Continuation Therapy with Tricyclic Antidepressants in Relapsing Depressive Illness

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An important problem in the management of patients suffering from depressive disorders is that many patients, having initially shown a good response to treatment, relapse when treatment is stopped. In recent years there has been an increasing interest in the treatment of relapsing disorders in other branches of medicine, as for example in recurrent myocardial infarction or relapsing ulcerative colitis. In the case of depressive disorders there have been two main approaches to drug treatment; the use of lithium salts and of the tricyclic drugs (Mindham, 1978). Earlier studies have examined the effects of tricyclic antidepressants in preventing recurrent depressive episodes following treatment with electroconvulsive therapy (Seager and Bird, 1962; Imlah et al., 1965; Kay et al., 1970). More recently studies of the continued administration of drugs following initial treatment with the same drug have been reported. I should like to outline a study with which I was concerned and to draw attention to what I see as its most important practical and theoretical implications (Mindham et al., 1973).

Method

The trial was conducted in eight centres in different parts of Great Britain under the aegis of the Medical Research Council; 42 consultant psychiatrists took part.

Definition of Depressive Illness

The definition of depressive illness used in the Medical Research Council’s trial of the treatments of depression was chosen. This trial showed imipramine to be of therapeutic value in depressive illness (Medical Research Council, 1965). The definition is as follows.

‘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).’
Eligible Patients

Patients were eligible for the study if they had been suffering from a depressive illness which fulfilled these criteria and which showed a marked subjective and objective improvement in response to treatment. The initial treatment consisted of either amitriptyline or imipramine in a dosage of at least 150 mg daily for between 3 and 10 weeks. The patients could have been treated in hospital or as out-patients or both. In addition to these main criteria, patients had not received other psychotropic drug treatment (apart from night sedation) during the final 3 weeks, electroconvulsive therapy during the previous 2 months. Patients of either sex between the ages of 25 and 69 inclusive were eligible. Patients suffering from an associated progressive disease or from structural cerebral disease or from physical disease which would preclude the use of amitriptyline or imipramine were excluded.

Procedure

When the patients had recovered from the depressive illness, eligible patients were allocated by a random procedure to one of two regimes 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 6 months. Both the patients and the psychiatrists were unaware of the allocation to the treatments.

Patients were assessed at the start of continuation therapy and on six subsequent occasions at intervals of about 1 month. If a patient had a further depressive episode during this period, which in the opinion of the psychiatrist required more active treatment, the continuation therapy was stopped. The criterion of effectiveness of continuation therapy was the relative frequency of relapses in the two series of patients.

Results

Patients Studied

A total of 92 patients fulfilled the admission criteria. An examination of the assessments before treatment and on the response date showed that there had been a marked reduction in the frequency of depressive symptoms.

Of the 92 patients, 50 were allocated to continuation therapy with the active drugs and 42 received the placebo. Random allocation to the treatment resulted in the two series being closely similar in most respects.

Relapses during Follow-Up

By the end of the period of continuation therapy 22% of the patients on active treatment had relapsed compared with 50% of those receiving the placebo (this difference is statistically significant). The percentages of patients remaining free of relapse in the two series at 4-week intervals are shown in figure 1. It is evident that there is an advantage to those receiving active treatment throughout the period of observation.

The data were examined to see what factors might predict an advantage
from continuation therapy with the active drugs. When those patients who were rated as ‘well’ and ‘not completely well’ in response to the initial treatment were considered separately; it was clear that those patients who had residual symptoms

Continuation Therapy in Depressive Illness 51

Fig. 1. Proportion of patients remaining free from relapse in the two trial groups at 4-week intervals.

at the time that continuation therapy was commenced had a greater advantage from receiving the active drugs than the patients without residual symptoms. There were no other predicting factors.

Unwanted Effects of Medication

Unwanted effects attributed to the treatment for the depressive episode were recorded for the week preceding the change to continuation therapy. A similar record was made at each monthly examination during continuation therapy. 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 patients who changed to the placebo, 32% still reported a dry mouth after a month of continuation therapy. For all other unwanted effects, however, the proportions reporting the presence of symptoms were similar in the active and placebo groups.

Yale Study

A rather similar study was conducted at Yale at about the same time as the study just described. In this study all the patients received amitriptyline initially and were then divided into three groups to receive amitriptyline, placebo or no medication for 6 months. These groups were further sub-divided into those groups who had supportive psychotherapy from a social worker in addition to other measures, and those who were followed by a psychiatrist routinely. Thus, there were six treatment cells in all. The trial showed an advantage to the patients who received amitriptyline, as far as relapse was concerned, irrespective of other measures (Paykel et al., 1975).

Mindham 52

Table I. Forecasts by participants and others of the likely outcome of the trial of continuation therapy in depressive illness.

Were the Studies Really Necessary?

Now that these trials have been completed it might well be asked ‘Were
these trials really necessary’? Could not these results have been foreseen? Shortly before completion of the British study, I wrote to all those who had been invited to participate and asked them to forecast the outcome. The answers make it plain that there was no consensus view of the likely effects of continuation therapy, prior to the results of the study being made known (table I).

Discussion

The results of the study show an advantage to those patients who received the active drugs. Some aspects of the study are of particular interest, and I should like to discuss them now.

The findings have some relevance to the effectiveness and mode of action of tricyclic antidepressants. When the tricyclic antidepressant drugs were first introduced, two main suggestions were made as to the mechanism of their clinical effects (as distinct from their biochemical effects). One hypothesis was that the drugs suppressed the symptoms of depression without altering the course of a postulated underlying disorder (Post, 1959); the implication of this hypothesis is that medication should be continued until the underlying disorder has reached a natural resolution. An alternative hypothesis is that the effect of the tricyclic drugs is to cure the morbid process which is responsible for the depressive symptoms; in which case medication would only be necessary until symptoms had been relieved and this would be taken to indicate a reversal of the underlying morbid process. Although the study does not bring direct support to either of

Continuation Therapy in Depressive Illness 53

these hypotheses; nor evidence of the presence of a more fundamental disorder underlying the depressive symptoms, the findings would appear to fit the first hypothesis more readily. The observation that patients who had residual symptoms at the ‘response date’ showed greater benefit from the active drug might be taken to suggest the continued presence of an underlying disorder while depressive symptoms were held partly in check by medication.

Clinical Relevance of the Findings

The clinical implications of the study are more clear-cut but certain reservations should be made. Medication with tricyclic antidepressants should clearly be continued until recovery of a depressive disorder is well established. In a depressive illness of the type covered by the definition given, drugs should be administered over a period of months. In the trial itself, patients received drugs for a period of up to 36 weeks, and even 6 months after the disappearance of most of the depressive symptoms there was an advantage to patients continuing to receive the active drugs. In this respect the study confirms a well-established clinical
practice. The study also showed that patients suffering from persistent symptoms had a particular advantage from receiving the active drug for an extended period.

An important finding was that many patients remained well without continued medication, so that it cannot be concluded that all patients require prolonged treatment. Unfortunately, we have limited information as to how those most likely to benefit may be identified. The presence of persistent symptoms, even if minor, is a clear indication for drug therapy to be continued.

In interpreting the results of this study it should not be forgotten that the patients studied were a special group: they all showed moderately severe, or severe symptoms initially; they had all responded to the drug which was given in continuation therapy before becoming eligible for the study, and they were closely supervised for an unusually long period of time.

In common with other methods of prophylaxis, such as the use of lithium salts, the tricyclic drugs have been reported to have some serious toxic effects. A few cases of sudden death among patients with heart disease receiving amitriptyline have been reported (Coull et al., 1970; Boston Collaborative Drug Surveillance Program, 1972). The drugs are known to have the property of altering electrical conductivity in the heart which may be relevant to these reports (Hamilton and Mahapatra, 1971). There may well be other, as yet unknown, effects of chronic administration of these drugs.

During the period of continuation therapy, unwanted effects of drugs were not an important practical problem, and although they were experienced by a majority of patients, only a small number of patients discontinued the treatment on account of them. This is probably attributable to the natural tendency for unwanted effects to subside as treatment is continued, as described by Åsberg et al., (1971), and to the lowering of the dosage of drugs in some patients when continuation therapy began. The finding that only the dry mouth produced by the drugs in some cases, allowed the active drug to be distinguished from the placebo with any degree of confidence is of some interest. It is also notable that unwanted effects were common amongst those receiving the placebo. In the past great stress has been placed on the possibility that the blindness of double-blind studies might be vitiated by the unwanted effects of the tricyclic drugs (Leyburn, 1967; Porter, 1971). The study shows that this risk is less than might have been expected.

Lithium Salts versus Tricyclic Antidepressants

Lithium salts have been shown to be of value in the prevention of both episodes of depressive illness and of mania. How do the tricyclic drugs compare? A
study by Prien et al. (1973) investigated this matter over a 2-year period. The findings show that in both unipolar and bipolar manic-depressive illness, lithium carbonate reduces the risk of relapse into both manic or depressive states; whereas imipramine protects only against relapse into depressive states. Thus, where a patient suffers from a bipolar manic-depressive illness lithium salts are to be preferred; but where a patient suffers from recurrent depressive illness the choice between the remedies can be made on the grounds of convenience (Prien et al., 1973).

Summary

Patients who have suffered a depressive illness frequently relapse when treatment is stopped. A controlled study of continued medication after clinical recovery was carried out. Of 92 patients studied, 22% of those who received amitriptyline or imipramine relapsed during 6 months of observation, compared with 50% of those who received placebo. Patients who experienced persistent residual symptoms derived more benefit from the active drug during continuation treatment than those who made a complete recovery from their illness.

References


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Continuation Therapy in Depressive Illness 55


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