

**DIAZEPAM**



*“Flapper with White Mink, Red Bead Earrings and Necklace”, Print, 1928, Alberto Vargas*

*"I'm going to fix everything, just the way it was before", he said, nodding determinedly. "She'll see".*

*He talked a lot about the past, and I gather that he wanted to recover something, some idea of himself perhaps, that had gone into loving Daisy. His life had been confused and disordered since then, but if he could once return to a certain starting place and go over it all slowly, he could find out what that thing was...*

*...One autumn night, five years before, they had been walking down the street when the leaves were falling, and they came to a place where there were no trees and the sidewalk was white with moonlight. They stopped here and turned toward each other. Now it was a cool night with that mysterious excitement in it which comes at the two changes of the year. The quiet lights in the houses were humming out into the darkness and there was a stir and a bustle among the stars. Out of the corner of his eye, Gatsby saw that the blocks of the sidewalks really formed a ladder and mounted to a secret place above the trees - he could climb to it, if he climbed alone, and once there he could suck on the pap of life, gulp down the incomparable milk of wonder.*

*His heart beat faster as Daisy's white face came up to his own. He knew that when he kissed this girl, and forever wed his unutterable visions to her perishable breath, his mind would never romp again like the mind of God. So he waited, listening for a moment longer to the tuning-fork that had been struck upon a star. Then he kissed her. At his lips' touch she blossomed for him like a flower and the incarnation was complete.*

*Through all he said, even through his appalling sentimentality, I was reminded of something - an elusive rhythm, a fragment of lost words, that I had heard somewhere a long time ago. For a moment a phrase tried to take shape in my mouth and my lips parted like a dumb man's as though there were more struggling upon them than a wisp of startled air. But they made no sound, and what I had almost remembered was uncommunicable forever.*

*F. Scott Fitzgerald, "The Great Gatsby", 1926.*

*Among the constellations of wonders of Homo Sapien neurophysiology lies an enigmatic set of receptors acted upon by an equally enigmatic chemical neurotransmitter known as gamma amino butyric acid. In general terms this system acts as an inhibitory one, attenuating, calming, moderating, in ways that are complex and only imperfectly understood. 21st century medicine can harness this system by the use of the drugs known as the benzodiazepines. But we manipulate this system only in the crudest of ways. Evolution over the countless ages has accreted many functions for it, some well known to us, yet others remain quite obscure. One effect of the benzodiazepines appears to be a suppression of memory, and in evolutionary terms this seems somewhat of a contradiction when we think in terms of a benefit to survival. This amnesia may simply be a result of our clumsy attempts to modify our own biochemistry, and so we call it a "side effect"; but are the benzodiazepines in fact showing us some deep primal purpose; the suppression of a memory too painful to endure. Perhaps some things "almost remembered" are best left "uncommunicable forever".*

## **DIAZEPAM**

### **Introduction**

**Diazepam** is a widely used *long acting* benzodiazepine.

In the ED it is primarily used for:

- Anxiolysis
- The termination of seizures
- Acute alcohol withdrawal
- The control of sympathomimetic symptoms in toxicology

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.

Diazepam has a number of *active* metabolites, that are also used in clinical practice

Diazepam → hydroxy-diazepam (**temazepam**) and nordiazepam (**oxazepam**)

### Classification

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

Length of Action	Half-life	Drugs
<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.

### Preparation

Diazepam as:

Tablets:

- 2 mg, 5 mg.

Ampoules:

- 5 mg/mL as 2 mL ampoules.

### 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:
  - More particularly an IV effect

## Pharmacokinetics

### Absorption:

- Diazepam can be given orally, rectally or IV
- IM absorption is erratic and unreliable and so is not generally given by this route.

### Distribution:

- Diazepam is 98% protein bound in the plasma.
- Diazepam and its metabolites readily diffuse across the blood brain barrier.
- Diazepam can cross the human placenta
- Diazepam is excreted into human breast milk.

### Metabolism and excretion:

- Metabolism:

Diazepam is metabolized in the liver to a number of active metabolites as follows:

Diazepam → hydroxydiazepam (**temazepam**) and nordiazepam (**oxazepam**).

The half-life of nordiazepam is prolonged at approximately 96 hours.

- Excretion:

Diazepam is excreted mainly (about 70%) in the urine in free form or as glucuronide and sulfate metabolites.

- Half-life:

The plasma concentration time curve for diazepam is biphasic.

There is an initial rapid and extensive distribution phase with a half-life of up to three hours, followed by a *prolonged* terminal elimination phase with a half-life of 20 - 48 hours).

The elimination half-life is increased in the elderly.

- Accumulation:

During repeated dosing of diazepam, accumulation of diazepam and its active metabolites may occur.

Accumulation continues until a steady state plasma concentration is reached, which usually takes five days to two weeks after initiation of therapy.

The elimination of diazepam after reaching steady state levels is slow since active metabolites may remain in the blood for several days or even weeks, possibly resulting in persistent effects.

## Indications

The most usual indications in the ED include:

1. Seizures:

- Including status epilepticus

2. Anxiolysis:

3. Sedation

4. Alcohol withdrawal symptoms.

5. Reduction of sympathetic hyperactivity

- In particular in toxicology in cases of sympathomimetic hyperactivity.

*Other indications include:*

5. Muscle spasm - skeletal muscle relaxation.
  - Including the spasm associated with tetanus.
6. As a premedication to anaesthesia
7. Hypnotic-sedative withdrawal syndromes.

### Contraindications/ 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

Diazepam is a category **C drug** with respect to pregnancy.

Category C drugs are classified as 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.

Case control studies have suggested that maternal benzodiazepines exposure in early pregnancy may be associated with an increased risk of fetal cleft lip and cleft palate.

However, other studies have refuted these findings.

The use of diazepam at or near term may increase the risk of adverse neonatal complications, such as floppy infant syndrome (e.g. intrauterine growth restriction, hypotonia, lethargy and sucking difficulties) and neonatal withdrawal symptoms (e.g. tremors, irritability, hypertonicity, vomiting, diarrhoea and vigorous sucking).

If diazepam is the treatment of choice, use the lowest effective dose for the shortest duration possible.

Consider tapering the dose of diazepam gradually at or near term if appropriate, to minimise the risk of neonatal withdrawal symptoms.

Neonatal care providers should be informed about the maternal use of diazepam as adverse effects or withdrawal signs may present in newborns.

### Breastfeeding

Small amounts of diazepam are excreted into breast milk, and accumulation of diazepam in the breastfed infant may occur due to the long half-life and slow clearance of the medicine.

One case has reported a breastfed infant experiencing drowsiness, weight loss, poor feeding and restlessness following maternal use of the medicine.

Another case series has reported mild jaundice in some infants exposed to diazepam via breast milk.

If diazepam is the treatment of choice, use the lowest effective dose for the shortest duration possible and 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 include:*

1. Excessive respiratory depression:
  - This is usually seen in association with other factors that impair respiratory drive, (eg COPD, other CNS depressants, sleep apnoea)
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.

*Additionally for diazepam:*

7. Administration effects:
- Thrombosis, phlebitis with intra-arterial injection.
  - Thrombosis, phlebitis with IV injection if given into a smaller vein..
  - Pain with IM administration.

### **Dosing**

#### **Oral:**

The usual adult oral dosing ranges from **5 - 40 mg/day** in 2 - 3 divided doses.

Higher daily doses may be required for the control of alcohol withdrawal symptoms.

#### **Rectal:**

The usual dose is **0.3 - 0.5 mg / kg**, (to a maximum of 10mg).

#### IV:

For seizures or sedation:

**Adults:** 2.5 -5.0 mg boluses (up to a maximum of 30 mg).

**Children:** 0.1 - 0.25 mg/kg IV <sup>2</sup> (up to a maximum of 20 mg).

**Doses should be reduced in the elderly where titrated 1 mg boluses will often be sufficient for sedation.**

Administer undiluted, - or if dilution is necessary for slow administration dilute until solution is **clear to 0.2 mg/mL or weaker.**

Diazepam precipitates at certain concentrations. *Cloudy* solutions should not be administered.

#### 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 2017
2. Diazepam in Australian Medicines Handbook, October 2013
3. Diazepam in MIMs October 2013.
4. Diazepam in RWH Pregnancy & Breastfeeding Guidelines, 25 July 2016.

Dr J. Hayes

Reviewed 1 June 2017.