Anticholinergic intoxication

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There are hundreds of substances with anticholinergic activity. Below are some of the most common and notable.

agents which function predominantly as anticholinergics

- Atropine.
- Glycopyrrolate (antisialogogue).

- Darifenacin, fesoterodine, flavoxate, oxybutynin, solifenacin, tolterodine, trospium (used for bladder spasm).
- Dicyclomine, hyoscyamine (used for irritable bowel syndrome).
- Scopolamine (used as an antiemetic or antialagogue).
- Benztropine, trihexyphenidyl (used for Parkinson's disease).
- Anticholinergic eye drops may rarely cause systemic toxicity (e.g., atropine, cyclopentolate).
- Numerous plants (e.g., various nightshade species including Atropa belladonna, Jimson weed).

agents with mixed effects, including anticholinergic activity

- First-generation antihistamines (e.g., brompheniramine, carboxamine, chlorpheniramine, clemastine, cyproheptadine, dimenhydrinate, diphenhydramine, doxepin, doxylamine, hydroxyzine, meclizine, triprolidine).
- Tricyclic antidepressants (e.g., amitriptyline, clomipramine, desipramine, imipramine, nortriptyline, protriptyline, trimipramine).
- Muscle relaxants: (e.g., cyclobenzaprine, orphenadrine).
- Antipsychotics, especially:
  - Typical agents: chlorpromazine, fluphenazine, loxapine, perphenazine, thioridazine, trifluoperazine.
  - Atypical agents: olanzapine, quetiapine.

epidemiology of anticholinergic intoxication

- This is extremely common, with various intents (suicidal, recreational, or inadvertent).
  - 15-20% of admissions for acute poisoning may be caused by anticholinergic delirium. [29956570](https://pubmed.ncbi.nlm.nih.gov/29956570/)
- Diphenhydramine is the sixth most commonly used medication in the United States, making it broadly available.

clinical presentation

"Mad as a hatter, blind as a bat, red as a beet, hot as a hare, dry as a bone, full as a flask.

anticholinergic toxidrome

- CNS effects:
  - Most often causes agitated delirium (often with hallucinations, incoherent speech, picking at the air or objects).
  - More severe cases may present with seizure and/or coma.
  - CNS effects may persist after peripheral features have resolved.
- Pupillary dilation, causing blurry vision and photophobia.
- Tachycardia.
- Hyperthermia with dry, flushed skin (examination may reveal no sweat in the armpits).
- Urinary retention.
- Ileus.
**core elements of the anticholinergic toxidrome**

- Key elements in the toxidrome are:
  - 😊 Dilated pupils
  - 😴 Delirium
  - 😍 Tachycardia
  - 🌱 Dry skin – This is an essential element, which helps separate anticholinergic toxidromes from sympathomimetic toxidromes.
- These four elements suggest an anticholinergic toxidrome.
  - Anticholinergic toxicity is often one *component* of tricyclic intoxication. An EKG may be helpful in sorting out a *pure* anticholinergic syndrome versus the *combination* of an anticholinergic syndrome plus sodium channel blockade.
Opsoclonus is rapid involuntary eye movements in all directions. It has a broad differential including infection, infarction, stroke, or intoxication (lithium, phenytoin, anticholinergics, organophosphates)\(^\text{8879053}\) (https://pubmed.ncbi.nlm.nih.gov/8879053/).

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**differential diagnosis**

- Sympathomimetic intoxication.
- Combined anticholinergic plus sodium channel blocker poisoning (e.g., tricyclic antidepressants).
- Combined antihistamine plus acetaminophen ingestion (many combination tablets contain both, such as Tylenol PM and NyQuil).
- Salicylate intoxication.
- Septic shock.
- CNS infections (e.g., meningitis).
- Other causes of delirium (more in the delirium chapter [here](https://emcrit.org/ibcc/delirium/#causes)).

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**evaluation**

*This will vary depending on the context, with common considerations including:*

- STAT fingerstick glucose, if mental status alteration.
- Electrolytes, Ca/Mg/Phos, complete blood count.
- Creatinine kinase level (with a repeat value if concern for the evolution of rhabdomyolysis).
- Serum acetaminophen and salicylate levels.
- Pregnancy testing as appropriate.

**EKG**

- This is essential to evaluate, especially for any evidence of sodium channel blocker activity (e.g., QRS widening and tall R-wave in aVR).
  - More on the EKG findings of sodium channel blockers [here](https://emcrit.org/ibcc/nacb/#EKG_findings_in_sodium_channel_blockade).
  - If evidence of sodium channel blockade is found, this has important clinical implications (more on this [below](#management_of_combined_anticholinergic_plus_sodium_channel_blocker_toxicity)).

**further investigation of altered mental status**

- Depending on the clinical context, additional studies may be considered (e.g., head CT scan and potentially lumbar puncture).
- If anticholinergic intoxication is strongly suspected, then a physostigmine challenge may be used diagnostically (more on this [below](#physostigmine)). If physostigmine causes a resolution of delirium, this establishes the presence of an anticholinergic toxidrome and removes the need for further neurodiagnostic testing.
physostigmine

physiology of physostigmine

Physostigmine is an acetylcholinesterase inhibitor. It inhibits degradation of acetylcholine within the synapse, thereby increasing acetylcholine signaling levels.

Physostigmine is extremely similar to neostigmine, which is commonly used in intensive care units for management of colonic pseudo-obstruction (more on neostigmine here). The difference between the two agents is that physostigmine penetrates the brain, whereas neostigmine doesn't. Administration of the two agents is similar.

controversy surrounding physostigmine

Physostigmine was enormously popular in the 1970s, when it was used with abandon for all sorts of toxicologic abnormalities (including administration in some "coma cocktails" which were broadly administered to comatose patients).

A handful of case reports from ~1980 suggested that physostigmine might cause bradyasystolic cardiac arrest. These cases generally involved the following elements:

- Patients had extremely severe tricyclic antidepressant intoxication.
- Patients were not treated based on modern standards of care (e.g., they didn't receive hypertonic bicarbonate).
- Physostigmine was pushed relatively rapidly (e.g., 2 mg over three minutes).

In the wisdom of hindsight, it shouldn't be surprising that many of these patients died, since they had extremely severe tricyclic intoxications that weren't treated appropriately. Perhaps overly rapid administration of physostigmine dropped their heart rates, precipitating cardiac decompensation. Perhaps not. Tricyclic intoxication often causes bradyasystolic arrest by itself, so it's impossible to determine causality.

These cases lead to widespread paranoia that physostigmine would assassinate patients. In reality, this fear is not evidence-based. Even in the 1970s-1980s, when physostigmine was being thrown around indiscriminately, serious side effects were rare.

Currently, physostigmine is experiencing a resurgence of popularity. It's a safe and effective medication when used properly (i.e., low-and-slow dosing) for the right patient (i.e., not patients with life-threatening tricyclic intoxication).

indications for physostigmine

Physostigmine may be utilized for patients in whom an anticholinergic toxidrome is known or strongly suspected.

Diagnostic benefit:
- Delirium resolution following physostigmine establishes the diagnosis of an anticholinergic toxidrome. This may allow the patient to be spared further diagnostic evaluation (e.g., CT scan and lumbar puncture).
- Note that improvement following physostigmine doesn't necessarily exclude all possible coingestions (e.g., acetaminophen). However, this explains the etiology of the patient's delirium, obviating the need for a delirium workup.

Therapeutic benefit:
- Physostigmine may reduce the need for intubation among patients with marked agitation.
- Physostigmine may help some patients avoid potentially deliriogenic medications (e.g., high-dose benzodiazepines).

potential contraindications

- The precise contraindications remain controversial. When in doubt, call a local toxicologist or poison control.
- (1) EKG demonstrating sodium channel blockade (e.g., wide QRS plus terminal right-axis deviation, with a deep S-wave in lead I and a tall R-wave in aVR).
• (2) Abnormally low heart rate within the context of anticholinergic toxicity (e.g., heart rate below ~60-80 b/m), or known cardiac conduction disease (e.g., AV block on EKG).
• (3) Anatomic obstruction of the urinary or gastrointestinal tract.
• (4) Frank coma with inability to protect the airway (physostigmine may rarely cause vomiting).
• (5) Epilepsy, recent seizure, or known coningestion with a proconvulsant substance.
• (6) Active asthma exacerbation or severe asthma.

**initial dosing**

• Physostigmine can cause bradycardia, so this should be done with telemetry monitoring and atropine available.
• (1) Start with 1 mg IV slowly over 5-10 minutes. ([12902007](https://pubmed.ncbi.nlm.nih.gov/12902007/))
  - Administering the physostigmine too rapidly will amplify side effects. One key to giving physostigmine safely and effectively is to give it s-l-o-w-l-y.
  - Observe for clinical signs of cholinergic excess (e.g., salivation, lacrimation, urination, defecation, emesis, bradycardia, diaphoresis). If any of these occur, they argue against an underlying anticholinergic toxidrome – so perhaps you have the wrong diagnosis. If cholinergic toxicity were to occur, atropine could be used to reverse it (the atropine dose is half of the amount of physostigmine which has been administered). Alternatively, glycopyrrolate could be used to selectively reverse physostigmine's peripheral cholinergic effects, without affecting CNS acetylcholine activity.
  - Observe for any clinical improvement. 1 mg should usually be a sufficient dose to see some improvement among patients with anticholinergic intoxication.
• (2) If no side effects are noted, an additional 1 mg IV may be given slowly, after 10-15 minutes.

**redosing**

• Redosing may be considered if the initial 1-2 mg of physostigmine caused a substantial clinical improvement.
• Physostigmine has a duration of action around an hour, so it may require redosing. The indication for redosing is if the patient develops substantial agitation.
  - Note that the goal isn't to eliminate all features of anticholinergic intoxication, but rather to alleviate distress. Using the minimal dose of physostigmine required to achieve this may optimize the benefit/risk ratio.
  - Consider using lower doses of physostigmine for redosing, as the underlying intoxication may be resolving.
  - As the underlying anticholinergic toxidrome resolves, the risk of side effects from physostigmine increases (there's less anticholinergic on board to "push back" against the cholinergic effects of physostigmine).

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**treatment of agitation**

**non-medication therapies**

• If bladder distension is driving agitation, this should be managed with Foley catheter placement.
• Consider dimming the room lights, as pupil dilation may cause photophobia.

**physostigmine**

• Pros:
  - Only agent which can be both diagnostic and therapeutic.
  - Only drug which offers to rapidly resolve delirium. This may assist, for example, in obtaining a better history & physical examination in order to avoid missing other traumatic or medical problems.
  - One retrospective series involving 52 patients found that physostigmine was 96% effective for treatment of agitation and 87% effective for delirium reversal, compared to benzodiazepines, which were only 24% effective for agitation and wholly ineffective at delirium reversal. ([10736125](https://pubmed.ncbi.nlm.nih.gov/10736125/))
• Cons:
  - Some contraindications limit the universal application of physostigmine (see above)
• Bottom line:
  - Physostigmine is arguably the treatment of choice for anticholinergic intoxication, in situations where it isn't contraindicated.
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### benzodiazepines

- **Pros:**
  - Can provide sedation and reduce the risk of seizure.

- **Cons:**
  - Benzodiazepines often fail to work in moderate to severe intoxication.
  - High doses of benzodiazepine may perpetuate delirium, by generating a vicious cycle of ongoing delirium and benzodiazepine administration.
  - Escalating doses of benzodiazepines are associated with increased frequency of intubation. ([26589572](https://pubmed.ncbi.nlm.nih.gov/26589572/))

- **Bottom line:**
  - Giving some benzodiazepine is reasonable, especially initially. Administration of a small dose of benzodiazepine (e.g., 1-2 mg lorazepam) prior to physostigmine might also theoretically reduce the risk of seizure after physostigmine administration. ([29956570](https://pubmed.ncbi.nlm.nih.gov/29956570/))
  - If the patient doesn't respond favorably to benzodiazepines, then consider switching to a different agent, such as physostigmine or dexmedetomidine (rather than escalating the benzodiazepine dose).
  - Benzodiazepine is not the treatment of choice for known anticholinergic delirium.

### dexmedetomidine

- **Pros:**
  - Titratable agent which doesn't cause respiratory suppression.
  - Short half-life reduces the risk of oversedation.
  - Unlike benzodiazepines, dexmedetomidine may be less likely to perpetuate sedation/delirium.
  - The main side effects of dexmedetomidine are bradycardia and hypotension, which is actually helpful here (because most of these patients are tachycardic and hypertensive to begin with). Dexmedetomidine may even reduce thermogenesis and thereby improve hyperthermia. ([26380573](https://pubmed.ncbi.nlm.nih.gov/26380573/))

- **Cons:**
  - Dexmedetomidine usually requires admission to ICU for monitoring.
  - Dexmedetomidine requires a little time to reach maximal effect, so it's not useful for emergent treatment of severe agitation.
  - Dexmedetomidine isn't supported by a large evidentiary basis. However, there is an increasing amount of evidence supporting its use. ([24943229](https://pubmed.ncbi.nlm.nih.gov/24943229/), [26380573](https://pubmed.ncbi.nlm.nih.gov/26380573/), [28491929](https://pubmed.ncbi.nlm.nih.gov/28491929))

- **Bottom line:**
  - Dexmedetomidine is potentially useful, especially in the following situations:
    - (1) Contraindication to physostigmine.
    - (2) Patient with a complex intoxication (e.g., anticholinergics plus sympathomimetics).
    - (3) Difficult-to-control agitation that requires numerous PRN boluses of medication.

### intubation

- **Pros:**
  - Achieves airway protection (if this is a problem).
  - Universally effective.
  - Propofol provides strong protection against seizures.

- **Cons:**
  - Risk of the intubation procedure itself.
  - Side effects involved with intubation and mechanical ventilation (e.g., may promote delirium, carries a risk of ventilator-induced pneumonia).

- **Bottom line:**
  - Intubation will rarely be needed for pure anticholinergic intoxication. However, intubation may be useful in the most severe cases with substantial seizures, hyperthermia, and/or coma.

### agents that may be suboptimal

[https://emcrit.org/ibcc/anticholinergic/](https://emcrit.org/ibcc/anticholinergic/)
Antipsychotics should arguably be avoided, as many have anticholinergic activity that could exacerbate the toxidrome.

### Other Management Issues

#### Hemodynamics

- Hypertension and tachycardia are generally mild and well tolerated. Before treating hypertension, the first step is to manage any agitation:
  - If agitation is driving the tachycardia, the best approach is to treat the agitation.
  - Avoid giving a beta-blocker up front, as this may impede the subsequent use of dexmedetomidine and/or physostigmine.
- Hypotension may occur, which may respond to fluid resuscitation.

#### Hyperthermia & Rhabdomyolysis

- Hyperthermia is occasionally severe and may require treatment:
  - Physical cooling (more in the chapter on hyperthermia).
  - Management of agitation as described above.
  - Avoid physical restraints, as this only worsens exertion and hyperthermia.
- Measure creatinine kinase and treat rhabdomyolysis as appropriate (more in the chapter on rhabdomyolysis).

#### Urinary Retention

- A Foley catheter may be required.
- Consider serial bladder scans to ensure that the patient doesn't develop urinary retention (if the patient is unable to communicate clearly).

#### QT Management

- Some antihistamines (e.g., diphenhydramine) can prolong the QT interval and cause torsade de pointes. ([21171853](https://pubmed.ncbi.nlm.nih.gov/21171853/))
- The QT interval should be monitored.
- Among patients with QT prolongation, maintaining Mg >3 mg/dL and K >4 mEq/L may reduce the risk of arrhythmia.
- If patients develop torsade de pointes, this should be treated as explored in the chapter on torsade de pointes.

#### Seizures

- Initial therapy is a benzodiazepine, for example:
  - Lorazepam 0.1 mg/kg IV.
  - Midazolam 10 mg IV/IM.
- Recurrent seizures may be managed by intubation and sedation with propofol.
- For recurrent seizures or status epilepticus, addition of levetiracetam may be reasonable. (Note that phenytoin is contraindicated, due to its potential to worsen sodium channel blockade.)
- More on the treatment of status epilepticus here.

### Management of Combined Anticholinergic Plus Sodium Channel Blocker Toxicity

#### Basics

- Several agents inhibit both muscarinic acetylcholine receptors and cardiac sodium channels, most notably:
  - First-generation antihistamines (e.g., diphenhydramine). In these patients, the overall clinical picture tends to be dominated by the anticholinergic toxidrome.
  - Tricyclic antidepressants. In this case, the more life-threatening aspects of the intoxication tend to be dominated by effects on sodium channels.
- These intoxications can be diagnosed based on a combination of an anticholinergic toxidrome plus EKG findings of sodium channel blockade (more on that here). Of course, in some cases the diagnosis may also be based upon a known history of ingesting a specific agent.
Some patients may be more susceptible to the sodium-blocking effect of antihistamines than other patients, possibly due to underlying genetic variability in their sodium channels (e.g., patients with Brugada syndrome variants). The EKG is the most accurate test to determine the physiologic impact that the intoxicant is having on an individual patient's heart.

**management**

- This is overall a *hybrid* of the management of anticholinergic (as above) and sodium channel blocker intoxications (described [here](https://emcrit.org/ibcc/nacb/#top)).
  - Some supportive elements discussed above may be helpful in these patients (e.g., Foley catheter to relieve urinary obstruction).
  - Sodium channel blockade is more worrisome than anticholinergic effects, since sodium channel blocker toxicity carries a greater mortality. Consequently, when in doubt, treatment should arguably focus more on adequate management of sodium channel inhibition (e.g., with hypertonic bicarbonate).
  - Physostigmine is relatively contraindicated in this situation (although multiple authors *do* recommend the use of physostigmine for patients with known antihistamine intoxication who have EKG evidence of sodium channel blockade).

**podcast**

Underutilization of physostigmine, leading to the administration of excessive doses of benzodiazepine (which may in turn promote intubation and ongoing delirium).

Failure to evaluate for acetaminophen coingestion.

Going further:


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The Internet Book of Critical Care is an online textbook written by Josh Farkas (@PulmCrit), an associate professor of Pulmonary and Critical Care Medicine at the University of Vermont.

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