British Journal of Psychiatry (1985), **146,** 515–519

An Evaluation of Alprazolam in the Treatment of Reactive or Neurotic (Secondary) Depression

NORMAN W. IMLAH

Summary: To investigate the effectiveness of a new benzodiazepine, alprazolam, and to compare this with amitriptyline (AMT) and with placebo, a trial was undertaken in 65 patients in whom depression was considered to be the dominating feature but not considered to be the primary cause of their condition; it was designed to exclude endogenous depressions. A consistent pattern was found favouring alprazolam over AMT both in rate of response and in total response, as well as significant differences in favour of both alprazolam and AMT over placebo. A comparison of side effects showed a definite trend in favour of alprazolam and placebo over AMT.

Alprazolam (8-chloro-1 methyl-6 phenyl-4H-S-triazalo-[4,3-a] [1,4]-benzodiazepine) belongs to the benzodiazepine group, and is distinguished from other drugs of this group in clinical use by having a triazole ring in its structure. The antidepressant trazodone also contains such a ring, and some animal models for antidepressants (Sethy & Hodges, 1982; O'Connor *et al,* 1984) show alprazolam to have similarities to the actions of tricyclic antidepressants, unlike diazepam.

Clinical studies in the United States on this drug suggest it is a more effective anxiolytic than placebo and as effective as diazepam. Two double-blind comparisons (Fabre & McLendon, 1979; Aden & Thein, 1980), suggested that the treatment of anxiety required a dose of alprazolam about one-tenth that of diazepam; at this dosage, it produced fewer side effects.

A double blind comparison (Fabre & McLendon, 1980) with imipramine and placebo in primary depression reports alprazolam as being as effective as impramine with fewer side effects. In a six week, double blind multicentre comparison of alprazolam, imipramine and placebo, 723 depressed patients (Feighner Diagnostic Criteria) were treated (Feighner *et al,* 1983). Both active drugs were statistically more effective than placebo and alprazolam was at least as effective as imipramine in relieving depressive symptoms, showing earlier onset of activity in some measures.

So far, there have been no reports of controlled studies in patients with secondary depression, although one uncontrolled trial (Fabre, 1976) in a small group noted moderate to marked improvement in 80% of patients.

This paper reports a trial carried out on a group of patients in whom depression was the dominating feature of their condition, but was not considered to be the primary cause. They were diagnostically labelled 'neurotic', 'reactive', or 'secondary' depression—i.e. a reaction to stress which took the form of an unnatural increase or prolongation of low spirits, or state of despondency. This could present in one of three clinical forms.

(a) As the predominating or exclusive symptom of the reaction.
(b) As a prominent fluctuating symptom of an anxiety state.
(c) As the predominant feature of a hysterical conversion syndrome.

The trial was designed to exclude, as far as possible, depressions which were predominantly primary or endogenous in character. The distinction between depressive neurosis with features of anxiety and anxiety neurosis with depressive symptoms was measured objectively by the use of both the Raskin (Raskin, 1970) and Covi (Lipman & Covi, 1976) Scales, and by a score of at least 2 on the depression component of the Hamilton Anxiety Rating Scale (Hamilton, 1959), in addition to the clinical diagnosis that depression and not anxiety was the predominating clinical feature of the neurosis.

The aims of the trial were: (1) To investigate the effectiveness of alprazolam in patients with predominating features of secondary depression. (2) To compare the effectiveness of the drug in this type of patient with amitrityline and with placebo. (3) To evaluate the safety of the drug, together with the incidence and type of side effects.

Method

The trial was conducted on a double-blind randomised group comparative basis, with a placebo wash-out period. There were several investigators, each of whom included cases according to the agreed diagnostic criteria, and each used the same instruments of evaluation. Each individual

case was evaluated by the same investigator throughout the trial period.

The investigators comprised both qualified psychiatrists and general practitioners with psychiatric experience. The trial was preceded by a series of briefing meetings to agree on inclusion criteria, evaluation methods, and procedure, and periodic meetings between the investigators took place throughout, to maintain consistency. The trial started when the co-ordinator was satisfied that there was consistency in rating between investigators on the basis of the pre-trial practice rating sessions. Ethical approval was obtained.

The inclusion criteria were:

1. Males or females, aged between 18 and 60 years.
2. In the opinion of the investigator, the patient required psychotropic medication for symptoms of reactive or neurotic depression, with or without anxiety.
3. Patients could be in-patients or out-patients, having symptoms present for at least one month.
4. At the end of the wash-out period, patients required a minimum score of 18 on the Hamilton Anxiety Rating Scale, with a rating of at least 2 on the Depressed Mood component.
5. All patients were required to give informed consent.

The following were excluded:

1. Patients with psychosis or psychopathy.
2. Patients whom the investigator diagnosed as having endogenous depression.
3. Patients with severe or uncontrolled physical disease.
4. Patients with epilepsy.
5. Patients with conditions for which tricyclic antidepressants are contra-indicated, e.g. glaucoma.
6. Patients who would concomitantly require anticholinergic, antihypertensive, thyroid regulation or other psychotropic medication.
7. Females of child-bearing age who were not taking adequate contraceptive precautions.
8. Patients with a history of alcohol or drug dependence.

Patients requiring hypnotics were offered a standard non-benzodiazepine hypnotic, started before the test medication, and at a constant dose throughout the trial period. All patients were counselled not to take other anxiolytic or antidepressant drugs during the trial, and to report any concomitant medication.

The following measurements of response were used for comparative evaluation:

1. Hamilton Anxiety Rating Scale; this was considered more appropriate to the patient population than the Depression Scale, which is more appropriate to endogenous depression. The scale was completed at the end of the wash-out period for inclusion criteria, and repeated at the end of weeks 1, 2, and 4.
2. The Leeds Self Assessment Scale (Snaith, *et al*, 1976) was completed by all patients at initial inclusion and at the end of weeks 1, 2, and 4.
3. The Raskin and the Covi Scales were rated at initial inclusion and at the end of week 4.
4. Severity of depression was rated on a five point scale at inclusion and at the end of weeks 1, 2, and 4.
5. Both investigators and patients recorded their global assessment of improvement at the end of the study.

The duration of the trial was four weeks, following an initial wash-out period of one week. Any patient who derived no benefit at the end of two weeks could be withdrawn as a treatment failure, at the investigator's discretion.

Side-effects were examined by two methods. Each patient was rated, using a symptom check list, on a four-point scale at each assessment time-point. A side-effect was designated as such when a symptom was rated at a higher score than at the initial assessment. The severity of the side-effect was designated as the maximum symptom score.

In addition, investigators were asked to rate side-effects on a four-point severity scale at the end of the trial, for statistical comparison. The frequency and severity of side-effects were recorded at each follow-up.

Dosage

During the wash-out period, one placebo capsule was given twice daily. In the trial, 0.5mg alprazolam was equivalent to 25mg AMT and to one placebo capsule. From day 1 to day 3, the dosage was three capsules daily, increasing, if required, to four capsules daily between days 4 and 6. The dosage was increased to two capsules tds, if necessary, from day 7 to day 28. It did not exceed six capsules per day, and an attempt was made to keep it constant over the last two weeks.

Statistical methods

Pre-trial demographic data were assessed by one way analysis of variance (ANOVA). Data obtained during and at the end of the trial were assessed as follows:

(a) Data obtained weekly during the trial.

For weekly assessments, the Hamilton Anxiety Rating Scale (total score and depression component), Physician Assessment of Severity of Illness, and Leeds Self-Assessment Scale were used. For each scale, the results were analysed and presented as follows:

(i) The total number of patients assessed (n) as well as the mean and standard deviation of the scores are given for each drug at each time point.

(ii) The significance level (P) of the difference between the initial and the last known score for each patient was determined for each drug using paired t-test. For patients who dropped out, the last known score was the one last recorded prior to discontinuation. A value of $P < 0.05$ was required to achieve statistical significance.

(iii) The total number of patients assessed and the mean of the individual changes in score from the initial one are given for each drug at each time point.

(iv) ANOVA was used to compare the effect of the three drug treatments on the change in score from the initial one at each time-point. A value of $P < 0.05$ was required to achieve statistical significance. When a significant level of variance was observed between the three treatment groups, pairs of treatment groups were compared by ANOVA, and a value of $P < 0.017$ set for significance.

(b) Data obtained initially and at the end of the trial.
For initial and final assessments, the Raskin Depression and Covi Anxiety scales were used; for each rating scale, the results were analysed and presented as above, except for point (iii), which was not presented.

(c) Data obtained at the end of the trial.
The rating scales used here were the Patient and Physician Evaluation of Therapeutic Effect and the Physician Assessment of Side-Effects. For each, the results were analysed and presented as follows:

(i) The total number of patients assessed, including drop-outs and the distribution of the patients between the possible ratings.

(ii) The χ^2 test was used to compare the effect of the three drug treatments on this distribution. A value of $P < 0.05$ was required to achieve statistical significance. When pairs of treatment groups were compared, a value of $P < 0.02$ was set for significance.

The χ^2 test was also used to compare the effect of the three drug treatments on the number of patients receiving medication at each time point.

Results

A total of 65 patients were enrolled into the trial, and 61 of these were evaluable. There were 15 females and eight males in the alprazolam group, 12 females and six males in the AMT group, and 14 females and six males in the placebo group. The mean ages of the patients in each treatment group were 36.2 years, 40.8 years and 40.5 years respectively. There was no significant difference between groups of either of these parameters. Four patients dropped out before the end of week 1 and could not be rated.

Within three years before entering the trial the following drugs had been prescribed for the subjects. In the alprazolam group – nine on benzodiazepines and three on tricyclics; in the AMT group – seven on benzodiazepines, four on tricyclics and one on phenothiazines; in the placebo group – nine on benzodiazepines, ten on tricyclics and one on phenothiazines. Three patients failed to complete the seven-day wash-out period.

Of the 61 patients who were deemed evaluable for analysis, eight dropped out during the course of the study. No patients in the alprazolam group dropped out, but three treated with AMT did so – one due to severe cardiovascular side-effects, one due to unrelated concomitant illness, and one was lost to follow-up. Five of the placebo treated patients dropped out (four due to their deteriorating condition) and one was lost to follow-up. The difference between groups was significant ($P = 0.046$, χ^2).

Only one patient was on concomitant therapy, receiving paracetamol 500 – 1000mg daily for headaches until week 3. No patient took hypnotics or other anxiolytic drugs during the trial period. No patient took an overdose during the trial.

Figures 1 and 2 illustrate the analysis of Total Scores and Depression Component Scores on the Hamilton Anxiety Scale. Analysis of the differences between the initial Raskin Depression Scale scores and the final assessment showed that all treatment groups were significantly improved (alprazolam $P < 0.001$, AMT $P < 0.001$, placebo $P < 0.05$). The only significant difference between groups was between alprazolam and placebo ($P = 0.002$).

Analysis of the difference between the initial Covi Anxiety Rating Scale scores and the final assessment showed that all treatment groups were significantly improved (alprazolam $P < 0.001$, AMT $P < 0.001$, placebo $P < 0.01$). The only significant difference between groups was between alprazolam and placebo ($P = 0.009$). The investigators' assessments of severity of depression and severity of illness are shown in Figure 3. Alprazolam was significantly better than placebo ($P = 0.01$) at Week 4.

The patients' self-assessment scores (Leeds Anxiety and Leeds Depression) were analysed; statistical tests of the former show that both the alprazolam and AMT groups had significant improvement between initial and final scores (alprazolam $P < 0.001$, AMT $P < 0.05$). However, the placebo group difference did not reach significance. The Depression score similarly showed a significant improvement noted by the patients in the

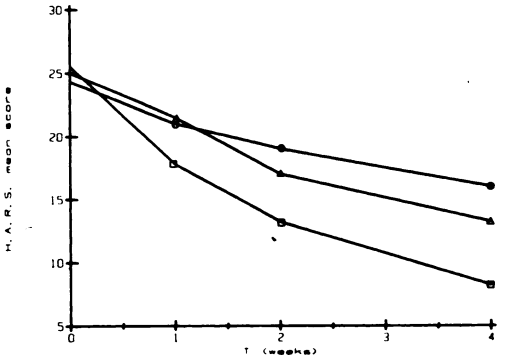

FIG. 1 Hamilton Anxiety Rating Scale (H.A.R.S.) mean scores during the study period.
Key: □ Alprazolam (A), △ Amitriptyline (B), ○ Placebo (C)
Significance of results: Week 1 $P = 0.007$ A vs B; $P = 0.003$ A vs C; Week 2 $P = 0.001$ A vs C; Week 4 $P = 0.0001$ A vs C

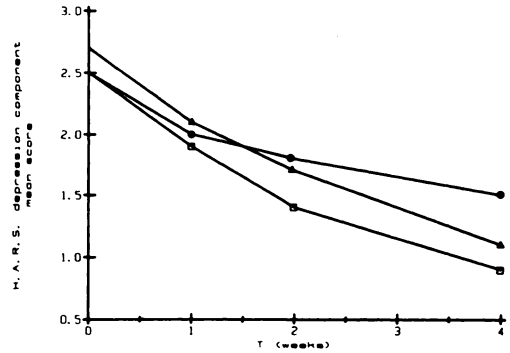

FIG. 2 Hamilton Anxiety Rating Scale (H.A.R.S.) depression component mean scores during the study period.
Key: □ Alprazolam (A), △ Amitriptyline (B), ○ Placebo (C)
Significance of results: Week 4 $P = 0.014$ A vs C; $P = 0.009$ B vs C

https://doi.org/10.1192/bjp.146.5.515 Published online by Cambridge University Press

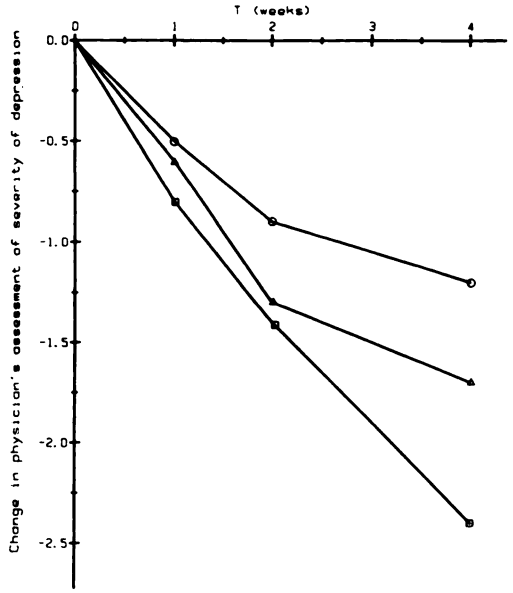

FIG. 3 Change in Physician's Assessment of Severity of Depression on a 7 point scale (1 = Normal 7 = Extremely Severe) during the study period.
Key: □ Alprazolam (A), △ Amitriptyline (B), ○ Placebo (C)
Significance of results: Week 4 $P = 0.01$ A vs C

alprazolam group ($P < 0.001$) and in the AMT group ($P < 0.001$), but not in the placebo group.

These various forms of assessment show a consistent pattern favouring alprazolam over AMT, both in the rate of response and in the total responses. There are also significant differences in favour of both alprazolam and AMT over placebo. The investigators' evaluations of therapeutic effect showed a significant difference only between alprazolam and placebo ($P < 0.005$); patients' assessments of therapeutic effect showed a trend in favour of alprazolam, but this did not reach statistical significance.

Analysis of side-effects and of the doctor's global assessments of the effect on patients well-being showed a significant difference ($P < 0.02$) between alprazolam and AMT with a high incidence of severe side-effects in the AMT treated patients. The symptom check list results showed a similar pattern: severe side-effects were recorded eight times for patients on AMT, four for placebo, and none for alprazolam; moderate side-effects were recorded 38 times for AMT, 27 times for placebo, and 20 times for alprazolam. The most common severe side-effects of AMT were tremor and dry mouth. Of the moderate side-effects of alprazolam recorded, four were drowsiness, three depression, two insomnia, and two headache; side-effects with alprazolam were less severe and less frequent than with AMT.

A study of laboratory data did not reveal any adverse reactions of any consequence.

Conclusions

A trial of a new benzodiazepine drug, alprazolam, against both AMT and placebo in a group of neurotic patients in which secondary depression was the predominant clinical feature, showed a very distinct trend in favour of alprazolam; patients receiving it responded faster, had a better overall response, and had less side-effects. Examination of the various objective measurements that were used showed statistically significant differences in a number of the comparisons.

Alprazolam was found to be relatively free of side-effects, and there were no adverse reactions. By contrast, AMT had a higher number of side-effects, and one patient had an adverse reaction requiring withdrawal from the study.

It was concluded that alprazolam is a very promising drug in patients of this kind, and that further clinical research on it is indicated; by virtue of the triazole component, it may have a specific antidepressant action which would make this drug clinically different from benzodiazepines in current use. In this study, there were strong indications that alprazolam has very potent anxiolytic effects, but it is not clear whether its antidepressant action was secondary to relief of anxiety or was a specific action.

Various anti-anxiety drugs have been credited with antidepressant properties, but to date, such claims have not been substantiated in extended investigations. The prevalent view is that the relief of secondary depression is due to the primary alleviation of anxiety. However, not all anxiolytic drugs relieve secondary depression, and in some cases, the depression increases as anxiety is relieved. In this investigation the use of alprazolam had a beneficial effect on secondary depression, though this does not in itself indicate that alprazolam has specific antidepressant activity as well as an anxiolytic action. Further research by controlled trials of the drug in primary depressive illness appear to be indicated.

Acknowledgements

Thanks for their help are expressed to: Drs. M. I. Akhter, H. M. Colabawalla, A. Kahn, K. Khan, R. Wall, A. C. Bajpai, C. Fernandez, K. P. Murphy, D. N. Rastogi, Surrinder Kaur, S. S. Venugopal and E. T. Wrigley, and to the Medical Department of Upjohn Limited.

References

ADEN, G. C. & THIEN, S. G. (1980) Alprazolam compared to diazepam and placebo in the treatment of anxiety. *Journal of Clinical Psychiatry*, **41**, 245–248.

FABRE, L. F. (1976) Pilot open label study with alprazolam in out-patients with neurotic depression. *Current Therapeutic Research*, **19**, 661–668.

—— & MCLENDON, D. M. (1979) A double-blind study comparing the efficacy and safety of alprazolam with diazepam and placebo in anxious out-patients. *Current Therapeutic Research*, **25**, 519–526.

—— & —— (1980) A double-blind study comparing the efficacy and safety of alprazolam with imipramine and placebo in primary depression. *Current Therapeutic Research*, **27**, 474–482.

FEIGHNER, J. P., ADEN, G. C., FABRE, L. F., RICKELS, K., SMITH, W. T. (1983) Comparison of alprazolam, imipramine and placebo in the treatment of depression. *JAMA*, **249**, 3057–3064.

HAMILTON, M. (1959) Hamilton Anxiety Rating Scale. *British Journal of Medical Psychology*, **32**, 50–55.

LIPMAN, R. S. & COVI, L. (1976) In *Evaluation of Psychological Therapies* (eds. R. L. Spitzer and D. S. Klein). Baltimore: Johns Hopkins University Press.

O'CONNOR, W. T., EARLEY, B. & LEONARD, B. E. (1984) Antidepressant properties of the triazolobenzodiazepines alprazolam and adinazolam: Studies on the olfactory bulbectomized rat model of depression. Presented at the 1st European Congress on "Recent Advances in Psychiatry". March 1984.

RASKIN, A. *ET AL* (1970) Raskin Depression Scale. *Archives of General Psychiatry*, **23**, 164–173.

SETHY, V. H. & HODGES, D. H. JR. (1982) Alprazolam in a biochemical model of depression. *Biochemical Pharmacology*, **31**, 3155–3157.

SNAITH, R. P., BRIDGE, G. U. K. & HAMILTON, M. (1976) Leeds Self Assessment Scale. *British Journal of Psychiatry*, **128**, 156–165.

Norman William Imlah, MB. ChB. FRCPsych. *Medical Director and Consultant Psychiatrist, All Saints Hospital, Birmingham B18 5SD*

(Received 14 May; revised 20 November, 1984)