**LORAZEPAM**

**Therapeutics**

**Brands**  •  Ativan  
*see index for additional brand names*

**Generic?**  Yes

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

**Commonly Prescribed for**  
(bold for FDA approved)
- Anxiety disorder (oral)  
- Anxiety associated with depressive symptoms (oral)  
- Initial treatment of status epilepticus (injection)  
- Preanesthetic (injection)  
- Insomnia  
- Muscle spasm  
- Alcohol withdrawal psychosis  
- Headache  
- Panic disorder  
- Acute mania (adjunctive)  
- Acute psychosis (adjunctive)  
- Delirium (with haloperidol)  
- 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  
- Inhibitory actions in cerebral cortex may provide therapeutic benefits in seizure disorders

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

**If It Works**
- For short-term symptoms of anxiety – after a few weeks, discontinue use or use on an “as-needed” basis

- 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 lorazepam 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  
- Not generally rational to combine with other benzodiazepines  
- Caution if using as an anxiolytic concomitantly with other sedative hypnotics for sleep

**Tests**
- In patients with seizure disorders, concomitant medical illness, and/or those with multiple concomitant long-term medications, periodic liver tests and blood counts may be prudent
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

Usual Dosage Range
- Oral: 2–6 mg/day in divided doses, largest dose at bedtime
- Injection: 4 mg administered slowly
- Catatonia: 1–2 mg per dose

Dose Forms
- Tablet 0.5 mg, 1 mg, 2 mg
- Liquid 0.5 mg/5mL, 2 mg/mL
- Injection 1 mg/0.5mL, 2 mg/mL, 4 mg/mL

How to Dose
- Oral: initial 2–3 mg/day in 2–3 doses; increase as needed, starting with evening dose; maximum generally 10 mg/day
- Injection: initial 4 mg administered slowly; after 10–15 minutes may administer again
- Take liquid formulation with water, soda, applesauce, or pudding
- Catatonia: initial 1–2 mg; can repeat in 3 hours and then again in another 3 hours if necessary

Dosing Tips
- One of the few benzodiazepines available in an oral liquid formulation
- One of the few benzodiazepines available in an injectable formulation
- Lorazepam injection is intended for acute use; patients who require long-term treatment should be switched to the oral formulation
- Use lowest possible effective dose for the shortest possible period of time (a benzodiazepine-sparing strategy)
- Assess need for continued treatment regularly
- Risk of dependence may increase with dose and duration of treatment
- For interdose symptoms of anxiety, can either increase dose or maintain same total daily dose but divide into more frequent doses
Can also use an as-needed occasional “top up” dose for interdose anxiety
Because panic disorder can require doses higher than 6 mg/day, the risk of dependence may be greater in these patients
Some severely ill patients may require 10 mg/day or more
Frequency of dosing in practice is often greater than predicted from half-life, as duration of biological activity is often shorter than pharmacokinetic terminal half-life

Overdose
- Fatalities can occur; hypotension, tiredness, ataxia, confusion, coma

Long-Term Use
- Evidence of efficacy up to 16 weeks
- Risk of dependence, particularly for treatment periods longer than 12 weeks and especially in patients with past or current polysubstance abuse

Habit Forming
- Lorazepam is a Schedule IV drug
- Patients may develop dependence and/or tolerance with long-term use

How to Stop
- Patients with history of seizure may seize upon withdrawal, especially if withdrawal is abrupt
- Taper by 0.5 mg every 3 days to reduce chances of withdrawal effects
- For difficult to taper cases, consider reducing dose much more slowly once reaching 3 mg/day, perhaps by as little as 0.25 mg per 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 10–20 hours
- No active metabolites
- Food does not affect absorption

Drug Interactions
- Increased depressive effects when taken with other CNS depressants (see Warnings below)
- Valproate and probenecid may reduce clearance and raise plasma concentrations of lorazepam
- Oral contraceptives may increase clearance and lower plasma concentrations of lorazepam
- Flumazenil (used to reverse the effects of benzodiazepines) may precipitate seizures and should not be used in patients treated for seizure disorders with lorazepam

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
LORAZEPAM (continued)

- History of drug or alcohol abuse often creates greater risk for dependency
- Use oral formulation only with extreme caution if patient has obstructive sleep apnea; injection is contraindicated in patients with sleep apnea
- 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 patient has angle-closure glaucoma
- If patient has sleep apnea (injection)
- Must not be given intra-arterially because it may cause arteriospasm and result in gangrene
- If there is a proven allergy to lorazepam or any benzodiazepine

Injection: safety and efficacy not established in children under age 18
- Long-term effects of lorazepam in children/adolescents are unknown
- Should generally receive lower doses and be more closely monitored

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, lorazepam 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

Breast Feeding
- Some drug is found in mother’s breast milk
- Recommended either to discontinue drug or bottle feed
- Effects on infant have been observed and include feeding difficulties, sedation, and weight loss

SPECIAL POPULATIONS

Renal Impairment
- 1–2 mg/day in 2–3 doses

Hepatic Impairment
- 1–2 mg/day in 2–3 doses
- Because of its short half-life and inactive metabolites, lorazepam may be a preferred benzodiazepine in some patients with liver disease

Cardiac Impairment
- Benzodiazepines have been used to treat anxiety associated with acute myocardial infarction
- Rare reports of QTc prolongation in patients with underlying arrhythmia
- Lorazepam may be used as an adjunct to control drug-induced cardiovascular emergencies

Elderly
- 1–2 mg/day in 2–3 doses
- May be more sensitive to sedative or respiratory effects

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages
- Rapid onset of action
- Availability of oral liquid as well as injectable dosage formulations

Children and Adolescents
- Oral: safety and efficacy not established in children under age 12
LORAZEPAM

Potential Disadvantages
- Euphoria may lead to abuse
- Abuse especially risky in past or present substance abusers
- Possibly more sedation than some other benzodiazepines commonly used to treat anxiety

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

Pearls

✽ One of the most popular and useful benzodiazepines for treatment of agitation associated with psychosis, bipolar disorder, and other disorders, especially in the inpatient setting; this is due in part to useful sedative properties and flexibility of administration with oral tablets, oral liquid, or injectable formulations, which is often useful in treating uncooperative patients
- Is a very useful adjunct to SSRIs and SNRIs in the treatment of numerous anxiety disorders
- Though not systematically studied, benzodiazepines, and lorazepam in particular, have been used effectively to treat catatonia and are the initial recommended treatment
- 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
- Because of its short half-life and inactive metabolites, lorazepam may be preferred over some benzodiazepines for patients with liver disease
- ✽ Lorazepam may be preferred over other benzodiazepines for the treatment of delirium
- ✽ When treating delirium, lorazepam is often combined with haloperidol, with the haloperidol dose 2 times the lorazepam dose
- ✽ Lorazepam is often used to induce pre-operative anterograde amnesia to assist in anesthesiology
- • May both cause depression and treat depression in different patients
- • Clinical duration of action may be shorter than plasma half-life, leading to dosing more frequently than 2–3 times daily in some patients
- • 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

Suggested Reading


