Acute Management of Nonprescription Drug Overdose

A Presentation for HealthTrust Members
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Learning Objectives for Pharmacists & Nurses

1. Identify signs and symptoms of a potential medication exposure using patient history and toxidromes
2. Recall the “ABCDEFG” patient treatment paradigm in toxicology
3. Recognize a plan of treatment for common over-the-counter (OTC) medication overdoses

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Learning Objectives for Pharmacy Technicians

1. Recall current burden of drug overdose in the United States
2. Identify key components of a thorough medication exposure patient history
3. Recognize the appropriate targeted treatment with an over-the-counter (OTC) medication overdose

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Background

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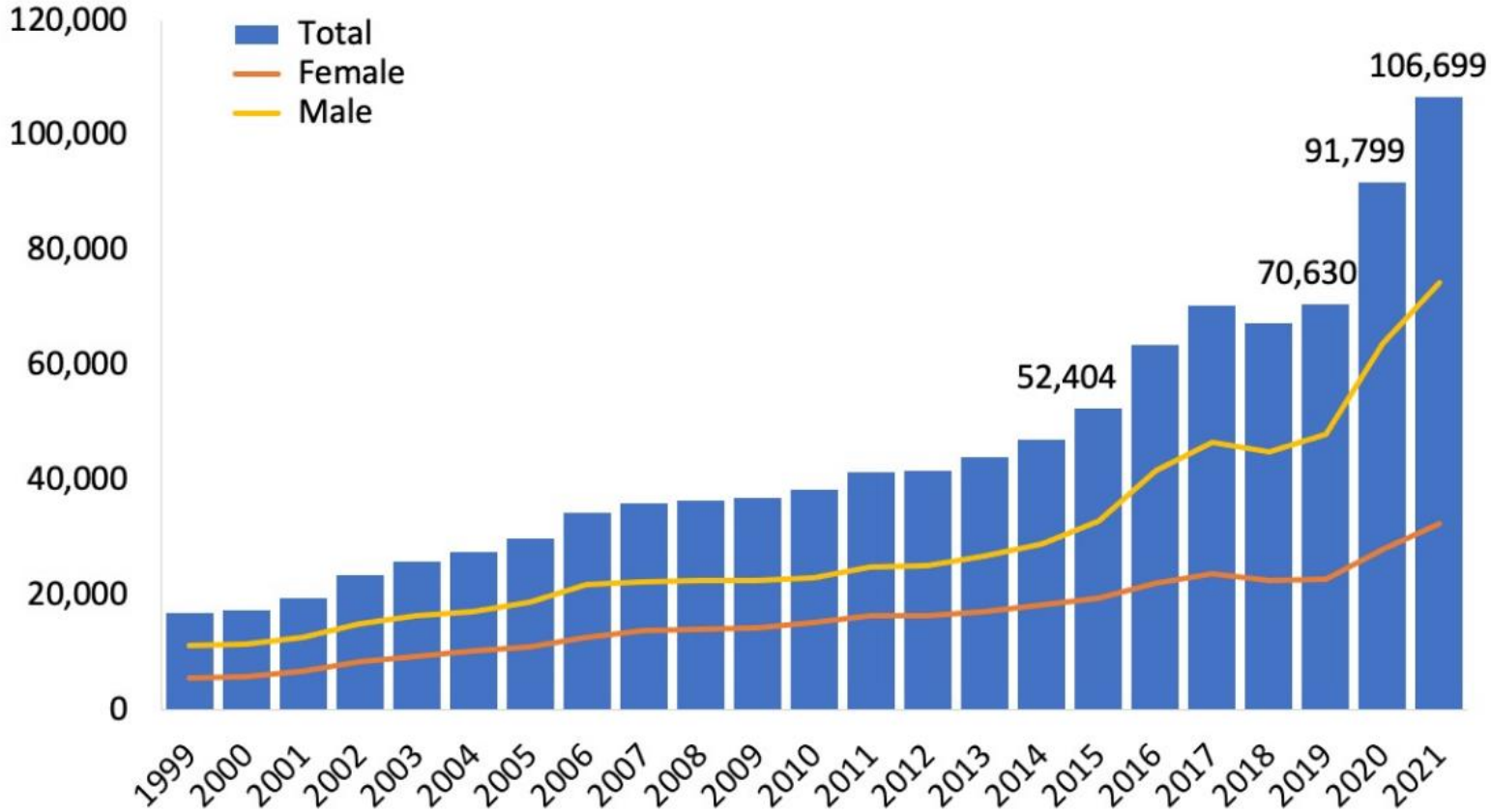
Background/Epidemiology

Drug overdose deaths rose by 51% from 2019 to 2021 with more than 106,000 drug overdose deaths reported in 2021

National Drug-Involved Overdose Deaths—Number Among All Ages, by Gender, 1999-2021



Source: National Institutes of Health. 2023.

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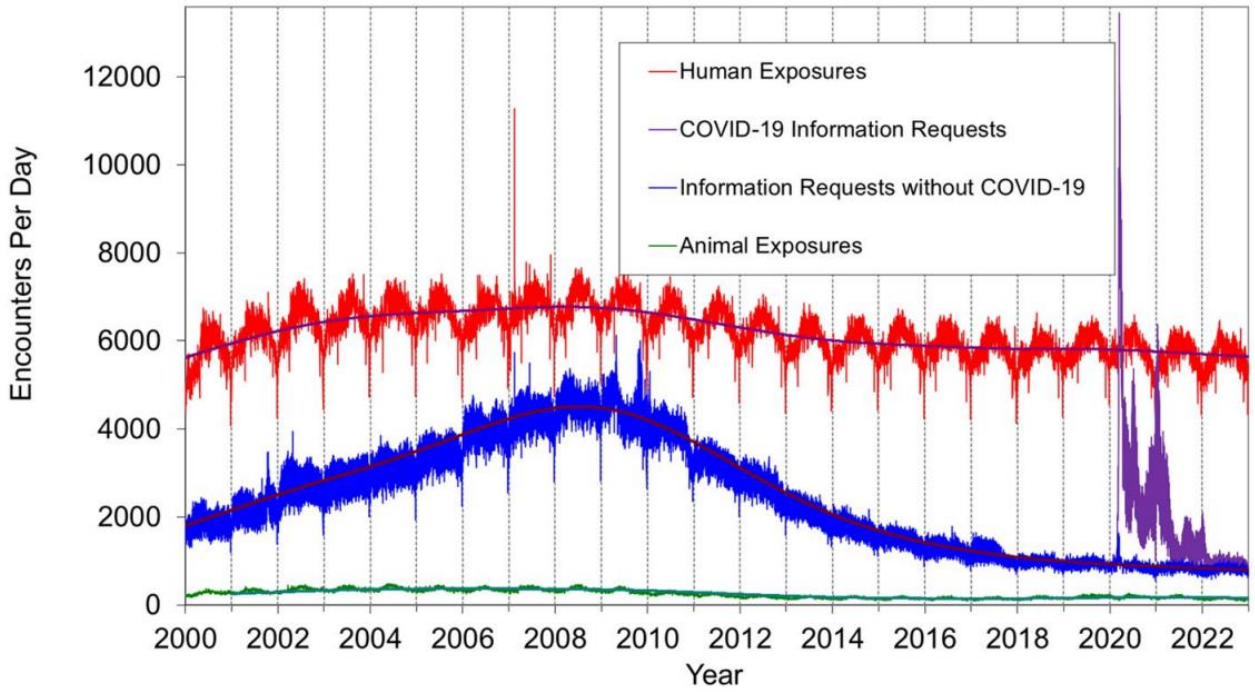
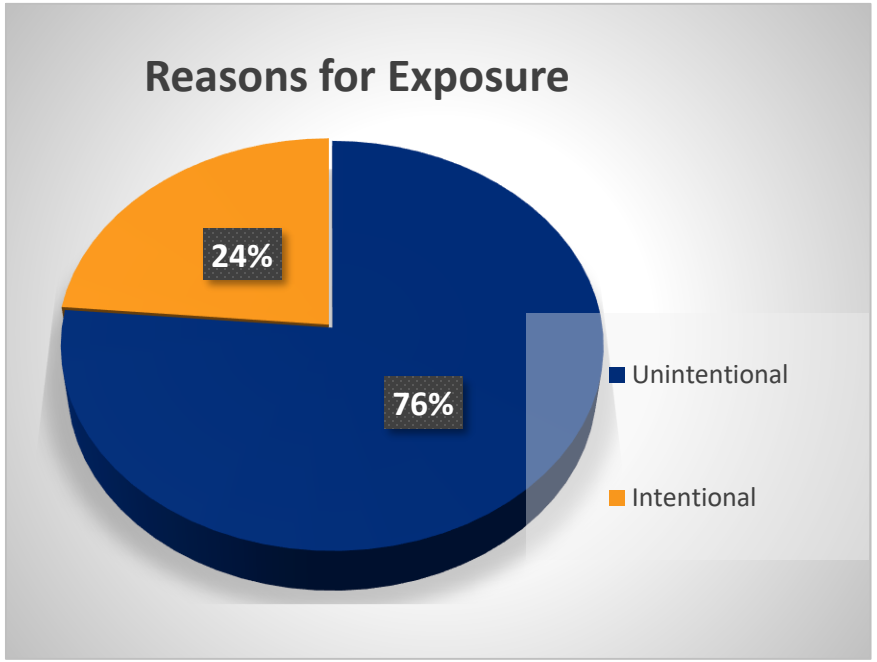
Background/Epidemiology

- The 2022 annual report of the National Poison Data System logged 2,064,875 human exposures in 2022
- Compared to 2021, human exposure cases <u>decreased by 0.771%</u>





Source: Gummin DD, et al. *Clin Toxicol (Phila)*. 2023;61(10):717-939.

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Top 25 Substances Involved in Human Exposures in 2022

Easily accessible or OTC substances

- ***Analgesics***
- Cleaning Substances (Household)
- ***Antihistamines***
- Cosmetics/Personal Care Products
- Vitamins
- ***Dietary Supplements***/Herbals/Homeopathic
- Alcohols
- Foreign Bodies/Toys/Miscellaneous
- ***Cold and Cough Preparations***
- Bites and Envenomation
- Chemicals
- Plants
- Other/Unknown Nondrug Substances

Prescription substances

- Antidepressants
- Cardiovascular Drugs
- Sedative/Hypnotics/Antipsychotics
- Stimulants and Street Drugs
- Pesticides
- Anticonvulsants
- Topical Preparations
- Hormones and Hormone Antagonists
- Gastrointestinal Preparations
- Antimicrobials
- Fumes/Gases/Vapors
- Electrolytes and Minerals

OTC=Over the counter

Source: Gummin DD, et al. *Clin Toxicol (Phila)*. 2023;61(10):717-939.

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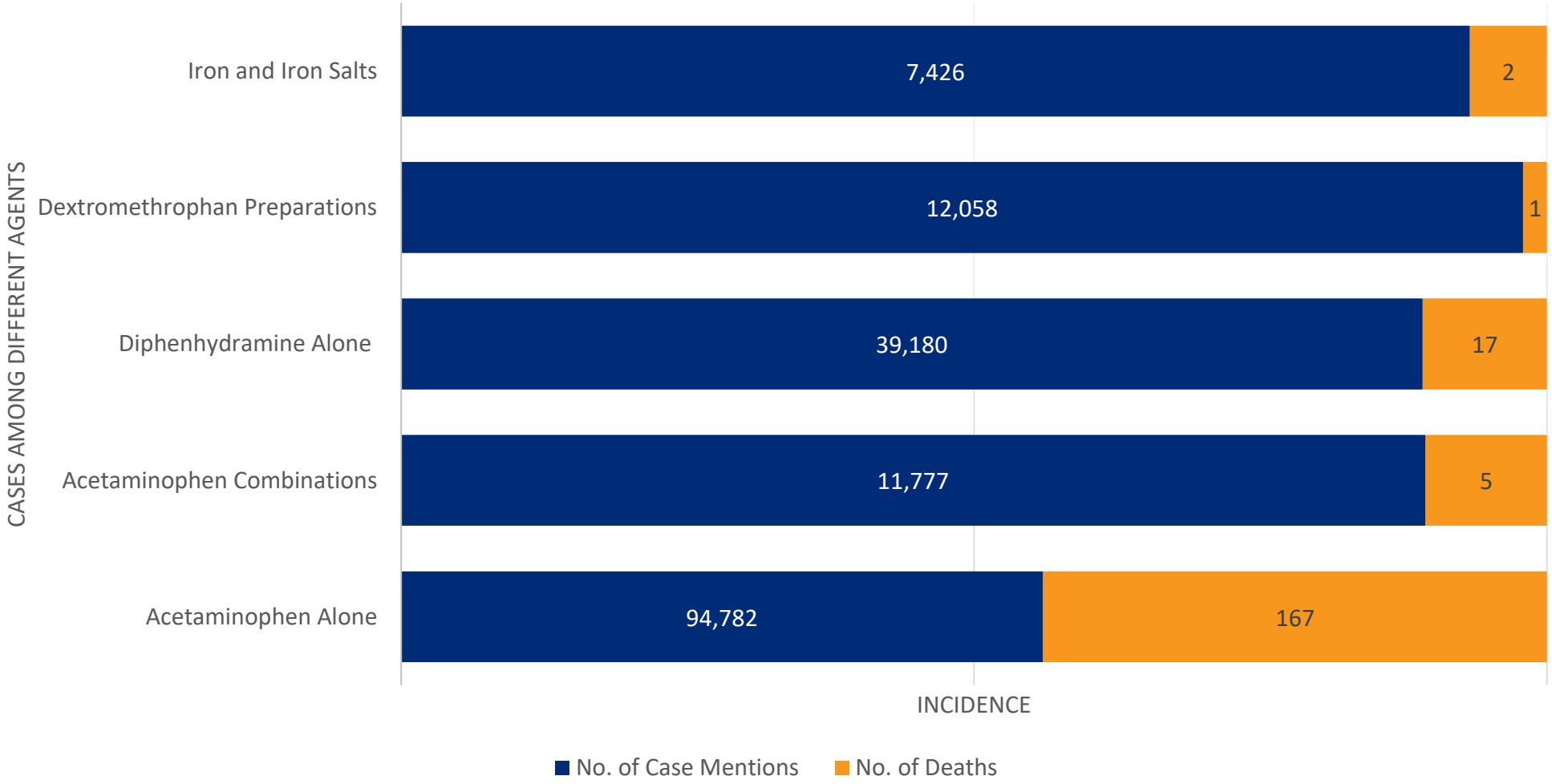
Common OTC Overdose Exposures and Deaths in 2022



Source: Gummin DD, et al. *Clin Toxicol (Phila)*. 2023;61(10):717-939.

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General Approach to Manage Overdose

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Treatment Paradigm -- “ABCDEFG”

- **A**irway
- **B**reathing
- **C**irculation
- **D**econtamination
- **E**nhanced elimination
- **F**ocused antidote
- **G**et help from a toxicologist or poison center

ABCs should be assessed in initial evaluation before obtaining a thorough history and physical exam

Source: Rech MA, et al. *Pharmacotherapy*. 2015;35(2):189-197.

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General Approach to Manage Overdose

Source: Frithsen IL, et al. *Am Fam Physician*. 2010;81(3):316-323.

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Exposure History

Components of Exposure History	Questions to Ask
Baseline medical status of the patient	**What** health conditions does patient have? (Any psychiatric illness or previous suicide attempts?)
Type of toxin or toxins	**What** agent(s) were taken in overdose?
Amount taken	**How much** was taken?
Time of exposure (acute versus chronic)	**When** was it taken?
Type of exposure occurred (accidental, suicide attempt, euphoria, therapeutic misadventure)	**Why** was it taken?
All medications patient has access to	**What** prescription, over-the-counter medications, vitamins, and herbal preparations are available at home?

Source: Erickson TB, et al. *Emerg Med Clin North Am*. 2007;25(2):249-vii.

Decontamination

Definition: Methods to prevention of further poison absorption

Gastrointestinal Decontamination Methods	Single-dose Activated Charcoal	Multiple-dose Activated Charcoal (MDAC)
Indications	Adsorb toxin in the stomach within 1h post ingestion	Life-threatening amount of ingestion of carbamazepine, dapsone, phenobarbital, quinine, or theophylline
Contraindications	Unprotected airway Intestinal obstruction	
Dosing	1 g/kg (50-100 g for adult and adolescent) If MDAC, followed by 25-50 g every 4 hours	
Administration	Dilute the powder with at least 8 mL of water per 1 g of charcoal Mix vigorously to form a slurry	
Complications	Aspiration into the lung	Aspiration into the lung Constipation Bowel obstruction Regurgitation

Source:
Mycyk MB. *Harrison's Principles of Internal Medicine, 21e*. McGraw-Hill Education; 2022.
Chyka PA, et al. *Clin Toxicol (Phila)*. 2005;43(2):61-87.
American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. *J Toxicol Clin Toxicol*. 1999;37(6):731-751.
Hoegberg LCG, et al. *Clin Toxicol (Phila)*. 2021;59(12):1196-1227.
Activated charcoal. *Lexicomp*. 2024.

Decontamination (Continued)

Gastrointestinal Decontamination Methods	Total Bowel Irrigation	Gastric Lavage
Definition	Enteral administration of large volumes of polyethylene glycol-electrolyte solution by nasogastric tube at rapid rates at least until the rectal effluent takes on the physical appearance of the infusate	Passage of a large bore orogastric tube and the sequential administration and aspiration of small volumes of liquid, with the intent of removing toxic substances present in the stomach
Indications	• Potentially toxic ingestions of sustained-release or enteric-coated drugs • Ingestion of substantial amounts of **iron** • Removal of ingested packets of illicit drugs	• Recent ingestion of a very toxic substance
Contraindications	• Ileus, bowel obstruction, bowel perforation, clinically significant gastrointestinal hemorrhage • Hemodynamic instability • Uncontrollable intractable vomiting • Unprotected compromised airway	• Ingestion of a corrosive substance such as a strong acid or alkali • Patients at risk of hemorrhage or gastrointestinal perforation
Complications	• Nausea, vomiting • Abdominal cramps • Bloating	• Aspiration pneumonia • Esophageal perforation • Hypoxia • Arrhythmia

Source:
Position paper: whole bowel irrigation. *J Toxicol Clin Toxicol*. 2004;42(6):843-854.
Vale JA, Kulig K. *J Toxicol Clin Toxicol*. 2004;42(7):933-943.

Toxidrome: a Hint to Targeted Treatment

Definition: a constellation of findings, either from the physical examination or from ancillary testing, which may result from any given poison

Anticholinergic

- Hyperthermia (**HOT as a hare**)
- Flushed (**RED as a beet**)
- Dry skin (**DRY as a bone**)
- Dilated pupils (**BLIND as a bat**)
- Delirium, hallucinations (**MAD as a hatter**)
- Tachycardia
- Urinary urgency and retention

Cholinergic
"DUMBELLS"

- **D**iarrhea, diaphoresis
- **U**rination
- **M**iosis
- **B**radycardia, broncho-secretions
- **E**mesis
- **L**acrimation
- **L**ethargic
- **S**alivation

Sympathomimetic

- Mydriasis
- Tachycardia
- Hypertension
- Hyperthermia
- Seizures

Opioid

- Miosis
- Bradycardia
- Hypotension
- Hypoventilation
- Coma

Source: Erickson TB, et al. *Emerg Med Clin North Am*. 2007;25(2):249-vii.; Holstege CP, Borek HA. *Crit Care Clin*. 2012;28(4):479-498.

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Acute Acetaminophen Overdose

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Acetaminophen (Tylenol®)

Uses	Analgesic	Antipyretic
Mechanism of Action	Activation of descending serotonergic inhibitory pathways in the CNS	Inhibition of the hypothalamic heat-regulating center
Common OTC Formulations & Dosing	**Immediate release** Regular strength (325 mg/tablet): 2 tablets (650 mg) every 4-6 hours as needed • Maximum daily dose: 10 tablets/day (3.25 g/day) Extra strength (500 mg/tablet): 2 tablets (1 g) every 6 hours as needed • Maximum daily dose: 6 tablets/day (3 g/day) **Extended release** (650 mg/tablet): 2 tablets (1.3 g) every 8 hours as needed • Maximum daily dose: 6 tablets/day (3.9 g/day)	

CNS= Central Nervous System
OTC= Over the Counter

Source: Acetaminophen. *Lexicomp.* 2024.

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Why is acetaminophen overdose so common?

Acetaminophen **combination products** accounted for ~70% of acetaminophen-induced acute liver failure cases in the United States.

Examples of OTC Combination Products	Examples of Prescription Combination Products
• Alka-Seltzer Plus LiquidGels® (**Acetaminophen**/Dextromethorphan/Phenylephrine) • Coricidin® (**Acetaminophen**/Chlorpheniramine) • Dayquil® (**Acetaminophen**/Dextromethorphan/Pseudoephedrine) • Excedrin® (**Acetaminophen**/Aspirin) • Midol® (**Acetaminophen**/Caffeine/Pyrilamine)	• Fioricet® (**Acetaminophen**/Butalbital/Caffeine) • Hydrocet®/Vicodin® (**Acetaminophen**/Hydrocodone) • Percocet® (**Acetaminophen**/Oxycodone)

Clinical Pearl: Max dose of 4g daily can be easily exceeded when patient uses multiple products containing acetaminophen

Source: Bunchorntavakul C, et al. *Clin Liver Dis*. 2018;22(2):325-346.

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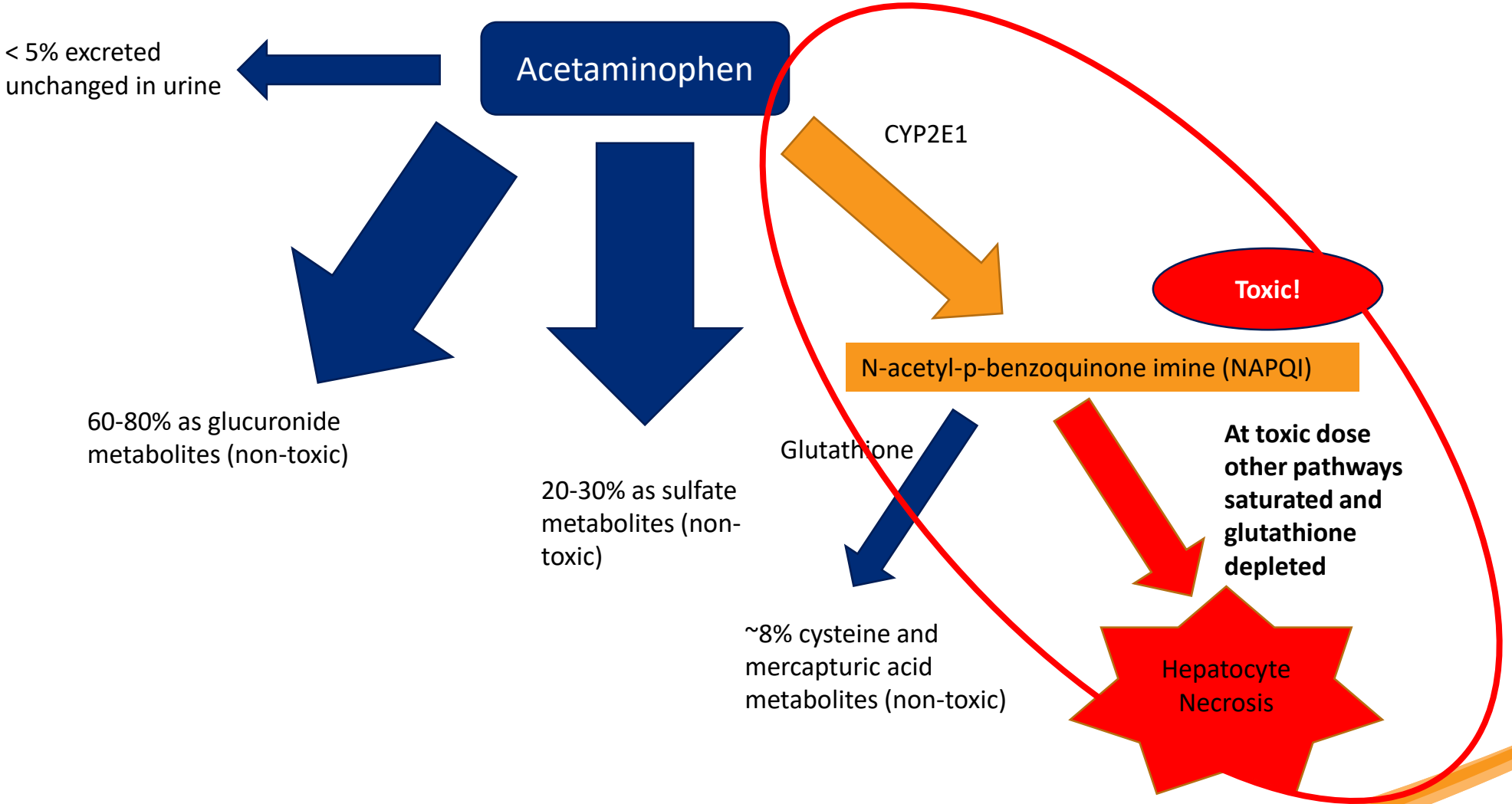
Metabolism & Toxicity



Source:
Acetaminophen. *Lexicomp.* 2024.
Bunchorntavakul C, et al. *Clin Liver Dis*. 2018;22(2):325-346.

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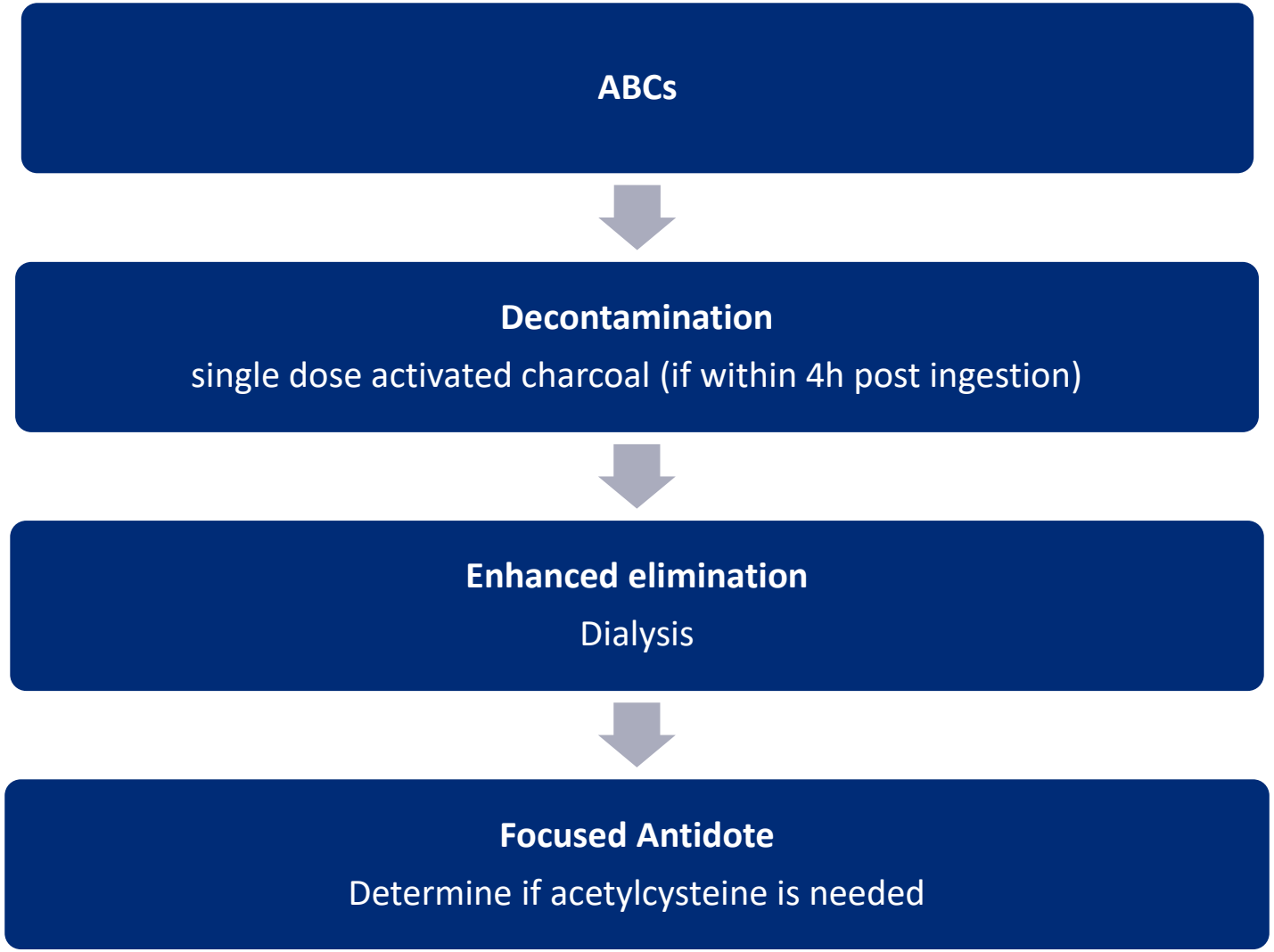
Clinical Stages of Acute Acetaminophen Overdose

Timeline post ingestion	Presentations	Labs
Stage I (0–24 hours)	Anorexia, nausea, vomiting	Normal
Stage II (24–72 hours)	Right upper quadrant abdominal pain	↑AST, ALT ↑bilirubin, PT, INR *[Severe poisoning]*
Stage III (72–96 hours)	Vomiting, liver failure (eg. jaundice, coagulopathy), renal failure, encephalopathy	Peaking of AST, ALT, bilirubin, and INR Hypoglycemia Confusion, stupor, death
Stage IV (>5 days)	Resolution of hepatotoxicity	Normalization

AST= Aspartate aminotransferase
ALT= Alanine transaminase
INR= international normalized ratio
PT= Prothrombin time

Source:
Malley GF, et al. *Merck Manuals*. 2022.
Bond G. *Tylenol professional*. 2023.

Management of Acute Acetaminophen Overdose



Source: Dart RC, et al. *JAMA Netw Open.* 2023;6(8):e2327739.

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Enhanced Elimination

- Dialysis is recommended if
  - ❑ Serum acetaminophen concentration >1000 mg/L and acetylcysteine is NOT administered
  - ❑ Patient presents with altered mental status, metabolic acidosis, with an elevated lactate, and a serum acetaminophen concentration
    - >700 mg/L and acetylcysteine is NOT administered
    - >900 mg/L (5960 µmol/L) even if NAC is administered

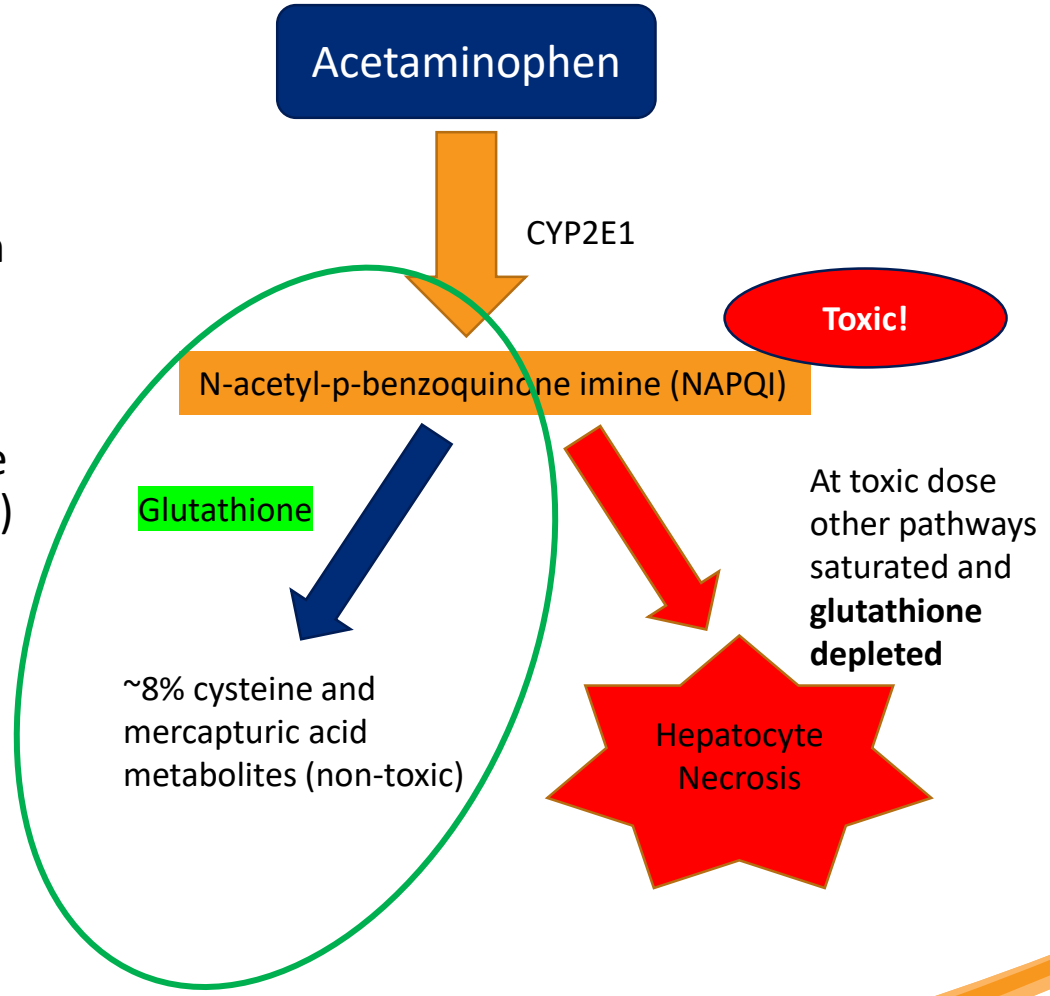
- *Choices of dialysis*
  - ❑ Intermittent hemodialysis (Preferred)
  - ❑ Intermittent hemoperfusion
  - ❑ Continuous renal replacement modalities

Source:
Dart RC, et al. *JAMA Netw Open.* 2023;6(8):e2327739.
Gosselin S, et al. *Clin Toxicol (Phila)*. 2014;52(8):856-867.

Focused Antidote – Acetylcysteine

Also known as N-acetylcysteine (NAC)

- **Mechanism of Action**
  - Restore hepatic glutathione by serving as a glutathione substitute and enhancing the nontoxic sulfate conjugation of acetaminophen
- **Dosage Forms**
  - Oral solution, IV solution
  - Solution for inhalation (avoid use routinely, use only if commercial IV formulation not available)
- **Adverse Effects**
  - Facial flushing
  - Urticaria or pruritis
  - Tachycardia
- **Pharmacokinetics**
  - Half-life: 5.6 h; Excretion: urine



Source: Acetylcysteine. *Lexicomp*. 2024.

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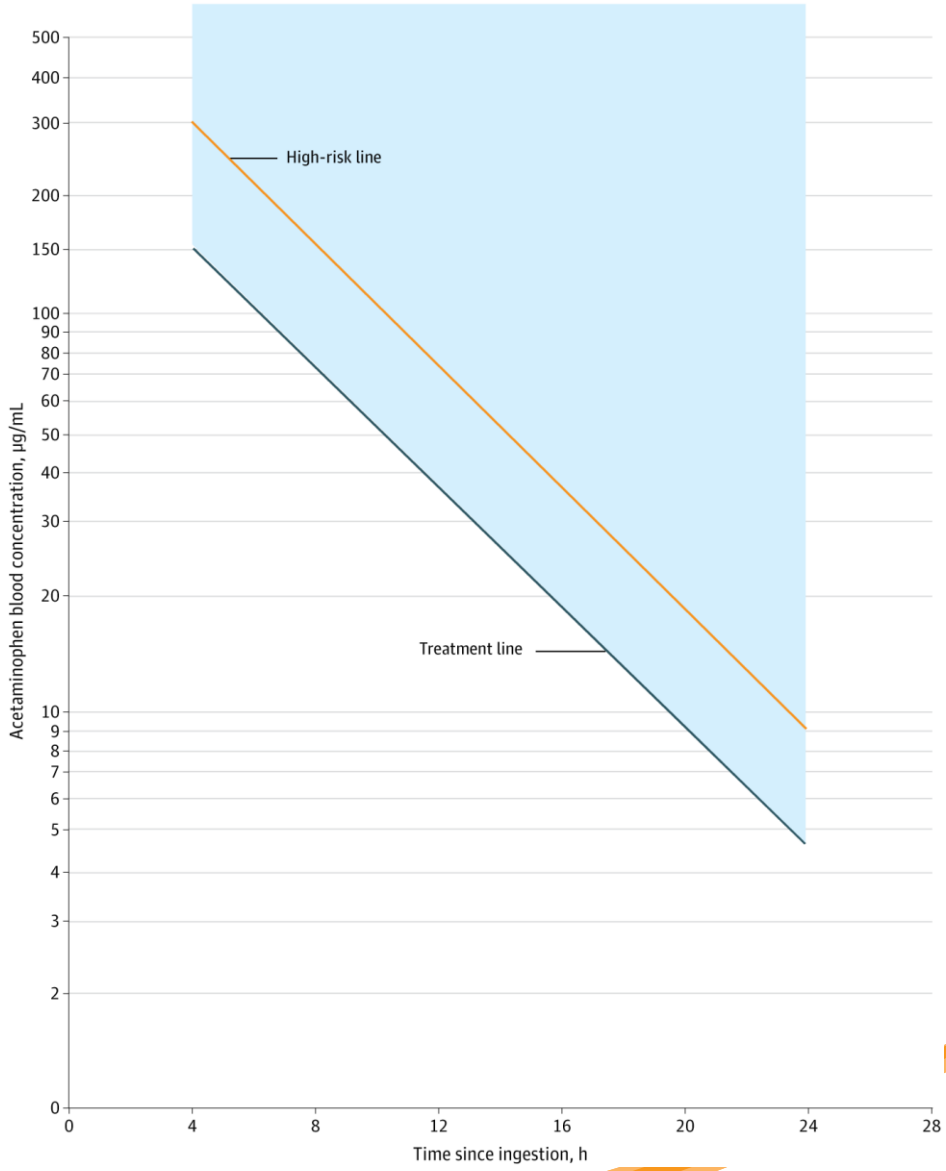
Focused Antidote – Acetylcysteine

When to use acetylcysteine?

- Ingestion ≥ 30g of Acetaminophen
- Acetaminophen concentration will return after 8h post ingestion
- Acetaminophen concentration drawn 4-24h post ingestion above treatment line on Rumack-Matthew nomogram



Source: Dart RC, et al. *JAMA Netw Open.* 2023;6(8):e2327739.

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Acetylcysteine Regimens (Oral)

Oral (72-hour regimen)	Administration	Storage
18 doses (total dose delivered: 1,330 mg/kg) • Loading dose: 140 mg/kg • Maintenance dose: 70 mg/kg every 4 hours; repeat dose if emesis occurs within 1 hour of administration	• Dilute the 20% solution 1:3 with a cola, orange juice, or other soft drink to prepare a 5% solution • Use within 1 hour of preparation • The unpleasant odor (sulfur-like) becomes less noticeable as treatment progresses • If patient vomits within 1 hour of dose, readminister • It is helpful to put the acetylcysteine on ice, in a cup with a cover, and drink through a straw; alternatively, administer via an NG tube	• Store unopened vials at room temperature • Once opened, store under refrigeration and use within 96 hours

The chosen regimen should deliver ≥300 mg/kg orally or intravenously during the first 20 to 24 hours of treatment. Acetylcysteine dose should be capped at 100 kg of body weight

Source:
Dart RC, et al. *JAMA Netw Open.* 2023;6(8):e2327739.
Acetylcysteine. *Lexicomp*. 2024.

Acetylcysteine Regimens (Intravenous)

Intravenous	Administration *Compatible diluents: D5W, 1/2NS, or SWFI*	Storage
Three bag method (total dose delivered: 300 mg/kg)		• Store intact vials at 20°C to 25°C (68°F-77°F) • Following reconstitution, solution is stable for 24 hours at room temperature • Discard unused portion
• Loading dose: 150 mg/kg infused over 1h • Second dose: 50 mg/kg infused over 4h • Third dose: 100 mg/kg infused over 16h	• Loading dose: Dilute dose in 200 mL diluent • Second dose: Dilute dose in 500 mL diluent • Third dose: Dilute dose in 1,000 mL diluent	
Two bag method (total dose delivered: 300 mg/kg)	*NS was used as the diluent in clinical study*	
• First dose: 200 mg/kg infused over 4h • Second dose: 100 mg/kg infused over 16h	• First dose: Dilute 200 mg/kg in 500 mL of a compatible diluent • Second dose: Dilute 100 mg/kg in 1,000 mL of a compatible diluent	
Single bag method (total dose delivered 430 mg/kg)		
Initiate therapy with 150 mg/kg infused over 1h; then decrease the rate to 14 mg/kg/h and infuse for an additional 20 h	Dilute 30 g in D5W 1,000 mL (total volume)	

The chosen regimen should deliver ≥300 mg/kg orally or intravenously during the first 20 to 24 hours of treatment. Acetylcysteine dose should be capped at 100 kg of body weight.

Source:
Dart RC, et al. *JAMA Netw Open.* 2023;6(8):e2327739.
Acetylcysteine. *Lexicomp*. 2024.

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Acetylcysteine Dose Adjustment During Dialysis

- **Oral Acetylcysteine**
  - No dose adjustment is needed

- **IV Acetylcysteine**
  - Dose need to be doubled
    - Up to 25% of NAC is extracted by CRRT
    - Up to 50% with intermittent hemodialysis
  - Infusion rate should be ≥12.5 mg/kg

NAC=N-acetylcysteine; CRRT=continuous renal replacement therapy

Source:
Dart RC, et al. *JAMA Netw Open.* 2023;6(8):e2327739.
Gosselin S, et al. *Clin Toxicol (Phila).* 2014;52(8):856-867.

Duration of Acetylcysteine Therapy and Goals of Therapy

- Serum acetaminophen concentration <10 mcg/mL
- INR <2
- Serum transaminases are normal for the patient or, if elevated, have decreased from the peak by 25% to 50%
- Patient is clinically well

Clinical Pearl

- Do not discontinue acetylcysteine after 20-21 hours of treatment without reassessment of the patient
- **Consider need to continue IV acetylcysteine at a rate ≥ 6.25 mg/kg/h until all criteria are met**

INR= international normalized ratio

Source: Dart RC, et al. *JAMA Netw Open*. 2023;6(8):e2327739.

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Acute Diphenhydramine Overdose

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Diphenhydramine (Benadryl®)

Uses	Allergic reaction, insomnia
Mechanism of Action	• Inverse agonist at the Histamine 1 (H1) receptor, reversing the effects of histamine on capillaries, reducing allergic reaction symptoms • Crosses the blood-brain barrier and inversely agonizes the H1 receptors in CNS, resulting in drowsiness
Dosing	Up to 50 mg every 4 hours as needed (maximum: 300 mg/day)
OTC Formulation	Tablets, capsules, oral solution
Cause of Overdose	• Unintentional (exists in various OTC combination products) • Intentional (suicidal or seeking euphoric effect)

OTC=Over the counter
CNS=central nervous system

Food and Drug Administration issued a warning on “Benadryl Challenge” on TikTok in 2020

Source:
Diphenhydramine. *Lexicomp*. 2024.
Huynh DA, et al. *Treasure Island (FL): StatPearls.* 2024
U.S. Food and Drug Administration. 2020.

Symptoms of Diphenhydramine Poisoning

- CNS depression

- Anticholinergic effects
  - Severe CNS anticholinergic toxicity: delirium, seizures, psychosis, hallucinations

- Cardiac arrhythmias
  - QT prolongation (delayed rectifier K channel inhibition)
  - QRS prolongation (fast Na channel inhibition)

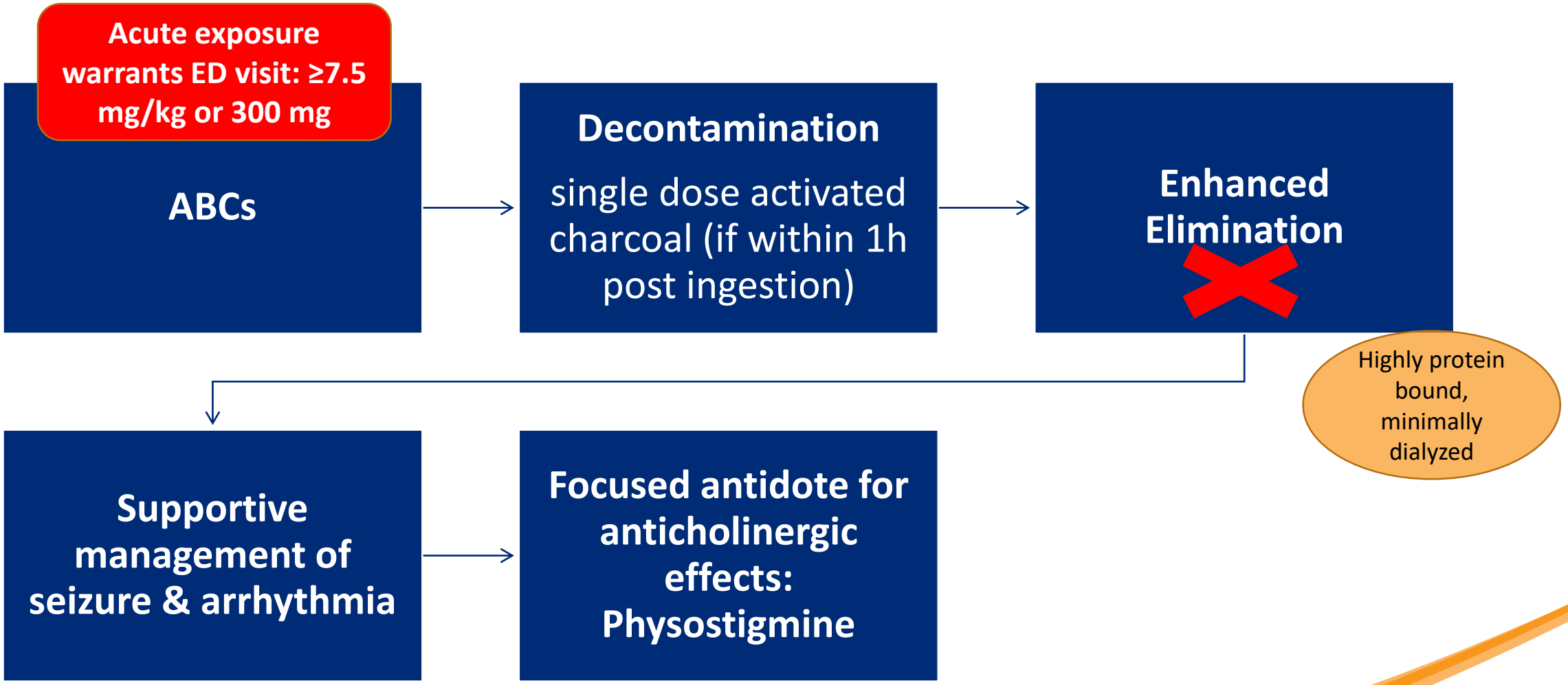
Anticholinergic

- Hyperthermia (**HOT as a hare**)
- Flushed (**RED as a beet**)
- Dry skin (**DRY as a bone**)
- Dilated pupils (**BLIND as a bat**)
- Delirium, hallucinations (**MAD as a hatter**)
- Tachycardia
- Urinary urgency and retention

CNS=Central Nervous System

Source:
Huynh DA, et al. *Treasure Island (FL): StatPearls.* 2024
Husain Z, et al. *Cardiol J.* 2010;17(5):509-511.

Management of Acute Diphenhydramine Overdose



Source:
Scharman EJ, et al. *Clin Toxicol (Phila)*. 2006;44(3):205-223.
Diphenhydramine. *Lexicomp*. 2024.

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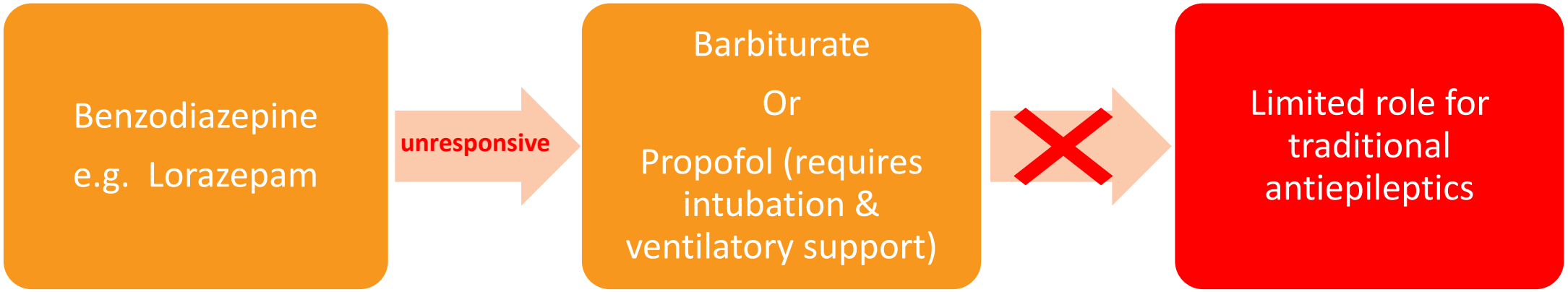
Management of Seizure



Medication	Mechanism of Action	Dosing
Lorazepam	**GABA-A receptor agonist** ↑frequency of chloride channel opening; neuronal hyperpolarization	2–4 mg IV; may repeat every 5–10 min (max rate: 2 mg/min)
Phenobarbital	**GABA-A receptor agonist** ↑duration of chloride channel opening and chloride ion influx	Initial: 5–15 mg/kg IV (max rate: 1 mg/kg/min) Followed by continuous infusion 0.5–5 mg/kg/h
Propofol	**GABA-A receptor agonist** ↑GABA binding to its receptor on the chloride channel **NMDA receptor antagonist**	Initial: 1–2 mg/kg IV Followed by continuous infusion 1.5–10 mg/kg/h

GABA= Gamma-aminobutyric acid; NMDA= N-methyl-D-asparate; IV= Intravenous

Source: Chen HY, et al. *Br J Clin Pharmacol*. 2016;81(3):412-419.

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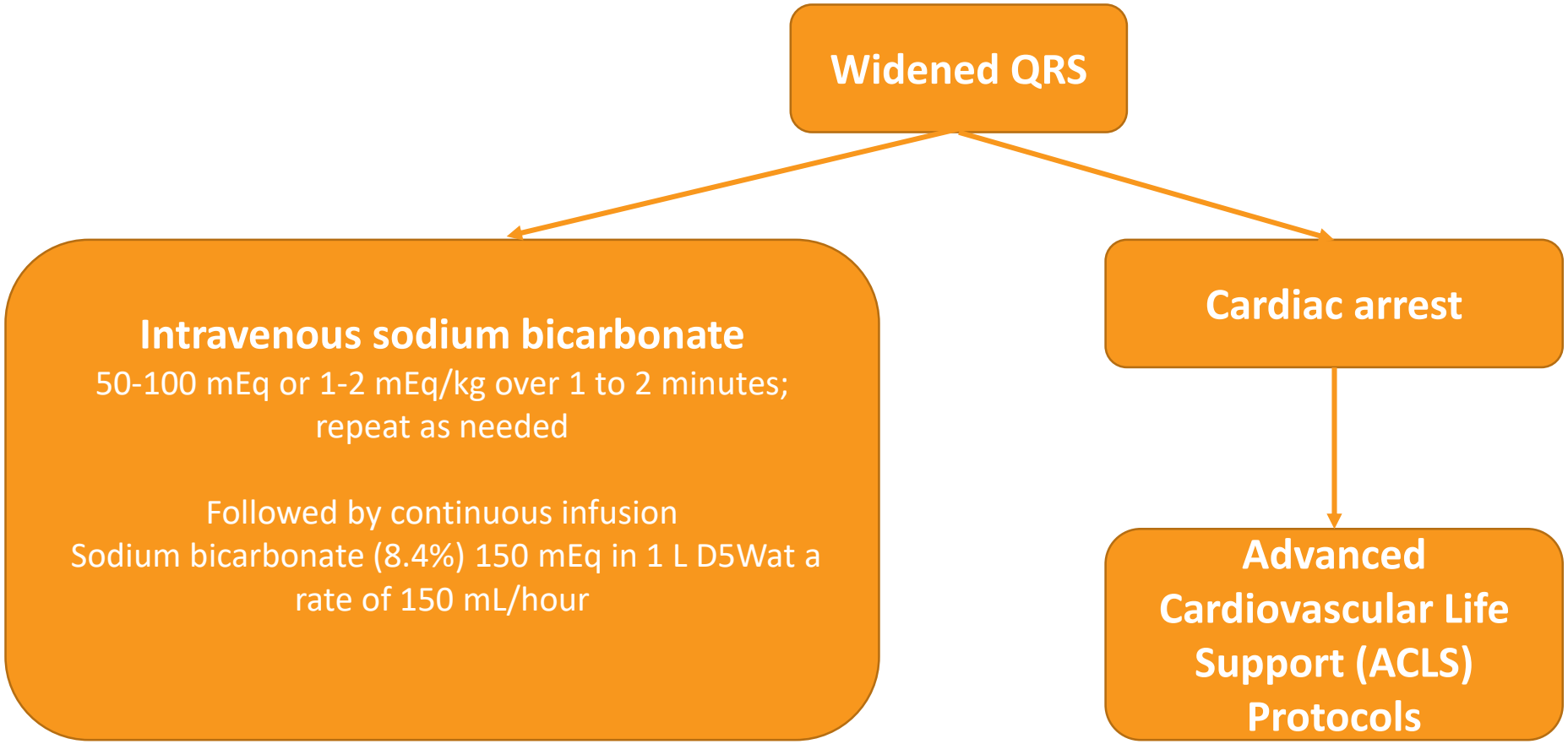
Management of Ventricular Arrhythmia



IV= Intravenous

Source:
Bruccoleri RE, et al. *J Med Toxicol*. 2016;12(1):121-129.
Sodium bicarbonate. *Lexicomp*. 2024.

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Focused antidote for anticholinergic effects: Physostigmine

Mechanism of Action	**Acetylcholinesterase Inhibitor** Inhibits the enzyme acetylcholinesterase that breaks down acetylcholine and prolongs the central and peripheral effects of acetylcholine
Dosing	2 mg IV administered over at least 5 minutes May repeat every 10-30 minutes until response occurs Generally, a single dose or a short duration of treatment (<6.5 hours) is sufficient
Administration	Infuse undiluted solution no more rapidly than 1 mg/minute [Available in 1 mg/mL] Too rapid administration may cause bradycardia, respiratory distress, and seizures
Adverse Effects	Hypersalivation, nausea, vomiting, diaphoresis, abdominal cramps, **seizure**, arrhythmia, and **bradycardia**
Pharmacokinetics	Onset of action: Within 3-8 minutes Duration: 45-60 minutes Metabolism: Via hydrolysis by cholinesterases Elimination half-life: 1-2 hours
Storage	20°C to 25°C (68°F to 77°F)

IV= Intravenous

Source:
Boley SP, et al. *Ann Pharmacother*. 2019;53(10):1026-1032.
Physostigmine. *Lexicomp*. 2024.
Rosenbaum C, et al. *J Med Toxicol.* 2010;6(4):386-392.
Arens AM, et al. *J Med Toxicol*. 2019;15(3):184-191.

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Acute Dextromethorphan Overdose

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Dextromethorphan (Robitussin®)

Uses	Cough (antitussive)
Mechanism of Action	**Prodrug; active metabolite dextrorphan** Decreases the sensitivity of cough receptors and interrupts cough impulse transmission by depressing the medullary cough center through sigma receptor stimulation
Dosing	10-20 mg PO every 4 hours or 20-30 mg PO every 6-8 hours Extended release: 60 mg PO twice daily Max: 120 mg/24 hours
OTC Formulation	Suspension, tablet, capsule, lozenge, orally disintegrating strips
Cause of Overdose	Dextromethorphan is a common component in various OTC cough and cold combination products Abuse for euphoria

OTC= Over the counter

Source:
Dextromethorphan. *Lexicomp*. 2024.
Burns JM, et al. *Subst Abuse Rehabil*. 2013;4:75-82.

Mechanism of Toxicity

- Dextromethorphan is metabolized by CYP2D6 to dextrorphan (major) and 3-methoxymorphinan (minor)
- **Dextrorphan** (active metabolite)
  - Therapeutic dose: binds with high affinity to σ-receptors to produce its antitussive activity without exhibiting classic opiate effects that occur from binding into μ and δ opiate receptors.
  - **Toxic dose**: antagonizes NMDA receptors (structurally similar to phencyclidine and ketamine) by binding to the calcium channel resulting in **dissociative, "out-of-body" experiences**

NMDA=N-methyl-D-aspartate

Source: Burns JM, et al. *Subst Abuse Rehabil*. 2013;4:75-82.

Dose-related Stages of Dextromethorphan Toxicity

Dose	Stage	Symptoms
1.5 mg/kg [adult dose: 100-200 mg]	Mild stimulation	• Neurobehavioral changes -- euphoria, hallucinations, inappropriate laughing, psychosis with dissociative features, agitation, and coma • Tachycardia • Dilated pupils • Diaphoresis (in the absence of anticholinergic co-ingestion) • "Zombie-like" ataxic gait
2.5 to 7.5 mg/kg [adult dose: 200-400 mg]	Euphoria and hallucinations	
7.5 to 15 mg/kg [adult dose: 300-600 mg]	Dissociative "out of body" state	
15 mg/kg [adult dose: >600 mg]	Complete dissociation with unresponsiveness	

Source:
White W. *The Vaults of Erowid*. 2002.
Burns JM, et al. *Subst Abuse Rehabil*. 2013;4:75-82

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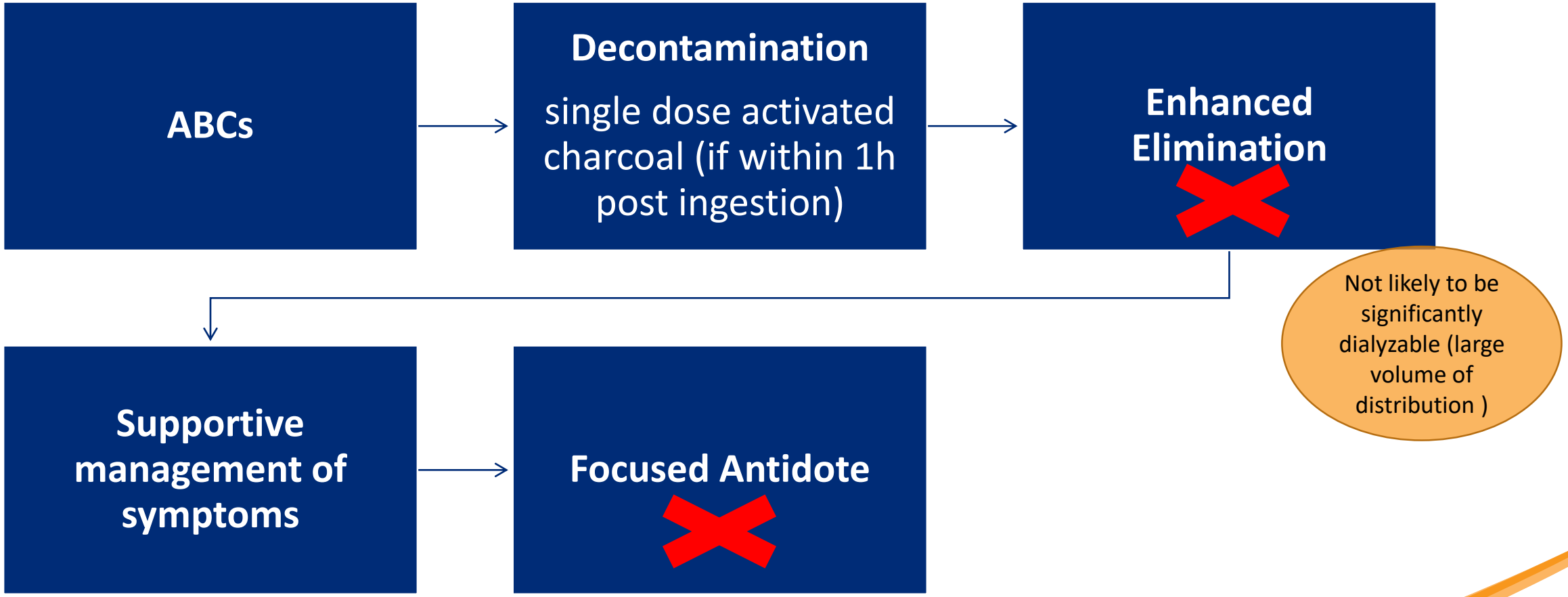
Management of Acute Dextromethorphan Overdose



Sources:
Journey JD, et al. *StatPearls* [Internet]. 2023.
Chyka P, et al. *Clin Toxicol (Phila)*. 2007;45(6):662-677.

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Supportive Management of Symptoms

- **Agitation/Violent Behavior/Psychosis**
  - Benzodiazepines (GABA-A receptor agonist)
    - E.g. Lorazepam 2 mg to 4 mg IV/IM; repeated doses every 10 minutes may be required for adequate sedation

- **Respiratory or CNS Depression**
  - Naloxone (Opioid Antagonist)
  - 0.04-0.2 mg/kg IV; may repeat with escalating doses every 2 to 3 minutes up to a cumulative dose of 10 mg

- **Hyperthermia**
  - Active cooling measures
  - E.g. Evaporative cooling, cold IV fluids

GABA=Gamma-aminobutyric acid
IV=intravenous
IM=intramuscular

Sources:
Journey JD, et al. *StatPearls* [Internet]. 2023.
Naloxone. Lexicomp. 2024.

Acute Iron Overdose

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Iron

- A mineral that is naturally present in many foods
- An essential component of hemoglobin and myoglobin
- Iron deficiency can cause anemia presenting with
  - Gastrointestinal disturbances
  - Weakness or fatigue
  - Difficulty concentrating
  - Impaired cognitive function, immune function, exercise or work performance, and body temperature regulation
- Available in many dietary supplements
  - With multivitamins
  - Iron-only supplements

Recommended Dietary Allowance (RDA)

Age	Male	Female	Pregnancy	Lactation
Birth to 6 months	0.27 mg*	0.27 mg*		
7–12 months	11 mg	11 mg		
1–3 years	7 mg	7 mg		
4–8 years	10 mg	10 mg		
9–13 years	8 mg	8 mg		
14–18 years	11 mg	15 mg	27 mg	10 mg
19–50 years	8 mg	18 mg	27 mg	9 mg
51+ years	8 mg	8 mg		

* Adequate Intake (AI)

Source: NIH Office of Dietary Supplements. 2023.

Toxic Dose

Elemental Iron Ingestion (mg/kg)	Potential Clinical Effect
< 20 mg/kg	Asymptomatic (non-toxic)
20-60 mg/kg	GI symptoms
≥ 60 mg/kg	Severe toxicity leading to morbidity and mortality

Common OTC Formulations

Formulation	Elemental Iron (%)
Ferrous sulfate	20%
Ferrous gluconate	12%
Ferrous fumarate	33%
Polysaccharide-iron complex (PIC)	The number in the name is the mg of elemental iron

GI: Gastrointestinal
OTC=Over the counter

Source: Klein-Schwartz W, et al. *Clin Pediatr (Phila)*. 1990;29(6):316-321.

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Stages of Iron Toxicity

Stages (time post ingestion)	Clinical Manifestations
Gastrointestinal toxicity (0-3h)	Vomiting, hematemesis, diarrhea, abdominal pain, restlessness, lethargy
Apparent stabilization (11-12h)	Symptoms subside
Mitochondrial toxicity (12-48h)	Shock, acidosis, coma, seizures, hyperglycemia, coagulopathy, acute tubular necrosis, hypoglycemia
Hepatic necrosis (>48h)	Jaundice, hepatic encephalopathy
Gastric scarring (2-4 weeks)	Gastric/pyloric strictures

Sources: Baranwal AK, et al. *Indian Pediatr*. 2003;40(6):534-540.

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Management of Acute Iron Overdose

Activated charcoal does NOT adsorb iron

ABCs

Decontamination:
Whole Bowel Irrigation

Enhanced Elimination

Patients with renal failure require hemodialysis to remove ferrioxamine-iron complex

Focused Antidote:
Deferoxamine

Sources:
Winchester JF. *Adv Ren Replace Ther*. 2002;9(1):26-30.
O'Malley GF, wt al. MSD Manual Consumer Version. February 16, 2022.

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Deferoxamine

Mechanism of Action	Chelate with trivalent ions (ferric ions) primarily in the vascular space to form **ferrioxamine**
Dosing & Administration	IV/IM: 1 g, may be followed by 500 mg every 4 hours for 2 doses • IV is the preferred route of administration • Initial infusion rate ≤ 15 mg/kg/hour, titrated up as tolerated • Subsequent doses infusion rate ≤ 125 mg/h
Preparation *SWFI: Sterile water for injection*	IV: • Reconstitute with SWFI (500 mg vial with 5 mL SWFI; 2,000 mg vial with 20 mL SWFI) to a final concentration of 95 mg/mL • Further dilute for infusion in NS, 1/2NS, D5W, or LR to a final concentration of 3-3.5 mg/mL IM • Reconstitute with SWFI (500 mg vial with 2 mL SWFI; 2,000 mg vial with 8 mL SWFI) to a final concentration of 213 mg/mL
Pharmacokinetics	• Metabolism: Plasma enzymes • Elimination half-life: 14 hours; plasma half-life: 20-30 minutes • Excretion: Primarily urine (as unchanged drug and ferrioxamine)
Storage	• Prior to reconstitution: store at 20°C to 25°C (68°F to 77°F) • Following reconstitution: Use within 3 hours of reconstitution (manufacturer labeling); may be stored at room temperature for 24 hours • Do NOT refrigerate reconstituted solution

Sources:
Baranwal AK, et al. *Indian Pediatr*. 2003;40(6):534-540.
Fine JS. *Curr Probl Pediatr*. 2000;30(3):71-90.
Deferoxamine. Lexicomp. 2024.

Deferoxamine

When to initiate	When to discontinue
• Serum iron concentrations >350 mcg/dL 6 hours post ingestion + other systemic symptoms OR • Serum iron concentrations >500 mcg/dL (even asymptomatic)	• Serum iron concentrations <350 mg/dL AND • Symptoms have resolved

Sources:
Baranwal AK, et al. *Indian Pediatr*. 2003;40(6):534-540.
Fine JS. *Curr Probl Pediatr*. 2000;30(3):71-90.
Deferoxamine. Lexicomp. 2024.

Key Takeaways

- Over-the-counter medications as the most accessible medications may cause significant toxicities that require emergent treatment
- A thorough history and toxidromes are essential to facilitate diagnosis
- “ABCDEFG” paradigm should be utilized to guide treatment in acute medication overdose
- Treatment for acute medication overdose relies primarily on supportive care while focused antidotes are only available for specific medications

Assessment Questions

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Assessment Question 1 for Pharmacists & Nurses

A 40 y/o male presented to the ED with altered mental status. He was found to have dilated pupil, tachycardia, hyperthermia, and dry skin. His wife was not sure what medication he was exposed to, but his home medications include quetiapine, alprazolam, ibuprofen, diphenhydramine, and lisinopril.

Based on the patient history, which of the home medications is the patient most likely overdosed on?

A. Alprazolam
B. Diphenhydramine
C. Ibuprofen
D. Quetiapine

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Assessment Question 1 for Pharmacists & Nurses: Correct Response

A 40 y/o male presented to the ED with altered mental status. He was found to have dilated pupil, tachycardia, hyperthermia, and dry skin. His wife was not sure what medication he was exposed to, but his home medications include quetiapine, alprazolam, ibuprofen, diphenhydramine, and lisinopril.

Based on the patient history, which of the home medications is the patient most likely overdosed on?

A. Alprazolam
B. Diphenhydramine (Correct Response)
C. Ibuprofen
D. Quetiapine

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Assessment Question 1 for Pharmacy Technicians

True/False: Over the past few years, both the incidence and the death rate of drug overdose has been increasing.

A. True
B. False

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Assessment Question 1 for Pharmacy Technicians: Correct Response

True/False: Over the past few years, both the incidence and the death rate of drug overdose has been increasing.

A. True
B. False (Correct Response)

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Assessment Question 2 for Pharmacists & Nurses

What does the “D” in ABCDEFG treatment paradigm stand for?

A. Disability
B. Dispute
C. Discuss
D. Decontamination

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Assessment Question 2 for Pharmacists & Nurses: Correct Response

What does the “D” in ABCDEFG treatment paradigm stand for?

A. Disability
B. Dispute
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D. Decontamination (Correct Response)

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Assessment Question 2 for Pharmacy Technicians

Which of the following is a key component of a thorough medication exposure history?

A. Baseline medical status of the patient
B. What medications were taken in overdose
C. When was it taken
D. Why it was taken
E. All the above

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Assessment Question 2 for Pharmacy Technicians: Correct Response

Which of the following is a key component of a thorough medication exposure history?

A. Baseline medical status of the patient
B. What medications were taken in overdose
C. When was it taken
D. Why it was taken
E. All the above (Correct Response)

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Assessment Question 3 for Pharmacists & Nurses

An 18 y/o female intentionally ingested 150 APAP 500mg tablets. In this ED, her labs were as follows: AST 19, ALT 8, serum APAP 180 mcg/mL @ 4h post ingestion. Serum ethanol and salicylate not detected. Urine drug screen negative.

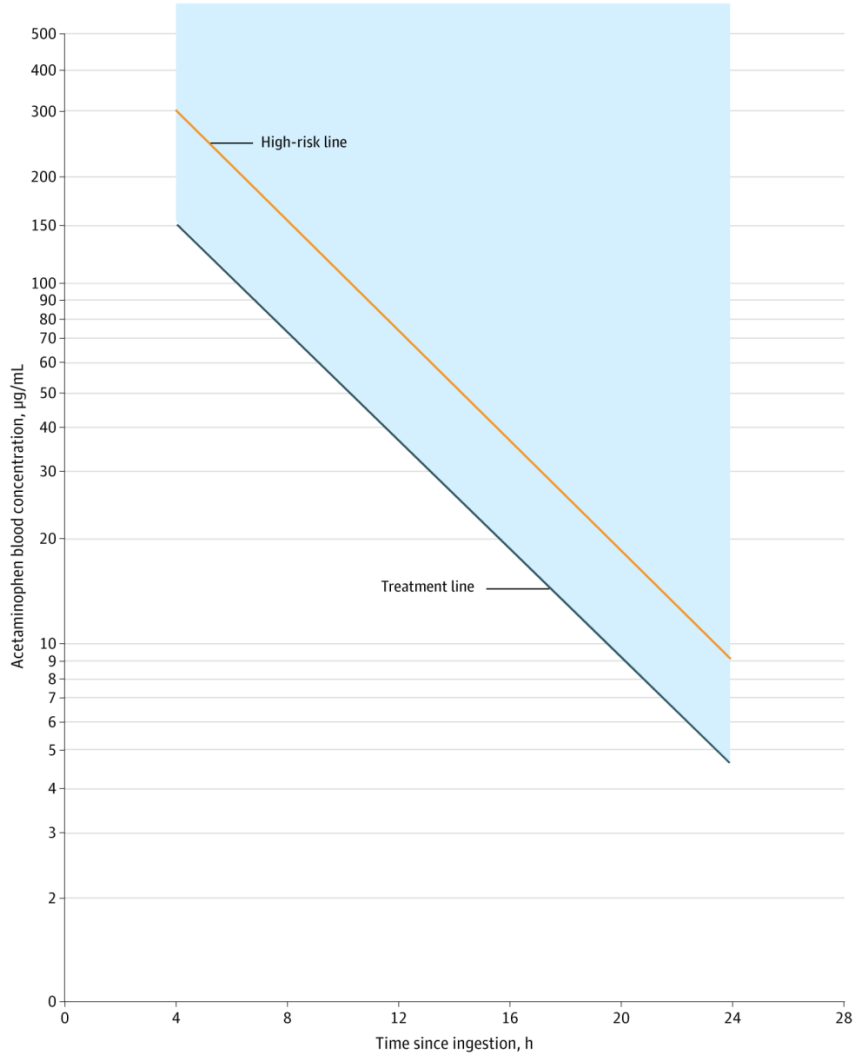
Based on the patient history and labs, how should we treat this patient?

A. Treatment is not needed at this time

B. Give N-acetylcysteine (NAC) IV 150 mg/kg over 1 hour, 50 mg/kg over 4 hours, then 100 mg/kg over 16 hours

C. Give fomepizole 15 mg/kg, followed by 10 mg/kg every 12 hours as needed

D. Contact liver transplant team



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Assessment Question 3 for Pharmacists & Nurses: Correct Response

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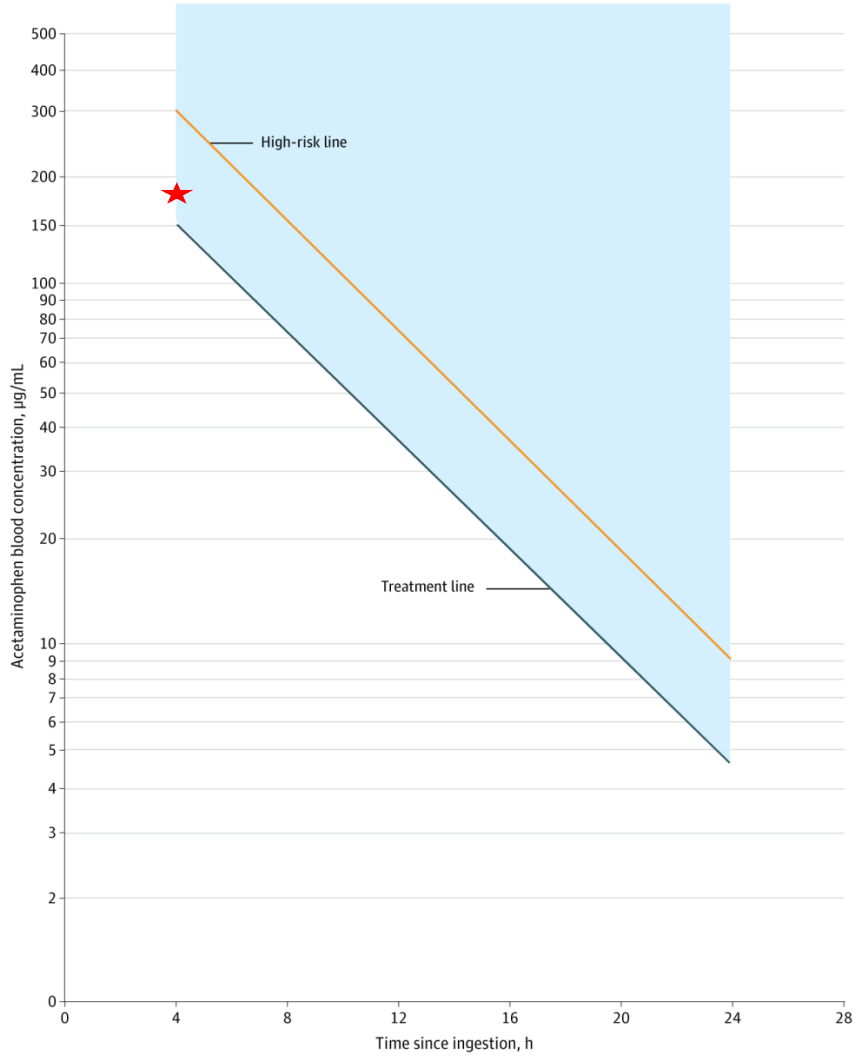

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Assessment Question 3 for Pharmacy Technicians

In the case of acetaminophen overdose, what medication needs to be prepared for treatment?

A. Lorazepam

B. Physostigmine

C. N-acetylcysteine (NAC)

D. Deferoxamine

Assessment Question 3 for Pharmacy Technicians: Correct Response

In the case of acetaminophen overdose, what medication needs to be prepared for treatment?

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B. Physostigmine

C. N-acetylcysteine (NAC) (Correct Response)

D. Deferoxamine

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Reference

1. Drug overdose death rates. National Institutes of Health. September 25, 2023. Accessed December 11, 2023. https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates.
2. Gummin DD, et al. 2022 Annual Report of the National Poison Data System® (NPDS) from America's Poison Centers®: 40th Annual Report. *Clin Toxicol (Phila)*. 2023;61(10):717-939.
3. Rech MA, Donahey E, Cappiello Dziedzic JM, Oh L, Greenhalgh E. New drugs of abuse. *Pharmacotherapy*. 2015;35(2):189-197. doi:10.1002/phar.1522
4. Frithsen IL, Simpson WM Jr. Recognition and management of acute medication poisoning. *Am Fam Physician.* 2010;81(3):316-323.
5. Erickson TB, Thompson TM, Lu JJ. The approach to the patient with an unknown overdose. *Emerg Med Clin North Am.* 2007;25(2):249-vii. doi:10.1016/j.emc.2007.02.004
6. Holstege CP, Borek HA. Toxidromes. *Crit Care Clin.* 2012;28(4):479-498. doi:10.1016/j.ccc.2012.07.008
7. Acetaminophen. In: *Lexi-Drugs.* Lexicomp; 2024. Updated March 16, 2024. Accessed March 18, 2024. http://online.lexi.com
8. Bunchorntavakul C, Reddy KR. Acetaminophen (APAP or N-Acetyl-p-Aminophenol) and Acute Liver Failure. *Clin Liver Dis*. 2018;22(2):325-346. doi:10.1016/j.cld.2018.01.007
9. Malley GF, Malley R. Acetaminophen poisoning. *Merck Manuals*. June 21, 2022. Accessed March 18, 2024. https://www.merckmanuals.com/professional/injuries-poisoning/poisoning/acetaminophen-poisoning.
10. Bond G. Guidelines for the management of acetaminophen overdose. *Tylenolprofessional*. 2023. Accessed February 21, 2024. https://www.tylenolprofessional.com/sites/tylenol_hcp_us/files/acetaminphen_overdose_treatment_info.pdf.
11. Dart RC, Mullins ME, Matoushek T, et al. Management of Acetaminophen Poisoning in the US and Canada: A Consensus Statement [published correction appears in JAMA Netw Open. 2023 Sep 5;6(9):e2337926]. *JAMA Netw Open*. 2023;6(8):e2327739. Published 2023 Aug 1. doi:10.1001/jamanetworkopen.2023.27739
12. Gosselin S, Juurlink DN, Kielstein JT, et al. Extracorporeal treatment for acetaminophen poisoning: recommendations from the EXTRIP workgroup. *Clin Toxicol (Phila)*. 2014;52(8):856-867. doi:10.3109/15563650.2014.946994
13. Center for Drug Evaluation and Research. FDA Drug Safety Podcast on Diphenhydramine Drug Safety Communication. *U.S. Food and Drug Administration.* 2020. Accessed March 19, 2024. https://www.fda.gov/drugs/fda-drug-safety-podcasts/fda-warns-about-serious-problems-high-doses-allergy-medicine-diphenhydramine-benadryl.
14. Huynh DA, Abbas M, Dabaja A. Diphenhydramine Toxicity. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; April 29, 2023.

Reference

15. Scharman EJ, Erdman AR, Wax PM, et al. Diphenhydramine and dimenhydrinate poisoning: an evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol (Phila)*. 2006;44(3):205-223. doi:10.1080/15563650600585920

16. Husain Z, Hussain K, Nair R, Steinman R. Diphenhydramine induced QT prolongation and torsade de pointes: An uncommon effect of a common drug. *Cardiol J*. 2010;17(5):509-511.

17. Chen HY, Albertson TE, Olson KR. Treatment of drug-induced seizures. *Br J Clin Pharmacol*. 2016;81(3):412-419. doi:10.1111/bcp.12720

18. Coralic Z, Kapur J, Olson KR, Chamberlain JM, Overbeek D, Silbergleit R. Treatment of Toxin-Related Status Epilepticus With Levetiracetam, Fosphenytoin, or Valproate in Patients Enrolled in the Established Status Epilepticus Treatment Trial. *Ann Emerg Med*. 2022;80(3):194-202. doi:10.1016/j.annemergmed.2022.04.020

19. Bruccoleri RE, Burns MM. A Literature Review of the Use of Sodium Bicarbonate for the Treatment of QRS Widening. *J Med Toxicol*. 2016;12(1):121-129. doi:10.1007/s13181-015-0483-y

20. Boley SP, Stellpflug SJ. A Comparison of Resource Utilization in the Management of Anticholinergic Delirium Between Physostigmine and Nonantidote Therapy. *Ann Pharmacother*. 2019;53(10):1026-1032. doi:10.1177/1060028019846654

21. Rosenbaum C, Bird SB. Timing and frequency of physostigmine redosing for antimuscarinic toxicity. *J Med Toxicol.* 2010;6(4):386-392. doi:10.1007/s13181-010-0077-7

22. Arens AM, Kearney T. Adverse Effects of Physostigmine [published correction appears in J Med Toxicol. 2019 Oct;15(4):310]. *J Med Toxicol*. 2019;15(3):184-191. doi:10.1007/s13181-019-00697-z

23. Burns JM, Boyer EW. Antitussives and substance abuse. *Subst Abuse Rehabil*. 2013;4:75-82. Published 2013 Nov 6. doi:10.2147/SAR.S36761

24. White W. The DXM Experience. The Vaults of Erowid. 2002. Accessed March 20, 2024. https://www.erowid.org/chemicals/dxm/faq/dxm_experience.shtml.

25. Chyka PA, Erdman AR, Manoguerra AS, et al. Dextromethorphan poisoning: an evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol (Phila)*. 2007;45(6):662-677. doi:10.1080/15563650701606443

26. Journey JD, Agrawal S, Stern E. Dextromethorphan Toxicity. [Updated 2023 Jun 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538502/

27. Iron - Fact Sheet for Health Professionals. NIH Office of Dietary Supplements. 2023. Accessed March 20, 2024. https://ods.od.nih.gov/factsheets/Iron-HealthProfessional/.

28. Klein-Schwartz W, Oderda GM, Gorman RL, Favin F, Rose SR. Assessment of management guidelines. Acute iron ingestion. *Clin Pediatr (Phila)*. 1990;29(6):316-321. doi:10.1177/000992289002900604

Reference

29. Baranwal AK, Singhi SC. Acute iron poisoning: management guidelines. *Indian Pediatr*. 2003;40(6):534-540.

30. Winchester JF. Dialysis and hemoperfusion in poisoning. *Adv Ren Replace Ther*. 2002;9(1):26-30. doi:10.1053/jarr.2002.30470

31. O'Malley GF, O'Malley R. Iron poisoning - injuries and poisoning. MSD Manual Consumer Version. February 16, 2022. Accessed March 20, 2024. https://www.msdmanuals.com/home/injuries-and-poisoning/poisoning/iron-poisoning.

32. Fine JS. Iron poisoning. *Curr Probl Pediatr*. 2000;30(3):71-90. doi:10.1067/mps.2000.104055

33. Mycyk MB. Poisoning and Drug Overdose. In: Loscalzo J, Fauci A, Kasper D, Hauser S, Longo D, Jameson J. eds. *Harrison's Principles of Internal Medicine, 21e*. McGraw-Hill Education; 2022. Accessed April 02, 2024. https://accessmedicine.mhmedical.com/content.aspx?bookid=3095&sectionid=264098477

34. Activated charcoal. In: *Lexi-Drugs.* Lexicomp; 2024. Updated March 11, 2024. Accessed April 2, 2024. http://online.lexi.com

35. Chyka PA, Seger D, Krenzelok EP, Vale JA; American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. Position paper: Single-dose activated charcoal. *Clin Toxicol (Phila)*. 2005;43(2):61-87. doi:10.1081/clt-200051867

36. Position statement and practice guidelines on the use of multi-dose activated charcoal in the treatment of acute poisoning. American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. *J Toxicol Clin Toxicol*. 1999;37(6):731-751. doi:10.1081/clt-100102451

37. Hoegberg LCG, Shepherd G, Wood DM, et al. Systematic review on the use of activated charcoal for gastrointestinal decontamination following acute oral overdose. *Clin Toxicol (Phila)*. 2021;59(12):1196-1227. doi:10.1080/15563650.2021.1961144

38. Position paper: whole bowel irrigation [published correction appears in J Toxicol Clin Toxicol. 2004;42(7):1000. Dosage error in article text]. *J Toxicol Clin Toxicol*. 2004;42(6):843-854. doi:10.1081/clt-200035932

39. Vale JA, Kulig K; American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. Position paper: gastric lavage. *J Toxicol Clin Toxicol*. 2004;42(7):933-943. doi:10.1081/clt-200045006

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