Antidepressants may not assist recovery in practice: a naturalistic prospective survey

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A total of 130 people attending psychiatric hospitals within 6 months of onset or relapse of an episode of depressive disorder were interviewed about their symptoms and treatment at the time of their initial contact. After a mean 4-month interval, 119 were reassessed to test the hypothesis that patients treated with antidepressants would be significantly more likely to be clinically improved compared with those untreated. Severity and duration of the episode emerged as the only significant clinical predictors of clinical improvement. Patients on treatment with antidepressants at the start of the study showed a nonsignificant trend for a lesser degree of clinical improvement, even when clinical severity and compliance were taken into account. Those who were not commenced on treatment until later in the study also fared no better than those who were never prescribed antidepressants. The effect of low doses of antidepressants (almost always a tricyclic) appeared to be less beneficial than either higher doses or clinical management without antidepressant drugs. The need for further experimental and naturalistic studies conducted over various periods of time and the implications for clinical practice, medical audit and the appropriate use of health outcome indicators are discussed.

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The effectiveness of the growing number of antidepressant drugs has been clearly demonstrated in a large number of well designed and conducted clinical trials, both in hospital and general practice patients (1–3). However, the efficacy of a treatment in carefully conducted trials does not guarantee that it will be properly or effectively used in clinical practice. This can only be shown by means of naturalistic studies on epidemiologically representative samples.

The study described here was primarily designed to investigate the effects of stressful life events and social support on the type and the course of depression in a clinically depressed population (4–6). To achieve this, other data capable of influencing course and outcome were collected, including sociodemographic, clinical and treatment details. Thus, information collected at two points in time made it possible to examine the longer term outcome of antidepressant drug treatment prospectively, in a cohort of psychiatric patients treated either by general practitioners or by psychiatrists in hospital practice.

Material and methods

Patients

A general description of the study and its design is provided by Bebbington et al. (4). As far as possible, our patients were consecutive series of men and of women from the Camberwell area presenting at the Maudsley Hospital outpatient and emergency clinics with new episodes of depression. The design required equal numbers of men and women (4). Men continued to be collected when the sampling target for women had been achieved and it proved necessary to top up with 14 men from adjacent and sociodemographically similar areas of south London (4). Altogether, 130 patients were assessed and follow-up clinical data were obtained on 120. Because of the selection criteria, the patients were a representative sample of those seeking psychiatric treatment for discrete and relatively recent episodes of depression.

Measures and procedures

Interviews with potential subjects were carried out by a research psychiatrist as soon as possible after they had been seen at the Maudsley Hospital. The first interview determined the subjects' mental state, clinical history, use of psychotropic medication prior to and since the onset of their episode of depression and basic sociodemographic characteristics. This was closely followed by a second interview with one of the other members of the team, concerning recent experience of adversity and details of social contacts. Social networks and social support were assessed by the Interview Measure of Social Relationships (IMSR). This instrument is described in detail elsewhere (7).

After a mean interval of 4 months (range 3–6 months), the subjects were contacted again, and their mental state was once more established at a third interview. Details of interim treatment and disposal were obtained.

Clinical assessment

The mental status of our subjects was established through the PSE-ID-CATEGO system (8, 9). For entry to the study, the subjects had to be diagnosed clinically as suffering from a depressive episode that dated from within 6 months of the interview with a period of at least 6 months free of symptoms prior to onset. The actual date of onset or relapse was carefully established, as was the number of previous episodes of depression in relapse cases.

The use of the PSE-ID-CATEGO system made it possible to assess clinical outcome in several different ways (5). In this study, 2 methods were used. The first used the difference between the 2 PSE-ID levels to divide subjects according to whether they had improved by at least 2 levels on the Index; and in the second method, used in the multiple regression analyses, the ID level at follow-up was the outcome variable and the initial ID level was included in the equation as a predictor. Both methods have the advantage that the initial severity of clinically significant symptoms is controlled, and that the assessment of recovery therefore takes into account change during the follow-up period.

Treatment received

At the first clinical interview, conducted by PD or TB, patients were asked about preceding treatment. A coding was made of the mode of referral to the Maudsley Hospital: self-referral; general practitioner referral; other doctor. Medication before onset and medication after onset were separately coded as: cyclic antidepressant; monoamine oxidase inhibitors (MAOI); benzodiazepine and other. The dosage of antidepressant was also coded (using dose equivalents for non-tricyclic preparations) as: none prescribed; equivalent of up to 100 mg of amitriptyline per day; equivalent of over 100 mg of amitriptyline per day. The interviewing psychiatrist also enquired about compliance with treatment, using his clinical judgement to make one of the following ratings: rigorous compliance; occasional lapses; failure to comply probably affected the efficiency of medication. The examination of this issue was carried out in some detail, and we tried to ensure that questioning was sympathetic and sensitive.

At the follow-up clinical assessment, which was also carried out by the same psychiatrist, patients were asked about interim treatment and disposal since the first interview. Patients were asked whether they were then being treated only by their general practitioner, or through psychiatric services of whatever type; a coding of lapsed from treatment was also available. We also coded whether electroconvulsive therapy (ECT) had been prescribed and if so, if the course had been completed. Drug use was coded as at the first interview, and again a judgement of compliance was made.

Statistical methods

The association between each predictor and the recovery index (or category) was examined independently in the whole sample. Multiple regression analysis was then carried out, including predictor variables that had been identified from the initial analyses. In building models the choice of variables and order of including them was specified beforehand. Because sampling procedures differed according to gender, the main effect of sex was included in multiple regression analysis on the total sample before the entry of other potential predictor variables. Checks were also made for violations of the necessary statistical assumptions, and for the presence of multi-collinearity.

Results

Details of the sociodemographic and clinical characteristics of the sample have already been described (4, 5). Briefly, the sample consisted of 33 men and 34 women with endogenous depression (that is, CATEGO Classes D and R) and 21 men and 42 women with neurotic depression (Classes N and A): 99 (76%) were definite cases at the first interview, and 30 were threshold cases on the Index of Definition. Altogether, 114 of the 130 patients fulfilled DSM-III-R criteria for major depressive disorder (10). Although we only included patients in the study

who had been well for at least 6 months before the start of this episode, 86 (67%) represented relapses in patients who had had previous mental illness from which they had recovered. The mean duration of the current episode was 11 weeks at the time of our initial assessment. Seventy-six (64%) of those reassessed with a PSE at the third interview had improved by at least two ID levels.

Preceding treatment

Of 130 patients initially assessed, 113 were on no maintenance medication prior to the onset of their episode of depression; 8 had been on a tricyclic antidepressant, 3 a benzodiazepine (alone) and 6 were on other drugs (which did not include an MAOI). The study included the 8 patients on maintenance tricyclics, each of whom developed a clear-cut relapse of depression: the reasons for this remain unclear.

Forty patients were self-referred: almost all of these had made direct contact with the walk-in Maudsley Hospital Emergency Clinic. Of the remainder, 78 were general practitioner referrals and 12 had been referred to the psychiatric service by another medical practitioner.

By the time we carried out our initial research interviews (130 patients), a total of 78 patients (63%) had been prescribed an antidepressant drug (which in 73 cases were tricyclics): however, at the time of interview, 50 patients were on a dosage that did not exceed 100 mg of amitriptyline, or its equivalent. Twenty-six were prescribed a benzodiazepine only. Thirteen were prescribed another drug and according to information obtained at the follow-up interview, at least 4 of these were non-tricyclic antidepressants such as mianserin. No MAOIs had been prescribed at this stage.

Patients prescribed an antidepressant differed from those not prescribed only with respect to age: those on antidepressants had a mean age that was almost 5 years older ($t = -1.83$, $P < 0.10$). Those on medication had exactly the same CATEGO-ID level (illness severity) as, and were no more likely to have an endogenous (CATEGO R or D) diagnosis, than those not prescribed; however, among those who commenced antidepressants, there was a nonsignificant trend for patients on higher doses (greater than 100 mg amitriptyline or its equivalent) to have endogenous depression ($\chi^2 = 2.1$, df = 1, $P = 0.12$). There were no differences with respect to treatment in relation to gender, social class, number of weeks depressed and size of primary social network. Thus, although treatment was decided by the responsible doctor and was not based on random assignment, we were unable to identify any difference between the two groups that might have affected subsequent outcome. Outcome was the same in neurotic as in endogenous depressives (5).

Our ratings of compliance with treatment prescribed before the first interview produced the following findings: 86 patients (66%) were rated as being rigorously compliant and only 14 (11%) were judged to be failing to comply to the extent that the efficiency of the medication was probably affected; 9 of these had been prescribed a tricyclic antidepressant.

Interim treatment and disposal at follow-up

A total of 119 patients were successfully followed up and reassessed about 4 months after their initial contact with the psychiatric service; however, complete treatment and outcome data were available on 115 patients only. Fifty-four continued in psychiatric outpatient care; 13 had been admitted to an inpatient unit and 3 to a day hospital; 29 had been referred back to their general practitioner and 19 had lapsed from treatment. One patient had been referred for psychotherapy. A total of 96 patients (83%) had improved by at least one level on the PSE ID scale; 3 patients (2.5%) had become worse and 26% were still at case level on the PSE ID scale.

Forty-seven patients had not been on an antidepressant but 9 of these had been prescribed nontricyclic antidepressants (with good compliance in 7). Seventy-two were on a tricyclic antidepressant, 59 with good compliance and 13 with doubtful compliance. Only one patient was prescribed a MAOI and 3 had had a course of ECT. Forty-one patients were on benzodiazepines: but 21 of these had also been on a tricyclic.

Table 1 summarizes the use of antidepressant treatment in these 119 patients at each stage of the study, regardless of type of drug, dosage and compliance. Just over half of the patients who were followed up had been taking an antidepressant prior to both the initial and the follow-up clinical assessments.

Table 1. Number of patients treated with an antidepressive at each stage of study (antidepressant = tricyclic, or MAOI or other antidepressant)

When treated	Frequency	(% of total followed up)
Treated before first interview only	12	(10)
Treated before follow-up interview only	16	(13)
Treated before first and before follow-up interview	63	(53)
Never commenced on treatment during study	28	(24)
Total	119	100%

Treatment and outcome

In an earlier report (6) 2 significant clinical predictors of outcome were found: the severity (ID level) of depressive symptoms and the duration of the episode prior to the initial assessment. After controlling for these predictors, a number of social support and social network variables were also significant predictors of outcome (6). It was also reported that the prescription of a tricyclic antidepressant drug was not related to outcome and, when taken into account, did not alter the significance of the other predictors of outcome. For the analysis reported here, we also computed an additional 3-level treatment index to make maximum possible use of the available data on medication (both at the initial and follow-up assessment), dosage and compliance. Patients were rated as adequately treated if they were taking an antidepressant with good compliance and at a dose in excess of 100 mg amitriptyline or its equivalent of another type of antidepressant (19 patients). Any patient who was not prescribed a tricyclic or whose compliance with medication was judged likely to have impaired efficiency was rated as untreated (39 patients). The remainder, all of whom had antidepressant treatment at some point but with suboptimal dosage or doubtful compliance, were rated as possibly treated (57 patients).

There was no association either between the initial dosage of antidepressant or the treatment index and clinical outcome; indeed, there was a weak trend for a worse outcome in those on drug treatment, which appeared to be accounted for by the low dosage and possibly treated groups (Tables 2 and 3). However, this analysis does not take into account the clinical predictors of outcome that we identified previously: the severity of the initial episode of depression and its duration. Multiple regression analysis was carried out in which these 2 clinical predictors were entered first into the model of clinical outcome together with gender. The treatment index was re-computed as a variate with 7 levels, with an approximately normal distribution. When this revised index of treatment was added to the above regression model, it was found to be unrelated to the follow-up PSE-ID level (clinical outcome). When the type of depression (neurotic *vs* endogenous) was also included in the model as a dummy variable, the same result was found. Thus, as previously reported, the type of depression was unrelated to outcome, but more importantly here, taking the type of depression into account did not alter the relationship between drug treatment and outcome. Nor was there evidence of a gender-treatment interaction effect or of a diagnosis-treatment interaction effect on clinical outcome. (A significant diagnosis-treatment interaction effect on clinical outcome would have been found if, for example, endogenous patients had responded well and neurotic patients poorly to antidepressants.) Other variables that also failed to alter the basic result were the patient's age, social class and social support.

It could be argued that only those treated with adequate dosages of antidepressants would be expected to recover. Of the patients treated with antidepressants, 55% of those on a lower dose and 70% of those prescribed a dose in excess of the equivalent of 100 mg of amitriptyline improved clinically (by 2 or more levels of the CATEGO-ID) at outcome. This difference was not statistically significant but was in the expected direction. A further multiple regression analysis, with the outcome CATEGO ID level as the dependent variable, was carried out only on treated subjects. The two dosage levels were incorporated as a predictor dummy variable, and age, gender, severity and duration of initial illness, and compliance were also entered as predictor variables. This showed the same association between dose level and outcome, but with two-tailed $P = 0.13$.

Although clinically no more ill than those on no medication, it might be suggested that those who were already on treatment when seen at the initial assessment (all of whom were then borderline or definite cases) were treatment-resistant, or had already failed to benefit from medication. However, there remained 44 patients in the study who were not

Table 2. Relationship to recovery (at least 2 points reduced on the PSE-ID) of initial antidepressant treatment (either amitriptyline or equivalent dose of another antidepressant)

Antidepressant dose	Still ill	Recovery index recovered	Total
Untreated	12	29	41
< 100 mg	21	26	47
⩾ 100 mg	8	19	27
Total	41	74	115

$\chi^2 = 2.82$, df=2, P=0.24.

Table 3. Relationship to recovery (at least 2 points reduced on the PSE-ID) of the treatment index

Treatment index*	Still ill	Recovery index recovered	Total
Untreated	11	28	39
Possibly treated	24	33	57
Adequately treated	6	13	19
Total	41	74	115

$\chi^2 = 2.11$, df=2, NS.

* Untreated: antidepressants not prescribed. Possibly treated: antidepressant prescribed at doses below 100 mg amitriptyline (or equivalent) or with uncertain compliance with treatment. Adequately treated: good compliance with antidepressants prescribed at dosages above 100 mg of amitriptyline or equivalent.

on treatment at the initial assessment: 16 of these had been started on treatment when re-visited for the follow-up interview (Table 1). We found that the recovery rate in those commenced on antidepressants was 30% and in those never treated it was 50% (NS). Once again, those treated were certainly no better off, although in this analysis we cannot rule out the possibility that delayed treatment was instituted because of protracted illness.

As only 3 patients had had ECT (all commenced and completed between the first and follow-up assessments), there were insufficient data to analyse the effect of ECT on outcome. The dosage of antidepressant at the initial assessment was known in two of these cases: one had not been on an antidepressant and the other was on a dose below 100 mg.

Discussion

The study reported here appears to indicate that, in an epidemiological sample of patients with clinical depression of recent onset, prescribed antidepressant drug treatment does not appear to have affected the clinical outcome over a period of follow-up of 4 months. This result applied both to patients who were already on treatment at the start of our study and also to those commenced on antidepressants during our study. How may this unexpected result be explained? If we accept the strong evidence that supports the clinical efficacy of antidepressant drugs, we must explain why we obtained a contrary result in this naturalistic study. The crucial distinction between a controlled clinical trial and a naturalistic study is that, in the former, treatment allocation is based on random assignment, whereas in the later it depends on a decision by the doctor to use a treatment and a decision by the patient to seek and accept that treatment. An obvious possibility is that treating psychiatrists were quite adept at identifying the more severe disorders that would be unlikely to improve without the benefit of antidepressants: because they treated the worst cases, a difference in outcome would be too much to expect. This does not seem to have been a significant explanation, because treated and untreated patients did not differ significantly either in the severity or type of their depression, and because controlling for both of these variables did not reveal an association between treatment and outcome. Similarly, we were unable to identify factors that might have affected patients' willingness to seek and or accept drug treatment. Clearly, a study like this cannot resolve the issue any further.

Another explanation is that the patients failed to comply with the medication prescribed. However, compliance appeared to have no influence on the effectiveness of medication in our analyses. There are real problems in assessing compliance in observational studies, as the more aggressive ways of doing this inevitably change what is being measured. We therefore limited ourselves to a neutral and understanding enquiry. This is likely to have overestimated the true level of compliance to an unknown degree.

A third issue that is likely to have influenced the efficacy of the antidepressant drugs prescribed for our patients is that of dose. Argument continues about the lower limit of effective dosage for antidepressant treatment (11), particularly in relation to the more long-established tricyclic preparations. Thompson (12) has recently reported a clinical trial showing that low dosages (75 mg per day of dothiepin) were ineffective in general practice depression. It is quite possible that the degree of depressive disorder seen in our patients is even more likely to require dosages above the equivalent of 100 mg of amitriptyline. When we compared outcome in those treated at the lower and higher dosages, there was a trend in the expected direction: those on lower doses appeared to have the worst outcome. However, the outcome in those treated with higher doses was almost exactly the same as that in the untreated patients (70% and 71% respectively recovered in the two groups).

Our study is open to criticism for a number of reasons. The investigation of drug utilization was not our prime objective, and thus there was a limit to the information gathered about drug selection, dosage and side effects, and about compliance (and reasons for noncompliance) over time. Nevertheless, we find it hard to avoid the conclusion that a clinical decision to commence antidepressant treatment that was accepted by the patient did not result in long-term clinical benefit in this population.

Our follow-up assessment was conducted 3–6 months after the initial assessment and not, as is usually the case with clinical trials of antidepressant drug treatment, 4–6 weeks following the commencement of treatment. We do not know the effect of drug treatment on these patients in the short term; it may well have been beneficial. Our analysis did show a nonsignificant trend towards an interaction between treatment and duration of illness, with those with a longer duration of illness being somewhat more likely to fare worse if a decision to use antidepressants had been made and implemented. Thus it may be that effective treatment with antidepressants depends not only on good compliance and adequate dosage but also on its early implementation. These are clinically important issues that are unlikely to be considered within the rigid design constraints of controlled clinical trials, but do suggest useful directions for future research.

The representativeness of our sample is of central

importance to the generalizability of these findings. In one sense it may have been atypical of patients with depression treated in psychiatric hospital out- and inpatient practice: we excluded patients unless they had been well for a period of at least 6 months before the start of their episode and the episode had to be of no more than 6 months duration when we conducted our first assessment. Although 4 of every 5 patients in the study had been ill previously, we would reject the suggestion that our sample was less likely to be responsive to drug treatment than patients treated by the psychiatric services as a whole. If anything, a nonselected series containing a substantial number of chronic cases would probably have been less responsive to medication and other efforts at treatment. It also seems improbable that patients seen by psychiatrists, albeit a selected group, are particularly unlikely to respond to antidepressants. They may indeed include a population who have failed to respond to antidepressants prescribed by their family doctors, yet trials establishing drug efficacy are usually conducted on patients referred to a psychiatrist. We would also make the point that clinical improvement had taken place in the majority of our patients, with 31 remaining at case level at follow-up; however, this improvement was not related to drug treatment.

This study does not prove that antidepressants do not work: it does provide naturalistic observations suggesting that, in clinical practice, their advantages may fail to be realized, at least in the longer term. Our conclusions must be tentative, but the best explanation for our results is probably that, in ordinary clinical practice, the psychiatrists and general practitioners who have taken the decision to use drug treatment may not prescribe adequate dosages of antidepressants (3). They may also be insufficiently diligent in explaining the rationale for drug treatment and encouraging and monitoring compliance. The importance of doing this may escape them because they can always reassure themselves that the treatment works because their patients recover anyway. However, the inefficient prescription of potentially toxic drugs (13) is pointless, and physicians who do not ensure adequate treatment may inadvertently prolong unnecessary suffering.

Although the relatively better outcome of those treated on higher doses of antidepressants is reassuring, the equally good outcome in those whose treatment did not include antidepressants is difficult to explain. These patients' doctors made the judgement, on whatever basis for them, that antidepressants were unnecessary or unlikely to be of benefit. Therefore it is possible that they paid more attention to other aetiological and pathogenic factors as well as providing more support to their patients. In this regard, it is of interest to note the comparatively good clinical outcome (at 16 weeks) recently reported in the results of the US NIMH Treatment of Depression Collaborative Research Program in the depressed outpatients who were treated with a placebo and clinical management (a minimal supportive therapy condition), in which the clinician provided "the patient with support and encouragement and direct advice if necessary" (14).

On the basis of this work, a case can be made for conducting clinical trials with a longer duration of follow-up, and for studying treatment effects more closely in naturalistic longitudinal studies with varying periods of follow-up. Since this study was completed, routine medical audit has become mandatory within the National Health Service in the United Kingdom and health authorities are increasingly likely to use data on treatment outcomes to determine health service funding through legally binding service purchasing contracts (15). The results of the present study may serve as a warning of the potential for misinterpretation of such data: they could be erroneously interpreted as undermining the requirement for this particular form of treatment rather than demonstrating that its effects may not be detectable long after the time it is expected to take effect, or alternatively, that its effective use depends on close attention to dosage and administration. On the basis of this study, we suggest that psychiatrists and general practitioners look to their practice of antidepressant treatment.

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