Medications That Pose Serious Risks to Our Kids: What Every Pediatric Healthcare Provider Should Know

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Oklahoma Poison Center

Objectives

1. Examine current trends in pediatric medication overdose and exposures.
2. Identify medications that pose significant risks to children, including those most commonly involved in overdose cases.
3. Understand the mechanisms of toxicity for these high-risk medications and the clinical signs of overdose in pediatric patients.
4. Develop a comprehensive approach to managing pediatric medication overdoses and exposure, including key interventions, antidotes, and when to seek toxicology consult.

THE VERY FIRST POISON CENTER

- A 1952 American Academy of Pediatrics study revealed that more than 50% of childhood “accidents” in the US were the result of unintentional poisonings.
- Edward Press, M.D. & Pharmacist Louis Gdalman
- Created the first poison center in1953 in Chicago, Illinois

Poison Control Center Enhancement & Awareness Act

- **Passed in 1999**
- **Directs Health Resources and Services Administration (HRSA) to provide assistance to regional poison centers**
- **Establish America's Poison Centers (APC) as accrediting body**
  - 53 accredited poison centers
- **Establish nation-wide toll-free number (800-222-1222)**
- **Stabilize funding through federal grants**
  - Funding only awarded to accredited centers
    - Operational 24 hours/day, 365 days/year by certified specialists in poison information (CSPIs)
    - Medical Toxicologist Back-Up
    - Professional and public education

What is a Poison Center?

- Public & professional guidance for poisoning treatment
  - Avoidance of unnecessary medical intervention
- Drug information resource
- Toxicology Research
- Collection of epidemiologic information
- Emergency treatment advice in event of disaster
- Medical professional training

Toxico-surveillance

- Poison centers auto-upload data on poison exposures to the National Poison Data System (NPDS) every 9.5 minutes
- Allows for real-time detection of surveillance anomalies and events of public health significance
- NPDS data is monitored with anomaly detection software by both APC and the Centers for Disease Control (CDC)
- NPDS data also gets shared with key regulatory agencies such as:
  - Food and Drug Administration (FDA)
  - Drug Enforcement Agency (DEA)
  - Consumer Product Safety Commission (CPSC)
  - Environmental Protection Agency (EPA)

10 CERTIFIED SPECIALISTS IN POISON INFORMATION (CSPIS); 1 SPECIALIST IN POISON INFORMATION (SPI)

12 POISON INFORMATION PROVIDERS (PIPS)

1 ADMINISTRATIVE ASSISTANT

Managing Director:
Kristie Edelen, PharmD, DABAT

1 PUBLIC EDUCATOR

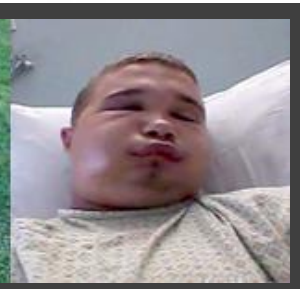
1 CLINICAL TOXICOLOGIST

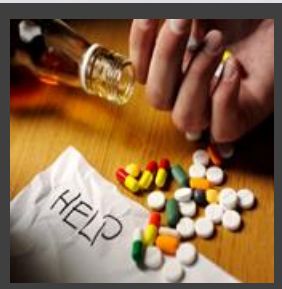
2 MEDICAL TOXICOLOGISTS

Medical Director:
William Banner, MD, PhD, DABMT

Associate Medical Director:
Claire Epperson, DO, DABMT

What Do We Deal With?





Oklahoma Poison Center Call Volume (2024)

- Total number of human exposures: 30,091
- Total number of animal exposures: 79
- Total number of confirmed non-exposures: 52
- Total number of informational calls: 4,692
- Total number of calls from all categories: 34,914
- Total number of follow-up calls: 30,593
- Total number of calls and follow-up calls: 65,507

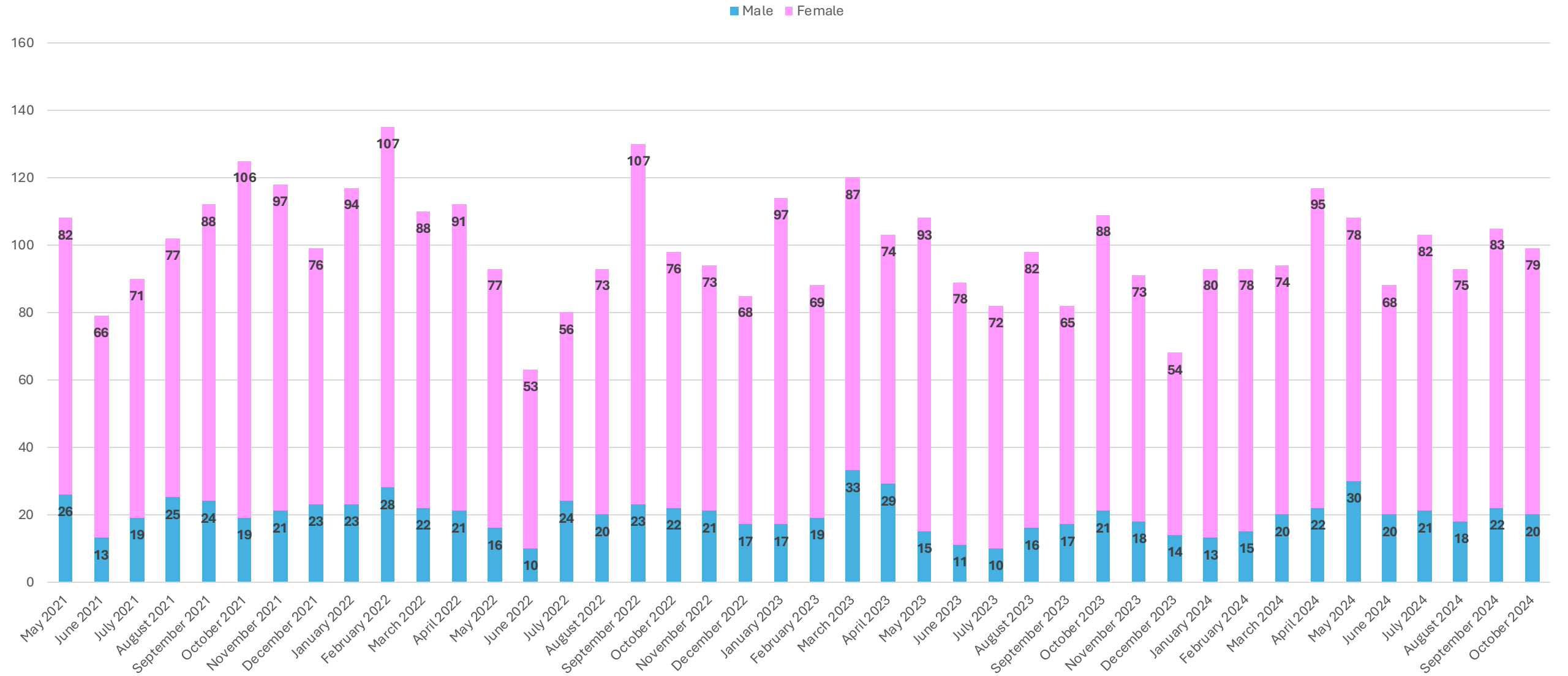
Pediatric Exposures (children ≤ 5 years of age)

- Total number of pediatric exposures: 13,994 (47% of all human exposure calls)
- Pediatric exposures to opioids: 66
- Pediatric exposures to marijuana: 264
- Pediatric exposures to other analgesics: 1,062
- Pediatric exposures to cold and cough preparations: 242
- Pediatric exposures to cleaning substances (household): 1,435
- Pediatric exposures to tobacco/nicotine/e-cigarette products: 302

The much bigger issue in our kids…

Intentional Self-Harm by Poisoning

Intentional Suspected Self-Harm Exposures Reported to the Oklahoma Poison Center By Month
12 – 18 years of age
May 2021 through October 2024



5 Teen Fatality Cases since May 2021

- Air Duster
- Bupropion/Acetaminophen
- Fentanyl
- Fentanyl/Methamphetamine
- Diphenhydramine

OKLAHOMA

POISON

CENTER

1-800-222-1222


Red Flag List: The Most Dangerous Drugs in Overdose

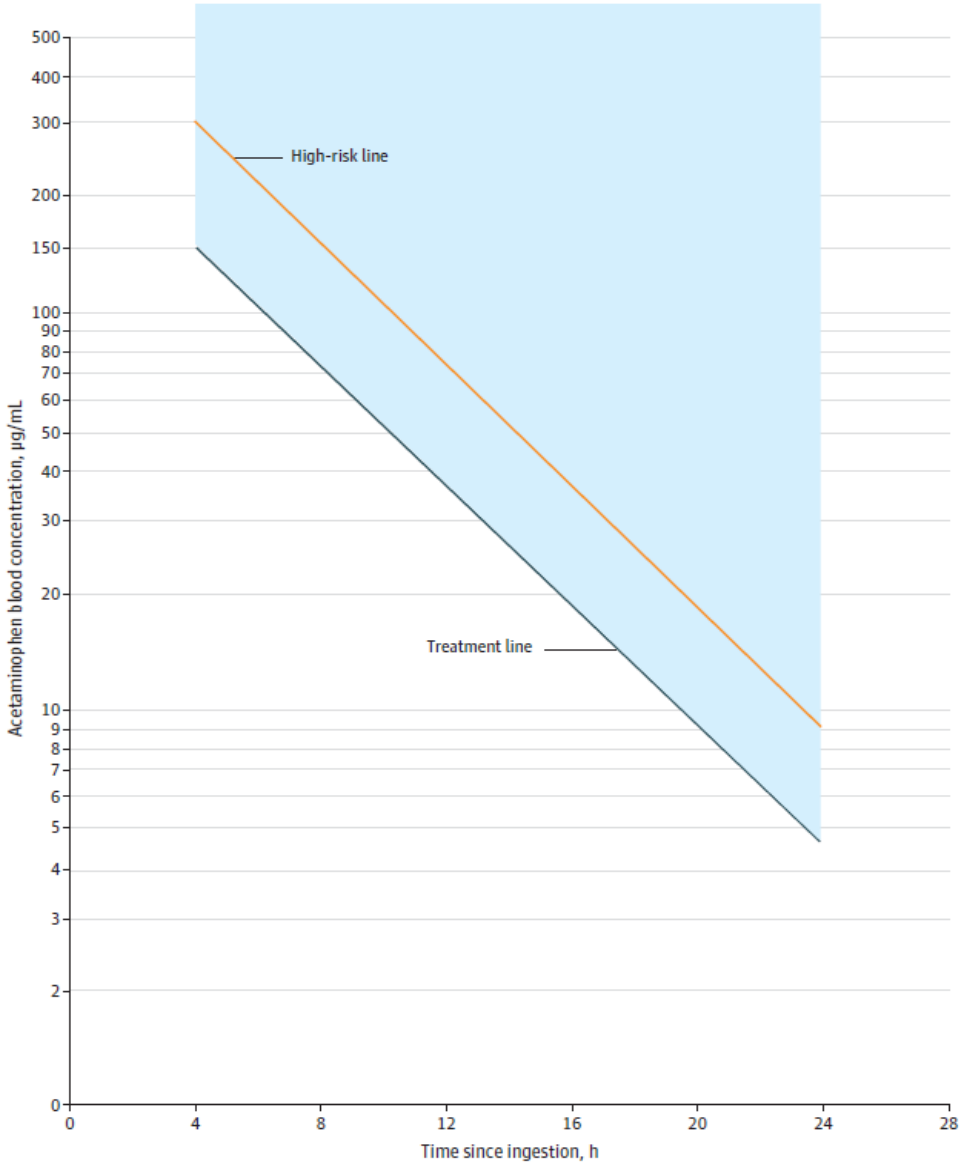
Acetaminophen

- Toxic Dose: 200 mg/kg or 10 g
- Readily accessible especially in the teenaged population
- Massive Ingestions
- 21 Acetaminophen-Related Deaths Since May 2021 (for all ages)
- We have a very good antidote, but it must be started within 8 hours of ingestion for good outcomes.

250 grams of APAP

Matthews – Rumack Acetaminophen Nomogram

Figure 2. Revised Rumack-Matthew Nomogram for the Acute Ingestion of Acetaminophen



The original Rumack-Matthew nomogram line, derived from patient data, begins at 200 µg/mL at 4 hours after ingestion.[7] The treatment line (safety line) beginning at 150 µg/mL at 4 hours was derived as 25% lower than the original nomogram line.[8] A line beginning at 300 µg/mL at 4 hours was derived as 50% greater than the original nomogram line to denote patients and increased risk of developing liver injury.[9] Acetylcysteine should be initiated if a serum or plasma acetaminophen blood concentration drawn 4 to 24 hours after ingestion falls on or above the treatment line. If the concentration falls on or above the high-risk line, many clinicians would provide an increased dose of acetylcysteine. However, the medical literature is insufficient to allow recommendation of a specific acetylcysteine dose in this circumstance.

High-Risk Acetaminophen Ingestion NAC Dosing:

- For patients with body weight above 40 kg,
  - Loading dose is 150 mg/kg in 200 mL of 5% dextrose (D5W), infused over 60 minutes
  - Second infusion is 50 mg/kg in 500 mL D5W, infused (12.5 mg/kg/h) until a reasonable endpoint is achieved (ALT and AST clearly trending down, an INR < 2 and an acetaminophen level <10 mcg/mL).
- For patients who present with a 4-hour acetaminophen level of 300 mcg/mL or greater or who meet or surpass the high-risk line on the revised Rumack-Mathew nomogram for the acute ingestion of acetaminophen.
- For patients whose acetaminophen aminotransferase multiplication product is equal to or greater than 10,000 at any time.
  - [AST or ALT (whichever is larger)] x [acetaminophen level]; if the multiplication product is equal to or greater than 10,000 at any time, high-risk NAC dosing should be considered in the patient's plan of care.
- Also recommend starting fomepizole: 15 mg/kg x1, then 10 mg/kg q12 hours

New 2-Bag NAC Dosing

Three-Bag Regimen

Table 2. Three-Bag Recommended ACETADOTE Dosage and Dilution for Patients 5 kg or greater

Body Weight	Bag 1 (Loading Dose)			Bag 2 (Second Dose)			Bag 3 (Third Dose)		
	Loading Dose	Diluent Volume*	Infusion time	Second Dose	Diluent Volume*	Infusion time	Third Dose	Diluent Volume*	Infusion time
5 kg** to 20 kg	150 mg/kg	3 mL/kg	Infused over 1 hour	50 mg/kg	7 mL/kg	Infused over 4 hours	100 mg/kg	14 mL/kg	Infused over 16 hours
21 kg to 40 kg	150 mg/kg	100 mL		50 mg/kg	250 mL		100 mg/kg	500 mL	
41 kg to 99 kg	150 mg/kg	200 mL		50 mg/kg	500 mL		100 mg/kg	1,000 mL	
100 kg or greater***	15,000 mg	200 mL		5,000 mg	500 mL		10,000 mg	1,000 mL	

* Dilute ACETADOTE in one of the following three solutions: sterile water for injection, 0.45% sodium chloride injection, or 5% dextrose in water.
**Recommended dosing for those less than 5 kg has not been studied.
***No specific studies have been conducted to evaluate the necessity of dose adjustments in patients weighing over 100 kg. Limited information is available regarding the dosing requirements of patients that weigh more than 100 kg.

Two-Bag Regimen

Table 3. Alternative Regimen for Patients 41 kg or Greater: Two-Bag Recommended ACETADOTE Dosage and Dilution

Body Weight	Bag 1 (Loading Dose)			Bag 2 (Second Dose)		
	Loading Dose	Diluent Volume*	Infusion time	Second Dose	Diluent Volume*	Infusion time
41 kg to 99 kg	200 mg/kg	1,000 mL	Infused over 4 hours	100 mg/kg	500 mL	Infused over 16 hours
100 kg or greater**	20,000 mg	1,000 mL		10,000 mg	500 mL	

*Dilute ACETADOTE in one of the following three solutions: sterile water for injection, 0.45% sodium chloride injection, or 5% dextrose in water.

Antiarrhythmics

- Quinidine (Ia), Flecainide (Ic), Propafenone (Ic)
  - Sodium Channel Blockers (wide QRS)
- Amiodarone (III), Sotalol (III), Dofetilide (III)
  - Potassium Channel Blockers (prolonged QTc)

Antiarrhythmics

- Quinidine (Ia) - Patients with an unintentional ingestion of an extra dose may be observed at home if asymptomatic.
- Flecainide (Ic) - There is no role for home management of flecainide overdose.
  - Patients with overdose (including children with inadvertent exposures) should be referred to a healthcare facility for evaluation and treatment.
  - Because of the potential for abrupt instability, patients should be transferred by ambulance.
  - Patients should be observed for at least 6 hours after exposure.
- Propafenone (Ic) - Cardiac dysfunction (ie, hypotension, dysrhythmias) and seizures may occur at doses just above a therapeutic dose. There is no data to support home management after overdose.
  - All patients with overdose and all children with ingestions should be sent to a health care facility for evaluation and treatment.
  - Patients ingesting immediate release preparations should be observed for at least 6 to 8 hours and those ingesting sustained release products for at least 10 to 14 hours, as toxic effects may be delayed/prolonged after overdose of modified release formulations.

Antiarrhythmics

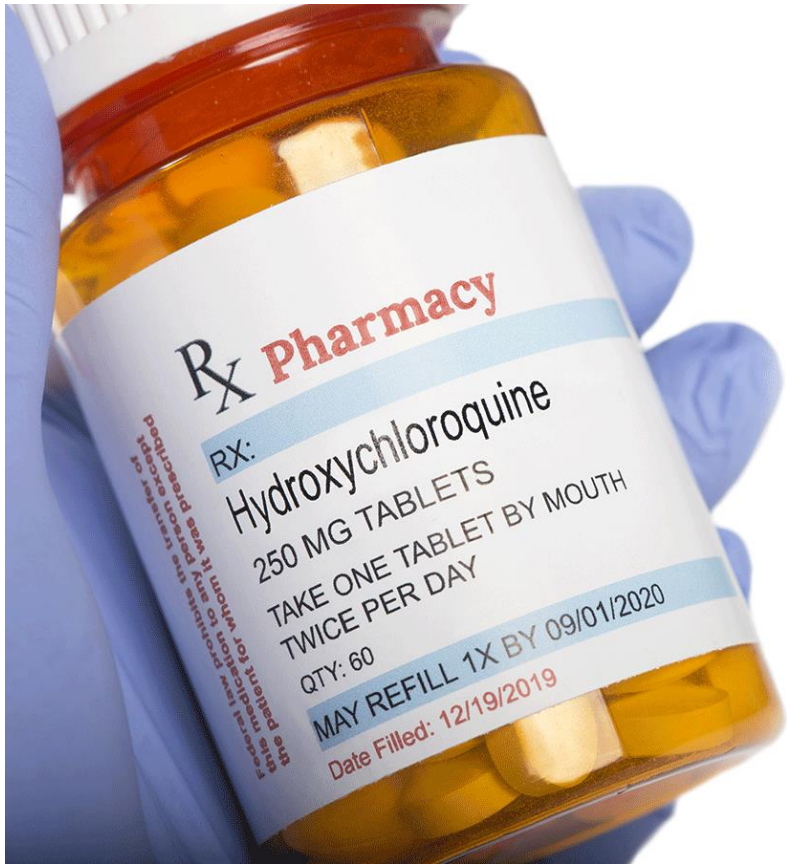
- Amiodarone (III) - For small, acute unintentional ingestions (a single extra dose, or less than a therapeutic dose for age and weight) or if patients are asymptomatic, they can be followed at home.
    - Due to the long half-life of amiodarone (31.5 hours [oral, single dose]; 26 to 107 days [oral, chronic dosing]), patients should be instructed that symptoms may be delayed and should recontact a healthcare provider if symptoms develop.
- Sotalol (III) - Healthy asymptomatic patients (including children) who inadvertently ingest less than or equal to a maximum single therapeutic dose for age (up to 160 mg in adults, or 4 mg/kg in children) may be observed at home and referred to a health care facility if symptoms develop.
    - Torsades de pointes has been reported in adults after therapeutic doses, although many of these patients had concomitant conditions (electrolyte abnormalities, cardiac disease, use of drugs that cause QT prolongation) that may have predisposed them to dysrhythmias.
    - Patients with a sotalol overdose who have an underlying cardiovascular disease or predisposing risk factors (ie, other antidysrhythmic drugs, diuretics) should be referred to a healthcare facility.
- Dofetilide (III) – Reported Overdoses:
    1. Doses greater than 500 mcg orally twice daily. OUTCOME: Increased risk of torsades de pointes.
    2. During a clinical study (n=9), 2500 mcg/day. OUTCOME: Ventricular bigeminy (n=1); headache, syncope and vasodilation (n=1).
    3. 2 500-mcg doses taken 1 hour apart. OUTCOME: Ventricular fibrillation and cardiac arrest.
    4. 22,500 mcg. OUTCOME: Ventricular tachycardia, frequent and multifocal premature ventricular beats, and ventricular bigeminy.
    5. 20 500-mcg tablets. OUTCOME: Torsades de pointes
    6. 28 500-mcg capsules. OUTCOME: No adverse effects; gastric lavage within 30 minutes of ingestion.

Antiarrhythmics

- Treatment:
  - Sodium bicarbonate for sodium channel blockers
  - Lipid emulsion therapy: Administer 1.5 mL/kg of 20% lipid emulsion over 2-3 minutes as an IV bolus
  - Extracorporeal Membrane Oxygenation (ECMO)

Antimalarials

- Chloroquine, Hydroxychloroquine, Quinine
- Sodium Channel Blockade > Dysrhythmias
- CHLOROQUINE:
  - ADULT: The lethal dose is estimated at 30 to 50 mg/kg. As little as 2.25 to 3 g may be fatal in an adult.
  - PEDIATRIC: Children have died after ingesting 1 or 2 tablets (dose as low as 300 mg).
- HYDROXYCHLOROQUINE: ADULT: Ingestion of 8 to 22 g by adults has caused life-threatening toxicity (ie, dysrhythmias, hypotension, and coma).



Antimalarials Treatment

- Benzos – specifically high dose diazepam at 2 mg/kg over 30 minutes after intubation has been shown to decrease mortality and lessen cardiotoxicity.
- Vasopressors – specifically epinephrine
- Consider IV lipid therapy early for patients with ventricular dysrhythmias or hypotension
- ECMO

Aspirin

It comes in many flavors!

The Peppermint Flavored

The Acetaminophen Flavored

The Wintergreen Flavored

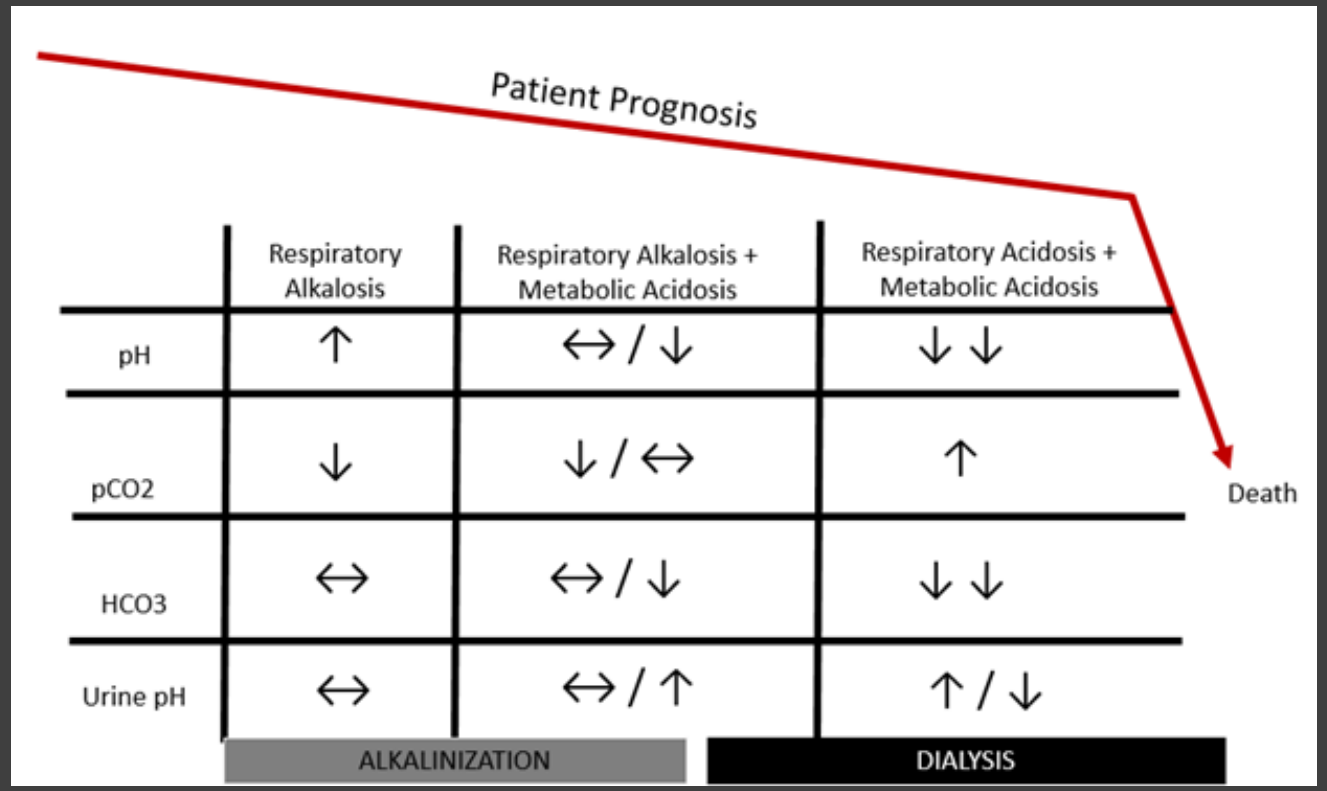
The Chalk Flavored… yum!

The Plop, Plop, Fizz, Fizz Flavored

Mechanism of Toxicity

- Toxic effect - impairs cellular energy production
  1. Interference with the Krebs cycle
  2. Uncoupling of oxidative phosphorylation
- Lactate and other organic acids accumulate and produce an elevated anion gap metabolic acidosis.
- Direct effect to stimulate the respiratory center in the brain leading to hyperventilation and respiratory alkalosis.

Mechanism of Toxicity



- Salicylate toxicity has a mixed acid-base disturbance – both respiratory alkalosis and metabolic acidosis
  - The actual blood pH reflects whichever process is dominant in the patient at the time.

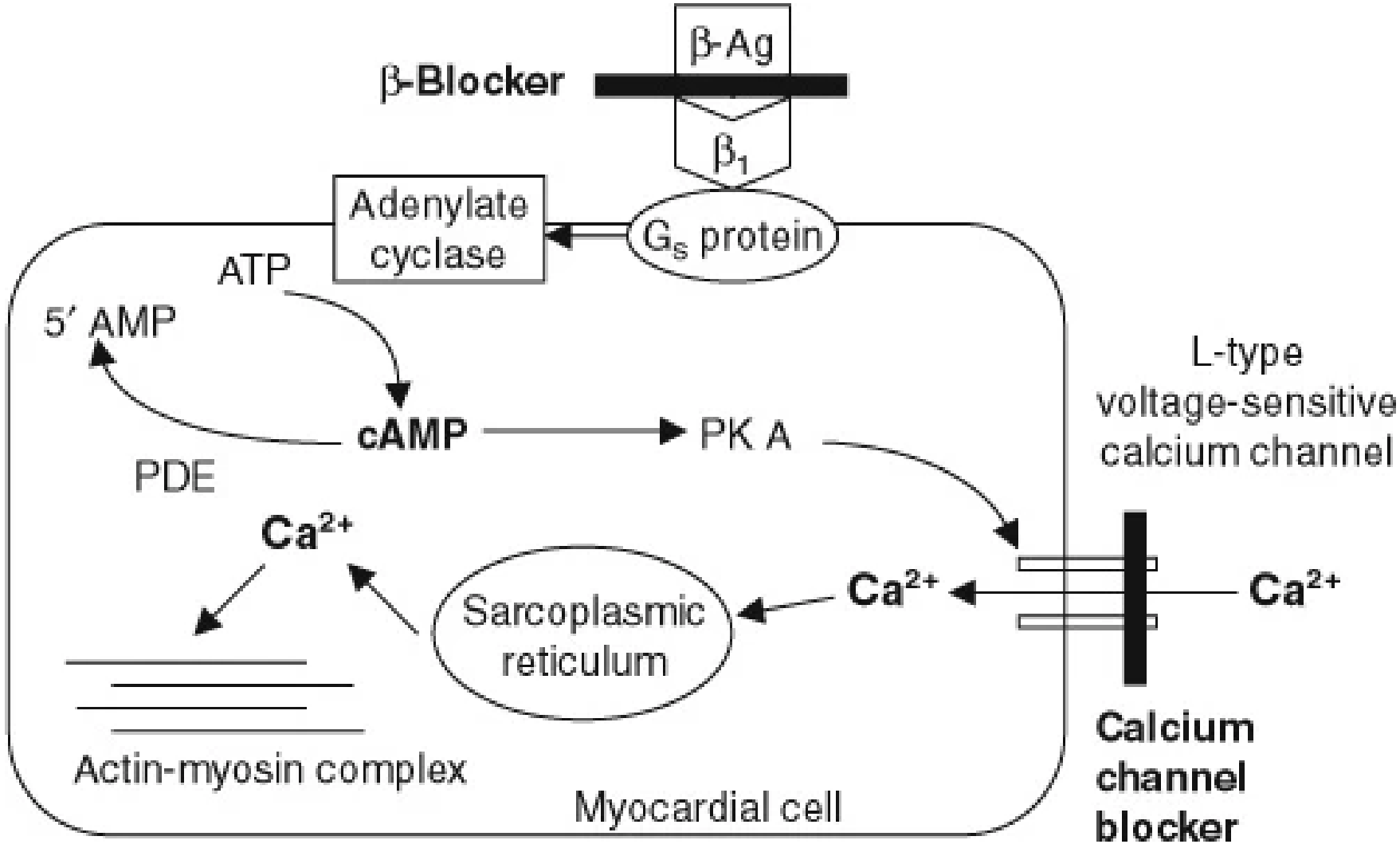
- Much attention is paid to acid-base status in salicylate poisoning because acidosis makes the problem worse.
  - More CNS penetration of salicylates in the acidotic patient
  - Puts the brain at even greater energy deficit.

Benzonatate

- Structure very similar to local anesthetics
- Sodium-channel blockade
- 1 to 2 benzonatate capsules (100 mg each) in a 12-month-old infant led to tonic-clonic seizures
- Seizures, ventricular dysrhythmias, cardiac arrest

CCB and BB Pharmacology

The role of calcium in myocardial contraction and the effects of β-agonists, β-blockers and calcium channel blockers on calcium influx.



DeWitt; Toxicol Rev 2004; 23 (4): 223-238

CCB Pharmacology

Heart

Myocytes and pacemaker cells of SA and AV nodes

Regulate contraction and conduction

More non-dihydropyridines

Vascular smooth muscle

Regulate vasoconstriction

More dihydropyridines

Pancreas – islet beta cells

Responsible for synthesizing and secreting insulin

Both dihydropyridines and non-dihydropyridines

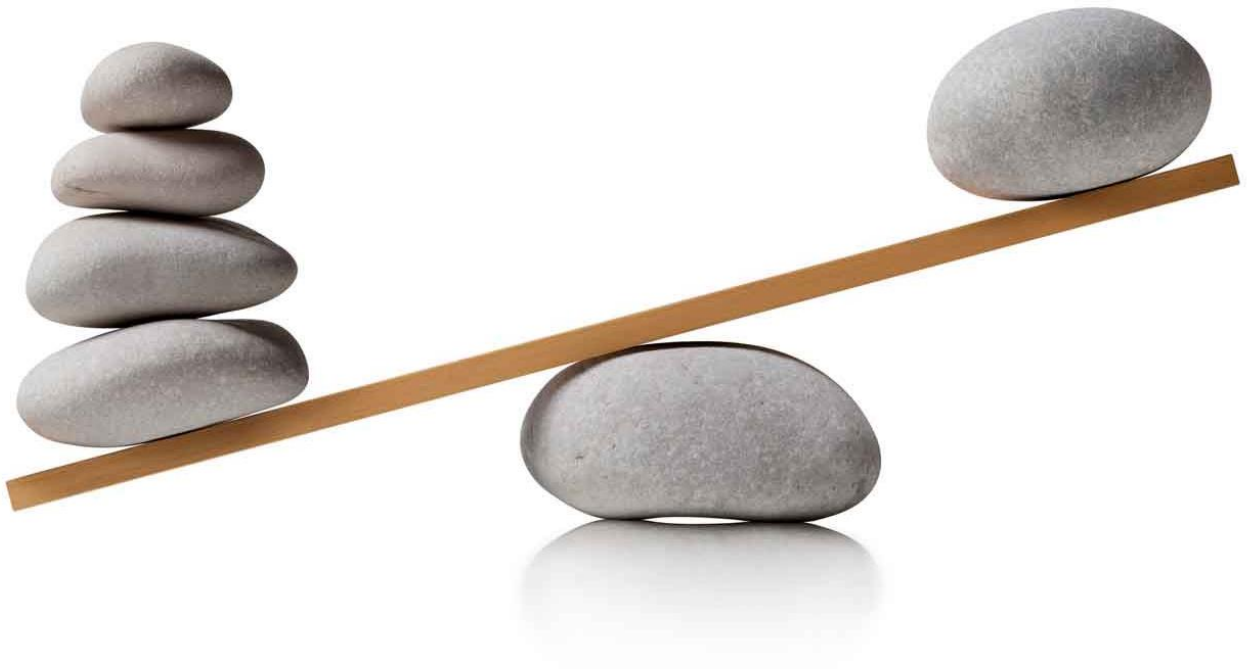
Assessment of hyperglycemia after calcium channel blocker overdoses involving diltiazem or verapamil*

Michael Levine, MD; Edward W. Boyer, MD, PhD; Charles N. Pozner, MD; Ann-Jeannette Geib, MD; Todd Thomsen, MD; Nathan Mick, MD; Stephen H. Thomas, MD

Hyperglycemia is Poor Prognostic Indicator

- Serum glucose concentrations correlate directly with the severity of the calcium channel blocker intoxication.
- The percentage increase of the peak glucose concentration is a better predictor of severity of illness than hemodynamic derangements.

IMPORTANT NOTE!



Not all CCB and BB are created equal!

Calcium Channel Blockers (CCB)

Non-Dihydropyridine

Primarily a pump issue*

- Diltiazem and Verapamil
- Block Ca^{2+} channels in myocardium
- Decreased inotropy and chronotropy

Dihydropyridine

Primarily a pipe issue*

- Nifedipine, amlodipine, nicardipine
- Block Ca^{2+} channels on vascular smooth muscle
- Vasodilation - tend to produce sinus tachycardia instead of bradycardia
- Fewer conduction disturbances

*Important – Selectivity is lost in significant overdose!

β-Blockers (BB)

- Wider array of properties influencing their toxicity compared with CCB.
- BB possessing membrane stabilizing activity are associated with the largest proportion of fatalities from BB overdose.
  - **Propranolol and carvedilol**
- **Sotalol** overdoses, in addition to bradycardia and hypotension, can cause torsade de pointes.

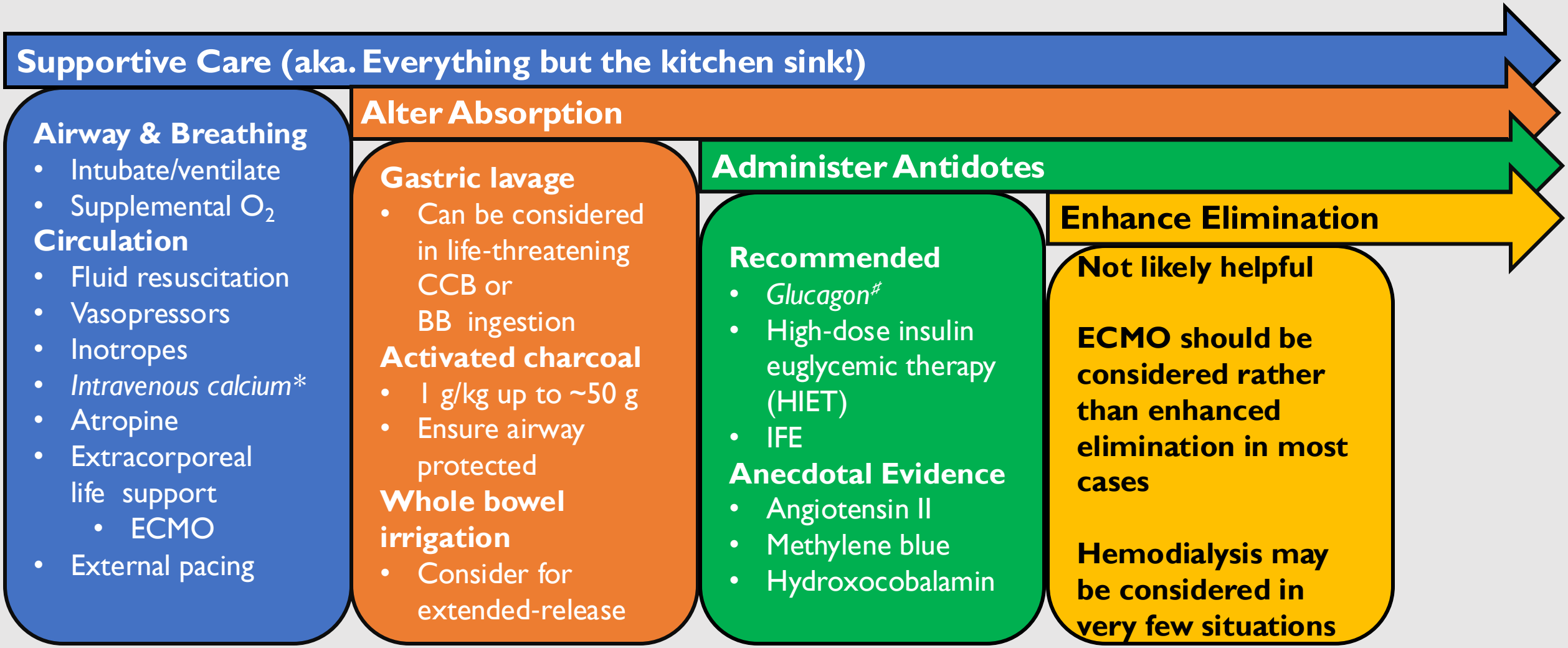
Table III. Pharmacological and pharmacokinetic properties of β-blockers[18,58]

β-Blocker	Receptor selectivity	Partial agonist activity (ISA)	Protein binding (%)	$t_{1/2}$ (h)	Bioavailability (%)	Vd (L/kg)	Lipid solubility	Metabolism/ elimination	Membrane stabilisation (MSA)
Acebutolol	β_1	Low	25	3–4	70	1.2	Low	Hepatic	Yes
Atenolol	β_1	No	5–10	6–9	50–60	1	Low	Renal	No
Betaxolol	β_1	No	50	14–22	90	5–13	Low	Hepatic	Low
Bisoprolol	β_1	No	30	9–12	80	3	Low	Renal	No
Cartelol	β_1, β_2	Yes	30	6	85		Low	Renal	Yes
Carvedilol	β_1, β_2, α_1	No	25–35	6–8	20	1–2	High	Hepatic	Yes
Esmolol	β_1	No	55	9 min	NA	2	Low	Erythrocyte esterases	No
Labetalol	β_1, β_2, α_1	No	50	6–8	90	9	Moderate	Renal	Yes
Metoprolol	β_1	No	10	3–4	90	4	Moderate	Hepatic	Low
Nadolol	β_1, β_2	No	25–30	20–24	30	2	Low	Renal	No
Oxprenolol	β_1, β_2	Yes	80	1–2	20–70	1.3	High	Hepatic	Yes
Penbutalol	β_1, β_2	Low	80–98	5	100	0.5	High	Hepatic	No
Pindolol	β_1, β_2	High	50	3–4	95	2	Moderate	Hepatic	Yes
Propranolol	β_1, β_2	No	90	3–5	90	4	High	Hepatic	High
Sotalol	β_1, β_2	No	0	7–15	80	2	Low	Renal	No
Timolol	β_1, β_2	No	10	4	90	2	Moderate	Hepatic	No

ISA = intrinsic sympathomimetic activity; **MSA** = membrane stabilising activity; **NA** = not applicable; $t_{1/2}$ = half-life; **Vd** = volume of distribution.

DeWitt; Toxicol Rev 2004; 23 (4): 223-238

Stepwise Treatment Approach



#Likely to be more beneficial in BB# **Likely to be more beneficial in CCB, considered a first line therapy**

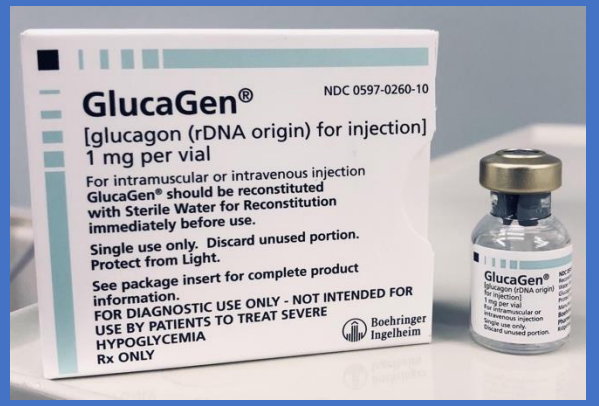
Short Term Therapies (Oh, Crap! Box)

- IV Fluid Bolus (10-20 mL/kg crystalloid)
- Calcium
- Glucagon
- Atropine
- Vasopressors
- Inotropes

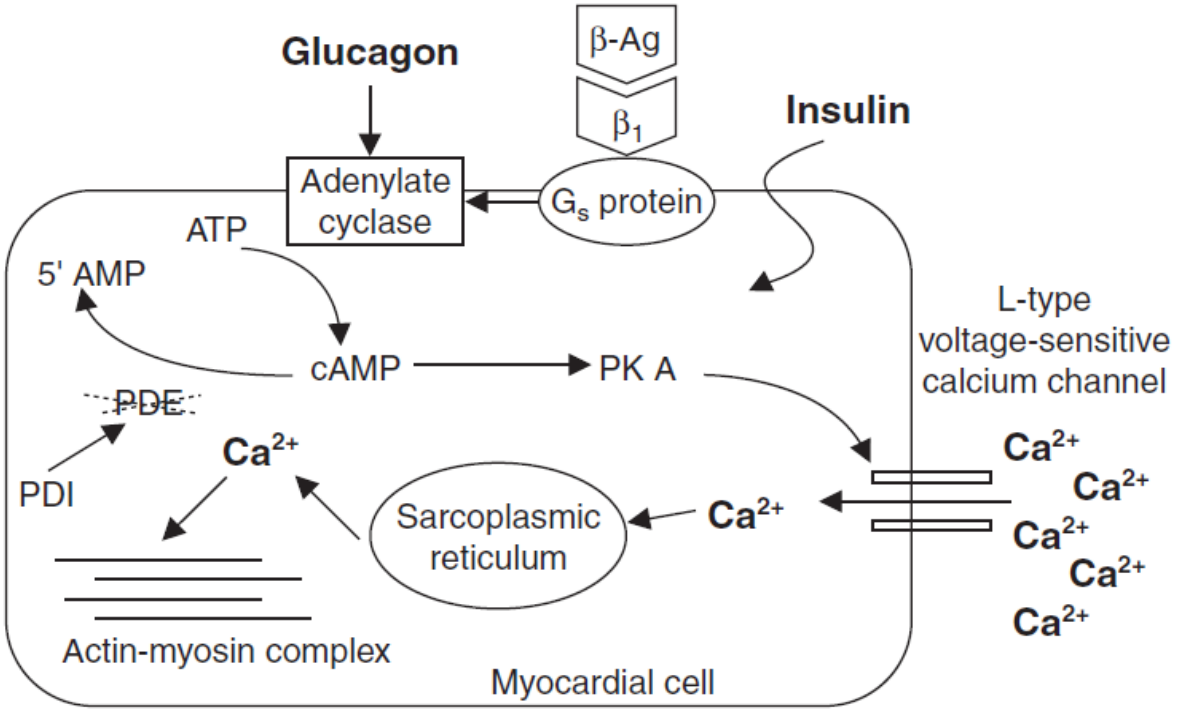
IV Calcium Salts

- GOAL: To increase the extracellular Ca^{2+} concentration in order to drive calcium influx into the myocardial cells & increase contractility.
- Calcium Gluconate - 1g (10 mL) of 10% = 4.6 mEq elemental Ca^{2+}
- Calcium Chloride - 1g (10 mL) of 10% = 13.6 mEq elemental Ca^{2+}
- Bolus Dose: start with an initial IV infusion of 13-25 mEq Ca^{2+}
- Drip Rate: 0.5 mEq/kg/hr of Ca^{2+} and titrate as needed
- BAD NEWS: tachyphylaxis

Glucagon



- MECHANISM – binds to glucagon receptors in cardiac tissue, leading to activation of adenylate cyclase & formation of cAMP
- DOSING – 5mg IV push, can repeat up to 15mg
  - 0.05 mg/kg in pediatrics
  - Continuous infusion @ 2-10 mg/hour **<u>if effective</u>**
  - **<u>Will deplete hospital supply quickly</u>**
- MONITORING
  - Your patient **<u>WILL PUKE – aspiration risk</u>**
    - AC/glucagon - not a good combination
  - Tachyphylaxis



DeWitt; Toxicol Rev 2004; 23 (4): 223-238

Vasopressors & Inotropes

- **Norepinephrine**
  - Reasonable first choice for patients with hypotension
  - ***Recommended* first line for symptomatic patients**
- **Epinephrine**
  - More beneficial than isoproterenol for BB toxicity but inferior to glucagon
  - *Recommended* first line for shock
- **Dobutamine**
  - Will likely cause hypotension at doses required to overcome adrenergic blockade
  - *Recommended* to increase contractility in cardiogenic shock
- **Vasopressin**
  - No benefit in animal studies
  - Only anecdotal evidence to support use in humans
  - Should not be used alone
- **Dopamine**
  - Paradoxical hypotension in BB/CCB toxicity
  - Inconsistent hemodynamic improvement found in expert reviews
  - Expert consensus guidance suggests against use

Holger et al. *Clin Tox*. 2007; 45: 396-401.
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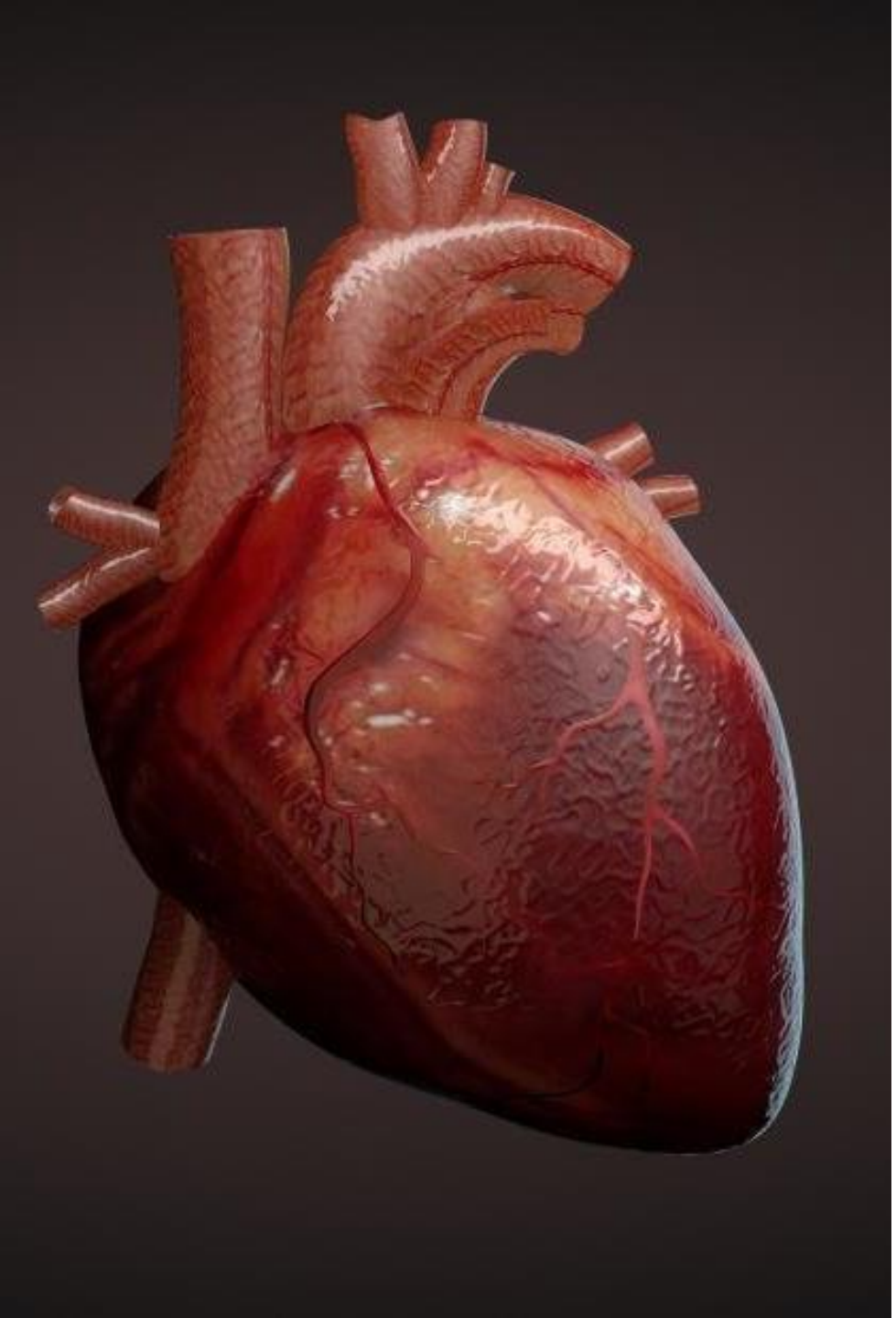
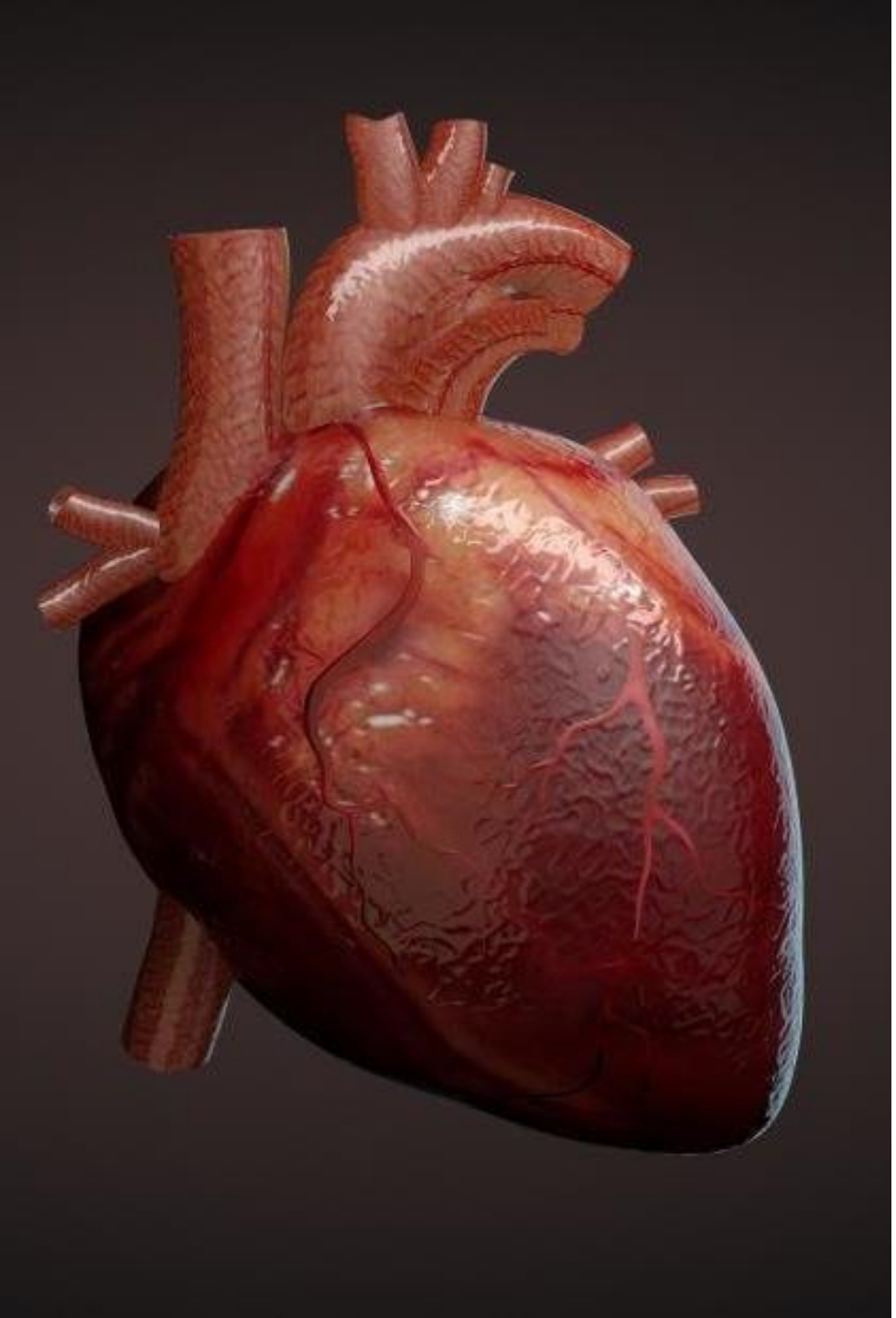


High Insulin Euglycemic Therapy (HIET)

- Administration of HIET may improve hemodynamic function
  - Improved contractility & organ perfusion
- Provides an energy source to the myocardium
- During stress, the myocardium shifts from predominantly free-fatty acid metabolism to carbohydrate metabolism.
- Insulin secretion is calcium dependent, and in overdose, CCBs will inhibit secretion of insulin in the pancreas, halting glucose uptake into myocardial tissues.
- Administration of exogenous insulin may provide the myocardium the energy required to sustain function until the offending agent is eliminated.



High Insulin Euglycemic Therapy (HIET)

Insulin Dosing: Initial bolus dose followed by continuous IV infusion

- BOLUS: 1 unit/kg regular insulin IV
- MAINTENANCE: 0.5 units/kg/hour regular insulin IV, titrating to clinical response
- MAXIMUM DOSE: Not established, but increased efficacy unlikely with doses > 10 units/kg/hour

- DON'T FORGET YOUR DEXTROSE!
  - BOLUS: 25gm dextrose (50 mL D50W) should be administered if initial blood glucose < 250 mg/dL
  - MAINTENANCE: Initiate dextrose infusion at 0.5 g/kg/hour (5 mL/kg/hour)
    - Titrate to maintain blood glucose > 150 mg/dL concomitantly with insulin infusion

IV Fat Emulsion (Intralipid 20%)

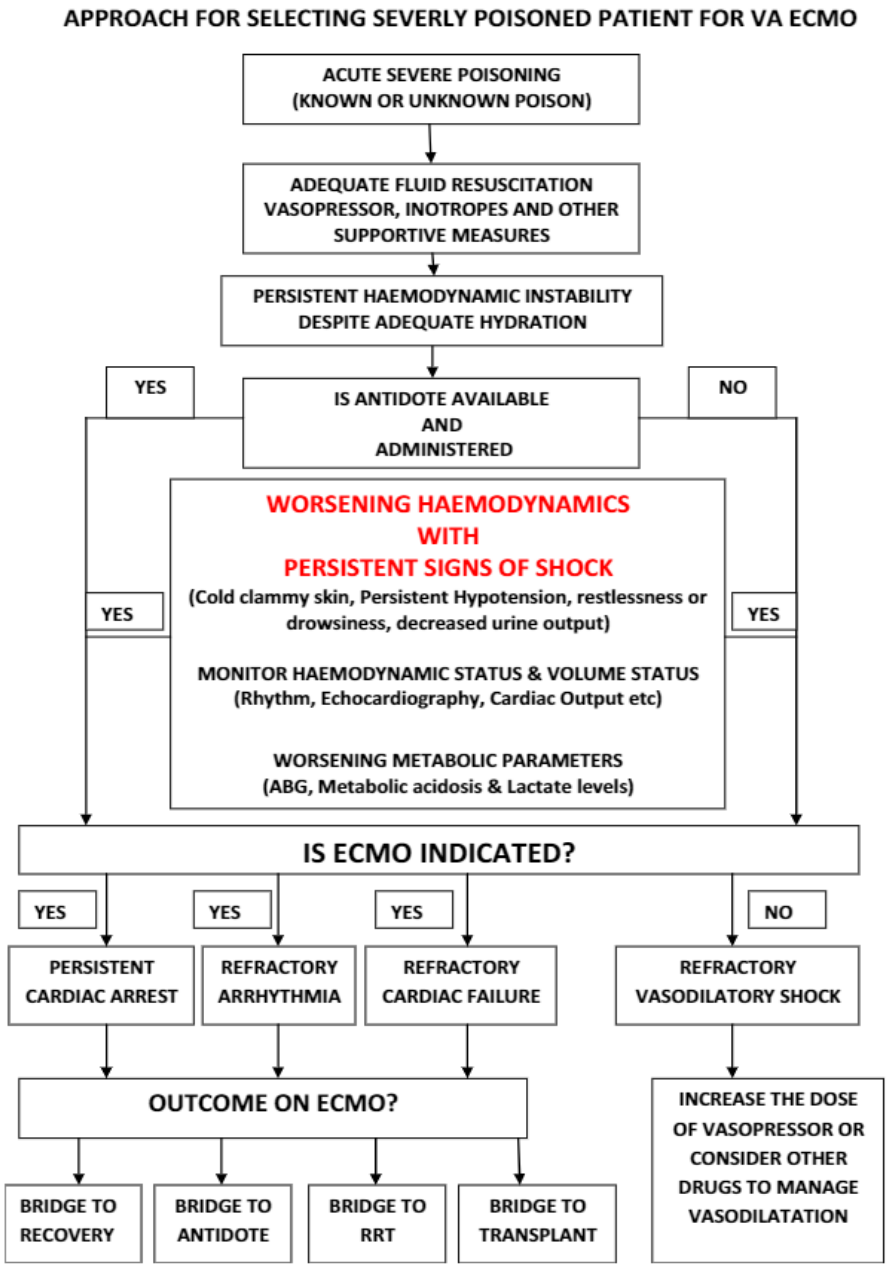
- Mechanism of Action: has not been fully elucidated.
  - Lipid Sink Theory – IFE creates a lipid compartment within the serum, sequestering lipid-soluble agents
  - Enhanced Fatty Acid Metabolism – IFE may counteract free fatty acid transport inhibition leading to increased free fatty acid metabolism and energy production to sustain myocardial funcion.

- Dosing: There are no validated, evidence-based dosing regimens.
  - BOLUS: 1.5 mL/kg of 20% IFE given slow IV push (over 3-5 minutes)
  - MAINTENANCE: 0.25 mL/kg/min of 20% IFE given as a continuous infusion for up to 60 minutes.

J. Med. Toxicol. (2017) 13:124-125

What is the Role for ECMO in these patients?

- ECMO helps in maintaining adequate cardiac output and tissue perfusion
- The duration of ECMO support depends on several factors such as severity of toxicity and recovery of cardiac function, half life of the toxin and organ dysfunction at the time of ECMO initiation.
- Venoarterial (VA) ECMO reduces cardiac oxygen consumption and provides hemodynamic and respiratory support as a bridge to recovery.



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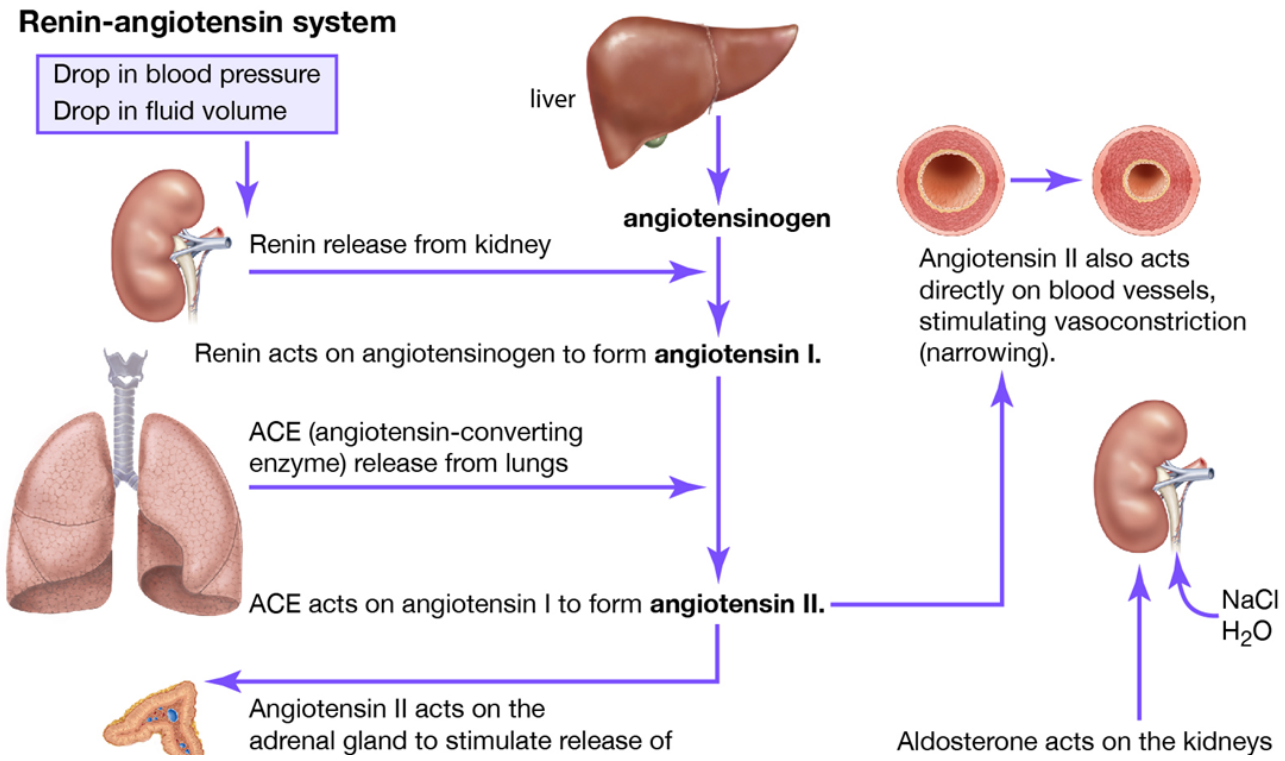
Angiotensin II (Giapreza)

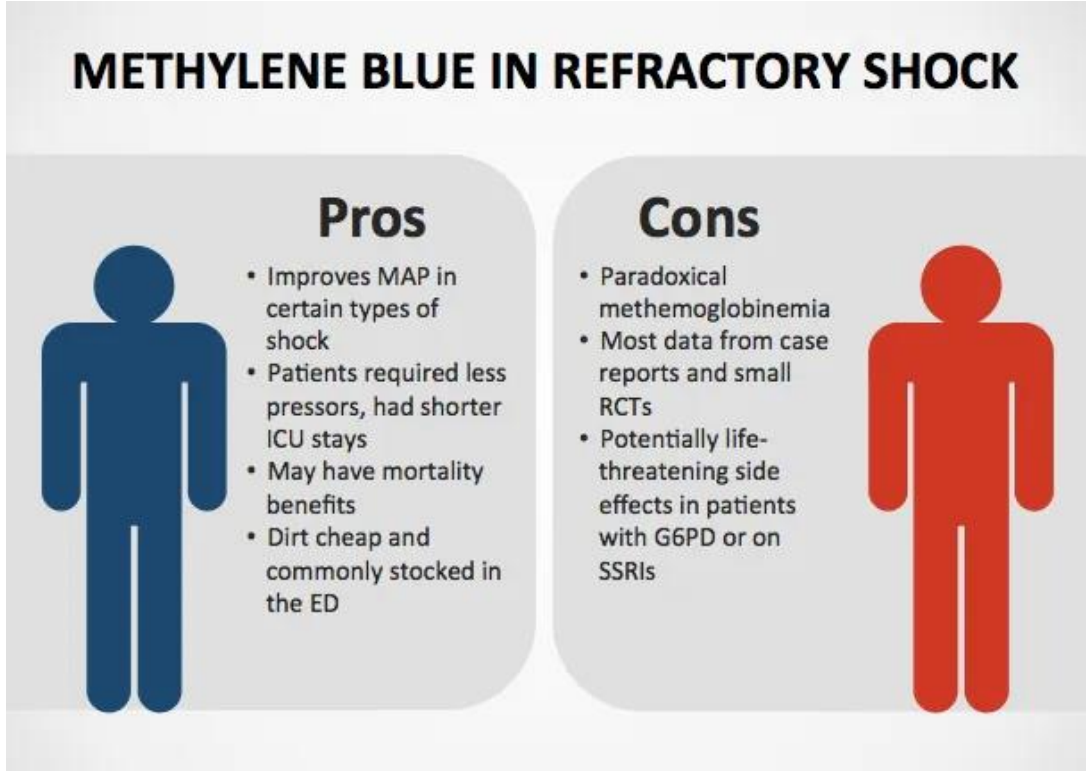


- 2.5 mg/mL IV solution
- Indicated for septic or other disruptive shock
- 20 ng/kg/minute continuous IV infusion
- Cost is approximately $1,800/vial

70kg x 20ng x 60 min = 84,000 ng/hour = 0.084 mg/hour
1 vial (2.5 mg) = approximately 30 hours of infusion time

Methylene Blue

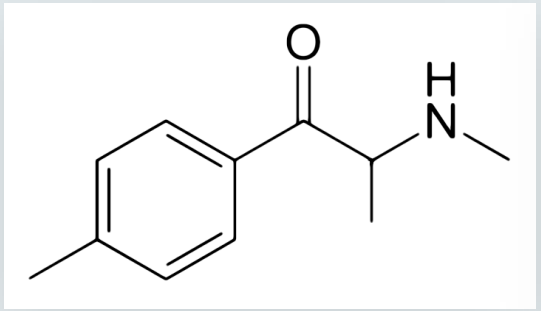
- Data suggest that methylene blue may be beneficial for the treatment of vasoplegic shock secondary to beta-blocker or calcium channel blocker overdose that is unresponsive to standard treatment.



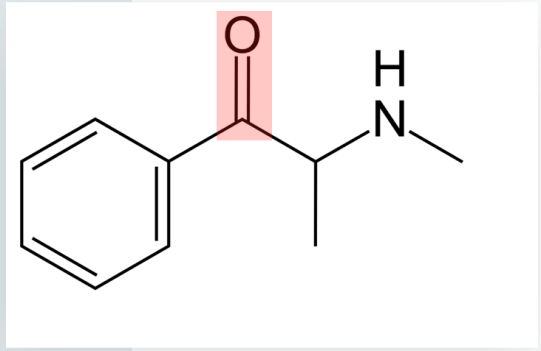
Hydroxocobalmin (CyanoKit)

- A few case reports and series have demonstrated that the postoperative administration of intravenous hydroxocobalamin **can be effective in restoring vascular tone and improving vasoplegia**.
- The starting dose of hydroxocobalamin in adults is 5g administered as an intravenous infusion over 15 minutes.
- Hydroxocobalamine inhibits nitric oxide synthase and scavenges for nitric oxide (NO), and it is this activity which has been linked to increases in mean arterial pressure (MAP).
- Will interfere with colorimetric testing including POC glucose.

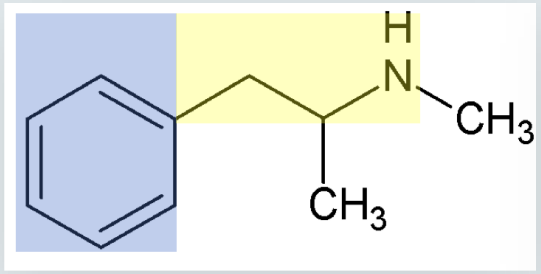
Bupropion (aka: Illbutrin)



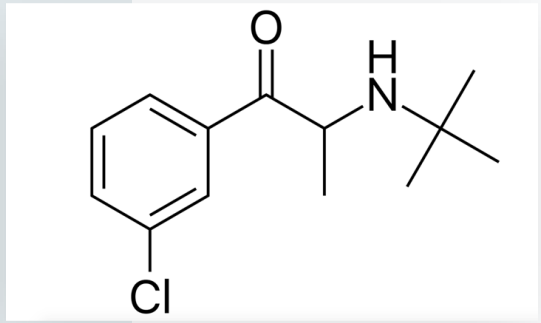
mephedrone



methcathinone



methamphetamine



bupropion

- I hate bupropion (Wellbutrin™)
- There is nothing “Well” about this drug
- It was first synthesized by Burroughs-Wellcome in 1966
- First approved by the FDA in 1989 as an antidepressant
- It was pulled off the market, as it was found in post-marketing studies to have a significantly higher rate of seizures (~0.4%) than other second-generation antidepressants
- Not willing to leave ill enough alone, they reformulated the drug as a sustained release version that lowered its seizure incidence rate to a more acceptable 0.1%.
- The drug that is written like candy to treat depression is a sustained release bath salt.

Bupropion Overview

- Bupropion is increasingly used for several indications:
  - Depression
  - Tobacco cessation
  - ADHD
- Immediate Release Tablets: 75mg and 100mg
- Extended Release Tablets: 100mg, 150mg, 174 mg, 200mg, 300mg, 348mg, 450mg, 522mg

Bupropion Overview

- **Bupropion is far more dangerous than other commonly used antidepressants.**
  - Bupropion can cause cardiogenic shock is somewhat unique.
- **Tricyclic antidepressants have largely fallen out of favor for treatment of depression, but bupropion remains commonly used.**
  - This makes bupropion one of the most dangerous antidepressants in widespread circulation.
- **The extended-release formulation of bupropion may cause *delayed* emergence of symptoms (a delayed "toxin bomb").**
  - Ongoing drug absorption can be relentless.

Bupropion Pharmacodynamics

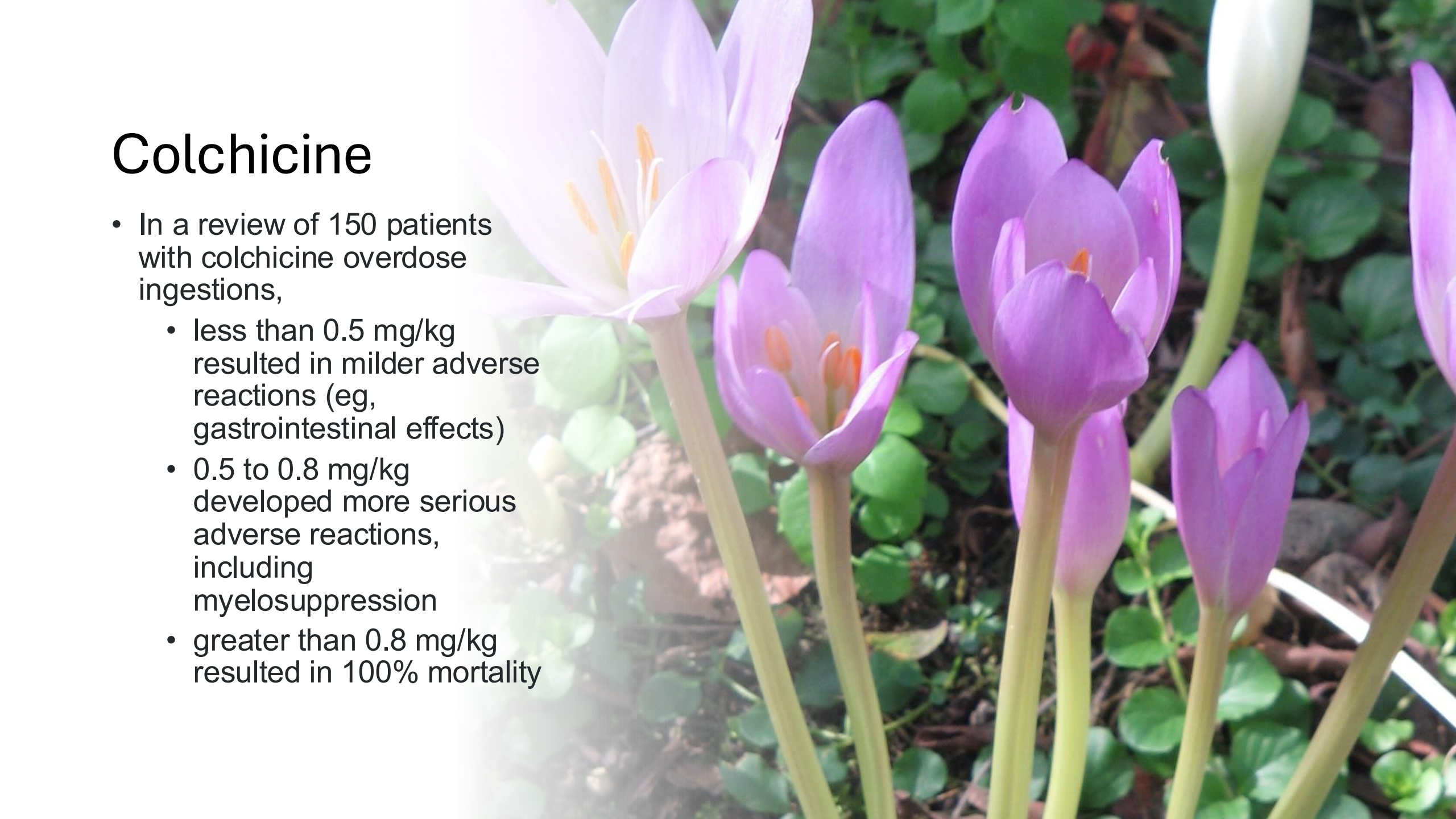
- **Inhibition of dopamine & norepinephrine reuptake**
  - This is the therapeutic mechanism of action of bupropion.
  - Structurally and pharmacodynamically, bupropion works similarly to *amphetamines* (specifically cathinones).
- **Cardiotoxicity**
  - The most notable effect is via **inhibition of gap junctions**.
    - Gap junctions are connections between adjacent cardiomyocytes involved in cell-cell signaling. Bupropion can inhibit them, impairing cardiac function (e.g. prolongation of QRS interval and systolic heart failure).
    - There is no way to counteract this. For example, sodium bicarbonate *won't* help (because sodium bicarbonate works on the sodium channels).
  - Another effect is blockade of cardiac potassium channels.
    - This may cause an increased QTc interval.
    - However, bupropion overdose doesn't seem to cause Torsades de pointes clinically.

Colchicine

- Who Remembers?
  - 1.2 mg at the first sign of a gout flare, then 0.6 mg every hour until diarrhea develops
- Current Dosing:
  - Gout, prophylaxis: 1.2 mg/day
  - Gout, treatment: 1.8 mg on day 1
- Phase 1 (0 to 24 hours): Diarrhea is an early sign of toxicity; nausea, vomiting, etc.
- Phase 2 (1 to 7 days): Myelosuppression, leukopenia, granulocytopenia, thrombocytopenia
- Phase 3 (> 7 days): recovery or death

Colchicine

- In a review of 150 patients with colchicine overdose ingestions,
  - less than 0.5 mg/kg resulted in milder adverse reactions (eg, gastrointestinal effects)
  - 0.5 to 0.8 mg/kg developed more serious adverse reactions, including myelosuppression
  - greater than 0.8 mg/kg resulted in 100% mortality



Colchicine

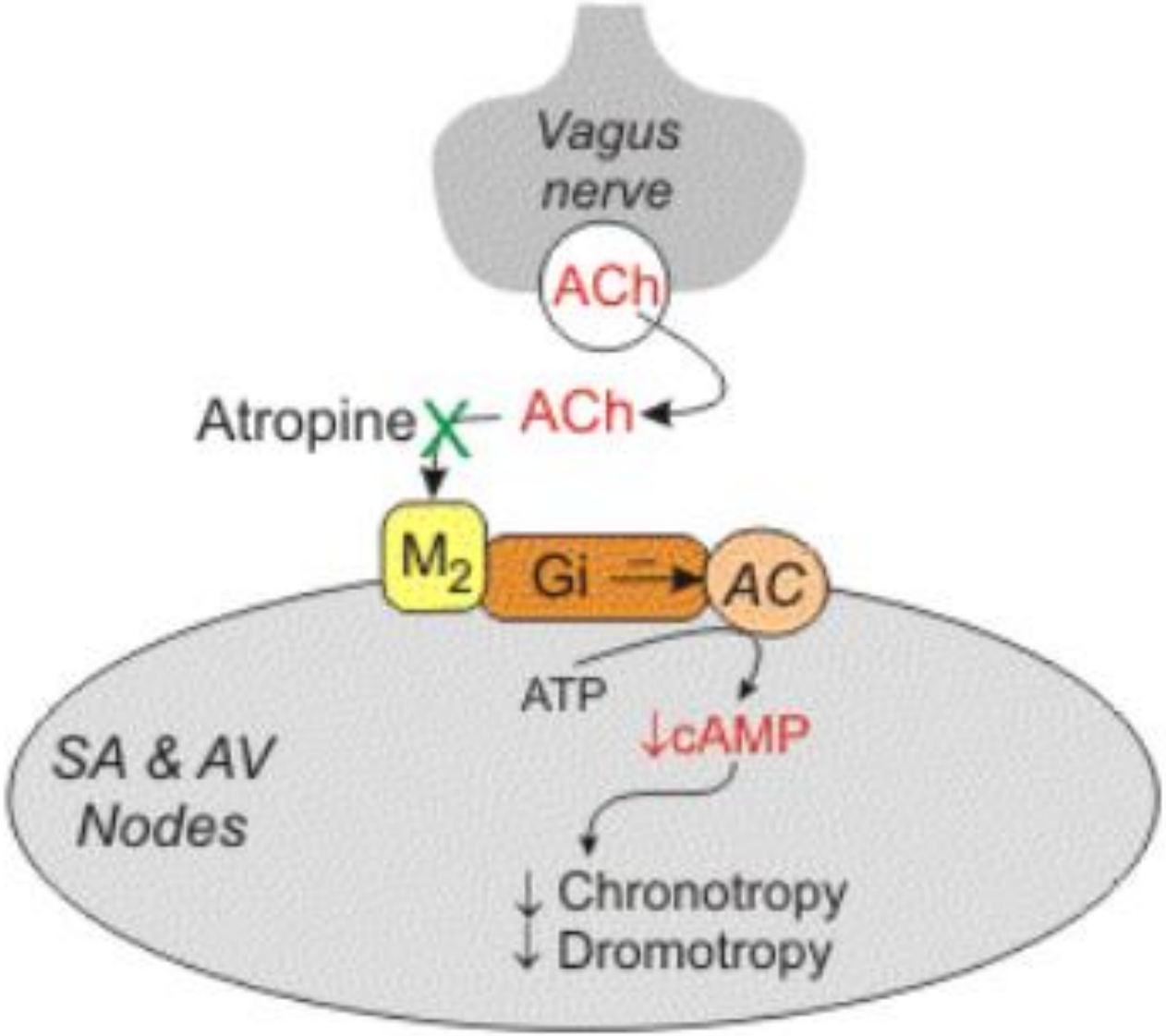
- Treatment is mainly treating multiorgan system failure.
- Treat with IV fluids, vasopressors, cardiac monitoring, intubation, antibiotics for sepsis, dialysis for acute renal failure as needed.
- For severe neutropenia, administer colony stimulating factor (e.g., filgrastim).
- If severe coagulopathy with bleeding develops transfuse with RBCs, platelets and fresh frozen plasma as indicated.

Diphenhydramine

- Massive ingestions
- Patients become severely anticholinergic

Anticholinergic Toxidrome Mechanism

- Acetylcholine (ACh) action is blocked at muscarinic receptors
- Muscarinic receptors are normally responsible for:
  - Secretions and sweating
  - GI motility
  - Releasing sphincters
  - Contracting the pupil of the eye
  - Slowing the heart rate



Anticholinergic Toxidrome Mechanism

When ACh is blocked at muscarinic receptors, we see:

- Dry membranes
- Hot flushed skin
- Quiet bowel
- Urinary retention
- Large pupils (mydriasis)
- Tachycardia

ACh receptors in the brain can be blocked and cause:

Agitation, confusion, hallucinations (anticholinergic delirium)

Anticholinergic Toxidrome

DRY as a BONE
- Dry mouth and nose, decreased sweating, urinary retention

RED as a BEET
- Flushing

BLIND as a BAT
- Mydriasis, blurred vision

MAD as a HATTER
- Confusion, agitation, hallucinations, seizures

HOT as HADES
- Increased body temperature

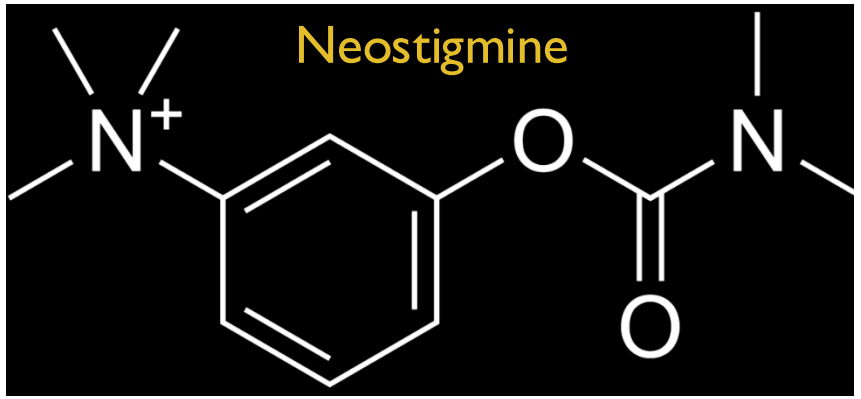
Anticholinergic Treatment

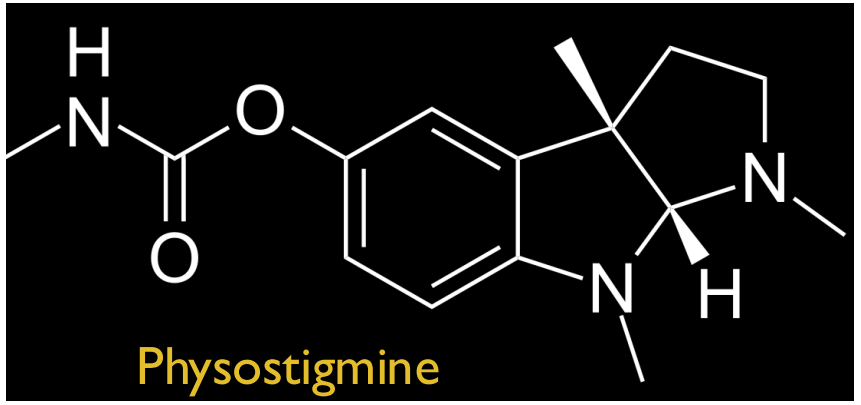
- Benzodiazepines (midazolam, lorazepam, diazepam, etc.) for any of the following:
  - Agitation
  - Tachycardia
  - Seizures
- Physostigmine (USE WITH CAUTION! – recommended to be given in ICU)
  - Carbamate - reversible inhibitor of acetylcholinesterase
  - ONLY a viable option if unable to control agitated delirium, severe tachycardia, or hyperthermia with benzodiazepines
  - Contraindicated for TCA overdose - may worsen cardiac conduction disturbances, cause bradyarrhythmias or asystole, and precipitate seizures

Physostigmine has been unavailable since February 2019

What are our carbamate alternatives?

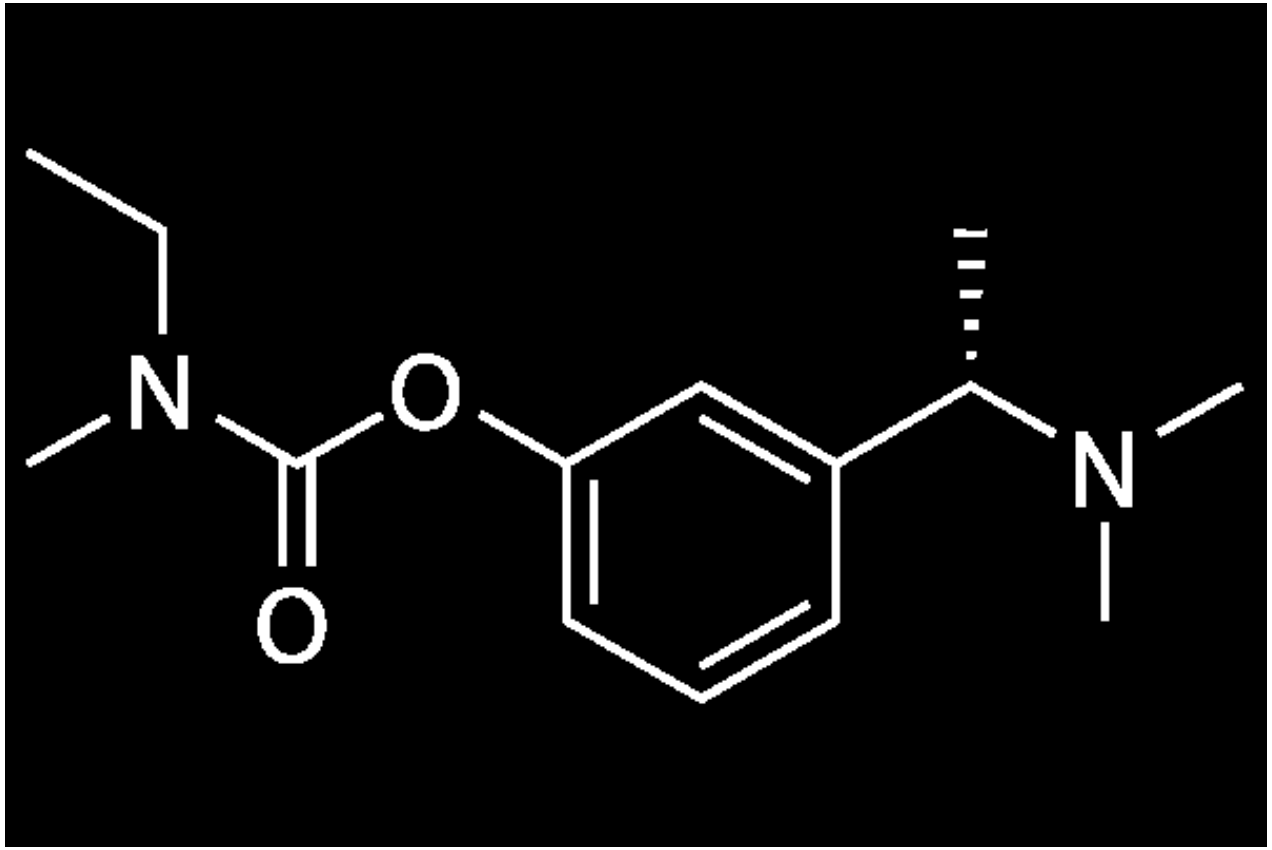
- Physostigmine is a carbamate with a tertiary amine. Its structure allows penetration into the CNS
- Neostigmine and pyridostigmine are carbamates with quaternary amine groups, which doesn't allow for easy passage through the blood brain barrier (BBB)





Rivastigmine

- FDA approved for Alzheimer's disease
- Same mechanism of action as physostigmine
- Structure contains a tertiary amine
  - This allows the drug to cross the BBB
- Rivastigmine has several therapeutic advantages compared to physostigmine



Comparison of Physostigmine and Rivastigmine

- Physostigmine inhibits acetylcholinesterase both peripherally and centrally, while rivastigmine is preferentially central
  - Rivastigmine is thought to have less peripheral toxicity
- Rivastigmine has a slower rate of CNS penetration, and a longer duration of action
  - Beneficial for prolonged delirium
- Physostigmine use is controversial due to its rare but serious side effects
  - Asystole, bradycardia, QTc prolongation, and seizures

Comparison of Physostigmine and Rivastigmine

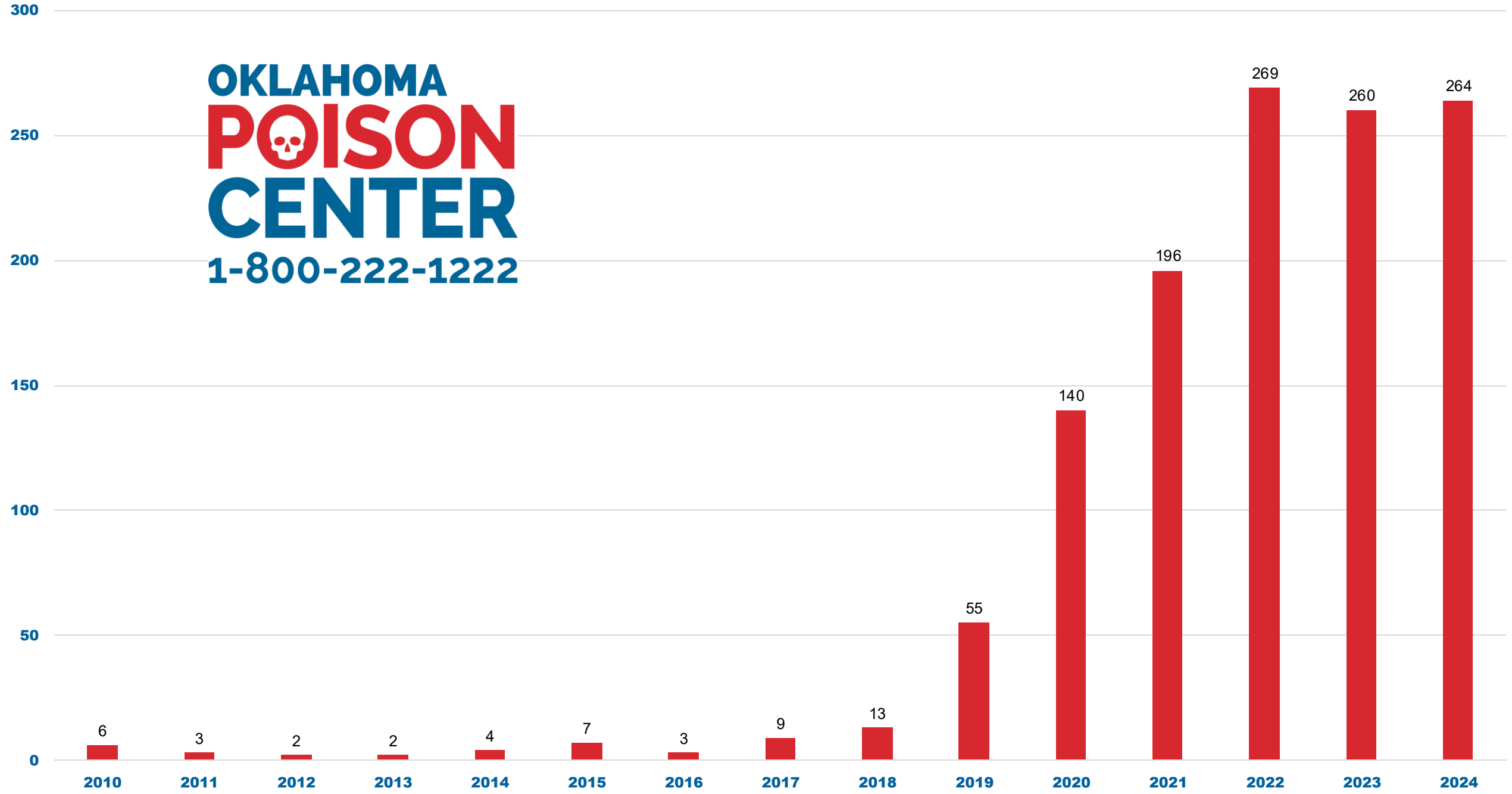
	IV Physostigmine	Oral Rivastigmine
Usual Dose	0.5-2 mg IV over 5 minutes	1.5-6 mg PO BID
Onset	2 minutes	1 hour
Duration	45-60 minutes	10 hours

Marijuana

- Comatose child (historically opioids > alpha-2 agonists > marijuana)

Pediatric (0-5 years) Marijuana Exposures Reported to the Oklahoma Poison Center

OKLAHOMA POISON CENTER
1-800-222-1222



Opioids

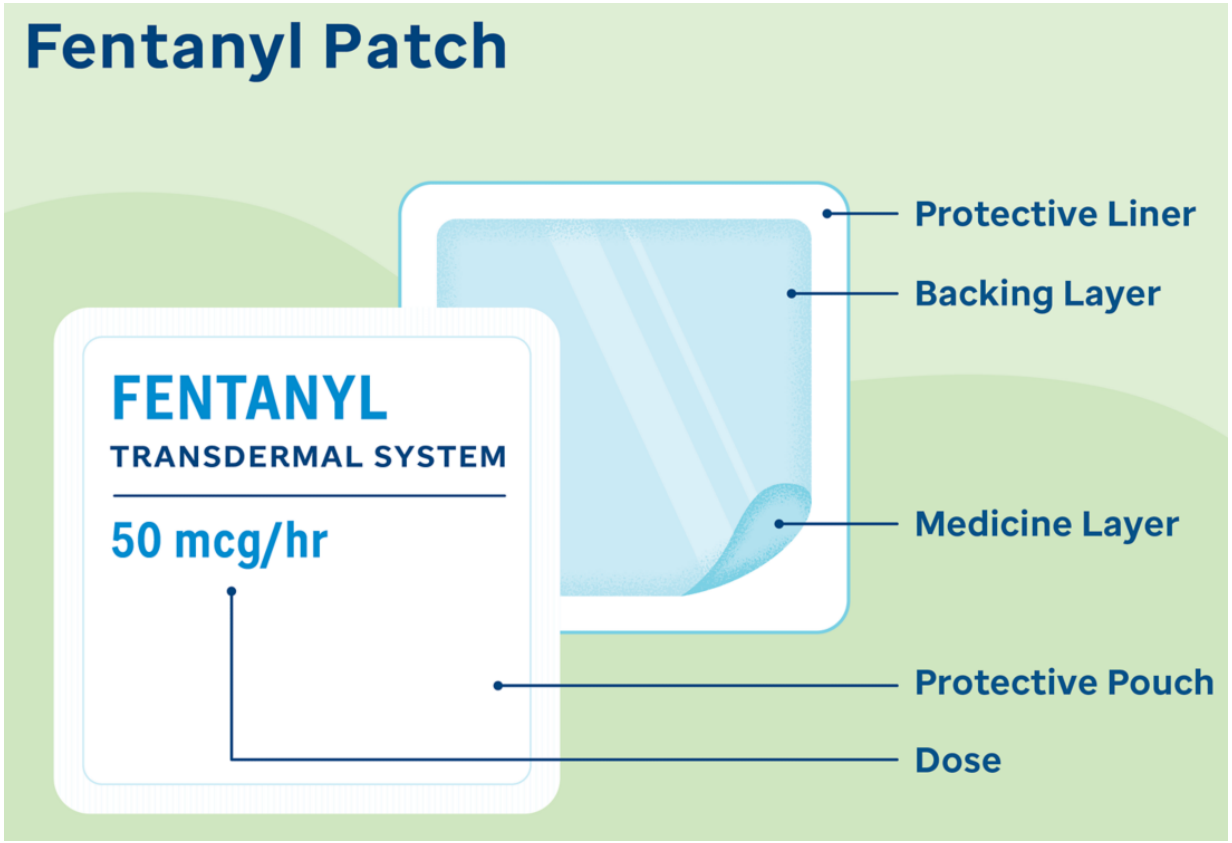
- “One pill can kill”
- Buprenorphine
  - Suboxone (buprenorphine/naloxone film and sublingual tablet)
  - Subutex (buprenorphine film, patch, sublingual tablet)

Fentanyl

- Available in many formulations
  - Sublingual Spray (Subsys) – 100 mcg, 200mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, 1600 mcg/spray
  - Patches (Duragesic) - 12.5 mcg/hr, 25 mcg/hr, 37.5 mcg/hr, 50 mcg/hr, 62.5 mcg/hr, 75 mcg/hr, 87.5 mcg/hr, 100 mcg/hr,
  - Lozenge on a Handle (Actiq) - 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, 1600 mcg
  - Buccal Tablets (Fentora, Abstral) - 100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg
- Highly lipid soluble and quickly crosses BBB

Abuse of Fentanyl Patches

- Inhalation:
  - Place patch in a glass container, heat, and smoke
  - Scratch and smoke the patches
- Ingestion
  - Remove gel contents and ingest
  - Cut frozen patches into pieces and chew or suck on them (“Chiclets”)
- Injection:
  - Remove gel contents and inject
  - Simmer patches in water and inject the liquid extract IV



Residual Amount of Fentanyl in Patch

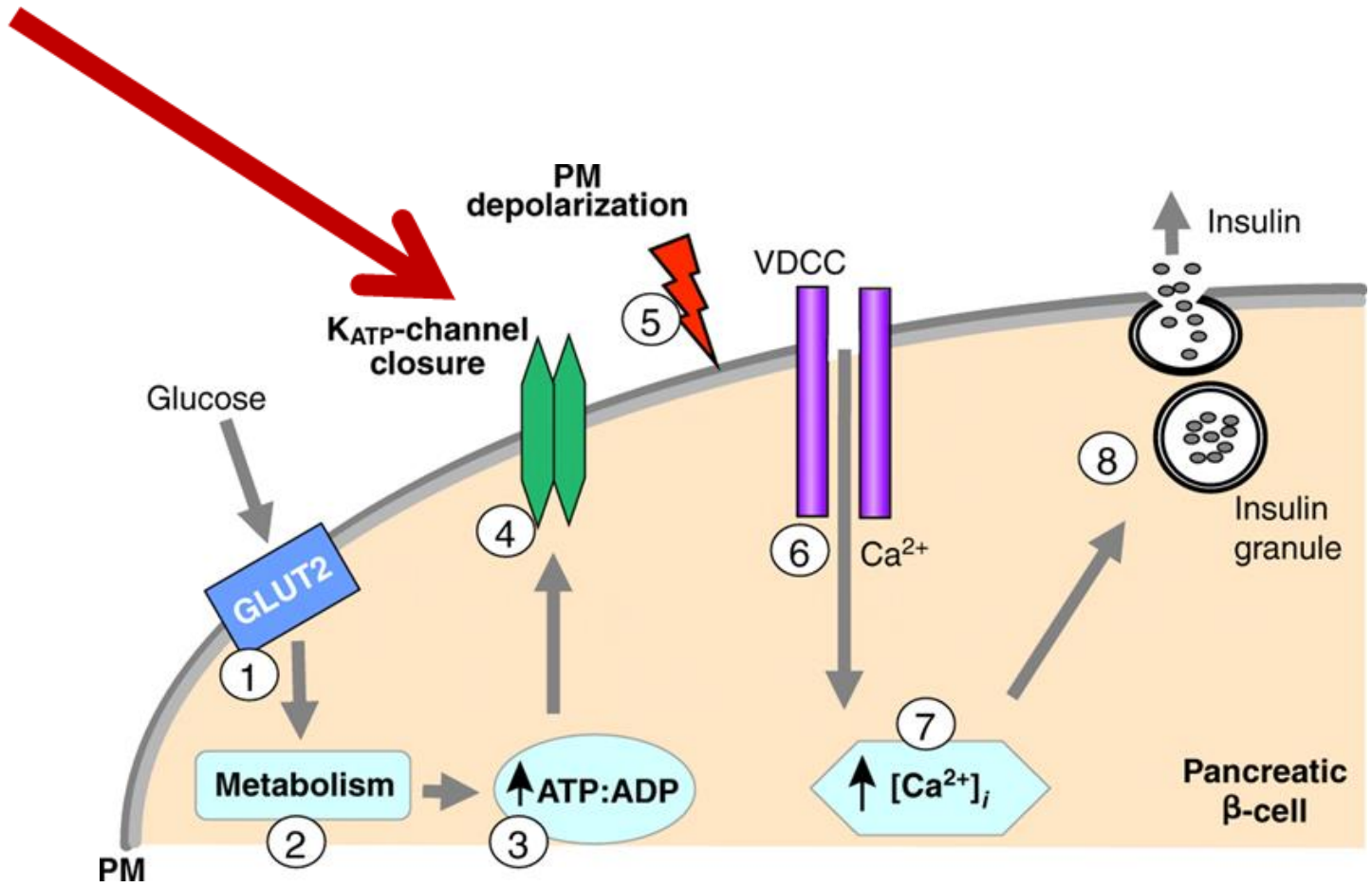
Patch Strength	Dose in Patch (mg)	Dose in Patch (mcg)	mcg used in 72 hours	Residual amount of drug in patch (mcg)
25 mcg/hour	2.75	2750	1800	950
50 mcg/hour	5.5	5500	3600	1900
75 mcg/hour	8.25	8250	5400	2850
100 mcg/hour	11	11000	7200	3800

Table of Comparative Opioid Potencies

Opioid	Potency Compared to Morphine	Potency Compared to Heroin
Morphine	1	~1/3
Heroin	2-5x	1
AH-7921	1.7x	
MT-45	3.5 x	
Butyrylfentanyl	7x	
U-47700	7.5x	
Acetylfentanyl	16-80x	5-15x
Fentanyl	50-100x	
3-methylfentanyl	1,000-7,000x	
Carfentanil	10,000x	4,000x

Sulfonylureas

- Glipizide, glyburide, glimepiride
- Stimulates pancreatic insulin secretion by closing K_{ATP} channels on beta cells.



Sulfonylureas

- Pediatric and geriatric patients are particularly sensitive to hypoglycemia
- Renally adjusted medications
- Usually observe patient for 12 hours minimum
    - Can have longer duration of hypoglycemia

Treatment for Sulfonylurea Ingestions

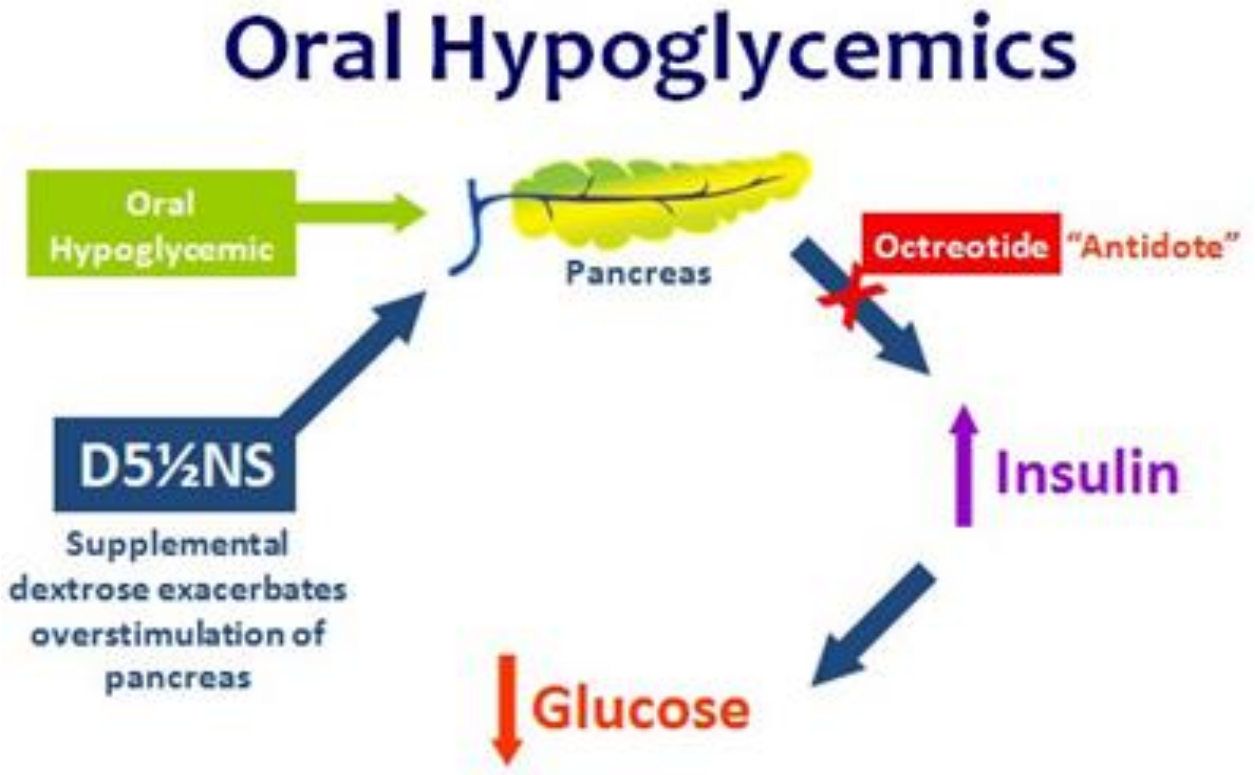
Asymptomatic patients need to be observed closely for signs or symptoms of hypoglycemia

Patients should be encouraged to eat, but should not be given prophylactic dextrose infusions

Bedside glucose determinations should be made every 1 to 2 hours for the first 8 to 12 hours after the initial exposure

Asymptomatic children should be observed with serial blood glucose monitoring for 24 hours following ingestion

Treatment with Octreotide



- Octreotide is a somatostatin analogue that inhibits insulin secretion and can be used for patients who are refractory to standard therapy with dextrose boluses and infusions.
- Octreotide should only be used after euglycemia has been achieved with IV dextrose
  - It will only prevent further episodes of hypoglycemia
- In children, a dose of 1 mcg/kg subQ every 6 hours can be used.
- A continuous infusion of octreotide can be administered in patients with prolonged, refractory hypoglycemia.
- Octreotide is generally considered to be well tolerated with local irritant effects predominating after subQ injection.

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