CHLORDIAZEPoxide

THERAPEUTICS

Brands
- Limbitrol
- Librium
- Librax

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 disorders
- Symptoms of anxiety
- Preoperative apprehension and anxiety
- Withdrawal symptoms of acute alcoholism
- 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 chlordiazepoxide 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
CHLORDIAZEPoxide (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
- Hyper-excitability, nervousness
- Pain at injection site
- 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**
- Unusual
- Rare or serious
- Common
- Problematic
- Reported but not expected

**Sedation**
- Unusual
- Not unusual
- Common
- Problematic
- 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
- 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

**Usual Dosage Range**
- Oral: mild to moderate anxiety: 15–40 mg/day in 3–4 doses
- Oral: severe anxiety: 60–100 mg/day in 3–4 doses

**Dosage Forms**
- Capsule 5 mg, 10 mg, 25 mg
- Injectable 100 mg/5 mL

**How to Dose**
- Injectable: acute/severe anxiety: initial 50–100 mg; 25–50 mg 3–4 times/day if necessary
- Injectable: alcohol withdrawal: initial 50–100 mg; repeat after 2 hours if necessary
- Injectable: preoperative: 50–100 mg 1 hour before surgery
- Patients who receive injectable chlordiazepoxide should be observed for up to 3 hours

**Dosing Tips**
- One of the few benzodiazepines available in an injectable formulation
- Chlordiazepoxide injection is intended for acute use; patients who require longer treatment should be switched to the oral formulation
- 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
- Some severely ill patients may require doses higher than the generally recommended maximum dose
- Frequency of dosing in practice is often greater than predicted from half-life, as duration of biological activity is often
CHLORDIAZEPOXIDE

1. Overdose
   - Fatalities can occur; hypotension, tiredness, ataxia, confusion, coma

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

3. 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)

4. How to Stop
   - Patients with history of seizure may seize upon withdrawal, especially if withdrawal is abrupt
   - Taper by 10 mg every 3 days to reduce chances of withdrawal effects
   - For difficult to taper patients, consider reducing dose much more slowly after reaching 20 mg/day, perhaps by as little as 5 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

5. Pharmacokinetics
   - Elimination half-life 24–48 hours

6. SPECIAL POPULATIONS
   - Renal Impairment
     - Oral: initial 10–20 mg/day in 2–4 doses; increase as needed
     - Injectable: 25–50 mg

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shorter than pharmacokinetic terminal half-life

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Drug Interactions

Other Warnings/Precautions

Do Not Use

If patient has angle-closure glaucoma

If there is a proven allergy to chlordiazepoxide or any benzodiazepine

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(continued) CHLORDIAZEPOXIDE
Hepatic Impairment
- Oral: initial 10–20 mg/day in 2–4 doses; increase as needed
- Injectable: 25–50 mg

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

Elderly
- Oral: initial 10–20 mg/day in 2–4 doses; increase as needed
- Injectable: 25–50 mg
- Elderly patients may be more sensitive to sedative effects

Children and Adolescents
- Oral: Not recommended for use in children under age 6
- Oral: initial 10–20 mg/day in 2–4 doses; may increase to 20–30 mg/day in 2–3 doses if ineffective
- Injectable: Not recommended for use in children under age 12
- Injectable: 25–50 mg
- Hyperactive children should be monitored for paradoxical effects
- Long-term effects of chlordiazepoxide 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 (PLLRL 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, chlordiazepoxide 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
- Unknown if chlordiazepoxide is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
* Recommended either to discontinue drug or bottle feed
- Effects of benzodiazepines on nursing infants have been reported and include feeding difficulties, sedation, and weight loss

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

Pearls
- Can be a useful adjunct to SSRIs and SNRIs in the treatment of numerous anxiety disorders, but not used as frequently as some other benzodiazepines
- 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
- Can 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

Remains a viable treatment option for alcohol withdrawal

- Though not systematically studied, benzodiazepines have been used effectively to treat catatonia and are the initial recommended treatment

Suggested Reading


