AN EVALUATION OF THE DOUBLE-BLIND TRIAL AS A METHOD OF ASSESSING PROMAZINE ("SPARINE") IN THE TREATMENT OF CHRONIC PSYCHOTIC PATIENTS

By

M. A. HARGREAVES, M.B., B.S., D.P.M.*

Warley Hospital, Essex

MOST people now accept the value of the tranquillizer or ataractic drugs, which play a major role in individual therapeutic results and in environmental change in major psychiatric hospitals. Numerous surveys have stressed the influence of these drugs and they have recently been confirmed by Brill and Patton (1959) in a twelve-year review of mental hospitals capable of dealing with over ninety-three thousand patients. As the number of patients on tranquillizing drugs (mainly chlorpromazine) increased, so the patients requiring restraint decreased, the discharges increased and the re-admissions decreased: a direct cause and effect relationship was established.

Few workers dealing with chronic psychiatric patients would like to return to the conditions before the introduction of the tranquillizers, and it may well become as unlikely for a medical student to see a chronic psychotic not under phenothiazine therapy as it is now for him to see a lobar pneumonia run its classical course.

Unfortunately chlorpromazine, which was the first of the phenothiazine tranquillizers and is probably still the most widely used, has a number of side-effects which may not only affect the patients but also the nursing staff. In this hospital a number of nurses developed proven skin sensitivity to chlorpromazine and it was decided to second them to a ward where this drug would not be used. The population of this ward were female chronic schizophrenics who were therefore denied treatment with chlorpromazine and were thus a virgin field for assessing other phenothiazines, as long as cross-sensitivity with chlorpromazine did not exist. This situation seemed to be ideal for conducting a clinical trial, as it would give a much more realistic picture of a drug's action than the trials commonly conducted nowadays where new drugs are given to groups of patients who have proved resistant to previous regimes with similar drugs.

When promazine ("Sparine") was introduced, preliminary trials demonstrated that nurses could handle the drug without recurrence of their chlorpromazine-induced skin sensitivity. Similar findings have been reported by Mitchell (1956), Fox (1956) and Morgan and Van Leent (1958). Patients have also been able to tolerate promazine although allergic manifestations occurred with chlorpromazine (Graffagnino *et al.*, 1956; Usdin, 1956). Cross-sensitivity is therefore not an important feature between these two phenothiazines, although occasional cases of allergic reactions to promazine have been observed (Azima and Durost, 1957; Ayd, 1957). It has been suggested

* Present address: United Birmingham Hospitals, Queen Elizabeth Hospital, Birmingham.

by Goodman and Cahn (1959) that the chlorine atom on the phenothiazine nucleus accounts for the skin reactions produced by chlorpromazine and drugs with a similar structure.

As promazine appeared to be acceptable to the skin-sensitive nursing staff and as conflicting results had been reported on its use in chronic psychotics, it was decided to conduct a pilot trial as a possible preliminary to a larger double-blind study.

Pilot Trial

Six of the most aggressive, and unco-operative patients who sadly neglected their personal hygiene and needed constant supervision and attention were selected for the pilot trial. The average age was 62 years and the average length of time in hospital was 31 years.

All were given promazine in the form of a concentrated solution which had been made into a pleasant elixir by the hospital pharmacist. Treatment was started at a dosage level of 300 mg. promazine daily and was increased slowly until beneficial or toxic effects appeared.

In all cases promazine was eventually given at 900 mg. daily and continued at that level for two to three months. No toxic effects were observed at this dosage level and the results were dramatic. Four out of the six patients improved sufficiently to be able to help with ward work, all lost their aggressiveness and destructiveness and became very much more co-operative so that they were easier to manage with minimum supervision. It was noticeable, however, that optimum results were not usually apparent until after six weeks' therapy.

This pilot trial was, of course, uncontrolled, but the results were sufficiently encouraging to proceed with a fully controlled double-blind trial using the dosages which had been found effective but safe.

Method

The ward to which the chlorpromazine-sensitive nurses were seconded and which was used for this trial accommodated sixty-four female patients of whom fifty were selected. All were chronic schizophrenics and had been in hospital for periods ranging from 2 to 41 years, the average duration of stay being 24 years. Ages varied from 30–70 years, with an average of 56 years. Of this population, forty-three completed the six months' trial, two were withdrawn because of side-effects and five for reasons beyond our control.

The medication used was promazine in solution at a concentration of 50 mg. per ml. and an inert solution with similar properties as far as taste and appearance were concerned. Both were formulated into palatable flavoured elixirs by the hospital pharmacist, who also held the key of the double-blind trial in an attempt to eliminate bias from the observations of the medical and nursing staff.

The trial was conducted over a six-months' period with each patient receiving promazine for three months and the identical placebo preparation for the other three months. Half of the patients started with promazine and half with placebo; the selection was made according to random tables.

In order to make the trial as realistic as possible and to mimic conditions of treatment in normal circumstances a variation in dosage was allowed in the design. Dosage started at 300 mg. daily in three divided doses and was increased within nine days to 900 mg. daily if permitted by the condition of the patient. Similarly the dose could be reduced if side-effects occurred. It was felt

that this device would reduce the shortcomings of the fixed-dose clinical trial which so often bears no relationship to the normal usage of drugs in clinical practice.

Assessments were made on charts as shown below (Fig. 1) with the senior nursing staff reviewing the patients daily and recording their findings weekly, as follows:

Much worse	0
Worse	1
No change	2
Good	3
Very good	4

The total scores for each patient on each assessment were then made omitting the first four weeks of each treatment because of the delay in effect mentioned earlier.

Results

During both halves of the trial a proportion of the patients receiving the active preparation could be distinguished from those on the placebo but this was more marked in the first three months when there was no continuing effect of the promazine during the placebo period.

It was noticeable that this difference between patients on active and patients on inert medication could only be made when the maximum dosage had been reached and when the drugs had been given for about six weeks. It was therefore confirmed early in the trial that there was a latent period before the drug's action was exerted, as had been shown earlier in the pilot study.

These observations may have interfered with the "blindness" of the double-blind trial but this is to some extent unavoidable with any potent treatment and really makes the use of the double-blind technique unnecessary for the evaluation of the drug.

In general about half of the original fifty patients improved on promazine and made sufficient progress to justify continuation of the drug. Apart from the specific factors listed in Figure 1, the overall improvement made the patients more manageable and accessible. This was particularly apparent from a nursing point of view and was illustrated by the ability of 28 of the patients to go on a day's outing organized by the hospital. The majority of these patients were schizophrenics of about 30 years standing and any similar outing could not possibly have been undertaken in the past. Despite this, the sister who accompanied them reported that they were all neatly dressed, behaved themselves extremely well and showed no signs of their previous degraded habits.

This improvement in so many patients made a great alteration in the ward generally so that untreated patients indirectly derived benefit.

Just as beneficial effects did not show themselves for four to six weeks on promazine, so these improvements continued for many weeks after the withdrawal of the active drug.

In addition to the day-to-day observations made on the patients which were recorded by the nursing staff, who put a cross on the chart in the appropriate square, a final assessment was made by the charge nurse of the condition and progress of the patient.

FIGURE 1

Name: ..... Age: ..... No. in Trial: .....
Ward: ..... Hospital No. .....
Clinical Condition: .....

(Please put a cross in the approp. square in each section.)	General Aggressive Behaviour					Over-Activity					Noisiness					Self-care					Drugs other than Susp. needed to control the patient
Date	Very bad	Bad	Average	Good	Very good	Very bad	Bad	Average	Good	Very good	Very bad	Bad	Average	Good	Very good	Very bad	Bad	Average	Good	Very good	
Initial Observations																					
	Much worse	Worse	No change	Better	Much better	Much worse	Worse	No change	Better	Much better	Much worse	Worse	No change	Better	Much better	Much worse	Worse	No change	Better	Much better	

Reverse of Proforma

DEFINITION OF TERMS:

General Aggressive Behaviour:

Very bad: Consistently aggressive, and impulsive towards other patients. Spiteful and resistive to nursing staff.
Bad: Aggressive and evasive most of the time, resisting efforts of nursing staff.
Average: Resenting interference and occasionally aggressive.
Good: Co-operative most of the time but occasionally resistant to supervision.
Very good: Never resistant or aggressive with co-operation practically all the time.

Over-Activity:

Very bad: Always destructive, tearing clothes and papers. Filling pockets with all sorts of rubbish. Talking and laughing to themselves. Requiring toilet supervision.
Bad: Frequently doing above.
Average: Sometimes shows useless activity.
Good: Quiet for most of the day with occasional bouts of over-activity.
Very good: Practically always quiet.

Noisiness: Self-explanatory.

Self-Care:

Very bad: Requiring all nursing attention, including washing, dressing and hand feeding. Is also doubly incontinent.
Bad: Remedies grosser defects such as spilt food on clothing, but no other efforts at self-care.
Average: On the whole uninterested in clothes or appearance, but fairly clean.
Good: Improves appearance with cosmetics, but will not wash or change clothing.
Very good: Takes fairly good care over personal appearance.

The total scores of the patients over the six-month period of the trial from the day-to-day assessments are given below, in Table I.

TABLE I

I. Sparine Given for First Three Months and Placebo for Latter Three Months

Case Number	General Aggressive Behaviour		Over-Activity		Noisiness		Self-Care	
	Sparine	Placebo	Sparine	Placebo	Sparine	Placebo	Sparine	Placebo
1 ..	11	23	11	23	24	24	8	18
2 ..	26	32	26	29	18	32	17	32
3 ..	16	16	16	16	16	24	26	24
5 ..	18	2	23	8	23	32	23	18
6 ..	16	31	20	31	20	31	17	31
8 ..	32	32	32	32	32	32	28	32
9 ..	14	31	14	25	14	31	21	31
12 ..	16	16	24	24	24	24	24	24
15 ..	22	32	22	32	20	18	22	32
18 ..	23	32	30	32	30	32	30	32
19 ..	21	Nil	22	16	22	8	22	24
21 ..	23	32	23	32	19	32	14	16
24 ..	32	8	32	13	32	32	32	32
25 ..	2	Nil	1	Nil	4	Nil	5	Nil
30 ..	32	32	32	32	32	32	32	32
34 ..	26	32	26	32	27	31	32	32
35 ..	28	32	28	32	28	32	28	32
37 ..	12	Nil	12	Nil	14	7	13	Nil
40 ..	32	11	32	25	32	32	32	24
46 ..	17	16	16	16	16	16	16	13
48 ..	Nil	16	16	16	Nil	16	16	16
50 ..	29	24	31	24	25	24	24	24
Totals ..	448	450	489	490	472	542	482	519

II. Placebo Given for the First Three Months and Sparine for the Latter Three Months

4 ..	32	32	32	32	32	32	32	32
7 ..	32	32	32	32	32	31	32	32
10 ..	25	20	24	32	21	24	26	10
11 ..	16	32	16	16	16	16	16	23
14 ..	16	15	16	16	16	16	16	16
16 ..	32	26	32	32	32	32	32	32
17 ..	21	2	21	2	29	2	20	2
20 ..	11	24	4	6	16	16	14	10
22 ..	26	24	26	24	26	24	26	32
23 ..	21	32	15	32	22	32	32	32
29 ..	5	2	6	Nil	3	4	10	Nil
31 ..	16	24	16	24	16	24	16	23
32 ..	22	32	20	32	20	32	26	32
33 ..	18	32	18	32	18	32	18	32
38 ..	32	32	32	31	32	31	32	29
41 ..	24	31	22	31	22	32	22	24
42 ..	23	8	23	18	23	9	18	4
43 ..	2	1	2	1	2	1	1	1
44 ..	31	26	31	22	31	29	32	32
45 ..	16	27	16	27	16	27	24	31
47 ..	19	24	19	24	19	24	22	20
Totals ..	440	478	423	466	444	470	467	449

https://doi.org/10.1192/bjp.107.448.529 Published online by Cambridge University Press

It will be seen from this that there is no significant difference between the scores on Sparine and the scores on the placebo. The total scores for all patients are as follows:

Sparine 3,754 Placebo 3,775

The natural assumption from this is that Sparine medication produced no improvement in the patients, a conclusion which is completely contradicted by the overall assessment of the ward atmosphere and the opinion of the experienced nursing staff. In fact the ward changed from a closed one with degraded patients in special clothing and needing almost constant supervision to an open ward with the majority of the patients helping in ward tasks, going to occupational therapy, feeding and dressing themselves and with a very marked decrease in incontinence and unclean habits.

The apparent paradox is further stressed by study of the individual cases, and comparison of the charge nurse's report with the total daily score taken during the trial. The following are typical illustrations:

G.B., aged 47, admitted 1941

Charge nurse's report:

Before trial. Very aggressive epileptic, makes constant clicking noises with mouth and cannot hold a conversation. Stays in side room in strong clothes and is unoccupiable. Has the most degraded habits (eating faeces) and is always noisy and untidy.

Since trial, and continued on Sparine suspension. Now goes to occupational therapy where the therapist commends her neat sewing. Understands orders, watches TV, goes to the cinema, concerts and church. She is no longer incontinent or dirty but tends to hoard in a paper bag. She has stopped making clicking noises and is really quite a likeable person.

Results from Proforma:

	General Aggressive Behaviour	Over-Activity	Noisiness	Self-Care	Total
Placebo	25	24	21	26	96
Sparine	20	32	24	10	86

E.C.R., aged 65, admitted 1921

Charge Nurse's report:

Before trial. Patient throws everything on the floor and is constantly covering herself with faeces. Solitary, with no emotions, grossly untidy and needs constant supervision.

Since trial, and continued on Sparine suspension. Clean and tidy with much less supervision. No longer incontinent and sleeps quietly in an open dormitory without any of the night sedation needed previously.

Results from Proforma:

	General Aggressive Behaviour	Over-Activity	Noisiness	Self-Care	Total
Placebo	32	32	32	32	128
Sparine	32	31	31	29	123

M.E.B., aged 59, admitted 1933

Charge Nurse's report:

Before trial. A wanderer needing a good deal of supervision and always kept in strong clothes. Too untidy and erratic to do ward tasks and sometimes incontinent. Usually mute and unco-operative.

Since trial, and continued on Sparine suspension. Wears a tidy outfit to all social functions, works well in the kitchen with little supervision, baths and dresses herself and has been given an allowance for cigarettes, etc. She has also been given false teeth, glasses and a perm. She talks sensibly and eats her meals with a knife and fork, which she could not do before. Her visitors had previously stayed away because they were afraid of her, but now come regularly and take her out into the country.

Results from Proforma:

	General Aggressive Behaviour	Over-Activity	Noisiness	Self-Care	Total
Placebo	32	32	32	32	128
Sparine	32	32	32	32	128

E.A.B., aged 72, admitted 1932

Charge Nurse's report:

Before trial. Aggressive, over-active and incapable of conversation. Dirty and untidy with considerable supervision needed.

Since trial, and continued on Sparine tablets. Now seems almost normal. Clean and tidy, works on the ward and goes to church and to the cinema. Needs very little supervision.

Results from Proforma:

	General Aggressive Behaviour	Over-Activity	Noisiness	Self-Care	Total
Placebo	32	29	32	32	125
Sparine	26	26	18	17	87

These illustrative cases are typical of those showing a considerable discrepancy between clinical results and proforma ratings in the formal double-blind trial.

Twenty-eight patients who had improved with Sparine therapy in a clear and undoubted way were reconsidered and analysis of the proforma results showed that, according to the formal trial, four had improved on Sparine, 3 had equal ratings with Sparine and placebo and 7 had apparently improved on the placebo. This confirmed the misleading impression given by the formal trial with its day by day assessments of the patient.

Side-Effects

When on a dosage of 900 mg. Sparine daily thirteen patients showed mild parkinsonian symptoms accompanied by some degree of undue lethargy and retardation. Reduction of dosage to 600 mg. daily retained the clinical benefit and the extra-pyramidal symptoms regressed satisfactorily.

Epileptiform convulsions were noted in six patients but three of these suffered from epilepsy in addition to schizophrenia, and one patient had coincident general paralysis of the insane.

No cases of allergy or skin reactions were noted in either patients or in the nursing staff even though these had previously shown skin sensitivity to chlorpromazine.

Discussion

This assessment of liquid oral Sparine in chronic schizophrenics demonstrated the clinical effectiveness of the phenothiazine in over half of the patients. The improvement in these patients was clear cut and definite and, as a result, the management of these patients was made easier and the atmosphere of the whole ward improved. Many of the patients not included in the trial improved due to the change in their immediate environment.

This improvement in the trial subjects could not be found when the results of a formal double-blind trial were analysed which suggested that there was no significant difference between Sparine and the placebo.

Many criticisms have been levelled at the double-blind controlled trial in the past but, nevertheless, it has become accepted as the method of proving therapeutic efficiency of a drug. In this particular trial an attempt was made to overcome some of the more obvious shortcomings, such as fixed dosage regimes, short-term treatment and no allowance for latent periods of drug action but, even so, the results are clearly unrealistic and bear no relationship to the actual clinical change.

Many factors may have contributed to these contradictory results, including the prolonged benefit noted in the group that were given the placebo in the second half of the trial, which meant that improvement brought about by the active drug was still being recorded in the placebo period. In addition the general improvement in ward atmosphere brought about clinical change that was not directly attributable to the drug being taken. The biggest factor, however, is probably the impossibility of accurately recording change in patients who are being seen every day and who vary within limits at different times during the day. The assessing nurse or doctor cannot give a realistic appraisal of a patient's state on such a day-to-day basis and can only give a worth-while impression of clinical change when the patient's behaviour over a reasonable period is surveyed.

Despite the statisticians' delight in the double-blind trial, it is possible that a more useful idea of therapeutic activity in chronic psychotics is gained by a clinical evaluation after a reasonable period of therapy.

Summary

Due to skin sensitivity of the nursing staff to chlorpromazine, a single ward contained female chronic schizophrenics who had not been treated with phenothiazines.

A pilot trial on six patients showed marked improvement with a liquid preparation of Sparine (promazine hydrochloride) without affecting the allergic state of the nursing staff, so a double-blind trial in a further 50 patients was started. This consisted of three months therapy with Sparine and three months with placebo. Assessments were made daily and at the end of the study.

Fifty-six per cent. of the patients made a clear-cut clinical improvement on Sparine, but this impression was not sustained by the analysis of the results of the double-blind trial.

The possible reasons for this contradictory state of affairs are discussed.

Acknowledgments

I would like to thank Mr. H. W. Layer, Chief Pharmacist, for his tremendous help, the nursing staff for their patient co-operation, and John Wyeth & Brother Limited for supplying the active material.

References

AYD, F. J., *N.Y. St. Med. J.*, 1957, **57**, 1742.
AZIMA, H., and DUROST, H., *Canad. M.A.J.*, 1957, **77**, 671.
BRILL, H., and PATTON, R. E., *Amer. J. Psychiat.*, 1959, **116**, 495.
FOX, V., *Amer. Pract. Dig. Treat.*, 1956, **7**, 1461.
GOODMAN, D., and CAHN, M. M., *J. Invest. Dermatol.*, 1959, **33**, 27.
GRAFFAGNINO, P. N., FREIL, P. B., and ZELLER, W. W., *Conn. St. Med. J.*, 1957, **21**, 1047.
MITCHELL, E. H., *J.A.M.A.*, 1956, **160**, 44.
MORGAN, D. R., and VAN LEENT, J. P., *Med. J. Australia*, 1958, **11**, 696.
USDIN, G. L., *J. Louisiana St. Med. J.*, 1956, **108**, 251.