# CRACKCast E150–Anticholinergics

## Key Points

- Symptoms of muscarinic receptor blockade may include delirium, mydriasis, a lack of sweating, dry mucous membranes, ileus, urinary retention, hyperthermia, tachycardia, and hypertension.
- Delirium may be the sole manifestation of toxicity and only one-third of patients manifest all of the classic autonomic  ndings of tachycardia, dry skin and axilla, and mydriasis.
- Physostigmine should be given to control severe agitation and delirium precipitated by muscarinic receptor antagonism.
- Physostigmine is relatively contraindicated in patients with bradycardia or AV block in the setting of possible TCA toxicity.
- Benzodiazepines should be used for symptom control when seizures occur or when physostigmine is contraindicated.
- Patients who develop hyperthermia despite treatment with evaporative cooling should be paralyzed, intubated, and cooled.
- Symptomatic patients should be observed until symptoms are clearly resolving. Accidental ingestion with mild symptoms can be expected to improve in less than 6 hours. Purposeful ingestions with mild to moderate symptoms will require admission to the hospital for extended observation (24 to 48 hours).

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## Core Questions

1) Describe the anticholinergic toxidrome
2) List 10 anticholinergic meds
3) List 15 DDx for Delirium
4) Describe the management of anticholinergic toxicity

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## Rosen's In Perspective

Here we are usually talking about anticholinergic = antimuscarinic

But in general Muscarinic receptors are on smooth muscle and the autonomic nervous system (SLUDGE & BBB)

Nicotinic receptors are on skeletal muscle NMJ

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| *Anticholinergic* | "Red as a beet<br>Dry as a bone<br>Blind as a bat<br>Mad as a hatter<br>Hot as hell<br>The bladder keeps its tone and the heart runs alone" | Antimuscarinic and antinicotinic properties - leading to a relative sympathomimetic (sympathetic overdrive because cholinergic tone is blocked)<br><br>Hyperthermia, cutaneous flushing, delirium, hallucinations, mydriasis, urinary retention, and **dry skin and mucous membranes** | Antihistamines, tricyclic antidepressants, cyclobenzaprine, orphenadrine, antiparkinson agents, antispasmodics, phenothiazines, atropine, scopolamine, belladonna alkaloids (eg, Jimson Weed) | Supportive, based on the specific agent |

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## [1] Describe the anticholinergic toxidrome

Box 145.1

1. Mydriasis: “Blind as a bat”
2. Altered mental status: “Mad as a hatter”
3. Dry mucous membranes: “Dry as a bone”
4. Dry, flushed skin: “Red as a beet”
5. Hyperthermia: “Hot as Hades”
6. Urinary retention: “Full as a flask”
7. Decreased bowel sounds/ileus
8. Tachycardia

See Figure 145.1 In Rosen’s (9th)

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## [2] List 10 anticholinergic meds

**In general the list you’ll see is:**

- ❑ Plants
  - ❑ Jimson weed
- ❑ belladonna alkaloids
  - ❑ Atropine
  - ❑ Scopolamine
- ❑ Antihistamines (H1 blockers)
  - ❑ Dimenhydrinate
  - ❑ Diphenhydramine
- ❑ Antiparkinson agents
  - ❑ Benztropine (Cogentin)
  - ❑ Procyclidine
- ❑ Tricyclic antidepressants
  - ❑ Cyclobenzaprine
  - ❑ Amitriptyline

Let's break this down into common antimuscarinic and antinicotinic drugs

**Antimuscarinic agents**

- ❑ Atropine
- ❑ Benztropine (Cogentin)
- ❑ Dimenhydrinate (Gravol, Dramamine)
- ❑ Diphenhydramine (Benadryl, Nytol, Advil PM, etc.)
- ❑ Doxylamine (Diclectin, Restavit, Unisom)
- ❑ Glycopyrrolate (Robinul)
- ❑ Ipratropium (Atrovent)
- ❑ Oxybutynin (Ditropan, Driptane, Lyrinel XL)
- ❑ Tiotropium (Spiriva)

- Tricyclic antidepressants (28 compounds with numerous trade names)
- Scopolamine
- Tropicamide

**Antinicotinic agents**

- Bupropion (Zyban, Wellbutrin) - Ganglion blocker
- Dextromethorphan - Cough suppressant and ganglion blocker

Plants of the Solanaceae family contain various anticholinergic tropane alkaloids, such as scopolamine, atropine, and hyoscyamine

Plants = The most common plants containing anticholinergic alkaloids (including atropine, scopolamine, and hyoscyamine among others) are:

- Atropa belladonna (deadly nightshade)
- Brugmansia species
- Datura species
- Garrya species
- Hyoscyamus niger (henbane)
- Mandragora officinarum (mandrake)

List source seen here

See Table 145.1 in Rosen's ($9^{th}$)

Note: In Canada the usual place you will see Doxylamine is in combination w/ pyridoxine (vitamin B6) which makes **Diclectin**, which is used to prevent morning sickness.

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## [3] List 15 DDx for "Hot & Bothered"

Box 145.2: **Common Differential Diagnosis Considerations With Overlapping Signs and Symptoms of Antimuscarinic Toxicity**

**Differential Diagnosis Considerations**

**Toxicological**

1. Sympathomimetic toxicity
2. Serotonin toxicity
3. Neuroleptic malignant syndrome
4. Lithium toxicity
5. Antidepressant toxicity
6. Antipsychotic toxicity

**Central Nervous System**

1. Intracranial hemorrhage (ICH)
2. Seizure

**Metabolic**

1. Hyperthyroid
2. Encephalopathy

**Infectious**

1. Sepsis
2. Central nervous system (CNS) infections

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## [4] Describe the management of anticholinergic toxicity

**Stabilization**

- ❑ Sodium bicarb for QRS widening (<100 in TCA, otherwise goal <110)
- ❑ Supportive care
- ❑ Fluid resuscitate
- ❑ Tx seizures & agitation w/ Benzos
- ❑ Aggressively treat temp (if evaporative cooling does not work, then go for intubation, deep sedation and paralysis)
- ❑ Physostigmine controversial see below

**Decontamination**

- ❑ Generally not needed
- ❑ There is no role for gastric lavage, whole bowel irrigation, or hemodialysis.
- ❑ Oral activated charcoalnot indicated UNLESS:
  - ❑ symptomatic patients w/ ingestion of **a highly toxic quantity of antimuscarinic plant seeds**
  - ❑ only if the patient presents early after ingestion (<2 hours) and
  - ❑ is anticipated to remain cooperative.
  - ❑ **** Administering AC is best made in consultation with a medical toxicologist or regional poison center. ***

**Elimination**

***In general no role***

**Antidote - Physostigmine**

- ❑ reversibly inhibits cholinesterases in the both peripheral nervous system and CNS
- ❑ allows for acetylcholine accumulation and subsequent com-petition with the antimuscarinic blocking agent occupying the receptor
- ❑ short half--life, approximately 20 minutes but clinical duration of physostigmine is 3 to 6 hours.
- ❑ Far more effective than Benzos at treating agitation / delirium
- ❑ Other cholinesterase inhibitors not used as they DO NOT CROSS BBB (eg pyridostigmine, neostigmine, edrophonium)

Classic indications are:

- ❑ Delirium / Coma / Seizure
- ❑ risk of harming themselves or staff
- ❑ requiring ongoing physical restraint, or
- ❑ interfering with effective treatment (eg, pulling out IV lines)

Contraindications:

- ❑ TCA overdose
- ❑ Wideined QRS >100
- ❑ AV blocks
- ❑ Bradycardia
- ❑ Unknown co-ingestions

See Box 145.3

## PHYSOSTIGMINE IN ANTICHOLINERGIC TOXICITY

Arens Clin Toxicol (Phila). 2017 In Press

| | | | |
|---|---|---|---|
| **CONTEXT** | Physostigmine is reversible acetylcholinesterase inhibitor that can rapidly reverse the central nervous system effects (delirium) present in anticholinergic toxicity. Historically, there was concern that profound bradycardia and seizures were common side effects yet evidence for this is lacking. | | |
| **STUDY DESIGN** | Retrospective cohort study<br>Descriptive statistics | | |
| **POPULATION** | Cases reported to California Poison Control Center between 2003-2012 who received physostigmine for anticholinergic toxidrome (N=191) | | |
| **CONTROL** | None | | |
| **OUTCOME** | Efficacy of physostigmine (patient response) | Plant (ex: jimsyn weed, belladonna, datura, etc) | 46/67 (68.7%); OR 0.7 (0.36-1.35) |
| | | Diphenhydramine | 43/56 (64.2%);OR 1.30 (0.63-2.68) |
| | | Combination products | 8/10 (80%); OR 1.48 (0.30-7.24) |
| | | Muscle relaxants | 3/4 (75%) |
| | | Antipsychotics | 4/4 (100%) |
| | Adverse events | Emesis | 4 (2.1%) |
| | | QTc prolongation | 2 (1%) |
| | | Seizure | 2 (1%) |
| | | Death | 1 (0.5%) **Diphenhydramine OD with wide complex tachycardia and death 6 hours after receiving 0.5 mg physostigmine (drug screen + for many other substances) |
| | | No serious clinical adverse effect | 186 (98.4%) |
| **LIMITATIONS** | This study suffers from likely selection bias as it only includes cases reported to the poison control center. Further, it typically takes much larger data sets to actually prove safety when looking for rare adverse events. | | |
| **BOTTOM LINE** | Physostigmine may be used to reverse anticholinergic delirium (adult 0.5-1 mg Q15 minutes if needed). The use of this antidote should be avoided in TCA overdose based on prior literature. | | |

@FOAMpodcast

Source: FOAMCAST

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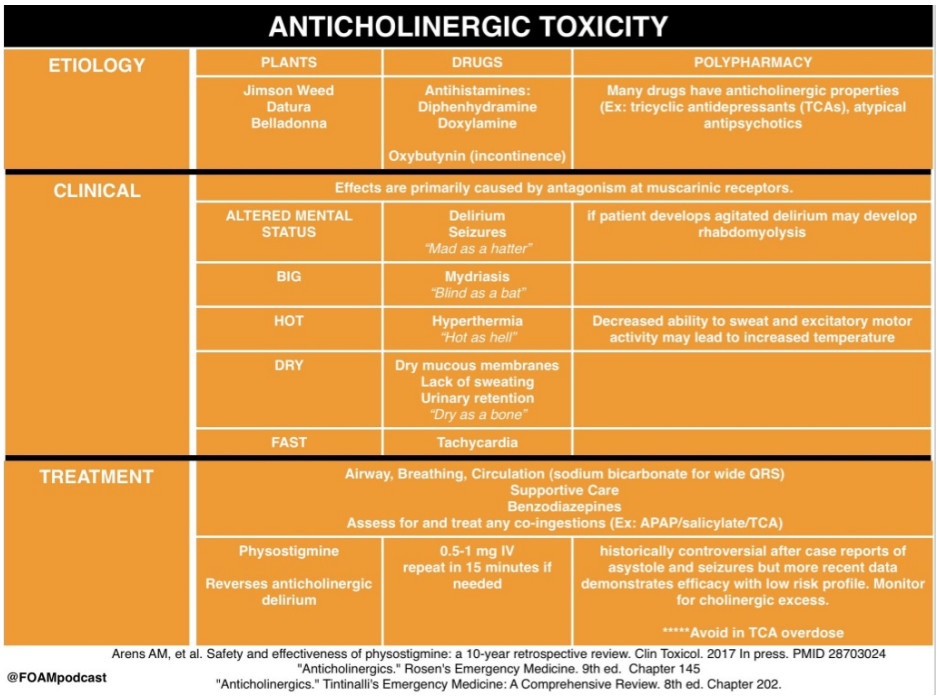
PODCAST Summary

A comparison of phisostigmine and benzoe tx of anticholernic

Berns & Linden

CrackCast Show Notes – Anticholinergics – February 2017
**www.canadiem.org/crackcast**



## ANTICHOLINERGIC TOXICITY

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|---|---|---|---|
| **ETIOLOGY** | **PLANTS** | **DRUGS** | **POLYPHARMACY** |
| | Jimson Weed<br>Datura<br>Belladonna | Antihistamines:<br>Diphenhydramine<br>Doxylamine<br><br>Oxybutynin (incontinence) | Many drugs have anticholinergic properties (Ex: tricyclic antidepressants (TCAs), atypical antipsychotics |
| **CLINICAL** | Effects are primarily caused by antagonism at muscarinic receptors. | | |
| | ALTERED MENTAL STATUS | Delirium<br>Seizures<br>*"Mad as a hatter"* | if patient develops agitated delirium may develop rhabdomyolysis |
| | BIG | Mydriasis<br>*"Blind as a bat"* | |
| | HOT | Hyperthermia<br>*"Hot as hell"* | Decreased ability to sweat and excitatory motor activity may lead to increased temperature |
| | DRY | Dry mucous membranes<br>Lack of sweating<br>Urinary retention<br>*"Dry as a bone"* | |
| | FAST | Tachycardia | |
| **TREATMENT** | Airway, Breathing, Circulation (sodium bicarbonate for wide QRS)<br>Supportive Care<br>Benzodiazepines<br>Assess for and treat any co-ingestions (Ex: APAP/salicylate/TCA) | | |
| | Physostigmine<br><br>Reverses anticholinergic delirium | 0.5-1 mg IV<br>repeat in 15 minutes if needed | historically controversial after case reports of asystole and seizures but more recent data demonstrates efficacy with low risk profile. Monitor for cholinergic excess.<br><br>*****Avoid in TCA overdose |

Arens AM, et al. Safety and effectiveness of physostigmine: a 10-year retrospective review. Clin Toxicol. 2017 In press. PMID 28703024
"Anticholinergics." Rosen's Emergency Medicine. 9th ed. Chapter 145
"Anticholinergics." Tintinalli's Emergency Medicine: A Comprehensive Review. 8th ed. Chapter 202.

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Source: FOAMCAST