Brief review of published alprazolam clinical studies

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1 The clinical efficacy of alprazolam has been evaluated in both anxiety states and depressive disorders. In anxiety neurosis, studies have been conducted *vs* placebo and/or other benzodiazepine tranquilizers. Reports, to date, with regard to panic/phobia disorders have been limited to open-label studies and a single report from a placebo-controlled study. In depression, both open-label and double-blind studies (*vs* tricyclic antidepressants) have been published.

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Anxiety and neurosis

A number of studies have consistently shown that alprazolam is significantly more effective than placebo in the treatment of anxiety neurosis in both adults (Aden & Thein, 1980; Chouinard *et al.*, 1982; Cohn, 1981; Davison *et al.*, 1983; Griess & Fogari, 1980; Maletzky, 1980; Rickels *et al.*, 1983) and geriatric patients (Cohn, 1984). At the end of 4 weeks of treatment, statistically significant improvement was reported on all outcome measures (rating scales). The more commonly reported side effects in these studies were extensions of alprazolam's pharmacological activity (e.g. drowsiness, etc.). As commonly noted with benzodiazepines, these usually occurred during the early phases of treatment and tended to dissipate with continued therapy. Several studies have been published which have compared alprazolam, diazepam and placebo. Of these, some found alprazolam and diazepam to be of comparable efficacy (Aden & Thein, 1980; Davison *et al.*, 1983; Rickels *et al.*, 1983) whereas two reported that alprazolam was superior to diazepam (Cohn, 1981; Maletzky, 1980). All five studies demonstrated both drugs to be superior to placebo. In all studies, the incidence of drowsiness was significantly less, or tended to be less, in the alprazolam group.

In studies which did not include a placebo group, alprazolam has been shown to be equally efficacious with diazepam (Perez Rincon *et al.*, 1981) and lorazepam (Botte *et al.*, 1981) in

anxious outpatients. Similar findings were reported in anxiety associated with the chronic phase of alcohol withdrawal where alprazolam has been compared to diazepam (Kolin & Linet, 1981) or chlordiazepoxide (McLendon & Fabre, 1979). In these studies, the incidence of side effects reports have been either similar in nature (Kolin & Linet, 1981; Perez Rincon *et al.*, 1981) or, again, suggested that it was lower during alprazolam treatment (Botte *et al.*, 1981; McLendon & Fabre, 1979).

Panic/phobic disorders

Studies of alprazolam in panic and phobic disorders have been limited. When compared to placebo, Chouinard and co-workers (Chouinard *et al.*, 1982) reported superiority of alprazolam in patients with a diagnosis of anxiety or panic disorder. Sheehan (1982) has reported that alprazolam is 'unique among benzodiazepines' with regard to anti-panic-attack properties in that it relieves not only anticipatory anxiety but prevents panic attacks as well as relieving the associated phobic behaviour. However, until double-blind data are available, it remains to be established as to whether alprazolam is more or less effective than tricyclic antidepressants and monoamine oxidase inhibitors in this disorder.

Depression

Aden (1983) has reported that alprazolam is effective in alleviating the depressed mood which often accompanies anxiety. In addition, a number of reports have appeared which suggest that it may also be effective in the treatment of primary depression. This again would indicate uniqueness among benzodiazepines as this group of drugs is usually considered to lack efficacy in depressive disorders (Schatzberg & Cole, 1978).

Feighner and co-workers (1983) conducted a large outpatient study in patients meeting the St Louis criteria (Feighner *et al.*, 1972) for primary depression. This study demonstrated that alprazolam and imipramine were equivalent (and superior to placebo) based on global measures of efficacy (total Hamilton Depression Scale score, Physicians' and Patient's Global Impressions and total Hopkins Symptom Checklist score). Importantly, alprazolam (and imipramine) was superior to placebo on subscale clusters suggestive of true antidepressant effects. In this trial, alprazolam produced more drowsiness than imipramine but clearly caused a lower incidence of anticholinergic side effects (dry mouth, blurred vision, constipation, tachycardia, etc.). More recently, Rickels and associates (1984) have reported results from a similar study comparing alprazolam, amitriptyline, doxepin and placebo. These authors also noted that alprazolam, amitriptyline and doxepin did not differ when patients were stratified based on a number of variables including: (a)

anxious vs agitated vs retarded subtype, (b) the presence or absence of endogenomorphic depression, (c) a high or low initial degree of retardation, core symptoms of depression or anxiety, (d) a history of prior episodes and (e) a family history of depression or alcoholism. In this study, alprazolam again produced a significantly lower incidence of anticholinergic side effects as compared to the tricyclics. The overall position of alprazolam in the treatment of depression remains to be established in that definitive data from more severely ill patients are not yet available. However, at least a portion of inpatients appear to respond based on reports from open-label studies (Feighner, 1983; France & Krishnan, 1983; Pitts *et al.*, 1983; Rush *et al.*, 1984). Of interest is Feighner's observation (1983) that those patients who do respond will do so rapidly. This would enable the clinician to rapidly shift to alternative therapy if the patient fails to respond to alprazolam.

Conclusion

The efficacy of alprazolam in the treatment of anxiety neurosis has been clearly established from a number of double-blind studies. Unlike other benzodiazepines, alprazolam appears to have utility in the treatment of panic/phobic and depressive disorders. The available data support its utility in at least a portion of such patients. However, the definitive position of alprazolam in these areas awaits further studies.

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