PHENOTHIAZINE SIDE-EFFECTS

COMPARISON OF TWO MAJOR TRANQUILLIZERS

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IN the six years since Delay and his associates first used chlorpromazine in psychiatry, at least forty-eight separate side-effects have been attributed to the drug. While many of these are minor, and indeed the majority are readily controlled in in-patients, the search for a phenothiazine of therapeutic value equal to or better than chlorpromazine, but with less or no side-effects, is well worth while. In out-patients there are two reasons for taking side-effects seriously. Firstly, they frequently lead to the patient ceasing to take the drug and thus relapse may occur. Secondly, they may be dangerous or even fatal if unreported —for example the signs of agranulocytosis.

We chose to compare chlorpromazine with a relatively new phenothiazine derivative, thioridazine (Melleril or Mellaril, Sandoz). Thioridazine is 3-methylmercapto-10-{2′-[N-methyl-piperidyl-(2″)]-ethyl-(1′)}-phenothiazine, usually provided as the hydrochloride. Chlorpromazine is well established as a therapeutic agent and therefore serves as a good standard for comparison.

The structural formulae of chlorpromazine and thioridazine are shown in Fig. 1 overleaf.

There are three main groups of phenothiazines and they may be described according to the side-chains in each (Hippius and Kanig, 1958).

The first is the dimethyl group, with a propyl side-chain. Chlorpromazine is the most widely used member of this group. The second is the piperazine group, having a piperazinyl propyl side-chain. Typical members are perphenazine ("Trilafon"), prochlorperazine ("Stemetil"), and trifluoperazine ("Stelazine"). The third group has either a piperidyl-methyl or piperidyl-ethyl side-chain. Such a drug is thioridazine.

The piperazine group includes very potent drugs—these have less adrenolytic and anticholinergic activity than the drugs in the dimethyl group, but they produce many and often marked extrapyramidal effects. By substituting a piperidine ring for a piperazine ring there was no increase in potency but the compound appeared to lose both its anti-emetic and its extrapyramidal effects (Kinross-Wright, 1959). One such drug (NP-207) was toxic to the retina. Replacing the halogen atom at the 2-position by a sulphur-containing radical

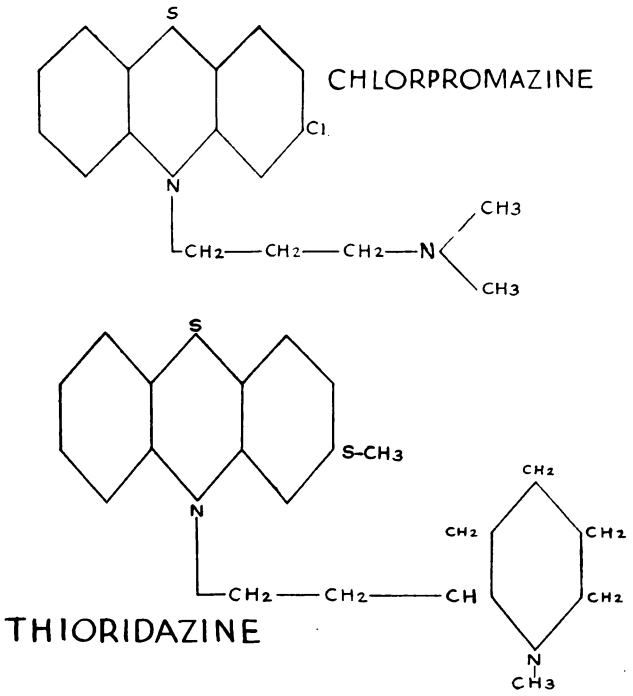

FIG. 1.

appears to have overcome the toxicity to the retina but retained all the other desirable properties—this is thioridazine.

The paucity of side-effects with thioridazine has been commented on by Cohen (1958), Fleeson *et al.* (1958), Remy (1958), Azima *et al.* (1959), Brunold (1959), Delay *et al.* (1959), Furtado (1959), Haug (1959), Judah *et al.* (1959), Kinross-Wright (1959) and Mayer (1959). Only Sauter (1959) states the contrary: "the side-effects were similar to those of other phenothiazines". Therefore we decided to investigate the nature and severity of side-effects with equivalent therapeutic doses of chlorpromazine and thioridazine in a group of in-patients.

METHOD

Sample

This was restricted to patients in long-stay wards who had received or were receiving a phenothiazine to control their periodically disturbed behaviour and to facilitate their nursing. Sixty patients were selected from similar wards (22 being moved to the treatment ward in the three weeks before the trial began) who were all females in the 20–60 age group, and reasonably homogeneous as far as diagnosis and prognosis were concerned. Fifty-six were suffering from schizophrenic or "paraphrenic" psychoses and 4 were manic-depressives.

As it was known that some months would be needed to evaluate the two drugs, patients were selected who were extremely unlikely to leave hospital during that time. Clinically, many showed much evidence of deterioration, many were grossly delusional, often with hallucinations, and their prognoses were considered very poor.

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Procedure

The sixty patients were taken off all drug treatment for one month. They were then assessed by one of us (D.M.S.) and the ward sister on the L-M Fergus Falls Behaviour Rating Scale (Lucero and Meyer, 1951), a rating scale described by these authors as suitable for use in mental hospitals. The L-M Fergus Falls Behaviour Rating Scale measures eleven aspects of behaviour, each of which is described by a five-point scale. The scale is so designed as to be usable by relatively untrained raters. Areas of behaviour measured by the scale include attitude to work and occupational therapy, response to meals, response to other persons (e.g. fellow patients, nurses and doctors), attention to dress, psychomotor activity, speech and toilet behaviour.

Four groups of fifteen were then matched by the psychologist (G.D.G.) according to the following criteria: total score on the above rating scale, age and duration of illness. In addition an attempt was made to include in each group an approximately equal number of patients attending occupational therapy and of patients who were described as "incontinent", "deteriorated" and "inaccessible".

A doctor who had no duties connected with the ward concerned allotted each of the groups to a particular therapy—by random choice: chlorpromazine, chlorpromazine placebo, thioridazine and thioridazine placebo. The two placebos were identical in appearance with the respective active tablets. The mean score of patients on the rating scale, the mean age and the mean duration of illness are given below (Table I):

Table I

Comparative Rating of Groups Before Trial

	Chlor-promazine	Thiori-dazine	Chlor-promazine Placebo	Thiori-dazine Placebo	Total Sample
Mean total score Fergus Falls ..	21·60	21·73	22·03	21·80	21·79
Mean age	41·0 years	41·3 years	41·4 years	40·3 years	41·0 years (range 24–58)
Mean duration of illness	10 years	10 years	9·5 years	8·45 years	9·5 years (range 3½ months–29 years)

The rating for response to electro-convulsive or insulin therapy has been omitted—these treatments were of course not used during the period. The occupational therapy rating has also been omitted because objective assessment by the raters was not practicable.

The dosage was as follows:

First 4 days: 200 mg. per day
Next 4 days: 300 mg. per day
Next 21 days: 400 mg. per day
Next 4 days: 600 mg. per day
Next 5 days: 700 mg. per day
Last 5 days: 800 mg. per day

43 days in all, total possible dose 20·3 grammes.

During the trial all patients were re-assessed on the rating scale by the same persons after two weeks and after six weeks, that is at the end of the trial.

There was daily observation and recording of side-effects and changes in behaviour by the psychiatrist, ward medical officer (P.H.C.) and nursing staff. Blood pressures and weights of patients were recorded before and during the trial and temperature and pulse charts drawn up.

It was planned that reduction of dosage when required by reason of severe side-effects would be by means of 100 mg. steps.

Special measures were taken to see that patients did not have any other drug treatment during the period, in particular for minor physical illnesses. Further, all tablets were swallowed in the presence of experienced nursing staff. Although a time-consuming procedure, it was felt that this was essential, as it has been reported that urine testing showed that as many as 10 per cent. of patients avoided taking their tablets (Pollack, 1958).

Nursing staff were given a list of all reported side-effects of both drugs and these were not differentiated. Nurses were drawn from a pool—all of them were informed that the side-effects of a new drug were being investigated and compared to those of chlorpromazine. They were not informed that placebos were being used. Even with "tranquillizing talks", nursing staff showed tremendous interest and enthusiasm, and one could readily forecast that some placebo improvement would occur.

At the end of the 43-day period, of the 15 patients in each group, 12 on chlorpromazine and 15 on thioridazine were further treated and observed for at least six weeks, and 12 chlorpromazine patients and 11 thioridazine patients for another 8 weeks.

Results

1. Side-Effects

We compared the side-effects from two points of view, general differences and specific differences.

(i) *General*

Chlorpromazine produced many more side-effects than thioridazine, at all dosage levels and at all stages of the trial.

Four patients on chlorpromazine were necessarily limited in their dosage by reason of side-effects, one was progressively reduced from 400 mg. a day to 100 mg. and one from 600 mg. to 400 mg. Two patients were unable to tolerate above 600 mg. a day. Only one patient on thioridazine was reduced in dosage —from 700 to 600 mg. We were very fortunate that this patient, who had never

Table II

Comparison of Side-Effects

Side-Effect	Number of Patients	
	Chlorpromazine	Thioridazine
Photosensitivity reactions (severe)	10	Nil
Oedema of the face, especially eyelids ..	4	Nil
Parkinsonism (severe)	1	Nil
Depression (severe)	1	Nil
Somnolence (severe)	5	3
Dryness of mouth (severe)	1	1
Pallor and syncope	Nil	2
Tachycardia (above 120)	10	2
Pyrexia	4	1

before tolerated a phenothiazine, happened to be in the thioridazine group. She had had chlorpromazine (Largactil), promazine (Sparine), mepazine (Pacatal) and trifluprомazine (Vesprin, Vespral).

(ii) *Specific*

The differences are summarized in Table II.

The word "severe" as used in the table indicates that such a patient would have taken herself off the medication if she were being treated on an out-patient basis.

Tachycardia and Pyrexia. Of the ten patients showing tachycardia above 120 on chlorpromazine, nine had other side-effects. The two thioridazine patients with tachycardia had pyrexia as well.

Increase in Weight. Significant weight gains occurred in both the active drug groups, after 4 weeks and after 6 weeks. The mean differences were:

Chlorpromazine: 4·8 and 6·0 pounds respectively.
Thioridazine: 3·2 and 4·6 pounds respectively.

In the control groups the mean differences were not statistically significant.

Blood Pressure. These readings were so irregular and inconsistent that it was not possible to draw any conclusions from them.

Photosensitivity. Each hot sunny day brought out a large number of reactions in chlorpromazine patients—all on 400 mg. a day or more—but none in thioridazine patients. In several patients the reaction was extremely severe and took many days to clear up.

Somnolence. With thioridazine this occurred in two patients on 200 mg. a day, and in one at 700 mg. (this was the patient whose dose had to be reduced to 600 mg. a day). With chlorpromazine somnolence occurred at all dosage levels in five patients.

Syncope. Two syncopal attacks occurred with thioridazine—in one patient before the first dose of tablets in the morning, but she had been clumsy and had dropped things the day before (dose 400 mg. a day). The other patient had her syncopal attack one hour after a dose of 100 mg. Neither patient had subsequent attacks.

Parkinsonism. The one severe reaction occurred on the 13th day at 400 mg. a day of chlorpromazine. This was an unexpectedly low incidence of Parkinsonism.

Placebo "Side-Effects"

No patient on placebo was reduced in dosage because of side-effects. Nevertheless eight patients on thioridazine placebo and six on chlorpromazine placebo showed tachycardia (above 120) and instability of temperature regulation—up to 100·6° F. axillary. One patient on thioridazine placebo had an axillary temperature above 99·0° F. on 15 days of the 43-day trial.

2. THERAPEUTIC

These are summarized in Table III overleaf.

Chlorpromazine Group. The mean difference in score after two weeks was +2·10 and, after six weeks, +4·87. The difference is significant in each case—in the former at the ·05 level of confidence and, in the latter, at the ·001 level of confidence.

TABLE III

Response to Treatment

Mean Total Score Fergus Falls	Chlor-promazine	Thiori-dazine	Chlor-promazine Placebo	Thiori-dazine Placebo
Initial rating	21·60	21·73	22·03	21·80
2nd rating (after 2 weeks) ..	23·70	23·26	21·77	21·73
3rd rating (after 6 weeks) ..	26·47	24·06	21·20	23·93
4th rating (after further 6 weeks)	—	26·73	—	—

Thioridazine Group. The mean difference in score after 2 weeks was +1·53, after 6 weeks +2·33 and, at the end of the treatment period, +5·0. After 2 and 6 weeks, the difference is significant at the ·05 level of confidence, and at the end of the treatment period, at the ·001 level of confidence.

Chlorpromazine Placebo. The mean difference in score after 2 weeks was −0·26 and, after 6 weeks, −0·83. These differences are not statistically significant.

Thioridazine Placebo. The mean difference in score after 2 weeks was −·07 and, after 6 weeks, +2·13. These differences are not statistically significant.

Individual Results

It would appear from Table IV that chlorpromazine was slightly more

TABLE IV

Individual Results of Trial After 6 Weeks—Fergus Falls

Changes in Ratings on Fergus Falls During Trial	Number of Patients			
	Chlor-promazine	Thiori-dazine	Chlor-promazine Placebo	Thiori-dazine Placebo
Much worse (−8→) ..	—	—	—	—
Worse (−4→−7)	—	—	4	3
Same (−3→+3)	5	9	7	8
Improved (+4→+7) ..	6	5	4	1
Much improved (+8→) ..	4	1	—	3

effective than thioridazine and that both chlorpromazine and thioridazine were more effective than their respective placebos. The differences, however, were too small to reach statistical significance. When, however, the response to the two active substances was combined and compared with the response to the two inert substances, the difference was significant at the ·05 level of confidence.

Ratings Based on Day-by-Day Observations of the Patients (at 6 Weeks)

Patients were rated as 5 (much improved), 4 (improved), 3 (remains the same), 2 (worse) and 1 (much worse) on the basis of the clinical data which was gathered on a day-to-day basis during the period of the study by the psychiatrist concerned.

The ratings were as shown in Table V.

It would appear from the table that response to treatment was most favourable among those who received chlorpromazine and least favourable among those who received its placebo. The response to thioridazine would seem less impressive. The differences in each case, however, were too small to

TABLE V

Individual Results of Trial After 6 Weeks—Clinical Rating

Clinical Rating		Number of Patients			
		Chlor-promazine	Thiori-dazine	Chlor-promazine Placebo	Thiori-dazine Placebo
Much worse	(1)	—	—	1	—
Worse	(2)	2	—	3	3
Same	(3)	5	10	10	6
Improved	(4)	6	5	1	6
Much improved	(5)	2	—	—	—

reach statistical significance. Even when the ratings for the two active substances were combined and compared with the ratings for the two inert substances, the difference was not statistically significant.

FURTHER TREATMENT PERIOD

As described under procedure above, daily observations were continued on the majority of patients who had received either chlorpromazine or thioridazine, for periods up to 14 weeks from the end of the controlled trial.

Side-Effects

Chlorpromazine: 7 patients showed side-effects, including two cases of Parkinsonism. These latter were reduced in dosage from 600 and 800 mg. respectively.

Thioridazine: 1 patient only showed a side-effect (oedema of the face and eyelids but with no redness) despite maintenance of dosage at the 500–800 mg. per day level.

Therapeutic

The period after the controlled trial was primarily intended for the observation of side-effects. However, the opportunity was taken to assess clinically the improvement of the two active treatment groups—and as all thioridazine patients remained on the drug for at least six weeks they were rated again on the Fergus Falls Scale. As only eleven of the original fifteen patients remained on chlorpromazine they were not re-assessed on this scale.

The patients on both drugs maintained their condition. In addition three other patients on thioridazine improved. Dosage was from 500 to 800 mg. daily. As shown in Table III, the difference in scores on the Rating Scale (before the trial compared with 12 weeks later) is significant at the ·001 level of confidence. Individual results on the scale showed that four patients remained the same, nine patients improved and two patients were much improved.

SUMMARY AND CONCLUSIONS

1. A controlled trial lasting six weeks was carried out on 60 female patients in the long stay wards of a mental hospital to compare the side-effects of chlorpromazine and thioridazine.

2. In this group of female patients, almost all chronic schizophrenics, and all with poor prognoses:

(*i*) Thioridazine produced far less side-effects than chlorpromazine at all doses between 200 and 800 mg. a day, at all stages of the trial, and during a subsequent period up to 20 weeks in all.

(*ii*) Thioridazine did not produce photosensitivity, Parkinsonism or depression.

(*iii*) Thioridazine was slower to act and required higher dosage than chlorpromazine. Results achieved with chlorpromazine in 6 weeks took some 12 weeks with thioridazine. Dosages of 600–800 mg. per day of thioridazine were roughly equivalent to 400 mg. per day of chlorpromazine.

(*iv*) The unexpected therapeutic response with thioridazine in these patients warrants its further trial in patients who are unable to tolerate chlorpromazine or who have failed to benefit from it.

3. Thioridazine is so well tolerated that it appears an excellent phenothiazine for ambulatory patients, in particular for maintenance of patients after they leave hospital.

4. Instability of temperature regulation was shown so frequently by patients on placebos that it seems unlikely to be a significant side-effect of the phenothiazines, that is when it occurs in isolation.

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REFERENCES

AZIMA, H., DUROST, H., and ARTHURS, D., *Canad. med. Ass. J.*, 1959, **31**, 549.
BRUNOLD, H., *Therap. Umschau.*, 1959, **16**, 90.
COHEN, S., *Amer. J. Psychiatr.*, 1958, **115**, 358.
DELAY, J., PICHOT, P., LEMPERIÈRE, T., and ELISSALDE, B., *Ann. méd.-psychol.*, 1959, **117**, 724.
FLEESON, W., GLUECK, B., HEISTAD, G., KING, J. E., LYKKEN, D., MEEHL, P., and MENA, A., *Univ. Minnesota Med. Bull.*, 1958, **29**, 274.
FURTADO, D., *Rev. neurol.*, 1959, **100**, 763.
HAUG, J. O., *Tschr. Norske Laegeforg.*, 1959, **79**, 317.
HIPPIUS, H., and KANIG, K., *Fortsch. Neur. Psychiat.*, 1958, **26**, 582.
JUDAH, L., MURPHREE, O., and SEAGER, L., *Amer. J. Psychiat.*, 1959, **115**, 1118.
KINROSS-WRIGHT, J., *J. Amer. Med. Ass.*, 1959, **170**, 1283.
LUCERO, R. J., and MAYER, B. T., *J. Clin. Psych.*, 1951, **7**, 250.
MAYER, K., *Medizinische*, 1959, 733.
POLLACK, B., *Amer. J. Psychiat.*, 1958, **115**, 1, 77.
REMY, M., *Schweiz. med. Wschr.*, 1958, **88**, 1221.
SAUTER, T., *Praxis*, 1959, **48**, 140.