Anticholinergic toxicity can occur from many common medications and xenobiotics. Examples include antihistamines and sleep aids, antipsychotics, and even specific plants. The common mnemonic to remember the symptoms of the anticholinergic toxidrome include:

*Mad as a hatter* (agitation, delirium)

*Blind as a bat* (mydriasis)

*Red as a beet* (flushed skin without perspiration)

*Hot as a hare* (hyperthermia)

*Dry as a bone* (dry mucous membranes)

*Stuffed as a pepper* (decreased bowel sounds, constipation, urinary retention)

Patient’s exhibiting anticholinergic toxicity after ingestion may have a prolonged course of delirium and agitation that is often waxing and waning in presentation. The mainstay of supportive care includes adequate administration of benzodiazepines and cooling measures. Physostigmine is the antidote for anticholinergic toxicity that acts as a carbamate to reversibly inhibit acetylcholinesterase with both peripheral and central nervous system (CNS) effects. It was first used in 1864 to counteract severe atropine poisoning. When given IV push, it has an onset of action within 5-10 minutes, a half-life of 16 minutes, with a duration of action that is typically 1-2 hours.

Physostigmine’s use was drastically reduced after two case reports published in 1980 described seizures, bradydysrhythmias, asystole, and death when administered in the treatment of tricyclic antidepressant (TCA) overdose. Over the past 2 decades, there have been multiple studies demonstrating not only the safety but also the efficacy of physostigmine for anticholinergic toxicity. Burns and colleagues conducted a retrospective review of 52 patients, comparing the control of agitation and reversal of delirium of patients who were treated with either physostigmine, benzodiazepines, or both. Physostigmine was found to control agitation and reverse delirium in 96% and 87% of patients, respectively. Benzodiazepines were able to control agitation in 24% of cases but were ineffective in reversing delirium. Patients treated with physostigmine compared to benzodiazepines also had a lower incidence of complications (7% vs. 46%; p<0.002) and a shorter time to recovery (median, 12 vs. 24 hours; p=0.004) but no difference in side effects (7% vs. 14%; p=0.06), or length of stay (median, 32 vs. 39 hours; p=0.15).

One of the largest studies published with 1,026 patients, by Rasimas et al, was a 6-year retrospective review, followed by a 1-year prospective observational study of bedside use of physostigmine. They demonstrated that >80% of patients demonstrated a positive response to physostigmine, with evidence of improved wakefulness, cleared cognition, and/or decreased agitation. Side effects were rare but included cholinergic symptoms of nausea, vomiting, diaphoresis, or diarrhea. Three patients had a seizure or an arrhythmia.
Finally, Boley and colleagues conducted a prospective observational study of 154 patients diagnosed with anticholinergic delirium and treated with consultation with a regional poison center. Based on a clinical guideline for Certified Specialists in Poison Information, physostigmine was recommended in 81% (125) cases and treatment teams administered it in 37% (57) of cases. Delirium control was observed in 79% of patients who received physostigmine, compared to 36% of patients who did not, with an OR of 6.6 for delirium control when treated with physostigmine. Adverse events, incidence of intubation, or need of restraint did not differ between the two groups.\(^6\)

Overall, physostigmine has well described positive antidotal effects for anticholinergic delirium when it is given in slow, intermittent bolus dosing or as a continuous IV infusion in rare instances:

- **Adults** → 1-2 mg over 5-10 minutes Q1 hour PRN
- **Pediatric** → 0.02 mg/kg (max 0.5mg for small children) over 5-10 minutes Q1 hour PRN
- **Continuous IV infusion** → 1-2 mg/hour for adults (for severe, recurrent symptoms. Recommended only with discussion from a toxicologist)

Since the duration of effect of physostigmine is much shorter than the duration of anticholinergic toxicity, additional doses may need to be given depending on the severity of the symptoms. Some practitioners may use physostigmine as a diagnostic tool to confirm the presence of anticholinergic toxicity with specific discussion from a toxicologist. In order to avoid its potential adverse effects, the patient should meet the following criteria before administering physostigmine:

- Heart rate >80 bpm and on cardiac monitoring
- QRS <100 ms

No history of TCA use or other sodium channel blocking agents (i.e. cocaine)
References: