

**ALPRAZOLAM**



*"Cafe Terrace at Night", oil on canvas, 1888, Vincent van Gogh*

*....I was only interrupted by my work on a new painting representing the exterior of a night café. On the terrace there are small figures of people drinking. An immense yellow lantern illuminates the terrace, the facade, the side walk and even casts light on the paving stones of the road which take a pinkish violet tone. The gables of the houses, like a fading road below a blue sky studded with stars, are dark blue or violet with a green tree. Here you have a night painting without black, with nothing but beautiful blue and violet and green and in this surrounding the illuminated area colours itself sulphur pale yellow and citron green. It amuses me enormously to paint the night right on the spot. Normally, one draws and paints the painting during the daytime after the sketch. But I like to paint the thing immediately. It is true that in the darkness I can take a blue for a green, a blue lilac for a pink lilac, since it is hard to distinguish the quality of the tone. But it is the only way to get away from our conventional night with poor pale whitish light, while even a simple candle already provides us with the richest of yellows and oranges...*

*.....You never told me if you had read Guy de Maupassant's Bel-ami, and what you now think of his talent in general. I say this because the beginning of Bel-ami is precisely the description of a starry night in Paris, with the lighted cafés of the boulevard, and it's something like the same subject that I've painted just now.....*

*Vincent van Gogh, Letter to his sister, Wilhelmina van Gogh,  
Arles, September 1888.*

*For Vincent there was nothing black about the night. In his "Cafe Terrace at Night" for example there is no pure black at all. Unable to form close and lasting relationships of any kind with anyone, apart from his beloved brother, Theo, he lived a desperately lonely life. Often on the road, travelling from place to place, his greatest friends were the stars at night, a recurring motif of his soulful and his haunting works. He loved the night, it protected him from the frantic and frightening modern pace of the day. Craving the company of others, yet at the same time terrified of them, at dusk he would set up his easel to paint the patrons of the night cafes, from a safe distance. Fascinated by watching strangers, but never daring to talk or interact with them directly, he would sit quite apart from them. People thought him quite odd, but on the whole harmless enough, and once used to his presence they simply ignored him and left him to his strange Art. In fact it was only very recently that Parisians had gotten used to seeing Impressionist Artists painting "en plein air". This however was during the day; to see an Impressionist producing the new modern works in the middle of the night was quite another novelty entirely! Though he complained of difficulty in catching the correct colours at night, this was never really a great problem for Vincent, his greatest inspiration came not so much from nature directly as with the majority of the Impressionists, but rather from within his own mind. He would be remembered as the father Post-Impressionism, and the prophet of the unprecedented and fabulous age of Twentieth century abstraction.*

*Art was the anaesthesia by which Vincent endured the anxieties of his tortured life. In the modern age most, sadly, resort to pharmacological agents rather than Art, in order to dull their daily anxieties. The night brings them no solace, indeed they may use the very same chemical agents to obliterate it altogether.*

## ALPRAZOLAM

### Introduction

**Alprazolam** is a **short acting** benzodiazepine.

It is primarily used in the treatment of **anxiety disorders** and **panic attack disorders**.

As with all benzodiazepines this agent has potential for abuse and both psychological and physical dependence.

Flumazenil is the specific antidote to overdose of benzodiazepines.

**See also separate Documents on:**

- **Benzodiazepine overdose, (in Toxicology folder)**
- **Benzodiazepine withdrawal syndrome, (in Toxicology folder)**
- **Flumazenil, (in Drugs folder)**

### History

The first benzodiazepine, chlordiazepoxide, was discovered by Croatian-born Jewish American chemist **Leo Sternbach** in 1955.

The Swiss pharmaceutical company Hoffmann-La Roche introduced chlordiazepoxide to clinical practice as “Librium” in 1959.

Diazepam was the second benzodiazepine developed and was marketed as “Valium” in 1963. It was described as a “minor tranquilliser” (as an alternative to the barbiturates).

By 1977 the benzodiazepines as a class were most the prescribed medications globally.

### Chemistry

**The Benzodiazepines** are a class of psychoactive drugs whose core chemical structure is the fusion of a benzene ring and a diazepine ring.

### Classification

The benzodiazepines can be most usefully clinically classified according to their duration of action, as follows:

<b>Length of Action</b>	<b>Half-life</b>	<b>Drugs</b>

<b>Very short</b>	< 6 Hours	Midazolam, Triazolam.
<b>Short</b>	6-12 Hours	Temazepam, Oxazepam, Alprazolam.
<b>Medium</b>	12-24 Hours	Lorazepam, Bromazepam.
<b>Long</b>	> 24 Hours	Diazepam, Nitrazepam, Flunitrazepam, Clobazam, Clonazepam.

### Preparations

#### Tablets:

- 0.25 mg, 0.5 mg, 1 mg, 2 mg.

### Mechanism of Action

The exact mechanism of action of the benzodiazepines is incompletely understood, but most current theories hold that they potentiate the action of the endogenous CNS inhibitory neurotransmitter gamma-aminobutyric acid (or **GABA**)

There are GABA-A and GABA-B receptors.

The antiepileptic action of the benzodiazepines involves modulation of the gamma-aminobutyric acid **type A (GABA-A) receptor**, which opens chloride channels and hyperpolarizes the cell, leading to postsynaptic inhibition.

### Pharmacodynamics

As with most other benzodiazepine agents, principle effects include:

1. Anxiolysis
2. Sedation
3. Hypnotic
4. Skeletal muscle relaxant
5. Antiepileptic effects:

- Benzodiazepines are the ideal agents in patients presenting with convulsive status epilepticus since they rapidly cross the blood–brain barrier to terminate seizures.

The *long-term* use of oral benzodiazepines in the treatment of epilepsy is limited by the development of tolerance and sedation.

## 6. Anterograde amnesia

### Pharmacokinetics

#### Absorption:

- Alprazolam is administered orally.

It is rapidly absorbed and has nearly complete bioavailability.

#### Distribution

- Alprazolam is 80 % bound to human serum protein, predominantly serum albumin.
- Small amounts are excreted into breast milk.

#### Metabolism and excretion:

- Alprazolam is extensively metabolised in humans, primarily by cytochrome P450 3A4 (CYP3A4), to two major metabolites in the plasma: 4-hydroxyalprazolam and alpha-hydroxyalprazolam.
- Alprazolam and its metabolites are excreted primarily in the urine.

### Indications

Indications include:

1. Anxiety syndromes (short term treatment)
2. Panic disorder

### Contra-indications/precautions

For the benzodiazepines as a group, these include:

1. CNS depressant effects are synergistic with other CNS depressants including alcohol.



2. Chronic obstructive airways disease with incipient respiratory failure, particularly those who are CO<sub>2</sub> retainers.
3. Sleep apnea.
4. Contraindicated in myasthenia gravis.
5. Children and the elderly are more susceptible to the effects of benzodiazepines in general
6. Contraindicated in severe hepatic impairment, particularly when hepatic encephalopathy is present. In mild-to-moderate impairment, use lower doses of a short-acting benzodiazepine to reduce risk of precipitating coma.
7. There is increased sensitivity to CNS effects in patients with severe renal impairment; use lower doses in severe impairment.
8. Known hypersensitivity to benzodiazepines or any of the components of the formulation
9. Caution must be exercised in prescribing any benzodiazepine to individuals known to be **addiction prone**.

### Pregnancy

Alprazolam is a category C drug with respect to pregnancy

Category C drugs are those drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Specialised texts should be consulted for further details.

Maternal use of alprazolam has not been associated with an increased risk of congenital malformations. However, some case control studies have shown maternal benzodiazepine exposure in early pregnancy is associated with an increased risk of fetal cleft lip and cleft palate, while other studies have refuted these findings. Maternal use of benzodiazepines during pregnancy may increase the risk of preterm delivery and low birth weight.

Infants exposed to alprazolam near term are at risk of experiencing mild and transient withdrawal symptoms, such as tremors, irritability, hypertonicity, vomiting, diarrhoea and vigorous sucking. This 1 - 2 week period of self-limiting neonatal withdrawal symptoms may present in the first 24 hours to several days after birth and may require supportive treatment.

If alprazolam is the treatment of choice during pregnancy, use the lowest effective dose for the shortest possible duration. Consider tapering the dose of alprazolam gradually at or near term if appropriate, to minimize the risk of neonatal withdrawal symptoms.

Neonatal care providers should be informed about the maternal use of alprazolam as adverse effects or withdrawal symptoms may present in the newborn. <sup>4</sup>

### Breast feeding

Compatible; but caution with chronic use, monitor infant for drowsiness

Small amounts of alprazolam are excreted into breast milk. A case report has described increased irritability in a 1 week old infant following the discontinuation of breastfeeding. The infant's mother had taken alprazolam during pregnancy and the post-partum period. <sup>4</sup>

Therefore, if alprazolam is the medicine of choice, use the lowest effective dose for the shortest duration possible. Closely observe the breastfed infant for potential adverse effects such as drowsiness, poor feeding and sleeping pattern changes. Inform neonatal care providers immediately if any adverse effects are noted in the breastfed infant.

### Adverse Effects

General adverse effects of the benzodiazepines as a group include:

1. Excessive respiratory depression:
  - This is usually seen in association with other factors that impair respiratory drive, (e.g. COPD, other CNS depressants, sleep apnea)
2. Excessive somnolence/ CNS depression:
  - Usually in the setting of excessive dosing or when used in association with other CNS depressants.
3. Physical dependence:
  - A benzodiazepine withdrawal syndrome is possible.
  - Patients who have been on longer term therapy of benzodiazepines should not have these *abruptly* withdrawn.
4. Psychological dependence:
  - Paradoxical hyper-excitement reactions are rarely seen, (mainly children or elderly).
5. Tolerance:
  - Tolerance, as defined by a need to increase the dose in order to achieve the same therapeutic effect, rarely occurs in patients receiving recommended doses under medical supervision.

- Tolerance may occur with longer term use, especially in those with drug seeking behaviour.
6. Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

### **Dosing** <sup>2</sup>

#### Anxiety:

*Adult*, initially 0.25 - 0.5 mg 3 times daily.

Usual range is: 0.5 - 4 mg daily.

#### Panic disorder:

*Adult*, initially 0.5 - 1 mg at night.

Increase by 0.25 - 1 mg every 3 days until symptoms are controlled.

Some evidence suggests that there is no need to use doses > 4 mg daily although the maximum recommended dose is **10 mg daily**.

#### Elderly and/or debilitated patient:

- Initially, 0.25 mg 2 - 3 times daily.

#### Reversal of effects:

Flumazenil is a specific benzodiazepine antagonist and will rapidly reverse the effects of benzodiazepines including depression of respiration and conscious state.



### References

1. eTG - March 2016
2. Alprazolam in Australian Medicines Handbook, Accessed July 2016.
3. Alprazolam in MIMs Website, 1 March 2014.
4. RWH Pregnancy and Breastfeeding Guidelines, 3 February 2016.

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