Indian J. Psychiat. (1991), 33(2), 131—135

A DOUBLE-BLIND EVALUATION OF ALPRAZOLAM AND IMIPRAMINE IN THE TREATMENT OF MAJOR DEPRESSION

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SUMMARY

This report describes the results of a multicentre collaborative study comparing the safety and efficacy of alprazolam with imipramine in patients suffering from major depressive disorder. Two hundred and eight patients diagnosed as major depression as per DSM-III criteria were randomly allocated to alprazolam (N=105) or imipramine (N=103) in a double-blind fashion. Detailed assessments were carried out for a period of six weeks. Results revealed that alprazolam was as effective as imipramine as an antidepressant. Side effects were less frequently reported with alprazolam.

Alprazolam is a new benzodiazepine compound that differs from classic benzadiazepines by the incorporation of a triazole ring in its basic structure. It has a different metabolic pathway with rapid absorption and elimination. The addition of the triazole ring to the basic structure is believed to have given antidepressant properties to alprazolam (Feighner, 1982). Compared to conventional antidepressants, alprazolam is reported to be less toxic (Fawcett and Kravitz, 1982). It is also free of anticholinergic side effects.

Several controlled trials have evaluated the efficacy of alprazolam in the treatment of major depression (Rickels et al., 1985; Rickels et al., 1987; Feighner et al., 1983 a and b). These studies have shown that alprazolam is as effective as conventional antidepressants like imipramine. Further the incidence of adverse effects have been noted to be lesser with alprazolam.

The present investigation is a double blind study carried out in four centres at Bangalore, Bombay, Madras and Delhi to assess the safety and efficacy of alprazolam in comparison with imipramine in patients with major depressive disorder.

Methodology

a. *Pre-trial meeting of the resear.h staff* : The investigators and research staff of the four participating centres had a pre-trial meeting to discuss the study protocol. Each of the study instrument was discussed in detail. Inter-rater reliability exercise were carried out using audiotaped interviews as well as live interviews. Research staff who joined the project afresh were provided similar exposure.

b. *Selection criteria* : Patients considered for participation were males and non pregnant females-using contraception or not-of childbearing potential. Only outpatients suffering from moderate to severe depression were included. Patients

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were required to meet the Feighner's criteria for primary depression (Feighner et al., 1972) as well as the criteria for major depression as per the Diagnostic and Statistical Manual (DSM-III) of the American Psychiatric Association (1980). In addition, they were required to have a minimum baseline score of 18 on the 21-Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960), a minimum score of 8 on the Raskin depression scale (Raskin et al., 1970) and a Covi anxiety rating scale (Lipman and Covi, 1976) score less than or equal to Raskin depression scale score. Patients with other psychiatric illness, alcohol or substance abuse, and concurrent use of other psychotropic medication were excluded. Similarly, patients with bipolar affective disorder and those with marked psychomotor retardation were excluded from the study.

Written informed consent was obtained from all the patients. Informed consent information was prepared in English and the local languages based on international guidelines (CIOMS and WHO, 1982), and this information was read out to all the potential participants. Doubts if any were clarified.

c. *Study procedure* : A three to seven day placebo washout period preceded the study proper. Patients who showed significant improvement during the washout period were eliminated from the study. The pre-trial screening involved collection of demographic, medical and psychiatric history; detailed physical examination and recording of vital signs; and biochemical investigations which included complete blood counts, urinalysis, estimations of serum creatinin, serum alkaline phosphatase, serum glutamic oxaloacetic transminase and serum bilirubin levels. All assessments were recorded in standard format data sheets.

Patients were allocated to alprazolam or imipramine in a double blind random fashion. The randomization was such that in each consecutive group of six patients, 3 were on alprazolam and 3 were on imipramine. The drugs were dispensed in identical capsules, each capsule containing alprazolam 0.5 mg or imipramine 25 mg. Patients were started with one capsule twice daily. Within three days, the dosage was adjusted to one capsule thrice daily. Dosage was further increased at weekly intervals, subject to a maximum of 3 capsules thrice daily. If significant side effects appeared, the dosage was reduced and if they persisted at the minimum dose, or when the clinical condition worsened, patient was withdrawn from the study. The drug code of each patient was kept in a sealed envelope which could be opened in case of an emergency. Once the drug code was broken, the data would be eliminated from further analysis.

Patients were requested to follow their regular eating habits. They were advised not to use alcohol or other psychotropic drugs. Follow up evaluation were done at the end of the first, second, fourth and sixth week of treatment using the following scales : Hamilton Depression Rating Scale (HDRS), Hamilton Anxiety Rating Scale (HARS) (Hamilton, 1959), Physician's Global Impression, and Patient's Global Impression. Treatment emergent symptoms were recorded at each evaluation and detailed physical examination and laboratory assays were repeated at the final evaluation. Treatment safety was assessed based on the number and severity of adverse reactions reported, physical examination and laboratory investigations. Statistical analysis of the data were performed using parametric and non parametric tests.

Results

A total of 208 patients were enrolled for the study from all the four centres.

There were 56 males and 49 females in the alprazolam group and 62 males and 41 females in the imipramine group. The mean age of the alprazolam group was 35.0±10.9 years, and that of the imipramine group was 32.3±9.3 years. There were no differences between the two groups with respect to age, sex, marital status, occupational adjustment, family life adjustment or precipitating stress factors.

Sixty percent of the alprazolam group and 62% of the imipramine group had an illness of more than one year duration, Thirty three percent of the alprazolam group and 35% of the imipramine group reported previous treatment for emotional problems.

Table 1 shows the dropout rates in the alprazolam and imipramine groups. The drop-out rate was significantly higher for the imipramine group during the first and second weeks. Overall 25% of the alprazolam group and 33% of the imipramine group dropped out of the trial.

TABLE 1—*Number of patients completing the different periods of assessment. (Percentage in parentheses)*

Period of Assessment.	Alprazolam	Imipramine
Initial	105 (100.0)	103 (100.0)
Week-I	98 (93.3)	86 (83.5)*
Week II	91 (86.7)	76 (73.8)*
Week IV	81 (77.1)	69 (67.0)
Week-VI	76 (75.2)	69 (67.0)

*The rate of drop out was higher in the imipramine group in the first week ($p<0.05$) and second week ($p<0.02$).

Table 2 and table 3 show the mean scores with standard deviation on the HRDS and HARS for the two groups. The two drugs were equally effective at all the periods of assessment. The drop in the mean HDRS scores was 59% for the alprazolam group and 61% for the imipramine group. On the Physician's Global Impression scale, 80% of the alprazolam and 83% of the imipramine group were rated as very much or much improved. Three patients in the alprazolam group and two patients in the imipramine group were rated as having showed no change or minimally worse at the end of six weeks of therapy. On the patient's Global Impression Scale 77% of the alprazolam group and 83% of the imipramine felt that they were very much or much better. Seventy eight percent of patients in both the groups evaluated the efficacy of the drugs as moderate to marked.

TABLE 2—*Mean±S. D. scores of the alprazolam group and imipramine group on the Hamilton Despression Rating Scale.*

Period of assessment.	Alprazolam Mean ± S. D.	Imipramine Mean ± S. D.
Initial	23.81 ± 14.95	23.44 ± 14.56
Week-I	16.65 ± 10.62	17.88 ± 11.18
Week-II	14.40 ± 8.77	14.11 ± 8.49
Week-IV	12.93 ± 7.17	11.26 ± 6.46
Week-VI	9.75 ± 4.63	9.20 ± 4.72

*The comparison of mean scores of the two groups at various period of assessment is statistically in significant (by 't' test).

The mean number of capsules per day (alprazolam 0.5 mg; imipramine 25 mg) in the first week was 3.2±0.8 of alprazolam and 3.4±0.9 of imipramine. This was 5.0±1.6 and 5.1±1.6 respectively at the end of six weeks. Eighty six percent of subjects, in either group required less than six capsules per day.

The frequency of side effects were higher with imipramine compared to alprazolam. Significantly higher number

of patients on imipramine reported insomnia ($p<0.01$) and tremor ($p<0.01$) as side effects. None of the side effects reported was significantly more in the alprazolam group. No significant changes in physical examination or laboratory data were observed in either of the groups.

Discussion

Depressive disorders constitute a significant proportion of mental health problems. A systematic epidemiological survey in Vellore town found the prevalence of depressive neurosis to be 33 per thousand population (Verghese and Beig, 1974). Pharmacotherapy forms an important component of the overall management of depression. Till recently two major groups of antidepressants were available, namely the tricyclic antidepressants and monoamine oxidase inhibitors. The frequent occurence of undesirable side effects is a disadvantage in the use of these drugs. Hence a drug like alprazolam with its reported antidepressant effect and lesser side effect profile would appear to be an advantage in the management of depression. The present study assumes importance in this context.

Although a number of factors might have contributed to the drop-out from the trial, the higher rate of drop-out in the imipramine group as well as the higher frequency of reported side effects in this group suggest that side effects of this drug might have contributed to non compliance.

The results of the present study show that alprazolam is as effective as imipramine in major depressive disorder. This finding is consistent with earlier reports which have used similar methodology (Rickels et al., 1985; Rickels et al., 1987; Feighner et al., 1983; a and b). Like the earlier studies, the present study found lesser incidence of undesirable adverse effects with alprazolam. This would especially favour the use of alprazolam in patients with cardiac disease and in elderly patients where tricyclic antidepressants are contraindicated. Further, since alprazolam shows a higher margin of safety compared to the other benzodiazepines, potential for fatal toxic reactions are less likely compared to tricyclic antidepressants.

Recently there have been reports of certain adverse effects of alprazolam like dependence (Juergens and Morse, 1986), emergence of depressive symptoms during the treatment of panic disorder (Lydiard et al., 1987) and exacerbation of symptoms of panic following discontinuation of alprazolam (Fyer et al., 1987). Since the present study was limited to an evaluation period of six weeks, more long term studies are required to understand the safety and efficacy of alprazolam.

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