would be interesting to know the results of such tests in which the total dose, whether of individual components or of the mixture, was the same.

Synergic action between antibiotics of this type has been thought not to occur, but one other example has been reported by Oskam (1956): using a very unusual *in vitro* method, he claims to have demonstrated synergy between tetracycline and erythromycin. Substantiation of this finding by other methods might raise the question whether a mixture of tetracycline and erythromycin could perhaps be therapeutically superior to one of tetracycline and oleandomycin.

Summary

The *in vitro* antibacterial activity of oleandomycin has been found to be somewhat less than that of erythromycin. The merits of these two antibiotics and of spiramycin are considered, and the conclusion reached is that neither oleandomycin nor spiramycin has been shown to be therapeutically superior to erythromycin: it is probable that the ratios of *in vitro* activity are reflected to some extent in their action in the body.

The repetition of tests showing that a mixture of tetracycline and oleandomycin exerts a synergic action *in vitro* did not confirm the claims made.

Studies of cross-resistance among antibiotics of the erythromycin group showed that, whereas complete cross-resistance develops in strains of staphylococci habituated *in vitro*, erythromycin-resistant strains isolated from patients may or may not be resistant to oleandomycin and spiramycin. Efforts to identify the factors determining which type of resistance is developed were fruitless. The behaviour of strains resistant to erythromycin only was peculiar in several ways. The presence of this antibiotic in a culture medium conferred on them resistance to each of the others.

For not only the execution of much of this work, but for the conception of many of the experiments, I am indebted to my assistant, Miss Pamela M. Waterworth, whose experience in the study of antibiotics has been extensive and continuous since she first worked with penicillin in my laboratory in 1943.

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The Wellcome Trustees have made a grant of £5,000 to McGill University, Montreal, for the purchase of books related to the history of medicine needed to fill important gaps in the Osler Library. The Trustees have also agreed to provide £1,200 annually for twenty-five years to assist the further development of this library. A new extension and reading-room for the library, to be known as "The Wellcome Camera," is to be provided by McGill University.

A TRIAL OF FIVE TRANQUILLIZING DRUGS IN PSYCHONEUROSIS

BY

M. J. RAYMOND, M.R.C.P.Ed., D.P.M.

C. J. LUCAS, M.B., M.R.C.P.

M. L. BEESLEY, B.M., D.P.M.

B. A. O'CONNELL, M.B., D.P.M.

Department of Psychiatry, St. George's Hospital, London

AND

J. A. FRASER ROBERTS, M.D., D.Sc., F.R.C.P.

Clinical Genetics Research Unit, Institute of Child Health, The Hospital for Sick Children, Great Ormond Street, London

Prolonged or disabling anxiety and tension are non-specific accompaniments of many psychiatric disorders. Conflict and frustration may be important contributory factors, and where they can be defined and resolved symptomatic relief may follow. Hence the most effective approach may often be by psychotherapy, especially if the symptoms are of recent origin. As an additional measure, where distress is severe or prolonged drugs are often prescribed. Recently there has been a striking increase of available tranquillizers, as the new preparations are termed. In this paper we report the results of a controlled trial of certain drugs claimed to reduce tension. We are not here concerned with the use of any of these drugs in the treatment of psychotic conditions, for which purpose they are given in much larger dosage to patients under strict hospital supervision.

Among clinical trials which have been reported chlorpromazine in daily dosage ranging from 75 to 300 mg. has been claimed to be of value for the relief of tension in psychoneurotics (Garmany *et al.*, 1954; Winkelman, 1954; Azima and Ogle, 1954). Selling (1955) and Borrus (1955) report favourably on the use of meprobamate in tension states. The usual dose in Selling's series was four tablets a day (each tablet = 400 mg.) and the maximum dose he used was eight tablets a day. Lasagna (1956) found its hypnotic effect equal to that of phenobarbitone, while Hollister *et al.* (1956) found that meprobamate provided effective relief of anxiety symptoms in half or more of the patients treated. Encouraging results with benactyzine in treating psychoneurosis have been reported by Jensen (1955), Munkvad (1955), Davies (1956), Raymond and Lucas (1956), and Hargreaves *et al.* (1957). Seager and Leitch (1956), however, reported unfavourably on its use on a series of 13 patients. A dosage of 2 mg. thrice daily is in line with the recommendations of most workers.

Method

The patients were selected from those attending the psychiatric out-patient department of St. George's Hospital. They comprise a heterogeneous group of psychoneurotic disorders, the criterion of selection being the presence in the symptomatology of a tension component. They were patients who, in the opinion of the referring consultant, had a definite load of symptoms, and they were comparable to those patients for whom sedation is commonly and properly prescribed in general practice. During the trial period we attempted to include all such patients who attended the department. Each patient served as his own control, and was given six medicaments (five tranquillizers and a placebo) for successive two-week periods. He was told that he was taking part in a trial to find out which of several tablets was best for him. He was asked to record his judgment of

the effect of each drug day by day on a five-point scale, as set out on the form reproduced here. He was not told that one of the tablets was inert.

Date Issued:**Patient's Name:**

This trial is designed to find out which of several tablets is best for you. At the end of the day please record how you have felt, using the following signs:

No effect (you do not think the drug has had any effect on you, good or bad)	..	..	..	..	= 0
Good effect	..	..	..	..	= +
Very good effect	..	..	..	..	= ++
Poor effect	..	..	..	..	= -
Very poor effect	..	..	..	..	= --

You may reduce your own tablets if you wish, but please do not stop taking them altogether, no matter how well you may feel. If you do change your dose, please record this below.

Any Other Observations

Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7
Day 8
Day 9
Day 10
Day 11
Day 12
Day 13
Day 14

PLEASE BRING THIS FORM WITH YOU WHEN YOU KEEP
YOUR APPOINTMENT

It will be noted that the patient was not asked to compare either one period with another, or his state with his concept of his own "norm." No objective rating by the interviewing psychiatrist was attempted, for the aim of the inquiry was to find out how the patient felt, and the simplest way was to ask him. Only the chief pharmacist knew the drug to which each code letter referred, and he also allotted the patients successively to the orders of treatment, which were unknown to the doctor (see below under Experimental Design).

We were particularly concerned that each drug should be made available in dosage generally considered adequate for out-patient treatment in this group of disorders, and also that the patient could reduce his dose if he thought it was too strong. We also considered it important that the number of tablets prescribed should be the same for each treatment (two tablets thrice daily).

Dosage

Drug	Dosage two tablets three times a day. Each tablet containing:
1. Amylobarbitone ("amytal") ..	$\frac{1}{4}$ gr. (50 mg.)
2. Benactyzine ("suavatil," "nutinal") ..	1 mg.
3. Chlorpromazine ("largactil") ..	25 mg.
4. Meprobamate ("equanil," "miltown," "mepavlon") ..	400 mg.
5. "Sedaltine" (a poly-pharmaceutical preparation) ..	Carbromal B.P.C., 195 mg. Bromvaletone B.P.C., 65 mg. Aluminium hydroxide, 100 mg. Rauwolfia B.P.C., 0.25 mg. (Total alkaloids 55%) Mephanezin B.P.C., 100 mg.
6. Placebo (lactose) ..	5 gr. (320 mg.)

Experimental Design

The order in which treatments are given may affect the result. It is therefore necessary to use a balanced design, so that each treatment can be fairly compared with each of the others. It is further desirable to partition the variation in the analysis, so that irrelevant causes can be eliminated in assessing the direct results of the treatments. Moreover, some of the other causes of variation are of interest on their own account.

There were six treatments, including the placebo, so successive sets of six patients were allotted at random to six orders of treatment, the design being a Latin square. In each set of six patients each treatment occurs once in the first, once in the second, once in the third, etc., two-week period. The variation due to the differing two-week periods might be important. For example, some patients might start off with enthusiasm and become progressively less interested towards the end of the twelve weeks. If so, the treatments given towards the end might be undervalued compared with those given earlier.

There is a further source of variation which has hitherto been little studied in drug trials, though on general grounds it might sometimes be expected to be important; it seemed particularly necessary to consider it in the present observations. This is a possible carry-over or residual effect of the preceding treatment. In the present instance any such residual effect would probably be psychological rather than pharmacological. Thus, if a patient considered that a particular drug had had a very good effect he might be inclined to undervalue the effect of the next drug. Conversely, a drug which followed one which was thought useless or was disliked might tend to be overvalued. A very useful method for studying residual effects has been elaborated by Williams (1949), though, so far as we are aware, it has not yet been used in pharmacological trials. The Latin square needed is one which has the further property that in each set of six patients each treatment follows each other treatment (or is the first treatment) once. It is then possible to assess the magnitude of residual effects of previous treatments and also to eliminate this source of variation when making the basic comparison, which is the direct effect of the treatments.

The Latin square used is one of those given by Williams, the six treatments being designated A, B, C, D, E, F.

Patients	Two-week Periods					
	1	2	3	4	5	6
1	A	C	B	E	F	D
2	B	D	C	F	A	E
3	C	E	D	A	B	F
4	D	F	E	B	C	A
5	E	A	F	C	D	B
6	F	B	A	D	E	C

As patients entered the trial they were allotted successively to the orders of treatment 1-6, the sequence starting again with the seventh patient, and so on.

Results

The total number of patients included in the trial was 79.

Four had filled in at least some of the forms so badly that these could not be used, so that they were eliminated from the analysis.

Twenty-four patients defaulted. Eight did not return to the hospital after the first treatment; the numbers defaulting at the end of the five further fortnights of treatment were respectively 3, 5, 6, 2, 0. It would seem, however, that defaulting was not related to any particular order of treatment or to any particular drug. Thus the numbers defaulting on the six orders of treatment were 6, 4, 4, 4, 4, 2. It is even more important that defaulting was apparently not related to the drug taken during the fortnight after which the patient failed to attend. The numbers defaulting after the six drugs (including the placebo) were 5, 5, 4, 4, 4, 2. Both these series of numbers are as near equality as could reasonably be expected, and do not suggest that in respect of drug treatment the defaulters are other than a random loss. The number available for analysis was thus 51. The sets of six were formed by taking the first patient who completed order of treatment 1, the first completing 2, etc. In this way seven complete sets of six were formed, leaving nine patients belonging to further incomplete sets. The first part of this analysis deals with the 42 forming the completed sets.

The responses were made numerical, as follows: very good effect = +2; good effect = +1; no effect = 0; poor effect = -1; very poor effect = -2. The 14 responses for each drug were averaged to give a single figure.

The great majority of patients returned a daily response for each drug—that is, 14 responses—but there were some omissions. Patients were allowed to reduce the dose but asked to continue taking some of the drug if possible. Some, however, did omit the drug altogether on some days. With the exception to be mentioned immediately, the minimum number of responses was seven. For these incomplete schedules the average response was accepted. The exception related to one drug, chlorpromazine. Six patients discontinued treatment after three to six days, but gave definite reasons for doing so; for example: "Made me feel terrible; I did try," and "More tense and depressed." As a definite explanation had been given, the forms were included, the score being, as before, the average of the responses before treatment was abandoned.

The analysis of variance, based on the seven complete sets of six patients, is shown in Table I. The first line shows the variation due to differences between patients in pattern of response. The mean square, compared with the mean square for remainder ("error" in the technical sense) is highly significant. It is, of course, only to be expected that patients should show significant differences in their patterns of response.

The variation due to differences between patients can be subdivided into two parts—namely, the differences between the six orders of administration of drugs and the differences between patients on the same order of administration. This is shown on the second and third lines. The mean squares are almost identical, so that the responses are independent of the order of treatment selected.

The fourth line shows the variation due to differences between the six fortnightly periods. There is no indication of any secular effect during the trial period. Incidentally, the overall means for the six two-week periods do not suggest any trend. It is interesting to find that the patients' evaluation of the drugs is unaffected by the period within the 12 weeks during which they were given.

Full details of the method for calculating direct and residual effects of treatment are given by Williams (1949). Briefly, an adjusted sum of squares is calculated for direct effects corrected for residual effects, and similarly an adjusted sum of squares for residual effects corrected for direct effects. This gives alternative analyses as indicated by the double columns under sum of squares in the Table.

The result for residual effects is particularly convincing. The mean square is smaller than would be expected by chance—that is, is smaller than the residual or "error" mean square. The patients' evaluation of a drug is thus quite independent of the preceding drug. This is a point of general interest, and may also be taken as lending some support to the plan of avoiding comparisons in asking patients to record responses. Presumably the patients did what they were asked to do—namely, assess each day what they thought the effect had been: very good, good, nil, poor, or very poor—and they were uninfluenced in this by what they had thought of the preceding drug and *a fortiori* in all probability of still earlier treatments.

The direct effects of the treatments stand out as showing highly significant variation. There are large and real differences in the average response of the patients to the different drugs. As is shown below, the outstanding difference is that between amylobarbitone and the other five. Accordingly in the last two lines of Table I the variation due to

TABLE I.—Analysis of Variance. Seven Sets of Six Patients

Source of Variation	Degrees of Freedom	Sum of Squares	Mean Square	Variance Ratio	P
Patients	41	52.4028	1.278	1.94	0.005-0.001
Between orders of treatment	5	6.5634	1.313	1.03*	>0.2
Within " " "	36	45.8394	1.273		
Two-week periods	5	4.1499	0.8300	1.26	>0.2
Treatments:					
Direct effects	5	13.3804	2.552†	3.88	0.005-0.001
Residual effects of preceding treatment	5	1.4935†	0.2987†	0.45	>0.2
Remainder	195	128.2345	0.6576		
Total	251	199.6611			
Further analysis of variation due to direct effects of treatments					
Between amylobarbitone and the other 5 treatments	1	8.6006	8.601	13.08	<0.001
Between the other 5 treatments	4	4.7798	1.194	1.82	0.2-0.1
Total	5	13.3804			

* Divisor 1.273. † Residual effects corrected for direct effects. ‡ Direct effects corrected for residual effects.

treatments is broken down into two parts: the difference between amylobarbitone and the others, and the differences amongst the five others. Partitioning the variation in this way, the whole of the differences due to treatments can be accounted for by the difference between amylobarbitone and the others, and when this highly significant part is removed there is no significant variation between the other five treatments.

The foregoing analysis shows that it is justifiable to make simple and direct comparisons between the treatments, and the nine additional patients can be added to the 42 previously used. The frequency distributions of the responses of the 51 patients are shown graphically.

The mean response to each treatment in order of preference is as follows:

Amylobarbitone ..	+0.392	Placebo	-0.018
Meprobamate ..	+0.090	Chlorpromazine ..	-0.251
Sedaltine ..	+0.025	Benactyzine ..	-0.280

The response to the placebo shows considerable variation, as shown in the Chart, but on the average at least the patients have drawn the right deduction, for the mean score is very nearly 0, no effect.

A comparison of the five drugs with the placebo is shown in Table II.

TABLE II.—Comparison of Five Drugs with the Placebo

	Mean Difference	S.E.	Diff./S.E.	Significance
Amylobarbitone—placebo ..	+0.4098	0.4352	3.03	++
Meprobamate— " ..	+0.1078	0.1499	0.72	—
Sedaltine— " ..	+0.0431	0.1492	0.29	—
Chlorpromazine— " ..	-0.2333	0.1546	1.51	—
Benactyzine— " ..	-0.2627	0.1631	1.61	—

++ = $P < 0.01$; + = $P 0.05-0.01$; — = $P > 0.05$.

In calculating the standard errors of the differences, the fact that each patient is his own control is, of course, allowed for, account being taken of the intercorrelations.

Table III gives a comparison of amylobarbitone with the other five treatments.

TABLE III.—Comparison of Amylobarbitone with the Five Other Treatments

	Mean Difference	S.E.	Diff./S.E.	Significance
Amylobarbitone—meprobamate ..	+0.3020	0.1189	2.54	+
" —sedaltine ..	+0.3667	0.1590	2.31	+
" —placebo ..	+0.4098	0.1352	3.03	++
" —chlorpromazine ..	+0.6431	0.1772	3.63	++
" —benactyzine ..	+0.6726	0.1691	3.98	++

The results of the trial may therefore be summed up very simply. In terms of patients' judgments amylobarbitone is highly significantly superior to the placebo; the other drugs do not differ significantly from the placebo. Amylobarbitone is highly significantly superior to benactyzine and chlorpromazine and significantly superior to sedaltine and meprobamate.

One final point may be mentioned. Three patients returned 0, no effect, for every drug on every occasion. It might be argued that as they refused to discriminate at all they should be omitted. It happened that all three fell into one of the sets of six, so the calculations of Table I were repeated, omitting that particular set. The changes, however, proved to be very slight and did not affect any conclusion. Similarly, the omission of the three patients from Tables II and III made practically no difference and did not affect the significance or non-significance of any comparison.

Comment

To evaluate the effect of a drug in the treatment of the psychoneuroses must always be difficult. We considered that, for the purpose of the present trial, a simple day-by-day rating by the patient of how he felt was more likely

to give a measure of the effect of the drug than a retrospective assessment made at intervals in conjunction with an interviewing psychiatrist.

Since this was an out-patient trial, no attempt could be made to keep environmental factors uniform; indeed, it would not have been desirable to do so, since the purpose of the trial was to assess the drugs as they are used in daily practice. In any case, environmental and other variations have been randomized.

We considered that the patient would be more co-operative, and his observations more carefully made, if he knew that he was trying a series of tablets in order to find something which suited him personally. Since the patient knew the nature of the trial, standardizing the appearance of the tablets did not seem a point of great importance. All the tablets were white but different in size, and some were sugar-coated. The prescribed number of tablets was the same for each drug. It is of some interest, perhaps, that the tablets of amylobarbitone were the smallest and least impressive of the series. Incidentally they were also the cheapest, not excluding the placebo.

Summary

The five drugs included in this trial are claimed to relieve tension. They were amylobarbitone, benactyzine, chlorpromazine, meprobamate, sedaltine. A placebo was also included. The patients were psychoneurotic out-patients selected as having a tension component in the symptomatology. Each patient received each drug for two weeks, being asked to record daily his assessment of the drug on a five-point scale.

Of 79 patients included in the trial, the records of four were faulty, and 24 defaulted. Reasons are given for supposing that the loss was probably random.

Only the chief pharmacist knew which drug was being given, and a randomized design was used. The scores based on the patients' assessments did not vary according to the particular period during the 12 weeks when the drug was administered. The scores were independent of the drug previously given. In terms of the patients' judgments the average score for the placebo was close to a nil response, neither good nor bad. The average score for amylobarbitone was highly significantly superior to that for the placebo. There was no significant difference between the other four drugs and the placebo.

We are indebted to Dr. Desmond Curran for his interest and constructive criticism. We also thank him and the other consultants who referred suitable cases for the trial. We are grateful to Mr. A. Stirling, lately chief pharmacist, and to his staff at St. George's Hospital for their close co-operation throughout the trial, and to the following drug houses for supplying the drugs: Clinical Products Ltd. supplied the sedaltine; Glaxo Laboratories Ltd. supplied the benactyzine (suavatil); John Wyeth & Bro. Ltd. supplied the meprobamate (equanil). The chart was drawn by Mrs. M. G. Young.

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