STELAZINE (TRIFLUOPERAZINE)
A PRELIMINARY REPORT ON A CLINICAL TRIAL

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TRIFLUOPERAZINE, which is 2-trifluoromethyl-10-(3′-[1″-methylpiperazinyl-4″]-propyl)-phenothiazine dihydrochloride—a preparation manufactured by Smith, Kline and French Laboratories Limited under the description SKF5019—is the most recent phenothiazine derivative reported to have a beneficial effect on certain types of mental illness. On the basis of animal tests trifluoperazine is described as having nine times the potency of chlorpromazine in blocking the conditioned response, and its specificity is greater than that of chlorpromazine.

Sixty patients were selected for this trial (40 females whose ages ranged from 20–72 years, the average being 42, and 20 males whose ages ranged from 24–50 years, the average being 38). The majority were chronic schizophrenics and the duration of their psychiatric illness averaged 11 years for females, ranging from 1–32 years, and 7 years for males, ranging from 2–14 years. They had failed to respond to the normally recognized forms of treatment. Many were of the disturbed hallucinated impulsive type whose prognosis was regarded as hopeless. Such long-stay patients constitute a problem in every mental hospital and their treatment by a new drug presents the severest test of its efficacy.

Trifluoperazine was given by mouth in capsule form. The initial dose was 5 mg. a day for three days. This was increased at intervals of three days to 5 mg. b.d. and 5 mg. t.d.s. and by 5 mg. steps to 10 mg. t.d.s. The maximum dose tried was 40 mg. a day. The usual maintenance dose in men was 25 mg. and in women 15 mg. a day. All patients had a maximum dose of 10 mg. t.d.s. except where toxic symptoms necessitated a reduction. Once stabilized on the appropriate dose, a double blind technique was introduced unknown to the nursing staff. Half of the patients were kept on Trifluoperazine and half were given a placebo which was identical in appearance with the drug. The choice of patients was determined solely by the pharmacist.

The results of the double blind technique will be the subject of a further communication.

The results of treatment were determined qualitatively with particular emphasis on such clinical observations as the lessening in activity of hallucinations and of aggressive conduct; and the emergence of alertness, interest, initiative, etc.

All patients showing improvement were ranked according to estimated degree of improvement and a rank order produced for the females and males separately. From this the following figures were obtained:

TABLE I

Improvement	Males		Females		Mean Percentage
	Number	Percentage	Number	Percentage	
Marked ..	6	30	7	17·5	23·75
Moderate ..	6	30	16	40	35
Slight	3	15	11	27·5	21·25
None	5	25	6	15	20

The figures for improvement were then broken down as follows. Table II shows the effect on symptoms.

TABLE II

	Number of Patients	Much Improved	Moderately Improved	Slightly Improved	No Change
Hallucinations ..	50	18	14	9	9
Aggression and noisiness	48	20	13	7	8
Withdrawal from surroundings ..	23	9	8	2	4
Thought disorder ..	32	11	13	2	6

Table III shows the effect on behaviour.

TABLE III

	Before Treatment Number of Patients	After Treatment Number of Patients
Spontaneity	13	42
Sociability	3	38
Speech	24	46
Occupation	11	40

COMMENTS

Improvement became noticeable approximately ten days after commencement of treatment. This was most striking in the fading of hallucinations, cessation of impulsiveness, an awakening of interest, a desire to take part in occupations and recreations of various kinds. It was also noted that many patients were moderately euphoric, in some appetite was increased, and a few became aware of their previous irrational conduct.

PSYCHOMETRIC INVESTIGATION

Clinical observations of the effect of trifluoperazine indicated changes in motor activity and general awareness in a small sample of patients.

From this evidence it was decided to measure quantitative changes in motor speed, hand-eye co-ordination and attention level.

The battery of tests used in the investigation were:

1. Modified Peg Board test of motor speed (3 trials).
2. Bead-threading test of co-ordination (3 trials).
3. Knox Cube test of attention level.

All three tests lend themselves to rapid individual administration and are sufficiently simple to be relatively unaffected by variations in intellectual level.

The battery was given to each patient a day or two before treatment commenced with a repeated administration three weeks later.

Differences between mean scores obtained on each test before and during treatment proved to be significant in the case of speed and attention tests for both men and women (see Table IV).

TABLE IV

Significance of Difference Between Means of Tests Before and During Treatment in Terms of Units of P.E. Difference

Test	Men (N=18) ×P.E. of Difference	Women (N=26) ×P.E. of Difference
Co-ordination	2·7	2·3
Speed	4·7	4·9
Attention	8·2	7·2

A similar comparison of coefficients of variation for the co-ordination and speed tests revealed a significant difference only in the case of the speed test (3·7 P.E. for men and 3·5 P.E. for women). The coefficient of variation yields in this case a measure of uniformity of performance over the three trials of each of these tests.

From the results to hand, the following changes have been observed during the period of treatment in both male and female groups:

1. A significant increase in speed of performance on the peg-board test.
2. A significant increase in the score on the Knox Cube attention level test.
3. A significant decrease in the scatter of speed over three trials of the peg-board test, i.e. a significantly more uniform performance on this motor speed test.

Further investigation is being carried out to exclude the possible effects of learning and environmental changes.

SIDE EFFECTS

These were noted in 28 patients (46·5 per cent.) of which 11 were males and 17 females.

The following occurred:

I. Parkinson-like symptoms:
   - (*a*) Mask-like face.
   - (*b*) Tremors.
   - (*c*) Muscle pains.
   - (*d*) General rigidity.
   - (*e*) Bent shoulders and shuffling gait.

In only 8 cases (13·23 per cent.) were these symptoms severe; the rest, 16 cases (26·6 per cent.) were of a mild character.

Other side effects were:

II. Drowsiness Male=1 Female=5.

III. Salivation Male=0 Female=6.

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IV.	Restlessness	Male=0	Female=1.
V.	Lachrymation	Male=0	Female=2.
VI.	Sweating	Male=0	Female=1.

Of these cases, side effects appeared between seven to thirty-two days after commencement of treatment, usually after twenty-one days. The dosage at the time of appearance of most side effects was 30 mg. per day, but a few cases occurred at a lower dosage, the lowest being 15 mg. per day. In eight cases all side effects disappeared on reduction of dose from 30 to 20 mg. per day. In three patients in whom it was necessary to stop treatment, resumption of treatment at a smaller dose (15 mg. per day) did not cause a re-appearance of side effects. In one case reduction of dose was combined with 2 mg. Artane b.d. but in the main alteration of dose only was effective. The beneficial effects of a reduction of dose was noted in 48 hours. In only two cases (female) was permanent cessation of treatment necessary for the abolition of Parkinsonism.

Other investigations showed that the blood pressure readings were unaffected, that in general there was a slight leucocytosis, and there were no cases of jaundice or urinary complications.

Discussion

The results so far obtained show that trifluoperazine is a powerful drug which has considerable beneficial effect when given to chronic psychotic patients. Although side effects are fairly numerous, the majority were overcome in general by reduction of dosage, and specific symptoms by their appropriate antidote. In some cases in which it was necessary to withdraw the drug completely, the improvement that had already taken place in the patients' condition was maintained for at least several weeks although, conversely, a patient who was discharged against advice while on 10 mg. t.d.s. relapsed and was back in hospital within ten days.

Concerning the site of action of Trifluoperazine, the sweating, lachrymation, salivation and drowsiness noticed in some patients suggest to us that one site might be the middle group of hypothalamic nuclei and likewise the interruption of the extra-pyramidal facilitatory pathway in the hypothalamus might account in part at least for some of the signs of Parkinsonism.

Our preliminary conclusions support the findings of Rudy *et al.* (1) and we feel that further research will reveal that Trifluoperazine will prove a great therapeutic advance in the treatment of mental disorders.

Summary

Sixty chronic psychotic patients were selected for this clinical trial. Observation showed that a high proportion were improved by Trifluoperazine.

The presence and control of side effects are discussed, as are the results of a parallel psychometric investigation.

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Reference

1. Rudy, L. H., *et al.*, *Amer. J. Psych.*, 1958, **114**, 747.