Double-blind placebo-controlled trial of amitriptyline among depressed patients in general practice

JULIE A. HOLLYMAN, BSc, MB, MRCPsych

P. FREELING, OBE, FRCGP

E.S. PAYKEL, MD, FRCP, FRCPE, FRCPsych

A. BHAT, MSc

P. SEDGWICK, BSc

SUMMARY. Depressed patients in general practice were included in a double-blind placebo-controlled six-week trial of amitriptyline (median dose 125 mg). The patients were relatively mildly ill and satisfied diagnostic criteria for depression and treatment with antidepressants in routine practice. Amitriptyline was found to be considerably superior to placebo after six weeks and significantly so as early as two weeks after the start of treatment. The effects of the antidepressant were on the core symptoms of depression, and were apparent in all but the most mildly ill patients. The findings suggest that tricyclic antidepressants are of considerable therapeutic benefit to depressed patients in general practice.

Introduction

GENERAL practitioners see many patients whom they recognize as suffering from depressive illness: an average of more than 50 each year.[1] Management of emotional disorder with drugs is common among family doctors,[2] and in 1985 more than 7.3 million prescriptions for antidepressants were filled by retail chemists in Great Britain. Nevertheless, general practitioners have been criticized for prescribing inadequate doses of tricyclic antidepressants, for using benzodiazepines instead and for obtaining poor compliance.[3,4] However, tricyclic antidepressants are dangerous in overdose and have unpleasant side effects and a delayed action. While the effectiveness of these drugs over placebo has been clearly demonstrated in psychiatric inpatient and outpatient samples,[5] there is ample evidence that depressed patients treated in general practice show milder illnesses with less evidence of an endogenous symptom pattern than those referred to psychiatrists.[3,4,6-9] The assumption that antidepressants will be effective in general practice patients may not be justified.

Few placebo-controlled studies of antidepressants have been conducted in general practice. Porter[10] found imipramine (75–150 mg) no more effective than placebo over a short treatment period of three weeks. He excluded patients whose mood seemed appropriate to events, who had concurrent anxiety or whose illness seemed self-limiting. Thomson and colleagues[11] found both amitriptyline and tryptophan to be superior to placebo in general practice patients. Studies in Australia and the USA[12,13] also show tricyclic antidepressants to be superior to placebo but it is unwise to extrapolate from results obtained in a different system of care.

There are alternatives to drug treatment for depressive illness but all involve considerable time on the part of patient and therapist. Blackburn and colleagues[14] found amitriptyline to be inferior to cognitive therapy in a non-blind comparison in a small general practice sample but Corney[15] found social work intervention among depressed women had only moderate effects on clinical or social outcome. It seems important, therefore, to determine the efficacy of adequate doses of amitriptyline taken by depressed patients in general practice.

Method

Forty-one general practitioners from south west London and Surrey agreed to participate in the study.

Patients

The general practitioners identified patients aged 18 to 64 years who were sufficiently depressed to require antidepressants and suitable for treatment in general practice. Patients were included in the study if they satisfied research diagnostic criteria[16] for probable or definite major, minor or intermittent depression and if their total score on the 17-item Hamilton depression scale[17] was at least six. Patients were excluded if they scored 27 or more on the Hamilton scale, required referral for psychiatric treatment or had been under psychiatric treatment or had received an adequate course of antidepressants in the previous three months. Other exclusion factors were a history of drug or alcohol problems or schizophrenia, significant language problems or a diagnosis of minor or intermittent depression accompanied by a diagnosis of phobic state, generalized anxiety disorder or obsessive–compulsive disorder, so as to exclude patients in whom depression was not the predominant feature of their disorder. Ethical approval was obtained and patients gave written informed consent to participating in the study.

Study design

After identification by the general practitioners, patients were interviewed within 48 hours, at home, by a research psychiatrist (J.A.H.). She was introduced as a doctor working from the department of general practice at St George's Hospital Medical School. Participating patients were assigned, double blind, to identical tablets of amitriptyline (25 mg) or placebo by previously prepared randomization schedules without any stratification by patient characteristics but with equal numbers assigned in each group of 20 patients. The latter was not known to the study team. Medication was administered to achieve a dose of 75 mg amitriptyline daily by the end of the first week, increasing to 100 mg

J.A. Hollyman, Clinical Research Fellow, Department of Psychiatry, P. Freeling, Professor of General Practice, Department of General Practice and Primary Care, A. Bhat, Lecturer in Biostatistics, Department of Psychiatry, and P. Sedgwick, Statistical Assistant, Department of Clinical Epidemiology and Social Medicine, St George's Hospital Medical School, London; E.S. Paykel, Professor of Psychiatry, University of Cambridge.

daily for the second week, and 125–175 mg daily, depending upon improvement, for the remaining four weeks of the study.

General practitioners were asked to prescribe no other psychotropic medication unless they felt benzodiazepines were necessary in which case they were asked to use only temazepam or lorazepam.

Further home visits were made by the research psychiatrist at one, two, four and six weeks. Symptoms were re-rated from two weeks onwards. At each visit compliance was checked and side effects recorded. Compliance was assessed by verbal enquiry, a return tablet count at each visit and by taking a blood sample for radioimmune assay at four weeks. Compliance was judged to be satisfactory if the patients took 75% of their prescribed dosage weekly.

Patients were withdrawn from the study if they were unable to achieve a dose of 75 mg daily, if their compliance with medication was poor, if they deteriorated markedly or if they withdrew their cooperation.

Following the final visit the code was broken and the patient's general practitioner was informed which group the patient had been in and the number of tablets being taken. The research team were kept blind to this information.

Patients who dropped out at four weeks were considered to have completed the study and their rating at four weeks was taken as the final rating. This tends to reduce rather than increase the differences between the two groups.

Measures

Data on personal history, social history and demographic characteristics were collected for all patients. The interview instrument, used in previous studies,[9] incorporated the present state examination,[18] the research diagnostic criteria,[16] the Hamilton rating scale for depression,[17] the clinical interview for depression,[19] the Newcastle diagnostic index[20] and the Raskin three area depression scale.[21] The interview used the present state examination questions and where these could not elicit sufficient information to rate the symptom on other instruments further questions were inserted. Self rating, visual analogue scales and the self-report 90-item Hopkins symptom check list[22] were also completed but will not be reported here.

All these measures were completed at the initial assessment interview. Symptoms were rated again at two, four and six weeks using the Hamilton depression scale, the clinical interview for depression, the Raskin three area depression scale and seven-point global ratings of severity and change.

Statistics

For qualitative variables the chi-square test (with continuity correction where necessary) was used to test for differences between groups. Two-tailed t-tests were used for continuous variables after having checked distributional assumptions. A two-tailed 5% level was taken to be significant.

Results

Two hundred and ninety patients were identified by the general practitioners and of these 178 (61%) were entered in the study — 90 in the amitriptyline group and 88 in the placebo group. These patients were identified by 33 doctors, with a mean of 5.4 patients per doctor (range 1–37). Of the remaining patients 53 were ineligible and 59 declined to enter the study after receiving a full explanation from the research interviewer.

Thirty seven patients failed to complete four weeks' treatment — 23 in the amitriptyline group, and 14 in the placebo group. This difference was not significant. Eighteen of the 23 dropouts in the amitriptyline group gave side effects, such as dry mouth, increased appetite or weight gain, as their main reason, while eight of the 14 dropouts in the placebo group had poor compliance and three suffered worsening depression.

Of the 141 patients who completed four weeks' treatment, 15 dropped out before six weeks and their four-week results are used in the analyses of end point. Five were taking amitriptyline and 10 placebo.

At four weeks the mean dose of amitriptyline being taken was 119 mg daily and the median dose 125 mg. At six weeks the figures were the same.

Only four patients in each group took a benzodiazepine regularly for a week or more. A total of 10 patients in the drug group and nine in the placebo group were taking benzodiazepines by the end of week one, and by week six, seven in each group were doing so.

Initial characteristics

The two groups were well matched and there was the expected predominance of female patients (Tables 1 and 2). The group who failed to complete four weeks' treatment was similar to the group who did, except that their mean Hamilton depression scale total was higher at 16.5 ($P<0.01$).

Table 1. Initial characteristics of patients who completed four weeks' treatment in the two groups.

	No. (%) of patients	
	Amitriptyline group ($n=67$)	Placebo group ($n=74$)
Sex		
Female	54 (*80.6*)	63 (*85.1*)
Male	13 (*19.4*)	11 (*14.9*)
Social class[a]		
1/2	19 (*28.8*)	25 (*35.2*)
3	36 (*54.5*)	35 (*49.3*)
4/5	11 (*16.7*)	11 (*15.5*)
Age (years)		
18–34	21 (*31.3*)	35 (*47.3*)
35–54	40 (*59.7*)	35 (*47.3*)
55–64	6 (*9.0*)	4 (*5.4*)
Duration of present episode		
Up to 1 month	8 (*11.9*)	12 (*16.2*)
1 month to 1 year	46 (*68.7*)	50 (*67.6*)
More than 1 year	13 (*19.4*)	12 (*16.2*)
Previous episode of psychiatric illness		
Yes	14 (*20.9*)	14 (*18.9*)
No	53 (*79.1*)	60 (*81.1*)
Diagnosis[b]		
Major depression	45 (*67.2*)	55 (*74.3*)
Minor or intermittent depression	22 (*32.8*)	19 (*25.7*)
Hamilton depression scale total[c]		
6–12	20 (*29.9*)	20 (*27.0*)
13–15	20 (*29.9*)	27 (*36.5*)
16–24	27 (*40.3*)	27 (*36.5*)

n = total number of patients. [a]n = 66 for amitriptyline group, n = 71 for placebo group. [b]According to research diagnostic criteria. [c]17-item version used.

Table 2. Initial ratings of patients who completed four weeks' treatment.

	Mean score (standard deviation)	
	Amitriptyline group ($n=67$)	Placebo group ($n=74$)
Hamilton depression scale total	14.7 (3.8)	14.8 (3.5)
Raskin three area depression scale total	8.2 (1.4)	8.1 (1.5)
Clinical interview for depression total	22.9 (4.7)	22.3 (3.8)
Global rating of severity	3.6 (0.5)	3.6 (0.5)

n = total number of patients.

One hundred patients were major depressives, but for 45 of these (32.2% of the total) this was at the probable rather than the definite level. The 'probable' diagnoses allow patients whose symptoms have been present for only a week to be included. However, the present episode had already lasted more than a month at entry for the majority of the patients in this study.

In an earlier study[9] the same interview schedule was used to survey characteristics of a representative sample of patients started on a new course of antidepressants by a general practitioner in routine practice. Comparisons were made between the earlier sample whose depressive illness had been confirmed and the sample reported here. The only difference was that the patients in the present study showed a higher mean total score on the Raskin three area depression scale (8.2 versus 7.7, $P<0.05$).

Overall outcome

Figure 1 shows the mean total scores on the Hamilton depression scale for the two groups. The difference at two weeks was 2.6 ($P<0.002$), at four weeks 2.8 ($P<0.004$) and at six weeks 3.2 ($P<0.001$).

Table 3 shows the reductions from the initial ratings at weeks two and six. Amitriptyline was significantly superior to placebo on all measures except the score for anxiety.

Table 4 shows the distribution of ratings on the seven-point scale for global change at six weeks. The effect of the drug was to increase the proportion of patients who had 'greatly improved'. The difference between the two groups was highly significant.

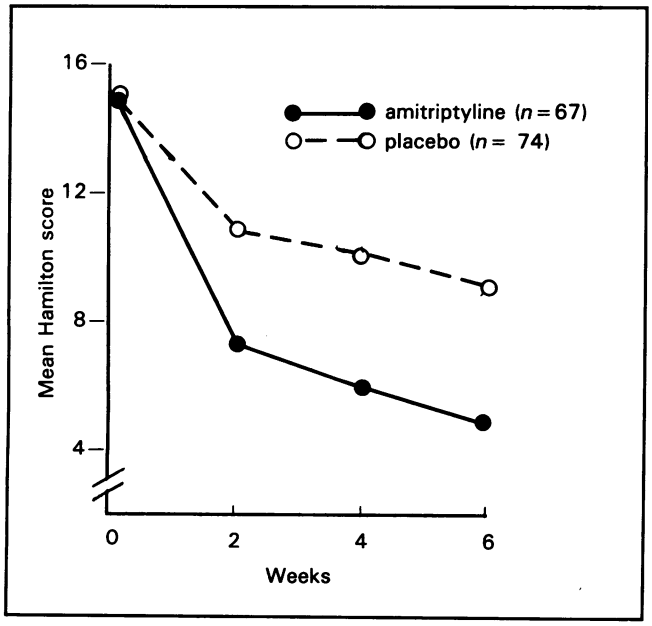

Figure 1. *Mean total scores on the Hamilton depression scale for the two groups over the six-week treatment period.* n = *number of patients in the group.*

Symptoms affected

Scores for individual items on the Hamilton depression scale and the clinical interview for depression were examined. At six weeks amitriptyline was superior to placebo for ratings of depressed mood, guilt, pessimism, loss of energy and fatigue, psychic anxiety, initial insomnia, delayed insomnia, depressed appearance and general somatic symptoms. At two weeks the drug was superior to placebo for depressed mood, guilt, pessimism, irritability, psychic anxiety, initial and delayed insomnia and genital symptoms of depression, such as loss of libido and disturbance of menstruation. The major benefit, particularly by week six, was in the core symptoms of depression. Improvement in insomnia and psychic anxiety might reflect either sedative or antidepressant effects but the reduction in reported loss of energy clearly showed the antidepressant effect.

Sub-group analysis

An extensive series of analyses was undertaken to seek subgroups showing varying differences between the effects of drug and placebo based on entry characteristics. The details are reported in full elsewhere[23] but are summarized here.

Using two-way analysis of covariance, no historical or demographic factors were found to be associated with differential response to amitriptyline. No differences were found between endogenous or reactive depression, whether defined by symptom pattern or occurrence of stress at onset. However, there were significant differences based on the initial severity of depression. The differences between drug and placebo were greatest in those with a diagnosis of probable or definite major depression, and patients with a score of at least 13 on the Hamilton depression scale at entry showed greater differences than those with scores of 12 or less.

Discussion

This study shows that amitriptyline, in recommended therapeutic dosage, is effective in patients whose depressive illness is typical of that usually managed in general practice. Among the patients who completed at least four weeks of adequate medication, amitriptyline was clearly superior to placebo. Further, the symptoms which benefited included those which are typical of depression rather than anxiety and which are largely affective rather than somatic.

Most trials of new antidepressants involving hospital outpatients require a threshold score of 17 on the Hamilton depression scale. The sample studied here, with a mean score of 15, was clearly a less severe group. An earlier study[9] identified depressed patients whom the general practitioners intended to treat with antidepressants and these patients had significantly less severe illness, fewer depressive symptoms, shorter illnesses and less primary and endogenous depressions than an outpatient sample. The issue of severity in the mild range of depression has not been addressed in other studies. Porter[10] made no assessment of severity for his sample. The groups treated by Thomson and colleagues[11] were more depressed than those studied here; they had a mean Hamilton depression scale score of about 21 at recruitment and all but one patient

Table 3. Mean reductions in scores from initial ratings at two and six weeks.

	Mean reduction in score at two weeks			Mean reduction in score at six weeks		
	Amitriptyline group ($n=67$)	Placebo group ($n=74$)	95% confidence interval[a]	Amitriptyline group ($n=67$)	Placebo group ($n=74$)	95% confidence interval[a]
Hamilton depression scale total score	6.9	4.4	1.2–3.9***	9.3	6.1	1.3–5.0***
Clinical interview for depression — total depression score	6.4	4.6	0.4–3.1*	9.2	6.2	1.1–4.9**
Raskin three area depression scale total score	2.2	1.5	0.3–1.3*	3.2	2.2	0.3–1.7**
Global rating of illness	0.9	0.6	0.1–0.6*	1.6	1.0	0.3–1.0***
Clinical interview for depression — total anxiety score	2.2	1.8	−0.4–1.2	2.6	2.3	−0.6–1.2

* $P<0.5$, ** $P<0.01$, *** $P<0.001$. n = total number of patients in group. [a]For differences between mean changes in scores.

Table 4. Distribution of ratings of global change at six weeks.

	No. (%) of patients	
	Amitriptyline group ($n=67$)	Placebo group ($n=74$)
Greatly improved	37 (*55.2*)	23 (*31.1*)
Moderately improved	16 (*23.9*)	16 (*21.6*)
Mildly improved	8 (*11.9*)	18 (*24.3*)
No change or worse	6 (*9.0*)	17 (*23.0*)

n = total number of patients in group. $\chi^2 = 12.06$, $P = 0.007$.

had a diagnosis of major depression. Thomson's finding of the advantage of active treatments over placebo was, therefore, extended here to include the less severely ill patients who make up the bulk of the general practitioner's work.

Given that the drug seems effective among a mildly ill sample it seems important to emphasize that 80% of the patients completed at least four weeks on recommended therapeutic dosages of amitriptyline. This was probably due in part to the frequency and duration of contact during treatment and because patients were seen after the first week, allowing encouragement to be given at a time when improvement is likely to be minimal. Nevertheless, 20% of the original sample taking amitriptyline dropped out owing to side effects. However, compliance was good on all measures for those in both groups who completed four weeks' treatment. The benefits obtained by the 80% who completed at least four weeks' active treatment seem marked enough for any general practitioner to prescribe amitriptyline with confidence and to encourage patients to tolerate the side effects.

An important finding which must help good compliance is the rapidity of response. There was a significantly greater improvement among patients taking amitriptyline than placebo at two weeks and four weeks as well as six. It is unclear whether this rapidity of response was related to the relative mildness of the illness.

This study did not determine the optimum dose of amitriptyline in general practice and it was assumed that the range used in psychiatric practice would be effective. The study design did not permit us to decide whether lower doses would work.

Many general practitioners believe that situational depression should not be medicalized. Nevertheless, the alternative treatments of depression are time consuming and, therefore, expensive to both patient and therapist. Although patients may be reluctant to take medication the findings reported here indicate that encouragement to try drugs in the first instance is appropriate. What would be inappropriate would be for doctors to avoid patient contact because drugs had been prescribed.

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Acknowledgements

We thank the Medical Research Council for funding the study, Parke-Davis for supplying amitriptyline and matched placebos, the general practitioners for allowing us to study their patients and Mr N. Tait for help with the statistical analysis.

Address for correspondence

Professor P. Freeling, St George's Hospital Medical School, Cranmer Terrace, London SW17 0RE.

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