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An evaluation of continuation therapy with tricyclic antidepressants in depressive illness[1]

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SYNOPSIS A double-blind clinical trial has been carried out to ascertain whether patients making a good recovery from depressive illness with tricyclic antidepressant medication derive any benefit from continuation of therapy with the same drug at a lower dose level. Of the 92 patients who entered the trial significantly fewer on active treatment relapsed during the six-month trial period: 23% as compared with 50% of patients receiving placebo. Patients with residual symptoms on entry to the trial derived more benefit from continuation therapy than patients who had made a complete recovery. The findings relate to a six-month trial period only, and any possible advantage of continuation therapy over a longer period remains uncertain.

Patients who have responded well to treatment for a depressive disorder, whether with drugs or with electro-convulsive therapy, are frequently prescribed further therapy with the aim of preventing a recurrence of depressive symptoms.

Although the efficacy of tricyclic antidepressants in the treatment of depressive illness is established (Medical Research Council, 1965; Wechsler, Grosser, and Greenblatt, 1965), very few studies have assessed the benefit of therapy after the disappearance of symptoms. Such therapy often consists of the continuation, usually at a lower dose, of a drug which has proved effective in the treatment phase. This type of further treatment will be referred to as 'continuation therapy'. This was chosen as a descriptive phrase which carries no assumptions as to the mechanisms involved, and is for this reason to be preferred to the more commonly used term, 'maintenance therapy', which is also used in other medical situations with a variety of connotations.

The trial reported here was designed to assess whether a six-month course of continuation therapy would prevent a recurrence of symptoms in patients successfully treated for a depressive episode with one of two tricyclic antidepressants —namely, imipramine and amitriptyline.

The few previous studies on these lines will be referred to in more detail later. However, in all of them electro-convulsive therapy was used as an integral part of the original treatment of the depressive episode, the further therapy being by drug alone. Strictly speaking, therefore, they

Report to the Medical Research Council Committee on Clinical Trials in Psychiatry. *Members of the Committee*: Professor Sir Austin Bradford Hill (Chairman), Dr. R. H. Awley, Professor M. G. Gelder, Professor D. A. Pond, Professor W. Linford Rees, Professor T. Ferguson Rodger, Professor Sir Martin Roth, Professor Michael Shepherd, J. I. Sutherland, Dr. M. H. Lader (Secretary).

The trial was undertaken in eight main centres (see below) and was coordinated by Dr. R. H. S. Mindham.

Regional organizers—Cardiff: Dr. A. C. Brown. *Chichester*: Dr. A. I. M. Glen, Dr. D. W. Pierce. *Edinburgh*: Dr. N. B. Fleitman. *Glasgow*: Dr. R. N. Herrington. *London*: Dr. R. H. Awley, Dr. R. H. S. Mindham. *Newcastle*: Professor J. L. Gibbons. *Oxford*: Dr. P. J. V. Beumont. *Sheffield*: Professor A. Jenner, Dr. I. B. Pearson.

The following psychiatrists participated in the trial—*Cardiff*: Dr. I. G. Pryce. *Chichester and region*: Dr. J. D. Carrissey, Dr. P. Sainsbury, Dr. J. P. Scrivener, Dr. D. W. Price. *Edinburgh and region*: Dr. J. W. Affleck, Dr. J. R. Crothies. *Glasgow and region*: Dr. A. Bruce, Dr. R. N. Herrington, Dr. P. W. Kershaw. *London and region*: Dr. R. H. Awley, Dr. J. J. Cockburn, Dr. J. L. Crammer, Dr. J. P. Crowsbery, Dr. Brenda Grant, Dr. K. Hamadah, Dr. E. A. Harvey-Smith, Dr. S. Jacobson, Dr. J. P. Leff, Dr. W. A. Lingman, Dr. C. McDonald, Dr. F. Post, Dr. E. Roderick-Jones, Dr. G. K. Shaw, Dr. D. C. Watt, Dr. R. H. Wheeler, Dr. J. W. P. Willis. *Newcastle and region*: Dr. K. Davison, Professor J. L. Gibbons, Dr. H. A. McClelland, Dr. D. D. Webster. *Oxford region*: Dr. P. J. V. Beumont. *Sheffield and region*: Dr. E. B. Gordon, Dr. E. Howarth.

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are not studies of continuation therapy, since the original response may have been due to the electro-convulsive therapy rather than to the drug treatment.

It was decided that there was a need for an assessment of continuation therapy, in the absence of other forms of treatment. The distinguishing features of the present trial are therefore that (1) it was confined to patients whose depressive episodes had shown complete, or nearly complete resolution, under treatment with a particular tricyclic antidepressant; and (2) it attempts to answer the question whether, if treatment with that drug alone results in the virtual disappearance of symptoms, there is any value in the continuation of therapy with the same drug at a lower dosage.

METHOD

The trial was conducted in eight different centres in different parts of Great Britain.

DEFINITION OF DEPRESSIVE ILLNESS

The study was confined to patients whose illness had revealed, as its primary manifestation, a persistent alteration in mood (with or without diurnal variation) which was evident to the examiner, which exceeded normal sadness, and which constituted a major symptom. This was supported by one or more of the following symptoms: self-depreciation with a morbid sense (or delusional ideas) of guilt; sleep disturbance; hypochondriasis, retardation of thought and action; agitated behaviour. The depression was the primary illness and did not constitute merely a secondary manifestation of some other psychiatric illness (such as schizophrenia or obsessional states). This definition was intentionally the same as that used in the previous trial (Medical Research Council, 1965) which had shown imipramine to be of therapeutic value in such cases.

ELIGIBLE PATIENTS

Patients were eligible for the study if they had been suffering from a depressive illness which fulfilled the above criteria and if they had shown a 'maximal response'—namely, unequivocal and sustained subjective and objective improvement with no room for further major improvement—to the initial treatment. This initial treatment had to consist of either amitriptyline or imipramine in a dosage of at least 150 mg daily for between three and 10 weeks. The patient could have been treated in hospital, or as an outpatient, or both. In addition to these main criteria, patients should not have received any other psychotropic drug treatment (apart from night sedation) during the final three weeks, nor electro-convulsive therapy during the previous two months. Patients of either sex between the ages of 25 and 69 inclusive were eligible. No patient suffering from an associated progressive disease, or with any indication of structural cerebral disease, or with a physical disease which would preclude the use of amitriptyline or imipramine was considered for the study. (Benign uncomplicated hypertension was not a contra-indication.)

GENERAL PLAN OF STUDY

The eligible patients were allocated by an essentially random procedure to one of two regimens of continuation therapy—namely, the same drug in a dosage of 75–150 mg daily, or a placebo of identical appearance, for a period of six months. The patient and the psychiatrist were both kept unaware of which regimen had been allocated.

Patients were assessed at the start of continuation therapy and on six subsequent occasions at intervals of about a month. If a patient had a further depressive episode during this period, which in the opinion of the psychiatrist required specific treatment, the continuation therapy was stopped and the psychiatrist started the treatment of his choice. The criterion of the effectiveness of continuation therapy was the relative frequency of such relapses in the two series.

CONTINUATION THERAPY

When the psychiatrist in charge was satisfied that the patient had shown a maximal response to the drug, and that the other criteria for eligibility were fulfilled, he took the decision to change to continuation therapy, and the patient was admitted to the trial. The day of this decision was referred to as the 'response date'.

Each centre held two series of numbered boxes of tablets for continuation therapy, one series for patients who had been treated with amitriptyline preparatory to the trial, and the other for patients who had been treated with imipramine. Each box contained the individual supply of continuation therapy for one patient. In each series about half the boxes contained tablets of the active drug; the remainder contained tablets of a placebo of identical appearance to the active tablets. The allocation of active and placebo tablets to the numbered boxes had been made jointly by the manufacturers and the MRC Statistical Research and Services Unit, in accordance with a prearranged list based upon random sampling numbers. As patients were admitted to the trial they were assigned to the next available number in the appropriate sequence (amitriptyline

or imipramine) and their continuation therapy was prescribed only from the box bearing the corresponding reference number.

The key to the allocations was retained in confidence by the manufacturers and the MRC Statistical Research and Services Unit, and was not available to the coordinator or anyone else connected with the treatment of patients in the trial. The psychiatrist in charge was, however, entitled to have this information on request, but only for a patient who had relapsed.

The prescribed dosage of the continuation therapy could be varied between three and six tablets daily, which corresponded to 75 to 150 mg of the active drug daily, at the psychiatrist's discretion; in practice, the dose was nearly always lower than during the initial treatment period. To minimize the risk of precipitating depressive symptoms by a sudden drop in dosage of active drug on entry to the trial, it was suggested that the dosage be gradually reduced during the latter part of the initial treatment period. Patients normally received their continuation therapy as outpatients. The psychiatrist supplied the patient, from the appropriate stock, with sufficient tablets to last a full month at the prescribed dosage, and the patient was instructed to return any unused tablets at the next examination. No additional medication apart from night sedation and aperients) was to be given. The patient's general practitioner was informed of this requirement, and was asked to notify any recurrence of depressive symptoms.

ASSESSMENTS

At the start of the initial treatment and on the response date the psychiatrist assessed the severity of eight individual symptoms (see Table 1), and made an overall rating of the severity of illness on a six-point scale. On the response date, the patient assessed his own condition on a four-point scale. Inquiry was also made about seven unwanted effects (see Table 5) during the preceding week. A note was made of the dosage of continuation therapy, and any permitted additional medication prescribed for the following month. Similar assessments, together with a count of returned tablets, were made at subsequent examinations of the patient, at intervals of about a month (these were usually four or five weeks, and sometimes six weeks). If a patient relapsed between set examinations, an extra progress assessment was made at the time of the relapse.

CRITERIA OF RELAPSE

If symptoms of depressive illness developed during continuation therapy which, in the opinion of the psychiatrist in charge, required specific treatment, the patient was regarded as having relapsed. In this context, specific treatment meant amitriptyline or imipramine in a dosage greater than 150 mg per day or the introduction of another psychotropic drug, or ECT, or admission to hospital with depressive symptoms. The psychiatrist was free to treat a relapsed patient as he saw fit.

Psychiatrists were urged not to remove patients from the trial in this way unless their condition gave rise to real concern, but it was emphasized that the decision in respect of any particular patient lay ultimately with the psychiatrist in charge.

RESULTS OF CONTINUATION THERAPY

PATIENTS IN TRIAL

Between November 1968 and December 1970 a total of 92 patients fulfilled the admission criteria. Table 1 presents the frequency of the individual symptoms and their severity, both at

TABLE I

CHANGES IN INDIVIDUAL SYMPTOMS DURING INITIAL TREATMENT PERIOD FOR THE 92 PATIENTS

	Start of initial treatment				*Response date*				
mptom	*Severe 3*	*Moderate 2*	*Slight 1*	*Absent 0*	*Severe 3*	*Moderate 2*	*Slight 1*	*Absent 0*	*Mean change in scores*
pressed mood	18	71	3	—	—	2	17	73	−1·9
xiety (psychic)	16	49	17	10	—	3	23	66	−1·5
matic symptoms (associated with mood change)	3	29	27	33	—	—	15	77	−0·9
somnia (any type)	26	43	15	8	—	4	21	67	−1·6
orexia	6	49	22	15	—	—	4	88	−1·5
ck of energy	24	50	13	5	—	1	23	68	−1·7
itability	7	35	35	15	—	2	13	77	−1·2
icidal ideas	4	26	30	32	—	—	1	91	−1·0

TABLE 2

COMPARISON OF TWO TREATMENT SERIES AT START OF CONTINUATION THERAPY

Characteristic	Active			Placebo		
	No. of subjects	% of total (50)	Mean value	No. of subjects	% of total (42)	Mean value
General						
Male	17	34	—	16	38	—
Female	33	66	—	26	62	—
Mean age (years)	—	—	45·8	—	—	48·3
Earlier depressive episodes						
None	30	60	—	24	57	—
As outpatient only	8	16	—	8	19	—
With hospital admission	12	24	—	10	24	—
Present depressive episode						
Initial severity (psychiatrist)						
Severely ill (rating 4 or 5)	11	22	—	11	26	—
Mean rating (on scale 0–5)	—	—	3·2	—	—	3·2
Treatment						
Electro-convulsive therapy	0	0	—	0	0	—
Amitriptyline	34	68	—	27	64	—
Imipramine	16	32	—	15	36	—
Mean duration (weeks)	—	—	7·5	—	—	7·5
Mean maximum daily dosage (mg)	—	—	166·0	—	—	175·0
Where treated						
As outpatient	28	56	—	17	40	—
Mean weeks in hospital (inpatients only)	—	—	5·0	—	—	4·4
Severity at response date (psychiatrist)						
Well (rating 0)	32	64	—	18	43	—
Minimal (rating 1)	14	28	—	19	45	—
Mean rating (on scale 0–5)	—	—	0·5	—	—	0·7

the start of the initial treatment and at the response date, and shows that improvements took place in all of the individual symptoms. The psychiatrists' overall rating of severity (on a 0–5 scale varying from well to extremely severe) averaged 3·2 at the start of the initial treatment and 0·6 at the response date.

COMPARISON OF ACTIVE TREATMENT AND PLACEBO SERIES AT START OF CONTINUATION THERAPY

Of the 92 patients, 50 were allocated to continuation therapy with the active drug and 42 received the placebo. The background characteristics of the active treatment and placebo series at the start of continuation therapy are summarized in Table 2. This comparison confirms that the random allocation procedure resulted in close similarity of the two series in terms of age, sex, history of earlier depressive episodes, and in the initial severity and treatment of the present depressive episode. However, by chance, a higher proportion of those allocated to the active treatment series were rated well at the response date (64%) than for the placebo series (43%). In nearly all the remaining patients (28% and 45% respectively) the severity of illness was minimal. Because of this disparity, the results for the patients who were rated 'well' and 'not completely well' are examined separately below.

RELAPSES DURING PERIOD OF CONTINUATION THERAPY

By the end of the period of continuation therapy 11 (22%) of the patients on active treatment had relapsed, compared with 21 (50%) of those receiving the placebo. This difference is significant at the 1% level (corrected $\chi^2 = 6{\cdot}70$ with 1 d.f.).

The percentages of patients remaining free of relapse in the two series at four-weekly intervals are shown in the Figure. In this Figure the data are presented in 'life-table' form, allowance having been made for the differing intervals between examinations and the consequent extension of the follow-up beyond 26 weeks for some subjects. The advantage shown to the active

reatment series throughout the whole period is lso significant at the 1% level (log rank test—'eto and Peto, 1972).

ELAPSE RATES IN DIFFERENT SUBGROUPS OF 'ATIENTS

Table 3 shows the relapse rates in the two series luring the period of continuation therapy for arious subgroups of patients.

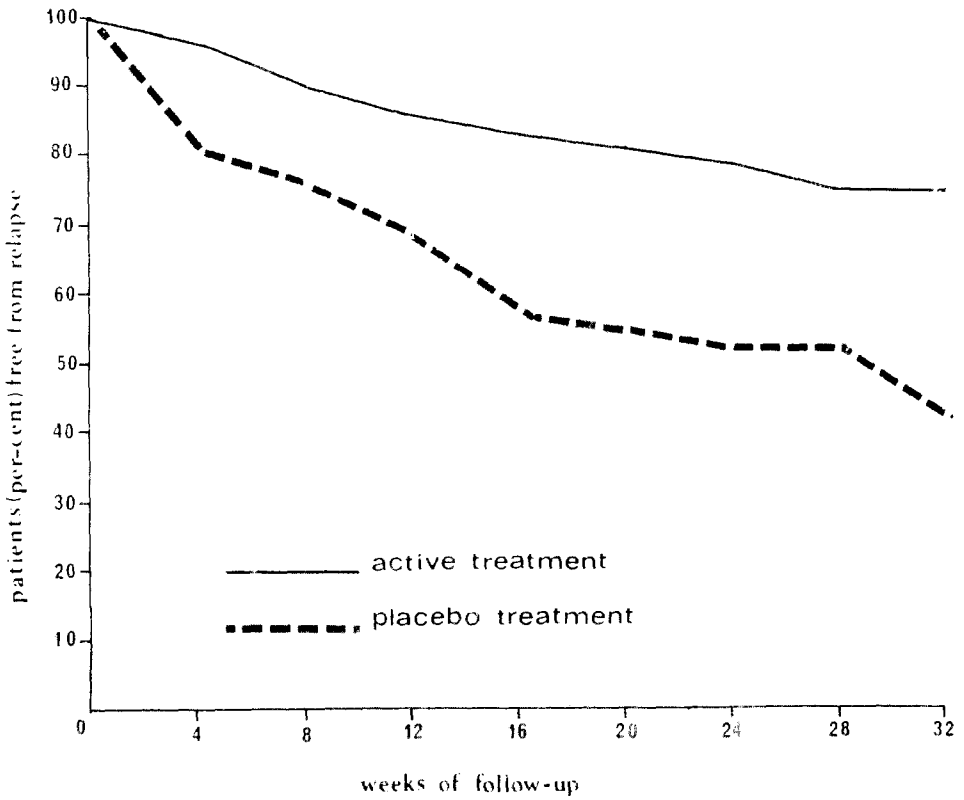
REATMENT CENTRES The response to continuation therapy was less marked in the patients dmitted to the Glasgow centre than in the atients admitted to other centres, but not to a tatistically significant extent.

EX Both sexes benefited from continuation herapy; the apparent advantage to males does ot attain statistical significance.

EARLIER DEPRESSIVE EPISODES The benefit from continuation therapy is apparently unrelated to the occurrence or severity of earlier depressive episodes.

INITIAL SEVERITY AND TREATMENT OF PRESENT DEPRESSIVE EPISODE Continuation therapy was of benefit both to those rated as severely ill and those not severely ill at the start of the period of initial treatment. It was of benefit both to those treated entirely as outpatients and to those who were admitted as inpatients for part or all of their treatment. For both characteristics the differences in benefit shown in Table 3 could well be due to chance.

TYPE OF ACTIVE TREATMENT The patients receiving continuation therapy with amitriptyline showed a very much lower relapse rate (24%) than those in the corresponding placebo group



GURE *Percentages of patients remaining free from relapse in the two trial groups at four-weekly intervals (Calculated standard actuarial methods.)*

TABLE 3

RELAPSE RATES IN VARIOUS SUBGROUPS OF PATIENTS

	Active			*Placebo*		
	No. of subjects	*Relapsed* No.	%	*No. of subjects*	*Relapsed* No.	%
All patients	50	11	*22*	42	21	*50*
Treatment centres						
London	21	4	*19*	15	8	*53*
Glasgow	16	3	*19*	15	4	*27*
Elsewhere	13	4	*31*	12	9	*75*
Sex						
Male	17	2	*12*	16	8	*50*
Female	33	9	*27*	26	13	*50*
Earlier depressive episodes						
None	30	8	*27*	24	11	*46*
As outpatient only	8	0	*0*	8	4	*50*
With hospital admission	12	3	*25*	10	6	*60*
Present depressive episode						
Initial severity (psychiatrist)						
Severely ill (rating 4 or 5)	11	3	*27*	11	7	*64*
Not severely ill	39	8	*21*	31	14	*45*
Where treated						
As outpatient	28	6	*21*	17	10	*59*
With hospital admission	22	5	*23*	25	11	*44*
Active treatment						
Amitriptyline	34	8	*24*	27	18	*67*
Imipramine	16	3	*19*	15	3	*20*
Severity at response date (psychiatrist)						
Well (rating 0)	32	6	*19*	18	6	*33*
Not completely well	18	5	*28*	24	15	*62*
Symptoms at response date (patient)						
No symptoms	30	7	*23*	16	4	*25*
Symptoms	20	4	*20*	26	17	*65*

(67%). However, the relapse rate in patients receiving continuation therapy with imipramine (19%) was almost the same as in the corresponding placebo group (20%). Thus, continuation therapy with amitriptyline appeared to be more effective than continuation therapy with imipramine. Because the contrast does not attain statistical significance (P=0·08 in the analysis outlined below[3]), this would normally be regarded as a rather large chance fluctuation and not as indicating a real difference in efficacy of continuation therapy.

It must, however, be remembered that initial treatment was not allocated at random. The psychiatrist had a free choice between amitriptyline and imipramine for the initial treatment, and that, as a consequence, the two series of patients may have been dissimilar at the start of continuation therapy. The patients selected for initial treatment with imipramine may have been clinically different from those selected for amitriptyline treatment; or the illness may have been more effectively treated with imipramine than with amitriptyline, so that the imipramine patients were less in need of continuation therapy. These possible differences could have either exaggerated or obscured a contrast in the effects of continuation therapy with the two drugs.

Relevant comparative information for the amitriptyline and imipramine patients is summarized in Table 4. There are no important differences between the two series of patients in terms of sex, age, history of earlier depressive episodes, and in the initial severity, treatment,

[3]Because of the disparity between the active and placebo groups that was noted above—namely, the differing numbers of patients who were rated well by the psychiatrist at the response date—relapse rates were calculated separately for the 'well' and 'not completely well' subgroups of amitriptyline and imipramine patients. The angular transformation was applied to the eight percentages, and the appropriate weighted linear contrast of the transformed percentages was tested as a normal deviate (Armitage, 1971, p. 375).

and response to treatment of the present depressive episode. There is thus no evidence either of clinical differences between the two groups of patients or of differing efficacy of the two drugs during the period of initial treatment.

As far as can be seen, the amitriptyline and imipramine series were closely similar at the start of continuation therapy. This analysis, therefore, does not help to decide whether the observed advantage of amitriptyline over imipramine is a result of a rather large chance fluctuation or a real difference in the efficacy of continuation therapy with the two drugs.

RESPONSE TO INITIAL TREATMENT

In addition to the classification of patients as 'well' or 'not completely well' at the response date, from the psychiatrist's ratings, the patients were also classified, according to their own assessment, as having 'no symptoms' of 'symptoms'. The relapse rates are shown for both subgroupings in Table 3.

Taking the psychiatrist's ratings, there is little evidence of a difference in benefit from active treatment between those rated 'well' and 'not completely well'. However, when the patients' own assessment is considered, it is apparent that those who reported symptoms at the response date received considerable benefit from active treatment, whereas those without symptoms derived little benefit. This difference is significant at the 1% level (in an analysis similar to that described in the footnote on page 000). The difference arises because patients reporting no residual symptoms had a relatively low subsequent relapse rate (about one quarter), which was not reduced by active continuation therapy, while, on the other hand, those reporting residual symptoms relapsed at a much higher rate (about two thirds) unless given continuation therapy.

In view of this finding, the possibility was considered that the slightly lower relapse rates at the Glasgow centre might be due to a preponderance of patients without residual symptoms, but this does not seem to be the explanation.

UNWANTED EFFECTS OF CONTINUATION THERAPY

Unwanted effects attributed to the treatment for the depressive episode were recorded for the week preceding the change to continuation therapy. A

TABLE 4

COMPARISON OF AMITRIPTYLINE AND IMIPRAMINE PATIENTS AT START OF CONTINUATION THERAPY

Characteristic	*Amitriptyline*			*Imipramine*		
	No. of subjects	*% of total (61)*	*Mean value*	*No. of subjects*	*% of total (31)*	*Mean value*
General						
Male	22	36	—	11	35	—
Female	39	64	—	20	65	—
Mean age (years)	—	—	47·6	—	—	45·6
Earlier depressive episodes						
None	35	57	—	19	61	—
As outpatient only	10	16	—	6	19	—
With hospital admission	16	26	—	6	19	—
Present depressive episode						
Initial severity (psychiatrist)						
Severely ill (rating 4 or 5)	16	26	—	6	19	—
Mean rating (on scale 0–5)	—	—	3·2	—	—	3·2
Treatment						
Electro-convulsive therapy	0	0	—	0	0	—
Mean duration of drug therapy (weeks)	—	—	7·5	—	—	7·5
Mean maximum daily dosage (mg.)	—	—	161·9	—	—	186·3
Where treated						
As outpatient	33	54	—	12	39	—
Mean weeks in hospital (inpatients only)	—	—	4·3	—	—	5·3
Severity at response date (psychiatrist)						
Well (rating 0)	35	57	—	15	48	—
Minimal (rating 1)	19	32	—	14	46	—
Mean rating (on scale 0–5)	—	—	0·6	—	—	0·6

similar record was made at each monthly examination during continuation therapy. Particular interest attaches to a comparison of the findings immediately preceding, and one month after, the change, since half the patients changed from an active drug to a placebo without being aware that this had occurred, and most of the patients had a reduction in the number of tablets prescribed. These findings are shown in Table 5.

Of 31 patients reporting a dry mouth in the week preceding the response date, 61% still reported a dry mouth after a month of active continuation therapy. Of 28 similar patients who changed to the placebo, 32% still reported a dry mouth after a month of active continuation therapy. The difference is significant at the 5% level ($\chi^2 = 3{\cdot}91$ with 1 d.f.). It will also be noted that among those who had not reported a dry mouth before the change to continuation therapy, this unwanted effect was reported by similar proportions of active drug and placebo patients a month later. It would, therefore, seem that few, if any, of the dry mouths reported with active drug in these patients could have been due to the drug.

As regards all the other unwanted effects listed, the proportions reporting these after a month of continuation therapy are similar in the active and placebo patients not reporting the effect earlier.

PATIENTS WHO DID NOT QUALIFY FOR ADMISSION TO THE TRIAL

The organization of the trial was complicated because arrangements had to be made for the prior identification of suitable patients and for their appropriate treatment, with a view to their eventual eligibility for this trial of continuation therapy. In total, 211 patients with depressive illness as defined above were so selected and started treatment with amitriptyline (141) or imipramine (70), although only 92 (43% of the amitriptyline and 44% of the imipramine patients) ultimately qualified for admission to the trial.

The reasons for the non-admission of the other 119 patients are shown in Table 6. In 49 (23% of the total) the drug treatment was discontinued by the physician, in 34 (16%) it was discontinued by the patient, and in 36 (17%) the patient did not satisfy one of the other admission criteria. The proportion of females in whom treatment was discontinued by the physician (28%) was much larger than the corresponding proportion for males (13%).

DISCUSSION

The finding that the tricyclic antidepressants are effective in the treatment of depressive illness has led to much speculation about their mode of

TABLE 5

UNWANTED EFFECTS OF TREATMENT REPORTED IN WEEK PRECEDING, AND ONE MONTH FOLLOWING, CHANGE TO CONTINUATION THERAPY

		Active			*Placebo*		
Type of unwanted effect	*Unwanted effect in week preceding response date*	*No. of subjects*	*Unwanted effect present at 1 month* (*No.*)	(%)	*No. of subjects*	*Unwanted effect present at 1 month* (*No.*)	(%)
Dry mouth	Present	31	19	*61*	28	9	*32*
	Absent	19	6	*32*	14	4	*29*
Constipation	Present	10	3	*30*	4	2	*50*
	Absent	40	4	*10*	38	2	*5*
Drowsiness	Present	10	3	*30*	8	2	*25*
	Absent	40	4	*10*	34	4	*12*
Blurring of vision	Present	8	1	*13*	8	1	*13*
	Absent	42	3	*7*	34	3	*9*
Sweating	Present	8	1	*13*	8	1	*13*
	Absent	42	3	*7*	34	2	*6*
Trembling	Present	9	2	*22*	7	1	*14*
	Absent	41	4	*10*	35	1	*3*
Difficulty in sleeping	Present	6	2	*33*	4	0	*0*
	Absent	44	1	*2*	38	2	*5*

TABLE 6

REASONS FOR NON-ADMISSION OF PATIENTS TO TRIAL OF CONTINUATION THERAPY

		All patients		*Males*		*Females*	
		(*No.*)	(%)	(*No.*)	(%)	(*No.*)	(%)
otal patients		211	*100*	70	*100*	141	*100*
reatment discontinued by physician:	Total	49	*23*	9	*13*	40	*28*
in favour of ECT		28		5		23	
worsening of condition (including hospital admission)		14		4		10	
because of side-effects		6		0		6	
for other reasons		1		0		1	
reatment discontinued by patient:	Total	34	*16*	17	*24*	17	*12*
response or partial response		8		3		5	
not responded		2		1		1	
not known		24		13		11	
ejected by criteria for admission to trial:	Total	36	*17*	11	*16*	25	*18*
responded too soon (within 3 weeks)		4		1		3	
not responded well by 10 weeks		29		9		20	
change in diagnosis		2		1		1	
not eligible because of age		1		0		1	
dmitted to trial	Total	92	*44*	33	*47*	59	*42*

ction. The various biochemical and pharmacological theories (Shepherd, Lader, and Rodnight, 968) are beyond the scope of the present paper, ut mention must be made of the two major inical contributions to this question. The rst is the hypothesis that the drugs suppress the mptoms of depression without altering the ourse of a postulated underlying disorder of nknown aetiology (Post, 1959); as a corollary f this hypothesis, medication must be continued ntil the underlying illness has come to a natural solution. Although this suggestion has gained any adherents, there has been little firm evience to support it. Secondly it has been suggested that the effect of an antidepressant drug ay be to cure the morbid process responsible r the depressive symptoms; in this case, conued medication after the complete remission symptoms can be regarded as prophylactic as much as the aim is to prevent the development of fresh depressive episodes.

REVIOUS CONTROLLED STUDIES OF CONTINUATION HERAPY

here have been few previous controlled studies continuation therapy. Seager and Bird (1962) lected a series of 43 depressed inpatients itable for electro-convulsive therapy (ECT): ey were allocated at random and without the owledge of the patients or doctors, to two oups which received either imipramine 50 mg t.d.s. or a placebo identical in appearance. After one week on this regime, ECT was given until an adequate clinical response had been achieved. Seven days later the patients were discharged and seen monthly for the next six months, continuing their medication throughout this period. Half the patients in each group were switched to the opposite drug treatment to that which they had received in hospital, so that there were four treatment regimens in all. Among 28 patients who completed the six month follow-up, relapse was recorded in two of the 12 on imipramine during the follow-up period, and 11 of the 16 on placebo.

Imlah, Ryan, and Harrington (1965) reported a study in which the treatment of depression by ECT was combined with either imipramine, phenelzine, or a placebo administered by random allocation. At the time of discharge from hospital the patients on drugs were instructed to continue taking the same drug in the same dosage for six months (although not all of them did); those on placebo were discharged without medication. Six months later the relapse rate among patients who had continued to take their medication was significantly lower than among those given no medication in the follow-up period. However, assessment of progress was not made without prior knowledge of the treatment regimens to which the patients had been allocated.

Kay, Fahy, and Garside (1970) reported a study in which depressed patients were treated

with electro-convulsive therapy and either amitriptyline or diazepam. After recovery the patients continued on the same drug treatment for a further seven months and were assessed at intervals of one month, four months, and seven months respectively after the completion of treatment with ECT. A large number of patients was lost to the study for a variety of reasons, but among those continuing under observation, the relapse rate in those receiving amitriptyline was markedly lower than in those on diazepam. However, since diazepam can exert a depressant action in its own right, its use as a control substance in such a study is inappropriate.

In 1968 a study was begun which was designed to compare the effects of amitriptyline, placebo, and no medication over a period of six months among inpatients who have made a good recovery from a depressive illness which has been treated initially with amitriptyline. This study also aims to compare the effect of twice weekly psychotherapy with a regimen involving minimal contact between the patient and the psychiatric team, and these two alternative methods of management are superimposed on the general design of the study. The six possible regimens will be compared for their effectiveness in preventing a recurrence of depressive episodes as shown by the relative frequency of relapse in the various groups, ratings of depression, and the social adjustment of the patients. A preliminary report of this study is in the press (Paykel, Klerman, Dimascio, Weissman, and Prusoff, 1972).

All the completed studies suggest that the tricyclic antidepressants may be partially effective in preventing relapse in patients who have been treated for depressive illness. However, that of Seager and Bird (1962) was on a very small scale, the assessments of Imlah *et al.* (1965) were not 'blind', and there are objections to the 'control' drug used by Kay *et al.* (1970). Moreover, in all these three trials the original treatment included electro-convulsive therapy, so that in none has it been possible to study the effect of continuation therapy with exactly the same treatment as was effective in the treatment of the depressive episode.

INITIAL TREATMENT

The present study was not designed to evaluate or compare the initial treatments. The psychiatrist had a free choice from two established tricyclic antidepressant drugs; the only stipulation was that the daily dosage should be 150 mg a day or more. It was striking that so large a proportion of patients failed to show satisfactory response to treatment: approximately 40% were given alternative treatment, and another 25 patients (about 14%) responded but were not sufficiently well at the end of 10 weeks' treatment to be eligible for continuation therapy in this trial. The failure of a substantial proportion of patients to respond well to antidepressants is well documented. The proportion in the present series is similar to the proportion of non-responders to imipramine in the MRC trial (1965), in which 29 of 63 patients (46%) failed to respond to imipramine after four weeks and required alternative treatment.

EFFECTIVENESS OF CONTINUATION THERAPY

Taking the frequency of relapse as the criterion of the effectiveness of continuation therapy, the results of this trial clearly show that those patients who received the active drugs had an advantage over those who received placebo.

The actual consumption of drugs is of some importance in this context. It has been shown that patients frequently fail to take their medication (Wilcox, Gillan, and Hare, 1965; Wilson and Enoch, 1967), and attention has been drawn to the need to ensure that treatment is taken as prescribed if the results of a trial are to be valid (Porter, 1970; Leff and Wing, 1971). In the present study, it was unfortunately not possible to obtain supplies of tablets with an added tracer substance such as riboflavin, because the safety of such a combination would have had to be tested beforehand, thereby considerably delaying the start of the trial. For this reason a less satisfactory technique—namely, a count of the tablets returned to the clinic each month—was employed but yielded too few data for useful analysis. Had the trial shown no advantage to patients on the active drug, the possibility that the finding was due to a failure to take medication would have been a major consideration in the interpretation of results. In the event, however, although any failure to take the treatment may have underestimated the value of continuation therapy at the prescribed dosage, it cannot have obscured its benefits.

Whereas these findings confirm the suggestive evidence from earlier studies, it should also be noted that many patients who received the active drug relapsed and that a substantial proportion of those patients who received the placebo remained well.

The high rates of relapse, even in those patients receiving continuation therapy with active drugs, may be explained in various ways. First, they might reflect the existence of discrete forms of mental disorder within the heterogeneous group of 'depressive illnesses', some of which are more responsive to drug treatment. Such a hypothesis cannot be tested directly by a study of this type. Secondly, they could be held to support the hypothesis that the effect of the drugs is merely to suppress depressive symptoms, rather than to relieve an underlying disorder, and that this is shown by the reappearance of symptoms when the drugs are withdrawn or the dosage reduced. This study provides no direct evidence of the existence of an underlying disorder of this kind. Finally, relapse might be related to such non-specific factors as the social circumstances of patients, the quality of care, the personalities of patients and staff, and other therapeutic factors unrelated to the pharmacological effects of the drugs used. The variation in the results furnished by the several centres in the investigation could be taken to support this notion.

The observations that so many patients remained well on the placebo and the possibility that prolonged administration of a tricyclic antidepressant may carry a danger of serious toxic effects (Coull, Crooks, Dingwall-Fordyce, Scott, and Weir, 1970; Boston Collaborative Drug Surveillance Program, 1972) serve as reminders that continuation therapy should not be undertaken unless there are good indications for it. Ideally, it would have been desirable to identify those patients likely to benefit from continuation therapy, but in the event it was not possible to specify any particular syndromes in which continuation therapy was of value. On the evidence of this study, all that can be stated is that the patients who show most benefit from continuation therapy are those who have made an incomplete recovery from a depressive illness and continue to show a few lingering symptoms.

The apparent differential effect of continuation therapy with amitriptyline and imipramine is surprising and calls for comment. It has already been pointed out that no significant differences between patient-groups were demonstrable before the start of continuation therapy, and that an unusual chance fluctuation could account for the differences shown in Table 3. On the other hand, in view of the possibility that the efficacy of the two drugs may have differed during the phase of continuation treatment, it is perhaps worth recalling the suggestion made by several workers that much of the therapeutic value of the antidepressants is non-specific, their main action being due to sedative or related effects (Hollister, Overall, Shelton, Pennington, Kimbell, and Johnson, 1967; Paykel *et al.*, 1968). Further to this argument, imipramine has been reported as having very little effect in controlling anxiety (Porter, 1970), whereas amitriptyline has a marked sedative action (Blashki, Mowbray, and Davies, 1971) and has been shown to have a marginal advantage in the treatment of the tense or agitated patient (Burt, Gordon, Holt, and Hordern, 1962). In addition, the antidepressant effect of the two tricyclic antidepressants, dothiepin and amitriptyline, has been shown to be closely related to their effect in controlling anxiety (Lipsedge, Rees, and Pike, 1971). It is possible, therefore, that any advantage to amitriptyline in continuation therapy could be largely attributable to its sedative effects rather than to its antidepressant properties. There is, however, no way of examining this proposition further on the basis of the data available.

It should be emphasized that all the patients studied had already shown a response to the drug given in continuation therapy and that the present study furnishes information on only the six months immediately following remission of symptoms. It does not necessarily follow, therefore, that continuation therapy with tricyclic antidepressants would be effective in patients initially treated by other methods, or for longer periods.

UNWANTED EFFECTS OF MEDICATION

The study has provided interesting data on the unwanted effects of amitriptyline and imipramine. Many unwanted effects were reported, both in the week before the response date and in the first month of continuation therapy. How-

ever, the incidence of most of the unwanted effects was as high among the patients receiving placebo as among those receiving the active drugs, and so cannot be attributed directly to the active drug. The exception was 'dry mouth', which did occur more frequently in the first month of continuation therapy in patients continuing on active treatment who had previously noted this unwanted effect.

These results have a bearing on the assertion that the 'blindness' of many trials of antidepressant drugs may be vitiated by a difference between the unwanted effects of the drug and the control treatment (Leyburn, 1967; Elkes, 1969; Porter, 1970). In the present study, the psychiatrist could not have discovered the nature of the tablets, with any degree of consistency, from observations of unwanted effects. This finding supports the value attaching to the 'blindness' of the assessments of relapse and so the validity of the comparisons of the active drug and placebo.

MULTI-CENTRE METHOD OF INVESTIGATION

The complex nature of the present investigation should be emphasized. It was conducted by means of a multi-centre collaborative approach, as in the MRC trial of treatments of depressive illness (1965). This approach was adopted here because of the need to identify a relatively large number of patients at the start of initial treatment in order to yield an adequate number of patients eligible for the trial of continuation therapy. This meant that it was necessary to record the relevant details and assessments for all patients who might become eligible for the trial. There have been few, if any, previous trials in which this preliminary step has had to be built into the structure of the investigation.

A full-time coordinator was appointed to deal with the administrative aspects of the study over a total period of about four years. In addition, regional organisers were appointed in the eight centres to make local arrangements and over 100 consultant psychiatrists were approached with a view to participation. Forty-two psychiatrists reported on patients receiving the initial treatment and 34 of them entered patients in the trial of continuation therapy. However, in the circumstances of the present study, there is no alternative to a multi-centre trial with an elaborate coordinating structure.

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REFERENCES

Armitage, P. (1971). In *Statistical Methods in Medical Research*. Blackwell: Oxford.

Blashki, T. G., Mowbray, R., and Davies, B. (1971). Controlled trial of amitriptyline in general practice. *British Medical Journal*, **1**, 133–138.

Boston Collaborative Drug Surveillance Program (1972) Adverse reactions to the tricyclic-antidepressant drugs. *Lancet*, **1**, 529–531.

Burt, C. G., Gordon, W. F., Holt, N. F., and Hordern, A. (1962). Amitriptyline in depressive states: a controlled trial. *Journal of Mental Science*, **108**, 711–730.

Coull, D. C., Crooks, J., Dingwall-Fordyce, I., Scott, A. M., and Weir, R. D. (1970). Amitriptyline and cardiac disease. *Lancet*, **2**, 590–591.

Elkes, A. (1969). *Mode of Action of Imipramine*, MD Thesis, University of London.

Hollister, L. E., Overall, J. E., Shelton, J., Pennington, V., Kimbell, I., and Johnson, M. (1967). Drug therapy of depression. Amitriptyline, perphenazine, and their combination in different syndromes. *Archives of General Psychiatry*, **17**, 486–493.

Imlah, N. W., Ryan, E., and Harrington, J. A. (1965). The influence of antidepressant drugs on the response to electroconvulsive therapy and on subsequent relapse rates. *Journal of Neuro-Psychopharmacology*, **4**, 438–442.

Kay, D. W. K., Fahy, T., and Garside, R. F. (1970). A seven-month double-blind trial of amitriptyline and diazepam in ECT-treated depressed patients. *British Journal of Psychiatry*, **117**, 667–671.

Kuhn, R. (1958). The treatment of depressive states with G 22355 (imipramine hydrochloride). *American Journal of Psychiatry*, **115**, 459–464.

Leff, J. P., and Wing, J. K. (1971). Trial of maintenance therapy in schizophrenia. *British Medical Journal*, **3**, 599–604.

Leyburn, P. (1967). A critical look at antidepressant drug trials. *Lancet*, **2**, 1135–1138.

Lipsedge, M. S., Rees, W. L., and Pike, D. J. (1971). A double-blind comparison of dothiepin and amitriptyline for the treatment of depression with anxiety. *Psychopharmacologia*, **19**, 153–162.

Medical Research Council. (1965). Report by Clinical Psychiatry Committee. Clinical trial of the treatment of depressive illness. *British Medical Journal*, **1**, 881–886.

Paykel, E. S., Price, J. S., Gillan, R. U., Palmai, G., and Chesser, E. S. (1968). A comparative trial of imipramine and chlorpromazine in depressed patients. *British Journal of Psychiatry*, **114**, 1281–1287.

aykel, E. S., Klerman, G. L., Dimascio, A., Weissman, M. M., and Prusoff, B. A. (1972). In *Psychopathology and Psychopharmacology*. Edited by J. O. Cole. John Hopkins Press: Baltimore. (In press.)

eto, R., and Peto, J. (1972). Asymptotically efficient rank invariant test procedures. *Journal of the Royal Statistical Society*, Series B, **135**, 185–206.

orter, A. M. W. (1970). Depressive illness in a general practice. A demographic study and a controlled trial of imipramine. *British Medical Journal*, **1**, 773–778.

orter, A. M. W. (1971). Clinical research in general practice. *British Medical Journal*, **1**, 600–602.

ost, F. (1959). Imipramine in depression. *British Medical Journal*, **2**, 1252.

eager, C. P., and Bird, R. L. (1962). Imipramine with electrical treatment in depression-controlled trial. *Journal of Mental Science*, **108**, 704–707.

Shepherd, M., Lader, M., and Rodnight, R. (1968). *Clinical Psychopharmacology*. English Universities Press: London.

Wechsler, H., Grosser, G. H., Greenblatt, M. (1965). Research evaluating antidepressant medications on hospitalized mental patients: a survey of published reports during a five-year period. *Journal of Nervous and Mental Disease*, **141**, 231–239.

Willcox, D. R. C., Gillan, R., and Hare, E. H. (1965). Do psychiatric out-patients take their drugs? *British Medical Journal*, **2**, 790–792.

Wilson, J. D., and Enoch, M. D. (1967). Estimation of drug rejection by schizophrenic in-patients, with analysis of clinical factors. *British Journal of Psychiatry*, **113**, 209–211.