### THERAPEUTICS

**Brands**
- Klonopin
  see index for additional brand names

**Generic?**
- Yes

**Class**
- Benzodiazepine (anxiolytic); antiepileptic drug (AED)

**Commonly Prescribed For**
(FDA approved in bold)
- Trigeminal neuralgia and painful tic disorders
- Burning mouth syndrome
- Panic disorder, with or without agoraphobia
- Lennox–Gastaut syndrome (petit mal variant)
- Akinetic seizure
- Myoclonic seizure
- Absence seizure (petit mal)
- Restless legs syndrome (RLS)
- Anxiety disorders
- Insomnia

**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
- 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
- There is often an immediate effect in treatment of epilepsy, periodic limb movement disorder (PLMD), RLS, insomnia, and panic disorders, but usually weeks are required for optimal dose adjustments and maximal therapeutic benefit

**If It Works**
- RLS, trigeminal neuralgia, painful tic disorders: continue to adjust dose to find the lowest dose that produces relief of symptoms with fewest AEs
- 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
- For long-term treatment of seizure disorders, development of tolerance dose escalation and loss of efficacy necessitating adding or switching to other antiepileptics is not uncommon

**If It Doesn’t Work**
- Trigeminal neuralgia, painful tic disorders: consider an AED–Na⁺ channel blocker (carbamazepine, oxcarbazepine, lamotrigine) as single agents or in combination with baclofen or tramadol or gabapentin
- RLS: change to or use combination with a dopamine agonist or an AED such as gabapentin
- Burning mouth syndrome: rule out iron deficiency; if obese, weight loss may be helpful
- Consider switching to another agent or adding an appropriate augmenting agent
- 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**
- RLS: dopamine agonists or gabapentin
- 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

**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
ADVERSE EFFECTS (AEs)

How Drug Causes AEs
- Same mechanism for AEs 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
- AEs are generally immediate, but immediate AEs often disappear in time

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

Life-Threatening or Dangerous AEs
- Respiratory depression, especially when taken with CNS depressants in overdose
- Rare hepatic dysfunction, renal dysfunction, blood dyscrasias
- Grand mal seizures

Weight Gain
- Unusual
- Reported but not expected

Sedation
- Not unusual
- Occurs in significant minority
- Especially at initiation of treatment or when dose increases
- Tolerance often develops over time

What to Do about AEs
- 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 AEs are severe or life-threatening

Best Augmenting Agents for AEs
- Many AEs cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range
- Trigeminal neuralgia: 0.25–1 mg every 8 hours
- RLS: 0.25–2 mg/night
- 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
- Trigeminal neuralgia, painful tic, burning mouth syndrome: start at 0.25 mg every 8–12 hours. Titrate to effect
- RLS: start at 0.25 mg at bedtime. Increase by 0.25 mg every few nights until symptoms improve to maximum of 2 mg at night
- 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
- Risk of tolerance and physical dependence may increase with dose and duration of treatment
- Assess need for continuous treatment regularly
- For anxiety disorders, use lowest possible effective dose for the shortest possible period of time (a benzodiazepine sparing strategy)
- For interdose symptoms of anxiety, can either increase dose or maintain same daily dose but divide into more frequent doses
- 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
- 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 (e.g. 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
● 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)
● 97% protein bound and bioavailability over 80%; mostly metabolized by CYP3A4 isoenzyme

Drug Interactions
● Increased depressive effects when taken with other CNS depressants
● Inhibitors of CYP3A4 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
● 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 abuse
● Use only with extreme caution if patient has obstructive sleep apnea
● Some depressed patients may experience a worsening of suicidal ideation

Do Not Use
● If patient has narrow 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 MI

Elderly
● Should receive lower doses and be monitored

Children and Adolescents
● 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
● Risk Category D: positive evidence of risk to human fetus; potential benefits may still justify its use during pregnancy, especially for seizure disorders
● Possible increased risk of birth defects when benzodiazepines taken during pregnancy
Because of the potential risks, clonazepam is not generally recommended as treatment during pregnancy, especially during the 1st 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.

**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

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**THE ART OF PAIN PHARMACOLOGY**

**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**
- Panic attacks
- Pain in RLS, trigeminal neuralgia
- Anxiety

**Pearls**
- Usually used in RLS only if dopamine agonists ineffective or poorly tolerated
- Is a very useful adjunct to SSRIs and SNRIs in the treatment of numerous anxiety disorders
- Easier to taper than some other benzodiazepines because of long half-life
- May cause less depression, euphoria, or dependence than some other benzodiazepines
- 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
- Longer half-life makes it easier to taper and may have less abuse potential than other benzodiazepines

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**Suggested Reading**


