

A CONTROLLED CLINICAL STUDY OF CHLORPROMAZINE AND RESERPINE IN CHRONIC SCHIZOPHRENIA

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Since their recent introduction into clinical practice, chlorpromazine and reserpine have been widely used in the treatment of the schizophrenias. Studies of schizophrenic patients treated with chlorpromazine have been published by Vaughan, Leiberman, and Cook (1955), Kinross-Wright (1955), Goldman (1955), Charatan (1954), Labhardt (1954) and Anton-Stephens (1954); treatment with reserpine has been reported by Foote (1955), Kline (1954), Hollister, Krieger, Kringel, and Roberts (1955), Kline and Stanley (1955), Tasher and Chermak (1955), Campden-Main and Wegielski (1955), Noce, Williams, and Rapaport (1955), Barsa and Kline (1955), and Glynn (1955). The claims made by these workers for the two drugs are not dissimilar, but only the study of Kinross-Wright attempts to compare their efficacy. It seemed desirable, therefore, to try and assess the relative merits of the drugs as accurately as possible.

Case Material and Method

For this trial, 24 of the most deteriorated and apathetic female schizophrenic patients in a county mental hospital (St. John's Hospital, Stone) were chosen. Their ages ranged from 27 to 52 years, with an average of 40.5 years. The age span on admission was 16 to 36 years, with an average age of 25.2 years. The length of stay in hospital varied from 7 to 29 years with a mean of 15.8 years; two patients only had been less than 10 years continuously in hospital.

A fairly uniform clinical picture was presented by this group of patients. Most were totally unoccupied, withdrawn and unsociable. They took no interest in their appearance or personal care and were incontinent of urine. Talk was so seriously disordered that an intelligible conversation was impossible. Many patients were mute; a few were noisy, interfering, hostile or destructive to clothing and property. The majority, however, were not predominantly over-active, aggressive or disturbing, but were characterized by long-standing apathy and inactivity.

The following case histories are representative:—

Case 9.—A telephone operator was admitted to the hospital in 1945, aged 18, after 12 months' illness. On admission she felt that her thoughts were being controlled

and were not really her own; she had impulses to destroy property and hit other people. Later she became stuporose. She was mute, incontinent, paid no attention to her personal appearance, and had to be fed. She frequently struck other patients, tore up her own clothing and resisted attention. Treatment with barbiturate narcosis and E.C.T. had produced limited, short-lived improvements.

Case 10.—A factory machinist was admitted in 1948, aged 28 years. On admission she would speak only in whispers. She grimaced and smiled meaninglessly. She displayed no interest in people or things around her. Later she became mute. She improved with a short course of insulin coma treatment and was discharged three months after admission. Four months later she was re-admitted. She thought she was under the power of a hypnotist, was auditorily hallucinated, and showed inappropriate facial expressions. She was sometimes aggressive. She degenerated to a state in which she was mute, unoccupiable, indifferent to her surroundings and her appearance. She was incontinent unless taken to the lavatory regularly.

Case 22.—This patient was admitted in 1935, aged 23. She had three years previously been in a mental hospital for one year. On admission she was restless and violent; she indulged in outbursts of abusive language and sometimes of hilarious laughter. She talked incoherently. She slowly deteriorated, finally becoming mute, untidy, and incontinent. She did a little knitting but was otherwise unoccupied. About once a month she had an outburst of laughing or abusive shouting. She sometimes struck other patients for no reason; at other times she would tear her clothes.

The 24 patients were divided into three groups of eight (A, B, and C) by random selection. The experiment lasted for 18 weeks during which time each group of patients received each of three substances—reserpine (R), chlorpromazine (C), and placebo (P)—in different orders of administration. The original latin square design had to be modified for reasons described below. Dosage was necessarily empirical and was determined by experience and a study of the relevant literature. Chlorpromazine, 150 mg., was administered twice daily. The initial dose of reserpine was 5 mg. three times daily but owing to the frequency of toxic reactions this was reduced to

5 mg. reserpine twice daily later in the experiment. Two kinds of inert substance were employed, one indistinguishable in appearance and taste from reserpine, the other from chlorpromazine. Nobody but the ward doctor allocating the drugs and the dispenser knew which patients were receiving drugs and which patients were on placebo. A sealed list containing the nature of each substance prescribed was available, in case of need, *e.g.*, at night. The pulse rate and blood pressure readings were recorded regularly.

Weekly clinical assessments were carried out by one of us (D. C. W.) who was unaware of the nature of the individual prescriptions. At the end of each six-weekly period all patients were rated after an interview with the patient and a discussion with the nursing staff. This rating, though it simply indicated whether the patient had improved, deteriorated, or remained unchanged during the six weeks, was the expression of a complex judgment of nursing and medical factors. The rating 0 was used as a base-line index, signifying the patient's condition before the start of the treatment. Degrees of improvement in descending order were indicated by a+, b+, and c+, though equal degrees of improvement are not implied by these symbols. Conversely, a-, b-, and c- pointed to three progressive stages of deterioration. Examples from the cases already described above illustrate the use of the scale. It may be seen from these examples that the degrees of improvement corresponded approximately to different stages of rehabilitation, although the clinical symptoms remained in every case.

Case 9.—During the six weeks on chlorpromazine, she became more friendly and talkative; she ceased to be destructive and aggressive; she ate normal meals and was no longer incontinent; she was occupied a little and was clean and tidy; her facial expression and bearing were friendly and responsive. The possibility of discharge was considered. She was rated a+.

Case 10.—While having reserpine, she spoke more freely although the content of her talk was often nonsensical. She required less supervision for washing and dressing and went to the lavatory unaided; she did a little work spontaneously and appeared to enjoy television and other entertainments more. Transfer to another ward was considered. She was rated b+.

Case 22.—While having reserpine she became very restless: she ate ravenously and sometimes stole food from other patients. She could not be occupied. Nevertheless, she was incontinent less often and was no longer noisy, aggressive, or destructive. She was, therefore, much easier to nurse. She was rated c+.

In almost every case negative ratings were made on patients who were suffering from toxic effects of the drug which brought about a marked deterioration in behaviour. In these cases administration of the drug was discontinued or the dose reduced; in view of the period of "turbulence" described by Barsa and Kline (1955) the drug was not withdrawn until it was clear that the toxic effects were serious and were increasing. In the former

instances the rating was made at the time when the drug was discontinued.

Results

The ratings made on the three groups after the administration of each substance are presented in Table I.

TABLE I
RATINGS ON ALL PATIENTS AFTER TREATMENT WITH RESERPINE, CHLORPROMAZINE, AND PLACEBO

A			
Case Number	Period 1	Period 2	Period 3
	Placebo (r)	Reserpine	Chlorpromazine
1	0	a-	0 (T)*
2	0	c- (T)	a-
3	c+	a-	b+
4	b+	c-	a+
5	a-	b+ (T)	a+
6	0	c+	c+
7	0	0	0
8	b+	b+	b+

B			
Case Number	Period 1	Period 2	Period 3
	Placebo	Chlorpromazine	Reserpine
9	0	a+	a+
10	0	a+	b+
11	0	c+	b-
12	c+	a-	a+
13	0	0	b- (T)
14	b+	b+ (T)	c- (T)
15	0	0	c+
16	c+	b+	c- (T)

C			
Case Number	Period 1	Period 2	Period 3
	Chlorpromazine	Placebo	Reserpine
17	b-	b-	b-
18	a-	a-	b+
19	a+	b+	a- (T)
20	b+	b+	c+
21	0	c+	0
22	b+	a-	c+ (T)
23	a+	a+	a+
24	c+	b+	c+ (T)

* T = toxic reaction.

A word of explanation must be offered about the sequence of drug administration in these tables. The original sequences, chosen to conform with a latin square design, had to be modified because of an administrative error which reduced the dose of reserpine in the first period from 15 mg. to 0.75 mg. daily in group A. This quantity of reserpine (here designated r) was regarded as resembling more an inert substance than the drug in the treatment of such severely ill patients and it was thought advisable to include chlorpromazine and reserpine in full dosage in the remaining periods. A rearrangement of the sequence of administration therefore became necessary.

If the patient's condition is assumed to rate as 0 at the start of each six-weekly period, the ratings

made at the end of each period can be used to assess whether the patients had improved (a plus rating), became worse (a minus rating) or remained unchanged after the administration of each of the three substances. Table II relates these changes in the clinical condition to the three substances.

TABLE II
CLINICAL RESPONSE TO ALL DRUGS ASSESSED BY RATINGS AND COMPARED WITH PRE-TREATMENT CONDITION

Drug Employed	Responses		
	Unchanged	Improved	Worse
Chlorpromazine	5	15	4
Reserpine	2	12	10
Placebo	9	11	4

It is apparent that the responses differ, though not significantly ($\chi^2 = 9.46$; d.f. = 4; $0.1 > P > 0.05$) and that by this token chlorpromazine proved to be better and reserpine worse than the placebo.

Similar calculations are recorded in Table III, where the response to each drug is considered relative to the rating actually obtained at the beginning of each period.

TABLE III
CLINICAL RESPONSE OF ALL PATIENTS TO ALL DRUGS ASSESSED BY RATINGS COMPARED WITH CONDITION BEFORE ADMINISTRATION OF DRUG

Drug Employed	Responses		
	Unchanged	Improved	Worse
Chlorpromazine	7	14	3
Reserpine	5	6	13
Placebo	13	8	3

The result shows a significant difference ($\chi^2 = 18.40$, d.f. = 4, $P < 0.002$) in the same direction as in Table II and so indicates that the order of administration did not exercise an influence on the responses observed.

The extreme rating categories are of some interest. Seven patients were rated as a+ at some time during the 18 weeks. If this response is attributed only to that substance given to a patient not rated as a+ before its administration, then the response was associated with six patients on chlorpromazine, one patient on reserpine, and no patient on placebo. It is unlikely that such a distribution among the substances is due to chance ($P = 0.02$). The mean length of stay of these seven patients up to the beginning of treatment was 12.5 years compared with 17.2 years for the remainder, a difference which just fails to achieve significance ($t = 1.81$; $0.1 > P > 0.05$). A rating of c- was only given to four patients who were receiving reserpine.

Discussion

The results serve to indicate that in this sample

of patients chlorpromazine was the drug of choice, for its administration was associated with a higher degree of improvement and a lower degree of toxicity than that of reserpine.

No precise comparisons can be made with the results of other workers as it was possible to extract relevant statistics from only one paper, that of Campden-Main and Wegielski (1955). Table IV displays the results obtained in the treatment of schizophrenia with both drugs, taken from several papers, expressed in percentages and arranged in three degrees of improvement corresponding approximately to our own. The different methods used by the various authors render stricter comparison impossible: controlled experiment was attempted in only two studies.

TABLE IV
COMPARISON OF PUBLISHED THERAPEUTIC RESULTS OBTAINED WITH CHLORPROMAZINE AND RESERPINE IN THE TREATMENT OF SCHIZOPHRENIA

Author	Number of Patients	Drug	% Marked Improvement	% Moderate Improvement	% Slight Improvement
Hollister <i>et al.</i>	127	Reserpine	17	29	31
Kline and Stanley	126	"	20.6	40.5	23.8
Kinross-Wright	27	"	29	40	—
Tasher and Chermak	214	"	36	30	—
Campden-Main <i>et al.</i> †	41*	"	9.5	29	67
Barsa and Kline	150	"	23	43	25
Noce <i>et al.</i>	165	"	36	28	20
Glynn	75	"	36	44	20
Present authors†	24	"	13 (a+)	17 (b+)	21 (c+)
Kinross-Wright	97	Chlorpromazine	35	37	20
Vaughan <i>et al.</i> †	103	"	27	43	—
Goldman	201	"	19	16	47
Labhardt	106	"	18	40	26
Present authors†	24	"	25 (a+)	25 (b+)	13 (c+)

† Controlled study.

* One-third of these were affective disorders.

It will be seen that the figures for chlorpromazine in the present study are within 10% of others published. Kinross-Wright (1955) has also compared the efficacy of reserpine and chlorpromazine in the treatment of schizophrenics and found that chlorpromazine produced marked improvement in a larger number of cases. The results we have obtained with reserpine, on the other hand, are less satisfactory than those in most studies published hitherto. The more frequent toxic effects of the drug were responsible for this finding. During the treatment of only one case was chlorpromazine discontinued because of toxic effects, which have been fully discussed by Lomas, Boardman, and Markowe (1955). Reserpine had to be reduced on this account from 15 mg. to 10 mg. daily in three cases and from

10 mg. to 5 mg. daily in four cases. In five cases it was withdrawn.

The most important evidence of toxicity was the appearance of a Parkinsonian syndrome, which was observed in six patients receiving reserpine and in one patient receiving chlorpromazine. These patients all exhibited tremor, rigidity, bowed posture, immobile facies, loss or diminution of associated limb movements, and excessive salivation, resulting in an unmistakable and striking clinical picture. It is noteworthy that in one case the Parkinsonian syndrome made its appearance while the patient was receiving chlorpromazine and became more severe when reserpine was administered. In every case the symptoms disappeared when the drug was withdrawn. The only other undesirable effect of chlorpromazine was an oedema of the face which developed in one patient and subsided when the drug was discontinued.

The undesirable side-effects of reserpine were more numerous and more disturbing. They included restlessness (one case), incontinence of faeces (one case), and of urine (two cases), excessive salivation (three cases), bulimia (five cases), oedema of the face and epilepsy (one case). All these complications have been described by other authors (Barsa and Kline; Kinross-Wright).

From our experience it would appear, therefore, that a daily dose of 10-15 mg. reserpine by the oral route is too large. This inference is not supported by the reports of other authors. Kinross-Wright (1955), using doses up to 60 mg. daily, found no evidence of Parkinsonism until a dose of 30 mg. daily had been reached. Noce and others (1955) employed 2.5-10 mg. daily, noted minor side-effects only, and did not report Parkinsonism at all. Barsa and Kline (1955) state that of 200 patients, treated with up to 13 mg. reserpine daily, only five developed epilepsy and 10 Parkinsonism. Hollister and others (1955) obtained poor results with an oral dose of 1 to 4 mg. which they therefore increased to 5 mg. daily parenterally with an additional 2-8 mg. by mouth: the side-effects were slight and necessitated withdrawal of the drug in only one case; no Parkinsonism or epilepsy was noted in 127 cases treated. Glynn (1955) noticed no untoward side-effects using 5-15 mg. daily. Finally, in a clinical trial recently carried out at Netherne Hospital toxic effects of the reserpine were frequent but less troublesome, though Parkinsonian symptoms were prominent (personal communication).

No satisfactory explanation for these differences can be offered because of the obscurity attending the mode of action of reserpine (*Lancet*, 1955). Clinically it may be significant that the schizophrenic patients of the present study were chosen not for their aggressiveness and over-activity, as in most of the other studies cited, but on account of their apathy and inertia: such symptomatic differences may be token factors in the nature or phase of the schizophrenic illness which bear on the response to the drugs employed. Within the group reactions to the placebo also occurred in a number of cases (see Table I) and individual variation in response to both drugs was evident. The shorter mean hospital stay of those patients who achieved an a+ rating may be of some significance in this regard. Labhardt (1954) has reported a similar finding in patients whose stay in hospital was shorter. An adequate interpretation of group and individual difference must, however, await the results of further research.

Summary

A clinical trial designed to compare the efficacy of chlorpromazine and reserpine in the treatment of 24 chronic schizophrenic patients has been described.

The results indicate that chlorpromazine was responsible for improvement in a significantly higher proportion of cases than reserpine and that, in the doses employed, reserpine was responsible for the great majority of toxic effects observed.

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