"RITALIN" AND CHLORPROMAZINE IN CHRONIC SCHIZOPHRENIA: A CONTROLLED CLINICAL TRIAL

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RITALIN (methylphenidate) is a drug which was developed by the firm of Ciba Limited. It resembles amphetamine in its central stimulant and sympathomimetic action but has quite a different chemical structure. Its general properties have been described by Meier *et al.* (1954) and by Drassdo and Schmidt (1954 a, b). Geller (1955) and Stier (1955) used Ritalin in the treatment of depressive states associated with apathy, while Ferguson (1955) found it of value in countering the depressive effects of reserpine therapy. Ferguson also notes that Ritalin seemed to have a beneficial action in cases of chronic schizophrenia and considered that his findings warranted a clinical trial.

The purpose of the present investigation was to determine, by a self-controlled trial, whether Ritalin was of value in the treatment of unselected chronic schizophrenic patients in a mental hospital ward. As there is fairly general agreement that chlorpromazine is of value in chronic schizophrenia, we also carried out a trial of this drug with the object of validating our methods of assessing clinical improvement.

METHOD

In a ward of 60 male chronic schizophrenic patients, 48 were arbitrarily chosen for the trial. The average age of the trial patients was 46, with a range of 28 to 64 years. The average time since their last admission to hospital was 18 years, with a range of 2 to 40 years. Fourteen patients had been subjected to leucotomy. In the opinion of the charge nurses and ward physician, thirteen were mainly overactive and aggressive, twenty-three were mainly apathetic. During the five months of the trial, patients received no other drugs or special methods of therapy with the exception that four who had at one time had epileptic fits continued to receive anti-convulsant drugs.

The drugs tested were: Ritalin 10 mg. t.i.d.; Ritalin 20 mg. t.i.d.; and chlorpromazine 50 mg. t.i.d. These were administered in a syrup which, when given without the addition of any drug, served as the inert control. Quassin was added to the control syrup to mimic the bitter taste of chlorpromazine. The trial lasted for five months (more precisely, for five periods of four weeks each). For the first month, all patients received only the control syrup; this enabled the nurses and physician to become accustomed to the methods used for assessing the patients' symptoms and behaviour. For the succeeding four months, each patient received each drug, including the inert control, for

a month at a time. The drug order for the 48 patients conformed to a Latin square design. Physician, nurses and patients were unaware of the order in which the drugs were given.

The effects of the drugs were assessed in two ways. At the end of each trial month the ward physician (B.J.S.) rated the severity of each patient's symptoms on a seven-point scale; a list of 18 symptoms common in chronic schizophrenia was used. It was intended that the assessment of symptoms should be made independently by two physicians but one physician left the hospital before the trial was completed. At the end of each week the nurses assessed the patients' behaviour on the Barrabee-Hyde behaviour rating scale; on this scale (Greenblatt and Solomon, 1953) seven general aspects of behaviour are rated on a five-point scale.

The 48 patients were divided into four groups, each group coming under the special care of two nurses; thus, though there were eight nurses on the ward, each patient was rated by the same two nurses throughout the trial. During the course of the trial there were no admissions to the ward, no patients were discharged or transferred, and none was physically ill.

RESULTS

The results were primarily recorded by comparing, for each patient, the rating score obtained during the month on a drug with that obtained during the control month; the drug score was then classed as "better than", "equal to" or "worse than" that of the control.

We may consider first the results of the physician's rating of symptoms. With Ritalin, the number of patients scoring "better" on the drug than on the control was not, for any of the 18 symptoms, significantly greater than the number of patients scoring "worse"; this was true for both doses of Ritalin. With chlorpromazine, on the other hand, the number of patients scoring "better" as compared with the control was significantly (at the 5 per cent level) greater than the number scoring "worse" in eight of the 18 symptoms. These eight symptoms and the scores are shown in Table I. The ten symptoms not

TABLE I

Number of Patients whose Symptoms were rated "Better", "Equal" or "Worse" during the Chlorpromazine Month as compared with the Control Month

Symptom	Better	Equal	Worse
Replies to questions vague, brief or careless	20	23	5
Incongruity of affect	21	20	7
Withdrawal from other people	19	22	7
Extent to which hallucinations and delusions influence behaviour	22	18	8
Paranoid attitude	24	14	10
Incontinence of urine and faeces	11	36	1
Flattening of affect	25	11	12
Aggressive behaviour	11	34	3

showing significant improvement on chlorpromazine were: lack of energy and initiative; hallucinations; delusions; incoherence of speech; emotional outbursts; impulsive behaviour; stereotypy of speech and/or behaviour; depression; anxiety, tension or agitation; and confusion.

These results may also be expressed in terms of the number of symptoms which, on the whole (i.e. in which more patients scored "better" than scored

"worse"), were rated better when the patient was receiving the drug. This is shown in Table II.

TABLE II

Number of Symptoms rated on the whole as "Better", "Equal" or "Worse" during the Drug Month as compared with the Control Month

Drug	Better	Equal	Worse
Chlorpromazine	17	1	0
Ritalin 10 mg. t.i.d.	11	0	7
Ritalin 20 mg. t.i.d.	8	2	8

The nurses' score for a patient during each drug-month was obtained by taking the mean of the two raters' scores for each week, and the mean of these four weekly scores. There was no instance for either Ritalin or chlorpromazine, in any of the aspects of behaviour, where the number of patients scoring "better" than on the control was significantly in excess of the number scoring "worse". There was, however, a clear general tendency for patients to score better on chlorpromazine than on the control, a tendency which was not present for Ritalin. This is shown in Table III, where it may be observed that, on chlorpromazine, more patients scored "better" than scored "worse" for each of

TABLE III

Number of Patients scoring "Better" or "Worse" for different aspects of Behaviour when scores on the Drug Month are compared with those on the Control Month

Aspect of Behaviour	Drug					
	Ritalin 10 mg. t.i.d.		Ritalin 20 mg. t.i.d.		Chlorpromazine	
	Better	Worse	Better	Worse	Better	Worse
Self-care	20	28	20	24	26	20
Co-operation	21	26	20	27	25	22
Productivity	21	21	18	25	22	19
Conversation	21	22	21	20	25	16
Group participation ..	25	23	26	21	29	18
Sociability	22	17	19	17	21	13
Initiative	22	23	21	25	28	16
	152	160	145	159	176	124

the seven aspects of behaviour studied; the excess of patients scoring "better" for initiative approaches the 5 per cent. level of significance.

A more detailed examination of the rating scores did not reveal any tendency for the over-active, aggressive patients to respond differently from the apathetic ones, either on Ritalin or on chlorpromazine. Thus of the 15 patients who showed most improvement on chlorpromazine, four were over-active and eight apathetic; and of the 12 who improved most on Ritalin, two were overactive and six apathetic.

Side Reactions

Sixteen patients were at some stage of the trial described by the nurses as markedly confused or drowsy; in 13 instances this occurred while the patient

was on chlorpromazine and in one case each while the patient was on Ritalin 10 mg. t.i.d., on Ritalin 20 mg. t.i.d. and on the control syrup. It may be observed that, of the thirteen patients who became markedly drowsy on chlorpromazine, only three showed any general improvement compared with the control month; this would seem to discount any marked bias towards favourable rating of patients thought to be on chlorpromazine. Fourteen patients were at some stage described as unduly restless or agitated; in ten instances this occurred while the patient was on Ritalin, in three while he was on chlorpromazine and in one while he was on the control. In five instances, the dose of the drug was halved for a few days because of the patient's untoward behaviour; in three of these instances, the patient was on chlorpromazine at the time, in one he was on Ritalin (20 mg. t.i.d.) and in one on the control. No other noteworthy complications occurred during the trial.

Discussion

The results do not confirm Ferguson's impression that Ritalin is of value in the treatment of chronic schizophrenia but they are in line with the controlled trials of Clark *et al.* (1956) and of Carey *et al.* (1956). On the other hand the results confirm the conclusion of several controlled studies that chlorpromazine is of some definite value (Vaughan *et al.*, 1955; Feldman *et al.*, 1956; Shepherd and Watts, 1956). In particular our findings agree with those of Shepherd and Watts and of Rockmore *et al.* (1956) that chlorpromazine is useful in apathetic schizophrenic patients; this is in contradistinction to such studies as those of Azima and Ogle (1954) who found the drug to have no useful effect in non-excited schizophrenics. Our figures did not show any significant improvement on chlorpromazine in the symptoms listed as "emotional outbursts" and "impulsive behaviour"; this is in agreement with Mitchell (1956) who found no difference between the number of "aggressive incidents" in chronic schizophrenic patients receiving chlorpromazine and those acting as controls.

A study of Table I suggests that chlorpromazine brought about improvement chiefly by reducing the severity of those symptoms that prevent the schizophrenic patient making social contact with other people; in particular, the coherent use of language was improved. This supports a common impression. Thus Vaughan *et al.* (1955) found that the basic schizophrenic symptoms were little influenced by chlorpromazine and that its main beneficial effect lay in better rapport and socialization; Azima and Ogle (1954) thought that chlorpromazine induces "a sense of decorum" in schizophrenic patients; Newbold and Steed (1956) considered that, by reducing emotional tension, the drug enabled the patient to communicate his thoughts more freely; while Rockmore *et al.* (1956), estimating by a controlled trial the effects of chlorpromazine on a hundred items of behaviour in chronic schizophrenics, found that the items showing significant improvement were those concerned with overactivity, communication and socialization.

Fullerton (1956) has recently shown by a controlled trial that the stimulant drug pipradol (Meratran) is apparently of no value in chronic schizophrenia and he refers to similar studies by other workers. These findings, together with those of the present study, tend to confirm the general view that central nervous stimulants are not of benefit in schizophrenia, but that drugs with a central depressant action may be so. This is of some theoretical interest because it suggests that the chronic schizophrenic suffers, not so much from a lack of

drive, as from a higher inhibition which prevents him making use of his energies.

Summary

1. A self-controlled, double-blind clinical trial of Ritalin, at two dosage levels, and of chlorpromazine was made in 48 chronic schizophrenic patients.

2. Compared with the control period, patients on Ritalin (at both dosages) showed no significant difference in behaviour or in the severity of their symptoms.

3. On chlorpromazine, however, a significant number of patients were improved, as compared with the control, in eight of the eighteen symptoms rated; behaviour also tended to improve, though taken singly none of the seven aspects of behaviour examined showed a significant degree of improvement.

4. The symptoms which showed most marked improvement with chlorpromazine were those concerned with sociability and the social use of language.

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