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TRIFLUOPERAZINE DIHYDROCHLORIDE ("STELAZINE") IN PARANOID SCHIZOPHRENIA

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Experience of phenothiazine derivatives in this hospital had prior to November, 1957, been mainly confined to chlorpromazine, which had been given in doses of up to 850 mg. daily together with electric convulsion therapy (E.C.T.). On the whole it can be said that some relief in symptomatology was obtained in patients with chronic schizophrenia, rather better success in patients suffering from involutional paranoid illness, but the results in cases of acute recent schizophrenia were minimal to moderate and did not obviate the necessity for insulin coma treatment (I.C.T.). It would be fair to criticize our experience with chlorpromazine in that perhaps we were too cautious, as better results have been reported with intensive chlorpromazine plus E.C.T. (Ollendorff, 1958). Nevertheless it appeared that a drug of similar action, more powerful, less toxic, and simpler in its administration, might give better or equally good results without the necessity for E.C.T. or, in acute cases, without the need for I.C.T.

Trifluoperazine dihydrochloride ("stelazine") was reputed to be such a drug. It is derived from prochlorperazine by the substitution of a trifluoromethyl group for the chlorine atom in the 2 position of the nucleus. According to the manufacturers it is reputed to be four times as powerful as prochlorperazine and between nine and ten times as powerful as chlorpromazine in blocking conditioned responses in animals.

In November, 1957, a trial of trifluoperazine was begun and its effect tested on a series of patients suffering from acute and chronic paranoid schizophrenia. The patients were treated under the conditions normally applying in this hospital, and no other treatment was given during the experiment except occasional night sedation, and all proceeded with the normal programme of rehabilitation.

The results of treatment in the first 50 patients so treated in the first nine months of the experiment are here recorded. They were divided into two groups.

Methods and Material

Group A.—There were 30 male patients suffering from chronic paranoid schizophrenia who had been in this hospital for a minimum period of two years. All had previously been treated by standard methods, such as I.C.T. and E.C.T., and had been given a prolonged trial with chlorpromazine and, in many cases, other tranquillizers available at the time. None of these treatments had materially altered the clinical picture. The duration of the illness varied from two to fourteen years.

Group B.—There were 20 patients admitted during the first attack of schizophrenia of less than six months' duration who had not had any previous treatment. They were admitted with a recommendation for I.C.T. by other consultants, and when initially examined in this hospital were thought to be cases that would normally have proceeded to I.C.T.

Treatment and Dosage.—Treatment was begun by suspending all other drugs. It was continued by administering 5 mg. of trifluoperazine daily for the first three days, thereafter increasing by 5 mg. daily at three-day intervals until gross side-effects appeared or a satisfactory therapeutic effect had been obtained. When the symptoms had been controlled by trifluoperazine the dosage was reduced to a maintenance level, on which patients were completely free from side-effects and at which the therapeutic effect seemed maximal. The maximum dose used was 45 mg. daily and the average maintenance dose 20–25 mg. daily. Those discharged have been maintained on dosages varying from 5 to 20 mg. daily.

Results

Assessment of the effect of trifluoperazine was made on the patient's capacity towards adjustment to normal social surroundings. These results are shown in the accompanying Table in terms of the degree of deterioration before and after treatment.

Group		(a)	(b)	(c)	(d)
A	Before treatment	26	4	—	—
	After " " "	9	12*	4	5
B	Before " " "	14	6	—	—
	After " " "	—	6†	—	14

* Two of these are fit for discharge but waiting placement.

† Three of these six made good initial improvement with trifluoperazine but proceeded to I.C.T. on the advice of other psychiatrists before trifluoperazine was given a full trial.

(a) Incapable of social living and requiring constant observation. (b) Able to adjust to social living in the hospital community (including parole, short leaves of absence, etc.). (c) Discharged from hospital and able to adjust socially but incapable of earning a living. (d) Discharged from hospital with return to full employment.

Follow-up.—All patients discharged have continued with a maintenance dose. No patients in Group B have reported a relapse. Three in Group A showed a return of symptoms when they had difficulty in obtaining the drug, but they quickly responded when the drug was recommenced. All have been out of hospital for from five to nine months.

Side-effects.—The only side-effects noted were, in order of frequency: drowsiness, Parkinsonism, increased motor restlessness, and increased salivation. No significant alterations were observed in blood pressure, white-cell counts, liver-function tests, or urinary analysis. Drowsiness and salivation occurred on dosages from 10 mg. daily, increased motor restlessness from 15 mg., and Parkinsonism of 20 mg. and above. The most troublesome side-effects, from the patients' point of view, were drowsiness and motor restlessness. The side-effects

were treated symptomatically by such drugs as amphetamine, barbiturates, and antihistamines without benefit. Benzhexol hydrochloride ("artane"), in doses of 6-8 mg. daily, proved effective in eliminating Parkinsonism and in greatly decreasing motor restlessness.

Discussion

Group A

We recognize that improved capacity for social adjustment is dependent on symptomatology, but it was interesting to note the effectiveness of trifluoperazine on specific symptoms. In general we found that the greatest effect was on aggression and general overactivity. Next in response were auditory hallucinations, then delusions; least of all affected were such symptoms as inability to concentrate, incapacity for sustained thinking or effort, abstract thinking, and comprehension in those who did not fully respond. If hallucinations and delusions did not clear up altogether they usually became less intense and the patients less troubled by them. There was often a remarkable degree of return of insight, and we were impressed when those patients who were relieved of their symptoms spontaneously attributed the improvement to the drug. The nursing staff and relatives were unanimous in describing the better rapport they were able to obtain with patients.

In general the improvement was gradual, but once the improved patients were able to graduate to a higher level in the programme of rehabilitation progress was rapid. This was to be expected. We believe that an adequate programme of rehabilitation remains a fundamental approach to the treatment of schizophrenia and that any physical method of treatment that will not only make such a programme more acceptable to a patient but make the patient more acceptable to others has a valuable place in psychiatric treatment.

We were unable to come to any conclusion on why some patients improved and others did not, except in the case of three of the patients who had had prefrontal leucotomy and who failed to show any response—an observation that has been made in the treatment of chronic katatonic schizophrenia in this hospital with prochlorperazine ("stemetil") (Storey, 1959); and Ollendorff (1958) quoted 11 leucotomized cases of chronic schizophrenia that had failed to respond to intensive chlorpromazine and E.C.T.

We cannot understand the findings of Forrester (1958). It is noted that eight of her cases had been leucotomized and two were oligophrenic, and we would not have expected improvement in these. She does not classify the type of schizophrenia in the other 15. The severity of the side-effects she quoted are very different from our experience and the experience of Madgwick *et al.* (1958), Milligan (1958), Rudy *et al.* (1958), and others with whom we have discussed the drug.

In our patients the only side-effect that gave rise to anxiety was motor restlessness. Patients were very aware of it and disturbed by it. Two patients with chronic schizophrenia, both of whom had a compulsive desire to escape from the hospital, became so restless that one jumped from a second-floor window and another jumped down several steps, fortunately without serious injury. Neither had any suicidal intent. This restlessness makes us feel that, certainly in large doses, treatment should only be carried out initially under good day-to-day observation. As we are becoming more familiar with the drug we find that we have been better able to control restlessness, and we are now less worried

about it. Parkinsonism is so easily controlled that no anxiety was felt about its occurrence.

Group B

The results of treatment in this group were surprisingly good. A similar pattern of response was found as with chronic patients, except that the response was more of a total one and all groups of symptoms tended to disappear more simultaneously. In those who had lost it, insight returned at a very early stage. All those discharged have maintained their improvement and have continued to take a maintenance dose of the drug. Comments that we have made on side-effects in Group A apply equally to Group B.

Comparison with I.C.T.

A comparison with the results of insulin treatment is desirable. For this purpose we have examined the results of I.C.T. in 24 male patients of similar clinical category treated during 1956. 23 of these were discharged from hospital after an average stay of 23½ weeks—12 returning to full employment, and the other 11 being able to live at home but unable to earn their living. Four of the latter subsequently relapsed. The average stay in hospital of those treated by trifluoperazine and discharged was 12½ weeks. The percentage of patients returned to full employment has been higher in the trifluoperazine group. Trifluoperazine would appear to be a cheaper and more pleasant method of treating acute paranoid schizophrenia than I.C.T., and just as effective, if not more so. A matter of some importance is how long patients should be kept on a maintenance dose. We are not in a position to say how many of these patients would have made a spontaneous recovery from acute attack, or how many are continuing to receive the drug unnecessarily if the attack has run its natural course. We have not taken any risks, but the matter is one that needs further study. We have, as yet, no evidence that the drug, if taken continuously, leads to complications. Of the three cases that proceeded to I.C.T., one made a complete recovery and the other two showed only moderate improvement. These later completely recovered with another course of trifluoperazine.

Summary

Thirty patients suffering from chronic paranoid schizophrenia and twenty from a first attack of paranoid schizophrenia were treated with trifluoperazine dihydrochloride. The results are shown in the capacity for social living before and after treatment, and the effect on different aspects of symptomatology is discussed.

Reference is made to a comparison of trifluoperazine and insulin coma treatment in acute paranoid schizophrenia.

Trifluoperazine should prove a valuable addition to the drugs available for the treatment of schizophrenia.

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