CLORAZEPATE

THERAPEUTICS

**Brands**
- Azene
- Tranxene

*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)
- Anxiety disorder
- Symptoms of anxiety
- Acute alcohol withdrawal
- Partial seizures (adjunct)
- 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 clorazepate 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

**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
CLORAZEPATE (continued)

- 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
- 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
- Many experience and/or can be significant in amount
- 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
- Anxiety: 15–60 mg/day in divided doses
- Alcohol withdrawal: 30–60 mg/day in divided doses

Dosage Forms
- Tablet 3.75 mg scored, 7.5 mg scored, 15 mg scored, 22.5 mg single dose, 11.25 mg single dose half strength

How to Dose
- Anxiety: initial 15 mg/day in divided doses; adjust dose as needed on subsequent days; single-dose tablet may be given once daily at bedtime after patient is stable; maximum generally 90 mg/day
- Alcohol withdrawal: initial 30 mg, then 30–60 mg in divided doses; second day 45–90 mg in divided doses; third day 22.5–45 mg in divided doses; fourth day 15–30 mg in divided doses; after fourth day decrease dose gradually and discontinue when patient is stable; maximum generally 90 mg/day
- Epilepsy: initial 7.5 mg 3 times/day; increase by 7.5 mg weekly; maximum generally 90 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
- Can also use an as-needed occasional “top up” dose for interdose anxiety
- Because anxiety disorders can require higher doses, the risk of dependence may be greater in these patients
- 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
Overdose
- Fatalities can occur; hypotension, tiredness, ataxia, confusion, coma

Long-Term Use
- Evidence of efficacy for up to 16 weeks
- Risk of dependence, particularly for periods longer than 12 weeks and especially in patients with past or current polysubstance abuse

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

How to Stop
- Patients with history of seizure may seize upon withdrawal, especially if withdrawal is abrupt
- Taper by 7.5 mg every 3 days to reduce chances of withdrawal effects
- For difficult to taper cases, consider reducing dose much more slowly after reaching 30 mg/day, perhaps by as little as 3.75 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
- Elimination half-life 40–50 hours

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

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
- 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 there is a proven allergy to clorazepate or any benzodiazepine

SPECIAL POPULATIONS

Renal Impairment
- Initial 7.5–15 mg/day in divided doses or in 1 dose at bedtime

Hepatic Impairment
- Initial 7.5–15 mg/day in divided doses or in 1 dose at bedtime
Cardiac Impairment
• Benzodiazepines have been used to treat anxiety associated with acute myocardial infarction

Elderly
• Initial 7.5–15 mg/day in divided doses or in 1 dose at bedtime

Children and Adolescents
• Not recommended for use in children under age 9
• Recommended initial dose: 7.5 mg twice a day

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 (PLLRR 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, clorazepate 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

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages
• Rapid onset of action

Potential Disadvantages
• Euphoria may lead to abuse
• Abuse especially risky in past or present substance abusers

Primary Target Symptoms
• Panic attacks
• Anxiety
• Incidence of seizures (adjunct)

Pearls
• Can be very useful as an 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
• More commonly used than some other benzodiazepines for treating alcohol withdrawal
• May both cause depression and treat depression in different patients
• 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

Effects of benzodiazepines on nursing infants have been reported and include feeding difficulties, sedation, and weight loss

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Suggested Reading


