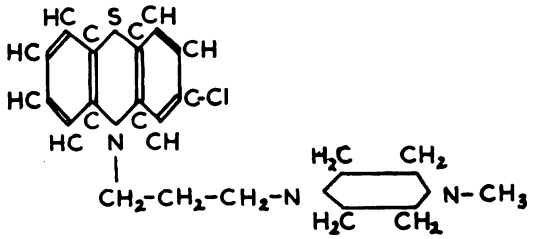
A CLINICAL TRIAL COMPARING PROCHLORPERAZINE ("STEMETIL") WITH CHLORPROMAZINE ("LARGACTIL") IN THE TREATMENT OF CHRONIC PSYCHOTIC PATIENTS

By

G. A. DRANSFIELD, M.B., B.S., D.P.M.
Assistant Psychiatrist
Warley Hospital, Brentwood, Essex

CHLORPROMAZINE ("Largactil") was introduced to this country some five years ago, and since that time a considerable number of reports on its clinical efficacy have appeared, including Anton-Stephens (1954) and Garmany *et al.* (1954). There is now general agreement that it is a useful form of treatment in chronic schizophrenia, especially for the aggressive, disturbed patient (Salisbury and Hare, 1957). More recently another phenothiazine derivative, incorporating a piperazine ring in the side chain, has been produced. This substance is Prochlorperazine ("Stemetil"), the full title of which is 2-chloro-10-(3-4′-methyl-1′-piperazinopropyl)-phenothiazine, the structural formula being:



It is prepared for use in the form of its dimaleate salt, which contains 62 per cent. of the active base. This compound has shown useful clinical activity in the treatment of Ménière's syndrome and migraine and as an anti-emetic, the last mainly in France. Pharmacologically, prochlorperazine has been shown to have an anti-emetic action, as measured against the action of apomorphine, approximately four times as powerful as that of chlorpromazine. On the other hand prochlorperazine has been found to be two or four times less powerful than chlorpromazine in its potentiating effect on general anaesthetics, hypnotics and analgesics, such as ether, hexobarbitone, and morphine. Prochlorperazine has been used in psychiatry in the United States (Vischer, 1957), and France (Borel *et al.*, 1957; Brousselle *et al.*, 1957; Lecompte *et al.*, 1957), but no reports on its psychiatric applications had, at the time of writing, yet been published in this country*. As the use of chlorpromazine is so widespread in psychiatric practice, and few, if any, psychiatrists have not by now reached

* An article on "A Clinical Trial of Stemetil" by H. B. Milne and F. Berliner appeared in the *Journal* for July 1958.

a conclusion as to its efficacy, it was felt that the most practical assessment of the value of prochlorperazine in psychiatry would be a clinical comparison of the two drugs. The trial now described is an attempt to compare the efficacy of prochlorperazine ("Stemetil") with that of chlorpromazine ("Largactil"), in the treatment of aggressive, disturbed, chronic psychotic male patients. In addition, a comparison of the incidence of side effects of the two drugs is made.

Fifty aggressive, disturbed, chronic male psychotic patients (forty-six schizophrenic, two G.P.I., and two M.D.) were selected for the trial on the grounds that they were the most aggressive and disturbed male patients in the hospital who were not at that time undergoing or had not recently undergone some other form of treatment. Two had previously been leucotomized. The patients had all been in hospital for a number of years, the most recent for five years, the longest for fifty-one years, the average being 19·5 years. All were regarded as of poor prognosis. The ages varied from twenty-seven years to seventy-six years with an average of 50·3. An initial assessment of each patient was made in regard to aggression, disturbance, deterioration, and apathy, on a four-point scale (severe, moderate, slight, none), and also for aptitude for social activity and occupation, again on a four-point scale (good, moderate, slight, none). The gradings used were defined as follows:

1. *Aggression*

   Severe—frequent physical attacks with minor effects, or occasional physical attacks with serious effects.
   Moderate—occasional physical attacks with minor effects, or frequent verbal abuse.
   Slight—occasional verbal abuse.

2. *Disturbance*

   Severe—frequently extremely noisy and/or frequently requires nursing in side room.
   Moderate—occasionally noisy and/or occasionally requires nursing in side room.
   Slight—noisy at times but not requiring nursing in side room.

3. *Deterioration*

   Severe—needs frequent supervision of toilet and/or appearance.
   Moderate—needs regular supervision of appearance.
   Slight—needs occasional supervision of appearance.

4. *Apathy*

   Severe—no response to efforts to stimulate interest.
   Moderate—shows some response to efforts to stimulate interest, but this is required frequently.
   Slight—requires only occasional stimulation of interest.

5. *Aptitude for Social Activity*

   Good—attends social activities and participates spontaneously.
   Moderate—attends social activities spontaneously but does not participate.
   Slight—needs encouragement to attend social activities and does not participate.

6. *Aptitude for Occupation*

Good—pursues occupation without supervision.
Moderate—pursues occupation but needs occasional supervision.
Slight—needs constant supervision to remain occupied.

These assessments were made on the basis of the Charge Nurse's estimate taken in conjunction with the author's evaluation. The patients were then divided into two groups, paired as far as possible for aggression, disturbance, deterioration, age, ward, amount of E.C.T. previously given, apathy, aptitude for social activity, and occupation. The first six of these items were regarded as the most important for the purpose of pairing. The amount of E.C.T. previously given was recorded because it had been suggested that there was a positive correlation between the amount of E.C.T. previously given, and the incidence of Parkinsonism and bizarre positions and movements (as described by French and American workers), and it was proposed to test this hypothesis.

The two groups were given one inert tablet t.d.s. for two weeks in order to provide control data establishing the essential similarity of the two groups.

The patients were seen at weekly intervals throughout the trial by the author, and overall progress on a purely clinical basis was noted on a four-point scale (much improvement, moderate improvement, slight improvement, no change) in addition to the noting of progress in the individual items as in the initial assessment.

In the third week one group was given prochlorperazine 12·5 mg. t.d.s. (37·5 mg. daily) whilst the other group was given chlorpromazine 25 mg. t.d.s. (75 mg. daily). The inert tablets and those containing prochlorperazine 12·5 mg. as well as those containing chlorpromazine 25 mg. were all identical, and only the author and the Chief Pharmacist were aware of the design of the experiment. The dosage was increased in each group by one tablet t.d.s. each week, except where there were clinical indications for the dose to be maintained at the previous level, reduced, or for the drug to be withdrawn completely. The maximum dosage in each group was four tablets t.d.s., which in the case of prochlorperazine represented 150 mg. daily, and in the case of chlorpromazine, 300 mg. daily, and was continued for five weeks. Side effects were noted as they occurred, and the numbers in each group which had to be withdrawn during the trial were recorded. At the end of the trial, a final assessment was made in each case, and a decision was taken as to whether clinical improvement warranted continuation of the drug. Records were kept of this decision and the dosage in each case.

Results

The clinical progress made in each group when the inert tablets were being given is shown by the figures in Table I.

Table I

Progress on Inert Tablets	Pre-prochlorperazine Group	Pre-chlorpromazine Group
Much improved	0	0
Moderately improved	0	0
Slightly improved	2	2
No change	23	23

https://doi.org/10.1192/bjp.104.437.1183 Published online by Cambridge University Press

The progress made when the active drugs were being given is shown in Table II.

TABLE II

Progress on Active Tablets	Prochlorperazine Group	Chlorpromazine Group
Much improved	1	1
Moderately improved	4	1
Slightly improved	11	17
No change	9	6

In neither case is there any statistically significant difference between the two groups in regard to clinical progress.

The incidence of side effects is given in Table III. The totals (excluding drowsiness) of eleven for the prochlorperazine group and four for the chlorpromazine group show a difference significant at the 5 per cent. level. If Parkinsonism alone is taken, then the difference in the incidence in the two groups is significant at the 0·1 per cent. level.

TABLE III

Side Effects	Prochlorperazine Group	Chlorpromazine Group
i. *Parkinsonism*		
Moderate	8	0
Slight	3	1
Total	11	1
ii. *Bizarre Positions*		
Total	1	0
iii. *Jaundice*		
Total	0	1
iv. *Syncopal Attacks*		
Moderate	0	1
Slight	0	1
Total	0	2
v. *Abdominal Distension*		
Total	1	0
vi. *Drowsiness*		
Severe	2	1
Moderate	4	3
Slight	11	10
Total	17 (68%)	14 (56%)
Totals in each group showing side effects other than drowsiness	11	4

In the group receiving prochlorperazine, one patient took up bizarre positions for a short time (not observed by the author) which seem to have been similar to those described by other workers. The symptom passed off spontaneously the dosage being maintained at 75 mg. daily. The same patient later developed Parkinsonism. The earliest feature of Parkinsonism most commonly noted was the immobility of the face, with resulting loss of expression, and occurred at dosages of prochlorperazine ranging from 75 to 150 mg. daily.

Shuffling gait was marked in some cases and cog-wheel rigidity was always present. Excess salivation with dribbling was rare. Tremor was marked only in a few cases, and when present was finer than is usually seen in Parkinsonism. In one of the cases showing Parkinsonism, unilateral rigidity of the flexibilitas cerea type occurred. The Parkinsonism in most cases responded to promethazine ("Phenergan") another phenothiazine derivative, in doses of 10 mg. t.d.s., but in several cases only partially. The effect of 10 mg. t.d.s. was found to be much superior to that of 25 mg. b.d. Another patient receiving prochlorperazine developed abdominal distension, which a consultant surgeon considered likely to be due to the drug. This symptom, which had followed the onset of Parkinsonism, did not respond to promethazine but subsided slowly on withdrawal of the prochlorperazine.

The case showing Parkinsonism whilst receiving chlorpromazine was not relieved by promethazine. The case of jaundice in the chlorpromazine group was of a moderately severe type with liver damage which was demonstrated by means of liver function tests (alkaline phosphatase 25 units per 100 ml., Van den Berg 3·0 mg./100 ml., serum protein 7·0G/100 ml., albumin 6·4 G and globulin 0·6 G.). One of the two cases of syncope in the chlorpromazine group was of minor degree and the other more severe, being accompanied by marked giddiness, necessitating withdrawal of the drug. A transient type of drowsiness was seen in a fairly large proportion of both groups, but in no way affected clinical progress. There was in fact no statistically significant difference in the incidence in the two groups. In two of the prochlorperazine group a moderate degree of restlessness occurred, although in neither case was it a disturbing feature. In one case it was transient, but in the other, who had some years previously been leucotomized, it proved more persistent.

TABLE IV

		Prochlorperazine Group	Chlorpromazine Group
Numbers withdrawn during trial		6	2
Numbers continued at end of trial		11	17
Dosages:			
Prochlorperazine group:	Continued at 150 mg. daily		9
	Continued at 112·5 mg. daily		1
	Continued at 75 mg. daily		1
Chlorpromazine group:	Continued at 300 mg. daily		16
	Continued at 150 mg. daily		1

From Table IV it will be seen that the numbers withdrawn from the trial are six and two, for the prochlorperazine and chlorpromazine groups respectively. These figures show a difference only marginally significant (at the 20 per cent. level). At the end of the trial, when each patient was considered with regard to continuation of the drug, the decisions and dosages were as shown in Table IV. The dosage of prochlorperazine varied from 75 to 150 mg. daily, whilst that of chlorpromazine varied from 150 to 300 mg. daily.

DISCUSSION

The results of treatment with prochlorperazine would not, in the author's opinion, on the evidence obtained in this trial, justify the substitution of this drug for chlorpromazine, in the treatment of the aggressive, disturbed, chronic psychotic (especially schizophrenic) male patient. Particularly is this so in view

of the fact that there would seem a much greater expectation of side effects, especially Parkinsonism, with prochlorperazine.

There has been some suggestion amongst American workers that the best clinical results are obtained when Parkinsonism occurs. This hypothesis is not supported by the findings in this trial, the relevant figures being given in Table V.

TABLE V

Clinical Progress of Patients in Prochlorperazine Group Who Developed Parkinsonism (11) *Compared with Those Who did not* (14)

	11 Patients Who Developed Parkinsonism	14 Patients Who *did not* Develop Parkinsonism
Much improved	0	1
Moderately improved	2	2
Slightly improved	5	6
No change	4	5

It has also been suggested that the incidence of Parkinsonism might show a positive correlation with the amount of E.C.T. previously given. This hypothesis is not supported by the findings as shown in Table VI. In regard to these claims however, larger series would be required to allow definite conclusions to be drawn.

TABLE VI

Incidence of Parkinsonism in Prochlorperazine Group According to Groupings on Basis of Number of E.C.T. Previously Given

	No E.C.T.	1–10	Over 10
Numbers of patients in each group	15	6	4
Parkinsonism:			
Moderate	3	4	1
Slight	3	0	0

On a purely clinical basis, reducing the dose of prochlorperazine when Parkinsonism occurred did not result in the improvement claimed by some American workers. Abdominal distension has been associated with prochlorperazine administration in the experience of French workers, and was considered by Delay, Deniker, Green and Mordret (1957), to be almost certainly due to spasm of the diaphragm. The clinical impression gained as a result of the weekly interviews during the trial, was that the two drugs were equally effective in the treatment of aggression, disturbance, and deterioration. In the treatment of the apathy found in the chronic schizophrenic patient, it was noted that chlorpromazine seemed very much superior to prochlorperazine. This effect of chlorpromazine on apathy was noted by Salisbury and Hare (1957).

From the experience gained in this trial it would seem that in psychiatric practice the dosage of prochlorperazine would be about half that of chlorpromazine. Table IV shows the doses given when the drugs were continued. The side effects of prochlorperazine, including Parkinsonism, which occurred in this trial, have been described and discussed by Delay *et al.* (1957), in a number of papers.

As originally planned it was intended that the trial should be over a longer period, and with reversal of the drugs received by the two groups. The high incidence of side effects in the prochlorperazine group led however to the curtailment of the trial.

Summary

An outline is given of the derivation, formula, and known pharmacology of prochlorperazine and of the use of chlorpromazine in the treatment of the aggressive, disturbed chronic psychotic patient. Fifty of this type of patient (mainly schizophrenic) were assessed and divided into paired groups. Inert tablets were given for two weeks, followed by increasing doses of prochlorperazine to one group and chlorpromazine to the other. The maximum doses were 150 mg. daily and 300 mg. daily respectively given for five weeks. Patients were interviewed at weekly intervals and a final assessment made. Side effects are described, especially marked being Parkinsonism in the prochlorperazine group.

The conclusion is reached that there is no advantage on clinical grounds in the use of prochlorperazine as opposed to chlorpromazine in the treatment of the aggressive disturbed chronic male psychotic, and that the greater incidence of side effects seems a contra-indication to its use in treating this type of patient. The dosage level of prochlorperazine would seem to be about half that of chlorpromazine in psychiatric practice.

Acknowledgments

I am indebted to Sir Geoffrey Nightingale, Bart., Physician Superintendent, Warley Hospital, for permission to conduct the trial; to Dr. J. Harper, of May & Baker Ltd., for advice and the provision of matching tablets; to Mrs. C. Williams, Senior Psychologist, for her help in the statistical evaluations; and to Mr. H. Layer, Chief Pharmacist, and the nursing staff for their interest and help.

References

Anton-Stephens, D., *J. Ment. Sci.*, 1954, **100,** 543.
Borel, Coiffer, B., and Dechosal, F., *Ann. Méd.-Psychol.*, 1957, **115,** 526.
Brouselle, P., *et al.*, *Presse Médicale*, 1957, **65,** 1628.
Delay, J., Deniker, P., Fourment, J., Green, A., and Ropert, —., *Ann. Méd.-Psychol.*, 1957, **115,** 510.
Idem, Deniker, P., Green, A., and Mordret, M., *Presse Medicale*, 1957, **65,** 1771.
Idem, Deniker, P., and Thuiller, J., *Ann. Méd.-Psychol.*, 1957, **115,** 506.
Garmany, G., May, A. R., and Folkson, A., *Brit. med. J.*, 1954, *ii*, 439.
Lecompte, G., Certoux, A., and Garrabe, J., *Ann. Méd.-Psychol.*, 1957, **115,** 922.
Salisbury, Barbara J., and Hare, E. H., *J. Ment. Sci.*, 1957, **103,** 830.
Vischer, T. J., *New Engl. J. Med.*, 1957, **256,** 26.