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Double-Blind Clinical Study Comparing Alprazolam and Doxepin in Primary Unipolar Depression

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Summary

The therapeutic effect and safety of alprazolam and doxepin were studied in 126 outpatients suffering from primary unipolar depression. The 6-week study was double-blind with a random allocation of treatment. Patients were treated with a flexible dose of 1.0–4.5 mg of alprazolam and 50–225 mg of doxepin per day. The mean final doses were 2.7 mg for alprazolam and 137.5 mg for doxepin. The results indicate that alprazolam and doxepin were equally efficacious. The incidence of side-effects was lower in the alprazolam treatment group.

Key words: *Alprazolam – Double-blind clinical study – Doxepin – Primary unipolar depression*

Introduction

Alprazolam (XANAX® – Upjohn) is a new triazolobenzodiazepine characterized by a triazol ring incorporated in the basic benzodiazepine structure [1]. Chemically and to a certain extent pharmacologically, the triazolobenzodiazepines represent a departure from the 'classic' marketed benzodiazepines (diazepam, chlordiazepoxide and oxazepam).

Previous clinical studies of alprazolam have shown that it was an effective anxiolytic, superior to placebo and at least as effective as standard benzodiazepines like chlordiazepoxide, diazepam or lorazepam [2–8]. The mean daily dose used ranged from 1.5 to 2.4 mg/day. Recent reports suggest that alprazolam possesses antidepressant activity superior to placebo and equivalent to imipramine [9–12]. In fact, true antidepressant activity has never been proven for any classic benzodiazepine. Due to its unique structure, alprazolam could possess some properties different from other benzodiazepines [13].

The purpose of this study was to compare the antidepressant activity of alprazolam and doxepin in outpatients with primary unipolar depression, to find the most effective doses for these patients and to compare the side-effects of the two drugs. For ethical and practical reasons a placebo group was not included.

Method

Selection of the patients

The double-blind study was conducted by 12 Belgian investigators especially trained for research in clinical psychopharmacology. Patients were seen in private psychiatric practices and in outpatient clinics of psychiatric departments. Most had been referred by general practitioners. The study was performed in outpatients who met the following criteria: both sexes, aged from 18 to 70, suffering from primary affective non-psychotic depression of at least moderate severity, where, in the opinion of the investigator, an anxiolytic antidepressant such as doxepin was warranted. Patients were required to have a Raskin Depression Scale score of 8 or more, at least 5 items on the Feighner Depression checklist, a Covi Anxiety Scale score equal to or less than the Raskin score and a 21-item Hamilton Psychiatric Rating Scale for Depression (HAM-D) score of at least 18.

Patients were excluded from the study who were psychopathic or psychotic, suffering from uncontrolled serious medical illnesses or in conditions where tricyclics are contraindicated. Individuals known to be sensitive to benzodiazepines or tricyclics, actively abusing alcohol or other drugs, or requiring other psychotropic or non-psychotropic medications were not enrolled. Patients receiving beta-blockers were admitted only if maintenance dosage had been reached prior to the start of the study and if that dosage was maintained unchanged throughout the trial, and thus assumed not to interfere with evaluation of treatment.

Procedure

Screening included patient history and physical examination, psychiatric background, intake form (Feighner Depression Checklist and Patient and Family History), Raskin Depression Scale, Covi Anxiety Scale, HAM-D and Hamilton Anxiety Scale (HAM-A).

All patients received a placebo for 4–7 days in order to identify placebo responders (patients who no longer fitted entry criteria) and to establish a symptom baseline. Patients were evaluated at the end of the 'wash-out' period and after the

first, second, fourth and sixth weeks on medication by the HAM-D, HAM-A, Physician's Global Impressions, Patient's Global Impressions, Beck Depression Inventory and Symptoms and Side-Effects Checklist. A drug evaluation report and a physical examination were completed at the end of the 42-day study.

Dose, regimen and duration

Patients were randomly assigned to treatment with alprazolam or doxepin. The initial dose of 2 tablets per day (1 mg alprazolam, 50 mg doxepin) was increased to 3 tablets within the first 3 days. The dose could be increased to a maximum of 9 tablets a day (4.5 mg alprazolam, 225 mg doxepin) until the patient's depression was adequately controlled or until significant side-effects appeared. Higher doses of alprazolam were not permitted because the study was conducted in outpatients, and at the time it began nothing was known about tolerance of doses over 4.5 mg/day.

Statistical methods

Contingency tables were constructed for comparing the two drug groups for categorical data, and analyzed using Fisher's Exact Test or the Exact Conditional Test. Continuous demographic and historical variables were analyzed using a one-way analysis of variance to determine if the two groups were equal before beginning drug therapy. Continuous efficacy variables were analyzed using a two-way analysis of variance including drug, investigator, and drug by investigator interaction terms in the model. All statistical tests were two-sided. The computations of the analyses done in this study were performed using SAS (Statistical Analysis System) except for the Exact Conditional Test which utilized a FORTRAN program.

Results

One hundred forty-five patients were enrolled in this study. Thirteen patients in the alprazolam group and 6 patients in the doxepin group were non-evaluable for the following reasons: HAM-D with a total score less than 18 at initial evaluation (1 alprazolam and 2 doxepin patients), no evaluation after the initial visit (4 alprazolam and 1 doxepin patients), interfering concomitant medication (3 alprazolam and 2 doxepin patients), noncompliance (4 alprazolam and 1 doxepin patients), and suicide attempt (1 alprazolam patient).

On demographic and historical data there were no statistically significant differences between the two treatment groups except for sex. There were 14 (24%) men and 45 (76%) women in the alprazolam group and 28 (42%) men and 39 (58%) women in the doxepin group ($P = 0.0493$). The mean age of the patients was 44.0 years in the alprazolam group and 43.7 years in the doxepin group.

The majority of the patients (71%) had taken at least one psychiatric drug prior to the study. Only one item on the psychiatric background differed between the two groups. Severity of precipitating stress was present or probably present in 47 (80%) of the alprazolam patients and 52 (77%) of the doxepin patients. This stress was mild in 11 (24%) alprazolam patients and 2 (4%) doxepin patients, moderate in 21 (46%)

TABLE I

SUMMARY OF RESULTS

	Initial		Week 1		Week 2		Week 4		Week 6	
	A	D	A	D	A	D	A	D	A	D
Hamilton Depression Scale [a]	24.9	25.1	−3.8	−2.4	−8.2	−7.2	−12.1	−11.3	−13.9	−14.1
Hamilton Anxiety Scale [a]	24.4	24.8	−2.5	−2.4	−6.5	−6.0	−10.6	−8.9	−11.9	−12.1
Beck Depression Inventory [a]	22.1	20.4	−1.9	−2.0	−6.0	−5.1	−8.9	−6.8	−10.3	−8.7
Physician's Global Impression										
Depression level [a]	4.5	4.6	−0.2	−0.2	−0.8	−0.8	−1.2	−1.3	−1.7	−1.8
Change level [b]	–	–	3.3	3.3	2.7	2.7	2.3	2.3	2.0	2.0
Therapeutic effect [c]	–	–	2.9	2.9	3.7	3.6	4.0	3.9	4.3	4.2

[a] Mean total scores at initial for alprazolam (A) and doxepin (D) and mean change from initial at each follow-up.

[b] Mean score on scale: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse.

[c] Mean score on scale: 1 = worse, 2 = unchanged, 3 = minimal, 4 = moderate, 5 = marked.

alprazolam and 33 (67%) doxepin patients, and severe in 14 (30%) alprazolam and 14 (29%) doxepin patients ($P = 0.0092$). For patient and family history, there were no statistically significant differences between the two treatment groups, nor were the initial scores on the rating scales or inclusion criteria statistically different between the two groups. Mean Raskin and Covi scores were 10.7 and 8.1 for the alprazolam group and 10.8 and 8.2 for the doxepin group.

The major efficacy measurements show that alprazolam and doxepin had similar effect on depression (Table 1). On the HAM-D, the mean total score decreased in each treatment group by 56% over the course of the study (Fig. 1). There were differences in favor of alprazolam at Week 1 for Somatic Symptoms - General ($P = 0.04$) and Genital Symptoms ($P = 0.01$), and in favor of doxepin at Week 6 for Work and Activities ($P = 0.04$) and Anxiety–Psychic ($P = 0.02$). There were no other significant differences on any of the individual items or the total score at any evaluation period.

The mean total HAM-A scores were approximately equal for the two groups throughout the study, decreasing 49% by the end of Week 6 (Fig. 2). Only one item showed a difference between groups in treatment response; autonomic symptoms favored alprazolam ($P = 0.04$) at Week 2. At the initial evaluation the alprazolam group had a lower score on insomnia ($P = 0.03$) and doxepin had a lower fears score ($P = 0.03$), but the changes from initial were not statistically significantly different between the groups.

According to the Physician's Global Impression, 88% of the patients in each treatment group were moderately to markedly depressed at the start of the study. Even the patients rated mildly depressed met the entry criteria. By the final evaluation, 76% of the alprazolam patients and 79% of the doxepin patients were normal or only mildly depressed. There were no statistically significant differences between the two treatment groups on any of the three questions from this evaluation form at any evaluation period (Table 1).

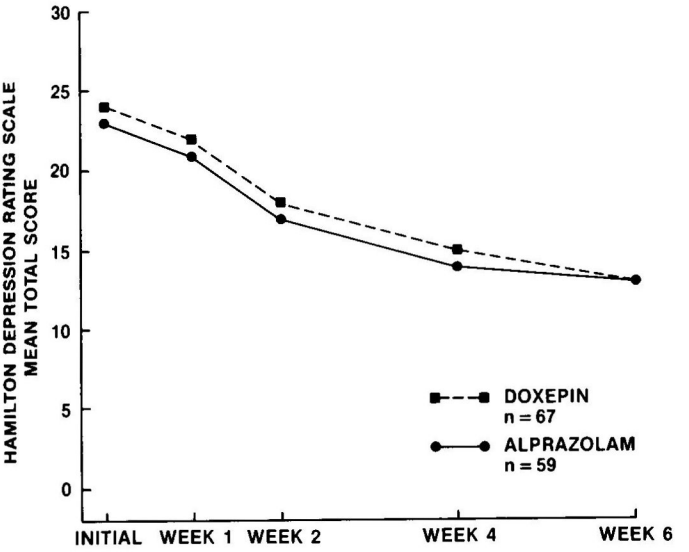

Fig. 1. Mean total scores on the Hamilton Depression Scale during treatment with alprazolam or doxepin.

The mean total Beck Score decreased 47% in the alprazolam group and 43% in the doxepin group over the course of the study. The two groups had similar total scores throughout the study and similar scores on all but two individual items. There was a difference ($P = 0.03$) favoring doxepin at the initial evaluation on 'sense of failure',

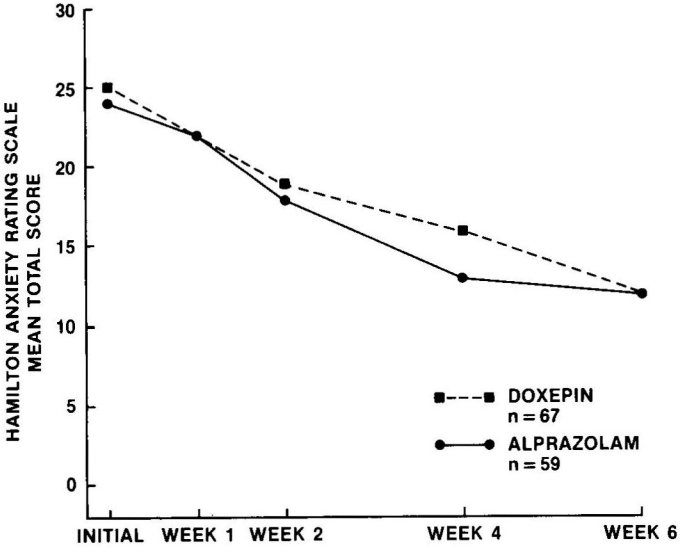

Fig. 2. Mean total scores on the Hamilton Anxiety Scale during treatment with alprazolam and doxepin.

TABLE 2

MOST COMMON SIDE EFFECTS

Side-effect	Alprazolam (n = 32)	Doxepin (n = 45)
Drowsiness	13	19
Dry mouth	6	24 *
Constipation	2	19 *
Lightheadedness	9	12
All others	112	283

* $P < 0.01$.

but not at any follow-up period, and favoring alprazolam on 'dissatisfaction' at Week 4 ($P = 0.02$) on the total score.

There were no statistically significant differences on either of the Patient's Global Impressions questions at any time in the final drug evaluation nor in vital signs.

Patient's symptoms and side-effects were rated on the symptoms and side-effects checklist as (0) = none, (1) = mild, (2) = moderate, and (3) = severe. Items were

TABLE 3

CONCOMITANT MEDICAL EVENTS

Patient number	Drug study	Adverse reaction	Severity	Investigator opinion [a]
Evaluable patients				
26	Doxepin	Hypotension		
63	Alprazolam	Nausea	Severe	Related
		Vomiting		
		Nightmares		
		Loss of weight	Severe	
65	Doxepin	Hypotension	Severe	Related
		Orthostatism		
67	Alprazolam	Hypotension	Severe	Related
85	Alprazolam	Cutaneous allergy	Mild	Possibly
109	Alprazolam	Stomach ache	Severe	Possibly
		Cramps		
		Emesis		
		Aorexia		
131	Doxepin	Thirst	Mild	Possibly
		Red cracked tongue	Severe	Probably
Nonevaluable patients				
25	Alprazolam	Suicide attempt	Moderate	Not related
61	Alprazolam	Choking feeling	Severe	Related
		Sternal constriction		
		Hot flashes		
94	Doxepin	Hypersexuality	Moderate	Probably
98	Alprazolam	Stomach ulcer	Severe	Possibly

[a] Investigator's opinion of event's relation to treatment.

TABLE 4

DOSE (MEAN CAPSULES/DAY)

	Alprazolam	Doxepin
Week 1	3.4 (1.7 mg)	3.4 (85 mg)
Week 2	4.6 (2.3 mg)	4.7 (117.5 mg)
Week 4	5 (2.5 mg)	5.5 (137.5 mg)
Week 6	5.3 (2.7 mg)	5.5 (137.5 mg)

defined as symptoms if they remained stable or improved at any follow-up time as compared to initial; items that appeared during therapy or became worse as compared to initial were defined as side-effects.

Patients taking alprazolam reported considerably fewer side-effects than the patients taking doxepin. For all periods, 32 alprazolam patients reported 142 side-effect episodes (a mean of 4.4 per reporting patient), while 45 doxepin patients reported 357 side-effect episodes (a mean of 8.5 per reporting patient). The most commonly reported side-effects were drowsiness, dry mouth, constipation, and lightheadedness (Table 2). With respect to the physician's evaluation of side-effects, 60% of the alprazolam and 43% of the doxepin patients were said to have had no side-effects, while side-effects outweighed the therapeutic benefit of the drug for two doxepin patients. Concomitant medical events, which may or may not have been adverse reactions to treatment, prompted the investigators to discontinue treatment for 11 patients (Table 3). Mean dose per day is presented in Table 4.

Discussion

Do the results of this study prove that alprazolam is the first antidepressant benzodiazepine? The equivalent efficacy of alprazolam and doxepin lend support to this hypothesis. However, it must be kept in mind that it is impossible to compare alprazolam's antidepressant activity to that of placebo and standard benzodiazepine as neither were included in the study. Moreover, the level of anxiety of the patients included in the study was rather high. This can be explained by the fact that the investigators selected patients suitable for treatment with doxepin, which is generally believed to be both antidepressant and anxiolytic [14], especially indicated in depression associated with anxiety. The inequality between treatment groups of severity of precipitating stress (alprazolam was higher) possibly compromises the results.

So far, no benzodiazepine has proven antidepressant activity. The early studies that attempted to demonstrate antidepressant efficacy generally enrolled patients labeled with such blurred concepts as 'anxious depression' [15,16], 'exogenous', 'mixed', or 'neurotic depression' [17–19], 'anxiety-depressive states' [20], 'depressive neurosis' [21,22] or 'anxiety-depressive neurosis' [23]. Actually, none of the older benzodiazepines have proven antidepressant activity. Indeed, benzo-diazepines have

never been found superior to standard antidepressants: in 24 studies comparing benzodiazepines and antidepressants no difference was found in 11 and benzodiazepines were inferior in 13 [24].

However, alprazolam seems to be pharmacologically different from the older benzodiazepines. The triazol ring may represent specific pharmacological properties: in the reserpine-induced biochemical model of depression (where chronic treatment with reserpine significantly increases the density of β-adrenoreceptor in the cerebral cortex of rats), alprazolam partially but significantly reduced the reserpine-induced increase in β-adrenoreceptors. Under similar conditions, diazepam had no significant effect [13]. However, this test has been criticized because it used the same doses of alprazolam and diazepam (10 mg/kg/day) although alprazolam is far more potent on a mg basis.

Several clinical studies report that alprazolam exerts an antidepressant effect comparable to imipramine's and with fewer side effects [9,10], and that it may be useful in treating severely depressed inpatients [11,12]. Our study concluded that there is equivalent efficacy between alprazolam and doxepin.

These pharmacological and clinical data strongly suggest some antidepressant activity for alprazolam. However, conclusive demonstration of such activity requires further studies. In particular, the drug must be studied in severely depressed inpatients who meet diagnostic criteria for endogenous depression or for melancholia and especially for the retarded subtype. The validity of the diagnosis could be increased by the use of biological markers for endogenous depression, such as non-suppression with dexamethasone suppression test [25] or shortened REM latency [26]. Such a study protocol must include a standard antidepressant and a standard benzodiazepine to demonstrate specific antidepressant activity for alprazolam.

Alprazolam, if it proves to be a reliable antidepressant, would provide real benefits for depressed patients. Standard tricyclic drugs possess a high rate of side-effects and potential toxicity in case of overdose, while alprazolam is devoid of anticholinergic side-effects and possesses a negligible toxicity, as this study clearly demonstrates.

Conclusion

In this study comparing alprazolam and doxepin in 126 outpatients with primary depression, both drugs were equally effective, but alprazolam was significantly better tolerated.

This study supports earlier reports that alprazolam may possess specific antidepressant properties and so could be the first benzodiazepine compound to be effective in the treatment of depression.

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