



**Drug Shortage Alert**  
**Physostigmine**

Date of last update: July 2023

*Recommendations and information provided in this drug shortage alert are compiled by experts in the field. Practitioners are advised to consult with their institution's staff to ensure that response to any drug shortage is in line with internal policies and procedures.*

**INTRODUCTION**

- Physostigmine is a naturally occurring tertiary amine reversible acetylcholinesterase inhibitor that readily crosses the blood-brain barrier. It is used for treatment of antimuscarinic (i.e., anticholinergic) toxicity (e.g., diphenhydramine overdose).
- The current physostigmine shortage, ongoing since March 2021, is caused by problems with the sole United States manufacturer, Akorn Pharmaceuticals, which ceased operations in February 2023.<sup>1</sup>
- This summary provides information in the event of a shortage and its impact on adult and pediatric patients by providing potential management strategies, pharmacotherapeutic considerations, and safety implications.
- The recommendations provided in this document are based on both current evidence, including a review of available literature by the SCCM Drug Shortages and Medication Safety Committee, and the need for physostigmine conservation during this shortage.

**MANAGEMENT STRATEGIES**

- Because of this shortage, institutions may need to reserve remaining stocks of physostigmine for patients with indications that will most likely benefit from this medication, such as severe and refractory antimuscarinic toxicity (e.g., severe delirium) and for the prevention of intubation.<sup>2</sup>
  - Rapid diagnosis of suspected antimuscarinic delirium and simultaneous exclusion of alternative life-threatening diagnoses (e.g., meningitis/encephalitis) is another potential indication.
  - Given physostigmine's scarcity and the need for careful patient selection, discussion with a toxicologist before use is recommended.
    - The use of physostigmine in patients with tricyclic antidepressant (TCA) overdose, seizure, or signs of sodium channel blockade on ECG is controversial and should be discussed with a toxicologist before use.
- Benzodiazepines may be used as initial management in patients with signs of central antimuscarinic toxicity, such as agitation associated with delirium or seizures (see [SCCM's December 2022 parenteral benzodiazepines drug shortage alert](#) for more information on this shortage).
  - Note that benzodiazepines may be deliriogenic.

- Dexmedetomidine may be considered in appropriate patients for suppression of agitation associated with antimuscarinic delirium.<sup>3,4</sup>
- Caution should be exercised with administration of antipsychotics, e.g., olanzapine, which may exacerbate antimuscarinic toxicity due to acetylcholine receptor antagonism.
- Centrally acting tertiary amine acetylcholinesterase inhibitors prescribed on-label for dementia (rivastigmine, galantamine, donepezil), which reverse the underlying pathophysiology of antimuscarinic delirium, may be considered in selected patients with antimuscarinic poisoning as an alternative or adjunct to physostigmine, benzodiazepines, and dexmedetomidine.
  - Similar to physostigmine, use of other centrally acting acetylcholinesterase inhibitors in the setting of TCA overdose, seizure, or ECG findings suggesting sodium channel blockade is controversial and should be discussed with a medical toxicologist before use.
  - Note that charged quaternary amine acetylcholinesterase inhibitors such as pyridostigmine will **NOT** cross the blood-brain barrier and therefore will only reverse peripheral, but not central, antimuscarinic toxicity.
    - Use of non-physostigmine centrally acting acetylcholinesterase inhibitors should be discussed with a medical toxicologist before administration.

**Table 1** describes selected indications for the above-mentioned drug shortage, specifically in critically ill patients.

**Table 1.** Potential management strategies for physostigmine shortage

Indication in critically ill patients	Suggested Strategies	Key Points
Antimuscarinic toxicity <sup>3,4</sup>	<ul style="list-style-type: none"> <li>• BZDs for central antimuscarinic toxicity, including agitation related to delirium, and seizure.</li> <li>• Dexmedetomidine for agitation related to delirium.</li> <li>• Non-physostigmine centrally acting acetylcholinesterase inhibitors may be considered in patients exhibiting antimuscarinic delirium and associated agitation.</li> </ul>	<ul style="list-style-type: none"> <li>• Available data for non-BZD alternative therapies are limited to case reports or series.</li> <li>• Cholinergic toxicity may occur with non-physostigmine acetylcholinesterase inhibitors due to lack of familiarity with dosing and monitoring; consultation with experts such as Poison Control or clinical toxicologists is recommended.</li> </ul>

BZD, benzodiazepine.

## PHARMACOTHERAPEUTIC CONSIDERATIONS

- The use of rivastigmine, donepezil, and galantamine, and management strategies in the setting of drug shortages is indication dependent. Please refer to the above review for more information.
- Important considerations for available therapeutic alternatives, compared to physostigmine:
  - Data suggest that physostigmine is associated with improved ability to manage delirium and associated agitation, compared to benzodiazepines.
  - Rivastigmine, donepezil, and galantamine are not available parenterally, leading to both a delayed time to peak (i.e., hours compared to minutes) and potential challenges in administration of enteral formulations due to aspiration risk in the setting of delirium.

- Delayed therapeutic effect due to antimuscarinic effects on gastrointestinal tract results in altered and erratic absorption.
- Inadvertent excessive dosing of alternative acetylcholinesterase inhibitors may lead to more prolonged cholinergic toxicity compared to physostigmine.

**Table 2. Pharmacokinetic Properties of Cholinesterase Inhibitors**

	Time to onset	Time to peak <sup>5-7</sup>	Elimination half-life <sup>5-7</sup>	Studied dosing	Notes
Rivastigmine (enteral) <sup>8-13</sup>	Within 1 hour	1 hour	1.5 hours	<ul style="list-style-type: none"> <li>• Pediatric: 0.75 mg, 6 mg</li> <li>• Adult: 1.5-12 mg</li> </ul>	<ul style="list-style-type: none"> <li>• 1.5 mg dosed twice daily × 7 days in an adult procyclidine overdose reported<sup>10</sup></li> </ul>
Rivastigmine (transdermal) <sup>12,14</sup>	1 hour	8-16 hours	3 hours (after patch removal)	<ul style="list-style-type: none"> <li>• Pediatric: 13.3 mg/24 hr patch</li> <li>• Adult: 9.5-13.3 mg/24 hr patch</li> </ul>	<ul style="list-style-type: none"> <li>• May provide selected patients with prolonged therapy, dependent on expected duration of toxidrome</li> <li>• Highest plasma concentrations are associated with administration to upper back, arm, or chest</li> </ul>
Donepezil, immediate release (enteral) <sup>15,16</sup>	Within 1 hour	3-8 hours	Up to 70 hours	5-10 mg daily	<ul style="list-style-type: none"> <li>• Only immediate release formulation has been studied</li> </ul>
Galantamine (enteral) <sup>17</sup>	Within 1 hour	1 hour	Up to 7 hours	Limited data available	<ul style="list-style-type: none"> <li>• Both immediate and extended release formulations available</li> <li>• Renally excreted and hepatically metabolized; dose adjustment may be necessary</li> </ul>

### SAFETY IMPLICATIONS

- Limited data support the use of the above non-physostigmine acetylcholinesterase inhibitors
  - Consultation with experts (e.g., Poison Control, toxicologists) is recommended
    - Poison Control phone number: 1-800-222-1222

- These stated acetylcholinesterase inhibitors are available only in enteral or transdermal formulations, which will affect the ability to both administer and monitor clinical benefit, compared to physostigmine
- The prolonged onset and duration of action of these acetylcholinesterase inhibitors may affect the ability to rapidly titrate to effect; iatrogenic cholinergic toxicity may be longer-lasting compared to physostigmine.

## IMPACT ON ICU CARE

- Alternative medications, such as benzodiazepines, dexmedetomidine, and non-physostigmine acetylcholinesterase inhibitors may be considered to conserve available physostigmine supply.
- Clear and constant communication (e.g., clinical decision support, email), is recommended to provide clinicians necessary information on how to appropriately prescribe these medications.
- Multiprofessional groups should be created to develop appropriate drug shortage mitigation strategies, including available drugs on formulary and appropriate education.
- Education of staff and caregivers is necessary to limit potential risks to patients.

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