift in group distribution during the three drug periods. The data for Factor 9 (hallucinations) and Factor 10 (delusions) are shown in Tables IX and X.

TABLE IX

Behaviour Rating Scale: Factor 9 (Hallucinations) Group Distributions During Three Drug Periods. Rating Scale Positions

		1	2	3	4	5	Totals
Drug Periods	Chlorpromazine	55	25	13	7	2	102
	Prochlorperazine	57	22	12	7	4	102
	Placebo	64	14	14	8	2	102
	Totals	176	61	39	22	8	306

$p = <0{\cdot}8 > 0{\cdot}7$ if n=8.

TABLE X

Behavioural Rating Scale: Factor 10 (Delusions). Group Distribution Along 5-Point Rating Scale During Various Drug Periods

	5-Point Rating Scale					
Drug periods	1	2	3	4	5	Totals
Chlorpromazine	72	5	17	8	0	102
Prochlorperazine	67	4	25	6	0	102
Placebo	69	5	20	7	1	102
Totals	208	14	62	21	1	306

$p = <0{\cdot}9 < 0{\cdot}8$ if n=8.

Discussion

Briefly our results indicate that of patients stabilized on chlorpromazine and then transferred to prochlorperazine less than one-quarter improved (23·5 per cent.) whereas 46·1 per cent. remained unchanged and 30·4 per cent. became worse. Our results do not, therefore, support the suggestion that prochlorperazine is going to prove of particular value in the hospitalized schizophrenic. Analysis of the group of 24 patients who did improve on prochlorperazine demonstrates that this group did not deviate significantly from the trial group as a whole. Nevertheless it may be significant that amongst those improving on prochlorperazine there were a disproportionate number of paranoid patients. It is well recognized that this group carries in any case a more favourable prognosis and does well with other neuroleptic drugs (McDonald and Watts, 1959). The interesting observation that comes out of this trial is that more than a quarter (26·5 per cent.) improved when transferred to placebo.

These results might be thought to cast doubts on the methods of assessment used. To check the reliability of the rating scale based on the structured interview we analysed the rating distribution for Groups A and B at the end of the first month. At this point all the patients had been on chlorpromazine for one month. As we know the degree of matching between the groups we postulated that calculation of the correlation co-efficient between the rating distribution for Groups A and B would give us an index of the reliability of the scale. The calculation shows that $r=0·729$ with a p value of $<0·17$.

In the same way we analysed the rating distributions for Groups A and B on the Behaviour Rating Scale for Factors 2 (under-activity) and 8 (disorder of speech function) at the end of the first month. Calculations of the correlation co-efficients give, for Factor 2, $r=0·96$ and $p<0·025$ while for Factor 8 $r=0·99$ and $p<0·005$. The much higher reliability of the Behaviour Rating Scales as compared with the global scale based on the structured interview is to some extent offset by the fact that the group distributions on the Behaviour Rating Scales show a bias to the left or normal end of the scale (see Table XI).

Table XI

Distribution on Behaviour Rating Scale of Groups A and B at the End of the Fourth Week (Factor 2 = Under-activity, Factor 8 = Disordered Speech Function)

		Rating Positions					
		1	2	3	4	5	Totals
Factor 2	A	18	24	4	5	0	51
	B	16	28	7	0	0	51
Factor 8	A	30	8	9	4	0	51
	B	32	5	8	5	1	51
Totals		96	65	28	14	1	204

Turning now to the literature on prochlorperazine it is conspicuous how few of the investigations reporting positive results employed adequate controls. Thus Riesenman and Pettit (1959), Denham (1958) and Galbraith *et al.* (1959) all reported good results with prochlorperazine. None employed satisfactory

controls. Goldman (1958) reported 27·5 per cent. complete recovery from all active psychotic symptoms out of a total of 320 schizophrenic patients treated and Frierson (1958) noted 60 per cent. improvement out of a total of 33 "chronic psychotic patients". Neither of these two authors used controls. Foulds (1958) has an interesting table analysing 72 papers reporting on the results of psychiatric treatment. Fifty-two projects had no controls and 43 gave positive results. Twenty projects used controls and only 5 gave positive results. Applying the usual tests of probability to these figures Foulds showed that this distribution could not have occurred by chance ($p < \cdot 001$). In other words uncontrolled drug trials in psychiatry tend to give positive results.

One of the better controlled studies on prochlorperazine in psychosis is that of King and Weinberger (1959). They compared three groups of schizophrenic patients over a period of ten weeks. One group received a lactose, one group received chlorpromazine and the third received prochlorperazine tablets. All three groups showed a significant improvement though this was greatest for those receiving chlorpromazine. The authors suggest, on the basis of their observations, that the therapeutic effects of the phenothiazines are not closely linked with their effect of producing parkinsonism. In our study only four patients developed parkinsonian rigidity (one of these also showed tremor and salivation). None of these patients showed any improvement in mental state or behaviour while receiving prochlorperazine. The parkinsonism was well controlled with benzhexol hydrochloride.

Neither did we encounter any significant side-effects (cf. Sainsbury, 1959). One patient experienced a mild cerebro-vascular incident while on prochlorperazine. He was taken off the drug and the symptoms of hemiparesis cleared up over a period of a week.

There are a few points concerning methodology which have emerged during this trial. Firstly, while we think that the Behaviour Rating Scale we employed is fairly reliable, yet the data on the 18 factors is very difficult to process. Each factor has to be analysed separately and the work involved in this analysis is not commensurate with the information derived. We are planning to construct a much simpler scale comprising five factors on a five-point scale.

Secondly the cross-over type of trial is subject to criticism. In this case the trial itself lasted three months to which must be added two weeks for preliminary study, so that the collection of sufficient suitable patients who are likely to remain in hospital for that period becomes a problem. In this trial the difficulty was minimized by the fact that three different hospitals were involved. Another factor to be noted is that the longer the trial continues the greater the chance of spontaneous fluctuation in the patient's condition. Nevertheless it is clear that in assessing the effect of phenothiazines in schizophrenia it is necessary to exhibit the drug for several weeks; nor can the trial be shortened by the omission of controls.

Finally, our results suggest that a certain proportion of hospitalized schizophrenics do not require drugs at all. While this may be self-evident to older and more experienced psychiatrists, it does seem that this point is not always recognized by younger staff members, and, if these expensive and in some cases potentially toxic drugs are to be used liberally on chronic schizophrenics, one would wish to see their value proved fairly conclusively. It seems justifiable here to quote Houston (1956) discussing the results of a controlled trial in schizophrenia; "The main lessons that emerge from the study are that caution and adequate control procedures are essential before any therapy or drug is accepted as beneficial in chronic psychotics . . ."

Summary

1. A controlled trial of prochlorperazine on chronic schizophrenic patients has been described.

2. The behavioural changes obtained did not differ significantly from those produced by placebo or chlorpromazine.

3. The methodology of the trial and the implications of the results have been discussed.

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