### Diazepam

#### Therapeutics

**Brands**
- Valium, Diastat, Dialar, Diazemuls, Rimapam, Stesolid, Tensium, Valclair, Alupram, Solis, Atensine, Evacalm

**Generic?**
- Yes

**Class**
- Benzodiazepine, antiepileptic drug (AED)

**Commonly Prescribed for**
(FDA approved in bold)
- **Seizure disorders.** Adjunctively and to control bouts of increased seizure activity
- **Anxiety disorders**
- **Acute alcohol withdrawal**
- **Muscle relaxant**
- **Preoperative medication**
- **Status epilepticus**
- **Tetanus**
- **Insomnia**
- **Agitation**
- **Stiff person syndrome**
- **Spasticity due to upper motor neuron disorders**
- **Irritable bowel syndrome**
- **Panic attacks**
- **Nausea and vomiting (from chemotherapy)**
- **Emergency treatment of preeclampsia**
- **Dystonia**
- **Vertigo**
- **Opioid or other drug withdrawal**
- **Acute mania in bipolar disorder**

#### How the Drug Works
- Benzodiazepines bind to and potentiate the effect of GABA-A receptors, boosting chloride conductance through GABA-regulated channels, and other inhibitory neurotransmitters. There are at least 2 benzodiazepine receptors, 1 of which is associated with sleep mechanisms, the other with memory, sensory and cognitive functions. They act at spinal cord, brainstem, cerebellum, and limbic and cortical areas.

#### How Long Until It Works
- Works quickly (minutes-hours depending on formulation) in the treatment of seizures, acute anxiety, drug withdrawal, and muscle relaxation. In patients with chronic disorders such as spasticity, dystonia or generalized anxiety it may take weeks to determine optimal dose for maximal therapeutic benefit.

#### If It Works
- **Seizures** – rectal diazepam is used intermittently as an adjunctive for patients with known epilepsy with increased seizure frequency. Intravenous diazepam is used for status epilepticus in conjunction with intravenous maintenance anticonvulsants. In patients with epilepsy who benefit from oral diazepam as an adjunctive medication, consider tapering the medication after 2 years without seizures, depending on the type of epilepsy.
- **Spasticity** – used as an adjunct medication. The cause of spasticity usually determines the duration of use. For acute muscle spasm, change to as needed use 1–3 weeks after onset.
- **Anxiety** – generally used on a short-term basis. Consider adding an SSRI or SNRI for long-term treatment.

#### If It Doesn’t Work
- **Epilepsy:** For acute use only. Status epilepticus is a medical emergency requiring immediate medical attention. After using diazepam, start maintenance AEDs such as phenytoin and evaluate for cause of worsening seizures.
- **Spasticity:** If not effective change to another agent.
- **Anxiety:** Consider a secondary cause, mania or substance abuse. Change to another agent or add an augmenting agent.

#### Best Augmenting Combos for Partial Response or Treatment-Resistance
- **Epilepsy:** often used in combination with other AEDs for optimal control but sedation can increase.
- **Spasticity:** tizanidine, baclofen, and other CNS depressants may be used.
- **Anxiety:** SSRI, SNRIs or tricyclic antidepressants are helpful for chronic anxiety. In most cases it is best to avoid combining with other benzodiazepines.
- **Insomnia:** may be combined with low-dose tricyclic antidepressants (amitriptyline), or tetracyclics (trazodone, mirtazapine).
Tests
• None required

ADVERSE EFFECTS (AEs)

How Drug Causes AEs
• Actions on benzodiazepine receptors including augmentation of inhibitory neurotransmitter effects

Notable AEs
• Most common: sedation, fatigue, depression, weakness, ataxia, nystagmus, confusion, and psychomotor retardation
• Less common: bradycardia, anorexia, hypotonia, and anterograde amnesia

Life-Threatening or Dangerous AEs
• CNS depression and decreased respiratory drive, especially in combination with opiates, barbiturates, or alcohol
• Rare blood dyscrasias or liver function abnormalities
• With injection there is a 1.7% risk of serious AEs, such as hypotension, respiratory and cardiac arrest

Weight Gain
• Unusual

Sedation
• Common

What to Do About AEs
• May decrease or remit in time as tolerance develops
• Lower the total dose and take more at bedtime
• For severe, life-threatening AEs administer flumazenil to reverse effects

Best Augmenting Agents for AEs
• Most AEs cannot be improved by adding an augmenting agent

USUAL DOSAGE RANGE
• Epilepsy: 2–10 mg 2–4 times daily
• Muscle spasm: 2–10 mg 3–4 times daily
• Panic/anxiety disorders: 2–10 mg 2–4 times daily

Dosage Forms
• Tablets: 2, 5, and 10 mg
• Oral Solution: 5 mg per mL
• Rectal Gel: 2, 5 and 10 mg
• Injection: 5 mg/mL

How to Dose
• Epilepsy: Used as adjunct in chronic epilepsy. Start at 2 mg 2–3 times daily and increase as tolerated to effective dose over days to weeks to maximum 10 mg 3–4 times daily
• Bouts of increased seizures in patients with epilepsy: Dose based on age and weight. In patients 12 or older, give rectal diazepam 5 mg if 14–27 kg, 10 mg if 28–50 kg, 15 mg 51–75 mg and 20 mg to patients 76 kg or more
• Status Epilepticus: 0.15–0.25 mg/kg in adults. Usually given 2–5 mg/min. IV or IM injection if no IV access available. After initial 5 or 10 mg, repeat every 10–15 minutes up to maximum of 30 mg in adults if seizures do not remit
• Spasticity: Start at 2 mg at bedtime. Increase by 2–5 mg every few days as tolerated to most effective/best tolerated dose
• Panic disorder: Start at 2 mg 2–3 times daily. Increase over 1–2 weeks as tolerated to most effective dose. Maximum 10 mg 4 times a day

Dosing Tips
• Children usually require higher doses per body weight for acute seizure control
• Rectal administration or injections are useful for acute seizures including exacerbations in patients with chronic epilepsy
• Assess need to continue treatment in all disorders

Overdose
• Confusion, drowsiness, decreased reflexes, incoordination, and lethargy are common. Ataxia, hypotension, coma, and death are rare. Coma and respiratory or circulatory
depression are rare when used alone. Use with other CNS depressants (such as alcohol, opioids or barbiturates) place patients at greater risk for severe AEs. Induce vomiting and use supportive measures along with gastric lavage or ipecac and in severe cases forced diuresis

- Flumazenil, an antagonist, reverses effect of diazepam
- Physostigmine can reverse some AEs but either can provoke seizures in patients with epilepsy

**Long-Term Use**

- Safe for long-term use with appropriate monitoring

**Habit Forming**

- Schedule IV drug with risk of tolerance and dependence. Dependence is common after 6 weeks or more of use. Patients with a history of drug or alcohol abuse have an increased risk of dependency

**How to Stop**

- Taper slowly. Abrupt withdrawal can cause seizures, even in patients without epilepsy. Seizures can occur over a week after stopping drug
- Taper 1–2 mg/day every 3 days to reduce risk of withdrawal. Once at a lower dose, decrease speed of taper to as little as 1–2 mg/week or less. Slow tapers are especially recommended for patient on diazepam for many months or years
- Monitor for re-emergence of disease symptoms (seizures, muscle spasm, or anxiety)

**Pharmacokinetics**

- Peak plasma level at 0.5–2 hours and elimination half-life 20–80 hours. 98% protein bound. Mostly metabolized by CYP3A4 isoenzyme. Highly lipid soluble with good CNS penetration

**Drug Interactions**

- Alcohol and other CNS depressants (barbiturates, opioids) increase CNS AEs
- Ranitidine may reduce GI absorption
- Inhibitors of hepatic metabolism (i.e., oral contraceptives, fluoxetine, isoniazid, ketoconazole, propranolol, valproic acid, metoprolol) can increase diazepam levels

**Antacids may alter the rate of absorption**
**May increase serum concentrations of digoxin and phenytoin, leading to toxicity**

**Other Warnings/Precautions**

- May cause drowsiness and impair ability to drive or perform tasks that require alertness
- Rare reports of death in patients with severe pulmonary impairment

**Do Not Use**

- Patients with a proven allergy to diazepam or any benzodiazepine. Significant liver disease or narrow angle-closure glaucoma

**SPECIAL POPULATIONS**

**Renal Impairment**

- Metabolites are renally excreted. Use with caution

**Hepatic Impairment**

- Do not use in patients with significant liver dysfunction

**Cardiac Impairment**

- No known effects

**Elderly**

- May clear drug more slowly and have lower dose requirement. Use lower doses than in younger adults

**Children and Adolescents**

- For bouts of increased seizures in epilepsy, dose by age and weight Age 2–5: 5 mg 6–11 kg, 10 mg 12–22 kg, 15 mg 23–33 kg and 20 mg 34–44 kg. Age 6–11: 5 mg 10–18 kg, 10 mg 19–37 kg, 15 mg 38–55 kg and 20 mg 56 kg and up
- Status epilepticus: 0.1–1.0 mg/kg total dose at 2–5 mg/min
- Used in children as young as 6 months (oral) and neonates under 30 days of age (injection)
- Paradoxical excitement and rage may occur in psychiatric patients and hyperactive children
Pregnancy

- Risk category D. Drug crosses placenta, and drug and its metabolites may accumulate. May increase risk of fetal malformations and infants can experience withdrawal. Use during labor can cause “floppy infant” syndrome with hypotonia, lethargy, and sucking difficulties.
- Consider changing to another AED in patients that use as a daily preventative, but can be used for status epilepticus.
- Do not use for treatment of anxiety.

Breast Feeding

- Drug is found in mother’s breast milk and may cause accumulation of drug and metabolites. Infants may become lethargic and lose weight. Do not breast feed on drug.

THE ART OF NEUROPHARMACOLOGY

Potential Advantages

- Rapid onset of action in epilepsy, spasticity, and anxiety disorders. Useful in the emergency treatment of seizures and as an adjunctive medication in spasticity disorders.

Potential Disadvantages

- Not a first-line maintenance agent in most patients with epilepsy. Development of tolerance and CNS depression often problematic. Significant potential for abuse due to quick onset of action compared to clonazepam.

Primary Target Symptoms

- Seizure frequency and severity
- Pain in spasticity disorders or dystonia
- Reduction in anxiety

Pearls

- Useful for treatment of acute seizures including status epilepticus, but patients typically require loading of a longer-lasting AED such as phenytoin.
- A first-line agent for symptoms in stiff person syndrome, but not curative.
- In cases of acute vertigo, works to suppress vestibular function and improve symptoms. Treat every 4–6 hours with 5–10 mg.

Suggested Reading


