TRIHEXYPHENIDYL

THERAPEUTICS

Brands
• Artane

Generic?
Yes

Class
• Antiparkinson agent, anticholinergic

Commonly Prescribed for
(FDA approved in bold)
• Extrapyramidal disorders
• Parkinsonism
• Idiopathic generalized dystonia
• Focal dystonias
• Dopa-responsive dystonia

How the Drug Works
• In PD, there is a relative excess of cholinergic input. Trihexyphenidyl is a synthetic anticholinergic with relatively greater CNS activity than most other anticholinergics
• May also inhibit the reuptake and storage of dopamine at dopamine neurons and transporters, prolonging dopamine action

How Long Until It Works
• PD/extrapyramidal disorders – minutes-hours

If It Works
• PD – do not abruptly discontinue or change doses of other PD treatments. Usually most effective in combination with other medications

If It Doesn’t Work
• PD – Generally trihexyphenidyl is an adjunctive medication for common PD symptoms, such as tremor, rigidity, and drooling. Other cardinal PD symptoms, such as bradykinesia and gait difficulties, are most likely to improve with other PD treatments, such as levodopa, dopamine agonists, amantadine, or MAO-B inhibitors
• Extrapyramidal disorders – increase to highest tolerated dose. Long-standing disorders are less likely to respond to treatment

Best Augmenting Combos for Partial Response or Treatment-Resistance
• For bradykinesia or gait disturbances causing significant functional disturbance, levodopa is most effective. For idiopathic PD patients, especially younger patients with normal cognition and milder disability, dopamine agonists are also a good first choice. Amantadine and MAO-B inhibitors may also be useful
• Depression is common in PD and may respond to low-dose SSRIs

Tests
• None

ADVERSE EFFECTS (AEs)

How Drug Causes AEs
• Prevents the action of acetylcholine on muscarinic receptors

Notable AEs
• Dry mouth, tachycardia, palpitations, hypotension, disorientation, confusion, hallucinations, constipation, nausea/vomiting, dilation of colon, rash, blurred vision, diplopia, urinary retention, elevated temperature, decreased sweating, erectile dysfunction

Life-Threatening or Dangerous AEs
• May precipitate narrow-angle glaucoma. Risk of heat stroke, especially in elderly patients. Can precipitate tachycardia, cardiac arrhythmias and hypotension in susceptible patients. May cause urinary retention in patients with prostate hypertrophy

Weight Gain
• Unusual

Sedation
• Common
**What to Do About AEs**

- Confusion, hallucinations – if possible stop trihexyphenidyl and any other anticholinergics
- Sedation – can take entire dose at night or lower dose
- Dry mouth – chewing gum or water can help
- Urinary retention: if drug cannot be discontinued, obtain urological evaluation

**Best Augmenting Agents for AEs**

- Most AEs cannot be improved with the use of an augmenting agent

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**DOSING AND USE**

**Usual Dosage Range**

- PD – 6–15 mg/daily
- Extrapyramidal reactions: 5–15 mg daily

**Dosage Forms**

- Tablets: 2, 5 mg
- Elixir: 2 mg/5 mL

**How to Dose**

- PD: start at 1 mg the first few days. Then increase in 2 mg increments every 3–5 days as tolerated or until clinical effect reached. Divide total dose and give 3 times daily, usually with meals. Patients on very high doses may elect to take 4 doses daily: with meals and at bedtime. Usual dose is 6–10 mg in idiopathic PD but higher on average (12–15 mg) in post-encephalitic PD
- Drug-induced extrapyramidal disorders: wait a few hours to assess effect and increase dose empirically as tolerated. The total daily dose varies from patient to patient. To achieve more rapid relief, temporarily lower dose of the offending agent (phenothiazine, thioxanthene, or butyrophenone) when starting

**Dosing Tips**

- Taking with meals may reduce AEs

**Overdose**

- Complications may include circulatory collapse, cardiac arrest, respiratory depression or arrest, CNS depression or stimulation, psychosis, shock, coma, seizures, ataxia, combativeness, anhidrosis and hyperthermia, fever, dysphagia, decreased bowel sounds, and sluggish pupils. Induce emesis, use gastric lavage or activated charcoal. Oxygen or intubation may be needed for respiratory depression. Catheterize for urinary retention. Treat hyperthermia appropriately with cooling devices, local miotics for mydriasis/cycloplegia. Use physostigmine to reverse cardiac effects and use fluids and vasopressors if needed

**Long-Term Use**

- Safe for long-term use. Effectiveness may decrease over time (years) in PD and AEs, such as sedation and cognitive impairment, can worsen

**Habit Forming**

- No

**How to Stop**

- No need to taper

**Pharmacokinetics**

- Half-life is 6–10 hours, but the time to peak effect is at 1–1.3 hours. Mostly urinary excretion. Bioavailability is about 100% but metabolism not well understood

**Drug Interactions**

- Use with amantadine may increase AEs
- Trihexyphenidyl and all other anticholinergics may increase serum levels and effects of digoxin
- Can lower concentration of haloperidol and other phenothiazines, causing worsening of schizophrenia symptoms. Phenothiazines tend to increase anticholinergic AEs with concurrent use
- Can decrease gastric motility, resulting in increased gastric deactivation of levodopa and reduction in efficacy

**Other Warnings/Precautions**

- Use with caution in hot weather – may increase susceptibility to heat stroke
- Anticholinergics have additive effects when used with drugs of abuse, such as cannabinoids, barbiturates, opioids, and alcohol
**Do Not Use**
- Known hypersensitivity to the drug, glaucoma (especially angle-closure type), pyloric or duodenal obstruction, stenosing peptic ulcers, prostate hypertrophy or bladder neck obstructions, achalasia, or megacolon

**SPECIAL POPULATIONS**

<table>
<thead>
<tr>
<th>Renal Impairment</th>
<th>Use with caution but no known effects</th>
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</thead>
<tbody>
<tr>
<td>Hepatic Impairment</td>
<td>Use with caution but no known effects</td>
</tr>
<tr>
<td>Cardiac Impairment</td>
<td>Use with caution in patients with known arrhythmias, especially tachycardia</td>
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<tr>
<td>Elderly</td>
<td>Use with caution. More susceptible to AEs</td>
</tr>
<tr>
<td>Children and Adolescents</td>
<td>Do not use in children aged 3 or less. Generalized dystonias may respond to anticholinergic treatment; young patients usually tolerate the medication better than the elderly</td>
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<tr>
<td>Pregnancy</td>
<td>Category C. Use only if benefit of medication outweighs risks</td>
</tr>
<tr>
<td>Breast Feeding</td>
<td>Concentration in breast milk unknown. May inhibit lactation. Use only if benefits outweigh risk</td>
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</tbody>
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**THE ART OF NEUROPHARMACOLOGY**

**Potential Advantages**
- Useful adjunctive agent for some PD patients, especially post-encephalitic and younger patients with bothersome tremor. First-line agent for generalized dystonias and well tolerated in the younger age groups

**Potential Disadvantages**
- Multiple dose-dependent AEs associated with muscarinic effects limit use. Not effective in most idiopathic PD patients. Patients with long-standing extrapyramidal disorders may not respond to treatment

**Primary Target Symptoms**
- Tremor, akinesia, rigidity, drooling, dystonia

**Pearls**
- Useful adjunct in younger PD patients with tremor
- Useful in the treatment of post-encephalitic PD
- Sedation limits use, especially in older patients. Patients with mental impairment do poorly
- Post-encephalitic PD patients usually tolerate higher doses better than idiopathic PD patients
- Generalized dystonias are more likely to benefit from anticholinergic therapy than focal dystonias
- Dystonias related to cerebral palsy, head injuries, and stroke may improve with trihexyphenidyl, especially in younger, cognitively normal patients
- Schizophrenic patients may abuse trihexyphenidyl and other anticholinergic medications to relieve negative symptoms, for a stimulant effect or to improve symptoms of drug-induced parkinsonism
Suggested Reading


