MAYO CLINIC

POISONS AND ANTIDOTES

TOXICOLOGY IN THE HOSPITALIZED PATIENT

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DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIP(S) WITH INDUSTRY

- Nothing to disclose

REFERENCES TO OFF-LABEL USAGE(S) OF PHARMACEUTICALS OR INSTRUMENTS

- Narcan

I work in the ICU so most of the cases will be ICU oriented, but the same principles apply to any hospitalized patient

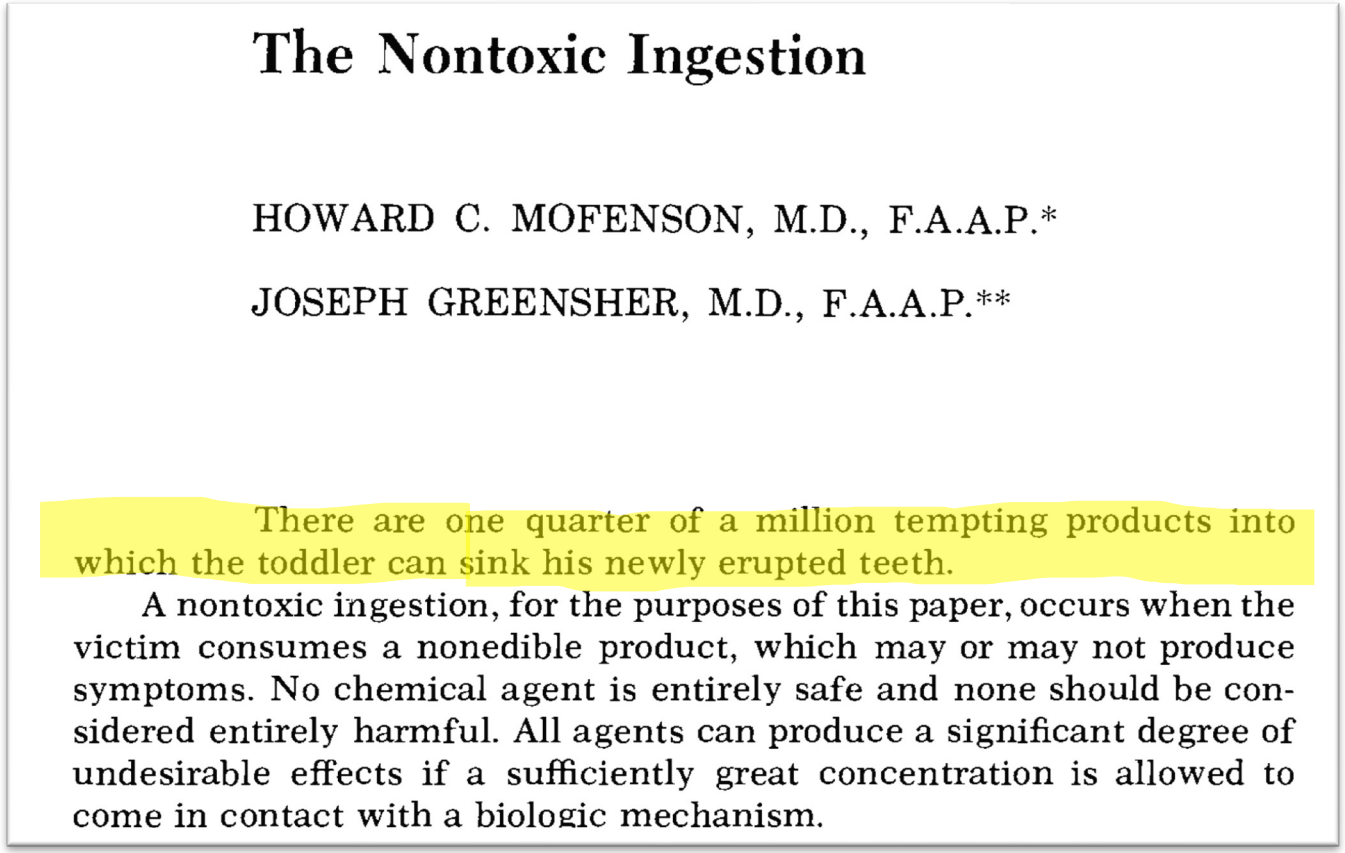
LEARNING OBJECTIVES

- Recognize the clinical features of commonly encountered toxidromes in the hospital
- Discuss treatment strategies for various intoxications
- Employ specific antidotes for select toxidromes and overdoses

TOXIDROMES:
WHAT ARE THEY?

- Blend of “toxic” and “syndrome”
- Coined in 1970 by Mofenson and Greensher [1]

- **Clinical Fingerprint**
  - Classic constellation of signs and symptoms due to toxins



The Nontoxic Ingestion

HOWARD C. MOFENSON, M.D., F.A.A.P.*

JOSEPH GREENSHER, M.D., F.A.A.P.**

There are one quarter of a million tempting products into which the toddler can sink his newly erupted teeth.

A nontoxic ingestion, for the purposes of this paper, occurs when the victim consumes a nonedible product, which may or may not produce symptoms. No chemical agent is entirely safe and none should be considered entirely harmful. All agents can produce a significant degree of undesirable effects if a sufficiently great concentration is allowed to come in contact with a biologic mechanism.

POISONINGS ARE COMMONLY ENCOUNTERED IN THE HOSPITAL

Some poisonings have specific antidotes

Many poisonings are treated with supportive care

BLUF: Treat the patient, not the toxin

"When in doubt, the best management generally consists of high-quality supportive care. Don't get too distracted by toxicological fanciness."

-EMCRIT: Approach to critically ill poisoned patient[2]

CASE #1

- 19yo M was arrested after a traffic violation and take to the local jail. After 1.5h he started having severe rigors and diaphoresis and EMS was called. He was able to talk initially and admitted to “one line a day” and his last use was at least 10h earlier. He became progressively less responsive. EMS took patient to the ED
- VS:

BP: 186/96 mmHg	HR 180 beats/min	RR 45/min
O2 sat: 98% on 10L	TEMP: 108F/42.2C	POC BG: 81 mg/dL

- On examination he was diffusely rigid and tremulous. Skin was hot and diaphoretic, pupils dilated, normal dolls eyes present, unresponsive to verbal or painful stimuli (GCS 3). Minimal UOP from foley

AUDIENCE QUESTION:

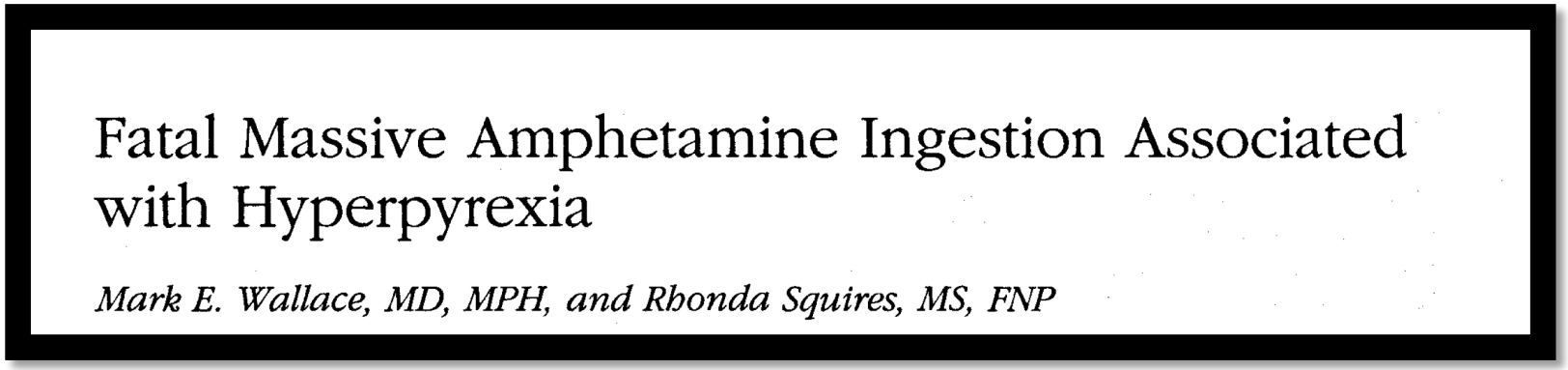
WHAT TYPE OF TOXIDROME IS THE PATIENT EXPERIENCING:

- A. Cholinergic
- B. Sympathomimetic
- C. Opioid
- D. Sedative/Hypnotic

- Ice packs applied. Given Ativan and labetalol and D50. Saturations dropped to 63%, requiring intubation. Gastric lavage produced a string but no pill fragments. Sorbitol and activated charcoal were administered. Rectal examination negative for pill fragments or foreign bodies. No overt track marks.
- CXR, CT head negative. ECG with sinus tachycardia.
- Admission Lab values: “essentially normal”; ABG: metabolic acidosis
- Transferred to ICU. His cell-mate had reported that the patient stated he ingested 8 “balls” (8g) of methamphetamine to avoid detection
  - Serum amphetamine level: 3,500ng/mL (3.5mg/L)

- Clinical Course:
  - Hyperthermia: Dantrolene (>104F), cooling measures, paralytic
  - Rhabdomyolysis, acute liver failure (AST>4K), acute kidney injury requiring dialysis
  - Multiple cardiac arrests, continued to spike fevers
  - Died from asystolic cardiac arrest on HOD 16

- Diagnosis: **Amphetamine Overdose**


Fatal Massive Amphetamine Ingestion Associated with Hyperpyrexia

Mark E. Wallace, MD, MPH, and Rhonda Squires, MS, FNP

SYMPATHOMIMETIC TOXIDROME

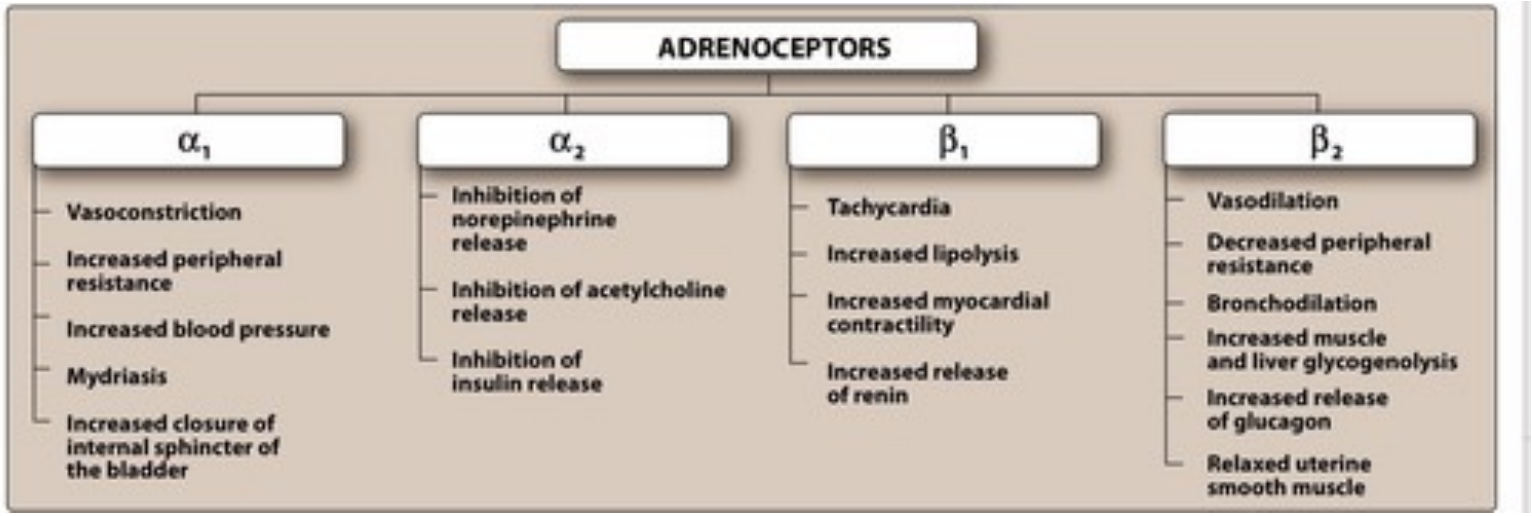
COMMON SYMPATHOMIMETIC DRUGS

- Caffeine
- Cocaine
- Ephedrine, pseudoephedrine
- Amphetamines: *Adderall, Ritalin, Concerta*
- Methamphetamines:
  - *Desoxyn (Rx)*
  - *Illicit: crystal meth, speed, Ice*
- MDMA *3-4 methylenedioxymethamphetamine*, a.k.a. “ecstasy” or “molly”
- Phentermine
- Cathinones: synthetic form – “bath salts”

Crystal meth from a patient’s purse

MECHANISM OF ACTION

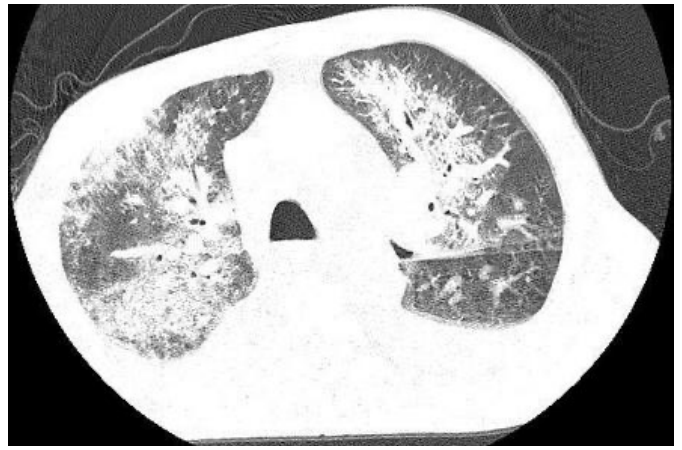
- Mimic the stimulation of the sympathetic nervous system – “Fight or flight” system
  - Directly activate adrenergic receptors *(α1, α2, β1, β2, β3)*
  - Indirectly by increasing NE/Epi levels
  - Mixed



SYMPTOMS

Box 2
Clinical manifestations of sympathomimetic intoxication

Central Nervous System	Cardiovascular	Pulmonary	Renal	Other
Agitation	Tachycardia	Hypoxia	Oliguria	Diaphoresis
Delirium	Hypertension	Tachypnea		Mydriasis
Hyperactivity	Dysrhythmia			
Psychosis				
Hyperthermia				



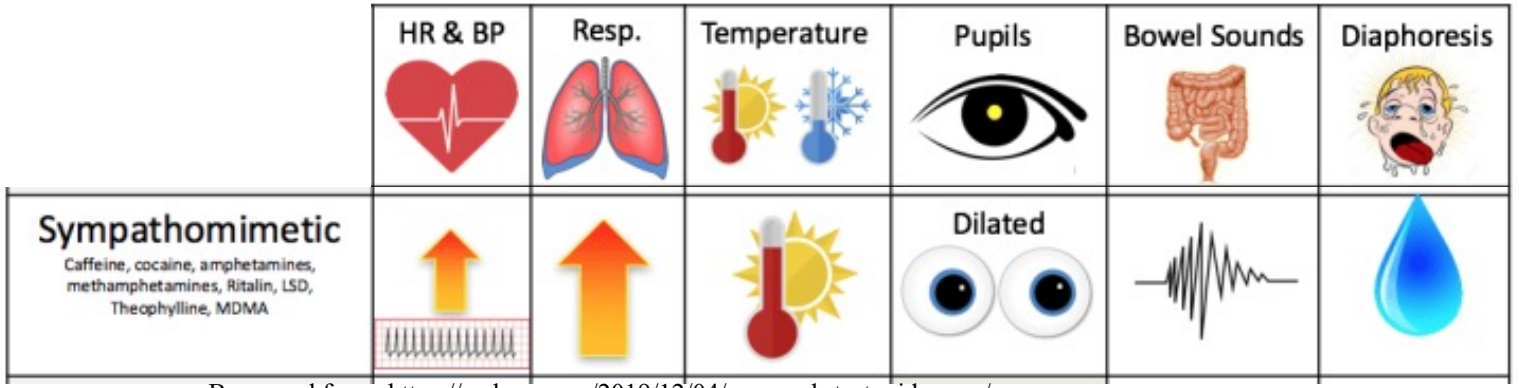
"Crack Lung" – Radiopedia.org

Table 1
Complications of sympathomimetic drugs by organ system

Central Nervous System	Cardiovascular	Pulmonary	Gastrointestinal	Renal	Musculoskeletal
Cerebral edema	Acute coronary syndrome	"Crack lung"	Bowel perforation	Acute kidney injury	Rhabdomyolysis
Hyperthermia	Aortic dissection	Pneumonia	Ischemic colitis	Acute renal failure	
Intracranial hemorrhage	Dysrhythmias	Pneumothorax	Mesenteric ischemia	Renal infarct	
Seizures	Hypertensive emergency	Pulmonary edema			
Stroke		Pulmonary hemorrhage			

Brown (2021), Crit Care Clin 37

HTN, Tachycardia, pupillary dilation, Hyperthermia, diaphoresis, hyperreflexia, agitated delirium → Coma



Borrowed from: https://wchcmr.org/2019/12/04/approach-to-toxidromes/

DIAGNOSIS

- Clinical history
- Standard labs
  - Electrolytes, CBC, coags
  - CK – *risk for rhabdomyolysis?*
  - LFTs
  - Troponins
  - Tylenol, salicylate levels
- Drug Screen
  - (-) UDS does NOT rule out
  - Numerous “designer” sympathomimetics which will not be detected by standard screens

TREATMENT[3]

- Avoid serotonergic medications (Zofran, Reglan, valproate, fentanyl)
- **Hyperthermia** (>104F or >40C) → emergent management
  - *Can cause brain injury, rhabdomyolysis, DIC*
  - Agitation control, physical cooling
- **SYMPATOMATIC MANAGEMENT**
  - **Hypertension/Tachycardia** – IV infusions
  - **Agitation**
    - Antipsychotics: Olanzipine or droperidol
    - Benzos: Versed
  - **Seizure**
    - Benzos, Keppra
    - *Avoid phenytoin and Valproic acid*

Critical care

SEROTONIN SYNDROME

- Too much serotonergic neurotransmission
  - Many sympathomimetics have serotonergic activity
- Presentation
  - **AMS** (anxiety, delirium, seizure, coma)
  - **Sympathetic hyperactivity** (hyperthermia, HTN, tachycardia, mydriasis)
  - **Neuromuscular hyperactivity** (clonus, especially ankles, ocular clonus, ultimately rigidity)
- Tx:
  - Stop offending medications, high quality supportive-care
  - Treat/prevent hyperthermia
  - Treat agitation
  - Medications: Cyproheptadine, precedex, benzos

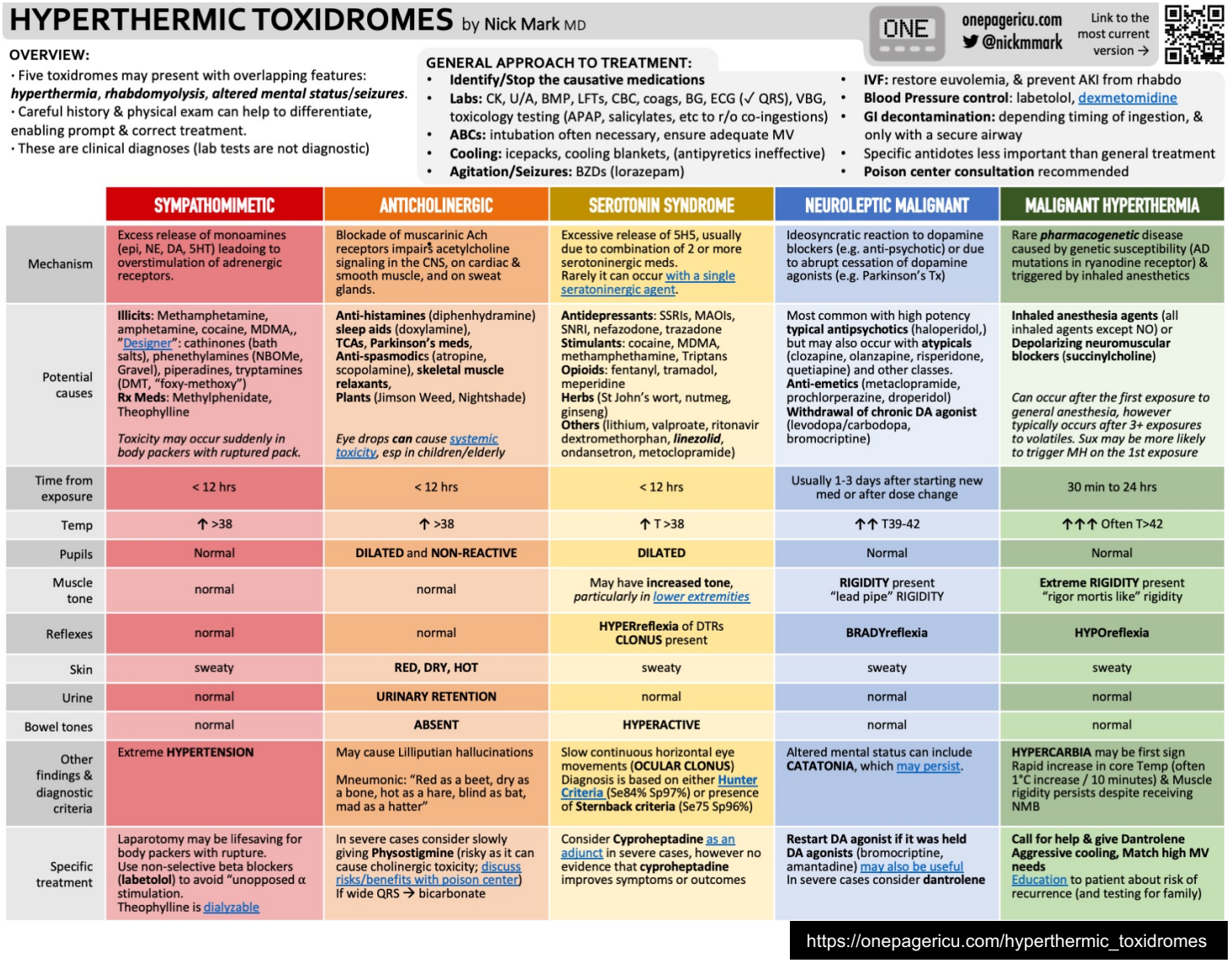
Celexa
Prozac
Lexapro
Paxil
Zoloft
Trazodone
Mirtazapine
Zofran
Reglan
Valproic Acid
Lamictal
Linezolid
Methylene Blue
St John's Wort

HYPERTHERMIC TOXIDROMES

Differential Diagnosis:

- Sympathomimetic Hyperthermia
- Anticholinergic
- Serotonin Syndrome
- Neuroleptic Malignant Syndrome
- Malignant Hyperthermia
- *Uncoupling syndrome*

ICU One Pager:



HYPERTHERMIC TOXIDROMES by Nick Mark MD

ONE onepagericu.com @nickmmark Link to the most current version →

OVERVIEW:

- Five toxidromes may present with overlapping features: ***hyperthermia, rhabdomyolysis, altered mental status/seizures.***
- Careful history & physical exam can help to differentiate, enabling prompt & correct treatment.
- These are clinical diagnoses (lab tests are not diagnostic)

GENERAL APPROACH TO TREATMENT:

- **Identify/Stop the causative medications**
- **Labs:** CK, U/A, BMP, LFTs, CBC, coags, BG, ECG (✓ QRS), VBG, toxicology testing (APAP, salicylates, etc to r/o co-ingestions)
- **ABCs:** intubation often necessary, ensure adequate MV
- **Cooling:** icepacks, cooling blankets, (antipyretics ineffective)
- **Agitation/Seizures:** BZDs (lorazepam)
- **IVF:** restore euvolemia, & prevent AKI from rhabdo
- **Blood Pressure control**: labetolol, dexmetomidine
- **GI decontamination:** depending timing of ingestion, & only with a secure airway
- Specific antidotes less important than general treatment
- **Poison center consultation** recommended

	SYMPATHOMIMETIC	ANTICHOLINERGIC	SEROTONIN SYNDROME	NEUROLEPTIC MALIGNANT	MALIGNANT HYPERTHERMIA
Mechanism	Excess release of monoamines (epi, NE, DA, 5HT) leadoing to overstimulation of adrenergic receptors.	Blockade of muscarinic Ach receptors impairs acetylcholine signaling in the CNS, on cardiac & smooth muscle, and on sweat glands.	Excessive release of 5H5, usually due to combination of 2 or more serotoninergic meds. Rarely it can occur with a single seratoninergic agent.	Ideosyncratic reaction to dopamine blockers (e.g. anti-psychotic) or due to abrupt cessation of dopamine agonists (e.g. Parkinson's Tx)	Rare ***pharmacogenetic*** disease caused by genetic susceptibility (AD mutations in ryanodine receptor) & triggered by inhaled anesthetics
Potential causes	**Illicits**: Methamphetamine, amphetamine, cocaine, MDMA,, "Designer": cathinones (bath salts), phenethylamines (NBOMe, Gravel), piperadines, tryptamines (DMT, "foxy-methoxy") **Rx Meds**: Methylphenidate, Theophylline *Toxicity may occur suddenly in body packers with ruptured pack.*	**Anti-histamines** (diphenhydramine) **sleep aids** (doxylamine), **TCAs, Parkinson's meds, Anti-spasmodics** (atropine, scopolamine), **skeletal muscle relaxants**, **Plants** (Jimson Weed, Nightshade) *Eye drops **can** cause systemic toxicity, esp in children/elderly*	**Antidepressants**: SSRIs, MAOIs, SNRI, nefazodone, trazadone **Stimulants**: cocaine, MDMA, methamphethamine, Triptans **Opioids**: fentanyl, tramadol, meperidine **Herbs** (St John's wort, nutmeg, ginseng) **Others** (lithium, valproate, ritonavir dextromethorphan, ***linezolid***, ondansetron, metoclopramide)	Most common with high potency **typical antipsychotics** (haloperidol,) but may also occur with **atypicals** (clozapine, olanzapine, risperidone, quetiapine) and other classes. **Anti-emetics** (metaclopramide, prochlorperazine, droperidol) **Withdrawal of chronic DA agonist** (levodopa/carbodopa, bromocriptine)	**Inhaled anesthesia agents** (all inhaled agents except NO) or **Depolarizing neuromuscular blockers (succinylcholine)** *Can occur after the first exposure to general anesthesia, however typically occurs after 3+ exposures to volatiles. Sux may be more likely to trigger MH on the 1st exposure*
Time from exposure	< 12 hrs	< 12 hrs	< 12 hrs	Usually 1-3 days after starting new med or after dose change	30 min to 24 hrs
Temp	↑ >38	↑ >38	↑ T >38	↑↑ T39-42	↑↑↑ Often T>42
Pupils	Normal	**DILATED** and **NON-REACTIVE**	**DILATED**	Normal	Normal
Muscle tone	normal	normal	May have **increased tone**, *particularly in lower extremities*	**RIGIDITY** present "lead pipe" RIGIDITY	**Extreme RIGIDITY** present "rigor mortis like" rigidity
Reflexes	normal	normal	**HYPERreflexia** of DTRs **CLONUS** present	**BRADYreflexia**	**HYPOreflexia**
Skin	sweaty	**RED, DRY, HOT**	sweaty	sweaty	sweaty
Urine	normal	**URINARY RETENTION**	normal	normal	normal
Bowel tones	normal	**ABSENT**	**HYPERACTIVE**	normal	normal
Other findings & diagnostic criteria	Extreme **HYPERTENSION**	May cause Lilliputian hallucinations Mneumonic: "Red as a beet, dry as a bone, hot as a hare, blind as bat, mad as a hatter"	Slow continuous horizontal eye movements (**OCULAR CLONUS**) Diagnosis is based on either Hunter Criteria (Se84% Sp97%) or presence of **Sternback criteria** (Se75 Sp96%)	Altered mental status can include **CATATONIA**, which may persist.	**HYPERCARBIA** may be first sign Rapid increase in core Temp (often 1°C increase / 10 minutes) & Muscle rigidity persists despite receiving NMB
Specific treatment	Laparotomy may be lifesaving for body packers with rupture. Use non-selective beta blockers (**labetolol**) to avoid "unopposed α stimulation. Theophylline is dialyzable	In severe cases consider slowly giving **Physostigmine** (risky as it can cause cholinergic toxicity; discuss risks/benefits with poison center) If wide QRS → bicarbonate	Consider **Cyproheptadine** as an adjunct in severe cases, however no evidence that **cyproheptadine** improves symptoms or outcomes	**Restart DA agonist if it was held DA agonists** (bromocriptine, amantadine) may also be useful In severe cases consider **dantrolene**	**Call for help & give Dantrolene Aggressive cooling, Match high MV needs** Education to patient about risk of recurrence (and testing for family)

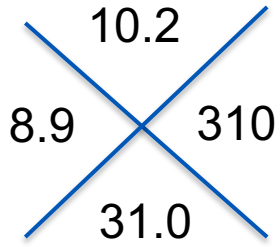
https://onepagericu.com/hyperthermic_toxidromes

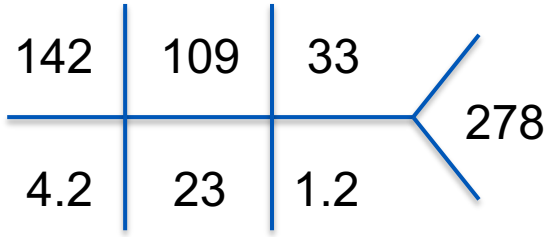
CASE #2

65yo F with PMHx scoliosis who is POD # 2 from a large corrective spine surgery. At 7:05pm day nurse notices the pt saturations are 86% and pt is very lethargic. Sternal rubbing patient and RRT called.

RRT RN arrives and places pt on NRB. HR 66, BP 110/76. Sternal rub, minimally responsive. Saturations still mid-80s. PCA pump next to pts hand.

AM labs:





- ICU team called, concerned about airway
- Night nurse reports patient was sleeping comfortably at last check. She had been taking scheduled oxycodone 10mg Q4h since last night at 8pm when cleared for PO.
- ICU team arrives.
  - Sats have improved to 91% on 15L NRB however pt minimally responsive (GCS 7- E1V2M4).
  - Pupils are 1mm.
  - Team concerned about mental status and possible need for intubation

- Narcan administered (0.4mg IV Push)
  - Patient opens eyes and starts shivering and and is nauseous
  - Mental status restored

- Diagnosis: **Opioid overdose**

	HR & BP	Resp.	Temperature	Pupils	Bowel Sounds	Diaphoresis
Opioid Morphine • Codeine • Tramadol • Heroin • Meperidine • Diphenoxylate • Hydromorphone • Fentanyl • Methadone • Propoxyphene • Pentazocine • DXM • Oxycodone • Hydrocodone	↓	↓	❄	Pinpoint	🚫	🌵

Source: https://wchcmr.org/2019/12/04/approach-to-toxidromes/

OPIOID TOXIDROME

OPIOID SYNDROME

- Opioids:
  - ALL substances that bind to opioid receptors
  - *Hydrocodone, hydromorphone, oxycodone, methadone, fentanyl*
- Opium isolated from the poppy plant
  - Opiates: Naturally derived narcotics found in opium *(morphine, codeine)*
- Receptors
  - Mu (OP_3), kappa (OP_2), and delta (OP_1)
    - Mu – sensation of euphoria; preferred for abuse
- "Classic" toxidrome:
  - **CNS and respiratory depression,** Miosis (pinpoint), dec GI motility

TREATMENT

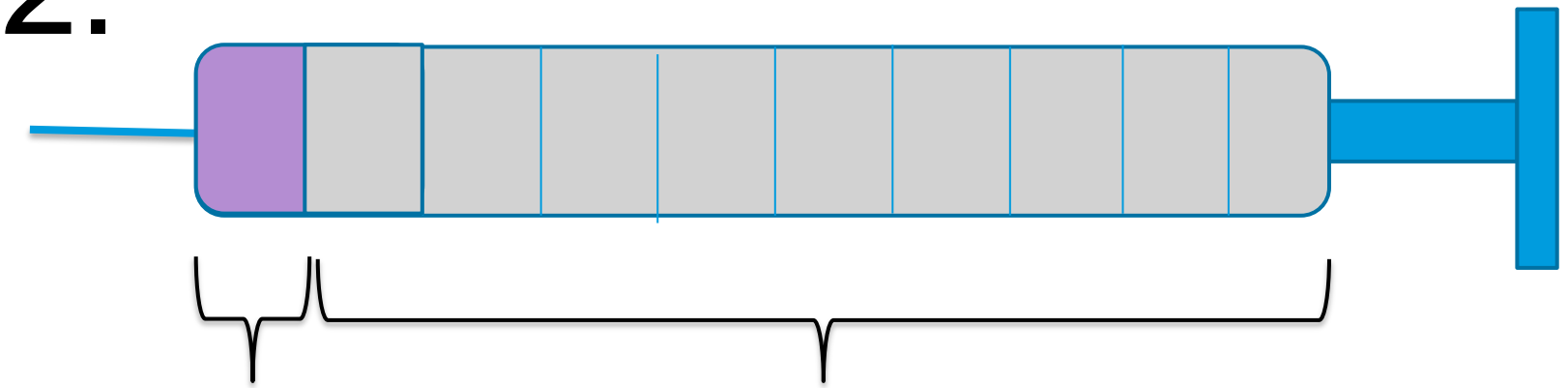
- **Opioid antagonist (**Naloxone, naltrexone)
- **Naloxone (Narcan):** **0.4** slow IV Push
  - Readministered at 2-3 min intervals
  - Desired endpoint => breathing, awake…
- **Observe patient for recurrent symptoms**
  - Narcan efficacy may only last 45 min
  - Narcan Drip[4]:
    - Infusion with 2/3 effective initial bolus
      - *(Bolus 0.3mg => infusion 0.2mg/hr)*

- CAUTION: Administration can precipitate opioid withdrawal symptoms

SIDENOTE – NARCAN IN THE POST-OP PATIENT

1.

2.



3.

Use the syringe you just created:

1cc = 0.04mg = **40mcg**

<u>Give 1 cc at a time (40mcg)</u>. Repeat every 1-3 min.

CASE # 3 -- CLINICAL VIGNETTES

55yoF, poor historian and hypochondriac who thinks she may have been told she has myasthenia gravis presents to ED with SOB, weakness and blurred vision. She is given edrophonium (Tensilon test) in the ED and develops extremely shallow respirations and hypoxia

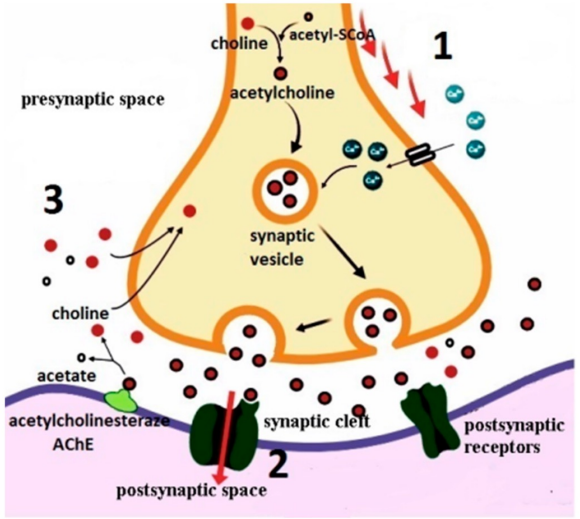
79yoF with Alzheimer's Dementia develops N/V, bradycardia to the 40s after inadvertently being given 50mg donepezil (Aricept) instead of usual 5mg dose*

40yoM migrant worker develops tremors, vomiting and diaphoresis spraying crops with pesticide for the past 3 days

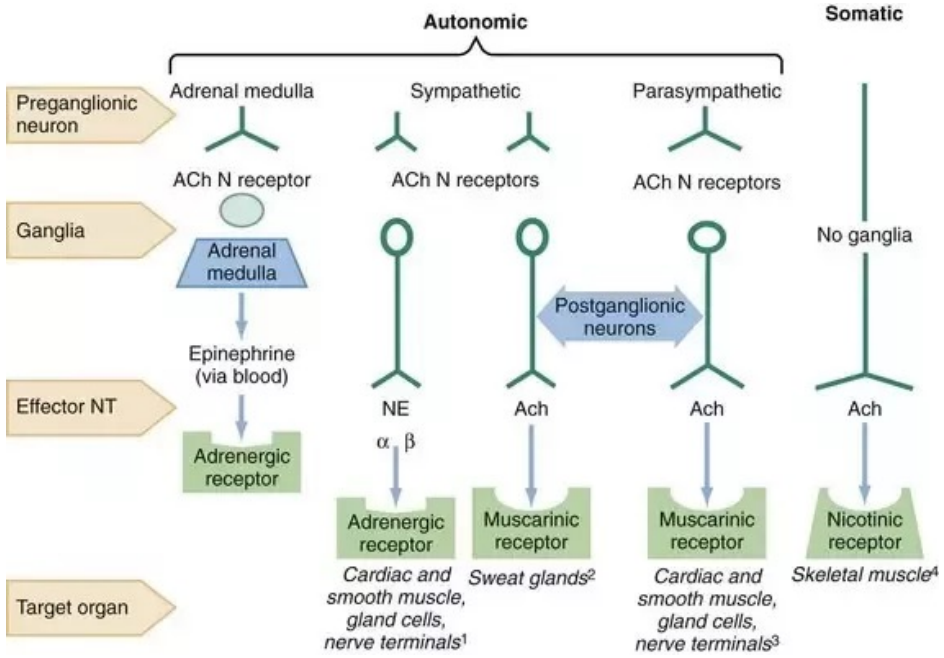
CHOLINERGIC TOXIDROME

CHOLINERGIC TOXIDROME

- **Cause:** Organophosphates, carbamate insecticides, cholinesterase inhibitors

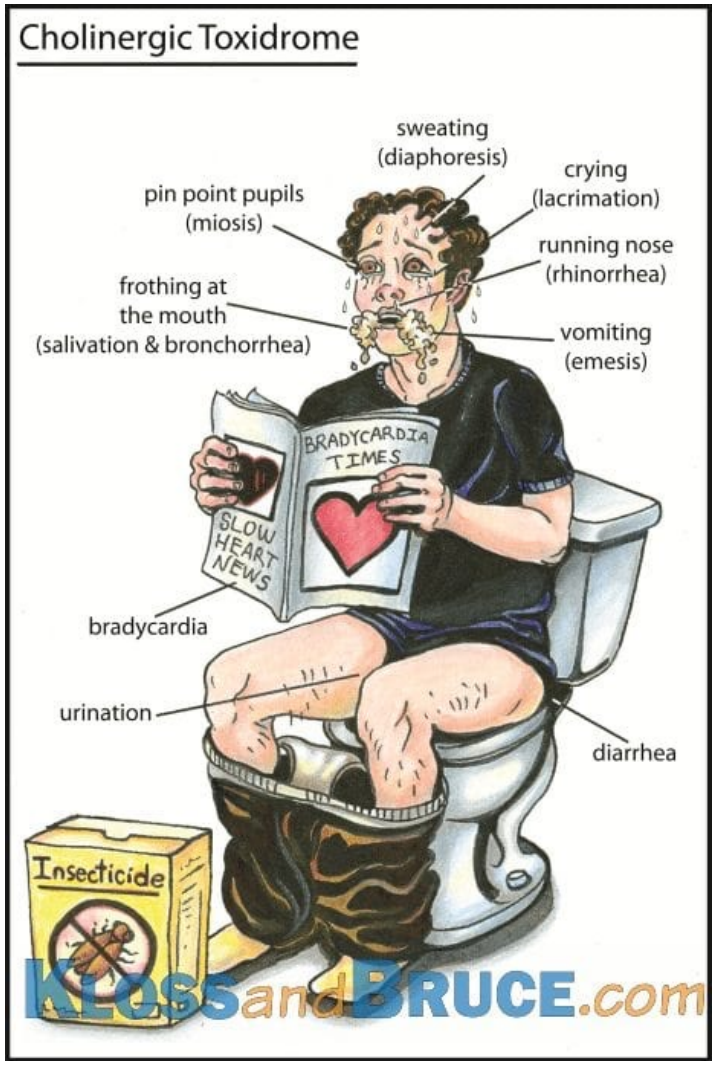


- **Pathophysiology**
  - **MOA: Acetylcholinesterase (AChE) inhibitors**
    - *AChE normally breaks down ACH in the synaptic cleft*
    - Organophosphates, carbamate insecticides are **AChE Inhibitors** => ACH not broken down => excessive ACH stimulation



CHOLINERGIC TOXIDROME

- **Symptoms**
  - **SLUDGE**
    - Salivation, lacrimation, urination, diarrhea, GI upset, emesis
  - **DUMBELLS**
    - Diaphoresis, urination, miosis (pinpoint) bronchorrhea/ bronchoconstriction, emesis, lacrimation, salivation
- **Severe poisonings:**
  - Resp failure: severe bronchospasm, bronchorrhea
  - Cardiovascular collapse: bradycardia
  - Seizures
  - fasciculations => flaccid paralysis



TREATMENT[5]

- ABCs
  - Intubation => Avoid succinylcholine *(prolonged paralysis)*
  - Clothing removed and discarded, skin wiped down
- **Atropine**
  - Direct antidote, can cross BBB
  - Muscarinic receptor antagonist → Antagonizes effects of excess ACH *(bronchorrhea, bradycardia, bronchoconstriction, etc)*
  - Dose: 2mg every 5 minutes until pulmonary symptoms improve
    - *Tachycardia is not a contraindication*
- Organophosphate poisoning
  - Pralidoxime chloride → reactivates AChE

CASE # 4

- 62yoM, history of HFrEF (30%), COPD on 3L O2, AF, CAD, HTN. He was discharged 10d ago from admission for COPD exacerbation. P/w inc SOB despite trial of albuterol/steroid inhalers for one week.

- Medications: lisinopril, sacubitril/valsartan(Entresto), furosemide, metoprolol, digoxin

<u>VS:</u>

BP 96/63mmHg Pulse 103 bpm RR: 25 Temp 96.5F

Sats: 88% on 3L

Exam: chronically ill, thin, respiratory distress with tachypnea. Irreregurarly irregular HR, B/L lower extremity edema, skin cool

LAB WORK

- K – 8.1mmol/L
- Phos – 12.7 mg/dL
- Mag – 3.5 mg/dL
- BUN – 124 mg/dL
- Cr – 3.84 mg/dL

- Hgb – 9.0 g/dL
- HCT – 28%
- WBC – 16K

- BNP – 5647 pg/mL
- Digoxin – 2.65 ng/mL

- ABG – WNL
- Troponin – WNL
- TSH – WNL
- Corsisol – WNL
- UA - WNL

CASE CONTINUED

- Diagnosed with cardiogenic shock, acute renal failure due and digoxin toxicity
- Vasopressors initiated
- Hyperkalemia treated
- Digoxin antibody - 2 vials
- Cards, neph consulted – no dialysis
- HOD 2
  - Pressors d/c'd
  - Electrolytes normalized
  - Renal function improved – Cr 1.99 mg/dL

A Case of Digoxin Toxicity Due to Acute Renal Failure

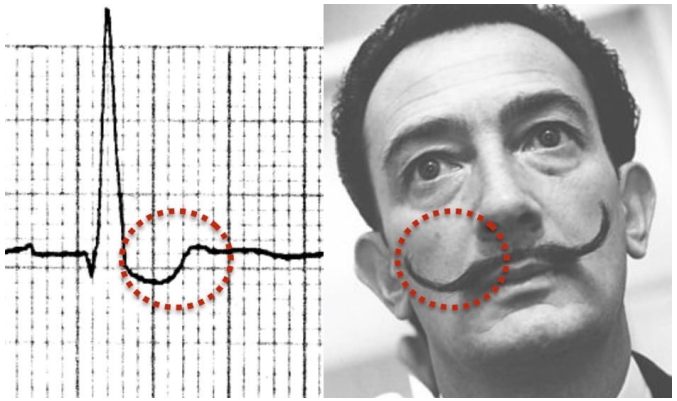
Monitoring Editor: Alexander Muacevic and John R Adler

Stephanie Digiovanni-Kinsley,[1] Brandon Duke,[1] Richard Giovane,[✉2] and Cameron Paisley[3]

DIGOXIN TOXICITY[6]

- MOA: Na/K pump inhibited → increased intracellular Na+ and increased extracellular K+
  - 1. hyperkalemia
  - 2. secondary mechanisms inc intracellular calcium → inc inotropy → inc vagal tone → in AF this decreases conduction rate through AV node → slows ventricular rate (bradycardia)
- Excretion:
  - Renal → AKI is big cause of toxicity
  - **Not dialyzable** (molecule too large)

- **Symptoms**
  - Arrhythmia – bradycardia, AF with a block. Ventricular arrhythmias
    - Scooped ST segment with ST depression
  - GI symptoms
  - Neuro – delirium, fatigue, visual changes
- **Digoxin Levels**[6]
  - 0.5-2 ng/ml; *chronic out-pt 0.5-1 ng/mL*
  - Worrisome:
    - Chronic intoxication: >4 ng/ml
    - Acute intoxication: >10 ng/ml
- Important!! Toxicity can occur with mild elevations!
- Serum digoxin levels don't correlate well with tissue levels and clinical toxicity!!



"Salvador Dali mustache"

Source: https://litfl.com/digoxin-effect-ecg-library/

TREATMENT[6]

- Indications
  - Significant dysrhythmia or HD instability
  - Hyperkalemia (>5.5)
- 2 brands : **Digibind and Digifab**
- Consult your pharmacist! *Multiple calculators/resources available*
  - Dosed in Vials
  - Vials contain 40mg of antibody fragments, which neutralize 0.5 mg
  - Different dosages for chronic vs acute ingestions
- **Words of CAUTION**
  - Calcium is CI for the management of hyperkalemia due to severe digoxin intoxication!
  - Cardiac pacing requires extreme caution

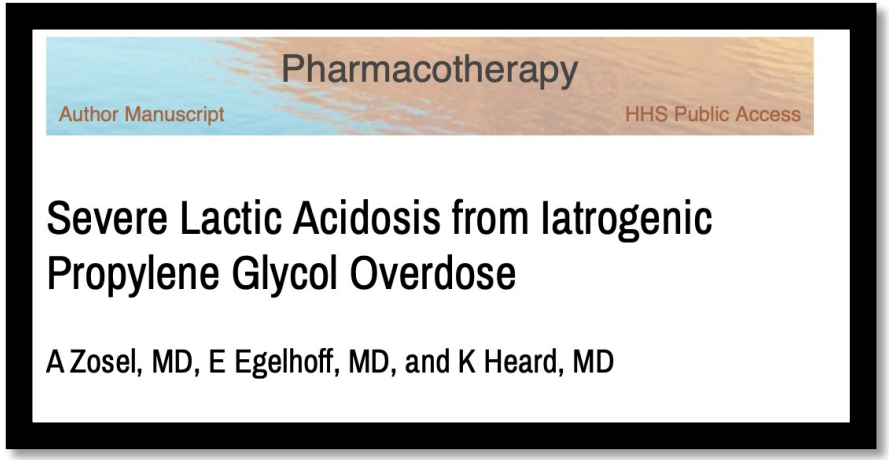
CASE # 5

- 50yoM presents to ED after cardiac arrest from choking on a large piece of meat. ROSC achieved. Transferred to the ICU for therapeutic hypothermia.
- Serum Ethanol level: 406 mg/dL
- After 12h he developed GTC, treated with IV lorazepam (Ativan)
- He was started on Ativan infusion. Over the next few hours he became hypotensive and acidemic (pH 6.9). Vasopressors were started.
- Staff member reviewing infusions and lorazepam was running at 2mg/minute instead of 2mg/hr (ordered rate)
  - Infusion stopped 10h after initiation

CASE CONTINUED

- Three hours later, pH remains 6.9, bicarbonate is 5meq/L
  - Sodium bicarb infusion started
  - Serum propylene glycol concentration: **659 mg/dL**
  - Lactate: 14.6 mmol/L
- Fomepizole administered (4h after), CRRT started (18h after)
- At 70h acidosis resolved, propylene glycol concentration: 45 mg/dL, and fomepizole was discontinued
- Ultimately he was found to have hypoxic brain injury and withdrawal of care was performed

PROPYLENE GLYCOL TOXICITY



- This patient had a 60-fold dosing error of Ativan
  - He received 500 gm of propylene glycol
- Propylene glycol is the solvent for IV lorazepam (Ativan) and Diazepam (Valium)
  - *Midazolam (versed) uses a different solvent*
- Normally propylene glycol is converted to lactic acid and cleared by the liver
- Treatment:
  - Fomepizole inhibits alcohol dehydrogenase (first step in metabolism of propylene glycol) → The metabolite **lactic acid is not formed**

SEDATIVE – HYPNOTIC TOXIDROME

SEDATIVE – HYPNOTIC TOXIDROME

- Common Drugs
  - **Benzos:** diazepam, lorazepam, midazolam
  - **Non-BZD GABA agonists ("Z" drugs):** zolpidem(Ambien), zaleplon (Sonata)
  - **Barbiturates:** Butalbital (Fiorcet), Thiopental
  - **Muscle relaxants:** Baclofen, carisoprodol (Soma), Methocarbamol (Robaxin)
- Symptoms:
  - CNS depression
  - Respiratory depression
    - More pronounced when co-ingestion with ETOH or other sedative
- Most cases of severe poisonings from attempted suicide

TREATMENT

- **Supportive Care**
- **Flumazenil[7]**
  - MOA: competitive antagonist on BZD receptor site
  - Effective antidote for BZDs, also "Z" drugs
  - Will not reverse effects of barbiturates
  - *Caution: Chronic BDZ users → can precipitate seizures*

Box 2
Sedating compounds for which Flumazenil is antidotal

Benzodiazepines
- Lorazepam
- Oxazepam
- Temazepam
- Clorazepate
- Alprazolam
- Clonazepam
- Diazepam
- Triazolam
- Estazolam
- Midazolam
- Chlordiazepoxide
- Meprobamate
- Flunitrazepam

Muscle relaxants
- Carisoprodol (Meprobamate)[a]
- Metaxalone
- Chlorzoxazone
- Methocarbamol

Nonbenzodiazepines
- Imidazopyridines
  - Zolpidem
- Pyrazolopyrimidines
  - Zaleplon
- Cyclopyrrolones
  - Zopiclone
  - Eszopiclone

Botanicals
- Uncaria hook (*Uncaria macrophylla*)
- Yokukansan (*Uncaria rhynchophylla*)

Ref: Assessment and Management of Toxidromes in the Critical Care Unit – J.J Rasimas

CASE # 6

36yo F with PMHx of hypothyroidism on levothyroxine is brought to the ED via EMS with active seizures. Prior to presentation she got into an argument with her husband and one hour later he found her lethargic in a locked room.

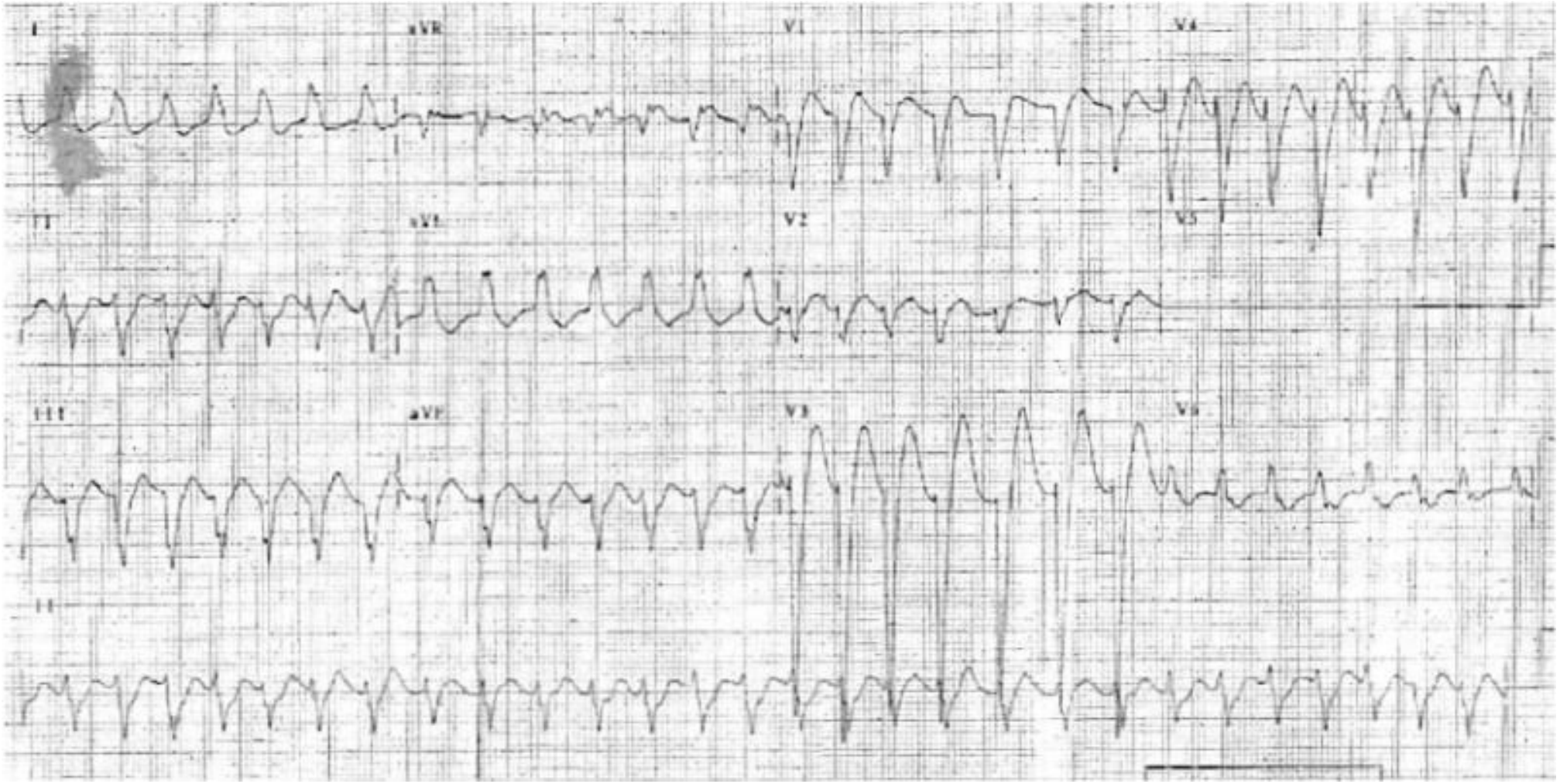
VS:

BP: 90/55 mmHg	HR 160 beats/min	RR 18
O2 sat: 99% on RA	TEMP: 99.8F	POC BG: 130 mg/dL

Interventions:

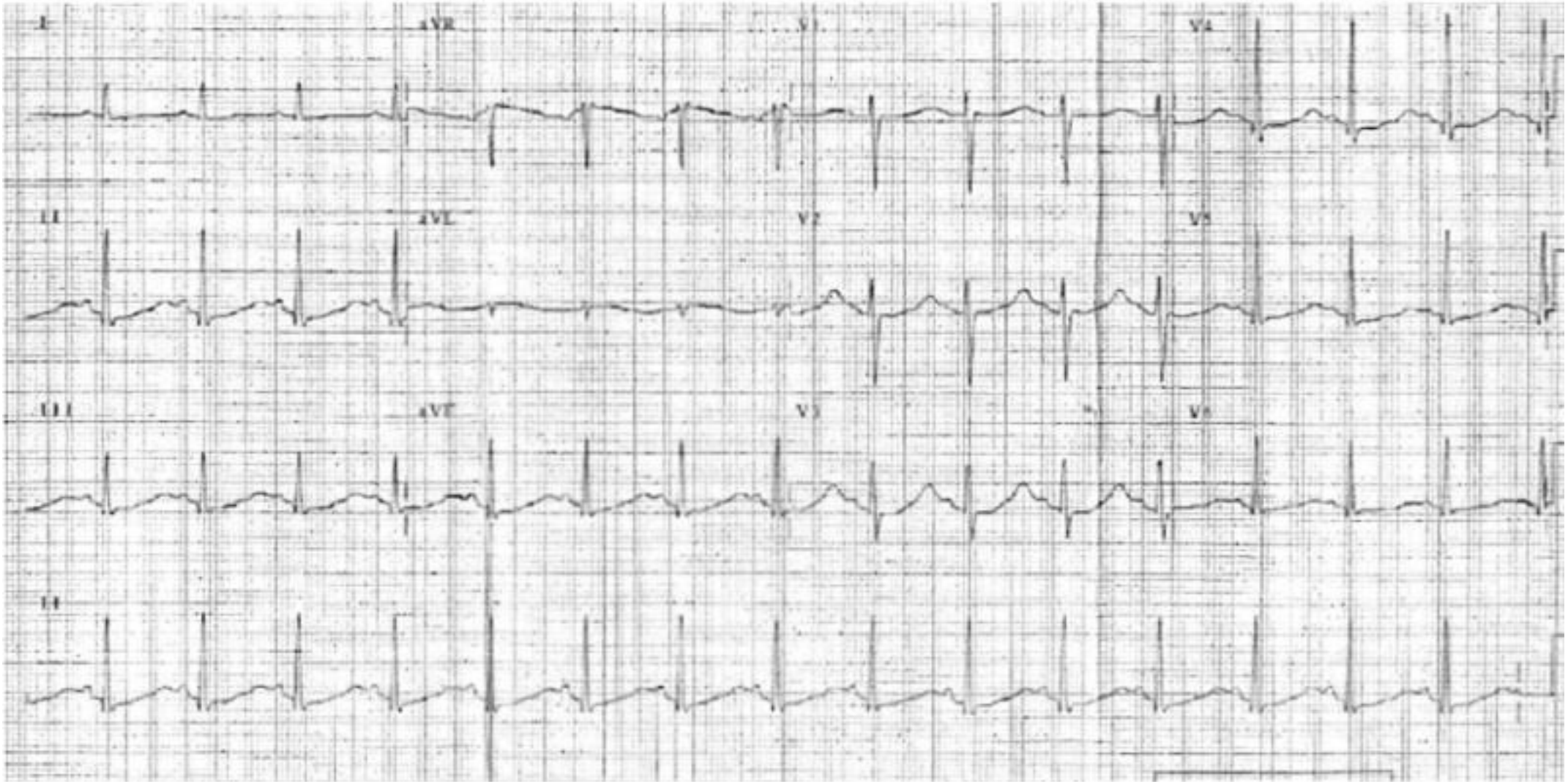
- 8mg IV Ativan given however GTC continued for 30 minutes
- Intubated and seizures stopped with propofol infusion
- ECG, labs obtained

INITIAL EGG



QRS: 127ms => 200 mEq of intravenous sodium bicarbonate was administrated

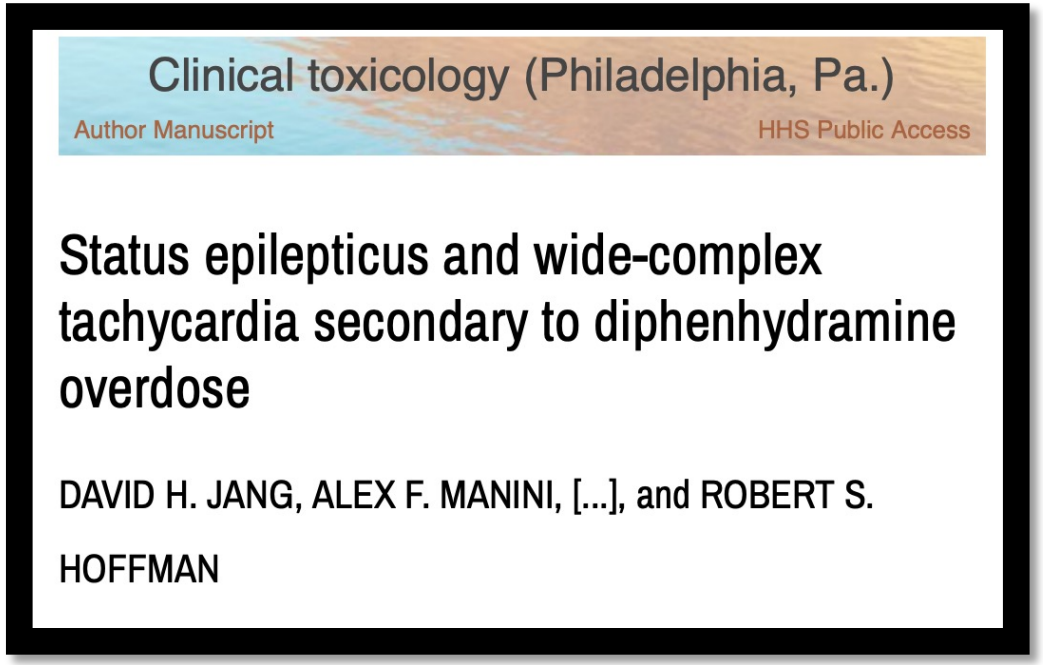
REPEAT ECG



QRS narrowed

COURSE CONTINUED

- Extubated HOD 2, neurologically intact
- Pertinent labs:
  - Serum diphenhydramine:
    - **1200 ng/mL** (9-120 ng/mL)
  - Tricyclic screen: negative
- Diagnosis: **Diphenhydramine Overdose**
  - Ingestions greater than 1-1.5g: delirium, seizures, coma, and death
  - Sodium channel blockade => widened QRS



ANTICHOLINERGIC TOXIDROME

ANTICHOLINERGIC MEDICATIONS ARE COMMON!

Anticholinergics:

- Atropine, Glycopyrrolate
- **Antispasmodics:** oxybutynin
- **IBS:** Dicyclomine, hyoscyamine
- Scopolamine
- **Parkinson's:** Benztropine, trihexyphenidyl

Anticholinergics with Sodium-channel blocking effects:

- **TCA:** amitriptyline, nortriptyline
- **Muscle relaxers:** cyclobenzaprine (Flexeril), orphenadrine (Norflex)
- **Parkinson's:** Amantadine
- **Antipsychotic:** Chlorpromazine(Thorazine), Quetiapine (Seroquel)
- **1st gen Antihistamines:** diphenhydramine, chlorpheniramine

ANTICHOLINERGIC TOXIDROME

- **Pathophysiology:**
  - Anticholinergic agents **inhibit muscarinic receptors**

- **Symptoms:**
  - Anhidrosis, mydriasis (dilated), flushing, hyperthermia, delirium, urinary retention

    "Dry as a bone, blind as a bat, red as a beet, hot as a hare, mad as a hatter, full as a flask"

  - Agitation, tachycardia, carphology (picking movements), mumbling speech, hallucinations

TREATMENT

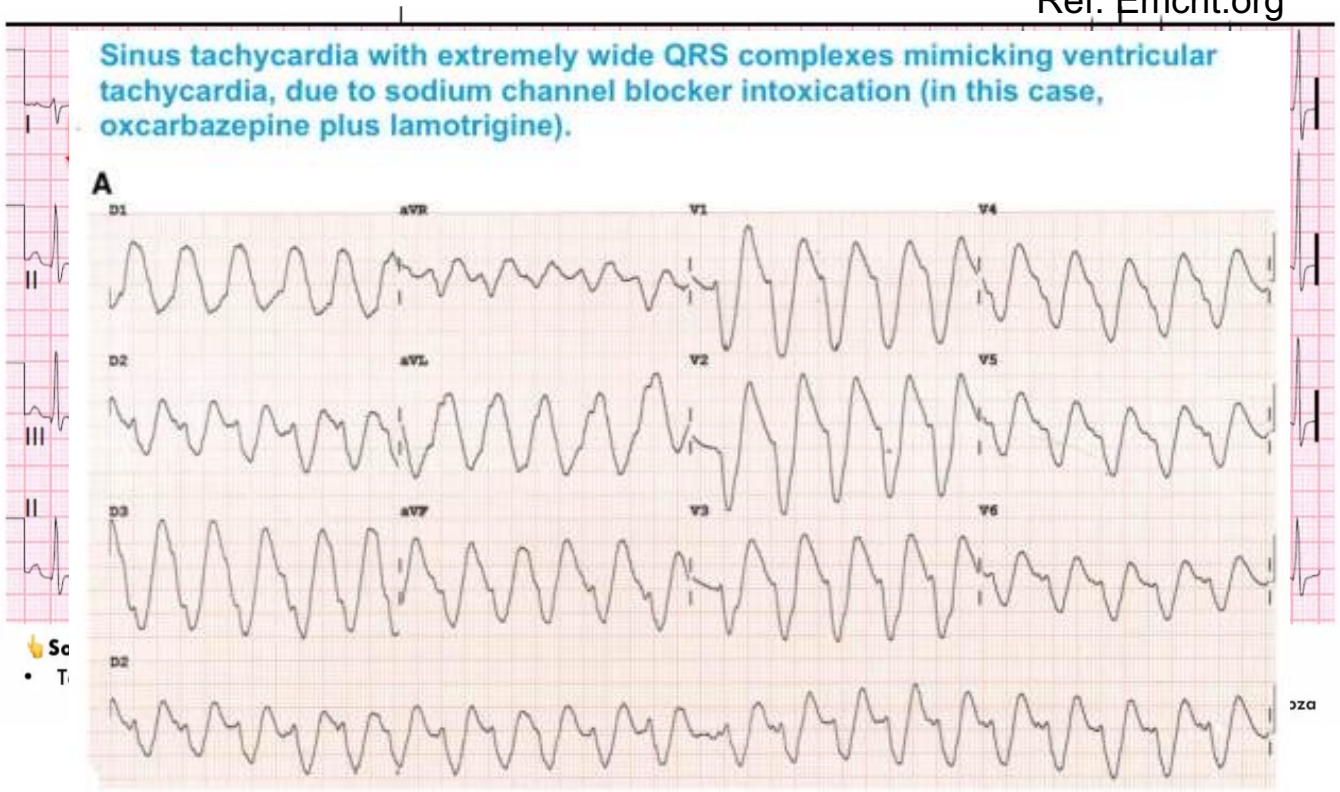
- **Remove offending agents, supportive therapy**

- **Physostigmine**
  - **Acetylcholinesterase inhibitor**
  - *Similar to neostigmine, however DOES cross BBB*
  - Heavily used in the 1980s, “coma cocktail, more recently fallen out of favor d/t adverse effects (bradycardic arrest)
  - Relative contraindications:
    - *QRS/QTC prolongation, Na-Channel blockade*
    - *Bradycardia*

TRICYCLIC ANTIDEPRESSANT TOXICITY[8]

- Pathophysiology:
  - Toxidrome is dominated by Sodium channel blockade
  - *Other effects: Anticholinergic properties (anticholinergic toxidrome); Vasodilate (block peripheral alpha-1 receptors); Somnolence (Central antihistamine activity); Seizures (Antagonize GABA receptors)*
- **Predictable ECG changes that can be lethal**
  - **Sodium channel blockade**:
    - Deep, terminal S-wave in Lead I
    - Terminal tall R-wave in aVR
    - **QRS widening**, >100ms

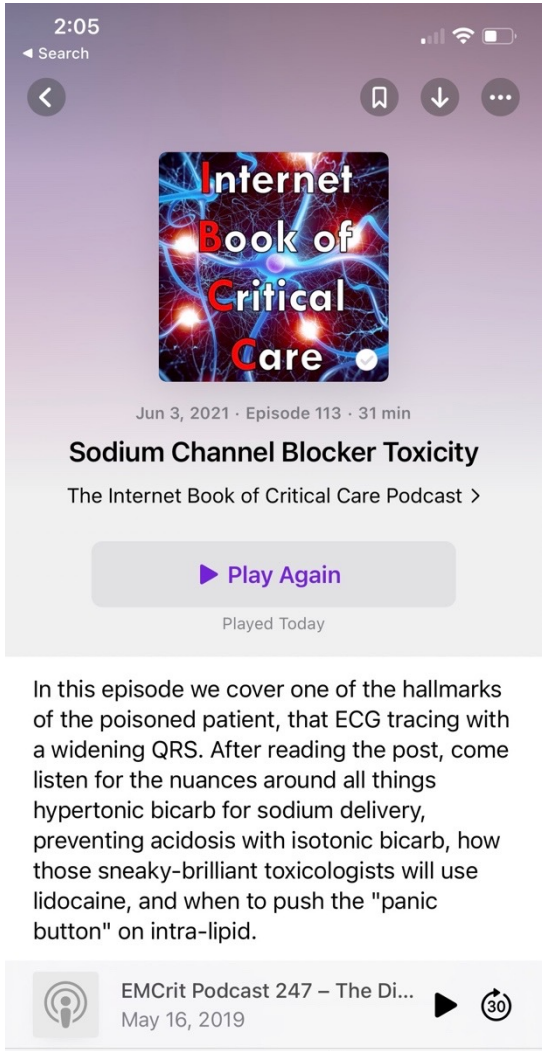
Ref: Emcrit.org



TREATMENT – TCA TOXICITY

- 1st line: Give **Hypertonic Bicarb** (code ampules) => repeat ECG
  - Improvement supports Na-channel blocker intoxication
- 2nd line: If recurrent ventricular arrhythmias: lidocaine
- 3rd line: lipid emulsions

- **Supportive care**
- Some literature supports Plasma Exchange (PLEX) for severe amitriptyline intoxication[9]



WHAT ABOUT ACTIVATED CHARCOAL?

- No controlled studies show reduced M&M[10]
- **May be helpful in select circumstances**
  - Within 2 h of ingestion
    - *Toxin still in stomach*
  - Large amount (enough to cause toxicity)
  - Awake, no risk of aspiration
    - *Do not intubate just to give AC*
- Formulations with and without sorbitol
- Dosing
  - **Optimal dose unknown**
  - 50g most common

CASE # 7

- 17 yoF presents with suicide attempt after infesting 97 tablets of her mother's 40mg propranolol tablets 1 hour prior. On arrival, lethargic and HR 75. Within minutes has two GTC and HR dropped to the 40s however hypotensive and no pulse dopplerable.
- CPR initiated. Intubated. Atropine, Narcan, calcium, bicarb, dopamine infusion with little to no effect.
- After 40 minutes, isoproterenol infusion transiently increased pulse to 80 with SBP 60s. NGT lavage revealed no pill fragments. Activated charcoal, Mg citrate was administered (50 minutes).
- At 1hr, given 2mg glucagon IV. SBP improved from 50 to 100 mmHg
  - Continued on glucagon, isoproterenol and dopamine infusions

CASE CONTINUED

- Continued to have intermittent seizures
- 10h mark began weaning chronotropic drips
- 18h post injection glucagon d/c'd. BP stabilized
- D/c'd to psychiatric unit

Case Reference: https://www.annemergmed.com/article/S0196-0644(85)81081-7/pdf

BB & CCB OVERDOSE[11]

- **Symptoms**
  - Bradycardia, HOTN, delirium, seizure
  - Hypo- or Hyper- glycemia
- **Treatment:**
  - Activated Charcoal – *w/in 2h*
  - Whole bowel prep – golytely infusion
    - *Prior to symptom (shock) onset*
    - *Glucagon will SLOW the gut ➔ not ideal to use both*
  - Beta blocker toxicity: Glucagon
  - Calcium Channel Blocker toxicity: Calcium

- **Glucagon**
  - Frequent emesis ➔ Caution!
  - Loading dose – 5mg IV over 5 min
  - If HD improvement → continuous infusion at effective dose (ex. 5mg/hr)
- **Calcium**
  - 1G CaCl or 3G CaGluconate, slow push over 5 minutes
    - Every 10-20 minutes, up to 3 doses
- **Atropine**
  - Often little to no response
  - 1mg IVP every 3 minutes, up to 3 doses
- Insulin: *Hyperinsulinemic euglycemia*
  - ***Rescue therapy*** *for cardiogenic shock. MC in CCB toxicity*
- Transvenous pacing tends to have poor results
  - *Myocardium is the problem, not the conduction system*

SUMMARY OF ANTIDOTES[12]

Assessment and Management of Toxidromes in the Critical Care Unit

J.J. Rasimas, MD, PhD, FAPM[a,*], Courtney M. Sinclair, BA[b]

Table 2
Emergency antidotes

Toxin	Antidote	Dosing
Acetaminophen	*N*-acetylcysteine (NAC)	IV *or* PO/NG: 140 mg/kg over 1 h, then 70 mg/kg over 1 h q4h × 5 doses; then reassess toxin clearance, PT/INR, and transaminases.[a]
Anesthetics (local) and some cardiotoxins	Lipid emulsion	IV: 1 mL/kg bolus of a 20% solution followed by 0.25 mL/kg per min infusion to maintain cardiovascular stability.[b]
Anticholinergics	Physostigmine	IV: 2 mg over 4 min in adolescents and adults, may repeat q1-2h prn; 20 μg/kg (1 mg maximum) in children, may repeat q1-2h prn.
Benzodiazepines and non-benzodiazepine hypnotics	Flumazenil	IV: 0.5 mg over 30 s in adults, Consider lower doses in children; may use 0.005–0.01 mg/kg at 0.2 mg/min rate in children; may repeat q30–60 min prn.
β-Adrenergic blockers	Glucagon[c]	IV: 50 μg/kg over 1–2 min up to 10 mg maximum followed by hourly infusion of half to full initial dose.
Calcium channel blockers	Calcium	IV: 1–2 g calcium (10% $CaCl_2$ solution) over 5 min in adults; 20–30 mg/kg per dose in children (may repeat).
	Insulin[c]	IV: 0.5–1 U/kg bolus followed by 0.5–1 U/kg per h continuous infusion.
	Glucose	IV: 25 g (as 50 mL of $D_{50}W$) in adults; 0.5 g/kg (as $D_{25}W$) in children (to maintain euglycemia in patients treated with insulin).
Cyanide, hydrogen sulfide	Sodium nitrite	IV: 300 mg over 2–5 min in adults; 0.2 mL/kg over 2–5 min in children.
	Sodium thiosulfate	IV: 12.5 g bolus in adults; 0.5 g/kg bolus (maximum 12.5 g) in children.
	Hydroxocobalamin (preferred)	IV: 70 mg/kg over 15 min.
Digitalis glycosides	Digoxin immune Fab	IV: 10–20 vials over 30 min for acute empiric dosing, otherwise based on serum digoxin concentration if known.
Ethylene glycol, methanol	Fomepizole (preferred)	IV: 15 mg/kg over 30 min, then 10 mg/kg q12h × 4 doses, then 15 mg/kg q12h as needed until nontoxic.
	Ethanol	IV: 10 mL/kg of 10% vol/vol solution, then 1.5 mL/kg per h continuous infusion until nontoxic; double rate during dialysis.
Iron	Deferoxamine	IV: start 5 mg/kg per h continuous infusion and titrate to 15 mg/kg per h as tolerated, total daily dose 6–8 g.
Isoniazid, hydrazine, and monomethylhydrazine	Pyridoxine	IV: 5 g in adults; 1 g in children.

Lead	Dimercaprol (BAL) $CaNa_2$ EDTA Succimer (DMSA)	IM: 75 mg/m^2 q4h, first dose to precede edetate calcium disodium ($CaNa_2$ EDTA). Contraindicated if peanut allergic. IV: 1500 mg/m^2/d by continuous infusion. PO: 10 mg/kg q8h for 5 d, then q12 h for 14 d in adults; 350 mg/m^2 in children (same course).
Methemoglobin-forming oxidants	Methylene blue	IV: 1–2 mg/kg over 5 min with 30 mL fluid flush, may repeat 1 mg/kg once.
Methotrexate	Folinic acid (leucovorin)	IV: 100 mg/m^2 over 15–30 min q3–6h for several days with absence/resolution of bone marrow toxicity.
Neuroleptics	Bromocriptine Dantrolene	PO: 5 mg q12h increasing to effect, as high as 10 mg q6h. IV: 3–10 mg/kg over 15 min with oral doses of 25–600 mg/d to maintain response.
Opioids and centrally acting α2 agonists (eg, clonidine, guanfacine, tizanidine)	Naloxone	IV: Start 0.05 mg with repeat dosing every 15 s to reversal of respiratory depression and/or unconsciousness; once achieved, repeat the same total dose q1h prn. Higher doses (1–2 mg or more) may be useful in α2-adrenergic agonist toxicity.[7]
Organophosphates and carbamates	Atropine Pralidoxime (2-PAM)	IV: 1–2 mg doubled every 3–5 min until bronchorrhea resolves in adults; 0.03 mg/kg in children, similar titration. IV: 1–2 g over 30 min, then up to 500 mg/h in adults; 25–50 mg/kg over 30–60 min, then 10–20 mg/kg per h in children.[d]
Snakebite (rattlesnake, copperhead, cottonmouth)	*Crotalidae* Polyvalent Immune Fab	IV: 4 vials typical minimum first dose in normal saline. Scheduled and prn regimens are effective going forward.
Sulfonylureas	Octreotide	SC: 50 μg q6-12h in adults, 1.25 μg/kg (max 50 μg) q6h in children.
Tricyclic antidepressants (and related compounds with sodium channel blocking properties)	Sodium bicarbonate	IV: 50 mEq per dose to address acidemia and/or ECG signs of sodium channel blockade. For an isotonic solution to continue alkaline fluid resuscitation, mix 150 mEq $NaHCO_3$ (typically 3 ampules) and 40 mEq KCl in 1 L D_5W. Goal serum pH 7.5–7.55.
Valproic acid	L-Carnitine	Clinically ill: IV: 100 mg/kg (max 6 g) over 30 min, then 15 mg/kg q4h. Clinically well: PO: 100 mg/kg per d (max 3 g) divided q6h.

Abbreviations: D_5W, a solution of 5% dextrose in water; $D_{25}W$, a solution of 25% dextrose in water; $D_{50}W$, a solution of 50% dextrose in water; ECG, electrocardiogram; IM, intramuscular; INR, international normalized ratio; IV, intravenous; PO, by mouth; NG, nasogastric; prn, as needed; q, every; SC, subcutaneous.

[a] This is one of many N-acetylcysteine regimens in use in the United States. The best regimen to use in different clinical situations remains under investigation.

[b] Intravenous lipid emulsion has been used in patients critically ill from a variety of different toxins using varying regimens.

[c] Glucagon is still used as a diagnostic aid in beta-blocker poisoning, but has largely been supplanted by other agents, including high-dose insulin, for ongoing treatment.

[d] Use of pralidoxime in carbamate poisoning is controversial, as there is some concern for worsening muscular weakness.

SUMMARY

"When in doubt, the best management generally consists of high-quality supportive care. Don't get too distracted by toxicological fanciness."

-EMCRIT: Approach to critically ill poisoned patient[2]

- Include toxidromes and overdoses in your differential
- Be careful about the satisfaction of the search
  - Patients can take multiple drugs
  - Patients can have simultaneous injuries that require attention despite being intoxicated
- **Treat the patient, not the toxin**

REFERENCES

1- Mofenson HC, Greensher J. The nontoxic ingestion. Pediatr Clin North Am. 1970 Aug;17(3):583-90. doi: 10.1016/s0031-3955(16)32453-1. PMID: 5491430.
2- https://emcrit.org/ibcc/tox/
3 - https://emcrit.org/ibcc/symp/
4 – UpToDate
5 - Holstege CP, Borek HA. Toxidromes. Crit Care Clin. 2012 Oct;28(4):479-98. doi: 10.1016/j.ccc.2012.07.008. Epub 2012 Aug 27. PMID: 22998986.
6- https://emcrit.org/ibcc/dig/
7 - Rasimas JJ, Sinclair CM. Assessment and Management of Toxidromes in the Critical Care Unit. Crit Care Clin. 2017 Jul;33(3):521-541. doi: 10.1016/j.ccc.2017.03.002. Epub 2017 Apr 23. PMID: 28601133.
8- https://emcrit.org/ibcc/nacb/
9- Sari I, Turkcuer I, Erurker T, Serinken M, Seyit M, Keskin A. Therapeutic plasma exchange in amitriptyline intoxication: case report and review of the literature. Transfus Apher Sci. 2011 Oct;45(2):183-5. doi: 10.1016/j.transci.2011.07.015. Epub 2011 Aug 26. PMID: 21872530.
10 - https://www.uptodate.com/contents/gastrointestinal-decontamination-of-the-poisoned-patient
11- https://emcrit.org/ibcc/ccb/
12 Rasimas JJ, Sinclair CM. Assessment and Management of Toxidromes in the Critical Care Unit. Crit Care Clin. 2017 Jul;33(3):521-541. doi: 10.1016/j.ccc.2017.03.002. Epub 2017 Apr 23. PMID: 28601133.

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QUESTIONS?

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