

THERAPEUTICS

Brands • Klonopin

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)

- **Panic disorder, with or without agoraphobia**
- **Lennox-Gastaut syndrome (petit mal variant)**
- **Akinetic seizure**
- **Myoclonic seizure**
- **Absence seizure (petit mal)**
- Atonic seizures
- Other seizure disorders
- Other anxiety disorders
- Acute mania (adjunctive)
- Acute psychosis (adjunctive)
- Insomnia
- 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 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
- For long-term treatment of seizure disorders, development of tolerance dose escalation and loss of efficacy necessitating adding or switching to other anticonvulsants is not uncommon

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 clonazepam 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
- Clonazepam is commonly combined with other anticonvulsants for the treatment of seizure 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
- Grand mal seizures

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

Best Augmenting Agents for Side Effects

- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- Seizures: dependent on individual response of patient, up to 20 mg/day
- Panic: 0.5–2 mg/day either as divided doses or once at bedtime

Dosage Forms

- Tablet 0.5 mg scored, 1 mg, 2 mg
- Disintegrating (wafer): 0.125 mg, 0.25 mg, 0.5 mg, 1 mg, 2 mg

How to Dose

- Seizures – 1.5 mg divided into 3 doses, raise by 0.5 mg every 3 days until desired effect is reached; divide into 3 even doses or else give largest dose at bedtime; maximum dose generally 20 mg/day
- Panic – 1 mg/day; start at 0.25 mg divided into 2 doses, raise to 1 mg after 3 days; dose either twice daily or once at bedtime; maximum dose generally 4 mg/day



Dosing Tips

- For anxiety disorders, use lowest possible effective dose for the shortest possible period of time (a benzodiazepine sparing strategy)
- Assess need for continuous 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 daily dose but divide into more frequent doses

- Can also use an as-needed occasional “top-up” dose for interdose anxiety
- Because seizure disorder can require doses much higher than 2 mg/day, the risk of dependence may be greater in these patients
- Because panic disorder can require doses somewhat higher than 2 mg/day, the risk of dependence may be greater in these patients than in anxiety patients maintained at lower doses
- Some severely ill seizure patients may require more than 20 mg/day
- Some severely ill panic patients may require 4 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
- * Clonazepam is generally dosed half the dosage of alprazolam
- Escalation of dose may be necessary if tolerance develops in seizure disorders
- Escalation of dose usually not necessary in anxiety disorders, as tolerance to clonazepam does not generally develop in the treatment of anxiety disorders
- * Available as an oral disintegrating wafer

Overdose

- Rarely fatal in monotherapy; sedation, confusion, coma, diminished reflexes

Long-Term Use

- May lose efficacy for seizures; dose increase may restore efficacy
- Risk of dependence, particularly for treatment periods longer than 12 weeks and especially in patients with past or current polysubstance abuse

Habit Forming

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

How to Stop

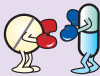
- Patients with history of seizures may seize upon withdrawal, especially if withdrawal is abrupt
- Taper by 0.25 mg every 3 days to reduce chances of withdrawal effects
- For difficult to taper cases, consider reducing dose much more slowly after

reaching 1.5 mg/day, perhaps by as little as 0.125 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

- Long half-life compared to other benzodiazepine anxiolytics (elimination half-life approximately 30–40 hours)
- Substrate for CYP450 3A4
- Food does not affect absorption



Drug Interactions

- Increased depressive effects when taken with other CNS depressants (see Warnings below)
- Inhibitors of CYP450 3A4 may affect the clearance of clonazepam, but dosage adjustment usually not necessary
- Flumazenil (used to reverse the effects of benzodiazepines) may precipitate seizures and should not be used in patients treated for seizure disorders with clonazepam
- Use of clonazepam with valproate may cause absence status



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
- Clonazepam may induce grand mal seizures in patients with multiple seizure disorders
- 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 has severe liver disease
- If there is a proven allergy to clonazepam or any benzodiazepine

SPECIAL POPULATIONS

Renal Impairment

- Dose should be reduced

Hepatic Impairment

- Dose should be reduced

Cardiac Impairment

- Benzodiazepines have been used to treat anxiety associated with acute myocardial infarction

Elderly

- Should receive lower doses and be monitored



Children and Adolescents

- Seizures – up to 10 years or 30 kg – 0.01–0.03 mg/kg per day divided into 2–3 doses; maximum dose 0.05 mg/kg per day
- Safety and efficacy not established in panic disorder
- For anxiety, children and adolescents should generally receive lower doses and be more closely monitored
- Long-term effects of clonazepam in children/adolescents are unknown



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, clonazepam 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
- Longer duration of action than some other benzodiazepines
- Availability of oral disintegrating wafer

Potential Disadvantages

- Development of tolerance may require dose increases, especially in seizure disorders
- Abuse especially risky in past or present substance abusers

Primary Target Symptoms

- Frequency and duration of seizures
- Spike and wave discharges in absence seizures (petit mal)
- Panic attacks
- Anxiety

**Pearls**

- * One of the most popular benzodiazepines for anxiety, especially among 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
- Generally used as second-line treatment for petit mal seizures if succinimides are ineffective
- Can be used as an adjunct or as monotherapy for seizure disorders
- Clonazepam is the only benzodiazepine that is used as a solo maintenance treatment for seizure disorders
- * Easier to taper than some other benzodiazepines because of long half-life
- * May have less abuse potential than some other benzodiazepines
- * May cause less depression, euphoria, or dependence than some other benzodiazepines
- * Clonazepam is often considered a “longer-acting alprazolam-like anxiolytic” with improved tolerability features in terms of less euphoria, abuse, dependence, and withdrawal problems, but this has not been proven
- 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
- Though not systematically studied, benzodiazepines have been used effectively to treat catatonia and are the initial recommended treatment

**Suggested Reading**

Davidson JR, Moroz G. Pivotal studies of clonazepam in panic disorder. *Psychopharmacol Bull* 1998;34:169–74.

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

Iqbal MM, Sobhan T, Ryals T. Effects of commonly used benzodiazepines on the fetus, the neonate, and the nursing infant. *Psychiatr Serv* 2002;53:39–49.

Panayiotopoulos CP. Treatment of typical absence seizures and related epileptic syndromes. *Paediatr Drugs* 2001;3:379–403.