CHLORPROMAZINE AND PECAZINE IN CHRONIC SCHIZOPHRENIA

By

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IN this paper the effect of chlorpromazine* is compared with that of pecazine† on the schizophrenic population of three chronic psychiatric wards.

Delay, Deniker and Harl (1952) introduced chlorpromazine into psychiatry. Pecazine was first used by Kline and Jacob (1955) and Hiob and Hippius (1955). Thorpe and Baker (1956), in a double-blind, controlled trial, found that both drugs reduced tension significantly in deteriorated, female, schizophrenic patients. Baker and Thorpe (1957) found that pecazine did not significantly reduce daytime incontinence in deteriorated psychotic patients. The trial was controlled and blind. Jones (unpublished), in a double-blind, controlled trial on disturbed psychotic patients, found chlorpromazine to be effective but could find no evidence that pecazine had any effect.

METHOD OF PRESENT TRIAL

Three locked wards for chronic, female, psychiatric patients were chosen. They were respectively a disturbed ward, a moderately disturbed ward and a ward in which 14 of the 57 patients worked in the hospital utility departments. The patients on these wards were diagnosed systematically by the present writer. The criteria for the differential diagnosis of schizophrenia were those of Mayer-Gross, Slater and Roth (1954).

The whole schizophrenic population of these three wards was studied, excluding cases of 60 years of age and over, and also excluding cases falling within Kraepelin's category of paraphrenia systematica.

Two patients had to be dropped from the investigation at an early stage. Ninety-two patients remained, 33 in the disturbed ward, 39 in the moderately disturbed ward and 20 in the workers' ward. Following Harries (1927) the patients were assigned to three groups—A, B and C—alternately, in order of their admission to hospital. This was carried out for each ward separately.

TABLE I

	Whole Series	Group A	Group B	Group C
Age range (to nearest year) ..	20–59 years	20–59 years	21–57 years	24–59 years
Mean age	42·25 years	42·00 years	41·20 years	43·70 years
Time since admission to hospital (to nearest month); range	3 months–33 years 8 months	3 months–24 years 9 months	6 months–33 years 8 months	6 months–29 years 5 months
Mean	11 years 4·23 months	11 years 1·10 months	11 years 4·77 months	11 years 6·93 months

* 2-chlor-10-(3-dimethylaminopropyl) phenothiazine hydrochloride. Largactil (May & Baker), Thorazine (Smith, Kline & French), Megaphen (German workers), Ampliactil (Spanish workers), Aminazine (Russian workers), 4560 RP, SKF 2601 A.

† 10-(1-methyl-3-piperidylmethyl) phenothiazine. Pacatal (Warner), Mepazine, Lacumin (Scandinavian workers), P 391, W 1224.

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Chlorpromazine was already familiar to the nursing staff; an unfamiliar, green, 25 mg. chlorpromazine tablet was used in order to overcome this difficulty. It was sweet tasting. The 25 mg. pecazine tablets were white and slightly bitter. The placebos were white, one being sweet and the other tasteless. Neither the ward doctor nor the nursing staff knew which drug the patients were having at any time.

The patients were rated initially and subsequently every four weeks. Each patient was rated on the fifteen most valid items of the Albany Behavioural Rating Scale (Shatin and Freed, 1955), and on an additional item relating to whether or not the patient was destructive. Each item was rated 1 or 0 by the two ward sisters in charge of the daytime shifts on each ward, a score of 1 indicating variation in the direction of mental health. In each case the average of the scores awarded by the two sisters was added to the score awarded by the ward doctor on two further items—mental tension and schizophrenic thought disorder. These were also rated as 1 or 0.

TABLE II

Course of the Investigation
(The tablets of the active drugs were each 25 mg. in strength)

Week of Investigation (inclusive)	Group A	Group B	Group C
1– 4	No tablets	No tablets	No tablets
5– 8	Placebo 3 tablets thrice daily	Placebo 3 tablets thrice daily	Placebo 3 tablets thrice daily
9–12	Pecazine 1 tablet thrice daily	Chlorpromazine 1 tablet thrice daily	Placebo 1 tablet thrice daily
13–16	Pecazine 3 tablets thrice daily	Chlorpromazine 3 tablets thrice daily	Placebo 3 tablets thrice daily
17–20	Chlorpromazine 1 tablet thrice daily	Pecazine 1 tablet thrice daily	Placebo 1 tablet thrice daily
21–24	Chlorpromazine 3 tablets thrice daily	Pecazine 3 tablets thrice daily	Placebo 3 tablets thrice daily

Each patient's score was adjusted as a fraction of the maximum possible score (18) for each rating.

The arbitrary nature of the rating scale made statistical methods suitable for normally distributed variables inappropriate here. The numbers of patients in each group falling into high (10–18) and low (0–9·9) scoring categories were compared at various times by means of the χ^2 test.

RESULTS

One case in group A developed agranulocytosis at the end of the 15th week, and had to have placebo subsequently. She was not dropped from group A as we were attempting to assess the proportion of chronic, schizophrenic patients who might be improved by the drugs. It was not necessary to interrupt treatment in the case of any other patient.

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TABLE III

In all cases, the active treatment groups showed better results than the control group C.

Week of Investigation	Groups A and C Compared		Groups B and C Compared	
0	$\chi^2=0{\cdot}03$	$P>0{\cdot}80$	$\chi^2=0{\cdot}87$	$P>0{\cdot}30$
4	$\chi^2=0{\cdot}03$	$P>0{\cdot}80$	$\chi^2=0{\cdot}87$	$P>0{\cdot}30$
8	$\chi^2=0{\cdot}17$	$P>0{\cdot}50$	$\chi^2=0{\cdot}17$	$P>0{\cdot}50$
12	$\chi^2=0{\cdot}18$	$P>0{\cdot}50$	$\chi^2=2{\cdot}83$	$P<0{\cdot}10$
16	$\chi^2=0{\cdot}84$	$P>0{\cdot}30$	$\chi^2=5{\cdot}64$	$P<0{\cdot}02$*
20	$\chi^2=5{\cdot}09$	$P<0{\cdot}05$*	$\chi^2=13{\cdot}7$	$P<0{\cdot}001$†
24	$\chi^2=3{\cdot}88$	$P<0{\cdot}05$*	$\chi^2=6{\cdot}04$	$P<0{\cdot}02$*

* indicates statistical significance beyond the 5 per cent. level.
† indicates statistical significance beyond the 1 per cent. level.

TABLE IV

Where the results have remained the same or deteriorated with time, the values of χ^2 and P are placed in parentheses. Where improvement has occurred, they are not.

Ratings Compared (given in weeks from the start)	Group A	Group B	Group C
0 and 4	($\chi^2=0{\cdot}00$ $P=1$)	($\chi^2=0{\cdot}00$ $P=1$)	($\chi^2=0{\cdot}00$ $P=1$)
0 and 8	$\chi^2=0{\cdot}07$ $P>0{\cdot}70$	($\chi^2=0{\cdot}00$ $P=1$)	$\chi^2=0{\cdot}00$ $P=1$
4 and 8	$\chi^2=0{\cdot}07$ $P>0{\cdot}70$	($\chi^2=0{\cdot}00$ $P=1$)	$\chi^2=0{\cdot}00$ $P=1$
8 and 12	($\chi^2=0{\cdot}00$ $P=1$)	$\chi^2=0{\cdot}58$ $P>0{\cdot}30$	($\chi^2=0{\cdot}00$ $P=1$)
8 and 16	$\chi^2=0{\cdot}07$ $P>0{\cdot}70$	$\chi^2=2{\cdot}36$ $P<0{\cdot}20$	($\chi^2=0{\cdot}00$ $P=1$)
12 and 16	$\chi^2=0{\cdot}26$ $P>0{\cdot}50$	$\chi^2=0{\cdot}28$ $P>0{\cdot}50$	$\chi^2=0{\cdot}00$ $P=1$
8 and 20	$\chi^2=0{\cdot}26$ $P>0{\cdot}50$	$\chi^2=4{\cdot}27$ $P<0{\cdot}05$*	($\chi^2=0{\cdot}71$ $P>0{\cdot}30$)
12 and 20	$\chi^2=0{\cdot}58$ $P>0{\cdot}30$	$\chi^2=1{\cdot}15$ $P>0{\cdot}20$	($\chi^2=0{\cdot}33$ $P>0{\cdot}50$)
8 and 24	$\chi^2=0{\cdot}26$ $P>0{\cdot}50$	$\chi^2=1{\cdot}00$ $P>0{\cdot}30$	($\chi^2=0{\cdot}31$ $P>0{\cdot}50$)
16 and 24	$\chi^2=0{\cdot}00$ $P=1$	($\chi^2=0{\cdot}07$ $P>0{\cdot}70$)	($\chi^2=0{\cdot}31$ $P>0{\cdot}50$)

* indicates statistical significance beyond the 5 per cent. level.

If the groups having active drugs are compared with the control group, as they are in many drug trials, the following observations may be made. During the initial four weeks on the active drugs, when the patients were having 75 mg. daily, the group which received pecazine (group A) remained no better than group C, whereas the group which received chlorpromazine (group B) improved relatively to group C. The latter difference was not significant statistically. After a further four weeks on the active drugs (225 mg. daily), the group receiving pecazine had improved, although it was not significantly better than group C. The group receiving chlorpromazine had improved further and was now significantly better than group C ($P<0{\cdot}02$).

During the last eight weeks of the investigation, when the active drugs had been changed round, groups A and B were significantly better than group C.

This method of analysis involves the danger of comparing actively treated groups with a control group which is deteriorating spuriously, as in this case. A better method is to allow each patient to act as her own control. This is permissible in chronic illness, when a fairly stable condition has been reached (Herdan, 1955). It is still desirable to retain a control group as an additional safeguard. Sharp changes unconnected with the drugs under trial may thereby be revealed.

If analysed from this point of view, group A improved slightly whilst on pecazine and chlorpromazine, but at no time did the change from the 8-week level approach significance.

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Group B improved during the period when the patients received chlorpromazine, though not significantly. Significance was reached during the subsequent four weeks on pecazine ($P<0\cdot05$), although this was followed by a decline during the final four weeks on pecazine.

The three groups showed no statistically significant change in thought disorder or mental tension during the investigation.

The reliability of the rating scale was tested. The coefficient of correlation between the scores awarded initially by the two sisters on each ward varied from 0·534 to 0·628. The repeat reliability, as measured by the scores awarded by each sister initially and after four weeks, gave values of r ranging from 0·583 to 0·835.

Side-Effects and Complications

In group A, more patients gained weight whilst on pecazine than had done so during a control period of the same length (8 weeks). The difference was not significant ($\chi^2=1\cdot94$, $P>0\cdot10$).

In the case of group B, more patients gained weight whilst on chlorpromazine than during the corresponding control period. The difference was highly significant ($\chi^2=7\cdot67$, $P<0\cdot01$).

Table V

Side-Effects and Complications

In each case, the number of patients is given

Side-Effect or Complication	Chlorpromazine (61 patients for 8 weeks)	Pecazine (62 patients for 8 weeks)	Placebo (30 patients for 16 weeks)
Parkinsonism	0	1	0
Grand mal attacks in patients with no previous history	2	0	0
Drowsiness	2	2	0
Tachycardia	2	0	0
Orthostatic collapse	1	0	0
Dizziness	2	1	0
Thirst	0	1	0
Vomiting	0	2	1
Constipation	0	1	0
Diarrhoea	1	7	4
Haematemesis	0	1	0
Skin rash	2	1	0
Erythema solare	2	1	0
Oedema	0	2	0
Difficulty in accommodation	1	2	0
Acute glaucoma	1*	1*	0
Agranulocytosis	0	1	0
Sub-clinical jaundice	1	0	0
Pyrexia	0	0	1

* The same patient.

The only serious complication encountered was one case of agranulocytosis. This occurred in a 41-year-old woman on the 47th day of pecazine. The patient complained of a sore throat at this time. She was apyrexial. The leucocyte count was 1,350/c.mm. (neutrophils 202, Stab cells 14, eosinophils 27, lymphocytes 1,026, monocytes 81 per c.mm.). Pecazine was stopped and penicillin started. Next day a sternal puncture was performed, and the count suggested the relatively benign maturation type of agranulocytosis. Thus there

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were 9 per cent. of premyelocytes and 6 per cent. of myeloblasts. By the 50th day, the leucocyte count had sunk to 925/c.mm. (neutrophils 65/c.mm.). Injection of nucleotides, 10 ml. four times daily, was commenced. The blood picture improved. Injection of nucleotides was stopped on the 58th day and penicillin on the 65th day. The patient made a good recovery. She was given no further phenothiazine medication.

Discussion

The group receiving chlorpromazine improved and was significantly better than the control group after eight weeks on the drug. The group which received pecazine improved, but was not significantly better than the control group. Pecazine and chlorpromazine thereafter were seen respectively to maintain and produce results which were significantly better than those obtained with the control group. These results were similar to those of other workers (Thorpe and Baker, 1956; Jones, unpublished).

If each patient was allowed to act as her own control, the results with chlorpromazine were very much less impressive than those obtained by other workers (Vaughan, Leiberman and Cook, 1955; Thorpe and Baker, 1956; Jones, unpublished; Shepherd and Watt, 1956; Abrams, 1958).

Moreover of the 61 patients who received chlorpromazine for eight weeks, only 14 patients improved by more than 3 points on the rating scale (maximum possible score 18). Seven of these patients showed scores which were virtually as labile during the control period, and they can probably be discounted. Of the 62 patients who received pecazine only 2 patients improved by more than 3 points whilst on pecazine, if those with labile scores during the control period are eliminated. An improvement of 3 points on the rating scale represents a very meagre social gain. The time was admittedly short, but 7 patients improved by more than 3 points in a series of 61 does not suggest that chlorpromazine is a treatment of wide application in chronic schizophrenia. In this connection it is interesting to note that, at the time of writing, some three years after the investigation here described, 51 of these 61 patients are still in hospital. No less than 40 of them are on one or other of the phenothiazine drugs.

It would seem that the use of these drugs is becoming excessive in chronic psychiatric wards. They should only be continued where clear improvement has occurred. Many chronic schizophrenic patients have benefited greatly from ataractic drugs, but many others have not. These drugs appear to have replaced paraldehyde and the barbiturates as a means of allaying the anxieties of the staff.

These results give no support to the conclusions of Baker and Thorpe (1957), who stated that sweet-tasting placebos might improve deteriorated, psychotic patients by improving the personal relationships between nurses and patients. In the present trial the initial placebo tablet was sweet-tasting.

Summary

The efficacy of chlorpromazine was compared with that of pecazine. A double-blind, controlled trial was carried out on 92 female patients, the whole schizophrenic population of under sixty years of age on three chronic psychiatric wards. The patients were divided into three groups and assessed every four weeks by a modification of the Albany Behavioural Rating Scale (Shatin and Freed, 1955). After eight weeks on the drugs, the group which had had chlorpromazine was significantly better than the control group. The group which

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had had pecazine was better than the control group, but not significantly so. A better method is to allow each patient to act as her own control. Analysed from this point of view, group A showed only slight improvement whilst receiving pecazine and chlorpromazine in turn. Significance was not approached. Group B showed improvement whilst on chlorpromazine, significance being approached after eight weeks on the drug. Improvement continued and significance was reached during the first four weeks on pecazine, immediately after the chlorpromazine, the group deteriorating once more during the final four weeks on pecazine. There was no significant change in the scores for mental tension or thought disorder during the investigation. The results with chlorpromazine are less impressive than those of most other workers. Only 7 out of 61 patients showed an improvement of over 3 points (out of a possible 18) whilst on chlorpromazine. It is suggested that phenothiazine derivatives are used too frequently with chronic schizophrenic patients. A case of agranulocytosis occurring with pecazine is described.

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