Confronting Scarcity: Management of Toxicities Amid Drug Shortages

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Disclosures

The authors of this presentation have no actual or potential disclosures to report related to this presentation. The following products will be described in an off-label manner as they are not approved by the FDA for their indication:

Anticholium® (physostigmine salicylate), rivastigmine, edetate calcium disodium, succimer

FDA: Food and Drug Administration

Objectives

Identify causes of drug shortages and the impact on patient care

Describe toxicities observed in the emergency department affected by drug shortages and discuss various approaches to their management

Explore drug shortage mitigation strategies and downstream impacts

Poll Everywhere

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- Text: **ERINBOWE361** to 37607

Drug Shortage

ASHP	FDA
• Supply issue that affects how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternative agent	• Demand or projected demand for the drug within the United States exceeds supply of the drug • Registered alternative manufacturer will not meet current and/or projected demands for potentially medically necessary use(s) at the patient level

ASHP: American Society of Health System Pharmacists
FDA: Food and Drug Administration

Food and Drug Administration, 2023.
American Society of Health System Pharmacists, 2023.

Why Do Drug Shortages Happen?

Nationwide Recall Issued for Acetaminophen Extra Strength Tablets Due to Mislabeling

July 1, 2021

Correspondence | Published: 08 April 2020

Potential of chloroquine and hydroxychloroquine to treat COVID-19 causes fears of shortages among people with systemic lupus erythematosus

Ozempic shortage hits diabetes patient after weight loss use

6th September 2023, 01:59 EDT

Share

Why Do Drug Shortages Happen?

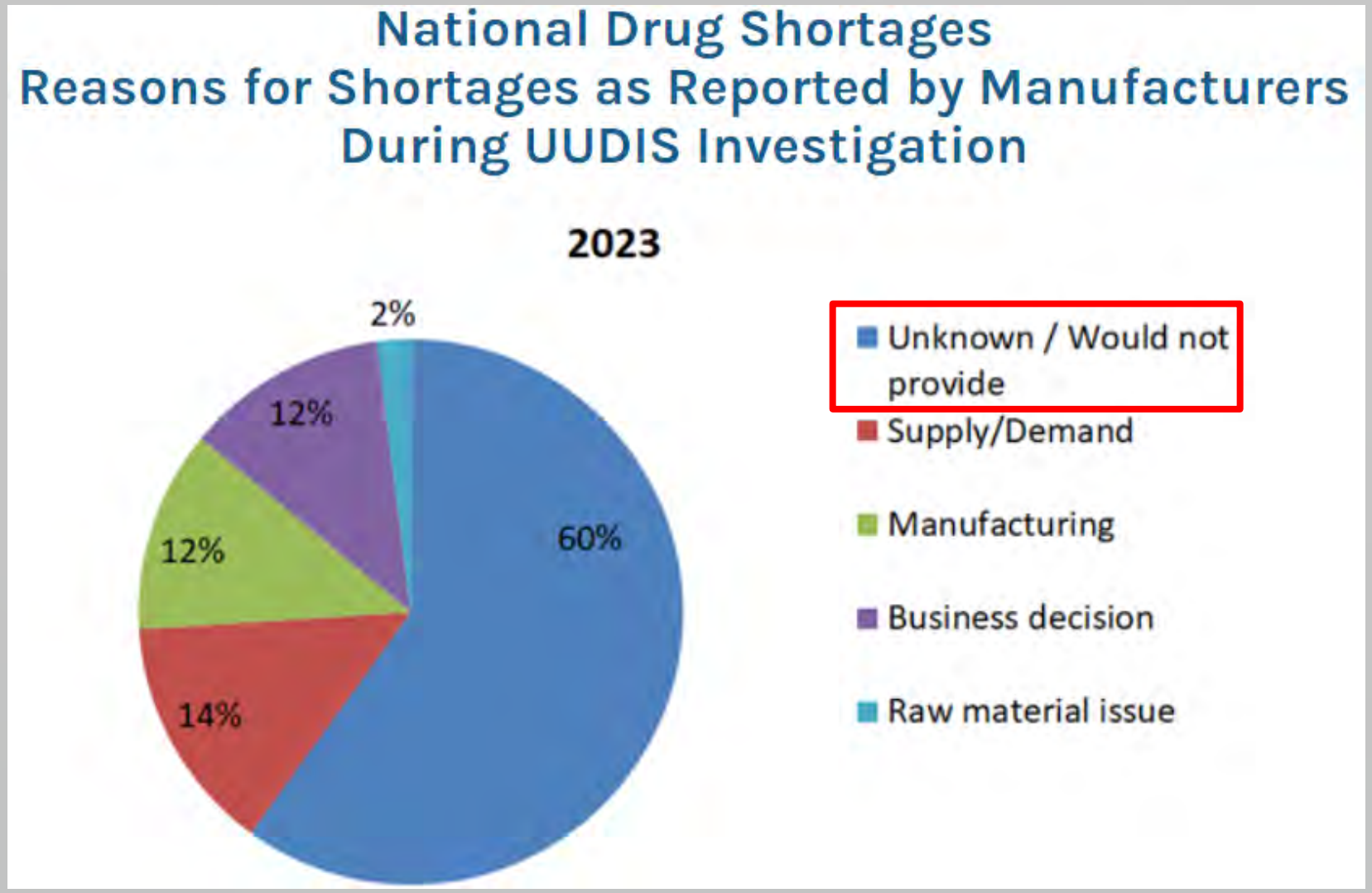
Tornado damage to Pfizer factory highlights vulnerabilities of drug supply

JULY 27, 2023 · 2:36 PM ET

AKORN

IN FEBRUARY 2023, AKORN OPERATING COMPANY LLC FILED CHAPTER 7 BANKRUPTCY. IN CONNECTION WITH THAT FILING, THE COMPANY HAS CEASED AND SHUTDOWN ALL OPERATIONS.

Why Do Drug Shortages Happen?



UUDIS: University of Utah Drug Information Service

ASHP. Drug Shortage Statistics, 2023.

Impact of Drug Shortages

- Healthcare systems
- Clinicians
- Patients

Impact of Drug Shortages on Patients

Mazer-Amirshahi, et al. 2015.

Study

- Analysis of drug shortage data from UUDIS from January 2001 – December 2013

Results

- 1751 drug shortages, 141 (8%) affecting poisoned patients

UUDIS: University of Utah Drug Information Service

Clinical Toxicology (2015), 53, 519-524.

Mazer-Amirshahi, et al. 2015.

Table 2. Types of medical toxicology drugs affected by shortages.

Type of medication	Number of shortages ($n=141$)*	Percent of drugs	Total shortage months**	Percent of study period on shortage***	Median shortage months (IQR)**
Anticholinergic antidotes	8	5.7	97	53	7 (4.5–13.5)
Antihypoglycemic antidotes	8	5.7	151	54	17.5 (7.5–28)
Antivenom/immune Fab	7	5.0	118	71	8 (4–37)
Chelators	6	4.3	86	44	15 (6–22)
Cholinergic antidotes	9	6.4	181	70	10 (4–31)
Cyanide antidotes	6	4.3	51	24	4.5 (2–5)
Decontamination products	2	1.4	27	17	27
Electrolytes	15	10.6	262	65	12 (5–31)
Hematologic	13	9.2	153	61	7 (3–23)
Other	24	17.0	396	81	12 (5–26)
Naloxone	6	4.3	37	24	5.5 (3–15.5)
Sedative/hypnotics	22	15.6	336	85	9 (4–22)
Vitamin/elements	15	10.6	78	44	3 (2–6)

*Includes both active and resolved shortages.
**Does not include products that were discontinued/withdrawn ($n=9$).
***Refers to the percentage of time during the study period when at least 1 drug of that type was on shortage.

Clinical Toxicology (2015), 53, 519-524.

Acute Toxicities

Anticholinergic Toxidrome

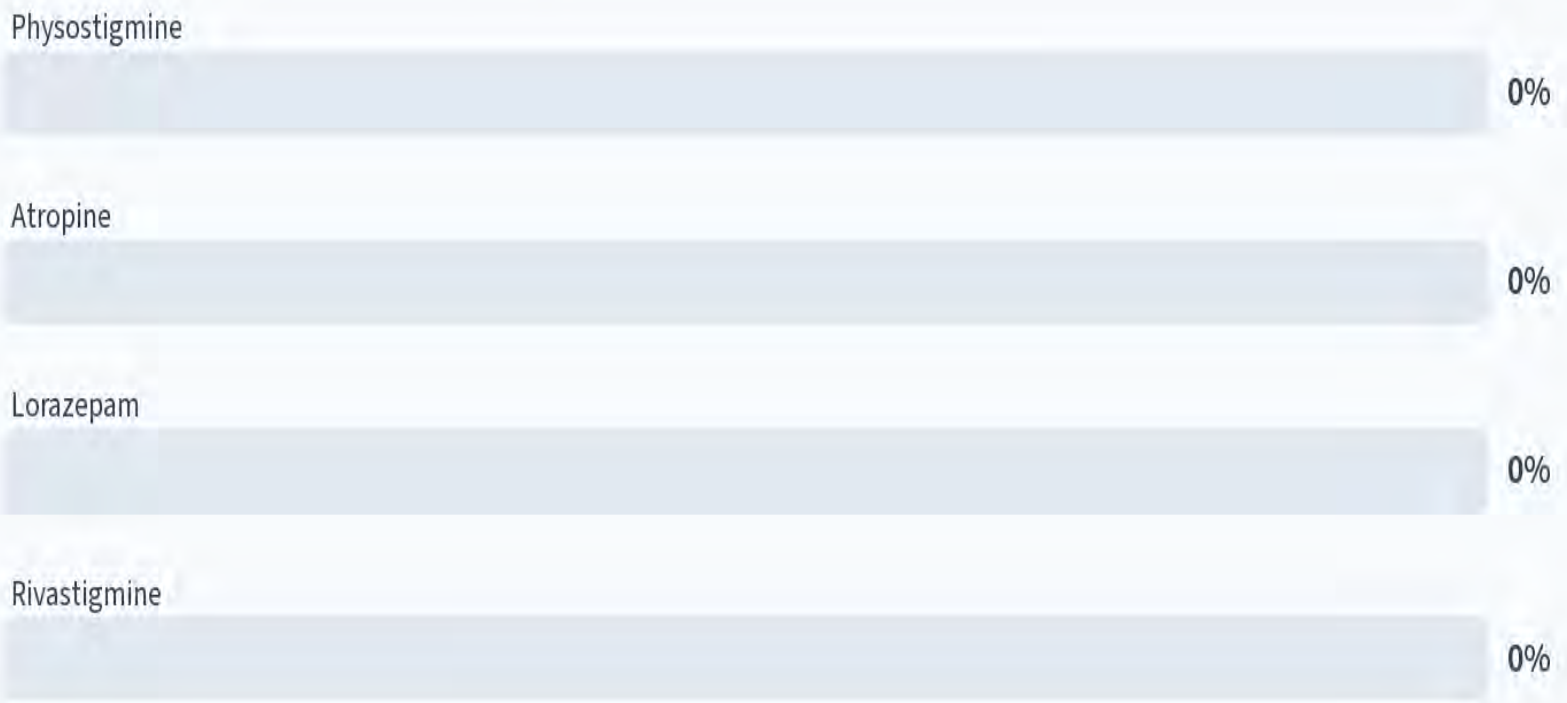
Lead Poisoning

Meet SB

37-year-old male presents to the ED after being found altered at home by his roommate. EMS reports an empty bottle of diphenhydramine was found in SB's room

Past Medical History	Home Medications
• Depression • Anxiety • Hypertension	• Buspirone • Losartan • Ibuprofen PRN

What initial therapy would you like to start for our patient?



Anticholinergic Toxidrome

- In 2023, ~7000 exposures to anticholinergic substances were reported to US Poison Centers
- Exposures rarely result in fatality
- Readily available OTC substances can produce anticholinergic toxicity

Clin Toxicol (Phila). 2024;62(12):793-1027.

Substances with Anticholinergic Activity

Class	Agent
Antipsychotics	Typical: chlorpromazine, haloperidol Atypical: olanzapine, quetiapine
Antiseizure	Carbamazepine, oxcarbazepine
First-generation Antihistamines	Diphenhydramine, hydroxyzine, doxylamine, cyproheptadine
Tricyclic Antidepressants	Amitriptyline, nortriptyline
Plants	Jimson weed, *Atropa belladonna*
Miscellaneous	Atropine, glycopyrrolate, cyclobenzaprine, scopolamine

*Not all inclusive

World J Emerg Med. 2017; 8(4): 297–301.

Clinical Presentation

Agitation, delirium, hallucinations, carphologia, seizure/coma

Hyperthermia, flushed skin, tachycardia

Xerostomia, dry skin, urinary retention

Mydriasis, blurry vision, photophobia

Br J Clin Pharmacol. 2016 Mar; 81(3): 516–524.

Diagnosis

History of ingestion

Clinical signs and symptoms

Serum drug levels

Additional labs

- EKG, CMP, CBC, HCG, urinalysis, urine drug screen, blood glucose, acetaminophen/salicylate levels

General Management

GI decontamination	• Case-to-case use
Supportive care	• Symptom management • Seizures • Delirium/agitation

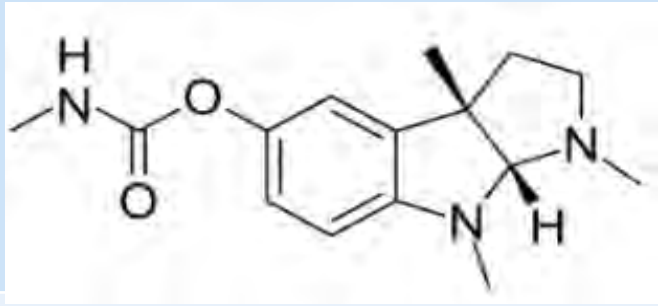
Br J Clin Pharmacol. 2016 Mar; 81(3): 516–524.

Management of Delirium

Benzodiazepines	Acetylcholinesterase Inhibitors	Non-Pharm
• Lorazepam • Midazolam	• Physostigmine • Rivastigmine	• Quiet • Dark room

Br J Clin Pharmacol. 2016 Mar; 81(3): 516–524.

Physostigmine

Mechanism	Reversible acetylcholinesterase inhibitor 
Dose	<u>Adult:</u> 0.5 – 2 mg IV over 5 – 10 minutes <u>Pediatric:</u> 0.02 mg/kg (max 0.5 mg) Repeat every 10 – 30 minutes
Adverse Effects	Bradycardia, respiratory depression, seizure, cardiac effects
Contraindications	TCA overdose, cardiac conduction disease, bradydysrhythmias, seizure

TCA: Tricyclic Antidepressant

Goldfrank's Toxicologic Emergencies, 11e. 2019.

Physostigmine Literature

Study	Intervention	Outcomes
Burns, et al. (2000) 52 patients with anticholinergic delirium	• Physostigmine • Benzodiazepines	Decrease in incidence of agitation (96%) and reversal of delirium (87%) in physostigmine group
Boley, et al. (201 154 patients with anticholinergic d		rium control in group (79%) versus idote (36%)
Wang, et al. (2021) 19 patients with anticholinergic agitation/delirium	• Physostigmine • Lorazepam	Less delirium and improved agitation scores in physostigmine group

Physostigmine is superior to benzodiazepines

Annals of Emergency Medicine (2000), 35(4), 374–381.
Clinical Toxicology (2019), Vol. 57, No. 1, 50–55.
Clinical Toxicology (2021), Vol. 59, No. 8, 698–704.

Physostigmine Drug Shortage

- ASHP announced shortage in March 2021
- Akorn Pharmaceuticals was sole manufacturer
- Non-FDA approved product (Anticholium®) imported from Germany through Provepharm Inc. and Direct Success

US Product

Import Product

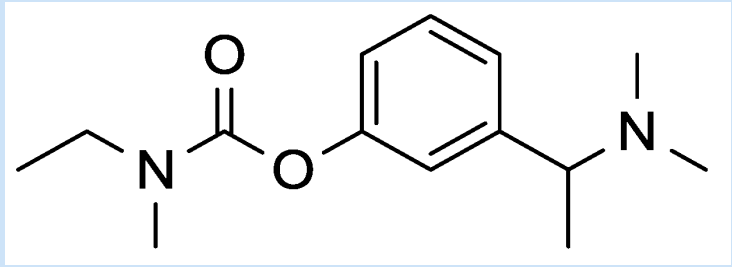
ASHP: American Society of Health System Pharmacists
FDA: Food and Drug Administration

Drug Shortages List. *ASHP* (2023).

Physostigmine: UK HealthCare's Experience

- Given FDA nod, UK HealthCare currently pursuing European product
  - Only available at WAC pricing from Direct Success
- Estimate treating 2 patients/month
  - 24 patients/year | 1 amp/patient | $625/5 amps
  - Drug Cost Estimate: $3000-$6000
  - Minimum quantity order of 15 amps from Direct Success
- Anticipated education needs: concentration differences

Rivastigmine

Mechanism	Reversible acetylcholinesterase inhibitor 
Indications	Alzheimer's disease Dementia Parkinson disease
Formulations	Oral capsule Transdermal 24-hour patch
Adverse Effects	Cholinergic adverse effects (SLUDGE), bradycardia, arrhythmias, dermatologic reactions (transdermal)

Goldfrank's Toxicologic Emergencies, 11e. 2019.

Rivastigmine Dosing Recommendations

- Oral
  - Adults and pediatrics:
    - 1.5 – 3 mg every 1 – 2 hours until symptoms resolve (max 12 mg/day)
    - Maintenance 3 – 6 mg twice daily
- Transdermal
  - Adults:
    - 9.5 – 13.3 mg/24 hours
  - Pediatrics:
    - 0.2 mg/kg/24 hours
- Combination

Drug shortage alert physostigmine - sccm.org. 2023.
Oxford Medical Case European Neuropsychopharmacology (2017) 27, 833–834.

Rivastigmine Case Reports

Study	Intervention	Outcomes
Sandia, et al. (2017) 6 adult patients with anticholinergic delirium	Transdermal rivastigmine 9.5 mg/24-hour x 5 days	Reduction in psychotic symptoms
Van Kernebeerk, et al. (2021) 1 adult patient with anticholinergic delirium	Rivastigmine 1.5 mg orally twice daily x 7 days	Decline in agitation within 24 hours
Fratta, et al. (2023) 1 adult patient with anticholinergic agitation and hallucinations	Rivastigmine 3 mg orally x 2 doses plus transdermal rivastigmine 13.3 mg/24-hour	Improvement in agitation at 27 hours
Chiew, et al. (2024) 50 adult patients with anticholinergic delirium	Transdermal rivastigmine 9.5 mg/24-hour or 9.2 mg/24-hour OR Rivastigmine 6 mg orally x1	Reduction in psychotic symptoms with transdermal and oral formulations at 5 hours and 2 hours, respectively

Clin Toxicol (Phila). 2021; 59(5): 447-448.
Oxford Medical Case European Neuropsychopharmacology (2017) 27, 833–834.
The Journal of Emergency Medicine, Vol. 65, No. 4, pp. e366–e368, 2023.
Clinical Toxicology 2024, VOL. 62, NO. 2, 82–87.

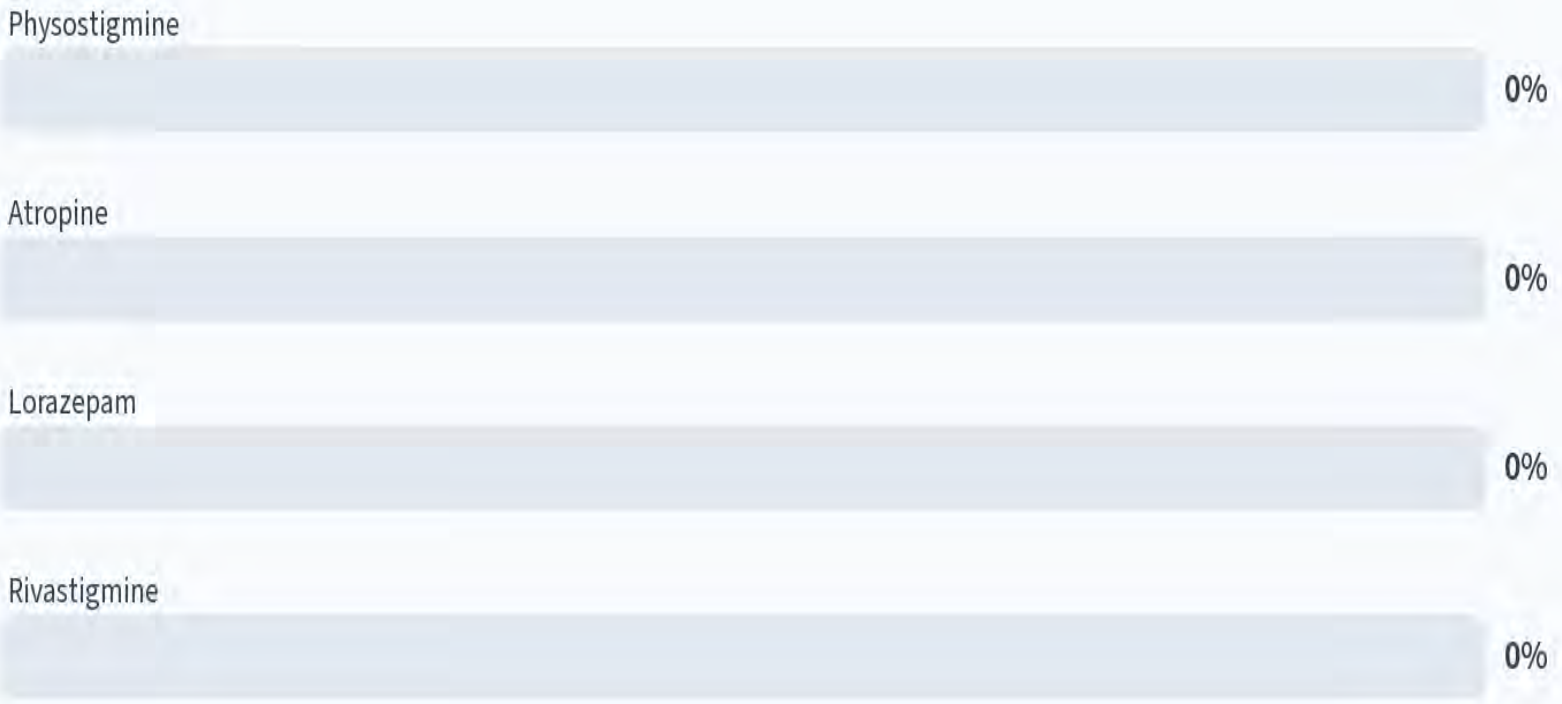
Rivastigmine: Ready for Primetime?

175. Cause for pause: bradycardia induced by transdermal rivastigmine in anticholinergic delirium

with verbal commands. Physical examination revealed dry skin, dilated pupils, and signs of delirium. Despite receiving lorazepam, the patient remained agitated, with her heart rate reaching 150 beats per minute (bpm). A 9.5 mg rivastigmine transdermal patch was applied, after which the patient developed asymptomatic sinus bradycardia, with a heart rate dropping to 40 bpm. After patch removal, the heart rate improved to 58 bpm. Over the course of several hours, the patient's mental status gradually improved, and she returned to her baseline hemodynamics prior to discharge.

- **Considerations**
  - Physostigmine preferred if available 2/2 titratability
  - Rivastigmine may have role if physostigmine unavailable
  - Consider lower dosing of rivastigmine
    - 1.5 - 3 mg oral q 2 hours NTE 12 mg | 4.6 - 9.5 mg patch

After being informed on current drug shortages, what initial therapy would you like to start for our patient?



Anticholinergic Toxidrome Key Points

Many substances have anticholinergic properties

Benzodiazepines are generally used first-line, although the literature favors physostigmine for the management of agitation

Rivastigmine (oral, transdermal, or combination) may be used as an alternative in the setting of physostigmine shortage for anticholinergic delirium

Acute Toxicities

Anticholinergic Toxidrome

Lead Poisoning

Meet NH

2-year-old male presents to the ED from an OSH after reports of an elevated surveillance blood lead level (BLL). Father reports recent home renovation. Subjective behavioral changes are also noted.

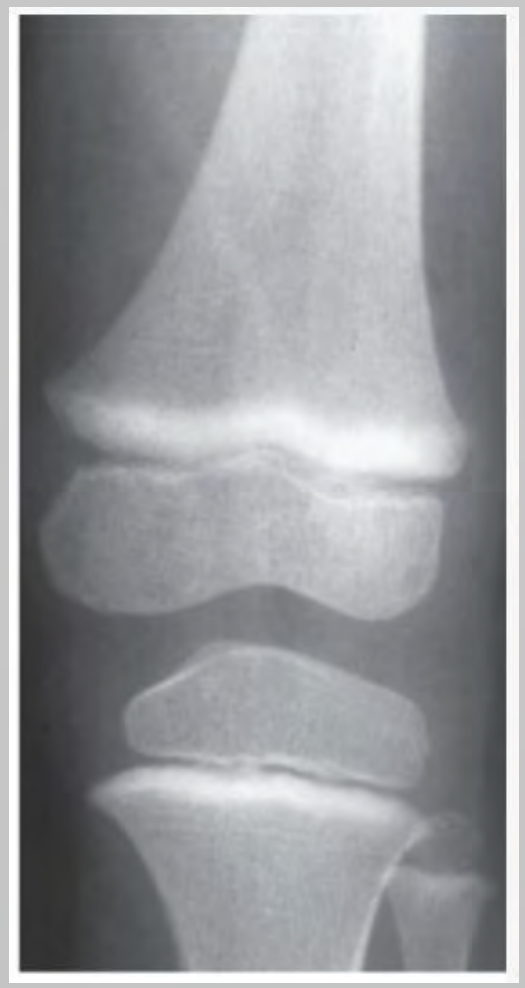
Past Medical History	Home Medications
• Pica • Iron deficiency	• Ferrous sulfate • Multivitamin

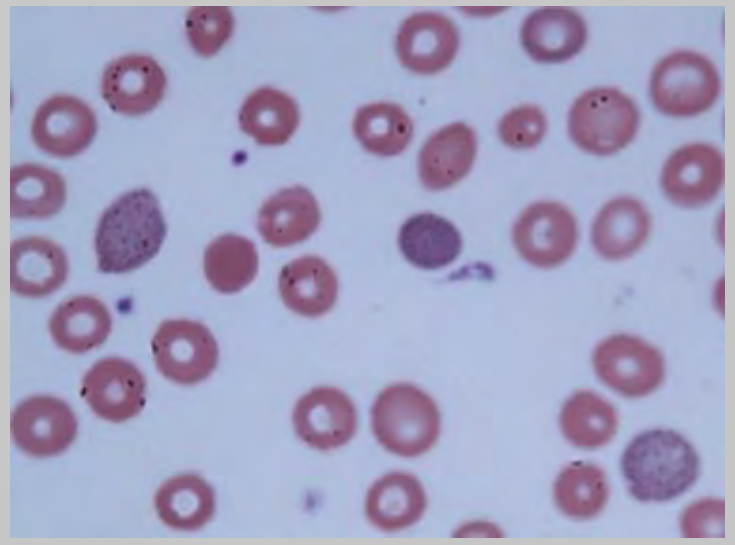
Meet NH

Abdominal pain, irritability, decreased "child's play"

Bands of increased metaphyseal density noted previously

Labs revealing anemia. Smear notes "basophilic stippling"





BLL = 85.9 mcg/dL

What therapies exist for the management of lead toxicity?

Dimercaprol 0%

Edetate calcium disodium 0%

Succimer 0%

All of the above 0%

Lead Poisoning

- Each year, approximately 1 million people die from lead poisoning
- Lead exposure is estimated to account for 21.7 million years lost to disability and death worldwide, due to long-term effects on health
- 1 in 3 children have blood lead concentrations greater than 5 mcg/dL

World Health Organization, 2022.
Goldfrank's Toxicologic Emergencies, 11e. 2019.

Sources of Lead Exposure

https://www.cdc.gov/nceh/lead/prevention/sources

Lead Toxicity

Dixon Ticonderoga Recalls Creativity Street Children's Assorted Craft Buttons Due to Violation of Federal Lead Content Ban

Investigation of Elevated Lead Levels: Cinnamon Applesauce Pouches (November 2023)

Do not eat, sell, or serve multiple brands of recalled apple cinnamon fruit pouches. FDA's investigation is ongoing.

Nazzaro Recalls Children Bowling Pin Sipper Cups Due to Risk of Lead Poisoning

Clinical Presentation

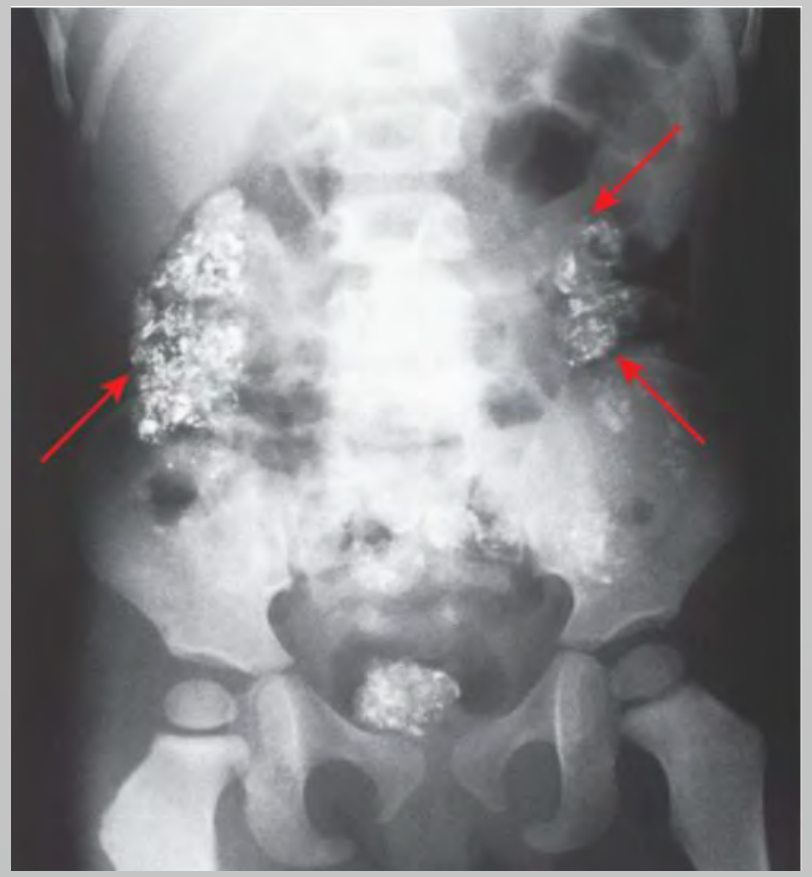
Typical Blood Lead Concentrations (mcg/dL)	Clinical Severity
20-69	**Mild** Fatigue, moodiness, hypertension, Burton lines, impaired cognition & growth
(≤49)*	
70-100	**Moderate** Headache, metallic taste, GI upset, myalgias, arthritis, hyperirritable behavior, decreased "child's play", intermittent vomiting, abdominal pain
50-70*	
>100	**Severe** Encephalopathy (coma, seizures), wrist/foot drop, abdominal colic, anemia, basophilic stippling, nephropathy, persistent vomiting
>70*	

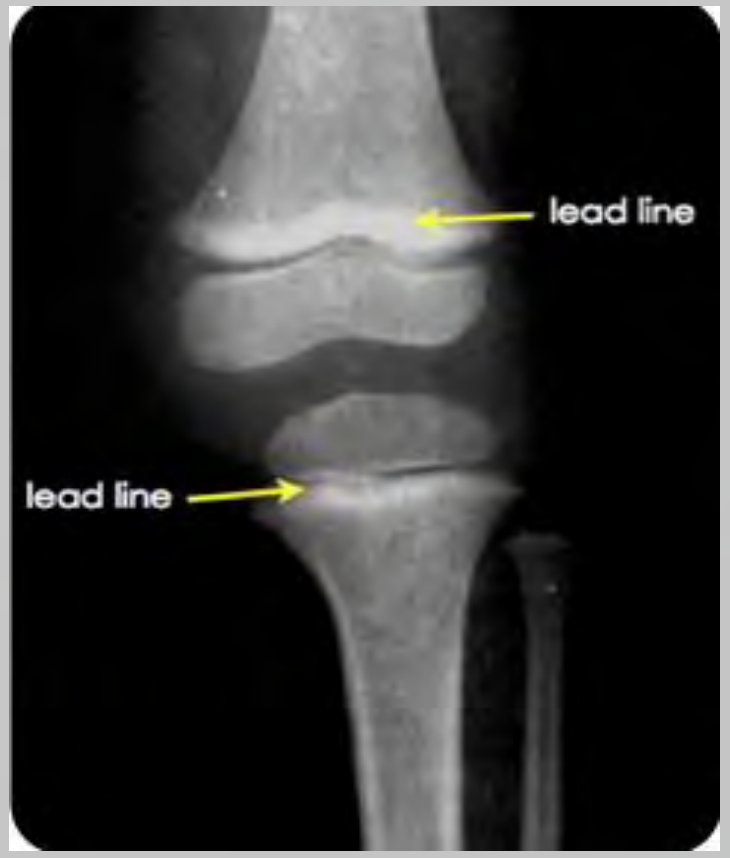
***Denotes pediatric thresholds**

Goldfrank's Toxicologic Emergencies, 11e. 2019.

Diagnosis

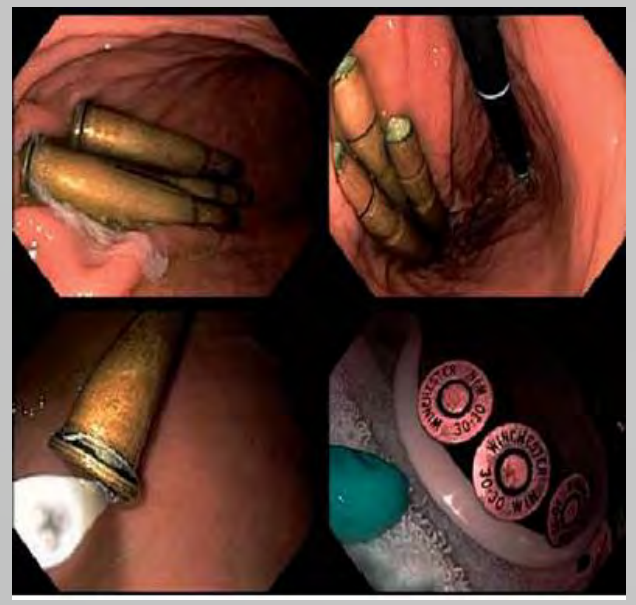
- Patient's history and clinical presentation
- Blood lead concentration
- Radiographic studies
- Pediatrics vs adults





Goldfrank's Toxicologic Emergencies, 11e. 2019.

Management of Lead Toxicity



- Limit exposure
- GI decontamination
- Supportive therapies
- Chelating agents

Chelating Agents Overview

Typical Blood Lead Concentrations (mcg/dL)	Clinical Severity	Chelating Agents
20-69	Mild	Usually not indicated
(≤49)*		
70-100	Moderate	Succimer or Edetate calcium disodium
50-70*		
>100	Severe	Dimercaprol + Edetate calcium disodium + Succimer
>70*		

*Denotes pediatric thresholds

Goldfrank's Toxicologic Emergencies, 11e. 2019.

Chelating Agents

- Dimercaprol
- Edetate calcium disodium
- Succimer

Dimercaprol

- Developed during World War II
- Also called British anti-Lewisite (BAL)
- Used in arsenic, gold, copper and mercury poisoning

Goldfrank's Toxicologic Emergencies, 11e.

Dimercaprol Shortage

- Shortage announced in May 2020
- Akorn Pharmaceuticals was the sole manufacturer

Dimercaprol

=

No longer available!

J Med Toxicol. 2021 Jul; 17(3): 321–322.

Chelating Agents

- Dimercaprol
- Edetate calcium disodium
- Succimer

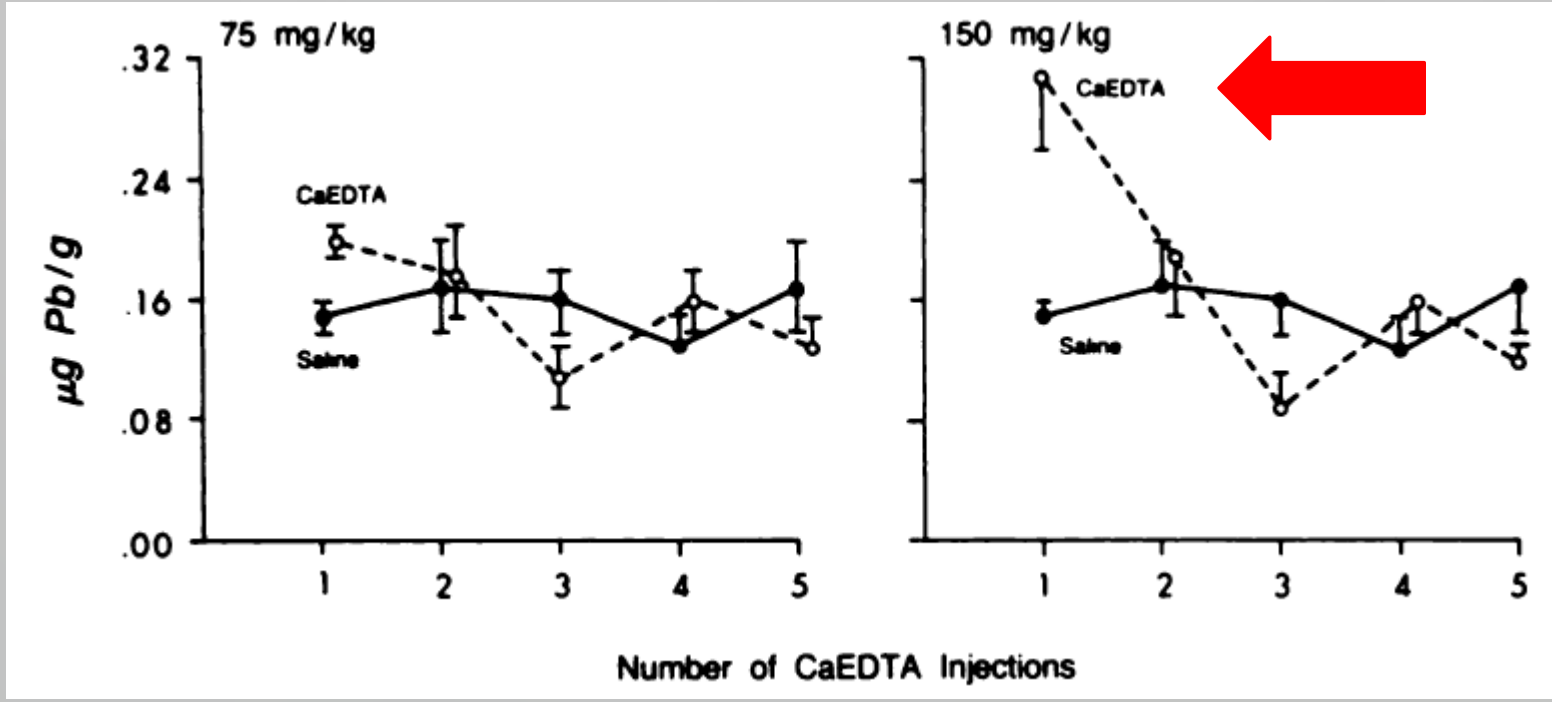
Edetate Calcium Disodium

Mechanism	Formation of nonionizing soluble complex with lead to be excreted in urine
Dose	<u>Encephalopathy:</u> 25 – 75 mg/kg/day (1000 – 1500 mg/m^2 /day) IV x 5 days (max 3000 mg/day)
Pearls	Can be administered as continuous infusion or in 2 – 4 divided doses Initial dose is started 4 hours after initiation of dimercaprol Treatment courses recommended to be repeated
Adverse Effects	Nephrotoxicity, malaise, fatigue, fever

Goldfrank's Toxicologic Emergencies, 11e. 2019.

Edetate Calcium Disodium

Mobilization and Redistribution of Lead Over the Course of Calcium Disodium Ethylenediamine Tetraacetate Chelation Therapy[1]



J Pharmacol Exp Ther. 1987;243(3):804-813.

Edetate Calcium Disodium

For brain, liver and kidney, wet tissue weights were recorded. After digestion with a 1:1 mixture of nitric and perchloric acids, samples were brought to a constant volume, and determination of tissue Pb content performed by graphite AAS (Hitachi 170-70). For each analysis, controls (blanks) and standards were carried in 0.7% nitric acid and calibration curves determined at the beginning and end of a sample run. Because extra tissue samples were not available, recoveries were based on standards carried through the digestion procedure, and resulting values were: 96 ± 9% for liver, 105 ± 5% for kidney and 110 ± 10% for brain.

- **Method no longer used**
- **Results disputed in other trials**
- **Risk vs benefit?**

In summary, this study utilized a sensitive stable Pb isotope tracer methodology to assess the effects of $CaNa_2EDTA$ chelation treatment on the reduction and redistribution of Pb in brain, blood, kidney, and bone tissues. Particular emphasis was placed on whether there occurred a significant redistribution of Pb into the brain following a single treatment of $CaNa_2EDTA$, as has been previously reported (Cory-Slechta *et al.*, 1987). Under the Pb exposure and chelation treatment regimens utilized here, there was no evidence of a measurable redistribution of Pb (as total Pb or labile ^{204}Pb tracer) into the brain after a single $CaNa_2EDTA$ dose. Further, $CaNa_2EDTA$ was not efficacious in measurably reducing brain or bone Pb levels, although brain levels of labile ^{204}Pb tracer were significantly reduced after 5 days of chelation. $CaNa_2EDTA$ treatment was effective in significantly reducing both blood and kidney Pb levels. Overall, these data substantiate the efficacy of $CaNa_2EDTA$ for reducing soft tissue Pb levels, but not total brain Pb, and they do not support concern for a transient increase in brain Pb levels with treatment (PDR, 1999).

J Pharmacol Exp Ther. 1987;243(3):804-813.
Appl Pharmacol. 1999;159(3):153-160.

Edetate Calcium Disodium Shortage

- Shortage announced in 2021
- BTG Pharmaceuticals and SERB temporarily imported non-FDA approved EDTA from France
- Wholesale acquisition cost: $3,500

Product Name	Strength	Dosage Form	Package Size	Lot Number	NDC Number
Calcium Edetate de Sodium Injection	500 mg/ampule	Injection, Solution (in ampules)	10 ampules	3081	50633-320-10

EDTA: Edetate Calcium Disodium
FDA: Food and Drug Administration

Edetate Calcium Disodium Shortage

- Rising Pharmaceuticals obtained FDA approval of EDTA and is now commercially available
- Wholesale acquisition cost: $32,000

EDTA: Edetate Calcium Disodium
FDA: Food and Drug Administration

Chelating Agents

- Dimercaprol
- Edetate calcium disodium
- Succimer

Succimer

Mechanism	Analog of dimercaprol, chelates lead to be renally excreted
Dose	10 mg/kg oral three times daily x 5 days, followed by 10 mg/kg twice daily x 14 days
Pearls	Oral capsule, can be opened and administered down feeding tube. **Pediatrics: chocolate pudding or syrup, applesauce.** Allow bottle to off-gas; round up. Switch to oral succimer after 5 days of IV Ca-EDTA Treatment courses recommended to be repeated
Adverse Effects	Nausea, vomiting, diarrhea, metallic taste, foul odor

EDTA: Edetate Calcium Disodium

Goldfrank's Toxicologic Emergencies, 11e. 2019.

NACCT Abstracts

235. Management of incidentally discovered massive bullet ingestion with associated lead toxicity

John DelBianco, Abigail Kerns and Matthew P. Stripp
Department of Emergency Medicine, Allegheny Health Network

275. A case of severe lead encephalopathy with cardiac arrest managed during a chelation shortage

Damilola Idowu[a], Zachary Gray[b], Matthew Stanton[c] and David Gummin[d]
[a]Department of Emergency Medicine, Division of Medical Toxicology, Medical College of Wisconsin; [b]Department of Pediatrics, University of Wisconsin School of Medicine and Public Health; [c]Froedtert and the Medical College of Wisconsin; [d]Wisconsin Poison Center

347. Plumbus still among us: a case report of lead encephalopathy presenting as status epilepticus in a pediatric patient

Trevor Cerbini[a], Iqra Kamal[b], Sophia Politis[a], Anh Tuyet Nguyen[a], Bruce Ruck[a], Howard Greller[a] and Diane Calello[a]
[a]Rutgers New Jersey Medical School; [b]Rutgers Health

357. Oral-only lead chelation therapy for severe lead toxicity in the United States

Karen Muschler[a], George Wang[b] and Laurie Halmo[b]
[a]Rocky Mountain Poison Center/Denver Health; [b]Children's Hospital Colorado/Rocky Mountain Poison Center

North American Congress of Clinical Toxicology (NACCT) 2023,
Clinical Toxicology, 61:sup2, 1-186

Lead Poisoning Treatment

Dimercaprol

- Prior standard of care treatment
- No longer being manufactured

Edetate calcium disodium

- Commercially available via Rising Pharmaceuticals
- Expensive
- Risk versus benefit of administration without dimercaprol

Succimer

- Commercially available
- Monotherapy option for mild to moderate toxicity
- Backbone therapy in severe toxicity

After being informed on current drug shortages, what initial therapy do you recommend for our patient?

Dimercaprol + edetate calcium disodium + succimer

0%

Edetate calcium disodium + succimer

0%

Succimer

0%

None of the above

0%

Lead Poisoning Key Points

Dimercaprol is no longer being manufactured; CaNaEDTA available but $$$

Chelator selection largely dependent on age, and clinical status

Succimer is widely available and can be used as monotherapy in the setting of drug shortages

EDTA: Edetate Calcium Disodium

Key Takeaways

Drug shortages affect a substantial number of agents critical in the management of poisoned patients

Communicate with your local Poison Control Center to assist in the management of acute toxicities

Pharmacists can assist in treating drug shortages to ensure safe and effective patient care

POISON Help 1-800-222-1222

Kentucky POISON Control Center of Norton Children's Hospital

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Emergency Medicine Clinical Pharmacy Specialists

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