DIAZEPAM

THERAPEUTICS

Brands
- Valium
- Diastat
see index for additional brand names

Generic? Yes (not Diastat)

Class
- Neuroscience-based Nomenclature: GABA positive allosteric modulator (GABA-PAM)
- Benzodiazepine (anxiolytic, muscle relaxant, anticonvulsant)

Commonly Prescribed for (bold for FDA approved)
- Anxiety disorder
- Symptoms of anxiety (short-term)
- Acute agitation, tremor, impending or acute delirium tremens and hallucinosis in acute alcohol withdrawal
- Skeletal muscle spasm due to reflex spasm to local pathology
- Spasticity caused by upper motor neuron disorder
- Athetosis
- Stiffman syndrome
- Convulsive disorder (adjunctive)
- Anxiety during endoscopic procedures (adjunctive) (injection only)
- Preoperative anxiety (injection only)
- Anxiety relief prior to cardioversion (intravenous)
- Initial treatment of status epilepticus (injection only)
- Insomnia
- Catatonia

How the Drug Works
- Binds to benzodiazepine receptors at the GABA-A ligand-gated chloride channel complex
- Enhances the inhibitory effects of GABA
- Boosts chloride conductance through GABA-regulated channels
- Inhibits neuronal activity presumably in amygdala-centered fear circuits to provide therapeutic benefits in anxiety disorders
- Inhibiting actions in cerebral cortex may provide therapeutic benefits in seizure disorders
- Inhibitory actions in spinal cord may provide therapeutic benefits for muscle spasms

How Long Until It Works
- Some immediate relief with first dosing is common; can take several weeks with daily dosing for maximal therapeutic benefit

If It Works
- For short-term symptoms of anxiety or muscle spasms – after a few weeks, discontinue use or use on an “as-needed” basis
- Chronic muscle spasms may require chronic diazepam treatment
- For chronic anxiety disorders, the goal of treatment is complete remission of symptoms as well as prevention of future relapses
- For chronic anxiety disorders, treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- For long-term symptoms of anxiety, consider switching to an SSRI or SNRI for long-term maintenance
- If long-term maintenance with a benzodiazepine is necessary, continue treatment for 6 months after symptoms resolve, and then taper dose slowly
- If symptoms reemerge, consider treatment with an SSRI or SNRI, or consider restarting the benzodiazepine; sometimes benzodiazepines have to be used in combination with SSRIs or SNRIs for best results

If It Doesn’t Work
- Consider switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy, especially cognitive behavioral psychotherapy
- Consider presence of concomitant substance abuse
- Consider presence of diazepam abuse
- Consider another diagnosis, such as a comorbid medical condition

Best Augmenting Combos for Partial Response or Treatment Resistance
- Benzodiazepines are frequently used as augmenting agents for antipsychotics and mood stabilizers in the treatment of psychotic and bipolar disorders
- Benzodiazepines are frequently used as augmenting agents for SSRIs and SNRIs in the treatment of anxiety disorders
**SIDE EFFECTS**

**How Drug Causes Side Effects**
- Same mechanism for side effects as for therapeutic effects – namely due to excessive actions at benzodiazepine receptors
- Long-term adaptations in benzodiazepine receptors may explain the development of dependence, tolerance, and withdrawal
- Side effects are generally immediate, but immediate side effects often disappear in time

**Notable Side Effects**
- Sedation, fatigue, depression
- Dizziness, ataxia, slurred speech, weakness
- Forgetfulness, confusion
- Hyperexcitability, nervousness
- Pain at injection site
- Rare hallucinations, mania
- Rare hypotension
- Hypersalivation, dry mouth

**Life-Threatening or Dangerous Side Effects**
- Respiratory depression, especially when taken with CNS depressants in overdose
- Rare hepatic dysfunction, renal dysfunction, blood dyscrasias

**Weight Gain**
- Reported but not expected

**DOSING AND USE**

**Usual Dosage Range**
- Oral: 4–40 mg/day in divided doses
- Intravenous (adults): 5 mg/minute
- Intravenous (children): 0.25 mg/kg every 3 minutes

**Dosage Forms**
- Tablet 2 mg scored, 5 mg scored, 10 mg scored
- Liquid 5 mg/5 mL, concentrate 5 mg/mL
- Injection vial 5 mg/mL; 10 mL, boxes of 1; 2 mL boxes of 10
- Rectal gel 5 mg/mL; 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg

**How to Dose**
- Oral (anxiety, muscle spasm, seizure): 2–10 mg, 2–4 times/day
- Oral (alcohol withdrawal): initial 10 mg, 3–4 times/day for 1 day; reduce to 5 mg, 3–4 times/day; continue treatment as needed
- Liquid formulation should be mixed with water or fruit juice, applesauce, or pudding
- Because of risk of respiratory depression, rectal diazepam treatment should not be given more than once in 5 days or more than twice during a treatment course, especially for alcohol withdrawal or status epilepticus
How to Stop

• Patients with history of seizure may seize upon withdrawal, especially if withdrawal is abrupt
• Taper by 2 mg every 3 days to reduce chances of withdrawal effects
• For difficult to taper cases, consider reducing dose much more slowly after reaching 20 mg/day, perhaps by as little as 0.5–1 mg every week or less
• For other patients with severe problems discontinuing a benzodiazepine, dosing may need to be tapered over many months (i.e., reduce dose by 1% every 3 days by crushing tablet and suspending or dissolving in 100 mL of fruit juice and then disposing of 1 mL while drinking the rest; 3–7 days later, dispose of 2 mL, and so on). This is both a form of very slow biological tapering and a form of behavioral desensitization
• Be sure to differentiate reemergence of symptoms requiring reinstitution of treatment from withdrawal symptoms

Benzodiazepine-dependent anxiety patients and insulin-dependent diabetics are not addicted to their medications. When benzodiazepine-dependent patients stop their medication, disease symptoms can reemerge, disease symptoms can worsen (rebound), and/or withdrawal symptoms can emerge

Pharmacokinetics
• Elimination half-life 20–50 hours
• Substrate for CYP450 2C19 and 3A4
• Food does not affect absorption

Drug Interactions
• Increased depressive effects when taken with other CNS depressants (see Warnings below)
• Cimetidine may reduce the clearance and raise the levels of diazepam
• Flumazenil (used to reverse the effects of benzodiazepines) may precipitate seizures and should not be used in patients treated for seizure disorders with diazepam

Other Warnings/Precautions
• Boxed warning regarding the increased risk of CNS depressant effects when benzodiazepines and opioid medications are
used together, including specifically the risk of slowed or difficulty breathing and death

- If alternatives to the combined use of benzodiazepines and opioids are not available, clinicians should limit the dosage and duration of each drug to the minimum possible while still achieving therapeutic efficacy

- Patients and their caregivers should be warned to seek medical attention if unusual dizziness, lightheadedness, sedation, slowed or difficulty breathing, or unresponsiveness occur

- Dosage changes should be made in collaboration with prescriber

- Use with caution in patients with pulmonary disease; rare reports of death after initiation of benzodiazepines in patients with severe pulmonary impairment

- History of drug or alcohol abuse often creates greater risk for dependency

- Some depressed patients may experience a worsening of suicidal ideation

- Some patients may exhibit abnormal thinking or behavioral changes similar to those caused by other CNS depressants (i.e., either depressant actions or disinhibiting actions)

**Do Not Use**

- If angle-closure glaucoma

- If there is a proven allergy to diazepam or any benzodiazepine

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**SPECIAL POPULATIONS**

### Renal Impairment

- Initial 2–2.5 mg, 1–2 times/day; increase gradually as needed

### Hepatic Impairment

- Initial 2–2.5 mg, 1–2 times/day; increase gradually as needed

### Cardiac Impairment

- Benzodiazepines have been used to treat anxiety associated with acute myocardial infarction

- Diazepam may be used as an adjunct during cardiovascular emergencies

### Elderly

- Initial 2–2.5 mg, 1–2 times/day; increase gradually as needed

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**Children and Adolescents**

- 6 months and up: initial 1–2.5 mg, 3–4 times/day; increase gradually as needed

- Parenteral: 30 days or older

- Rectal: 2 years or older

- Long-term effects of diazepam in children/adolescents are unknown

- Should generally receive lower doses and be more closely monitored

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**Pregnancy**

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001

- Possible increased risk of birth defects when benzodiazepines taken during pregnancy

- Because of the potential risks, diazepam is not generally recommended as treatment for anxiety during pregnancy, especially during the first trimester

- Drug should be tapered if discontinued

- Infants whose mothers received a benzodiazepine late in pregnancy may experience withdrawal effects

- Neonatal flaccidity has been reported in infants whose mothers took a benzodiazepine during pregnancy

- Seizures, even mild seizures, may cause harm to the embryo/fetus

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**Breast Feeding**

- Unknown if diazepam is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk

  - Recommended either to discontinue drug or bottle feed

- Effects of benzodiazepines on nursing infants have been reported and include feeding difficulties, sedation, and weight loss
Diazepam is often the first choice benzodiazepine to treat status epilepticus, and is administered either intravenously or rectally. Because diazepam suppresses stage 4 sleep, it may prevent night terrors in adults. May both cause depression and treat depression in different patients. Was once one of the most commonly prescribed drugs in the world and the most commonly prescribed benzodiazepine. Remains a popular benzodiazepine for treating muscle spasms. A commonly used benzodiazepine to treat sleep disorders. Remains a popular benzodiazepine to treat acute alcohol withdrawal. Not especially useful as an oral anticonvulsant. Multiple dosage formulations (oral tablet, oral liquid, rectal gel, injectable) allow more flexibility of administration compared to most other benzodiazepines. When using to treat insomnia, remember that insomnia may be a symptom of some other primary disorder itself, and thus warrant evaluation for comorbid psychiatric and/or medical conditions. Though not systematically studied, benzodiazepines have been used effectively to treat catatonia and are the initial recommended treatment.

**THE ART OF PSYCHOPHARMACOLOGY**

**Potential Advantages**
- Rapid onset of action
- Availability of oral liquid, rectal, and injectable dosage formulations

**Potential Disadvantages**
- Euphoria may lead to abuse
- Abuse especially risky in past or present substance abusers
- Can be sedating at doses necessary to treat moderately severe anxiety disorders

**Primary Target Symptoms**
- Panic attacks
- Anxiety
- Incidence of seizures (adjunct)
- Muscle spasms

**Pearls**
- Can be a useful adjunct to SSRIs and SNRIs in the treatment of numerous anxiety disorders, but not used as frequently as other benzodiazepines for this purpose
- Not effective for treating psychosis as a monotherapy, but can be used as an adjunct to antipsychotics
- Not effective for treating bipolar disorder as a monotherapy, but can be used as an adjunct to mood stabilizers and antipsychotics

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Suggested Reading


