

**CLONAZEPAM**



*“Matilda immerses Dante into the waters of the River Lethe”, woodcut print, 1865,  
Gustave Dore.*

*All the streams that run the purest here on  
Earth would seem defiled beside that  
stream, which reveals all that it contains*

*even though it flows in darkness,  
dark beneath perpetual shade  
that never lets the sun or moon shine  
through.*

*Though my feet stopped, my eyes pass on  
beyond the rivulet to contemplate  
the great variety of blooming boughs,*

*and there appeared to me, as suddenly  
appears a thing so marvelous it drives  
away all other thoughts,*

*a lady, who went here and there alone,  
singing and picking flowers from among  
the blossoms that were painted all along  
her way...*

*“The water you see here does not spring  
from a vein that is restored by vapour  
when condensed by cold, like a river that  
gains and loses flow,*

*“but issues from a sure, unchanging  
source, which by God’s will regains as  
much as it pours forth to either side.*

*“On this side it descends and has the  
power  
To take from men the memory of sin.  
On the other it restores that of good deeds.*

*“Here it is called Lethe and on the other  
side Eunoe, but its water has no effect  
until they are both tasted....*

*I lowered my eyes to the clear water.  
But when I saw myself reflected, I drew  
them back towards the grass, such shame  
weighted on my brow....*

*Then when my heart restored my vital  
signs, I saw the lady I first found alone  
above me, saying “Hold on to me and hold  
me fast!”*

*she drew me into the river up to my throat  
and, pulling me along behind her, moved  
upon the water as lightly as a skiff.*

*When I had come close to the blessed shore  
I heard “Asperges me” so sweetly sung  
that I cannot recall nor write it down.*

*The lovely lady spread her arms,  
Then clasped my head, and plunged me  
under, where I was forced to swallow  
water...*

*Dante Alighieri, Purgatorio Canto XXVIII, 28 - 42; 121-132, Canto XXX 76 - 78, Canto  
XXXI, 91-102, (1306-1317)*

*Dante has finally completed his journey through Purgatory, but even though much humbled, he is not worthy of entering the final stage of his journey - that of Paradise. He has reached the top of the mountain of Purgatory and finds himself in the primal garden of Eden. There he is met by a beautiful mysterious, nymph named Matilda, who is keeper of the garden. Virgil, Dante’s guide through Hell and Purgatory is not permitted to go any further, and his new guide through Paradise is to be the secret love of his Earthly life, Beatrice. But she cannot take Dante any further in his current state of “impurity”. Matilda offers to help purify Dante by immersing him into the magical rivers of Lethe which erases all memory of the bad things someone has done in their life, and then the River Eunoe, which recalls the memory of all the good they have done. Dante undergoes this ritual, and is then free to accompany Beatrice into Paradise! A touch of amnesia is sometimes a very useful thing for those who need to undergo a painful procedure in the ED. Waters from the River Lethe are somewhat difficult to procure in this imperfect earthly existence - fortunately however we have a range of magical potions, that can assist us in the form of the benzodiazepines, such as clonazepam.*

## **CLONAZEPAM**

### **Introduction**

**Clonazepam** is a *long acting* benzodiazepine.

In the ED it is primarily used for:

- Seizures, including:
  - ♥ Status epilepticus and refractory seizures.
  - ♥ Myoclonic seizures
- Occasionally as an oral medication for acute sedation/ anxiolysis.

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)**

### **Preparation**

Preparations include: <sup>4</sup>

**Tablets:** 0.5 mg, 2.0 mg

**Ampoules:** 1 mg/mL (1 mL):

- Reconstitute immediately before use with *1 mL of diluent provided*

**Liquid formulations are available for children:** 2.5 mg/mL (1 drop = 0.1 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.

## Classification

Clonazepam is classified as a **long acting** benzodiazepine,(see **Appendix 1 below**).

## Pharmacokinetics

### Absorption:

- Clonazepam can be given **orally** or **intravenously**.  
Efficacy by IM route has *not* been demonstrated.
- It is rapidly and completely absorbed after oral administration, (slightly more quickly in liquid for compared to tablet form).
- The absolute bioavailability of clonazepam is about 90%.
- Maximum plasma concentrations of clonazepam are reached within 1 - 2 hours after oral administration.
- With *chronic* dosing, *accumulation* can occur.

### Distribution:

- Clonazepam enters the cerebral tissues rapidly.
- Benzodiazepines cross the placenta and may cause effects on the fetus.
- The plasma protein binding of clonazepam is around 85%.

### Metabolism and excretion:

- The absorption half-life is 24 minutes.  
The distribution half-life is approximately between 0.5-1 hour  
The mean elimination half-life is 39.0 +/- 8.3 hours.
- Clonazepam is primarily metabolised in the liver.

## Pharmacodynamics

As with most other benzodiazepine agents, principle effects include:

- Anxiolysis
- Sedation
- Hypnotic

- Skeletal muscle relaxant
- Antiepileptic effects.

### Indications

*Clonazepam indications in the ED include:*

1. Seizures:
  - Clonazepam can be used for the treatment of seizures including status epilepticus and refractory seizures.
  - Sedation is less common in children than adults.
  - However, behavioural changes and excess salivary and bronchial secretions are more common in children with this agent.
2. Seizure prophylaxis:
  - Can be used for prophylaxis for certain type of seizure activity, such as myoclonus.
3. Sedation/ anxiolysis.

*Clonazepam indications outside of the ED include:*

4. Adjunctive treatment for epilepsy refractory to other antiepileptic drugs, in particular absence and myoclonic seizures, and infantile spasms
  - Note however that benzodiazepines are not generally suitable for long-term treatment of epilepsy because of their sedative effect and the development of tolerance in a high proportion of people.

Treatment should be stopped if clear and lasting therapeutic benefit cannot be demonstrated. Withdraw treatment *slowly*.

### Contraindications/ Precautions

Contraindications and Precautions include:

- CNS depressant effects are synergistic with other CNS depressants including alcohol.
- Chronic obstructive airways disease with incipient respiratory failure, particularly those who are CO<sub>2</sub> retainers.
- Sleep apnea.

- Contraindicated in myasthenia gravis.
- Children and the elderly are more susceptible to the effects of benzodiazepines in general
- 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.
- There is increased sensitivity to CNS effects in patients with severe renal impairment; use lower doses in severe impairment.
- Known hypersensitivity to benzodiazepines or any of the components of the formulation
- Caution must be exercised in prescribing temazepam to individuals known to be **addiction prone**.

### Pregnancy

Clonazepam 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.

However there have been some reports that benzodiazepines may have an increased risk of congenital malformations if taken in the first trimester.<sup>3</sup>

### Breastfeeding

Avoid repeated doses; this may cause lethargy and poor feeding in the 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, (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.

*Additionally:*

7. With clonazepam paradoxical excitability reactions, (such as irritability/ aggression/ nervousness) may be seen that necessitate cessation of the drug. <sup>4</sup>
8. Salivary and bronchial hypersecretion can occur in infants and small children. <sup>4</sup>

## **Dosing**

### **Sedation/ Anxiolysis:**

- The standard oral dose is generally **0.25 - 0.5 mg - 1.0 mg daily** (usually in 2 divided doses)

Oral doses can be increased by 0.5-1 mg every third day to **maximum of 20 mg/day**. <sup>4</sup>

### **For generalized seizures/ status epilepticus:**

- Adults           **0.5 - 2.0 mg bolus up to 10 mg.**
- Children       **0.25 - 0.5 mg bolus up to 5.0mg** <sup>1</sup>

For infants smaller doses are used (0.1 mg)

For epilepsy prophylaxis:<sup>2</sup>

- *Adult*, oral, initially 0.5 - 1 mg at bedtime for 4 days, increase gradually over 2 - 4 weeks to 2 - 8 mg daily in divided doses.
- *Child*, oral, initially 0.01- 0.03 mg/kg in divided doses, increase gradually up to 0.1- 0.2 mg/kg 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.



## Appendix 1

### Classification of Benzodiazepines:

<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.

### References

1. eTG - November 2014
2. Clonazepam in Australian Medicines Handbook, October 2013
3. Clonazepam in MIMs October 2013.
4. Clonazepam in RCH Pharmacopoeia, 13<sup>th</sup> ed 2002.

Dr J. Hayes  
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