1

Financial Disclosure and Resolution

- Under guidelines established under the Standards for Integrity and Independence in Accredited Continuing Education, disclosure must be made regarding relevant financial relationships with ineligible companies within the last 24 months.

Kristie Edelen, Pharm.D., DABAT

- I have no relevant financial relationships with ineligible companies to disclose.

2

Professional Practice Gap

Toxicology is a very specialized area of pharmacy practice that is not familiar to most retail and hospital pharmacist, but many pharmacists may be asked questions about the potential toxicity of exposures from antidepressant and neuroleptic medications as well as lithium. Due to the nature of these drug classes, they tend to be a leading culprit in intentional self-harm cases. The appropriate action is to consult the Oklahoma Poison Center, but this presentation will help pharmacists to identify life-threatening exposures from antidepressant and neuroleptic medications and lithium and select the appropriate treatment modalities for a patient case.

3

Learning Objectives

Describe	Describe the mechanisms of toxicity and clinical effects of antidepressant and neuroleptic medications
Develop	Develop a treatment strategy for a patient suffering from antidepressant and neuroleptic overdose
Choose	Choose effective treatment plans for serotonin toxicity and neuroleptic malignant syndrome

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Call comes into the poison center from an emergency physician…

- 56 y/o male
- Possible ingestion?
- Patient found unresponsive in bed this morning
- Paramedics picked him up and he had a seizure enroute to ED with tachycardia and hypotension
- Patient's QRS is 133 after 5 amps of sodium bicarbonate
- Patient had 2 seizures in the ED

5

Patient Case Continues

- Patient went into v-tach
- Becoming more somnolent; comatose – not responsive to pain
- Paramedics were bagging him on arrival
- BP 70s/30s
- HR 160s
- RR 6-8
- Wide complex tachycardia

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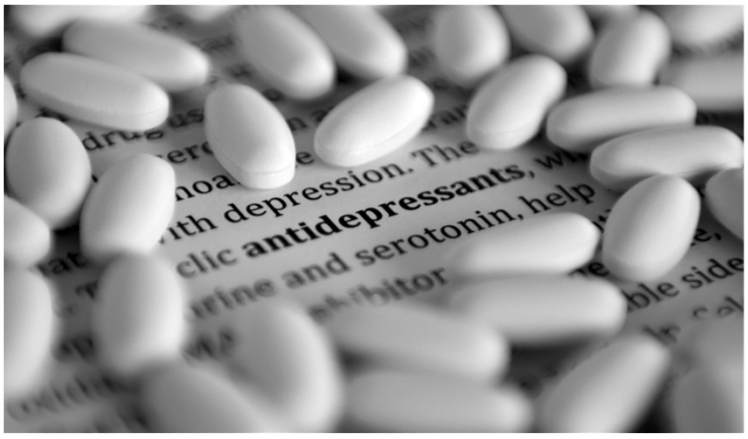
Antidepressants



- Tricyclic Antidepressants (TCAs)
- Selective Serotonin Reuptake Inhibitors (SSRIs)
- Serotonin/Norepinephrine Reuptake Inhibitors
- Atypical Antidepressants
  - Bupropion, trazodone

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Tricyclic Antidepressants

Generic Name	Brand Name
amitriptyline	Elavil
amoxapine	Asendin
clomipramine	Anafranil
desipramine	Norpramine
doxepin	Sinequan/Prudoxin/Silenor/Zonalon
imipramine	Tofranil
nortriptyline	Pamelor
protriptyline	Vivactil
trimipramine	Surmontil

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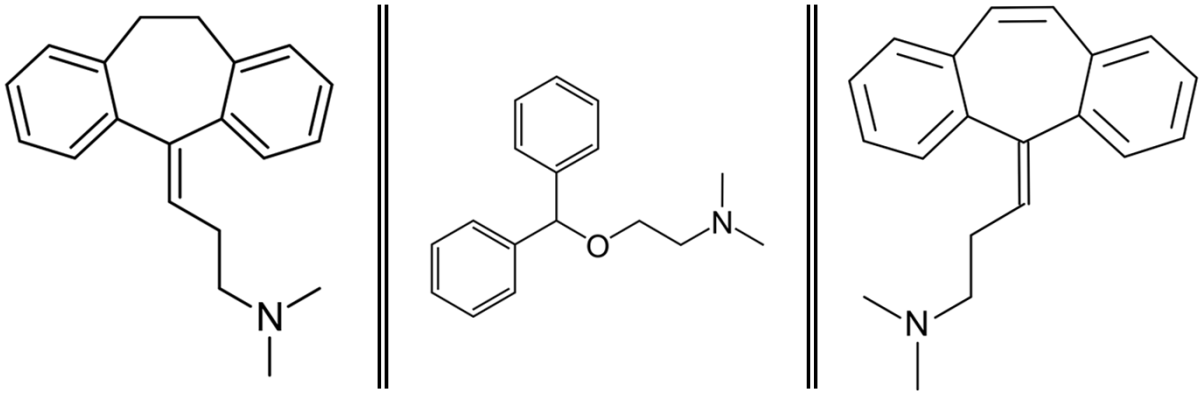

amitriptyline diphenhydramine cyclobenzaprine

Structural Relationships

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False Positives for TCAs

- carbamazepine (Tegretol)
- cyclobenzaprine (Flexeril)
- cyproheptadine (Periactin)
- diphenhydramine
- hydroxyzine
- quetiapine (Seroquel)

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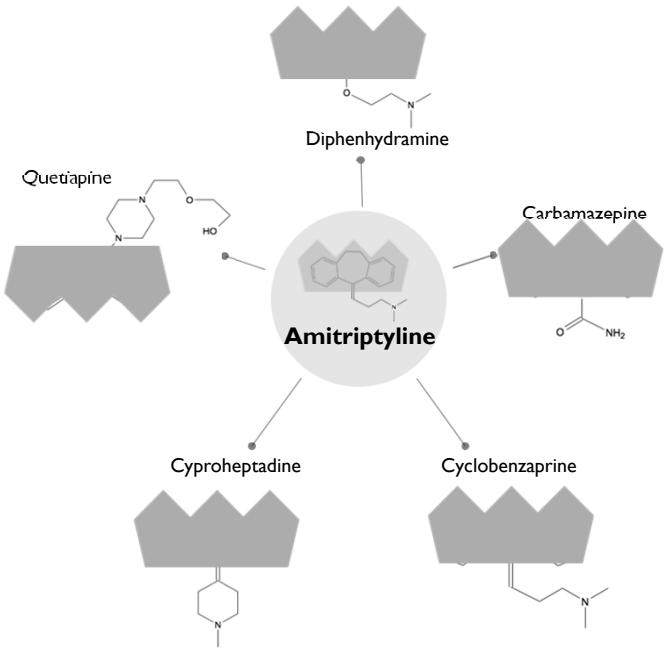

False Positives: TCA's

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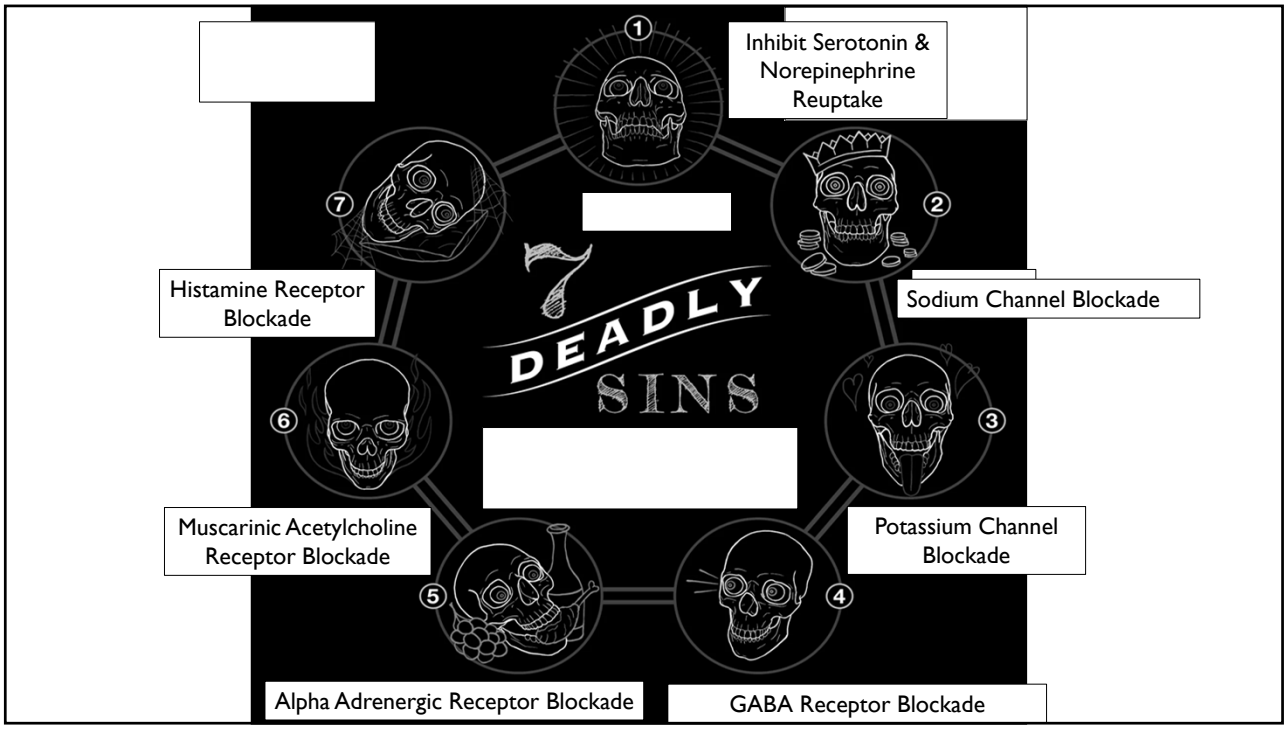

13

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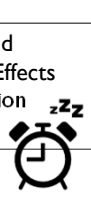
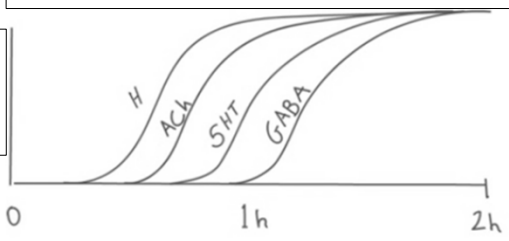
TCA Toxicologic Effects

CNS Effects

Antihistamine and Anticholinergic Effects
- CNS depression
- Tachycardia

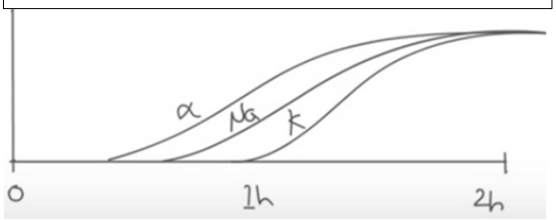




Seizures

Cardiac Effects

Hypotension



Wide Complex Tachycardia > Cardiac Arrest

https://www.thoracic.org/professionals/clinical-resources/video-lecture-series/critical-care/tricyclic-acid-overdose.php

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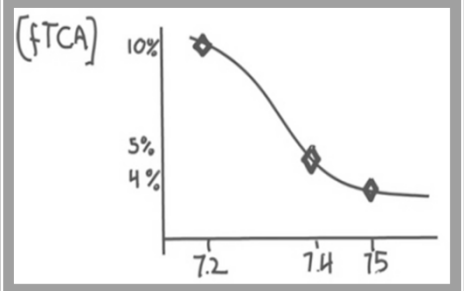
TCA Toxicologic Effects



Lower pH increases the amount of free TCA concentration [fTCA] creating a death spiral

90% of the binding of TCAs to the sodium channel occurs in the ionized state

Alkalinizing the blood facilitates the movement of the TCA away from the hydrophilic sodium channel and into the lipid membrane

Death Spiral: seizure > metabolic acidosis > increased free drug > cardiac arrest

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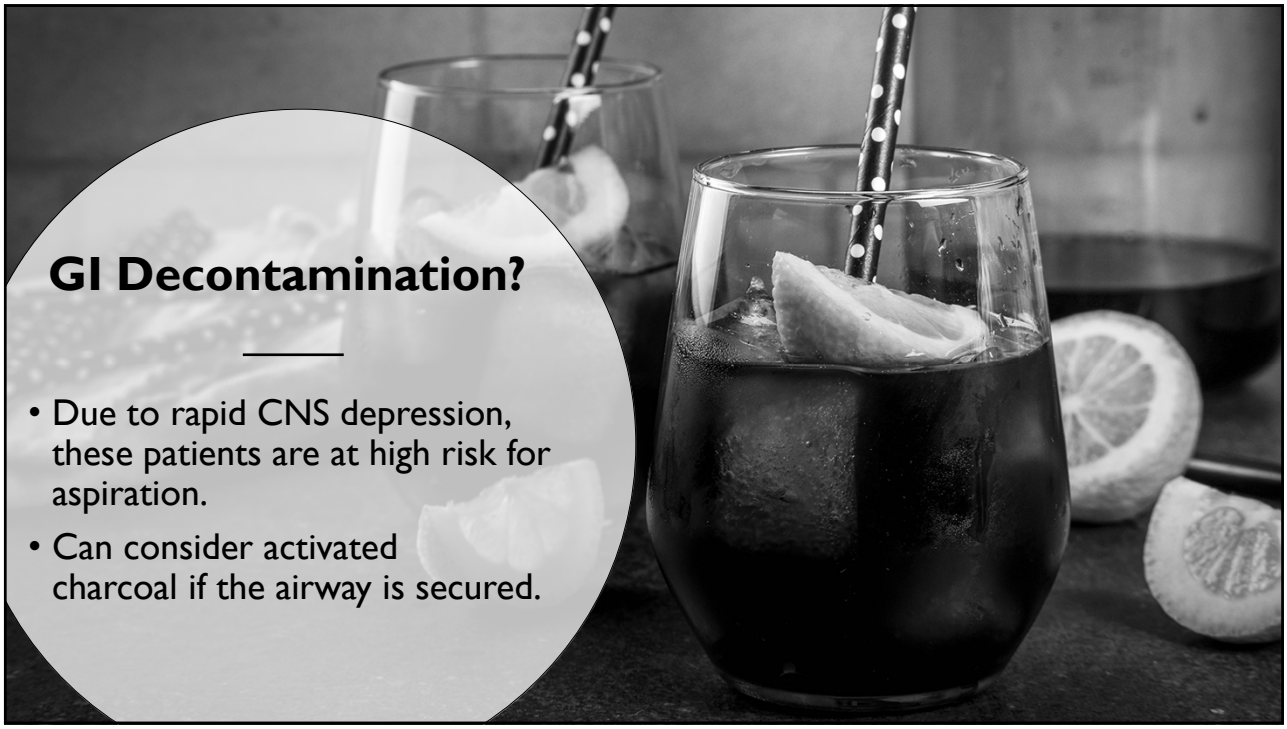

GI Decontamination?

- Due to rapid CNS depression, these patients are at high risk for aspiration.
- Can consider activated charcoal if the airway is secured.

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Treatment

Antihistamine and Anticholinergic Effects

Don't give physostigmine! Can precipitate seizures.

Supportive Care/Time

Seizures

Benzos > Propofol

Sodium bicarbonate

Hypotension

Fluids

Norepinephrine

Phenylephrine

Wide Complex Tachycardia > Cardiac Arrest

Sodium bicarbonate

Hypertonic saline

Intralipid

Lidocaine

Sodium bicarbonate drip: D5 + 40mEq K + 3 amps bicarb (150 mEq) + 2x maintenance + 1 bag

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VALUE OF THE QRS DURATION VERSUS THE SERUM DRUG LEVEL IN PREDICTING SEIZURES AND VENTRICULAR ARRHYTHMIAS AFTER AN ACUTE OVERDOSE OF TRICYCLIC ANTIDEPRESSANTS

MARK T. BOEHNERT, M.D., AND FREDERICK H. LOVEJOY, JR., M.D.

1. Serum drug levels failed to predict the risk of seizures or ventricular arrhythmias
2. Seizures occurred at any QRS duration of 0.10 second or longer
3. Ventricular arrhythmias were seen only with a QRS duration of 0.16 second or longer
4. Determination of the QRS duration predicts the risk of seizures and ventricular arrhythmias in acute overdose with TCAs
5. Patients who acquired symptoms (seizures or ventricular arrhythmias) did so by six hours after the overdose

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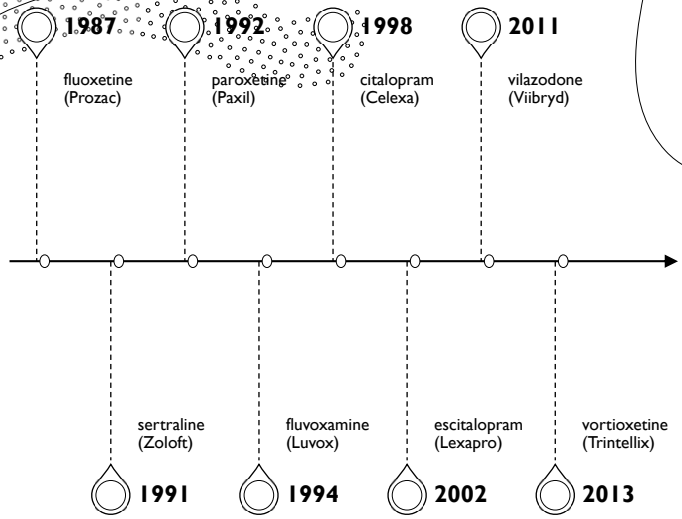
Selective Serotonin Reuptake Inhibitors (SSRIs)



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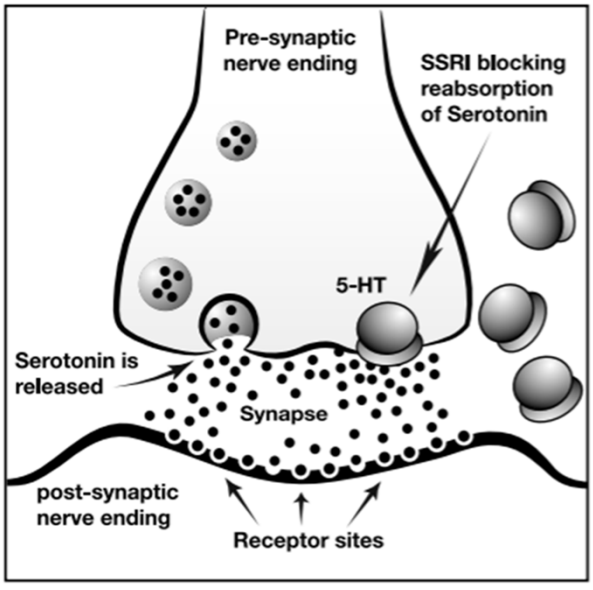
SSRI MECHANISM OF ACTION

- Antidepressant
- SSRIs selectively inhibit presynaptic serotonin reuptake
- They have minimal effects on NE and DA uptake
- Serotonin more readily available



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BACKGROUND

- Just as effective as TCAs and MAOIs for major depression
- Few side effects, less problematic in overdose
- Different PK profiles and metabolites that are substrates or inhibitors of CYP enzymes
- Diverse elimination patterns

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PK PROFILES

SSRI	Half-Life (hours)	Metabolite Half-Life	Peak Plasma Level (hours)	% Protein Bound	Bioavailability (%)
Citalopram (CeleXA)	35	S-desmethyl-citalopram: 59 hours	4	80	80
Escitalopram (Lexapro)	27 to 32	S-desmethyl-citalopram: 59 hours	5	56	80
FLUoxetine (PROzac, PROzac Weekly, Sarafem, Selfemra)	Initial: 24 to 72 Chronic: 96 to 144	Norfluoxetine: 4 to 16 days	6 to 8	95	72
FluvoxaMINE (Luvox CR)	14 to 16	N/A	3 to 8	80	IR: 53 ER: 84
PARoxetine (Paxil, Paxil CR, Pexeva)	21	N/A	5	95	>90
Sertraline (Zoloft)	26	N-desmethyl-sertraline: 62 to 104 hours	5 to 8	98	88

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PK PROFILES

Drug	Typical Daily Dose Range (mg)	$t_{1/2}$ (h)	Major Metabolic Mechanism	Major Active Metabolites	Major Active Metabolite $t_{1/2}$	Drug (d) or Metabolite (m) Inhibits CYP
SSRIs						
Citalopram	20–60	33–37	2C19, 3A4, 2D6	Monodesmethylcitalopram, didesmethylcitalopram	59 h	None or unknown
Escitalopram	10–20	22–32	2C19, 3A4, 2D6	S(+)-Desmethylcitalopram	59 h	None
Fluoxetine	10–80	24–144	2C9, 2D6	Norfluoxetine	4–16 d	2D6 (d,m), 2C19 (d,m), 2D6 (d,m), 3A4 (m)
Fluvoxamine	100–300	15–23	1A2, 2D6	None	N/A	1A2, 2C9, 2C19, 3A4
Paroxetine	10–50	2.9–44	2D6	None	N/A	2D6
Sertraline	50–200	24	2C9, 2B6, 2C19, 2D6, 3A4	Desmethylsertraline	62–104 h	2C19 (d,m)

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SSRI TOXICITY

- Drowsiness, tremor, nausea, & vomiting
- Less common: CNS depression and sinus tachycardia
- Seizures, prolongation of QRS complex and QT interval duration have been reported but very rare
- Seizures & QT interval prolongation more commonly with citalopram and escitalopram
- > 600mg of citalopram or more than 300 mg escitalopram
- 8-12 hour observation time usually sufficient

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SSRI TOXICITY MANAGEMENT

Supportive care: benzos for seizures; replace Mag for QTc prolongation

IV fluids containing dextrose and thiamine – for altered mental status

12-lead ECG to identify other cardiotoxic drugs

Cardiac monitor for citalopram or escitalopram

AC after stabilization – especially for citalopram and escitalopram

100mg citalopram & 50mg of escitalopram can be managed at home for children and adults; up to 5x therapeutic dose

Fatalities are rare and are usually associated with co-ingestants

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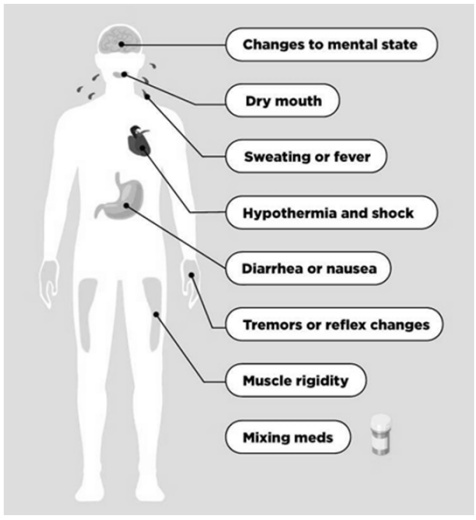
Serotonin Syndrome

- Serotonin syndrome can result from an overdose or drug interaction involving one or more of the many drugs that increase serotonergic activity.
- The Hunter Criteria is often used for the diagnosis of serotonin syndrome.

- To fulfill the Hunter Criteria, a patient must have taken a serotonergic agent and meet ONE of the following conditions:
  1. Spontaneous clonus
  2. Inducible clonus PLUS agitation or diaphoresis
  3. Ocular clonus PLUS agitation or diaphoresis
  4. Tremor PLUS hyperreflexia
  5. Hypertonia PLUS temperature above 38°C PLUS ocular clonus or inducible clonus



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Treatment of serotonin syndrome

- In addition to supportive care, benzodiazepines are given to eliminate agitation, tremor, clonus, and elevations in heart rate and blood pressure.
- Cyproheptadine, an anti-serotonergic antihistamine can be given as well.
  - Give 12 mg orally or by orogastric tube as the initial adult dose.
- Patients with severe serotonergic effects such as muscle tremors, hyperthermia*, and seizures may require:
  - Intubation
  - Aggressive sedation and cooling
  - Possibly neuromuscular blockade

*When patients reach body temp of 106-107°F, there is about a 7–9-minute window before they start denaturing proteins.

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Bupropion Overdose

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Bupropion Overview

- Bupropion is increasingly used for several indications:
  - Depression
  - Tobacco cessation
  - ADHD
- Immediate Release Tablets: 75mg and 100mg
- Extended Release 12-Hour Tablets: 100mg, 150mg, 200mg
- Extended Release 24-Hour Tablets: 150mg, 174mg, 300mg, 348mg, 450mg, 522mg

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Bupropion Overview

- **Bupropion is far more dangerous than other commonly used antidepressants.**
  - Bupropion can cause cardiogenic shock - 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.

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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.

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Bupropion Pharmacokinetics

- *Bupropion (especially the XR formulation) is a pharmacokinetic slug.*
  - *It takes a long time to be absorbed, and even longer to be excreted.*
- **Absorption**
  - With therapeutic dosing:
    - With **immediate release** formulations, serum levels may peak after ~1.5 hours.
    - With **extended release** formulations, serum levels may peak after ~5 hours.
  - A *toxic* dose of bupropion may take far *longer* to reach peak levels (due to ongoing absorption).
- **Metabolism & Elimination**
  - Bupropion is largely metabolized by CYP2B6 in the liver.
  - Metabolism occurs very slowly, with a half-life of about a day (for the extended-release formulation). In overdose, this could occur even more slowly.
  - Hydroxybupropion is a potentially toxic metabolite.

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Bupropion GI Decontamination

- Activated Charcoal:
  - Bupropion is lipophilic, so it should bind to activated charcoal.
  - For a large bupropion ingestion, the amount of charcoal needed to bind all of the bupropion may be excessive.
- Whole Bowel Irrigation:
  - Whole bowel irrigation may be a rational approach to large intoxications of *sustained-release* bupropion.
  - The main goals of whole bowel irrigation are roughly two-fold:
    - (1) **Avoid death due to cardiogenic shock.** Massive bupropion ingestion can be refractory to all conventional therapies (there is no effective antidote).
    - (2) **Minimize time on mechanical ventilation.** Patients with large overdoses of bupropion XR can require prolonged support on mechanical ventilation due to coma or seizures. Minimizing the absorbed dose and avoiding persistent drug absorption could accelerate weaning off ventilation.

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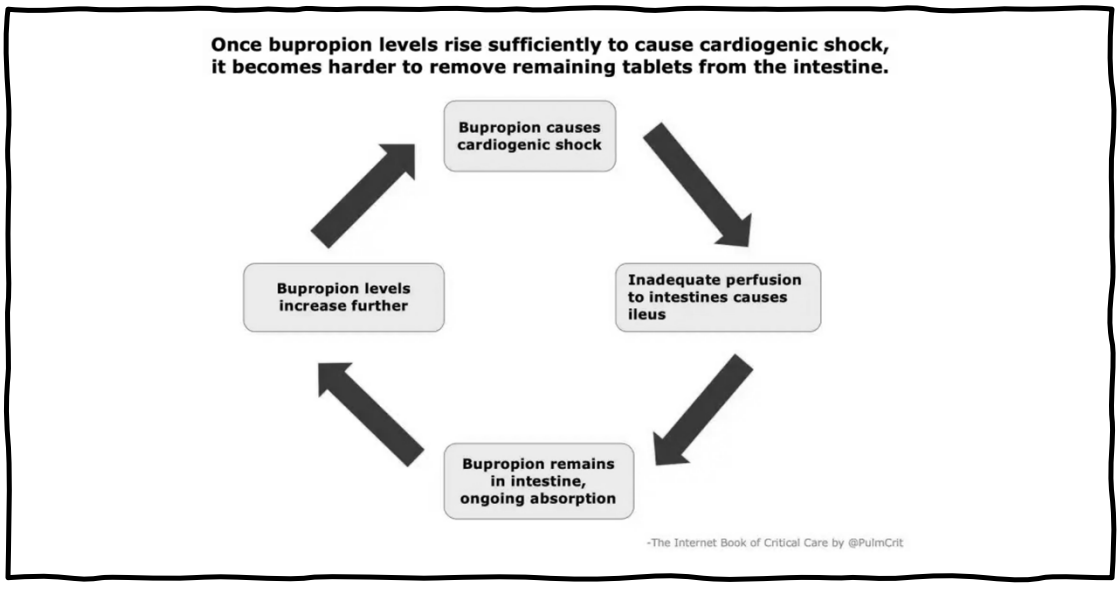

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Treatment of Neurotoxicity

Agitation/Delirium

- Front-line therapy is benzodiazepines (which could potentially reduce the risk of seizure)

Seizure

- Front-line therapy is benzodiazepines.
- For recurrent seizures or status epilepticus, consider intubation and propofol infusion.
- Levetiracetam is often used to prevent seizure recurrence (although no good evidence exists regarding this).
- It might be ideal to avoid the following therapies:
  - (1) Definitely avoid phenytoin (may promote bradycardia, hypotension; generally not a favored agent for seizures due to intoxication).
  - (2) Phenobarbital might not be an ideal option due to its potential hypotensive effects (if patients progress into a cardiotoxic phase, phenobarbital cannot be withdrawn).

Brain-Death Mimic

- Continue aggressive supportive care (these patients will generally make a full recovery).
- Wait for bupropion to metabolize (which may take days).
- Video EEG monitoring to surveil for seizure might be considered.

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Treatment of Cardiotoxicity

Catecholamine Vasopressors

- These are often required.
- There is no evidence regarding the optimal agent.
- Norepinephrine is often a good choice, but this may also depend on the individual patient's hemodynamics.

Intralipid

- Intralipid is supported by a handful of case reports.
- One case study did demonstrate increased blood bupropion levels following administration of intralipid, supporting the concept that intralipid functions as a "sink" to remove bupropion from the myocardium.

VA ECMO

- This is an excellent option for patients with bupropion-induced *cardiogenic* shock refractory to other treatments (e.g. with profoundly reduced ejection fraction).

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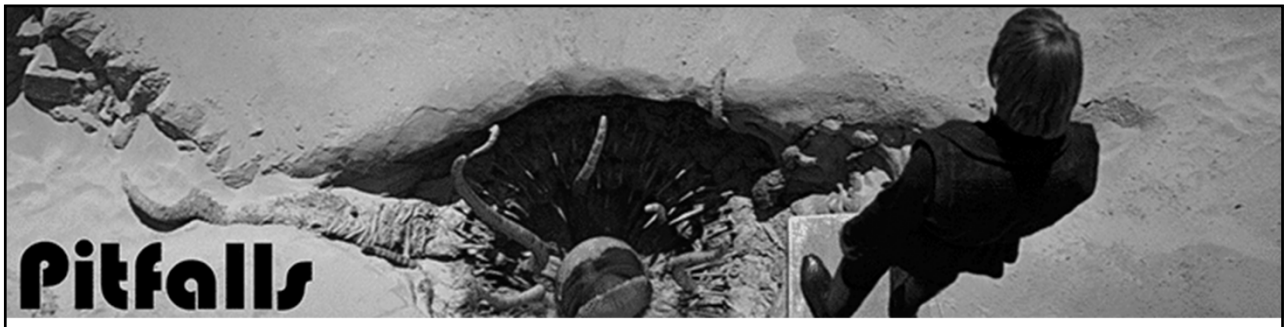

1. Lack of awareness that bupropion intoxication can be life-threatening (and far more severe, for example, than selective serotonin reuptake inhibitors).
2. Failure to understand the latent phase of bupropion intoxication, leading to inappropriately early discharge.
3. Failure to consider whole bowel irrigation for an intubated patient with massive bupropion XR intoxication (especially at a non-ECMO center, where this intoxication can outrun all available therapies).
4. Incorrect diagnosis of brain death in a patient with bupropion intoxication, leading to inappropriate withdrawal of life-sustaining therapy.

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NEUROLEPTICS

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OUTLINE

- Butyrophenones
- Phenothiazines
- Atypical Antipsychotics
- EPS and NMS

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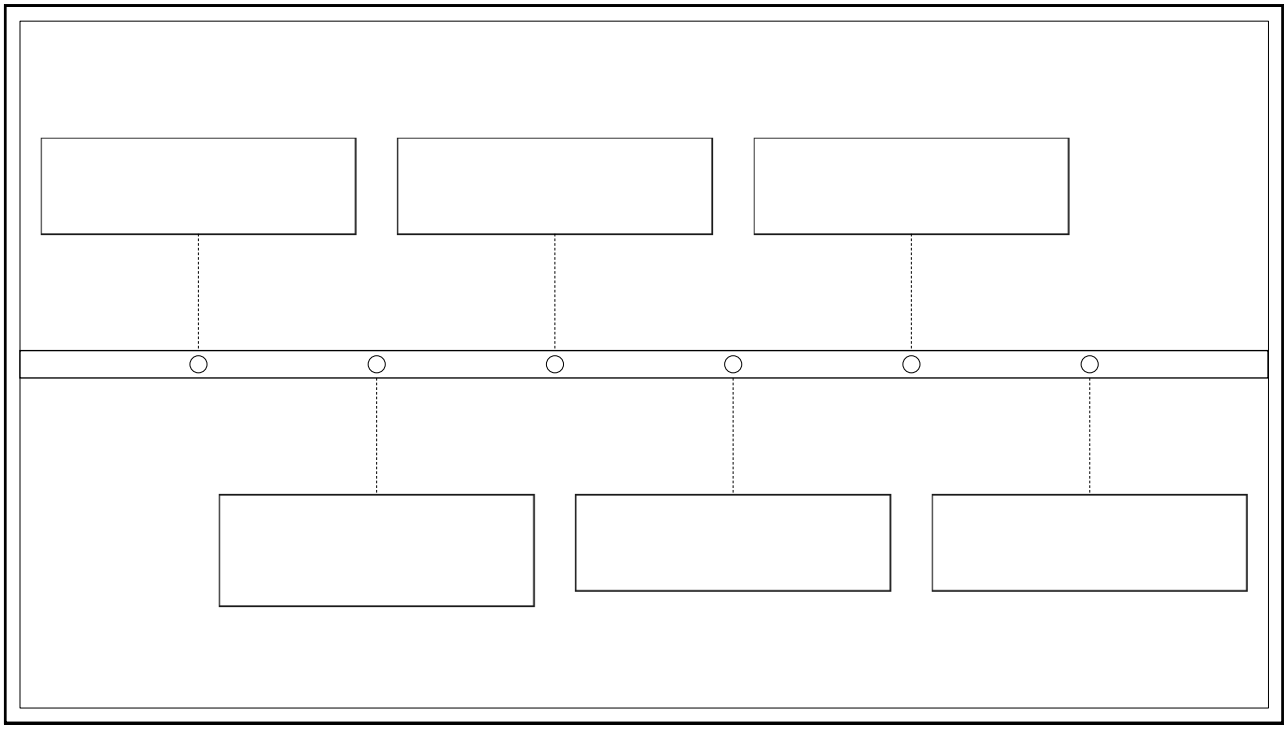

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FIRST GENERATION / TYPICAL ANTIPSYCHOTICS

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FIRST GENERATION / TYPICAL ANTIPSYCHOTICS

- Droperidol (Inapsine)
- Haloperidol (Haldol)
- Chlorpromazine (Thorazine)
- Fluphenazine (Prolixin)
- Perphenazine (Trilafon)
- Prochlorperazine (Compazine)
- Thioridazine (Mellaril)
- Thiothixene (Navane)

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FIRST GENERATION / TYPICAL ANTIPSYCHOTICS

- Droperidol (Inapsine) → **BUTYROPHENONES**
- Haloperidol (Haldol)
- Chlorpromazine (Thorazine)
- Fluphenazine (Prolixin)
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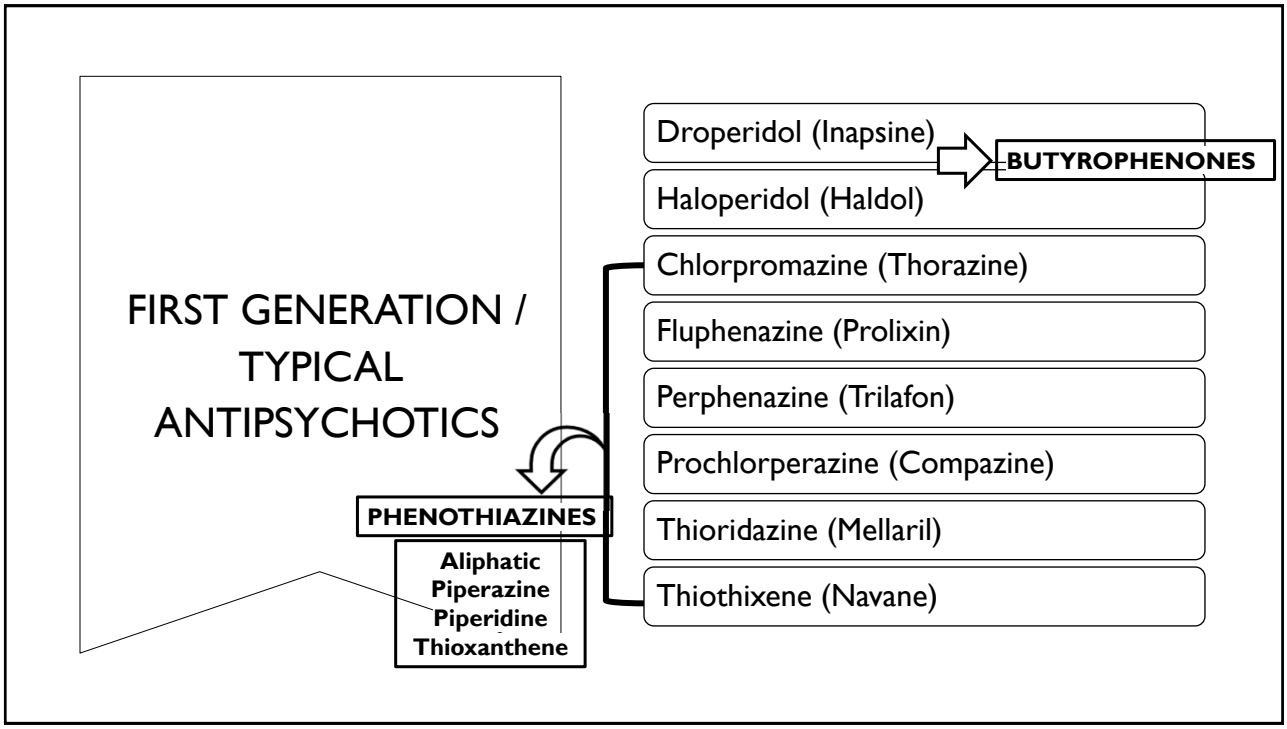

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BUTYROPHENONES

Nonselective Postsynaptic Blockade Of D2 receptors

DROPERIDOL	HALOPERIDOL
• Vd: 2-3 L/kg • T1/2: 2-10 hours • 90% protein binding • No active metabolite	• Vd: 18-30 L/kg • T1/2: 14-41 hours • 99% protein binding • Active metabolite

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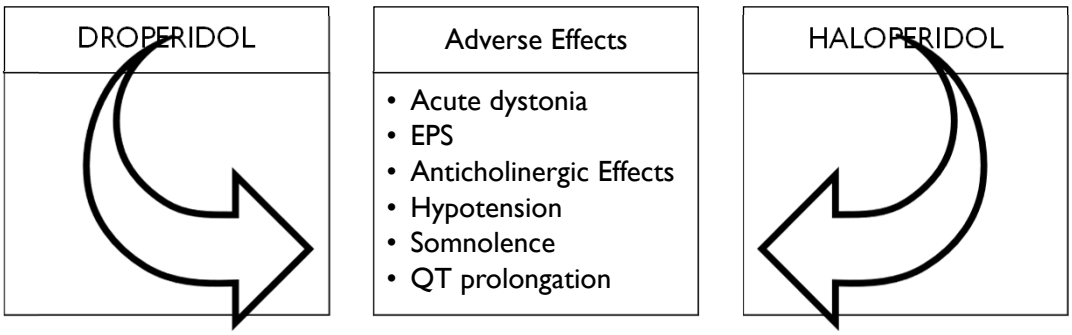
BUTYROPHENONES

Nonselective Postsynaptic Blockade Of D2 receptors



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PHENOTHIAZINES

D2 Receptor Blockade

Class	Name	Vd	T1/2 (hours)	Protein binding
Aliphatic	Chlorpromazine	10-35 L/kg	18-30 hours	98%
Piperazine	Fluphenazine	220 L/kg	13-58 hours	99%
	Perphenazine	10-35 L/kg	8-12 hours	> 90%
	Prochlorperazine	13-32 L/kg	17-27 hours	> 90%
Piperidine	Thioridazine	18 L/kg	26-36 hours	96%
Thioxanthene	Thiothixene	?	12-36 hours	> 90%

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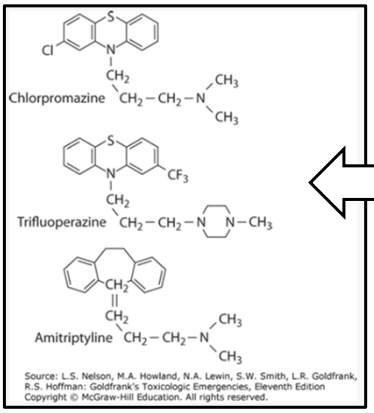
PHENOTHIAZINES MECHANISM OF ACTION



D2 Receptor Blockade

- Mesolimbic/Mesocortical Pathways – Antipsychotic Effects
- Chemoreceptor Trigger Zone – Antiemetic effects
- Hypothalamus - ↑Prolactin
- Nigrostriatal Pathway – Movement Disorders

Structural similarity to TCAs

- Alpha-1 adrenergic antagonism - Hypotension
- Muscarinic antagonism – Anticholinergic effects
- Fast Sodium Channel (INa) Blockade – QRS widening & Myocardial depression
- Delayed Rectifier (IKr) Current Blockade – QT prolongation & Torsades de Pointes

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PHENOTHIAZINE CLINICAL MANIFESTATIONS

Dopamine Blockade

- Somnolence, coma, EPS (occurs at therapeutic doses), sexual dysfunction

Muscarinic Blockade

- Mydriasis, urinary retention, blurred vision, dry mouth, impaired peristalsis, tachycardia, hyperthermia

Central Anticholinergic Blockade

- Agitation, delirium, psychosis, hallucinations

Alpha Adrenergic Blockade

- Hypotension

Sodium Channel Blockade

- QRS complex widening

Potassium Channel Blockade

- QT interval prolongation
- Torsades de Pointe

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Clinical and Toxicologic Manifestations of Typical Neuroleptics

	Hypotension	Anticholinergic Effects	QRS complex widening	QT interval prolongation
Chlorpromazine	+++	++	++	++
Fluphenazine	-	-	+	+
Haloperidol	-	-	+	++
Loxapine	+++	++	++	+
Mesoridazine	+++	+++	+++	++
Perphenazine	+	-	+	++
Pimozide	+	-	+	++
Thioridazine	+++	+++	+++	+++
Trifluoperazine	+	-	+	++

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PHENOTHIAZINE TOXICITY MANAGEMENT

ABCs
- Gastric decontamination
  - Agents do adsorb to AC
- Screen for co-ingestants
  - Not just typical APAP/ASA/EtOH
  - Consider lithium, valproate, etc.
- EKG and CCM warranted
- Drug levels not clinically useful

Hypotension
- Aggressive fluid resuscitation
- Refractory: Norepi or phenylephrine

- Seizure
  - Benzos first line
  - Refractory: phenobarb or propofol
  - Avoid phenytoin
- Anticholinergic effects
  - Physostigmine has been used successfully in antipsychotic overdose
    - 1-2 mg slow IV push, can repeat every 10-25 min
    - Use caution in patient with EKG abnormalities
- EKG changes
  - Sodium bicarb for QRS > 120 msec
  - Refractory arrythmias: can use lidocaine (avoid Class Ia, Ic, and III)
  - Magnesium for TdP

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ATYPICAL ANTIPSYCHOTICS

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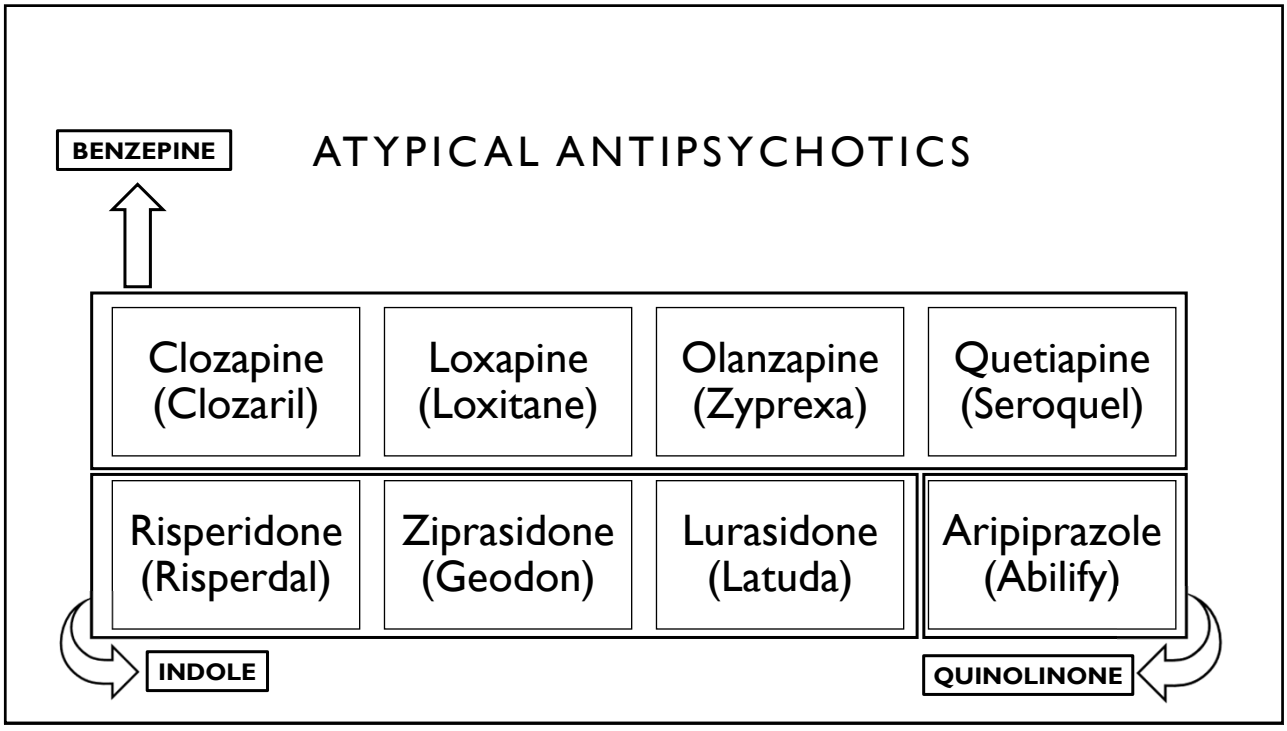

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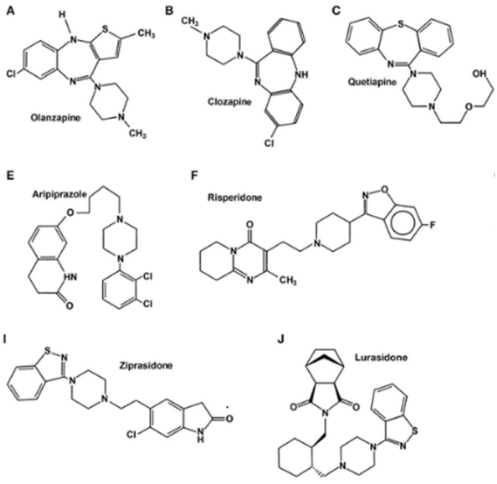
ATYPICALS MECHANISM OF ACTION



D2 Receptor Blockade

- Mesolimbic/Mesocortical Pathways – Antipsychotic Effects
- Atypicals are much more specific for D2 receptor
  - ↓ Prolactin
  - ↓ Antiemetic effects
  - ↓ Movement disorder

Not just specific for dopamine receptor

- Interferes with signalling at muscarinic receptors, histamine receptors, and alpha-adrenergic receptors
- Fast Sodium Channel Blockade
- Delayed Rectifier Potassium Channel Blockade
- 5-HT2A Receptor Blockade

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ATYPICAL ANTIPSYCHOTICS CLINICAL MANIFESTATIONS

CNS

- Somnolence, coma, respiratory depression, hyperthermia, EPS, central anticholinergic effects

Cardiovascular

- Tachycardia, hypotension, QRS widening, QT interval prolongation, TdP

Anticholinergic

- ↓ Bowel sounds, dry, flushing, mydriasis, tachycardia

Neuroleptic Malignant Syndrome

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Clinical and Toxicologic Manifestations of Atypical Neuroleptics

	Hypotension	Anticholinergic Effects	QRS complex widening	QT interval prolongation
Amisulpride	-	-	-	++
Asenapine	++	-	-	-
Aripiprazole	++	-	-	-
Clozapine	+++	+++	-	+
Iloperidone	+++	-	-	++
Lurasidone	-	-	-	-
Olanzapine	++	+++	-	-
Paliperidone	++	-	-	+
Quetiapine	+++	+++	+	- to +
Remoxipride	-	-	-	-
Risperidone	++	-	-	-
Sertindole	+	-	-	++
Ziprasidone	++	-	-	+++

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ATYPICALS TOXICITY MANAGEMENT

ABCs
- Gastric decontamination
  - Agents do adsorb to AC
- Screen for co-ingestants
  - Not just typical APAP/ASA/EtOH
  - Consider lithium, valproate, etc.
- EKG and CCM warranted

Hypotension
- Aggressive fluid resuscitation
- Refractory: Norepi or phenylephrine

- Seizure
  - Benzos first line
  - Refractory: phenobarb or propofol
  - Avoid phenytoin
- Anticholinergic effects
  - Physostigmine has been used successfully in antipsychotic overdose
    - 1-2 mg slow IV push, can repeat every 10-25 min
    - Use caution in patient with EKG abnormalities
- Tachydysrhythmias
  - Lidocaine is treatment of choice
  - Refractory: consider lipid rescue
  - Sodium bicarb for QRS > 120 msec
  - Magnesium for TdP

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EXTRAPYRAMIDAL SYNDROME(EPS)AND NEUROLEPTIC MALIGNANT SYNDROME (NMS)

61

Acute Dystonia
- Occurs within hours to days
- Sustained involuntary muscle contraction (dopamine/cholinergic imbalance)
- Tx: benzos or anticholinergic agents

Akathisia
- Occurs within hours to days
- Restless and unease (mesocortical dopamine antagonism)
- Tx: propranolol, benzos, or anticholinergic agents

Parkinsonism
- Occurs weeks after initiation of medication
- Resting tremors, bradykinesia, shuffling gait (postsynaptic striatal dopamine antagonism)
- Tx: dopamine agonists or anticholinergic agents

Tardive dyskinesia
- Occurs months to years after initiation of medication
- Involuntary choreiform movements, orobuccal, lingual, masticatory stereotypic movements (excessive dopamine activity)
- Discontinue offending agent, largely irreversible

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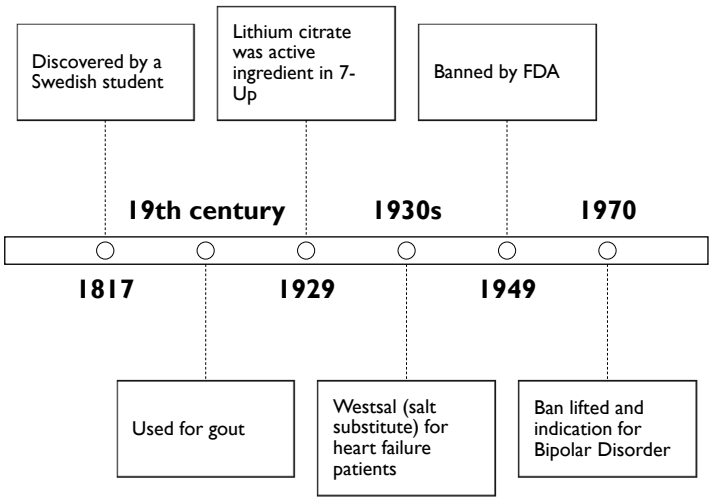
HISTORY OF LITHIUM



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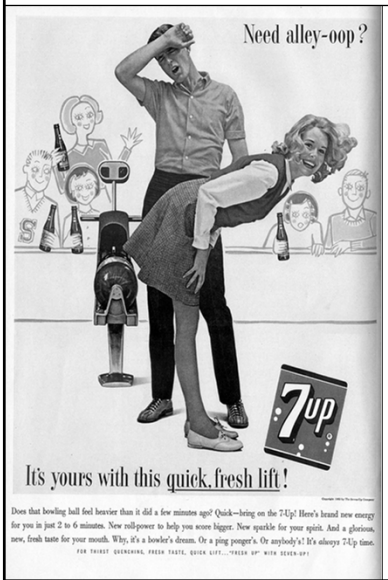

History and Epidemiology

- The soft drink 7-Up originally contained lithium as its "active ingredient."
- Considered the most effective long-term therapy for treatment and prevention of relapse of bipolar affective disorders.
- Demonstrated anti-suicidal effect and the ability to improve manic and depressive symptoms.
- Effective for compulsive gambling
- Has shown promise for use in neurodegenerative disorders such as Alzheimer's disease, ischemic stroke multiple sclerosis, and traumatic brain injury.

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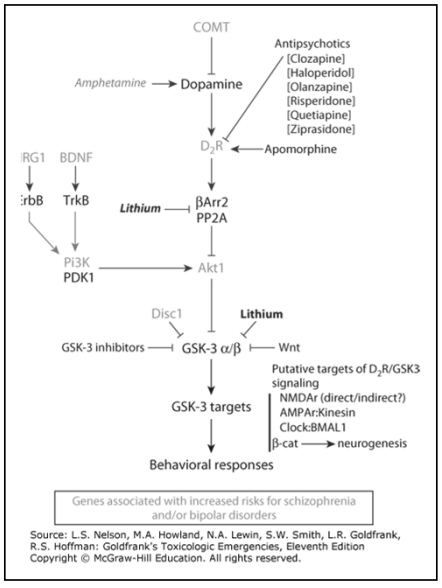
Pharmacology

- Lithium chemically is the simplest xenobiotic in the modern pharmacopeia.
- Complex mechanism of action that "eludes complete explication" after more than 50 year of clinical use and study.
- Direct inhibitor of glycogen synthase kinase 3 (GSK-3β)
- Postmortem tissue from the ventral prefrontal cortex of patients with MDD showed elevated GSK-3β activity.
- GSK-3β is inadequately inhibited in association with mood disorders and is inhibited in humans treated with lithium.



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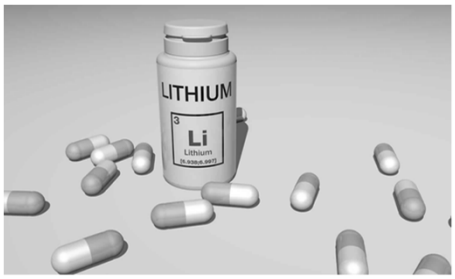
Pharmacokinetics & Toxicokinetics

- Vd = 0.6-0.9 L/kg
- No protein binding
- Distributes in total body water

- Distribution into CNS is active transport involving Na+/Li+ exchange

Tmax:
- Therapeutic: 1-2 hours IR; 4-5 hours SR
- Overdose > 12 hours

- Not metabolized
- Eliminated almost entirely (95%) by the kidneys, with a small amount eliminated in the feces
- Handled by the kidneys much in the same way as sodium
- Excretion is dependent on factors that affect the GFR or decrease serum sodium concentration.



Therapeutic range of serum lithium concentrations is 0.6 to 1.2 mmol/L

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Acute

Chronic

Acute-on-Chronic

Overdose Comes in Three Flavors

70

Clinical Manifestations

- Acute Toxicity
  - Patient has no body burden of lithium present at the time of ingestion
  - Predominant early GI effects – nausea, vomiting, and diarrhea are prevalent
  - Neurologic symptoms occur several hours after ingestion in acute toxicity because the lithium redistributes into the CNS from the serum.

71

Clinical Manifestations

- Chronic Toxicity
  - Patient has a stable body burden of lithium as the serum concentration is maintained in the therapeutic range, and then some factor disturbs this balance, either by enhancing absorption, or more commonly decreasing elimination.
  - Lithium is primarily a neurotoxin.
  - Approximately 27% of patients using lithium develop tremor.
    - Tremor diminishes over time with continued therapy but increases with toxicity.
  - Other finding of chronic toxicity include fasciculations, hyperreflexia, clonus, dysarthria, nystagmus, and ataxia
  - The mental status is often altered and progresses from confusion to stupor, coma, and seizures.
  - Syndrome of irreversible lithium-effectuated neurotoxicity (SILENT) - irreversible neurologic and neuropsychiatric sequelae of lithium toxicity.

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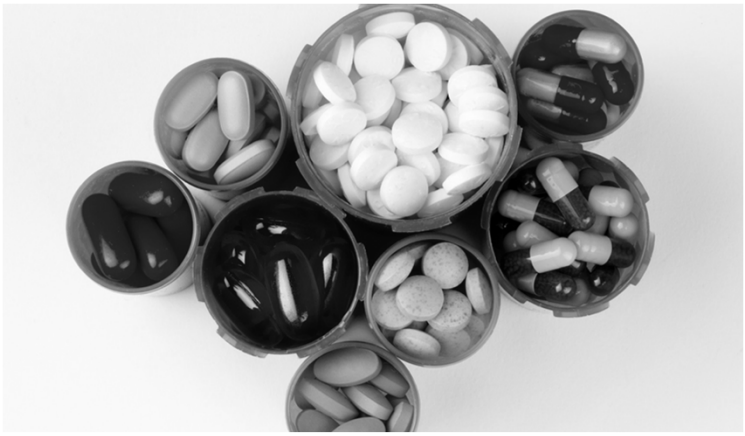
Clinical Manifestations



- Acute-on-Chronic Toxicity
  - Patient ingests an increased amount of lithium (intentionally or unintentionally) in the setting of a stable body burden.
  - With tissue saturation, any additional lithium leads to signs and symptoms of toxicity.
  - These patients display prominent GI and neurologic effects

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Clinical Manifestations

- Other Systemic Manifestations of Chronic Lithium Therapy
  - Nephrogenic diabetes insipidus (NDI)
  - Chronic tubulointerstitial nephropathy – AKI and/or CKD
  - Endocrine disorders: hypothyroidism
  - EKG abnormalities – T-wave flattening or inversion

74

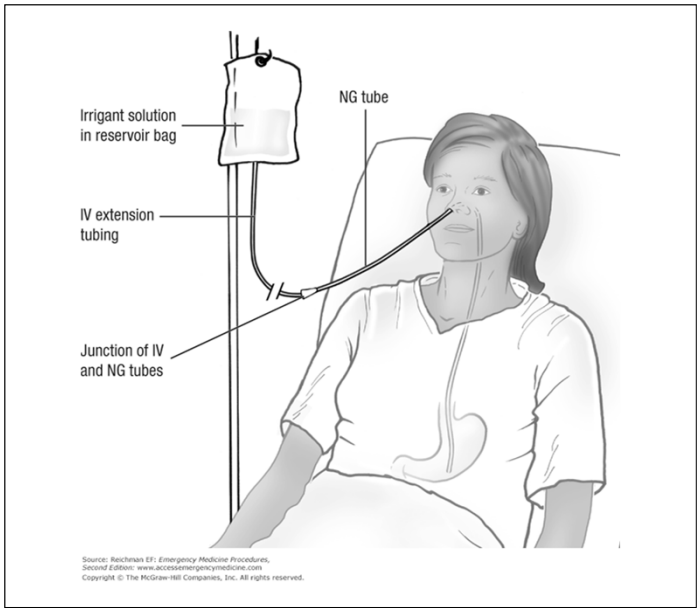
Diagnostic Testing

- Serum concentrations are usually readily obtainable
- Lithium concentration should be determined upon patient presentation and serial measurements obtained in most instances in which overdose or toxicity is likely.
- Emphasis should be placed on the lithium concentration as a marker of exposure and response to therapy, but not necessarily as a determinant of toxicity or treatment.
- The history, symptoms and clinical signs, rather than the absolute lithium concentration, should guide therapy.

75

Management

- Gastrointestinal Decontamination
  - AC will not adsorb to lithium
  - WBI recommended for patients manifesting significant toxicity (ie, neurologic dysfunction) and who have sustained release lithium preparations and have no contraindications (eg, protected airway, no obstruction or ileus)



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Management

- Fluid and Electrolytes
  - The critical initial management of the lithium-poisoned patient should focus on restoration of intravascular volume, both in those with acute poisonings with GI losses and in chronic poisonings with toxic effects that are often the result of disturbances of kidney function and lithium elimination.
  - NS at 1.5 to 2 times the maintenance rate
  - This will increase renal perfusion, and GFR, which will increase lithium elimination.
  - When the patient is hyponatremic, the kidney with retain lithium!
  - Same family!

77

Management

Extracorporeal Drug Removal

STRENGTH OF RECOMMENDATION	CONCENTRATION	OR CLINICAL FEATURES
Recommended	>4.0 mEq/L with ↓GFR	Decreased level of consciousness, seizures, or life-threatening dysrhythmias
Reasonable	>5.0 mEq/L	Confusion or [Li^+] not expected to fall to <1.0 mEq/L with optimal management in 36 h

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Summary

- Lithium is a simple ion with extensive current usage and extremely varied and complex clinical and pathophysiologic effects.
- Lithium is available in multiple formulations, both immediate release and sustained release, and has an essential role in clinical psychiatry.
- Because of the complexity of the pharmacokinetic profile of lithium, toxicity develops in a wide range of conditions and is precipitated by both intentional overdose and therapeutic misadventure.

79

Summary

- The care of lithium-poisoned patients should be based on rapid clinical evaluation of the condition of the patient coupled with identification of the type of poisoning.
- Management includes the use of volume resuscitation, WBI and/or hemodialysis, when indicated, to prevent or treat severe neurologic morbidity and mortality.
- Syndrome of irreversible lithium-effectuated neurotoxicity (SILENT) is a persistent neuropsychiatric consequence of lithium toxicity with predominant cerebellar findings that continue at least 2 months after cessation of lithium.

80

Anticholinergic vs. Sympathomimetic vs. Neuroleptic Malignant Syndrome vs. Malignant Hyperthermia vs. Serotonin Syndrome

81

Medical Resident Calls About A Patient Case

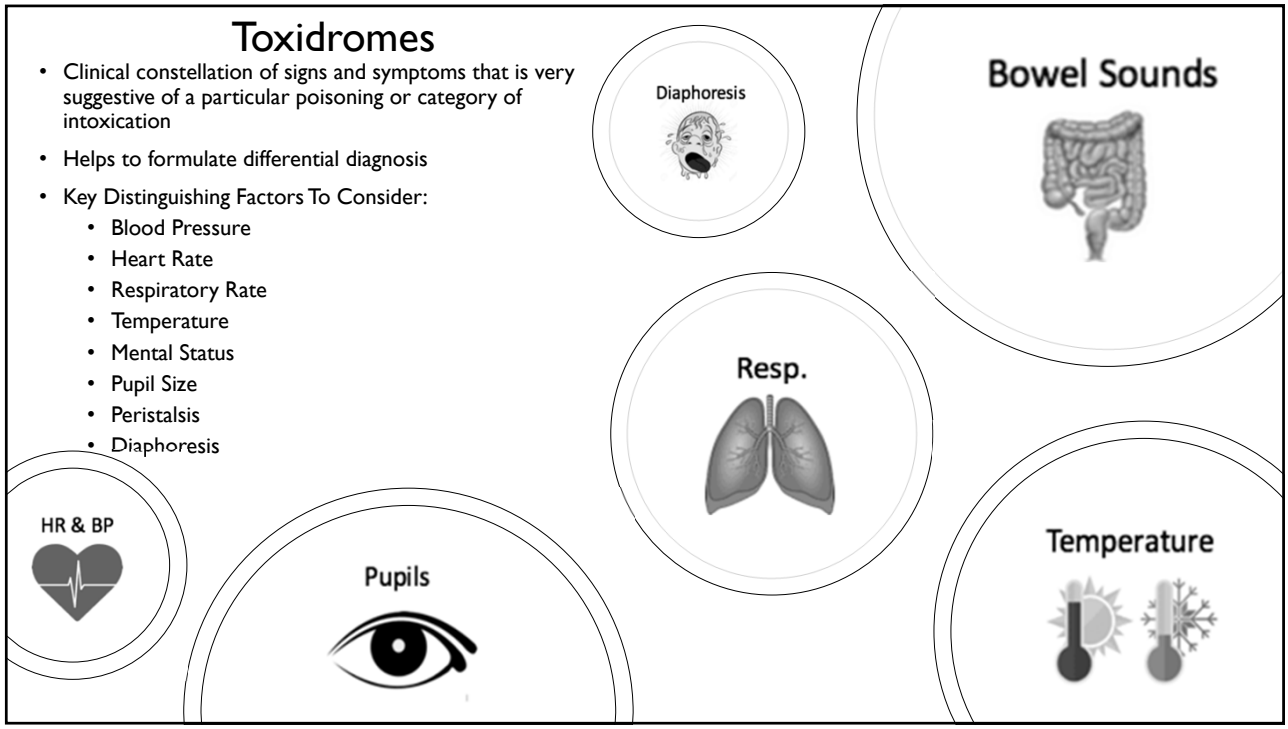
A 44 year-old woman presents to the emergency department with altered mental status. The patient is agitated but sleepy-appearing. She appears to be uncomfortable, shifting on the stretcher and unable to lie still. Her initial vitals are HR 141, rectal temperature 103.6F, BP 194/110, RR 22, SpO2 98% in room air.

Is my patient having serotonin syndrome?

82

Toxidromes

- Clinical constellation of signs and symptoms that is very suggestive of a particular poisoning or category of intoxication
- Helps to formulate differential diagnosis
- Key Distinguishing Factors To Consider:
  - Blood Pressure
  - Heart Rate
  - Respiratory Rate
  - Temperature
  - Mental Status
  - Pupil Size
  - Peristalsis
  - Diaphoresis



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Thermal Regulation

- Core body temperature is tightly regulated by negative feedback system
- Aims to maintain a "set point"
- ~0.5°C– 1°C around normal body temperature of 37°C
- Mediated by norepinephrine, serotonin, dopamine, acetylcholine, prostaglandins, neuropeptides
- Regulated through the pre-optic region of the hypothalamus
- As core temperature rises, efferent fibers of autonomic nervous system stimulated → sweating, cutaneous vasodilation

84

Patient Case

History

- A 27 year-old man was found acting abnormally in Bricktown.
- When approached by police he seemed to be hallucinating and answered questions inappropriately.
- When the paramedics arrived they recorded the following:
  - BP 148/92 mm Hg
  - HR 142 beats/min
  - RR 16 breaths/min
  - dilated pupils and disorientation
- IV was started
- Placed on 4L oxygen
- No further history obtained as patient could not be understood.

85

Patient Case

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Patient Case

Physical Examination

- On arrival to OU Medical Center, the patient appeared to be a well-nourished, appropriately dressed man in significant distress.

- Vital signs:
  - BP 152/92 mm Hg
  - HR 155 beats/min
  - RR 22 breaths/min
  - Temperature 99.4°F
  - O_2 sats 100% on 4 L/min by NC
  - Glucose 117 mg/dL

87

Patient Case

Physical Examination

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- Vital signs:
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  - RR 22 breaths/min
  - Temperature 99.4°F
  - O_2 sats 100% on nasal canula at 4 L/min
  - Glucose 117 mg/dL

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Patient Case

Physical Examination

- Normal head without signs of trauma
- Pupils were 7 to 8 mm and not reactive
- EKG showed sinus tachycardia
- Abdomen was distended and tender with absent bowel sounds
- His skin was warm and dry

89

Patient Case

Physical Examination

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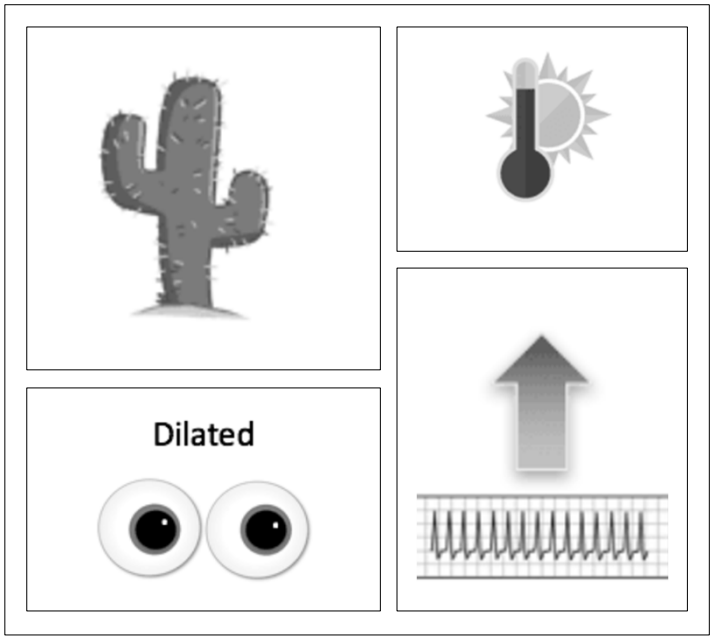

What Is the Differential Diagnosis?

Patient presentation notable for:	The toxicologic differential diagnosis of these findings includes:
• Hallucinations • Hypertension • Tachycardia • Tachypnea • Dilated pupils • Warm, dry skin • Fever • Absent bowel sounds	• Anticholinergics and antihistamines • Certain antipsychotics and antidepressants • Alcohol and sedative–hypnotic withdrawal • Sympathomimetics such as cocaine and amphetamines • Hallucinogens

Exam is suggestive of ...

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ANTICHOLINERGIC TOXIDROME

VITAL SIGNS
- HYPERTENSION
- TACHYCARDIA

CNS
- HALLUNINATIONS
- AGITATION

METABOLIC
- FEVER
- FLUSHING
- DRY

OCULAR
- MYDRIASIS
- NON-REACTIVE PUPIL

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WHY NOT SYMPATHOMIMETIC TOXIDROME?

ANTICHOLINERGIC

DRY
DECREASED BOWEL SOUNDS
NON-REACTIVE PUPILS
SLIGHTLY HYPERTHERMIC

SYMPATHOMIMETIC

DIAPHORETIC
NORMAL BOWEL SOUNDS
REACTIVE PUPILS
CAN BE VERY HYPERTHERMIC (>40°C)

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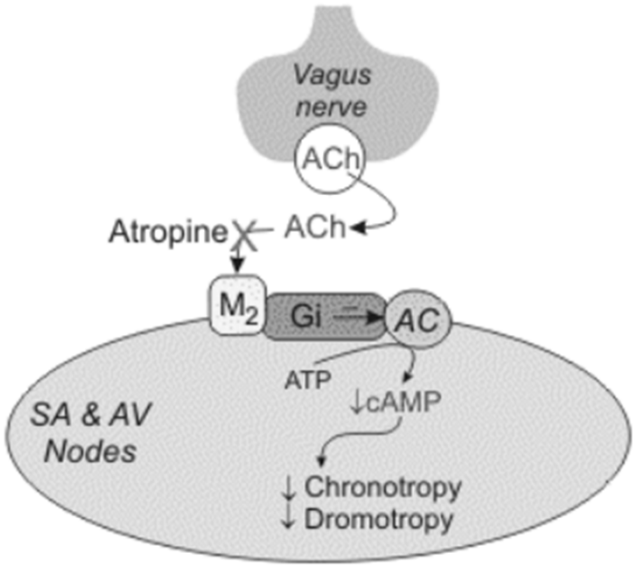
Anticholinergic Toxidrome Mechanism

- 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



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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)

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Anticholinergic Toxidrome

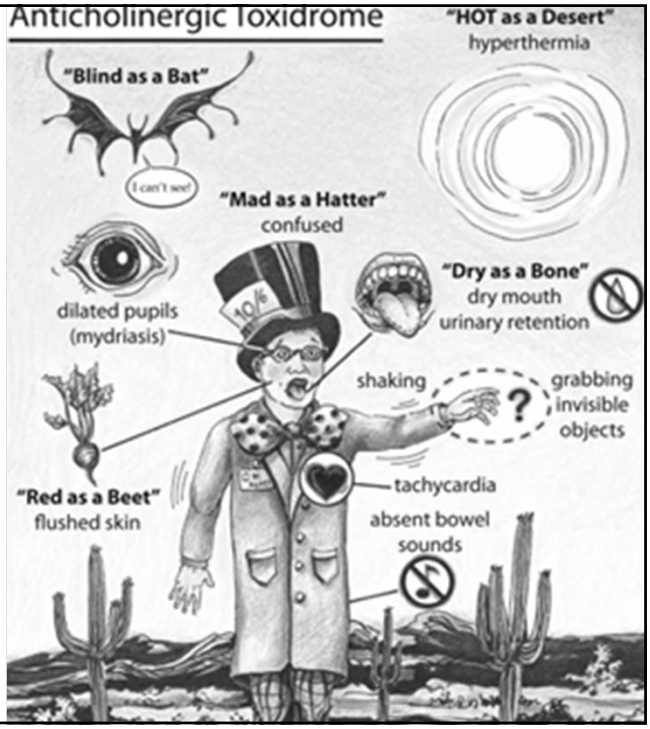
–DRY as a BONE
- Dry mouth and nose, decreased sweating, urinary retention

–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



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Anticholinergic Causative Agents

- Atropine, scopolamine
- Antihistamines (1st generation H_1 blockers)
  - diphenhydramine, doxylamine
- Antipsychotics (1st and 2nd gen. agents)
  - Phenothazines (promethazine, prochlorperazine)
  - Atypicals (clozapine, olanzapine, quetiapine)
- Antiepileptics (carbamazepine)
- Benztropine (Cogentin)
- Antispasmodics (Donnatal®, dicyclomine)
- Muscle relaxants (cyclobenzaprine (Flexeril®))
- Tricyclic Antidepressants (amitriptyline, doxepin)
- Plants – belladonna alkaloids (Jimson Weed, Deadly Nightshade)

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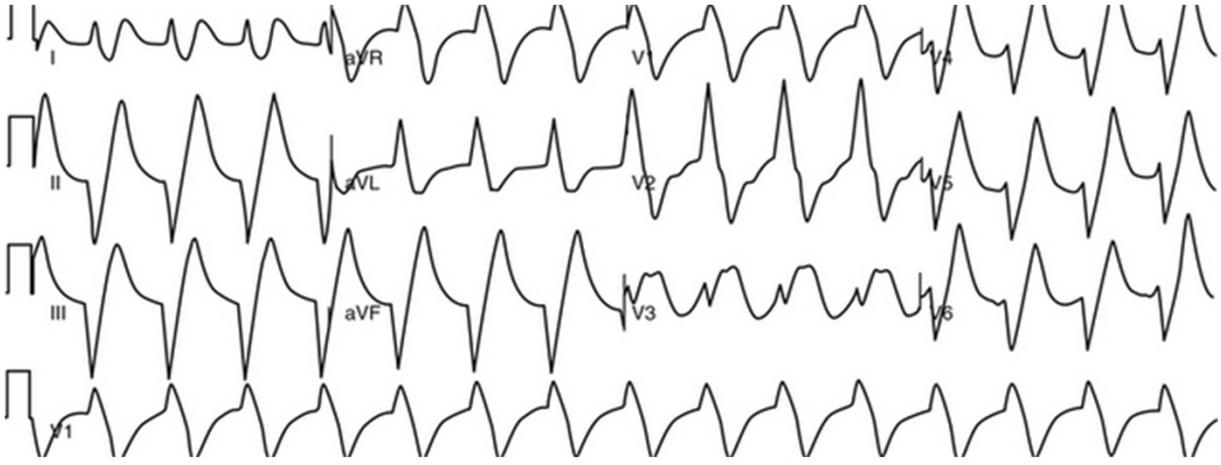

Patient Case #1

Assessment and Management

- Obtain an EKG to identify signs of sodium channel blockade
  - Characteristic of TCA overdose!
    - Can occur with phenothiazines and diphenhydramine
  - A prolonged QRS complex duration would indicate the need for sodium bicarb
- Obtain UDS and APAP level

Observe patient for hyperthermia, seizures, and rhabdomyolysis!

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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

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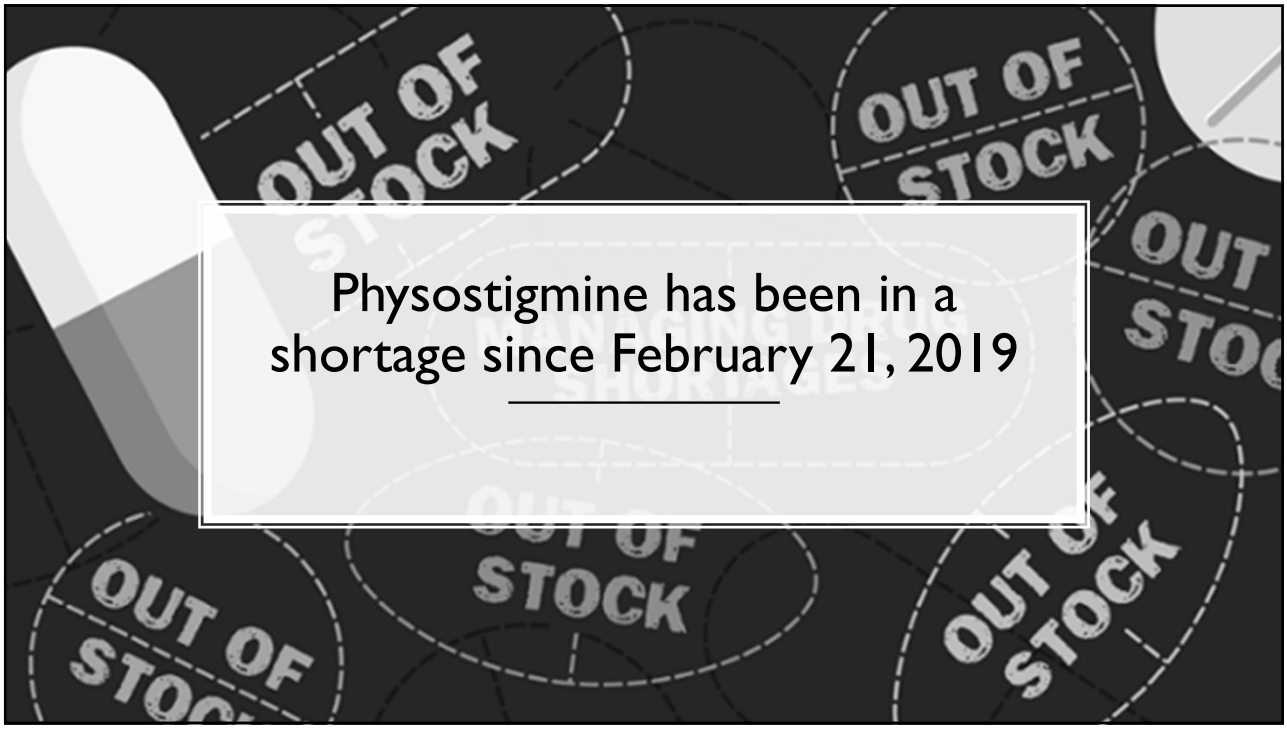

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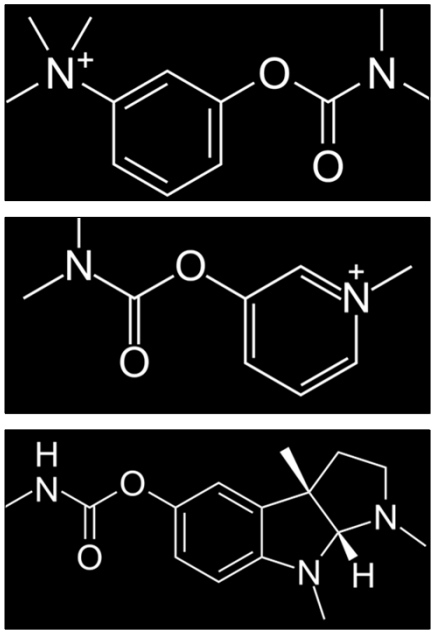
What are our carbamate alternatives?

- 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)



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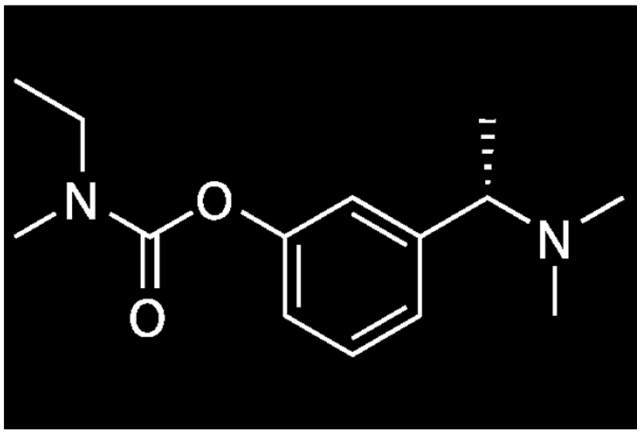
Rivastigmine

- 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



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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

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Patient Case

History

- Police were called to State Fair Park on a rainy October afternoon where an adolescent male was acting bizarrely.
- The man appeared confused and was pacing and gesturing as if he was hallucinating.
- When the police approached him, he began to run away, but after a struggle he was subdued.
- The paramedics were called because of his behavior.

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Patient Case

Immediate Assessment and Management

- When paramedics arrived, they found an agitated/confused man
- He was diaphoretic with 6 to 7 mm pupils and breathing rapidly
- He had a pulse of 180 beats/min
- Due to agitation, no other vital signs were obtained
- On arrival to Integris Baptist ED, a team of physicians, nurses, and hospital security personnel were required to restrain him
- An intravenous (IV) line was inserted
- Blood was obtained for analysis, and midazolam was given.

105

Patient Case

Immediate Assessment and Management

- When paramedics arrived, they found an agitated/confused man
- He was diaphoretic with 6 to 7 mm pupils and breathing rapidly
- He had a pulse of 180 beats/min
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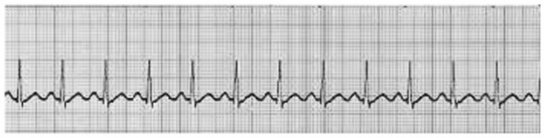
106

Sinus Tachycardia



Patient Case

The patient became more calm, and the following vital signs were obtained:

- blood pressure, 198/122 mm Hg
- pulse, 188 beats/min
- respiratory rate, 38 breaths/min
- tympanic temperature, 104.6°F (40.3°C)
- oxygen saturation, 98% on room air
- glucose 187 mg/dL

107

Patient Case

Physical Exam

- Diaphoretic young man
- Mumbling incoherently
- Hot to the touch
- No signs of trauma
- Pupils were 7 mm and reactive to light
- Heart was regular and tachycardic without extra sounds
- Abdomen was soft and nontender with normal bowel sounds
- Muscle tone was increased symmetrically
- Reflexes were brisk, 3-4 beats of clonus at both ankles

108

SYMPATHOMIMETIC TOXIDROME

VITAL SIGNS

HYPERTENSION

TACHYCARDIA

CNS

EXCITATION

AGITATION

SEIZURES

RESTLESS

TREMOR

METABOLIC

HYPERTHERMIA

DIAPHORESIS

109

Sympathomimetic Causative Agents

Illicit Drugs	Decongestants	Stimulants	Thyroid Hormones (T3, T4)	Dieting Agents
• Amphetamines • Cocaine • MDMA (ecstasy or Molly) • Cathinone derivatives (aka: bath salts) • Synthetic cannabinoids (aka: K2 or Spice)	• pseudoephedrine • phenylephrine	• Adderall • Concerta • Ritalin	• Liothyronine (T3) • Levothyroxine (T4)	• Ephedrine (banned in 2004) • Caffeine

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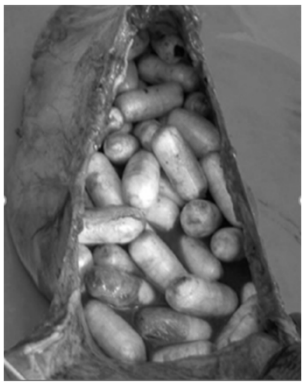

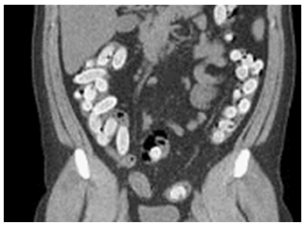
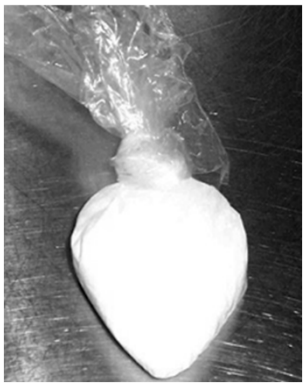

Body Packers vs. Body Stuffers

- Body Packer – "Professional" carriers of well packed illicit drugs.
- Body Stuffer - Swallowing or inserting relatively small amounts of loosely wrapped drug because of fear of arrest.
- WBI indicated in these patients.

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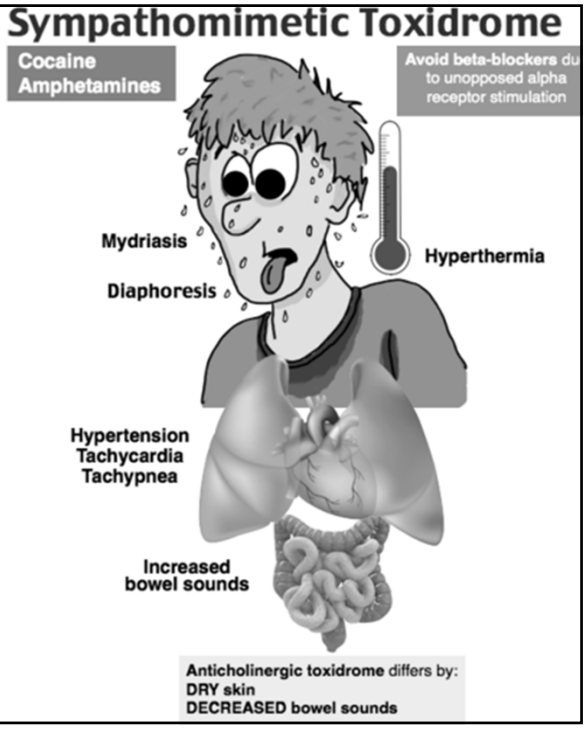
Sympathomimetic Toxidrome

- Treatment:
  - Supportive measures
    - Cooling
    - IV Fluids
  - Benzodiazepines (midazolam, lorazepam, diazepam, etc.) for:
    - Agitation
    - Restlessness
    - Tachycardia
    - Palpitations
    - Hypertension



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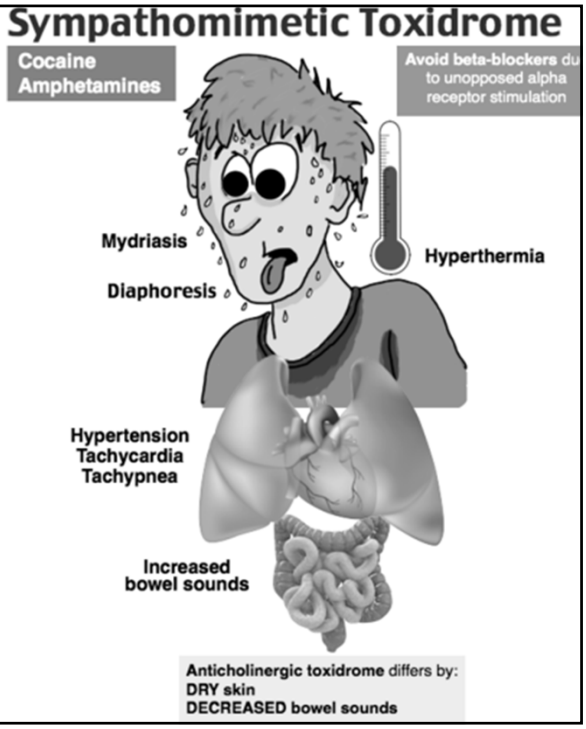
Sympathomimetic Toxidrome

- Treatment:
  - Cardiac dysrhythmia:
    - If no response to benzodiazepine follow ACLS protocol
  - Hypertension:
    - If no response to benzodiazepine try direct acting vasodilator like nitruprusside
    - **Caution**: Do not use beta blockers alone to treat hypertension, or unopposed alpha stimulation may shoot blood pressure higher
  - Dantrolene NOT indicated for sympathomimetic patients!



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ANTICHOLINERGIC VS. SYMPATHOMIMETIC

ANTICHOLINERGIC

DRY
DECREASED BOWEL SOUNDS
NON-REACTIVE PUPILS
SLIGHTLY HYPERTHERMIC

SYMPATHOMIMETIC

DIAPHORETIC
NORMAL BOWEL SOUNDS
REACTIVE PUPILS
CAN BE VERY HYPERTHERMIC (>40°C)

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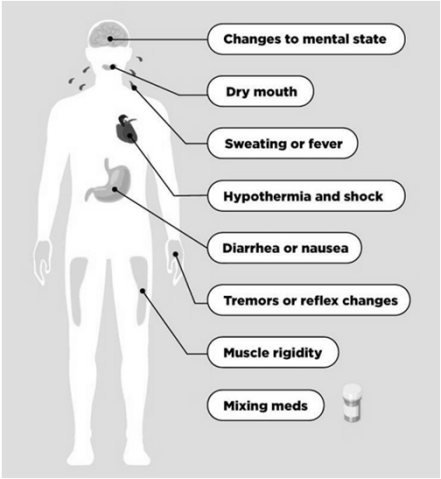
Serotonin Syndrome

- Serotonin syndrome can result from an overdose or drug interaction involving one or more of the many drugs that increase serotonergic activity.
- The Hunter Criteria is often used for the diagnosis of serotonin syndrome.
- To fulfill the Hunter Criteria, a patient must have taken a serotonergic agent and meet ONE of the following conditions:

1. Spontaneous clonus
2. Inducible clonus PLUS agitation or diaphoresis
3. Ocular clonus PLUS agitation or diaphoresis
4. Tremor PLUS hyperreflexia
5. Hypertonia PLUS temperature above 38°C PLUS ocular clonus or inducible clonus



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Treatment of serotonin syndrome

- In addition to supportive care, benzodiazepines are given to eliminate agitation, tremor, clonus, and elevations in heart rate and blood pressure.
- Start with 1 or 2 mg of IV lorazepam or midazolam and titrate the dose to effect.
- Cyproheptadine, an anti-serotonergic antihistamine can be given as well.
  - Give 12 mg orally or by orogastric tube as the initial adult dose.

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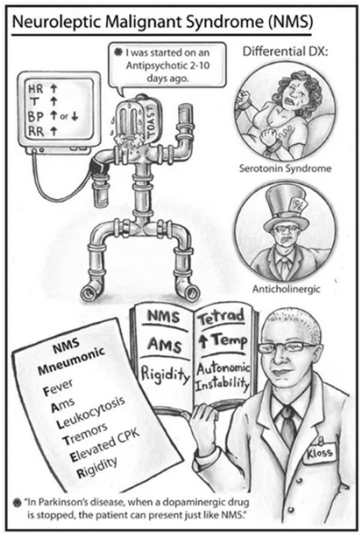
Neuroleptic Malignant Syndrome

- Review of the patient's current and recent medications and HPI to differentiate between the NMS and SS.
- SS develops over 24 hours, whereas NMS develops over a period of days.
- SS is accompanied by neuromuscular hyperreactivity (tremor, hyperreflexia, and myoclonus)
- NMS is accompanied by sluggish neuromuscular responses (rigidity and bradyreflexia).



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Neuroleptic malignant syndrome

The slow onset of neuroleptic malignant syndrome (mental status changes occurring over one to three days) generally distinguishes it from MH or SS.

NMS does not generally occur during administration of general anesthesia.

NMS is defined by its association with a class of medications that block dopamine transmission and 4 distinctive findings:

Fever
Rigidity
Mental status changes
Autonomic instability

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Suggested Diagnostic Criteria for Neuroleptic Malignant Syndrome

Criterion	Priority Score
Exposure to a dopamine antagonist or withdrawal of a dopamine agonist in previous 72 hours	20
Hyperthermia (> 100.4°F or 38°C on at least two occasions), measured orally	18
Rigidity	17
Mental status alteration (reduced or fluctuating level of consciousness)	13
Creatine kinase elevation (at least four times the upper limit of normal)	10
Sympathetic nervous system lability, defined as at least two of: • Blood pressure elevation (SBP or DBP ≥ 25% above baseline) • Blood pressure fluctuation (≥ 20% DBP change or ≥ 25% SBP change in 24 hours) • Diaphoresis • Urinary incontinence	10
Hypermetabolic state (defined as heart rate increased ≥ 25% above baseline and respiratory rate increase ≥ 50% above baseline)	5
Negative workup for other toxic, metabolic infectious, or neurologic causes	7

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Treatment of neuroleptic malignant syndrome

- Aggressive supportive care in NMS is essential.
- It is likely that mechanical ventilation, IV fluids, antihypertensives, and benzodiazepines will be required.
- Maximally aggressive surface cooling should be used, including cooling blankets and axillary ice packs.
- Recommended treatments for NMS are based upon case reports and clinical experience, not upon data from clinical trials.
- Commonly recommended medications are bromocriptine and amantadine.
  - Their use is controversial and largely unsupported. However due to lack of other proven treatments and high morbidity and mortality of the disorder, it is likely one or more of these medications will be tried for a patient who develops NMS.

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Malignant Hyperthermia

Syndrome characterized by extreme skeletal muscle hypermetabolism.

Malignant hyperthermia occurs rarely after exposure to halogenated volatile anesthetics (halothane) or a depolarizing neuromuscular blocker (succinylcholine), which triggers a cycle of abnormal calcium release from the skeletal muscle sarcoplasmic reticulum.

Classic presentation is increased skeletal muscle concentrations, increased carbon dioxide production (hypercapnia), rigor mortis-like muscle rigidity, tachycardia, hyperthermia, anaerobic metabolism, and metabolic acidosis.

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Treatment of malignant hyperthermia

In addition to supportive ventilator strategies and rapid cooling, dantrolene should be given immediately to patients with MH.

Dantrolene is the only known antidote for MH.

loading dose of 2.5 mg/kg IV

subsequent bolus doses of 1 mg/kg IV until the signs of acute MH abate

Be prepared for the development of hyperkalemia

Acute potassium release from skeletal muscle cells produce life-threatening hyperkalemia.

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Dantrolene

- Partially blocks calcium release from skeletal muscle sarcoplasmic reticulum.
- Exact mechanism is not known.
- Modulates several calcium pathways.
- Before the introduction of dantrolene, the mortality rate of MH was 64%.
- When patients with acute MH are treated immediately with dantrolene, removal of triggering agents, and supportive measures (volume resuscitation, active cooling, control of hyperkalemia) the mortality rate is less than 5%.

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Conclusion and Clinical Pearls

- Never hesitate to contact the poison center for any drug information questions or assistance in treating an overdose patient.
- Antidepressant and neuroleptic medications are often taken in overdose in attempt to self harm.
- Pharmacists should be able to identify common signs and symptoms of overdose and develop a treatment strategy for a patient suffering from antidepressant and neuroleptic overdose.
- Patient medical and medication history is imperative when trying to diagnose serotonin syndrome vs. neuroleptic malignant syndrome.
- Treatment of patients with serotonin syndrome and neuroleptic malignant syndrome is primarily supportive with aggressive cooling and sedation.

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Additional Resources

- Nelson LS, Howland MA, Lewin NA, Smith SW, Goldfrank LR, Hoffman RS. Goldfrank's Toxicologic Emergencies, 11e; Chapters 67-70.
- Oklahoma Poison Center. https://oklahomapoison.org/ 1-800-222-1222

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The Ins and Outs of Ups and Downs: Antidepressant, Neuroleptic and Lithium Overdoses

Kristie Edelen, Pharm.D., DABAT
Managing Director
Oklahoma Poison Center

Walter E. Scheffe CPE Series

October 28, 2023

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