## CYCLOBENZAPRINE

### THERAPEUTICS

<table>
<thead>
<tr>
<th>Brands</th>
<th>Flexeril, Fexmid, Amrix, Apo-Cyclobenzaprine</th>
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<tbody>
<tr>
<td>Generic?</td>
<td>Yes (except once-daily form)</td>
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<tr>
<td>Class</td>
<td>Skeletal muscle relaxant, centrally acting</td>
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<tr>
<td>Commonly Prescribed For (FDA approved in bold)</td>
<td>Muscle spasm, Neck pain/lower back pain, Myofascial pain, Fibromyalgia</td>
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#### How the Drug Works
- A tricyclic compound with actions and structure similar to TCAs. Blocks serotonin and norepinephrine reuptake pumps and has anticholinergic effects. Acts within the CNS at the brainstem, not at the spinal cord, neuromuscular junction, or skeletal muscle level. Reduces tonic somatic motor activity.

#### How Long until It Works
- Pain – May work within hours but maximal effect occurs in 4–14 days.

#### If It Works
- Titrate to effective tolerated dose.

#### If It Doesn’t Work
- Increase to highest tolerated dose. If ineffective, consider alternative medications or other modalities.

#### Best Augmenting Combos for Partial Response or Treatment Resistance
- Use other centrally acting muscle relaxants with caution due to potential additive CNS depressant effect.
- Combine with nonpharmacologic treatments such as exercise/physical therapy, message, heat/ice, or acupuncture.

#### Tests
- Consider checking ECG for QTc prolongation at baseline and when increasing dose.

### ADVERSE EFFECTS (AEs)

#### How Drug Causes AEs
- Anticholinergic and antihistaminic properties are causes of most common AEs.

#### Notable AEs
- Dry mouth, dizziness, fatigue, constipation, weakness, sweating, and nausea are most common. Somnolence is more common with the intermediate-acting form.

#### Life-Threatening or Dangerous AEs
- Orthostatic hypotension, tachycardia, QTc prolongation, and rarely death.
- Increased intraocular pressure.
- Paralytic ileus, hyperthermia.
- Rare activation of mania or suicidal ideation.
- Rare worsening of existing seizure disorders.

#### Weight Gain
- Not unusual.

#### Sedation
- Common.

#### What to Do about AEs
- For somnolence or fatigue, change to once-daily formulation or decrease dose. For any serious AEs, discontinue.

#### Best Augmenting Agents for AEs
- Most AEs cannot be improved by use of augmenting agent.

### DOSING AND USE

#### Usual Dosage Range
- 15–30 mg/day.

#### Dosage Forms
- Tablets: 5, 7.5, 10 mg.
- Extended-release capsules: 15, 30 mg.
**How to Dose**
- Start at 5 mg 3 times a day and increase as tolerated (for best effect) to 7.5 or 10 mg 3 times day. The extended-release capsule should be taken 4–6 hours before bedtime.

**Dosing Tips**
- Take the largest dose in the evening to avoid somnolence with the immediate-release form. The extended-release capsule peaks at about 6–8 hours. Taking the extended-release form just before bedtime can lead to excess fatigue before awakening. Peak concentrations are greater when taking with food.

**Overdose**
- Cardiac arrhythmias and ECG changes; death can occur. CNS depression and tachycardia are most common. Convulsions or severe hypotension are less common. Least commonly, agitation, ataxia, tremor, vomiting, or coma can occur. Patients should be hospitalized. Sodium bicarbonate can treat arrhythmias and hypotension. Treat shock with vasopressors, oxygen, or corticosteroids.

**Long-Term Use**
- Not studied but probably safe

**Habit Forming**
- No

**How to Stop**
- Not usually tapered but may cause withdrawal similar to tricyclic antidepressants (insomnia, nausea, headache) after extended use.

**Pharmacokinetics**
- Metabolized by CYP450 system, especially CYP3A4, CYP1A2, and to a lesser extent CYP2D6 and excreted as glucuronides via the kidney. All forms take 3–4 days to reach steady state and at usual doses exhibit linear pharmacokinetics.

**Drug Interactions**
- Use with anticholinergics can increase AEs (e.g. risk of ileus)
- May enhance effects of CNS depressants
- Use with MAOI, such as rasagiline or selegiline, can cause hypertensive crisis, seizures, or death
- May alter effects of antihypertensive medication, such as guanethidine (blocking effect)
- Use with tramadol may increase seizure risk

**Do Not Use**
- Proven hypersensitivity to the drug or other tricyclic antidepressants
- Contraindicated with MAOIs
- In acute recovery after MI or uncompensated heart failure
- In conjunction with antiarrhythmics that prolong QTc interval

### SPECIAL POPULATIONS

**Renal Impairment**
- Use with caution. May need to lower dose.

**Hepatic Impairment**
- Increased plasma concentrations with moderate–severe liver dysfunction. Use with caution at low does if at all.

**Cardiac Impairment**
- Do not use in patients with recent MI, severe heart failure, a history of QTc prolongation, or orthostatic hypotension.

**Elderly**
- Plasma levels are higher and may be at greater risk of AEs. Use with caution, especially in patients over age 65.

**Children and Adolescents**
- Not studied in children under age 15.

**Pregnancy**
- Category B: use only if there is a clear need.

**Breast-Feeding**
- Unknown if excreted in breast milk. Do not use.

### THE ART OF PAIN PHARMACOLOGY

**Potential Advantages**
- Effective antispasmodic with effectiveness in acute muscle spasm and pain
- Low risk of addiction/dependence compared to carisoprodol
- Available as once-daily dose
Potential Disadvantages

- Sedation can be problematic, especially with immediate-acting form
- Not effective for spasticity due to CNS disorder, e.g. multiple sclerosis

Primary Target Symptoms

- Muscle spasm, pain

Pearls

- Similar to TCA class in structure, pharmacology, and AEs. In long-standing pain disorders such as migraine, chronic neck pain, or fibromyalgia, consider using TCAs for long-term treatment
- Do not use for spasticity related to CNS disorders, including MS, spinal cord injury, and cerebral palsy. Baclofen or tizanidine are more effective agents for these conditions
- Usually used as a short-term adjunctive agent (2–6 weeks) for acute muscle spasm and pain. No longer-term studies have been done, but due to similarities with TCAs, probably safe to use for months or years
- Reasonable first-line alternative agent for fibromyalgia although has no FDA approval for this

Suggested Reading


