ALPRAZOLAM

THERAPEUTICS

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

Generic? Yes

Class

- Neuroscience-based Nomenclature: GABA positive allosteric modulator (GABA-PAM)
- 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

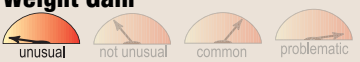
Notable Side Effects

- ✻ 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

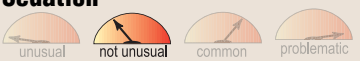
- Respiratory depression, especially when taken with CNS depressants in overdose
- Rare hepatic dysfunction, renal dysfunction, blood dyscrasias

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 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

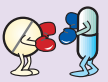
- Alprazolam is a Schedule IV drug
- Patients may develop dependence and/or tolerance with long-term use

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 and 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

Pharmacokinetics

- Metabolized by CYP450 3A4
- Inactive metabolites
- Elimination half-life 12–15 hours
- Food does not affect absorption



Drug Interactions

- Increased depressive effects when taken with other CNS depressants (see Warnings below)
- 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

- 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
- Hypomania and mania have occurred in depressed patients taking alprazolam
- 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
- 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 are taken during pregnancy
- Because of the potential risks, alprazolam is not generally recommended as treatment for anxiety during pregnancy, especially during 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
- ✻ Alprozolam 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

DeVane CL, Ware MR, Lydiard RB. Pharmacokinetics, pharmacodynamics, and treatment issues of benzodiazepines: alprazolam, adinazolam, and clonazepam. Psychopharmacol Bull 1991;27:463–73.

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