ALPRAZOLAM

THERAPEUTICS

Brands • Xanax, Xanax XR
see index for additional brand names

Generic? Yes

Class • Benzodiazepine (anxiolytic)

Commonly Prescribed for (bold for FDA approved)
• Generalized anxiety disorder (IR)
• Panic disorder (IR and XR)
• Other anxiety disorders
• Anxiety associated with depression
• Premenstrual dysphoric disorder
• Irritable bowel syndrome and other somatic symptoms associated with anxiety disorders
• Insomnia
• Acute mania (adjunctive)
• Acute psychosis (adjunctive)
• 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

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 — 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 alprazolam 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
• Could consider augmenting alprazolam with either gabapentin or pregabalin for treatment of anxiety disorders

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

SIDE EFFECTS

How Drug Causes Side Effects
• Same mechanism for side effects as for therapeutic effects – namely due to excessive actions at benzodiazepine receptors
Usual Dosage Range
- Anxiety: alprazolam IR: 1–4 mg/day
- Panic: alprazolam IR: 5–6 mg/day
- Panic: alprazolam XR: 3–6 mg/day

Dosage Forms
- Alprazolam IR tablet: 0.25 mg scored, 0.4 mg (Japan), 0.5 mg scored, 0.8 mg (Japan), 1 mg scored, 2 mg multiscored
- Alprazolam IR orally disintegrating tablet: 0.25 mg, 0.5 mg, 1 mg, 2 mg
- Alprazolam IR solution, concentrate: 1 mg/mL
- Alprazolam XR (extended-release) tablet: 0.5 mg, 1 mg, 2 mg, 3 mg

How to Dose
- For anxiety, alprazolam IR should be started at 0.75–1.5 mg/day divided into 3 doses; increase dose every 3–4 days until desired efficacy is reached; maximum dose generally 4 mg/day
- For panic, alprazolam IR should be started at 1.5 mg/day divided into 3 doses; increase 1 mg or less every 3–4 days until desired efficacy is reached, increasing by smaller amounts for dosage over 4 mg/day; may require as much as 10 mg/day for desired efficacy in difficult cases
- For panic, alprazolam XR should be started at 0.5–1 mg/day once daily in the morning; dose may be increased by 1 mg/day every 3–4 days until desired efficacy is reached; maximum dose generally 10 mg/day

Dosing Tips
- 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, or give as extended-release formulation
- Can also use an as-needed occasional “top up” dose for interdose anxiety
- Because panic disorder can require doses higher than 4 mg/day, the risk
of dependence may be greater in these patients
• Some severely ill patients may require 8 mg/day or more
• Extended release formulation only needs to be taken once or twice daily
• Do not break or chew XR tablets as this will alter controlled release properties
• 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
• Alprazolam and alprazolam XR generally dosed about one tenth the dosage of diazepam

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**Overdose**
• Fatalities have been reported both in monotherapy and in conjunction with alcohol; sedation, confusion, poor coordination, diminished reflexes, coma

**Pharmacokinetics**
• Metabolized by CYP450 3A4
• Inactive metabolites
• Elimination half-life 12–15 hours

**Drug Interactions**
• Increased depressive effects when taken with other CNS depressants
• Inhibitors of CYP450 3A, such as nefazodone, fluvoxamine, fluoxetine, and even grapefruit juice, may decrease clearance of alprazolam and thereby raise alprazolam plasma levels and enhance sedative side effects; alprazolam dose may need to be lowered
• Thus, azole antifungal agents (such as ketoconazole and itraconazole), macrolide antibiotics, and protease inhibitors may also raise alprazolam plasma levels
• Inducers of CYP450 3A, such as carbamazepine, may increase clearance of alprazolam and lower alprazolam plasma levels and possibly reduce therapeutic effects

**Other Warnings/Precautions**
• 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
• Hypomania and mania have occurred in depressed patients taking alprazolam

**Long-Term Use**
• Risk of dependence, particularly for treatment periods longer than 12 weeks and especially in patients with past or current polysubstance abuse

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

**How to Stop**
• Seizures may rarely occur on withdrawal, especially if withdrawal is abrupt; greater risk for doses above 4 mg and in those with additional risks for seizures, including those with a history of seizures
• 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 after reaching 3 mg/day, perhaps by as little as 0.25 mg per week or less (not for XR)
• 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. Not for XR
• 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

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**Pharmacokinetics**
• Metabolized by CYP450 3A4
• Inactive metabolites
• Elimination half-life 12–15 hours
• Use only with extreme caution if patient has obstructive 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 is taking ketoconazole or itraconazole (azole antifungal agents)
• If there is a proven allergy to alprazolam or any benzodiazepine

• Possible increased risk of birth defects when benzodiazepines taken during pregnancy
• Because of the potential risks, alprazolam 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

Use only with extreme caution if patient has obstructive sleep apnea

**Renal Impairment**
• Drug should be used with caution

**Hepatic Impairment**
• Should begin with lower starting dose (0.5–0.75 mg/day in 2 or 3 divided doses)

**Cardiac Impairment**
• Benzodiazepines have been used to treat anxiety associated with acute myocardial infarction

**Elderly**
• Should begin with lower starting dose (0.5–0.75 mg/day in 2 or 3 divided doses) and be monitored closely

**Children and Adolescents**
• Safety and efficacy not established but often used, especially short-term and at the lower end of the dosing scale
• Long-term effects of alprazolam in children/adolescents are unknown
• Should generally receive lower doses and be more closely monitored

**Pregnancy**
• Risk Category D [positive evidence of risk to human fetus; potential benefits may still justify its use during pregnancy]

• One of the most popular benzodiazepines for anxiety, especially among primary care physicians and psychiatrists
• Is a very useful adjunct to SSRIs and SNRIs in the treatment of numerous anxiety disorders

**THE ART OF PSYCHOPHARMACOLOGY**

**Potential Advantages**
• Rapid onset of action
• Less sedation than some other benzodiazepines
• Availability of an XR formulation with longer duration of action

**Potential Disadvantages**
• Euphoria may lead to abuse
• Abuse especially risky in past or present substance abusers

**Primary Target Symptoms**
• Panic attacks
• Anxiety

**Pearls**
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## Suggested Reading


### Suggested Reading

- Alprazolam XR may be dosed less frequently than immediate-release alprazolam, and lead to less interdose breakthrough symptoms and less “clock-watching” in anxious patients
- Slower rises in plasma drug levels for alprazolam XR have the potential to reduce euphoria/abuse liability, but this has not been proven
- Slower falls in plasma drug levels for alprazolam XR have the potential to facilitate drug discontinuation by reducing withdrawal symptoms, but this has not been proven
- Alprazolam XR generally has longer biological duration of action than clonazepam
- If clonazepam can be considered a “long-acting alprazolam-like anxiolytic,” then alprazolam XR can be considered “an even longer-acting clonazepam-like anxiolytic” with the potential of improved tolerability features in terms of less euphoria, abuse, dependence, and withdrawal problems, but this has not been proven
- Though not systematically studied, benzodiazepines have been used effectively to treat catatonia and are the initial recommended treatment

### Clinical Considerations

- **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**
- **May both cause depression and treat depression in different patients**
- **Risk of seizure is greatest during the first 3 days after discontinuation of alprazolam, especially in those with prior seizures, head injuries, or withdrawal from drugs of abuse**
- **Clinical duration of action may be shorter than plasma half-life, leading to dosing more frequently than 2–3 times daily in some patients, especially for immediate release alprazolam**
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### Alprazolam XR

- **Alprazolam XR may be less sedating than immediate-release alprazolam**

### Additional Considerations

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