2024 ACMT
Board Review Course
Interactive Cram Session #4
July 26, 2024

Interactive Cram Session

Today's goal is to be **interactive**, **engaging**, and **educational**:

- Introductions
- 5-min "Key Takeaways"
- Q&A with Speakers
- Pop Quiz

Today's session is being recorded and will be accessible on-demand.

DISCLAIMER

According to ABEM policy, the planning committee and faculty for this course are not allowed to have intimate knowledge of the exam or write exam questions. The content of this course is based on the expertise of ACMT members, who are specialists in Medical Toxicology.

We do not have direct knowledge of the exam content. ABEM test question writers are prohibited from participating in any board review or preparatory course. The study materials, including the Quiz Bank and pop quiz questions, are based on years of collective experience from the Board Review Course committee, but we do not guarantee that these questions fully represent the exam content.

CRAM SESSION TOPICS | FRI. JULY 26, 2024

Classic Toxicology

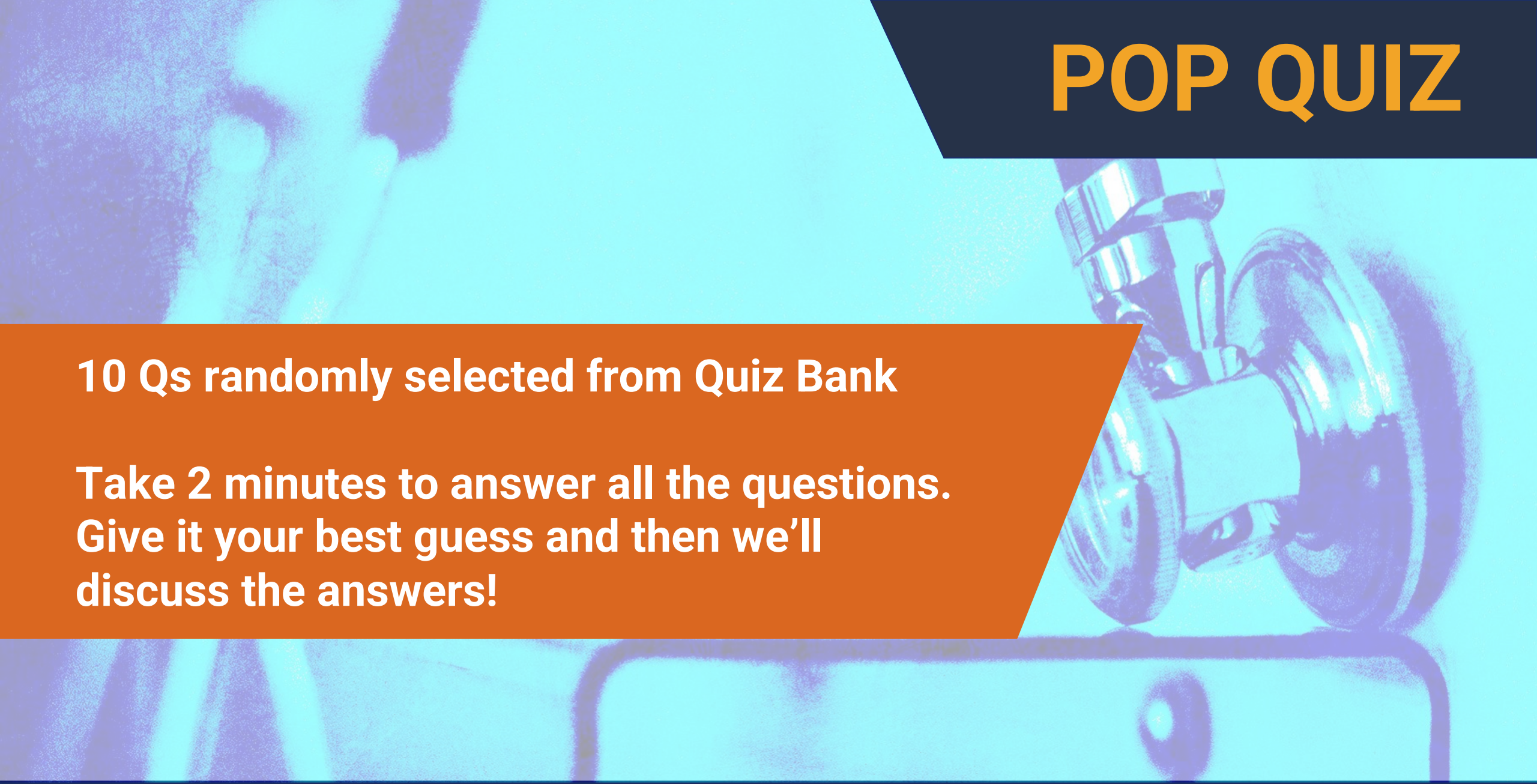
Antipsychotics

Psychotropics

Endocrine

Herbals, Vitamins & Supplements

POP QUIZ



10 Qs randomly selected from Quiz Bank

Take 2 minutes to answer all the questions. Give it your best guess and then we'll discuss the answers!

Question 1

A 17-year-old female presents in status epilepticus after an acute isoniazid overdose. What is the antidote's mechanism of action?

A. Blockage of sodium channels

B. Facilitating the removal of the offending agent from hemoglobin

C. Removal of the toxin from acetylcholinesterase

D. Replenishment of the cofactor for glutamic acid decarboxylase

E. Stimulation of a Gs protein that will cause the phosphorylation of Protein kinase A

Question 1 - Answer

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D. **Replenishment of the cofactor for glutamic acid decarboxylase**

E. Stimulation of a Gs protein that will cause the phosphorylation of Protein kinase A

EXPLANATION: Isoniazid (INH) creates a functional deficiency of pyridoxine. Hydrazines such as INH inhibit pyridoxine phosphokinase and increases renal excretion of pyridoxine. This leads to inhibition of glutamic acid decarboxylase, the enzyme which converts glutamic acid to GABA. Without endogenous GABA, benzodiazepines will be ineffective in terminating convulsions; therefore, these patients should be treated with pyridoxine. Glucagon stimulates a Gs protein activating PKA and increases cardiac myocyte calcium influx and release from the sarcoplasmic reticulum. Hydroxocobalamin removes cyanide from hemoglobin to make cyanocobalamin (vitamin B12). Pralidoxime removes organophosphates that have not yet been hydrolyzed from acetylcholinesterase. Phenytoin blocks sodium channels and is effective in treating seizures due to 4-aminopyridine (Avitrol).

Question 2

Patient presents after an acute ingestion of phenibut and is comatose upon arrival to the ED. What is the mechanism of action for this medication?

A. GABAa agonist

B. GABAb agonist

C. Glycine agonist

D. NDMA antagonist

Question 2 - Answer

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A. GABAa agonist

B. GABAb agonist

C. Glycine agonist

D. NDMA antagonist

EXPLANATION: Similar to GBH and baclofen, phenibut is a GABAb agonist and can present similar to the others with this mechanism of action. Phenibut was developed in the Soviet Union in the 1960s, and used there as a pharmaceutical drug to treat post-traumatic stress disorder, anxiety, depression, insomnia, alcoholism, stuttering, and vestibular disorders, and other conditions. In the rest of the world, phenibut is not approved for clinical use, and is instead sold as a nutritional supplement. Withdrawal from this product can be severe and life threatening after chronic use.

Question 3

Which of the following antipsychotics is the most cardiotoxic in an overdose?

A. Fluphenazine

B. Haloperidol

C. Loxapine

D. Thioridazine

E. Thiothixine

Question 3 - Answer

Which of the following antipsychotics is the most cardiotoxic in an overdose?

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B. Haloperidol

C. Loxapine

D. Thioridazine

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EXPLANATION: Thioridazine is the most cardiotoxic. It has a higher association with QT prolongation than most of the other antipsychotics. Loxapine is most likely to result in seizures.

Question 4

What is the most commonly described ECG abnormality in patients on chronic lithium therapy?

A. Bidirectional VT pattern

B. Inverted T wave pattern

C. Peaked T wave pattern

D. Prolonged QTc interval

E. Widened QRS complex

Question 4 - Answer

What is the most commonly described ECG abnormality in patients on chronic lithium therapy?

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B. Inverted T wave pattern

C. Peaked T wave pattern

D. Prolonged QTc interval

E. Widened QRS complex

EXPLANATION: Patients chronically on lithium will often have inverted T waves. The most common agents on the toxicology differential for a widened QRS complex would be TCAs, class IA antiarrhythmics, diphenhydramine, chloroquine, older phenothiazines such as thioridazine, cocaine and propoxyphene. A prolonged QTc interval can be seen with cisapride, amiodarone, terfenadine, arsenic, and the antipsychotics. Peaked T waves suggest hyperkalemia and bidirectional VT can be seen in cardiac glycoside poisoning.

Question 5

Acute overdoses of selective serotonin reuptake inhibitor (SSRI) antidepressant medications happen most often in which of the following?

A. Cardiac dysrhythmias

B. CNS depression and tachycardia

C. Hallucinations and delirium

D. Profound hyperthermia and rigidity

E. Seizures

Question 5 - Answer

Acute overdoses of selective serotonin reuptake inhibitor (SSRI) antidepressant medications happen most often in which of the following?

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B. CNS depression and tachycardia

C. Hallucinations and delirium

D. Profound hyperthermia and rigidity

E. Seizures

EXPLANATION: Patients with acute exposures to SSRI medications typically do well with CNS depression and tachycardia being the most common symptoms encountered. Cardiac dysrhythmias, seizures, and hallucinations and delirium are not routinely seen in acute overdose. Hyperthermia and rigidity may be seen as a part of the serotonin syndrome but true serotonin syndrome is seen in ~15% of isolated SSRI overdoses.

Question 6 - Answer

A 2-year-old presents to the ED with a dystonic reaction. GCMS was performed. Which of the following medications is most likely responsible?

A. Carbamazepine

B. Dextromethorphan

C. Lamotrigine

D. Phenytoin

E. Valproic acid

Question 6 - Answer

A 2-year-old presents to the ED with a dystonic reaction. GCMS was performed. Which of the following medications is most likely responsible?

A. Carbamazepine

B. Dextromethorphan

C. Lamotrigine

D. Phenytoin

E. Valproic acid

EXPLANATION: Carbamazepine is structurally similar to TCAs and, in the pediatric population, has a higher incidence of choreoathetosis, seizures, and dystonias.

Question 7 - Answer

Which antidiabetic medication was withdrawn by the manufacturer secondary to hepatic toxicity in the US in 2000?

A. Miglitol

B. Repaglinide

C. Sitagliptin

D. Troglitazone

Question 7 - Answer

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D. **Troglitazone**

EXPLANATION: The FDA directed the manufacturer of Troglitazone to withdraw the drug in 2000 because of associated liver toxicity.

Question 8

Which of the following agents will most likely result in euglycemia after an overdose?

A. Glipizide

B. Glyburide

C. Metformin

D. Repaglinide

E. Unripe Bilghia sapida

Question 8 - Answer

Which of the following agents will most likely result in euglycemia after an overdose?

A. Glipizide

B. Glyburide

C. **Metformin**

D. Repaglinide

E. Unripe Bilghia sapida

EXPLANATION: Glipizide and glyburide (in addition to insulin) are considered “hypoglycemic agents” and regularly result in hypoglycemia after overdose. Sulfonylureas act to promote insulin release from pancreatic beta cells. Unripe Bilghia sapida (Ackee fruit) causes hypoglycemia via “Hypoglycin A” which inhibits gluconeogenesis. It is also the agent responsible for Jamaican Vomiting Sickness. Repaglinide (Prandin) is considered a Meglitinide which binds to its own receptor on beta cells and promote insulin secretion. Metformin (glucophage) is a Biguanide agent that does not regularly result in hypoglycemia in overdose. It is considered an “antihyperglycemic” agent that may result in severe acidemia and elevated lactate levels in poisoning.

Question 9

Kava (Piper methysticum) hepatotoxicity is best described as:

A. Idiosyncratic

B. Ito cell necrosis with Vitamin A deficiency

C. Kava is associated with renal disease, liver disease is not reported

D. Portal vein thrombosis

E. Veno-occlusive disease

Question 9 - Answer

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C. Kava is associated with renal disease, liver disease is not reported

D. Portal vein thrombosis

E. Veno-occlusive disease

EXPLANATION: Kava hepatic toxicity is rare and idiosyncratic. It does not appear to be dose-related but overdose, prolonged treatment, and comedication with synthetic drugs and dietary supplements have been associated. (Kava hepatotoxicity--a clinical review Ann Hepatol. 2010 Jul-Sep;9(3):251-65). Both hepatocellular necrosis and cholestatic hepatic injury have been described.

Question 10

Vitamin K1 is the antidote for which of the following group of plants:

A. Aesculus spp (horse chestnut)

B. Angelica polymorpha (Dong quai)

C. Echinacea purpurea (Coneflower)

D. Lathyrus sativus (grass pea)

E. Nepeta cataria (catwort)

Question 10 - Answer

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E. Nepeta cataria (catwort)

EXPLANATION: Dong Quai, Angelica polymorpha, has anticoagulant effects and is used as a blood purifier and to improve circulation as well as for menstrual disorders.

FEEDBACK SURVEY

Before you leave, please fill out the feedback survey.

This survey should appear in your browser when the meeting ends.

Let us know how we can improve the next interactive cram session!

COMING UP!

Interactive Cram Session #5
August 9, 2024

ACMT
American College
of Medical Toxicology

CRAM SESSION TOPICS | FRI. AUG 9, 2024

Inhalational Toxins & Asphyxiants

Carcinogenesis

Reproductive & Developmental Toxicology

Epidemiology & Population Health

Statistical Measures

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ACMT BOARD REVIEW COURSE

Antipsychotics / Psychotropics Cram Session

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Dalhousie University, University of Minnesota & Penn State College of Medicine
Consultation - Liaison Psychiatry, Addiction Medicine, & Medical Toxicology
Mental Health & Addictions Co-Occurring Disorders Program Lead, Nova Scotia Health

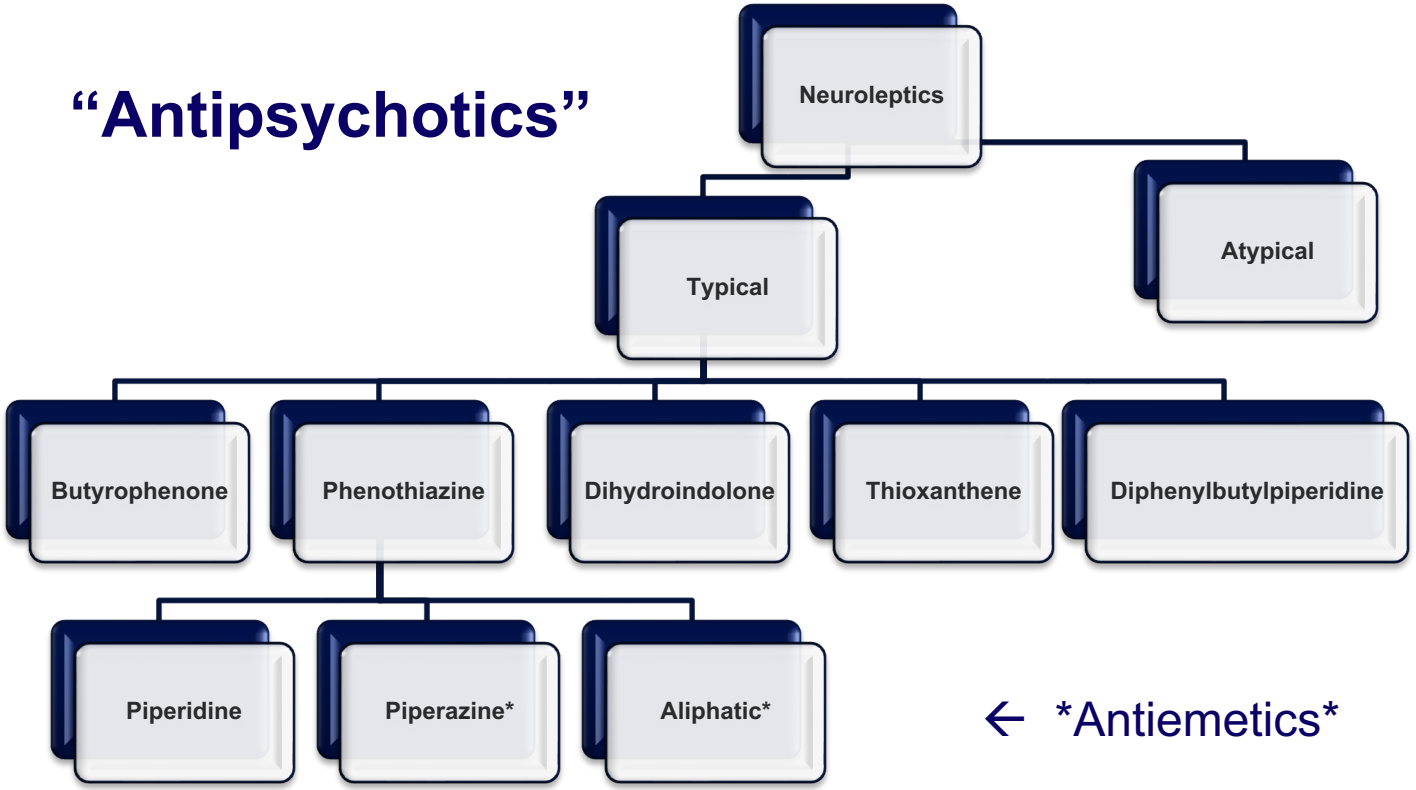
ACMT

ANTIPSYCHOTICS

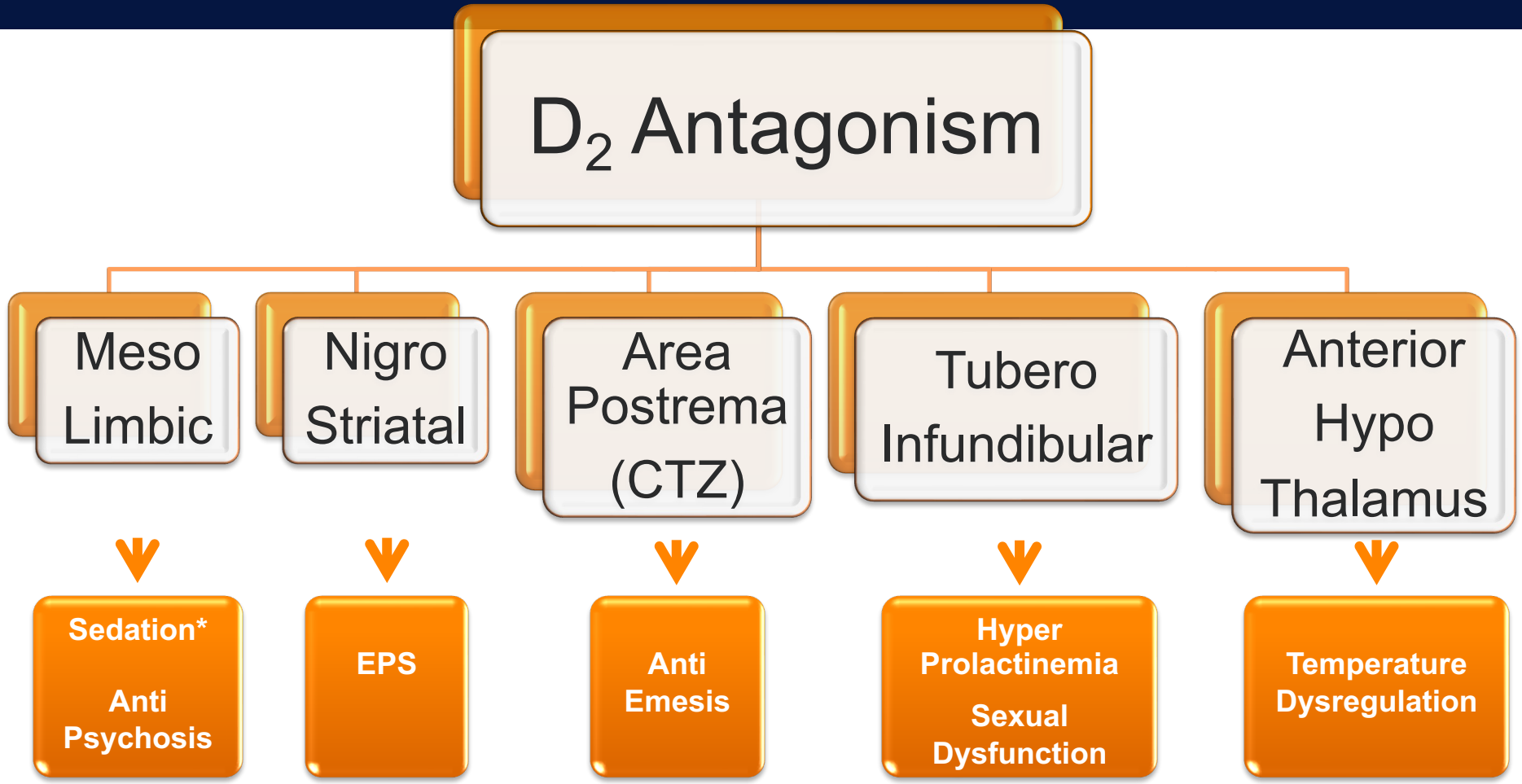
- Typical antipsychotics (FGAs)
  - D_2 antagonists
  - Alpha antagonists
- Atypical antipsychotics (SGAs)
  - Preferential binding to 5-HT_{2A} over D_2 → less EPS
  - Mixed DA receptor affinities (D_1,D_2, D_4 etc.)
  - Perhaps more selective for limbic vs. EP sites
  - Mixed affinity for DA, 5-HT, **α**,…

DOPAMINE ANTAGONISTS

“Antipsychotics”



← *Antiemetics*


D2 Antagonism
Meso Limbic
Nigro Striatal
Area Postrema (CTZ)
Tubero Infundibular
Anterior Hypo Thalamus
Sedation*
Anti Psychosis
EPS
Anti Emesis
Hyper Prolactinemia
Sexual Dysfunction
Temperature Dysregulation

Manifestations of Toxicity

- Peak effects typically evident within **2 to 6 hours**
- Most common clinical manifestations:
  - Dopamine (and histamine) blockade: slurred speech, ataxia, cognitive impairment, lethargy, sedation, and **coma**
  - α Adrenergic blockade: tachycardia and **hypotension**
  - Muscarinic blockade: tachycardia, **delirial agitation**, hallucinations, blurry vision, retention, and sicca
  - Potassium Channel Antagonism: **arrhythmias**

EPS may be the only presenting manifestation especially in children (rigidity, bradykinesia, tremors and/or akathisia).

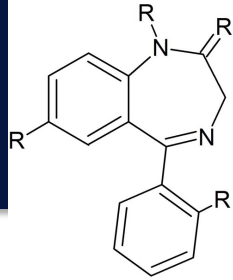
TYPICAL ANTIPSYCHOTIC PEARLS

- Thioridazine (Mellaril)
  - Peak serum level can be delayed 120 hours
  - QTc but not QRS correlates closely with peak concentration
  - Most lethal in overdose (mesoridazine close behind) – Na^+ channel blockade
- Loxapine (Loxitane, Adasuve)
  - Seizures in overdose, new inhaled preparation for acute agitation
- Chlorpromazine (Thorazine)
  - Cholestatic jaundice, Agranulocytosis
- Chlorprothixene (Taractan)
  - Acute reversible oliguria
- Haloperidol (Haldol)
  - Most common cause of NMS (> 90% of reported cases)

Second Generation Agents

- Clozapine (Clozaril)
- Olanzapine (Zyprexa)
- Quetiapine (Seroquel)
- Risperidone (Risperdal)
- Paliperidone (Invega)
- Ziprasidone (Geodon)
- Aripiprazole (Abilify)
- Cariprazine (Vraylar)

BENZODIAZEPINES

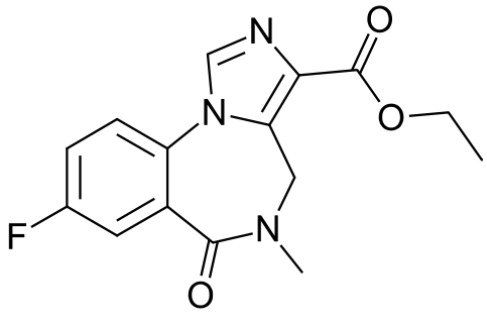


- Over 50,000 benzodiazepine OD cases reported annually
- 65% intentional
- Few deaths
  - Essentially ”never” in mono-ingestion
  - Problematic in combination exposures, but also potentially protective (CNS, Cardiac)
  - Mixed sedative OG or IV exposure increases morbidity

BENZODIAZEPINES

- All are indirect agonists at post-synaptic GABA-A receptors
  - BZD_1 (arousal) and BZD_2 (memory/cognition) receptors in the brain
  - Increase ***frequency*** of chloride channel opening
  - Channel will not open without GABA present
- BZD_2 agonism in spinal cord effects muscle relaxation
- All produce tolerance with cross-reactivity
- Predispose to physical dependence (BZD_2 mediated)
  - Withdrawal is generally worse for short half-life agents; alprazolam being the exception – redistribution & two-phase elimination kinetics

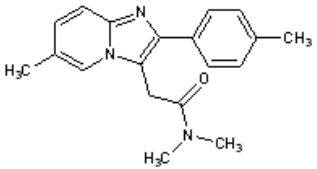
BENZODIAZEPINE PEARLS

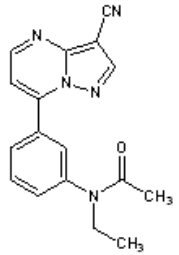


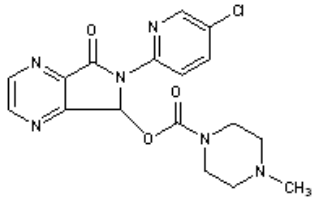
- Antidote for CNS effects – Flumazenil
  - BZD Receptor antagonist, inverse agonist at high doses
  - Patient selection guided by physical exam renders seizures rare
- Propylene glycol: Lorazepam
- Clonazepam: Anticonvulsant and “Mood stabilizer”
- Flunitrazepam (RoHypnol): “Date Rape”
- EMIT: Oxazepam -- false negatives (ALP, LRZ, TMZ…)

‘Z’ DRUGS: Nonbenzodiazepine sedatives

- Zolpidem (Ambien, Stilnox) – imidazopyridine
- Zaleplon (Sonata) – pyrazolopyrimidine
- Zopiclone (Imovane) – cyclopyrrolone
- Eszopiclone (Lunesta, Estorra)







Selective for GABA-A BZD_1 receptors

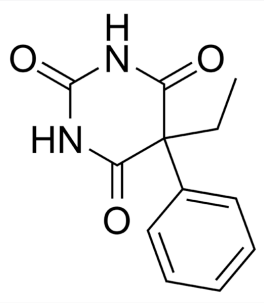
Less physical dependence than BZDs

Flumazenil is antidotal

BARBITURATES

- GABA-A receptor agonists
  - Direct increase in ***duration*** of chloride channel opening
  - GABA **not** needed for pharmacologic function
- 4 Categories
  - Ultrashort: methohexital, thiopental
  - Short: pentobarbital, secobarbital
  - Intermediate: butalbital
  - Long-acting: phenobarbital
- Cytochrome enzyme induction → drug interactions

PHENOBARBITAL (PHB)



- Long-acting barbiturate, chemically a weak acid
- Steady-state therapeutic range 15-40 mg/L
- CNS tolerance does not usually yield respiratory tolerance
- Levels > 80 mg/L typically result in coma
- Death is uncommon with good supportive care
  - Urine alkalinization, MDAC enhance elimination
- Primidone
  - Metabolized to PEMA and PHB

TCA MECHANISMS OF ACTION

- Inhibition of serotonin reuptake
- Inhibition of norepinephrine reuptake
- Antihistamine (central and peripheral)
- Antimuscarinic – CNS M_1 antagonism, in particular
- Sodium channel blockade
- Potassium channel blockade
- Peripheral alpha-adrenergic (α_1) antagonists
- Interferes with GABA complex – effective antagonism
- Alters function of beta-adrenergic receptors

TCA TOXICITY

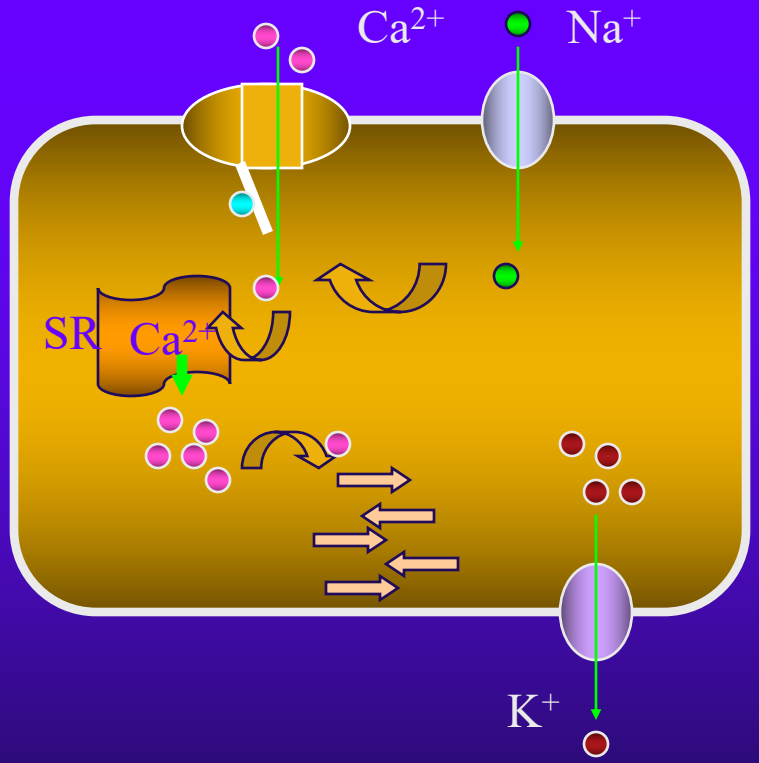
- Rapid onset of symptoms
- Early sedation → coma
- Early antimuscarinic symptoms → delirium
- Seizures next
- Cardiovascular next
  - Decreased inotropy
  - Hypotension
  - Dysrhythmias

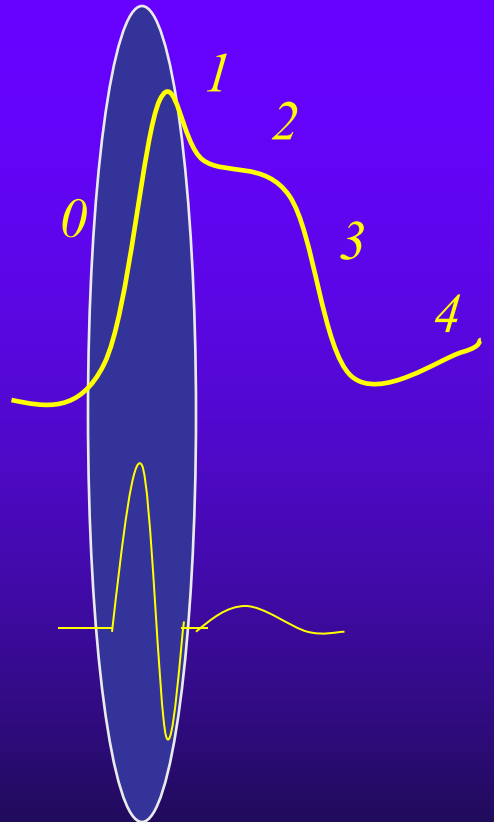
"T" = Tremor (seizures)

"C" = Cardiovascular

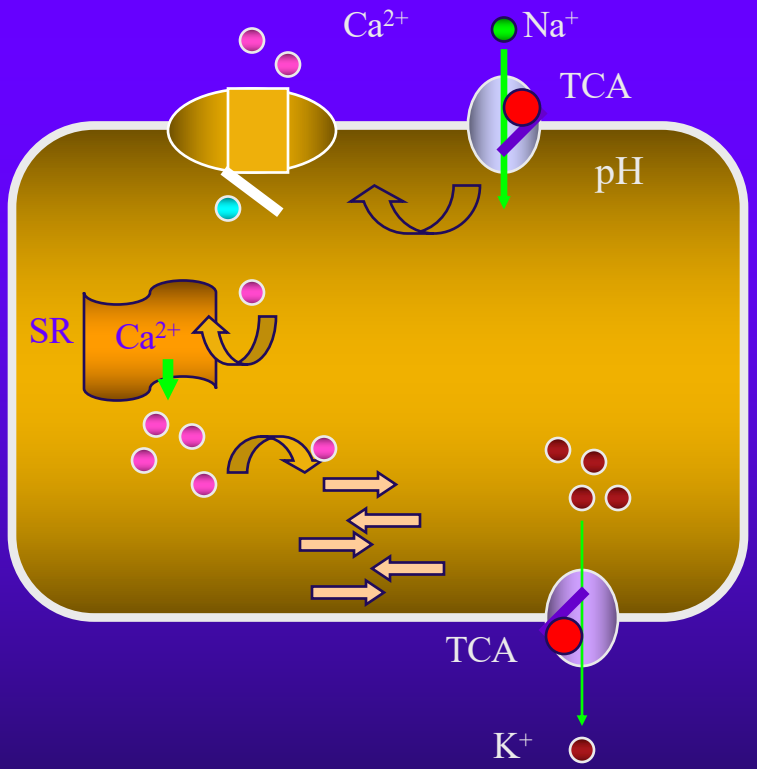
"A" = Antimuscarinic

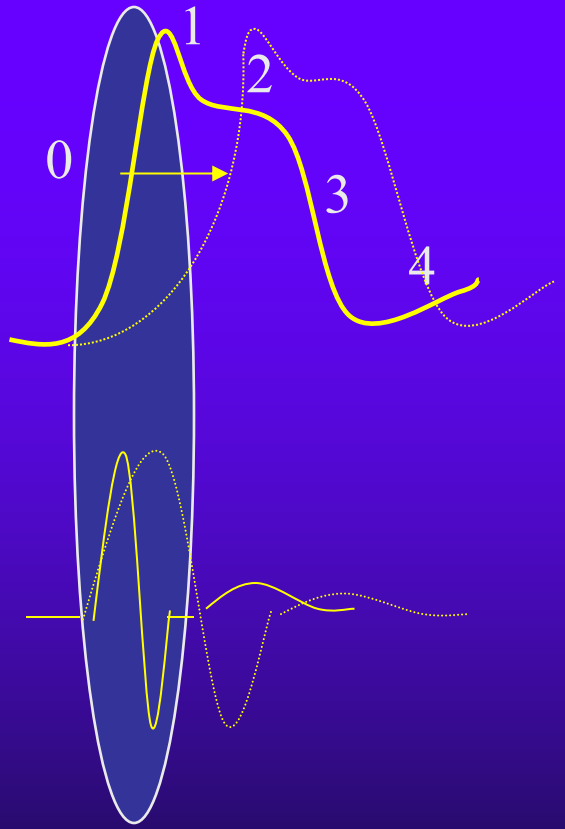
Myocardial Cell Electrophysiology





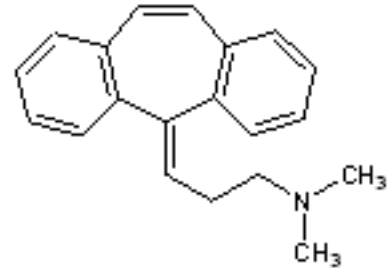
TCA Membrane Effects

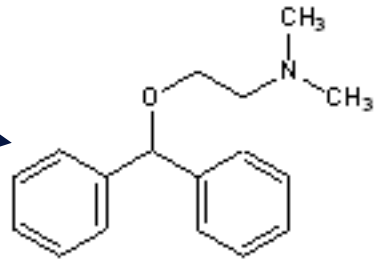


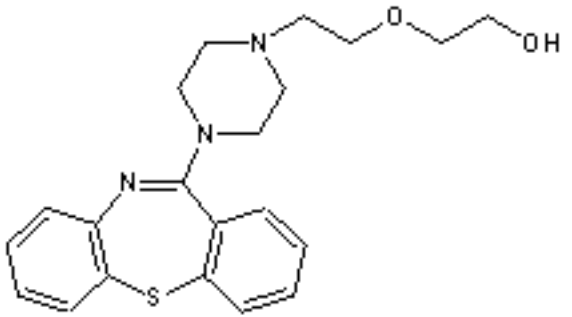


TCA SCREEN CROSS REACTIVITY

- Cyclobenzaprine (Flexeril)
- Carbamazepine (Tegretol)
- Diphenhydramine (Benadryl)
- Thioridazine (Mellaril)
- Olanzapine (Zyprexa)
- Quetiapine (Seroquel)

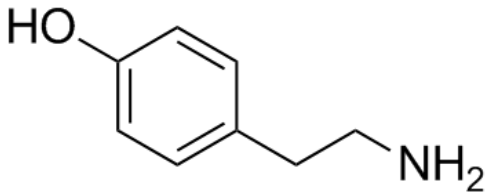






MAOI - TYRAMINE REACTION

- Not typically an overdose scenario
- Onset within 2 hours after eating
- Ingested tyramine normally inactivated by gut MAO-A
- Inhibition of gut MAO-A
  - Absorption of dietary tyramine and byproducts
  - Tyramine releases NE formed by inhibition of neuronal MAO-A
- Hyperadrenergic state
- Treat symptomatically



SIGNS AND SYMPTOMS (MAOI OVERDOSE)

Phase I

- Latent period: 6-12 hours in patients already on medication
- 24-36 hours in “naïve” patients

Phase II

- Excitatory phase
  - Hyperadrenergic
  - “Ping-pong” nystagmus, hippus
  - Hyperreflexive with rigidity
  - Writhing, opisthotonos, facial grimacing
- Progression
  - CNS depression
  - Fever, diaphoresis, salivation
  - Rigidity, myoclonus, carpopedal spasm
  - Myocardial ischemia, ICH, seizures

SEROTONIN REUPTAKE INHIBITORS

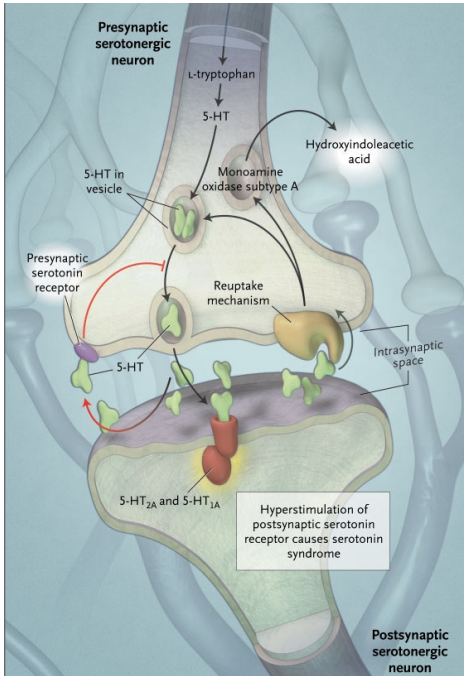
- Paroxetine (Paxil)
- Fluoxetine (Prozac, Sarafem)
- Citalopram (Celexa)
- Escitalopram (Lexapro, Cipralex)
- Sertraline (Zoloft)
- Fluvoxamine (Luvox)
- Fluoxetine + olanzapine (Symbyax)

PEARLS

- Citalopram and escitalopram: reports of seizures and widened QT interval (CIT > ESC)
- Fluvoxamine inhibits CYP1A and CYP2C
- Paroxetine, fluoxetine, and their metabolites are strong inhibitors of CYP2D6
- SSRIs in overdose: CNS depression and tachycardia most common findings **(not SS)**

SEROTONIN SYNDROME

- Stimulation of post-synaptic 5-HT_{1A} and certain 5-HT_2 receptors ***within the CNS***
- Mechanism
  - Two or more serotonergic agents
    - SSRI + agent with serotonergic properties
    - In one acute toxicology study, SSRI + an abused stimulant accounted for 1/3 of cases
  - One agent with multiple 5-HT mechanisms (DXM)
  - Change in dose of one or more agents
  - Metabolic inhibition



Serotonin Syndrome vs NMS

		Serotonin Syndrome	Neuroleptic Malignant Syndrome
Precipitated by		Serotonergic agents	Dopamine antagonists
Onset		Variable, usually < 24 hours	Variable
Similar features	Vital signs	HTN, tachycardia, tachypnea, hyperthermia (>40°C)	
	Mucosa	Sialorrhea	
Overlapping features	Skin	Diaphoresis	Diaphoresis, pallor
	Mental status	Variable: agitated state, coma	Variable: stupor, coma, alertiveness, delirium
	Muscles	Increased tone, particularly in lower extremities	"Lead pipe" rigidity in all muscle groups
Differentiating features	Reflexes	Hyperreflexia, clonus	Hyporeflexia
	Pupils	Mydriasis	Normal
	Bowel sounds	Hyperactive	Normal- decreased

Serotonin vs Anticholinergic Syndromes

	Serotonin Syndrome	Anticholinergic Toxicity
Inciting Agents	5-HT agonists	Anticholinergics • Atropine-like drugs • Anti-histamines • Parkinson's meds • Many others
Onset	<24 hrs	<24 hrs
Symptoms	• Hyperreflexia • Rigidity • ~~Hyperthermia~~ • Increased bowel sounds • Diaphoretic	• ~~Normal reflexes~~ • Normal muscle tone • Decreased bowel sounds • Dry skin

OTHER REUPTAKE INHIBITORS

- SNRIs – Nausea, HTN…Seizures, QRS prolongation
  - Venlafaxine (Effexor), Desvenlafaxine (Pristiq): 5-HT > NE
  - Duloxetine (Cymbalta): 5-HT ~ NE
  - Milnacipran (Savella), Levomilnacipran (Fetzima): 5-HT < NE

- Bupropion (Wellbutrin, Zyban, Aplenzin, Forfivo, Budeprion)
  - “NDRI”
  - Meet SS Criteria, Seizures, QRS and severe QT prolongation
  - XL products may warrant enhanced elimination

OTHER ANTIDEPRESSANTS

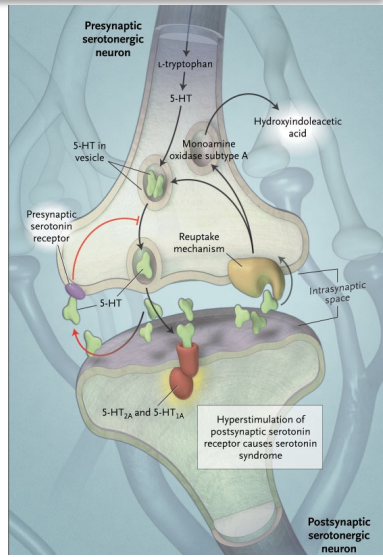
- Vilazodone (Viibryd)
  - SRI and 5-HT_{1A} Partial agonist (think SSRI plus buspirone)
  - Serotonin toxicity risk potentially greater (mono-ingestion)
- Vortioxetine (Brintellix / Trintellix)
  - Antagonist of 5-HT_3, 5-HT_7, and 5-HT_{1D} receptors
  - Partial agonist activity of 5-HT_{1B} receptors
  - Agonist of 5-HT_{1A} receptor
  - Some inhibition of the 5-HT transporter (SRI)
  - Serotonin toxicity risk potentially greater (mono-ingestion)

OTHER ANTIDEPRESSANTS

- Mirtazapine (Remeron): H_1, α_1 and α_2 antagonist
  - Sedation, Some anticholinergic effects, Mild symptoms in overdose
- Trazodone (Desyrel): SRI, α_1 antagonist, α_2 agonist (?)
  - Prolonged QT, orthostatic hypotension, priapism
- Nefazodone (Serzone): SRI, α_1 antagonist, 5-HT_2 antagonist
  - Prolonged QT, orthostatic hypotension, priapism
  - Boxed warning based on risk of hepatotoxicity
- Reboxetine (Edronax)
  - NRI – Hypertension and seizures might be expected

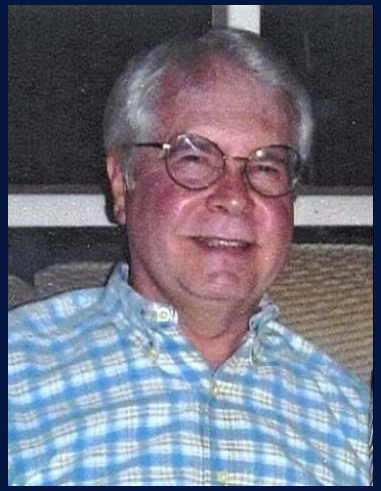
LUMATEPERONE (Caplyta)

- Serotonin Transporter Inhibitor
  - Serotonin signs → SS ?
- 5-HT_{2A} antagonist
  - Fatigue, dizziness, hypotension
- Partial D_2 agonist / antagonist
  - Sedation, movement side effects ?
- Indirect glutamatergic modulator (NMDA and AMPA)
- **Possible adrenal damage (animal models) via aniline lumateperone metabolite deposition – Rx quercetin ?**



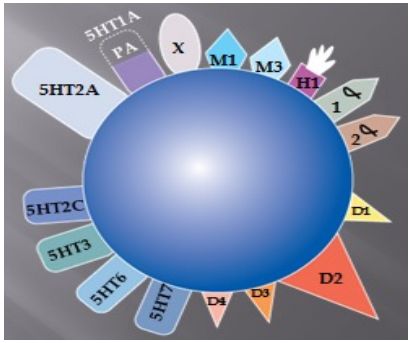
Acknowledgment to:

J. Ward Donovan, M.D.



Questions?

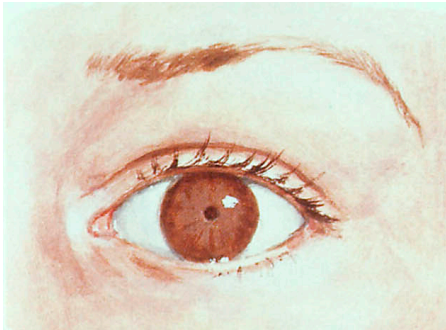
ATYPICAL ANTIPSYCHOTICS (1)



- Clozapine (Clozaril, Fazaclo)
  - Highly variable metabolism (CYP1A2)
  - Agranulocytosis / aplastic anemia (REMS)
  - Myocarditis, Sz (5-10%), Drooling, DM / Metabolic effects
  - Low D_2 affinity, high M_1 affinity → used to manage EPS
- Olanzapine (Zyprexa)
  - Highest incidence of NMS of SGAs
  - High antimuscarinic activity, DM / Metabolic effects
- Quetiapine (Seroquel)
  - High **α**-adrenergic blockade
  - Most sedating of class – antihistaminic / antimuscarinic activity
  - Short t ½ that increases to ~22 hours in overdose

ATYPICAL ANTIPSYCHOTICS (2)

- Risperidone (Risperdal)
  - Highest rate of dystonia in SGAs
  - Potent alpha blockade, no antimuscarinic activity
  - Seizures, unusual dysrhythmias for class (a-flutter, heart blocks)
- Paliperidone (Invega): active CYP2D6 metabolite of risperidone
- Ziprasidone (Geodon)
  - Highest rate of increased QT (~20 msec in outpatients)
- Lurasidone (Latuda)
  - Hypotension, leukopenia
- Iloperidone (Fanapt)
  - Hypotension, QT prolongation



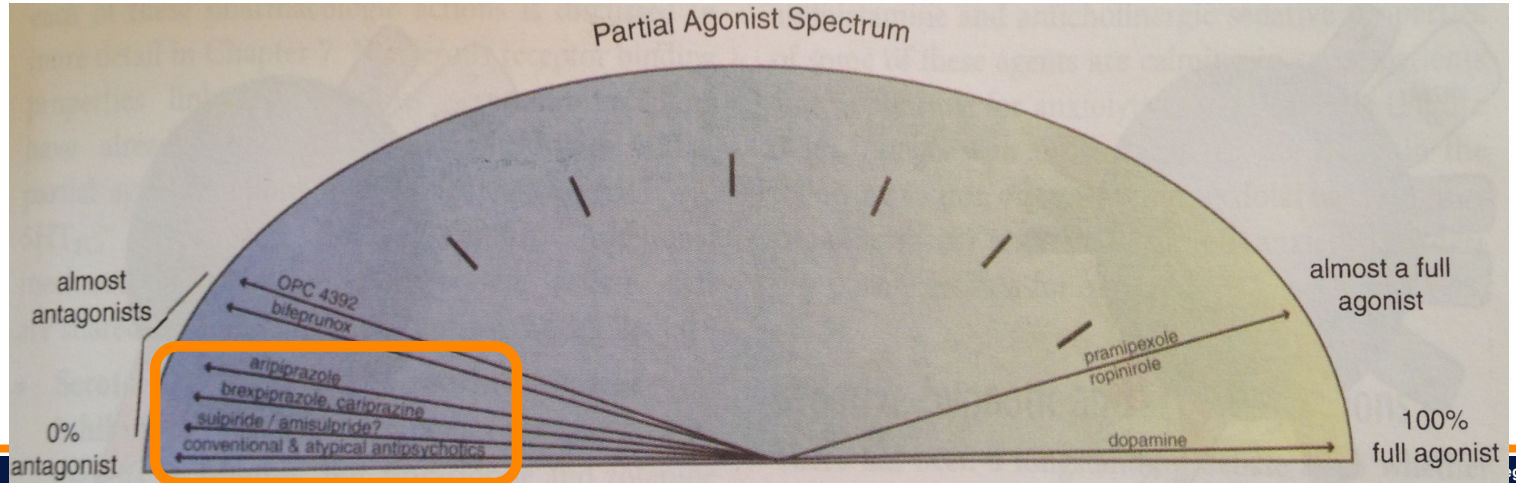
ATYPICAL ANTIPSYCHOTICS (3a)

Int J Clin Pract, November 2015, 69(11):1211-20.

Stahl, S. M. (2013). Stahl's essential psychopharmacology: Neuroscientific basis and practical applications.

- Phenylpiperazines
  - Partial agonists at D_2 and 5-HT_{1A} receptors
    - Extremely high affinities for those receptors
    - Active metabolites, very long half lives (longer in OD)

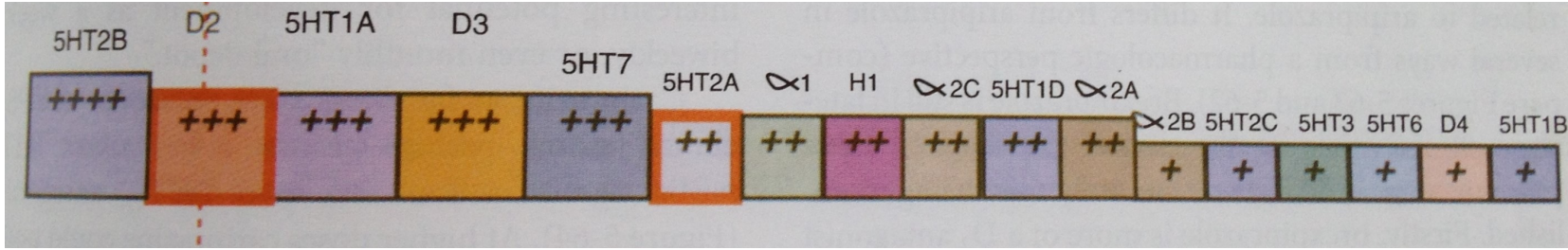
Aripiprazole (Abilify), Brexpiprazole (Rexulti), Cariprazine (Vraylar)



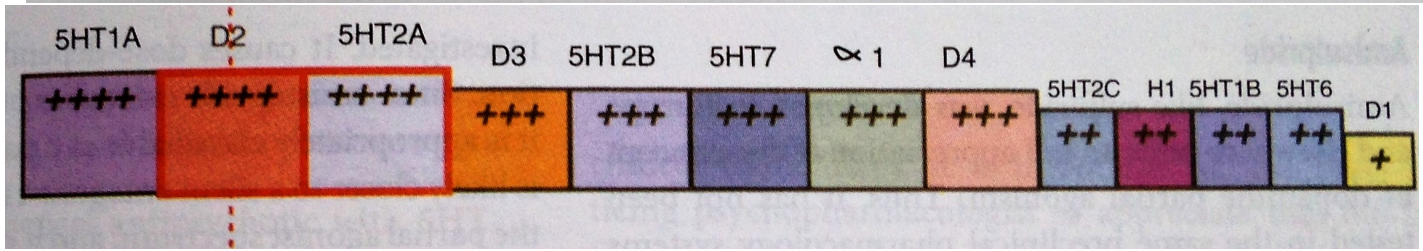
ATYPICAL ANTIPSYCHOTICS (3b)

- Phenylpiperazines all cause more akathisia, less QT prolongation

Ari

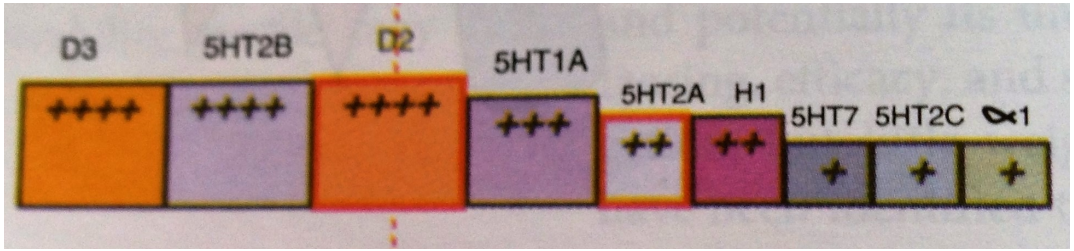


Brex



Orthostasis
↑ SS risk

Car

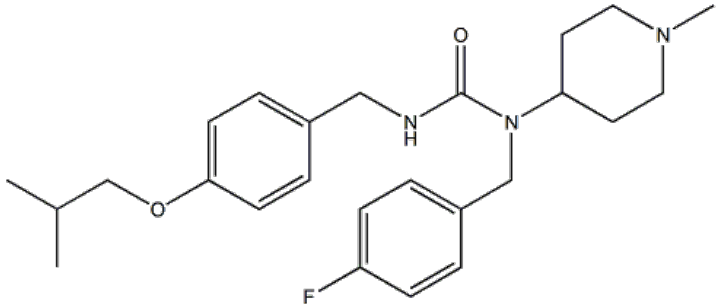


Greatest akathisia risk, least sedating

D_3 partial agonism role unclear – improved cognition ?

Lower 5-HT_7 activity may account for lack of efficacy in depression

ANTIPSYCHOTIC ?



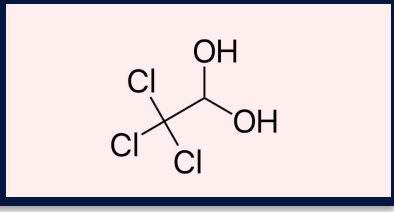
- Pimavanserin (Nuplazid)
  - Rx Psychosis associated with Parkinson Disease
  - Works around the tradeoff between movement and perceptions
- Inverse agonist and antagonist at 5-HT_{2A} receptors
  - 30-fold greater selectivity for 5-HT_{2A} over other serotonin receptors
  - No appreciable affinity for dopaminergic, adrenergic, histaminergic or muscarinic receptors
- CYP3A4/5 substrate with active metabolite
  - Long t ½ of 57 hours, 200 for N-desmethylpimavanserin
- QT prolongation 7.3 msec above placebo at therapeutic dose
- Nausea, ataxia, peripheral edema
- No overdose data

Cruz MP. P T. 2017;42(6):368-371.

SEDATIVE - HYPNOTICS

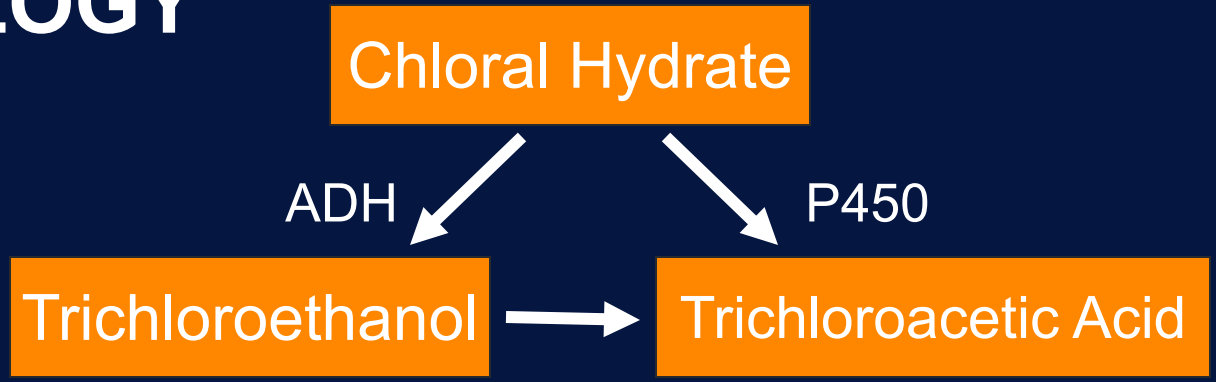
- Ramelteon (Rozerem)
  - MT_1 and MT_2 agonist; may alter testosterone, prolactin levels
- Chloral hydrate (Noctec, Felsules)
- Meprobamate (Miltown, Equanil, Meprospan)
- Methaqualone (Quaalude, Sopor)
- Glutethimide (Doriden)
- Ethchlorvynol (Placidyl)

CHLORAL HYDRATE



- Common use by alcoholics in late 19th century → sleep
  - Solutions EtOH and chloral hydrate often called “knockout drops”
  - Slip a “Mickey Finn” = covertly adding chloral hydrate to a drink
- Minimal respiratory depression or hypotension
- Used recreationally only by a small number of people
  - Historical users: Nietzsche, William James, Oliver Sacks
- Still clinical uses in sedating children / intellectually disabled
  - Mostly dentistry

PHARMACOLOGY



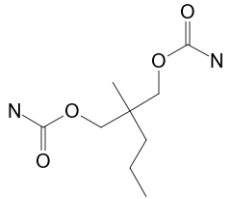
- Trichloroacetic acid
  - Highly protein bound
  - May displace acidic drugs from plasma proteins
- 2,2,2-Trichloroethanol exerts barbiturate-like effects on the GABA-A receptor channel
- 2,2,2-Trichloroethanol inhibits ethanol metabolism

CLINICAL HIGHLIGHTS

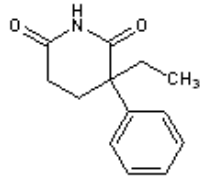
- Hemorrhagic gastritis
- Cardiac arrhythmias
  - Attributed largely to trichloroethanol
  - Myocardium sensitized to circulating catecholamines
- Radio-opaque

SEDATIVE - HYPNOTIC PEARLS

- Meprobamate
  - Concretions/bezoars in overdose
  - Has benzodiazepine-like activity (flumazenil is antidotal)
  - Active metabolite of carisoprodol (antimuscarinic muscle relaxant)

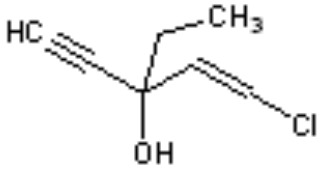


- Glutethimide
  - 2D6 inducer – enhances codeine abuse
  - “Doors and Fours” with Tylenol#4 (APAP & Codeine)

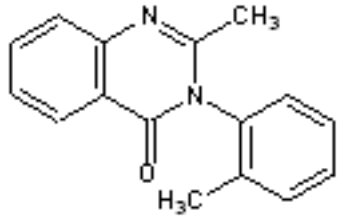


SEDATIVE - HYPNOTIC PEARLS

- Ethchlorvynol – “Jelly-bellies”
  - Oversedation is followed by withdrawal restlessness
  - Used by William Rehnquist



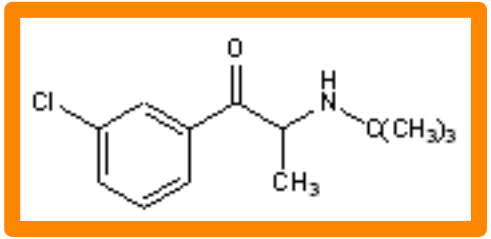
- Methaqualone – “Ludes”
  - Originally synthesized as an antimalarial agent
  - Recent abuse in South Africa
  - Can see hypertonia, hyperreflexia, clonus in overdose
  - Residual paresthesias and polyneuropathies after overdose
  - Mandrax: a combination product with diphenhydramine (“Mandrakes”)



ANTIDEPRESSANTS

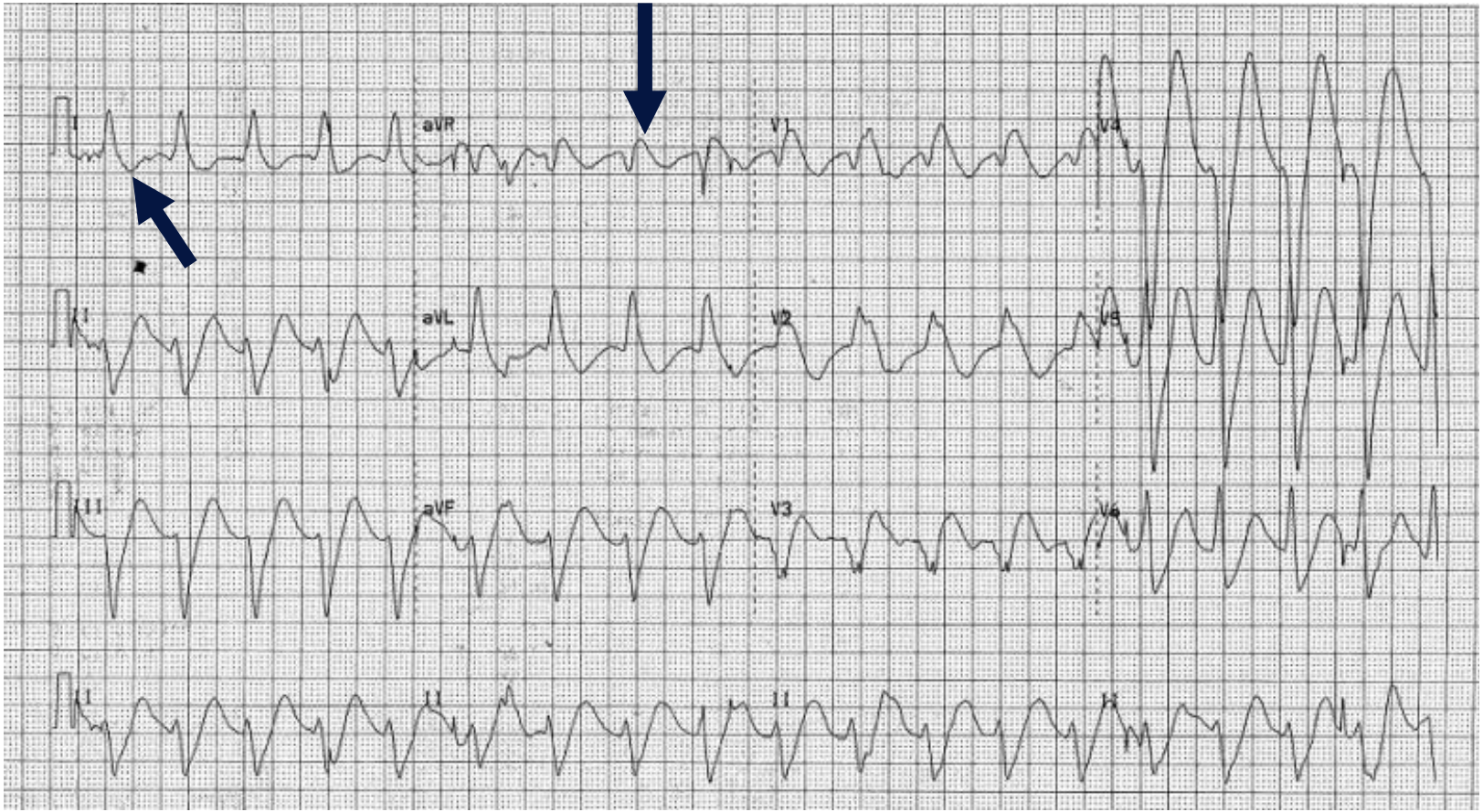
- (Tri)cyclic antidepressants (TCAs)
- Monoamine oxidase inhibitors (MAOIs)
- Selective Serotonin reuptake inhibitors (SSRIs)
- Dual reuptake inhibitors (SNRIs)
- Miscellaneous

Mirtazapine	Reboxetine
Trazodone	Vortioxetine
Nefazodone	Vilazodone

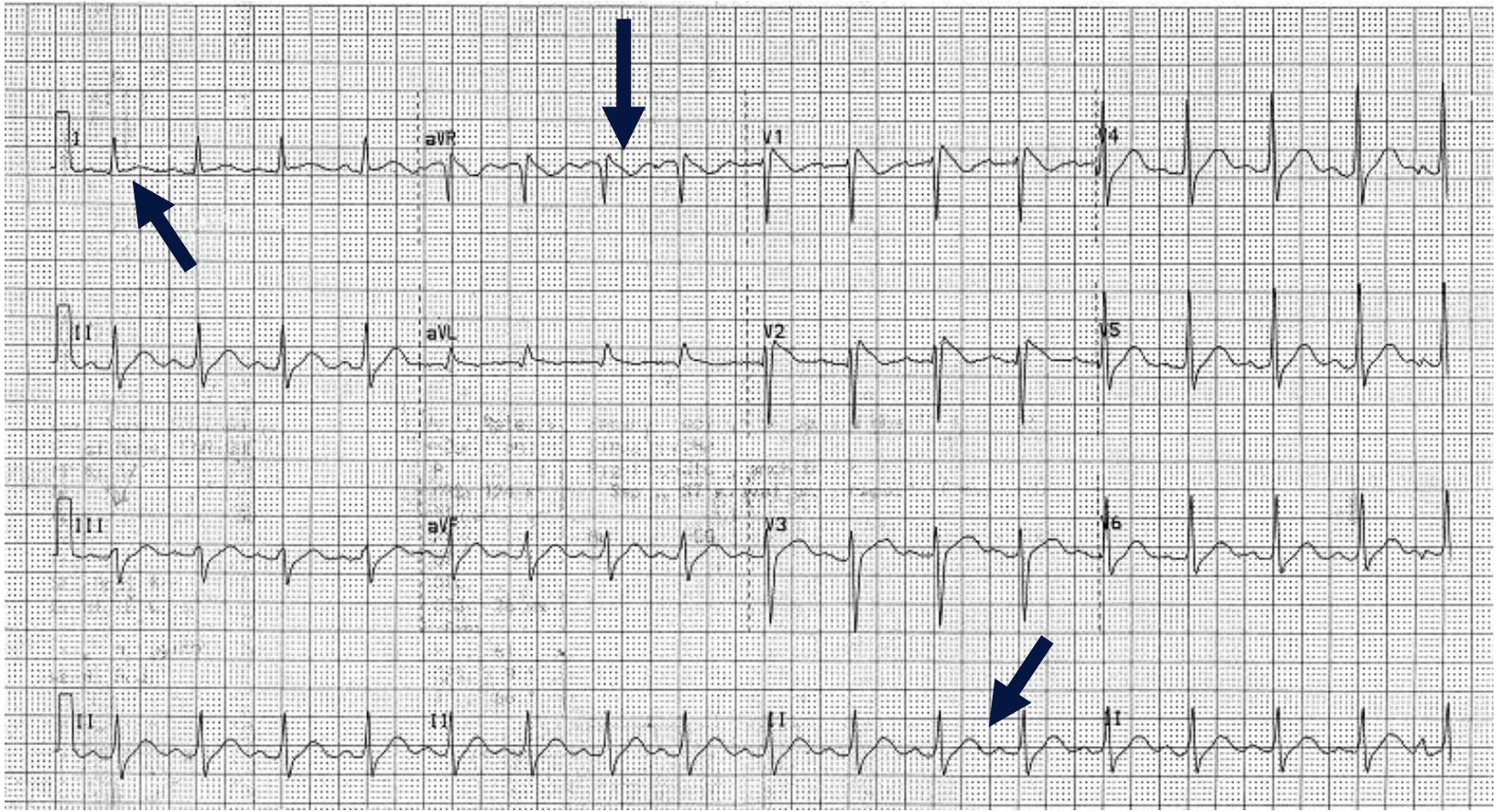


Bupropion

TCA TOXIC EKG



Rx Sodium Bicarbonate



MAOI PHARMACOLOGY

- Monoamine oxidase (MAO)
- Intracellular enzyme found on mitochondrial membranes
- Degrades biogenic amines
  - MAO-A: DA, NE, Tyramine, and 5-HT
  - MAO-B: DA
- Inhibition increases CNS neurotransmitter activity
  - Down-regulates post-synaptic 5-HT & adrenergic receptors
  - Post-synaptic DA receptor populations unaffected

MAOI PHARMACOLOGY

Irreversible binding

- Phenelzine
- Tranylcypromine
- Isocarboxazid
- Selegiline
- Pargyline
- Rasagiline

Reversible binding

- Moclobemide
- Brofaromine
- Cimoxatone
- Toloxatone
- Harmaline

MAOI PHARMACOLOGY

Selective

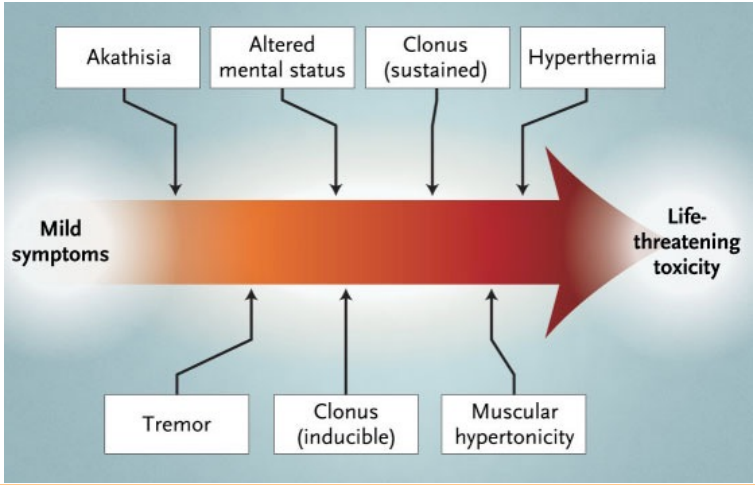
- Moclobemide (A)
- Toloxatone (A)
- Harmaline (A)
- Selegiline (B > A)
- Pargyline (B)
- Rasagiline (B)

Nonselective

- Tranylcypromine
- Phenelzine
- Isocarboxazid

SEROTONIN SYNDROME

- Modified Sternbach criteria (all 3 must be met)
  - Syndrome occurs after addition of known serotonergic agent
  - List of symptoms AND other causes ruled out
  - No neuroleptic involved
- NEJM Boyer & Shannon article
  - Emphasizes spectrum of presentation
  - Hyperthermia
  - Autonomic instability
  - Delirium
  - CLONUS – the ankle, mostly



NEONATAL SRI WITHDRAWAL

- Fetus exposed to an SRI late in the third trimester
  - Paroxetine & Venlafaxine most common (shortest t ½)
- Symptoms
  - Tremors, jitteriness, irritability
  - Respiratory distress, cyanosis, apnea
  - Feeding difficulties, vomiting
  - Hypoglycemia
- Onset hours to days after delivery, which resolved in days or weeks
- Prolonged hospitalization, respiratory support, and tube feeding
  - Consider clonidine or SRI replacement and taper

ACMT BOARD REVIEW COURSE

Herbals, Vitamins & Supplements CRAM SESSION

Nima Majlesi, DO
Director of Medical Toxicology
Staten Island University Hospital, Northwell Health

ACMT

VITAMINS

Fat-soluble

- A
- D
- E
- K_1

Water-soluble

- B_1
- B_3
- B_6
- B_{12}
- C

Differentiating Vit A and D

Both cause hypercalcemia and bone pain

Vit A: **hepatotoxicity and alopecia**

Vit D: **soft tissue calcifications**

THIAMINE Deficiency

- Congestive heart failure (“wet beriberi”)
- Wernicke-Korsakoff (“dry beriberi”) syndrome
  - Ataxia, altered mental status and ophthalmoplegia
  - Korsakoff psychosis- amnesia and confabulation preceded by the signs of Wernicke encephalopathy
  - Metabolic acidosis, elevated lactate, hyporeflexia, hypothermia also seen

VITAMIN B_6 (PYRIDOXINE)

- Pyridoxal phosphate is the active form
- Required in the synthesis of GABA
- Antidote for INH, hydrazine (*Gyromitra esculenta*) toxicity, or intractable seizures
- Deficiency: cheilosis, stomatitis, glossitis, blepharitis, seborrheic dermatitis, **peripheral neuropathy**, and is associated with seizures

VITAMIN B_6 (PYRIDOXINE) Toxicity

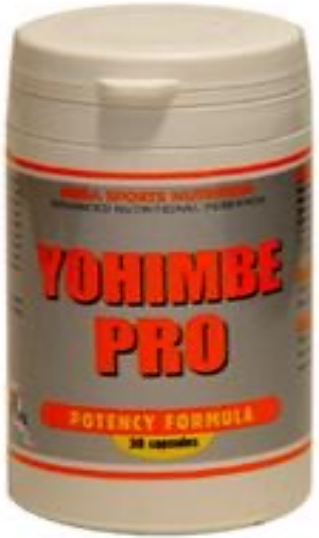
- Chronic excessive dosing
  - Although reports of acute massive iatrogenic IV overdoses are in the literature-- 2-3g/kg
- **Peripheral neurotoxicity affecting dorsal root ganglia**
  - Producing sensory ataxia
  - Impairment of proprioception
  - Impaired vibratory sensation

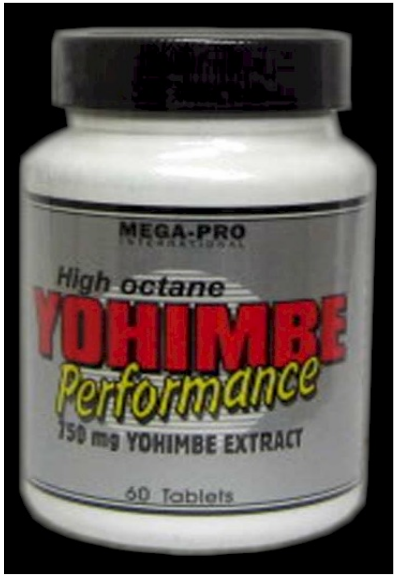
VITAMIN B_{12} (CYANOCOBALAMIN)

- Essential for DNA and myelin synthesis
- Transfers a methyl group from methyl-tetrahydrofolate to homocysteine to form methionine
- Functional deficiency from N_2O abuse
  - Resulting in bone marrow depression and **dorsal column degeneration** and **sensory polyneuropathy**
  - Check homocysteine and methylmalonic acid levels

YOHIMBE (*PAUSINYSTALIA YOHIMBE*)

- Uses - Bodybuilding, hallucinogen, aphrodisiac
- Alkaloid
  - Yohimbine (alkaloid) from bark
- Alpha-2 antagonists (presynaptic)
- Adverse Events
  - Hypertension
  - Weakness/paralysis
  - Abdominal pain





ST. JOHN'S WORT (*Hypericum perforatum*)

- Leaves, stems, and flowers are used
- Uses:
  - Depression
  - Infections
  - Healing wounds
  - Anxiety
  - Headaches
- Hypericin and hyperforin
  - inhibit reuptake of 5-HT, NE, DA, GABA, glutamate and acts as weak MAO-I

ST. JOHN'S WORT

Side effects:

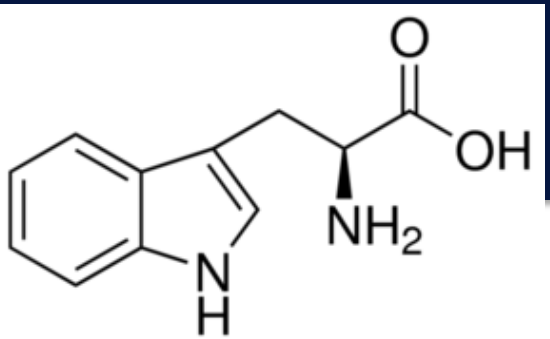
- Photosensitivity; can be severe
- Dizziness
- Confusion
- GI upset

CYP 3A4 Inducer

Interactions:

- **SSRI's – serotonin syndrome**
- Cyclosporin – reduced levels
- Digoxin – reduced levels
- Some narcotics – increased effects
- Oral contraceptives – decreased effectiveness
- Protease inhibitors – decreased effectiveness
- Warfarin – decreased INR

L-TRYPTOPHAN



- Amino acid precursor to 5HT used as a sleep aid
- Eosinophilia myalgia syndrome
  - myalgias, eosinophilia, edema, dyspnea, arthralgias, skin changes, neuropathy, and weight loss
- In 1989 >1500 people who used a supplement
- Outbreak traced to a single manufacturer likely due to a contaminant

GINGKO (*Gingko biloba*)

- Leaves and bark
- Uses:
  - Dementia, memory
  - Claudication
  - Arthritis
  - Sexual dysfunction
  - Acute mountain sickness
- Side effects:
  - Headaches, palpitations, diarrhea, dermatitis
- Interactions:
  - Potentiates anticoagulants

Ginkgo biloba

- Contains Ginkgolide B has antioxidant properties, **inhibits platelet activating factor**, increased bleeding times
  - Bleeding diatheses assoc. with post-op bleeding, SAH, hyphema, cerebral and retrobulbar hemorrhage

- Exploratory ingestions in children resulted in coma and szs

- Raw seeds contain 4-methoxypyridoxine a competitive antagonist of PLP with resultant inhibition of glutamate decarboxylase and impaired GABA synthesis

GINSENG (*Panax quinquefolia*)

- Root
- Uses:
  - Stimulant
  - Memory improvement
  - Treat menopause symptoms
  - Erectile dysfunction
- Interactions:
  - Decrease INR in warfarin users

GINSENG (*Panax ginseng*)

- Active ingredient: ginsenosides (panaxin, panax acid, panaquilin, sapogenin, ginsenin)
- Associated with hirsutism in females in utero
- Ginseng abuse syndrome: diarrhea, anxiety, insomnia, depression, dermatitis, amenorrhea and HTN in those taking >3 g/d (transient and self-limited)

BLACK COHOSH (*Cimicifuga racemosa*)

- Used as an abortifacient and for menstrual irregularity
- Contains triterpene glycosides
- Appears largely safe
- Excessive dosing may cause nausea, vomiting, headache, and dizziness

BLUE COHOSH (*Caulophyllum thalictoides*)

- Used as an abortifacient and for dysmenorrhea
- N-methylcytisine a nicotinic alkaloid
- Causes N/V, diaphoresis, mydriasis, weakness, and fasciculations

ARISTOLOCHIC ACID

- Birthwort, heartwort, fangii
  - (Aristolochia spp)
- Ingredient in Chinese herbal products
- Use: Uterine stimulant
- Aristolochic acid
  - Nephrotoxicity (renal fibrosis)
  - Carcinogen (urothelial cancer)
- FDA warning April 2001. Banned in 7 European countries and Egypt, Japan, and Venezuela.

PYRROLIZIDINE ALKALOIDS

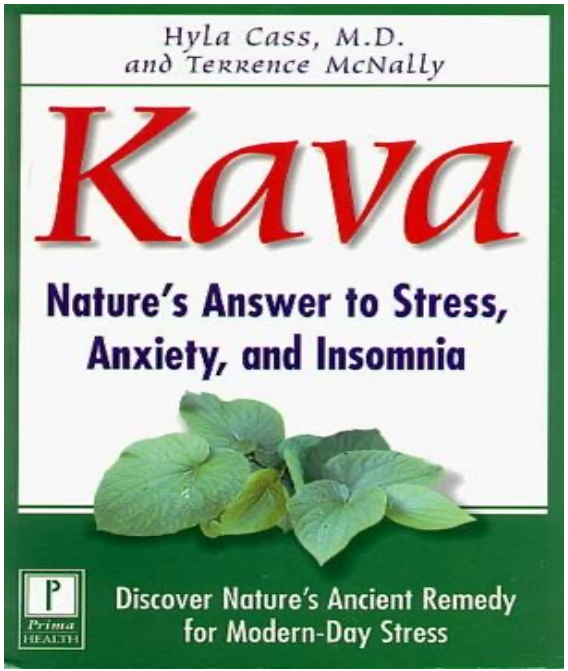
- Includes:
  - Comfrey (Symphytum officinale)
  - Heliotrope (Crotalaria specatabulis)
  - Gordolobo yerba
  - Most dangerous class is retronecine type PA's
- Liver Venoocclusive disease
  - (Sinusoidal hypertrophy & venous occlusion)
- Association with hepatic CA
- Treatment: supportive, transplant

KAVA (*PIPER METHYSTICUM*)

- GABA-agonism, NE/5-HT reuptake blockade, Na^+ channel blockade, MAOI-B inhibition

- Uses:

  Sleeping aid, stress reliever, muscle relaxant, arthralgias, headache, asthma, dysuria



KAVA

- CNS depression
- Kava dermopathy or Kavaism
  - Chronic, high-dose
  - Flaky, dry, and yellowing of the skin, hair loss
  - Ataxia, hearing loss, decreased appetite
- Hepatotoxicity
  - 2002 - 70 cases, including 4 deaths → FDA issued advisory warning
  - Sales restricted in many countries.

EPHEDRA

- Side effects:
  - Sudden death
  - Coronary vasospasm/ MI
  - CVA
  - Arrhythmias
  - Agitation
- Attempted ban in 1997
- Banned by FDA Feb 6, 2004

WHY AREN'T THEY REGULATED?

- Dietary Substance Health Education Act 1994
  - Congress defines herbs as "dietary supplements" not drugs
  - No FDA regulation
  - Safety and efficacy tests **NOT** required
  - No adverse event reporting system
  - Indication claims are acceptable, but not treatment claims
  - FDA can stop sale of an herb if it is determined to be unsafe

ADVERSE REACTIONS

- Hepatotoxicity – comfrey, kava-kava, chaparral, germander
- CVA: ma huang, guarana, yohimbine, bitter orange
- Carcinogen - aristolochic acid, androstenedione, aflatoxin
- Nephrotoxicity - aristolochic acid

Thank you

ACMT BOARD REVIEW COURSE

Endocrine – Rapid Fire

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ACMT

DISCLOSURES

I am a substitute presenter

ANTIDIABETIC AGENTS

- Know your agents—and their MOA

- **Hypoglycemic**
  - Insulin – peaks/timing
  - Meglitinides
  - Sulfonylureas

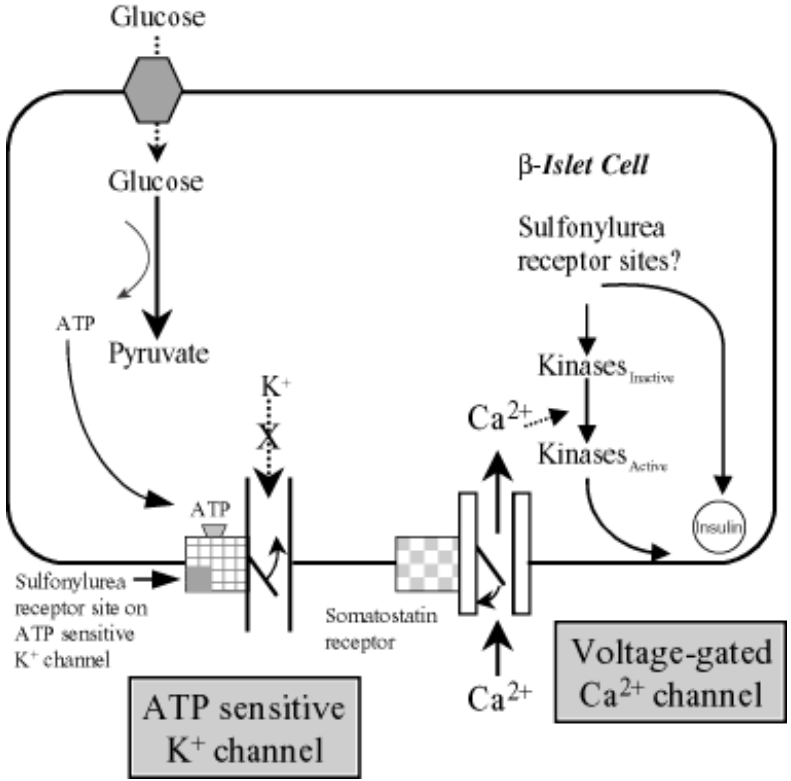
- **Antihyperglycemic**
  - Biguanides--MALA
  - α glucosidase inhibitors
  - Thiazolidinediones
  - GLP 1 analogs
  - Gliptins
  - SGL2 -- Euglycemic DKA

Oral Agents

Xenobiotic	Duration of Action	Active Hepatic Metabolite	Active Urinary Excretory Product	Likelihood of Hypoglycemia in Overdose
Sulfonylureas				
First-generation				
Acetohexamide	12–18 h	(++)	(++)	H
Chlorpropamide	24–72 h	(+)	(++)	H
Tolazamide	10–24 h	(++)	(++)	H
Tolbutamide	6–12 h	(+)	(++)	H
Second-generation				
Glimepiride	24 h	(++)	(++)	H
Glipizide	16–24 h	(–)	(+)	H
Glyburide	18–24 h	(++)	(++)	H
Meglitinides				
Nateglinide	4–6 h	(++)	(+)	H
Repaglinide	1–3 h	(–)	(–)	H
Low Risk: GLP-1 Analogs, SGLT-2 Inhibitors, Amylin Analogs, DPP-4 inhibitors, α-Glucosidase Inhibitors, Biguanides				

SULFONYLUREAS

- Stimulate pancreatic insulin release
- Bind to receptors that result in closure of the K^+ATP channels



BIGUANIDES

- MALA
  - Primary toxicity is type B lactic acidosis
- Inhibits pyruvate carboxylase
  - Pyruvate accumulates → lactic acid
- ARF Patients. → Poss. Need for HD

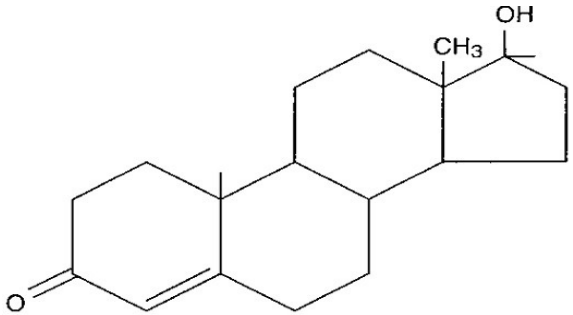
ANABOLIC STEROIDS

- 1990 Anabolic Steroid Control Act
  - Amended the Substance Control Act
  - Made AAS schedule III
- 2004 Anabolic Steroid Control Act
  - Added certain precursors (like androstenedione) to the list of substances

ILLICIT STEROID CHEMISTRY 101

Testosterone is rapidly degraded in the liver

Esterify 17-hydroxy position → oil that can be injected IM for depot release



Alkylate 17-hydroxy position → compounds resistant to hepatic metabolism and suitable for PO administration

DHEA

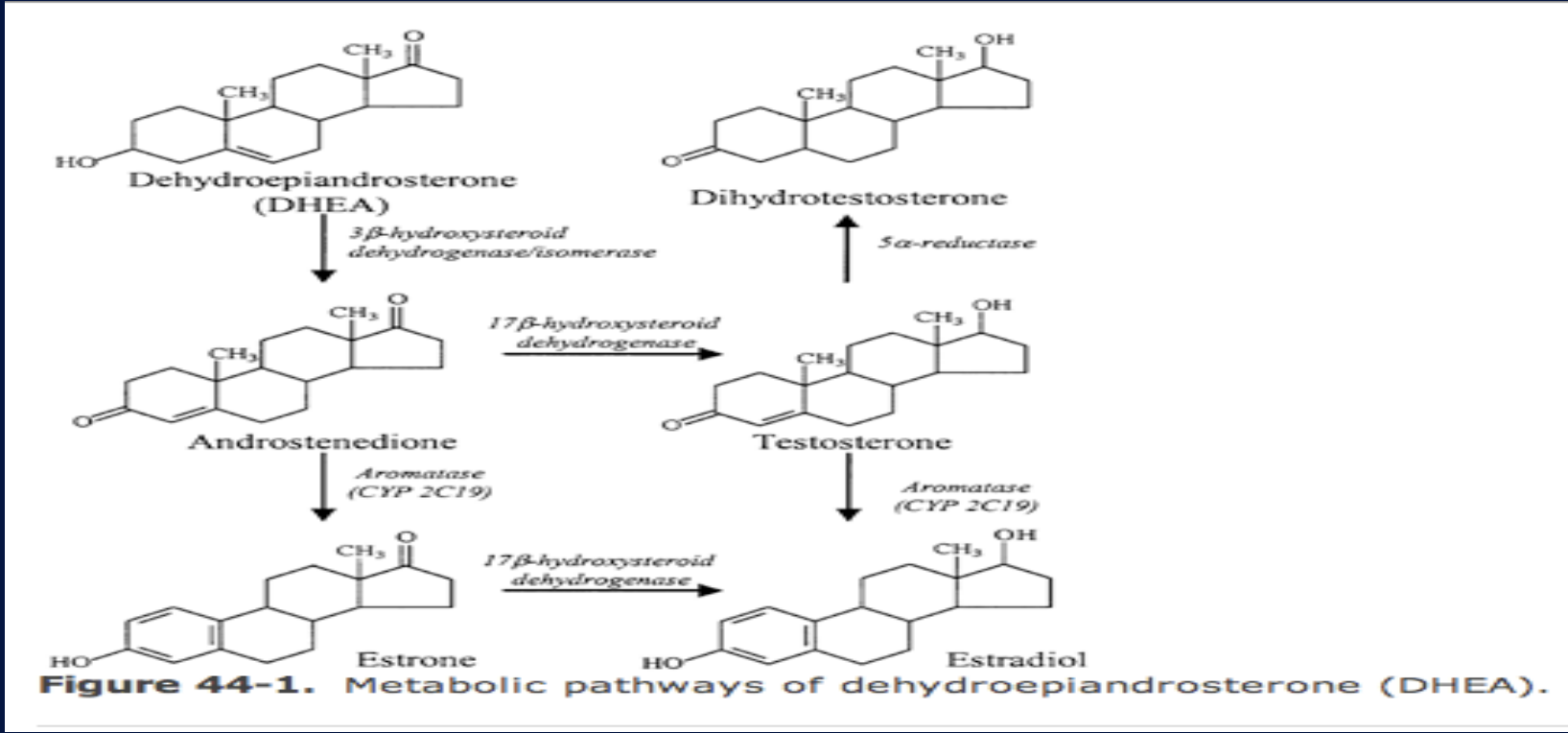


Figure 44-1. Metabolic pathways of dehydroepiandrosterone (DHEA).

TESTING

- Chromatography/MS
- Urinary ratio of testosterone to its endogenous epimer, epitestosterone: Normally, the ratio is less than 6 to 1.
- Athletes taking exogenous testosterone (suppresses the production of both testosterone and epitestosterone) have higher ratios

THYROID EXPOSURE

Acute

- 7-10 day delay
- Most remain asymptomatic or only mildly symptomatic
- Treatment: Supportive care, beta-blockers

Chronic

- Thyrotoxicosis factitia (healthcare workers)
- Meat from neck of animals
- Manifestations
  - Accelerated osteoporosis
  - Dysrhythmias (a. flut/fib, tachy, CHF)
  - Tachycardia disproportionate to fever
  - Neurologic = anxiety, agitation, seizure
  - Death in up to 20% with thyroid storm

IODIDES

- Iodide salts were used before Thioamides were available
- Inhibit T3/T4 release
- **Block thyroid uptake of radioactive iodine**

IODISM

- Rare occurrence with iodides
  - Prolonged treatment
  - High doses
- Rash, laryngitis, bronchitis, esophagitis, conjunctivitis, drug fever, metallic taste, ↑ salivation, headache, bleeding diathesis