

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

- 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

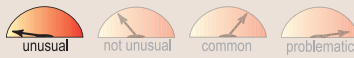
- * Sedation, fatigue, depression
- * Dizziness, ataxia, slurred speech, weakness
- * Forgetfulness, confusion
- * Hyperexcitability, nervousness
- Rare hallucinations, mania
- Rare hypotension
- Hypersalivation, dry mouth



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

Sedation



- Occurs in significant minority
- Especially at initiation of treatment or when dose increases
- Tolerance often develops over time

What to Do About Side Effects

- Wait
- Wait
- Wait
- Lower the dose
- Switch to alprazolam XR
- Take largest dose at bedtime to avoid sedative effects during the day
- Switch to another agent
- Administer flumazenil if side effects are severe or life-threatening

Best Augmenting Agents for Side Effects

- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

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

* Alprazolam and alprazolam XR generally dosed about twice the dosage of clonazepam

Overdose

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

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

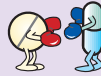
- Seizures may rarely occur on withdrawal, especially if withdrawal is abrupt; greater risk for doses above 4 mg and in those with additional risks for seizures, including those with a history of seizures
- Taper by 0.5 mg every 3 days to reduce chances of withdrawal effects
- For difficult to taper 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 reinstatement 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

- 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

ALPRAZOLAM (continued)

- 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

SPECIAL POPULATIONS

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]

- 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

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

- ✳ 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

- 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
- Adding fluvoxamine, fluoxetine, or nefazodone can increase alprazolam levels and make the patient very sleepy unless the alprazolam dose is lowered by half or more
- 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
- * Alprazolam XR may be less sedating than immediate-release alprazolam
- * 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



Suggested Reading

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