

Alprazolam

AN ANXIOLYTIC, AN ANTIDEPRESSANT OR BOTH?

**Dr. Frank Pace B.Sc., (Hons) M.Sc., M.I.Biol., D.Biol. (Pisa),
Dip.Ed. (Lond.), A.Inst.M., Dip.M. (U.K.), M.Inst.A.M. (Dip.)**

Alprazolam or 8-chloro-1-methyl-6-phenyl-4H-s-triazolo (4-3a) (1-4) benzodiazepine has recently been launched locally. It has been available in the U.S.A. for the last five years. Alprazolam, because of its very special pharmacological properties is a useful addition to the armamentarium of the benzodiazepines already available to psychiatrists and general practitioners.

The Anxiety Syndrome

Patients frequently present themselves to the General Practitioner and Psychiatrist with a cluster of symptoms which may include amongst others:

Sleep disturbances, fears of fainting, places, crowds and impeding disasters, pessimism, tense aching muscles, trembling or shaking, emotional distress, frequent crying without any particular reason, restlessness and fidgeting, heart beating fast or pounding chest pains, feelings of a lump in the throat or choking, cold clammy hands, dry mouth, stomach 'gas', nausea, or upset stomach, tingling sensation in hands and feet..... the list seems endless. Once clinical tests show that there is no serious underlying organic disease, the diagnosis is usually quite simple..... ANXIETY.

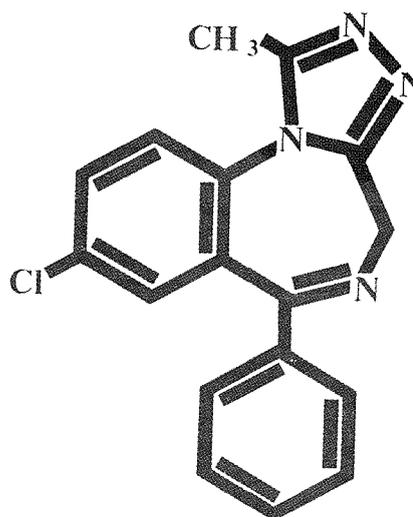
Notwithstanding the rapidity of this diagnosis the relationship between such a diagnosis and the therapeutic choice is made difficult and complicated by the multiple manifestations of the anxiety syndrome. Apart from clear-cut anxiety, treatment must be able to cover the patient from the somatic expressions of anxiety and in most cases, symptoms of depression are very frequently encountered.

There have been in the past, unjustified claims that once the patient is prescribed an anxiolytic (usually a benzodiazepine) then the depression symptoms cluster disappear. Modern psychiatric literature and clinical experience of general practitioners with patients on traditional long-term therapy with benzodiazepines completely disprove this school of thought. In fact use of anxiolytics usually unmasks the underlying depressive symptoms and the doctor in such

cases would have to combine two drugs to cover both the anxiety and the depression which is associated with the anxiety. The usual combination therapy takes the form of a benzodiazepine, a tricyclic or an anti-MAO antidepressant. Before Alprazolam, there has been no benzodiazepine which could be prescribed with confidence to cover both the anxiety and anxiety associated with depression..... and this is precisely what Alprazolam offers to the doctor who frequently has to treat such patients!

Properties of Alprazolam

Formula:—



alprazolam

Alprazolam is a triazolo-benzodiazepine with very direct metabolism, and without accumulation of metabolites common to other benzodiazepines⁽⁶⁾ (see table 1). Its half-life is of intermediate length 12 to 15 hours, which according to modern psychiatric literature is optimal for an anxiolytic. Longer acting anxiolytics, may offer the advantage of a once daily convenient dosage regimes but usually have accumulation of metabolites which is frequently not desired!^(10 & 9)

Clinically superior in efficacy and with a reduced incidence of side effects, when compared with the standard benzodiazepine, diazepam as proven in 24 clinics

Clinical Trials

Multi-centre double-blind clinical trials have shown the superiority of alprazolam as an anxiolytic to other traditional benzodiazepines. Alprazolam has been studied extensively on thousands of patients and has been shown to be superior to diazepam (the yardstick) ($p < 0.025$) not only from a global medical assessment but also using ⁽¹²⁾ the Hamilton Scale of Anxiety ⁽³⁾. Studies comparing Alprazolam with the popular lorazepam has shown ⁽⁴⁾ that patients continue to improve after the second week of therapy, whilst the dramatic improvement also associated with lorazepam in this induction treatment tends to level off. The somatic manifestations of anxiety quantified by a scale of self-evaluation of the symptoms have been controlled by alprazolam to a much greater extent than for lorazepam even when studies were extended to 16 weeks of therapy ⁽⁴⁾. Similar studies have also shown that Alprazolam is also superior to bromazepam when the anxiety syndrome cluster and the general patient's response were compared for a duration of 4 weeks of therapy ⁽¹²⁾.

Laboratory studies and clinical trials have shown an extreme tolerance of the drug when taken in therapeutic doses. In fact no clinically significant effects on the cardio-vascular and respiratory ⁽⁵⁾ systems or depression of renal and liver functions have been observed. Any side effects, which have been observed were always dose-related and were always simple extensions of its pharmacological activities. Somnolence and slight hypotension (as expected) usually disappeared after the second or third day of therapy.

Major Breakthrough

The major breakthrough of Alprazolam has been however the discovery that it is also clinically effective as an antidepressant beyond that explained by its anxiolytic action alone ⁽⁸⁾. Comparing it with Imipramine (A Tri-cyclic antidepressant) and placebo, Feighner et al, have demonstrated that it is at least as effective as Imipramine in relieving depressive symptoms, significantly more effective in controlling the somatic symptoms of depression and shows an earlier onset of activity in some measurements!

According to previous reports the classic benzodiazepines are not effective in treating patients with major ⁽¹³⁾ depression, although they relieve the symptoms of anxiety often related to depression. The implications of such a discovery makes Alprazolam a unique benzodiazepine in its class!

Tricyclic antidepressants are indispensable in the treatment of severe depression but patients on TCAs often experience anti-cholinergic side effects, orthostatic hypotension, dry mouth, constipation and drowsiness. Moreover TCAs' if taken in high doses (especially by patients who have suicidal tendencies) have severe cardiotoxic effects. There is moreover a two-week lag for onset on activity ⁽²⁾.

Advantages of Alprazolam

Alprazolam offers the possibility of prescribing safe and unique anxiolytic which has comparable if not superior properties to the other traditional benzodiazepines but with a strong

direct antidepressant action as well. In most cases therefore, a cocktail of two or more drugs may no longer be indicated if the patient is suffering from anxiety and/or anxiety associated with depression. This not only effectively lowers the cost of therapy, but also and more important still, ensures maximum safety without the suspicion that the patient would on anxiolytic therapy develop depressive symptoms!

Dosage

Alprazolam is available in two-doses 0.25mg and 0.50mg tablets. Clinical experiences in European countries show that most adult patients respond to the 0.50mg tablet with an

Initial Dosage Guide

Anxiety	0.25mg	t.i.d.
Anxiety associated with Depression	0.25-0.5mg	t.i.d.
Elderly Patients	0.25mg	b.i.d. or t.i.d.

Dosage may be increased, if necessary, to a maximum of 4 mg/day.

initial t.i.d. dosage. This dose can be increased even up to 4.0mg daily until the patient responds favourably. The 0.25 mg is perhaps more suitable for elderly patients who may require smaller initial doses. Both tablets are scored and this increases the flexibility of the dosage regime which ultimately would have to be discovered by the doctor for every individual patient.

Availability

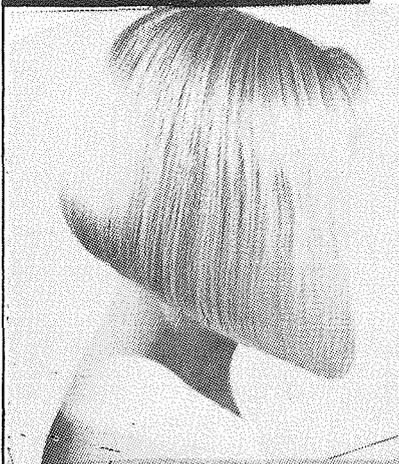
Alprazolam is marketed under the trade name XANAX. It is a product of original research by THE UPJOHN COMPANY.

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