A CONTROLLED TRIAL OF METHYL PHENIDATE (RITALIN) IN THE TREATMENT OF DEPRESSIVE STATES

BY

A. A. ROBIN and S. WISEBERG

From Runwell Hospital, Wickford, Essex

α Phenyl α piperidyl acetic acid methyl ester hydrochloride (methyl phenidate, "ritalin") has recently been introduced as a central nervous system stimulant. Animal experiments have shown that it increases psychomotor activity and has a pressor effect. Its effectiveness in counteracting the effects of hypnotics in man, experimentally and in cases of poisoning, has been reported, as has its usefulness in treating reserpine-induced depression. It has also been used in other depressive states where its action was considered to be beneficial in reducing the disorder of mood and in increasing confidence and speed of activity (Meier, Gross, and Tripod, 1954; Heiss, Becker, Hiltman, and Honsberg, 1956; Ferguson, 1955; Geller, 1955; Stier, 1955). None of these conducting clinical reports so far has utilized controls, and this paper describes a "blind" trial in which, in addition to general out-patient management and supervision, two comparable groups of depressed patients were given either the drug or a placebo over a period of four weeks.

Selection of Cases

All the patients treated were suffering from mild or moderately severe depressive reactions. Cases were selected by the following criteria: (a) Complaint of depression as a prominent symptom; (b) evidence of depression at interview, *e.g.* sad, careworn expression, general bearing, and lack of spontaneity.

In addition, all patients showed four or more of the following abnormalities: (a) Sleep disturbance; (b) loss of appetite and weight; (c) impairment of interests; (d) lack of confidence; (e) reduced alertness; (f) retardation or agitation.

Care was taken to exclude from the group cases where the anxiety component was sufficiently large to contraindicate stimulant medication or where symptoms of a physical nature were prominent.

Method

Sealed envelopes were prepared containing the prescription of placebo or methyl phenidate (10 mg. tablets) and were thoroughly shuffled. The placebo tablets were

identical in appearance with the active tablets. The psychiatrist and patient were thus unaware of the true nature of the tablets the patient received during the course of the trial.

Each patient was examined at an initial interview and the actuarial data, diagnosis, prognosis rating, etc., and the results of the modified Minnesota multiphasic personality inventory (M.M.P.I.) (Hathaway and McKinley, 1951), the Kent oral intelligence test (Kent, 1946), and an adapted Porteus maze test (Porteus, 1952) recorded. The initial prescription of 1 tablet b.d. was then given.

The patient was seen again after a maximum period of a fortnight and the dose of tablets raised from 1 b.d. to 2 b.d. if improvement was not evident.

The patient was seen a third time after four weeks and after neutral conversation the psychiatrist entered his rating of the results of treatment. The patient was then asked to rate his own improvement and was finally retested with the M.M.P.I. and the Porteus maze test.

Group Matching.—Forty-five cases were treated in all. Of the 23 control patients, none failed to complete treatment. Of the 22 drug-treated cases, two failed to return. Observed, therefore, over one month were 23 control patients and 20 drug-treated patients.

The groups corresponded closely in their sex distribution, age, civil state, personality type, precipitating factor, duration of illness, type of treatment given previously and concurrently, intelligence as measured by the Kent oral test, prognosis as estimated by the psychiatrist, and depth of depression as measured by the version of the M.M.P.I. devised by the authors (Table I).

The personality type was defined as obsessive or hysteroid according to which characteristics predominated. Obsessive characteristics were excessive cleanliness, orderliness, conscientiousness, vacillation, submissiveness, and lack of confidence. Hysteroid characteristics were over-demonstrativeness, impulsiveness, changeability, exhibitionism, and a tendency to vivid phantasy.

The prognosis rating was, after Davies and Shepherd (1955), simply based on a three-point scale from 1, indicating the best prognosis, to 3, indicating the worst.

The Kent oral test is a rapid clinical intelligence test. The examiner puts a number of questions ranging from, "What are houses made of?" or "What metal is

TABLE I
COMPARISON OF TREATMENT AND CONTROL GROUPS

	Drug	Placebo	Probability
Sex			
Male	4	10	$n = 1$
Female	16	13	$\chi^2 = 1.74$
			$P \geq 0.2$
Civil State			
Single	4	4	
Married	14	16	
Widowed, separated, or divorced	2	3	
Age			
< 20	1	3	
21 - 30	5	3	
31 - 40	6	7	
41 - 50	5	3	
51 - 60	2	6	
60 +	1	1	
Mean age in years ..	37.5 ± 11.5	39.5 ± 13.9	$t = 0.49$ $P = 0.6$
Duration of Illness			
3 months	8	9	
4 - 12 months	5	6	
13 months	7	8	
Mean duration in months	12.3	13.9	
Precipitant			
Social (finance, housing)	6	4	$n = 2$
Interpersonal (marital, death)	5	12	$\chi^2 = 3.35$
Physical (health, menopause)	9	7	$P \geq 0.2$
Personality			
Predominantly hysteroid	6	10	$n = 1$
Predominantly obsessive	14	13	$\chi^2 = 0.53$ $P \geq 0.5$
Modified M.M.P.I. Score	83.9 ± 4.5	81.9 ± 12.3	$t = 0.67$ $P = 0.5$
Kent Oral Test (2 untested in each group)			
Mental age in years ..	11.5 ± 2.1	11.9 ± 2.0	$t = 0.29$ $P = 0.8$
10	5	4	
11 - 13	10	13	
13	3	4	
Prognosis			
1	16	11	$n = 2$
2	3	8	$\chi^2 = 3.44$
3	1	4	$P \geq 0.2$
Previous Treatment			
In-patient	3	3	
Out-patient	8	12	
None	9	8	
Concurrent Treatment			
Night sedation	13	15	
No night sedation	7	8	

attracted by a magnet ?" to "Give me the names of four large cities" or "Name some birds". The raw scores of the four sub-tests (1, 3, 4, and 5) are added in two combinations (1, 3, and 4, and 1, 4, and 5) and from a scale the mental age may be derived.

To support the clinical judgment, a numerical estimate of the degree of depression was obtained using the depressive scale of the Minnesota multiphasic personality Inventory. Fifty-nine cards which constitute the depressive scale were extracted from the total of 550 which make the full test. Each card contains a statement of which examples are: "I seldom worry about my health", "I am happy most of the time", and "I cannot under-

stand what I read as well as I used to". In the full test the patient is asked to sort these statements into three groups: "True", "False" and "Cannot Say". The "Cannot Say" group was not used in the modified test in order to limit the number of indefinite responses so that the part-test should not be invalidated. The cutting line of normality in the full test is a score of 70, scores above this being regarded as abnormal. The modified test was tried on 11 controls of whom none scored over 70 (mean score 53.3 ± 7.7), while of 45 patients, 39 scored over 70 (mean score 84.1 ± 14.3) ($t = 6.71$; $P < 0.01$). Five patients later rated as "much improved" had a mean score of 60.0 ± 7.7 , 18 as "improved" had a mean score of 73.7 ± 15.6 , and 17 as "not improved" a mean score of 81.5 ± 12.7 . (Comparing "much improved" and "improved" $t = 1.83$, $P > 0.05$; comparing "improved" and "not improved" $t = 1.12$, $P = 0.3$; comparing "much improved" and "not improved" $t = 3.35$, $P < 0.01$).

To show whether the drug had any demonstrable effect on speed of performance, a set of Porteus mazes was used with the alternative paths blocked so that the subject merely had to trace a line as quickly as possible, avoiding the sides of the maze.

Results of Treatment

The results of treatment were assessed by (1) the rating scale administered by the psychiatrist; (2) the patient's rating of his own condition (in the rating scales a 5-point scale was used with +2 much improved, +1 improved, 0 no change, -1 worse, and -2 much worse); (3) re-testing with the M.M.P.I. and, (4) the Porteus maze test was repeated.

As has been remarked, of the 23 control patients none failed to complete treatment. Of the 22 cases treated with methyl phenidate, two failed to return at all. Three further cases failed to complete one month of treatment. Two of these three cases abandoned the drug because of ill-effects, primarily increased tension, one because she felt no effects from the tablets and thought them superfluous.

The results in the 40 patients who completed treatment are shown in Table II.

The results of the psychiatrists' ratings were added to give a sum in each case. These sums were written out in rank order and the median obtained. The number of methyl phenidate-treated cases and placebo-treated cases scoring more than and less than the median is given in Table II. Those scoring more than the median were assessed as "good results" and those less than the median as "poor results". The patients' symptom ratings were dealt with in the same way. The difference in time between the first and second maze performance was expressed as a percentage of the first performance and finally also dealt with as above, being classified as "speeded up" or "not speeded up or slower"

TABLE II
RESULTS OF TREATMENT IN DRUG-TREATED AND CONTROL GROUPS

	Drug					Placebo					Result	
<i>General Improvement</i>	+2	+1	0	-1	-2	+2	+1	0	-1	-2		
Psychiatrist's rating ..	3	7	7	0	0	2	11	10	0	0		
Patient's rating ..	5	8	1	3	0	4	11	7	1	0		
<i>Depression</i>												
Psychiatrist's rating ..	2	7	8	0	0	3	11	10	0	0		
Patient's rating ..	5	5	5	2	0	4	12	6	1	0		
<i>Symptomatic Improvement</i>												
Psychiatrist's rating:												
Retardation ..	0	5	11	1	0	1	7	13	2	0		
Confidence ..	2	7	8	0	0	2	8	12	1	0		
Alertness ..	1	2	14	0	0	0	3	20	0	0		
Range of interests ..	2	7	8	0	0	1	10	12	0	0		
Patient's rating:												
Sleep ..	3	7	6	1	0	4	5	14	0	0		
Confidence ..	3	4	9	1	0	1	8	12	2	0		
Alertness ..	1	10	6	0	0	0	6	16	1	0		
Range of interests ..	1	12	4	0	0	2	8	13	0	0		
<i>Sum of Symptom-sign Ratings</i>												
Psychiatrist's rating:												
Good result ..	10					13					$n = 1$	
Poor result ..	7					10					$x^2 = 0.02$	
Patient's rating:											$p \cong 0.8$	
Good result ..	10					12					$n = 1$	
Poor result ..	7					11					$x^2 = 0.18$	
											$p \cong 0.7$	
<i>M.M.P.I. Re-test</i>												
Scoring less than the median score of both groups	7					12					$n = 1$	
											$x^2 = 0.47$	
Scoring more than the median score of both groups	10					11					$p \cong 0.5$	
Mean score and S.D.	79.0 $\pm$ 9.9					73.6 $\pm$ 13.2					$t = 1.38$	
Mean reduction from original score ..	-4.9					-8.3					$p = 0.2$	
<i>Porteus Mazes</i>												
Speeded up ..	7					13					$n = 1$	
Not speeded up or slower ..	10					10					$x^2 = 0.8$	
											$p \cong 0.3$	

(Table II). The M.M.P.I. scores were also placed in rank order and the median obtained.

It will be seen that methyl phenidate in doses of 10 to 20 mg. b.d. was no more effective than the

placebo in its general effect on the patient, in the treatment of the depression, and in the treatment of other symptoms, and that methyl phenidate did not produce any speeding up of performance on the modified maze test.

Summary

A controlled trial of methyl phenidate was undertaken on 45 patients. The patients in the treatment and control groups were shown to be comparable. Two patients abandoned the drug because of unpleasant side-effects and three others did not complete the month's treatment period. In the remaining 40 patients, methyl phenidate, in doses of 10 to 20 mg. b.d., was shown to have no advantage over a placebo in the treatment of depression or associated symptoms and no increase in rate of performance was demonstrated with the drug. As well as clinical assessments, the patients were tested with a number of quickly performed tests which may have value in standardizing the results of out-patient studies.

We wish to thank Dr. R. Strom-Olsen and Dr. Henry Wilson for permission to publish, Dr. A. K. Pittman of Messrs. Ciba Laboratories Ltd. for supplies of methyl phenidate and placebo and other help in organizing this trial, and the pharmacists at the various hospitals at which the trial was carried out—Miss A. R. M. Foulds, M.P.S., Messrs. W. S. Hodgson, M.P.S., C. R. Wiseman, M.P.S., D.B.A., D. C. Phillips, M.P.S., H. W. Bartless, M.P.S., R. Bird, M.P.S.—for their careful co-operation throughout.

REFERENCES

- Davies, D. L., and Shepherd, M. (1955). *Lancet*, 2, 117.
 Ferguson, J. T. (1955). *Ann. N.Y. Acad. Sci.*, 61, 101.
 Geller, W. (1955). *Medizinische*, p. 606.
 Hathaway, S. R., and McKinley, J. C. (1951). *Minnesota Multiphasic Personality Inventory Manual*. Psychological Corporation, New York.
 Heiss, R., Becker, H., Hiltmann, H., and Honsberg, I. (1956). *Medizinische*, p. 260.
 Kent, Grace H. (1946). *Kent Series of Emergency Scales*. Psychological Corporation, New York.
 Meier, R., Gross, F., and Tripod, J. (1954). *Klin. Wschr.*, 32, 445.
 Porteus, S. D. (1952). *The Porteus Maze Test Manual*. Harapp, London.
 Stier, C. (1955). *Therap. d. Gegenw.*, 94, 92.