ALPRAZOLAM

THERAPEUTICS

Brands
- Xanax
- Xanax XR

Generic
Yes

US FDA Approved for Pediatric Use
- None

Off-Label for Pediatric Use
- Approved in adults
- Generalized anxiety disorder (IR)
- Panic disorder (IR and XR)
- Other off-label uses
  - 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

Class and Mechanism of Action
- Neuroscience-based Nomenclature: GABA positive allosteric modulator (GABA-PAM)
- Benzodiazepine (anxiolytic)
- As positive allosteric modulators of GABA-A receptors, benzodiazepines (in the presence of GABA) increase the frequency of opening of the inhibitory chloride channels (although it does not increase the conductance of chloride across the individual channels or the time that the channel is open). This enhances the inhibitory effects of GABA.
- Inhibits neuronal activity presumably in amygdala-centered fear circuits to provide therapeutic benefits in anxiety disorders

SAFETY AND TOLERABILITY

Notable Side Effects
- Sedation, fatigue, depression
- Dizziness, ataxia, slurred speech, weakness
- Forgetfulness, confusion
- Agitation and irritability
- Sialorrhea, dry mouth
- Rare hallucinations, mania
- Rare hypotension

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

Growth and Maturation
- Not studied

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
- 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

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

Warnings and 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)

When Not to Prescribe

- 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

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

Overdose

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

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 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

Options for Administration

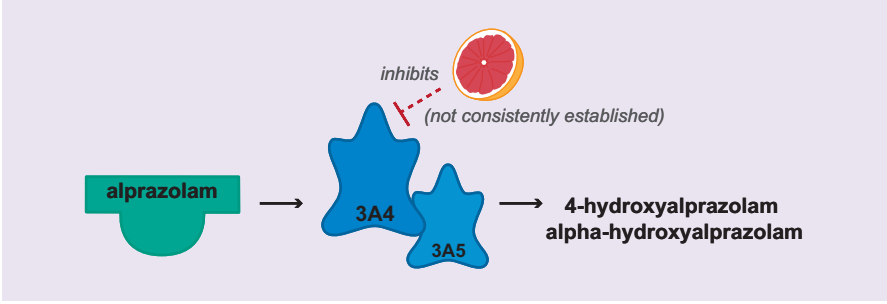
- Available as an extended-release formulation

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

Pharmacokinetics

- Alprazolam is well absorbed after oral administration
- The onset of action is relatively rapid, with peak plasma concentrations occurring within 1 to 2 hours. Factors such as the formulation of the medication



and individual variations can affect the absorption.
- Alprazolam is highly lipophilic, which allows it to distribute widely throughout the body, including the central nervous system; however, this also means that it leaves the CNS quickly
- Protein binding of alprazolam is about 80%
- Alprazolam undergoes extensive hepatic metabolism primarily via CYP3A4 (major) and to a lesser extent CYP3A5
- The major metabolites of alprazolam are 4-hydroxyalprazolam and α-hydroxyalprazolam. Of these, α-hydroxyalprazolam is the primary active metabolite
- Half-life of alprazolam in adults is 12–15 hours; there are limited data on its kinetics in youth

Pharmacogenetics

- No recommendations

Drug Interactions

- Increased depressive effects when taken with other CNS depressants
- Inhibitors of CYP3A, 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 CYP3A, such as carbamazepine, may increase clearance of alprazolam and lower alprazolam plasma levels and possibly reduce therapeutic effects

Dosing Tips

- For anxiety disorders, use lowest possible effective dose for the shortest possible period of time (a benzodiazepine sparing strategy). In adolescents, these medications may be administered prior to some anxiety-producing situations and can help to facilitate returning to school in patients with school refusal.
- Assess need for continuous treatment regularly
- Risk of dependence may increase with dose and duration of treatment and with more lipophilic benzodiazepines (e.g., alprazolam)
- For interdose symptoms of anxiety, can either increase dose or maintain same daily dose but divide into more frequent doses, or give as extended-release formulation
- Frequency of dosing in practice is often different than predicted from half-life, as duration for benzodiazepines is often related to redistribution (Stimpfl et al., 2023)
- 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
- Alprazolam and alprazolam XR are generally dosed about one-tenth the dosage of diazepam
- Alprazolam and alprazolam XR are generally dosed about twice the dosage of clonazepam

How to Switch

Use the accompanying equivalence table to convert from the alprazolam dose to the dose of the new benzodiazepine

Approximate equivalent dosage (mg)	
Alprazolam (Xanax)	0.5
Chlordiazepoxide (Librium)	25
Clonazepam (Klonopin)	0.25–0.5
Diazepam (Valium)	5
Lorazepam (Ativan)	1

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)
- Be sure to differentiate the 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

WHAT TO EXPECT

Onset of Action

- Some immediate relief with first dosing is common; can take several weeks with daily dosing for maximal therapeutic benefit

Duration of Action

- Duration of action varies for benzodiazepines, including alprazolam, in pediatric patients, but is generally considered to be from 10–12 hours

Primary Target Symptoms

- Panic attacks
- Anxiety

What Is Considered a Positive Result?

- The goal of treatment for anxiety is complete remission of current symptoms as well as prevention of future relapses
- If treatment works, it most often reduces or even eliminates symptoms, but is not a cure since symptoms can recur after medicine is stopped

How Long to Treat

- For short-term symptoms of anxiety – after a few weeks, discontinue use or use on an "as-needed" basis
- 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

What If It Stops Working?

- If anxiety symptoms reemerge, consider an SSRI and re-trying psychotherapeutic approaches

What If It Doesn't Work?

- Consider a trial of an SSRI
- When treating youth with anxiety disorders, many patients will have had significant anxiety for years prior to beginning treatment. As such, when anxiety is treated with alprazolam, their symptoms may be improved, but the patient has likely missed important developmental milestones (e.g., spending the night with friends, being able to ask questions in class). Developing these skills will take time. Beyond this, the family may have lived with the anxious child for years, and following treatment of the child, the family may need to readjust.
- Be mindful of family conflict contributing to the presentation; sometimes treating parental depression or anxiety disorders improves psychiatric and social function without any treatment of youth. Also, accommodation is common in families of youth with anxiety disorders and may need to be addressed specifically, as it can perpetuate symptoms.

TALKING TO PATIENTS AND CAREGIVERS

What to Tell Parents About Efficacy

- While the medicine helps by reducing symptoms and improving function, it is not a cure, and it is therefore necessary to keep taking the medication to sustain its therapeutic effects
- Since every treatment consideration depends on a risk/benefit analysis, parents should fully understand short- and long-term risks as well as benefits
- Often it is a good idea to tell parents whether the medication chosen is specifically approved for the disorder being treated, or whether it is being given for "unapproved" or "off-label" reasons based on good clinical practice, expert consensus, and/or prudent extrapolation of controlled data from adults

What to Tell Children and Adolescents About Efficacy

- We are trying to make you feel better
- It may be a good idea to give the medication a try; if it's not working very well, we can stop the medication and try something else
- Medications don't change who you are as a person; they give you the opportunity to be the best person you can be

What to Tell Parents About Side Effects

- Explain that mild side effects are expected at initiation or when increasing the dose and are usually transitory
- Predict side effects in advance (you will look clever and competent to the parents, unless you scare them with too much information and cause nocebo effects, in which case you won't look so clever when the patient develops lots of side effects and stops medication; use your judgment here); a balanced but honest presentation is an art rather than a science
- Ask parents to support the patient while side effects are occurring
- Parents should fully understand short- and long-term risks as well as benefits
- Explaining to the parents what to expect from medication treatment, and especially potential side effects, can help prevent early termination of medication

What to Tell Children and Adolescents About Side Effects

- Even if you get side effects, most of them get better or go away in a few days to a few weeks; however, we will likely not use this medication for a long time
- Explaining to child/adolescent what to expect from medication treatment, and especially potential side effects, can help prevent early termination of medication

What to Tell Teachers About the Medication (If Parents Consent)

- Alprazolam can make children/adolescents sleepy and make it difficult for children or adolescents to pay attention. In these situations, it is important to notify the clinician so that the dose can be decreased.
- Alprazolam may interfere with children's ability to engage in some activities at recess and in physical education class
- Encourage dialogue with parents/guardians about any behavior or mood changes

SPECIAL POPULATIONS

Renal Impairment

- 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

- No data available

Pregnancy

- 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 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 breast milk
- Recommended either to discontinue drug or formula 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

- Abuse especially risky in past or present substance users

Pearls

- Despite trials of benzodiazepines in adults with anxiety disorders consistently demonstrating benefit, trials of benzodiazepines in pediatric patients have produced mixed results:
  - Small double-blind, placebo-controlled trials and meta-analyses do not reveal differences between benzodiazepines and placebo for the management of anxiety disorders. However, these studies were small and included very young children and high doses of short-acting benzodiazepines (e.g., alprazolam).
  - By contrast, for acute anxiety in children and adolescents, a meta-analysis of nearly 1,500 patients suggests that benzodiazepines are more effective than placebo in treating acute anxiety; in this meta-analysis, there was no significant difference in the risk of developing irritability or behavioral changes between benzodiazepine and control groups (Kuang et al., 2017)
  - In the pediatric benzodiazepine trials, the poor tolerability – particularly in younger patients – may be connected to age-related pharmacodynamic factors (Strawn and Stahl, 2023)
- The pharmacodynamics of the GABA receptor in children and adolescents differ from adults, with adult expression/function not being achieved until age 14–17½ years for subcortical regions and 18–22 years for cortical regions, although girls reach adult expression of GABA receptors slightly earlier than boys (Chugani et al., 2001)
- In adults with anxiety disorders, benzodiazepines may be a very useful adjunct to SSRIs and SNRIs in the treatment of numerous anxiety disorders; however, the evidence for this is limited in children and adolescents
- Grapefruit significantly affects the pharmacokinetics of most benzodiazepines (and other medications that are metabolized by CYP3A4). In fact, grapefruit increases peak benzodiazepine blood levels (Cmax) by almost 60%, increases the time to maximum concentration (Tmax) by 80%, and boosts absorption by up to 50%.
- 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. This is primarily related to alprazolam's rapid redistribution.
- 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 alprazolam 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 "clockwatching" 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
- 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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