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Continuation Therapy with Amitriptyline in Depression

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SUMMARY Thirty-two patients who had responded to amitriptyline (150 mg daily) when suffering from a depressive illness were allocated either to receive placebo or to remain on the same medication for one year.

Plasma concentrations of the drug were regularly estimated. There was no correlation between plasma concentration and subsequent residual affective morbidity. In spite of considerable encouragement, three of the patients did not take the prescribed amitriptyline and they all relapsed. Five out of sixteen patients who received placebo relapsed. None of the patients who continued to take amitriptyline relapsed.

It is emphasized that the patients studied were selected, inasmuch as they were apparent responders to amitriptyline. It is concluded that this group of patients should continue to be treated with antidepressant medication for eight months after apparent recovery, and care should be taken to ensure the patients' compliance.

The value of maintenance therapy in recurrent affective disorders has been investigated in numerous trials. Lithium has been investigated under double-blind conditions and has been found to be superior to placebo in both unipolar and bipolar illness (e.g. Baastrup *et al*, 1970; Coppen *et al*, 1971; Prien *et al*, 1973), and also to the antidepressant maprotiline in unipolar illness (Coppen *et al*, 1976).

The present investigation is concerned with the value of continued tricyclic medication after apparent recovery from a depressive episode. Most investigators (e.g. Seager and Bird, 1962; Imlah *et al*, 1965; Kay *et al*, 1970; Mindham *et al*, 1974; Paykel *et al*, 1976), have shown the advantage of continuing medication for periods of up to eight months. However, none of these investigators estimated plasma concentration of tricyclics and the dosage of drug was not always defined. Because of this, and because of a high rate of non-compliance, especially in out-patients who feel well (Blackwell, 1976), the benefits of continued medication are still not satisfactorily delineated.

The following is a report of a placebo-controlled, double-blind study of the continuation of amitriptyline after recovery from a depressive episode, with regular monitoring of plasma tricyclic concentration.

Patients and Methods

The investigation was carried out as a double-blind study in which the antidepressant efficacy of amitriptyline was compared with placebo tablets in patients after they had recovered from a depressive episode following treatment with amitriptyline. During the depressive episode 23 patients were treated as in-patients and 9 as out-patients. They all recived only amitriptyline. The continuation study was conducted when the patients attended the follow-up out-patient clinic at six-weekly intervals for one year.

Patients

Male and female patients with ages ranging between 33 and 70 years were included in the study (Table I). They were all suffering from

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TABLE I

Details of patients in the study

Treatment Group	N	Sex		Age (yr)		Weight			
						Pre-Entry		End of Study	
		M	F	Mean	S.E.	Mean	S.E.	Mean	S.E.
Placebo	16	3	13	51.6	3.5	59.7	2.9	60.0	3.6
Amitriptyline	16*	3	13	55.3	2.7	62.8	3.2	65.4‡	3.8

* 3 of these patients were non-compliers and each was treated as an in-patient for relapse.

‡ Paired comparison (from pre-entry) $p < 0.01$ (using the 13 patients who took amitriptyline).

primary depressive illness (MRC Trial, 1965). In the case of 11 patients this was the first episode, and the other 21 had had one or two previous episodes. In these 21 patients the interval between the present episode and the last episode ranged from 8 months to 16 years (mean 44 months). None of them had any history of mania. A patient was considered clinically recovered when the Hamilton Rating Scale (HRS), (Hamilton, 1960) score was six or less, using the first sixteen items of the scale. Patients had to maintain recovery for at least six weeks. At the end of this period, the patients were selected randomly either to receive identically looking placebo tablets or to continue with amitriptyline in the previous dosage.

Assessment of affective morbidity

The patients were seen in the out-patient clinic every six weeks, and their psychiatric state was assessed by interview during which the patient was rated on the HRS (the first sixteen items only).

Any patient who showed increased morbidity during the study was treated, if the symptoms were mild, by supportive psychotherapy; if more serious the patient was admitted to hospital. A relapse was defined in this study as an increase in morbidity sufficiently severe to warrant admission to hospital. If their condition so demanded, a decision to give electro-convulsive therapy (ECT) was made. During a relapse the amitriptyline or placebo was continued as before. No additional physical therapy other than ECT was used. These patients after clinical improvement were subsequently followed up in the out-patient clinic during the rest of the trial year. No other psychotropic drugs were administered except nitrazepam, as a hypnotic and in a few cases diazepam as a daytime anxiolytic.

Subjective side-effects

These were measured by means of a standardized check list (Braithwaite *et al*, 1971) which was administered initially before starting the continuation trial (baseline side-effects score). The check list was completed at each visit, and the baseline score was subtracted from the subsequent scores to indicate change in side-effects. Weight was measured regularly during this one year assessment period at each attendance.

Plasma concentration of tricyclics

Heparinized blood samples were collected for the estimation of the plasma concentrations of amitriptyline and its metabolite nortriptyline during each attendance at approximately 09.00 hrs. The plasma was stored at −20°C until analysis. The plasma concentrations following initial clinical recovery and prior to the random allocations of active and placebo medications were considered as the baseline drug concentration. The tricyclic concentrations were estimated by a gas chromatographic method, using a sensitive nitrogen detector (Jorgensen, 1975).

Results

In both groups the patients' mean age and weight were similar at the beginning of the study (Table I). At the beginning of the study the two groups had similar mean HRS (Table II).

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TABLE II

Mean Hamilton Rating Scale during the First and Second 6-Month Period

Treatment Group	N	Hamilton Rating Scale Pre-Entry Mean	S.E.	First 6 months Mean	S.E.	Second 6 months Mean	S.E.
Placebo	16	2.13	0.4	5.40*	1.1	3.53	0.9
Amitriptyline	13	2.46	0.6	3.83	0.9	3.92	1.0

* Significant increase from pre-entry $p < 0.005$.

Psychiatric morbidity

Three female patients in the amitriptyline group who relapsed during the trial were subsequently found to have nil plasma concentration of the drug. They were admitted to the hospital and successfully treated with ECT. These patients we referred to as non-compliers, and they were not included in the amitryptyline group for the purposes of analysis. Table II summarizes the affective state of the two groups of patients. There was significant increase ($P < 0.005$) in the mean HRS (compared to baseline scores) during the first six months in the placebo treatment group. There was no significant change in mean HRS for the first or second six months period in the 13 patients treated with amitriptyline (omitting the non-compliers). Five female patients in the placebo group as shown in Table III and Table IV relapsed between 5 and 23 weeks and were then treated with ECT. During the rest of the trial period they remained well. If one excludes the non-compliers, none of the patients in the amitriptyline group relapsed during the one year follow-up period. This is significantly different ($P > 0.01$) from the placebo group ('G' Test: Sokal and Rohlf, 1969). Thus, 8 patients who did not take amitriptyline (5 from the placebo group and 3 non-compliers from the active group) relapsed.

Subjective side-effects

It will be seen in Table V that there was a progressive reduction in the side-effects score in patients receiving inactive medication. The patients treated with amitriptyline reported side-effects significantly higher than those patients receiving placebo tablets.

Weight gain

The mean weight of patients treated with amitriptyline was significantly higher than that of the group treated with placebo (Table I).

TABLE III

Relapse and admission to hospital

Treatment	Relapsed	No relapse
Placebo group	5	11
Amitriptyline group	0	13

3 Non-compliers in the amitriptyline group required admission but are not included in the table.
All 8 patients admitted to hospital received ECT.
'G' test: 6.79: $p < 0.01$.

TABLE IV

Details of patients (female) who relapsed

Placebo group Age	Placebo group Time of relapse	Amitriptyline group (3 non-compliers) Age	Amitriptyline group (3 non-compliers) Time of relapse
43	19 weeks	61	45 weeks
66	20 weeks	40	17 weeks
33	17 weeks	40	10 weeks
43	5 weeks		
56	23 weeks		

TABLE V

Change in side-effects during the trial

Treatment group	N	Side-effects score Difference from baseline 1st six months Mean	S.E.	2nd six months Mean	S.E.
Placebo	16	−3.83	1.3	−5.13	1.4
Amitriptyline	13	+1.92*	1.1	+1.44*	1.7

* Placebo vs Amitriptyline $p < 0.01$.

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Plasma tricyclic concentrations

The plasma concentrations of amitriptyline and nortriptyline of 13 patients (again excluding the non-compliers) treated with amitriptyline during the study are shown in Table VI. There was a slight but progressive increase in the mean plasma concentrations of both these tricyclics. There were significant correlations between the basal concentration, the mean of the first 6 months and the mean of the second 6 months plasma concentrations of amitriptyline, nortriptyline and the total tricyclic concentrations (Table VII).

Relationships of the plasma tricyclics concentrations with clinical state

There was no significant correlation between the residual psychiatric morbidity (mean HRS of first and second 6 months period) and the plasma concentrations of AT, NT or total tricyclic (Table VIII).

TABLE VI

Plasma concentrations of tricyclics for 13 patients who took active medication

Plasma Concentration (ng/ml)	Baseline		During first six months		During second six months	
	Mean	S.E.	Mean	S.E.	Mean	S.E.
Amitriptyline	97.9	8.6	106.0	10.0	118.9	15.2
Nortriptyline	91.2	11.0	99.2	15.2	121.1	22.2
Amitriptyline + Nortriptyline	189.1	13.8	205.1	22.2	240.0	34.1

TABLE VII

Correlations between plasma levels of amitriptyline and nortriptyline at baseline and the mean of the First and Second and Second 6 Month Period

			Plasma concentration			
			Amitriptyline		Nortriptyline	
			r	p	r	p
Baseline	vs	1st six months	0.68	0.01	0.82	0.001
Baseline	vs	2nd six months	0.81	0.001	0.84	0.001
1st six months	vs	2nd six months	0.92	0.001	0.97	0.001

TABLE VIII

Correlation between plasma levels of tricyclics and morbidity

Correlation			1st Six Months r	2nd Six Months r
Amitriptyline concentration	vs	Morbidity (mean HRS)	−0.112	−0.134
Nortriptyline concentration	vs	Morbidity (mean HRS)	0.224	0.243
Amitriptyline + Nortriptyline concentration	vs	Morbidity (mean HRS)	0.103	0.055

All correlations between plasma drug concentration and morbidity—not significant.

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Discussion

This study has shown the value of continuation therapy. Over one year patients taking amitriptyline remained well, while no less than 42 per cent of those not taking the drug relapsed. All the relapses but one in the patients not taking amitriptyline occurred within six months after starting the study.

Amitriptyline 150 mg taken at night seemed an adequate dose, and within these limits there was no correlation between amitriptyline, nortriptyline and plasma concentration and clinical response. The side-effects were not excessive and seemed a small price to pay for prevention of relapse.

All but one of the relapses occurred within six months of starting the trial, which actually commenced six weeks after apparent recovery from a depressive episode. There was one relapse which occurred at 45 weeks, but this happened with a non-complier. Although one would be tempted to suggest a continuation period of one year, we feel that eight months will be a reasonable period as all but one of our patients who relapsed did so within seven and a half months after apparent recovery. In view of the cardiotoxicity of tricyclic drugs (Burrows *et al*, 1976), it is obviously not in the patient's interest to continue for longer than necessary.

The question of compliance is important, as no less than 3 out of 16 patients (19 per cent) did not comply in spite of considerable encouragement. In lithium therapy one can get immediate information on the patients' drug state, but tricyclics are expensive, time-consuming and difficult to estimate. Perhaps the addition of a simply estimated marker would be the best method of ensuring compliance.

Our sample was of patients who had responded to amitriptyline. We would suggest that probably the same situation exists after recovery by any treatment, i.e. that the patient remains vulnerable to further attacks for at least six months. Similar continuation treatment in the form of regular supervision and adequate dosage with tricyclics or other antidepressants would therefore seem desirable and a very worth while form of preventive medicine after the acute attack has subsided. In the case of patients who have had three or more attacks of depression we would recommend lithium prophylaxis (Coppen *et al*, 1971; Coppen *et al*, 1976). The management of patients who did not respond to tricyclic medication remains a problem. Whether patients who have responded to electro-convulsive therapy would be kept well during the subsequent eight months period of high risk of relapse by being given amitriptyline remains to be established.

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