Psychotropics

G. Patrick Daubert, MD

Some (most) material plundered from various mentors and other talented toxicologists, with permission

MENU

2.1.11.9 Psychotropics
  2.1.11.9.1 Anxiolytics and sedative-hypnotics
  2.1.11.9.2 Antidepressants
  2.1.11.9.3 Antipsychotics
  2.1.11.9.4 Mood stabilizers

Anxiolytics and Sedative-hypnotics

- Benzodiazepines
- Barbiturates
- Sedative-Hypnotics
Benzodiazepines

"There are very few toxicological problems that cannot be solved through the suitable (and liberal) application of benzodiazepines."

Suzanne White, MD

Benzodiazepines

- Roughly 50,000 benzodiazepine OD cases reported annually
- 65% intentional
- Few deaths
- Most are combination exposures
- Mixed drug overdose or IV administration = increased morbidity

Benzodiazepines

- About 15 types marketed in the US
- 50 types worldwide
- Vary in half-life and metabolism
  - All rapidly absorbed
  - CNS redistribution varies
  - Half-life ≠ duration of action
  - Conjugation only
    - Oxazepam, lorazepam, temazepam
  - IM administration
    - Lorazepam, midazolam
Benzodiazepines

- All are indirect agonists at post-synaptic GABA-A channels
- Can’t open the channel without GABA
- $BZD_1$ receptors
- Increase frequency of Cl channel opening
- $BZD_2$ receptors (spinal cord) affect muscle relaxation
- All produce tolerance with cross-reactivity
- Predispose to physical dependence
- $BZD_2$ receptors
- Withdrawal: worse for short half-life agents

Benzodiazepine Overdose

- Nonspecific
- CNS: drowsiness, dizziness, slurred speech, nystagmus, confusion, ataxia, coma (rare)
- Children: 17% isolated ataxia
- Other: respiratory depression, hypotension with IV administration

Benzodiazepine Pearls

- Increase frequency of Cl channel opening
- Propylene glycol: lorazepam
- Clonazepam:
  - Anticonvulsant
  - Mood stabilizer
- Flunitrazepam (RoHypnol): “Date Rape”
- EMIT: Oxazepam false negatives
Barbiturates
- GABA<sub>A</sub>
  - Direct increase in duration of channel opening
  - GABA not needed
- 4 Categories
  - Ultrashort: methohexital, thiopental
  - Short: pentobarbital, secobarbital
  - Intermediate: butalbital
  - Long-acting: phenobarbital
- Enzyme induction: drug interactions

Barbiturate Toxicity
- Symptoms similar to other sedatives
- More likely to see respiratory depression
  - CNS tolerance ≠ Respiratory tolerance
- Common
  - Nystagmus, dysarthria, ataxia, drowsiness, respiratory
    depression, and coma
- Less common
  - Hypotension, cardiovascular collapse, and hypothermia
  - Bullous skin lesions ("barb burns"), noncardiogenic
    pulmonary edema

Phenobarbital (PHB)
- Long-acting barbiturate
- Normal range 15-40 mg/L.
- PHB tolerance does not usually involve respiratory tolerance
- Levels > 80 mg/L typically result in coma
- Death is uncommon with good supportive care
- Primidone
  - Metabolized to PEMA and PHB
Treatment

- Supportive care
- Passive warming
- Positive barbiturate on urine drugs of abuse screen
- Phenobarbital vs butalbital
- IVF, norepinephrine for hypotension
- Urinary alkalinization
  - Stop alkalinization when PHB < 40 mg/L.
- MDAC
  - Listed on MDAC position statement (The 'A' list)
  - MDAC demonstrates better elimination than urine alkalinization.

‘Z’ Drugs

- Zolpidem (Ambien, Stilnox)
- Zaleplon (Sonata)
- EcZopiclone (Lunesta, Estorra)
- Ramelteon (RoZerem)
- Non-benodiazepine sedatives
- Selective for GABA_BZ-1 receptors
- Less physical dependence
- Flumazenil may precipitate withdrawal
- Ramelteon may alter testosterone and prolactin levels

“Z” Drug Overdose

- CNS depression, coma
- Respiratory depression
- Nausea and vomiting
- Hypotension
- Miosis, mydriasis
- Hallucinations
- Flumazenil reverses Z agent effect and may precipitate withdrawal
  - Same precautions as with benzodiazepines
Sedative-Hypnotics

- Buspirone (Buspar)
- Chlordiazepoxide
- Meprobamate
- Methaqualone
- Glutethimide
- Ethchlorvynol

Chloral Hydrate

- Commonly used by alcoholics in the late 19th century to induce sleep
- Solutions of alcohol and chloral hydrate often called “knockout drops” or “Mickey Finn”
- Sedation with minimal respiratory depression and hypotension
- Used recreationally only by a small number of people
- Common trade names are Noctec, Somnos and Felsules

Pharmacology

- Trichloroacetic acid
  - Highly protein bound
  - May displace acidic drugs from plasma protein
- Trichloroethanol exerts barbiturate-like effects on the GABA<sub>A</sub> receptor channels
- Trichloroethanol inhibits ethanol metabolism
Clinical Highlights

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

Sedative-Hypnotic Pearls

- Meprobamate (Miltown, Equanil, Meprospan)
  - Active metabolite of carisoprodol
  - Concretions/bezoars in overdose
- Glutethimide (Doriden)
  - 2D6 inducer – codeine abuse
  - "Doors and Fours" with Tylenol#4

- Ethchlorvynol (Placidyl)
  - "Jelly-bellies"
  - Used by William Rehnquist (oversedation then withdrawal)
- Methaqualone
  - Quaaludes, Mandrax
  - Recent abuse in South Africa
  - Can see hyperreflexia, clonus
  - Residual paresthesias and polyneuropathies after overdose
Antidepressants

- Cyclic antidepressants
- Monoamine oxidase inhibitors (MAOIs)
- Serotonin reuptake inhibitors
- Miscellaneous
  - Bupropion
  - Citalopram/Escitalopram
  - Mirtazapine
  - Trazodone
  - Venlafaxine

Usual Suspects

- Tertiary amines
  - Amitriptyline
  - Clomipramine
  - Doxepin
  - Imipramine
  - Trimipramine
- Secondary amines
  - Desipramine
  - Nortriptyline
  - Protriptyline
- Tetracyclic
  - Amoxapine
  - Maprotiline

TCA Screen Cross Reactivity

- Cyclobenzaprine (Flexeril)
- Diphenhydramine (Benadryl)
- Cyproheptadine (Periactin)
- Carbamazepine (Tegretol)
- Thioridazine (Mellaril)
- Quetiapine (Seroquel)
Pharmacokinetics

- Peak serum concentration 1-8 hrs
- Antimuscarinic = delayed gastric emptying
- Lipophilic = large Vd
- Hepatic phase I: Demethylation
  - Imipramine $\rightarrow$ desipramine
  - Amitriptyline $\rightarrow$ nortriptyline
- Hydroxylation: CYP2D6
  - Slow vs Rapid
  - Desipramine 81-131 vs 12-23 hours

CA Toxicity

- Rapid onset of symptoms
- Early sedation and coma
- Early antimuscarinic symptoms
- Cardiovascular
  - Hypotension
  - Dysrhythmias

Cardiovascular Toxicity

- Rapid inward Na$^+$ current
- QRS prolongation
  - HH more susceptible (leads V1, V2, aVR, V)
- Rate dependent
- pH dependent
- R axis deviation in terminal 40 msec
- AV node blocks
- K$^+$ channel blockade (Ih)
- Increased QT but TdP uncommon with tachycardia
- Seen with therapeutic dosing
Cyclic Antidepressants Toxicology

- Membrane effects
  - Blockade of fast Na\(^+\) channels phase 0 of the action potential

Axis Change in Toxicity

V1 R aVR Terminal R
MAOI pharmacology

- Intracellular enzyme found on mitochondrial membrane
- Degrades biogenic amines
- Increases neurotransmitter activity in CNS, down-regulates post-synaptic 5HT and adrenergic receptors
- Post-synaptic DA unaffected

MAOI pharmacology

- Irreversible binding: Phenelzine, Tranylcypromine, Isocarboxazide, Selegiline, Pargyline
- Reversible binding: Moclobemide, Toloxatone, Harmaline
**MAOI pharmacology**

- **Selective**
  - Clorgyline (A)
  - Moclobemide (A)
  - Toloxatone (A)
  - Harmaline (A)
  - Selegiline (B)
  - Pargyline (B)
- **Nonselective**
  - Tranylcypromine
  - Phenylephrine
  - Isoxcarbazazid

**Signs and Symptoms (Overdose)**

- **Phase I**
  - Latent period: 6-12 hrs in pts on medication.
  - 24-36 hrs in "naïve" patients.

- **Phase II**
  - Excitatory phase
    - Hyperadrenergic appearing
    - "Ping-pong" nystagmus
    - Hyperreflexive with rigidity
    - Writhing, opisthotonus, facial grimacing
  - Progression
    - CNS depression
    - Fever, diaphoresis, salivation
    - Rigidity, myoclonus, carpopedal spasm
    - Myocardial ischemia, ICH, seizures

**Treatment**

- Expect prolonged period of toxicity
- ICU for 24 hrs after resolution of signs and symptoms
- Restricted diet for 2-3 weeks
- Check ALL medications for interactions
- Treat as signs and symptoms appear
  - Use SHORT acting agents
  - Use DIRECT acting agents-COMT metabolism
MAO-Tyramine reaction

- Not an overdose
- Onset within 2 hrs 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

Serotonin Reuptake Inhibitors

- Paroxetine (Paxil)
- Fluoxetine (Prozac, Sarafem)
- Citalopram (Celexa)
- Escitalopram (Lexapro)
- Sertraline (Zoloft)
- Fluvoxamine (Luvox)
- Fluoxetine + olanzepine (Symbyax)
**Pearls**

- SSRI in overdose: CNS depression and tachycardia most common
- Citalopram and escitalopram: reports of seizures and widened QT interval
- Fluvoxamine inhibits CYP1A and CYP2C
- Paroxetine, fluoxetine, and metabolites strong inhibitors of CYP2D6

**SSNRI and Others**

- Bupropion
  - Excitation in overdose, SEIZURES, XL products
- Mirtazapine (Remeron)
  - Sedation, mild symptoms in toxicity
- Nefazadone (Serzone), Trazadone (Desyrel)
  - Prolonged QT, orthostatic hypotension, priapism
- Venlafaxine (Effexor, aka side-effectson)
  - Seizures, QRS prolongation

**Serotonin Syndrome**

- Stimulation of post-synaptic 5HT_1a_ and 5HT_2 brain receptors
- Mechanism
  - Two or more serotonergic agents
  - SSRI + neuroleptic
  - SSRI + agent with serotonergic properties
  - Change in dose
  - Metabolic inhibition
Serotonin Syndrome

- Modified Sternbach criteria: A, B, C must be met:
  - A. Syndrome occurs after addition of known serotonergic agent
  - B. List of symptoms to be met (at least 3) and other causes ruled out
  - C. No neuroleptic involved
- NEJM M. Shannon article

- Hyperthermia
- Mental status changes
- Autonomic instability
- CLONUS

Serotonin Syndrome - Treatment

- Good supportive care
- Benzodiazepines
- External cooling
- Paralyzation with a nondepolarizing agent

Specific agents
- Cyproheptadine: nonspecific 5HT1 antagonists (4-8 mg q1h)
- NTG: nitric acid mediated downregulation of 5HT (drip titrated to effect)
- Propranolol: 5HT1 antagonist (1-5 mg IV)
- Chlorpromazine: 5HT2 antagonist

SS vs NMS

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<tr>
<th>Signs/Symptoms</th>
<th>SS</th>
<th>NMS</th>
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</thead>
<tbody>
<tr>
<td>Onset</td>
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<td>Resolution</td>
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<td>Days</td>
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<td>Myoclonus</td>
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<td>--</td>
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<tr>
<td>Hyperreflexia</td>
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<tr>
<td>Metabolic acidosis</td>
<td>*/+</td>
<td>++++</td>
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<tr>
<td>Muscle rigidity</td>
<td>++</td>
<td>++++</td>
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<tr>
<td>Altered mental status</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td>Autonomic dysfunction</td>
<td>+++</td>
<td>++++</td>
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Neonatal SSRI Withdrawal

- Fetus exposed to an SRI late in the third trimester
- Symptoms:
  - Respiratory distress (apnea)
  - Cyanosis, apnea
  - Feeding difficulties
  - Vomiting
  - Hypoglycemia
  - Tremors, jitteriness, irritability
- Onset hours to days after delivery, which resolved in days or weeks
- Prolonged hospitalization, respiratory support, and tube feeding

Question

Acute overdose of selective serotonin reuptake inhibitor (SSRI) antidepressant medications most often result in
A. Cardiac dysrhythmias
B. CNS depression and tachycardia
C. Hallucinations and delirium
D. Profound hyperthermia and rigidity
E. Seizures
Antipsychotics

- Traditional antipsychotics
  - D2 antagonists
- Atypical
  - Selective for limbic vs EP sites
  - Mixed DA receptor affinities (D1,D2 etc)
  - Mixed affinity for DA, 5HT, alpha
  - Looser binding to D2, less EPS

Antipsychotic Classification

- Low potency (sedating, antimuscarinic, miosis)
  - Chlorpromazine (most sedating in overdose)
  - Chlorprothixene
  - Mesoridazine
  - Thioridazine (most cardiotoxic in overdose)
- Medium potency
  - Droperidol
  - Loxapine (more seizures in overdose)
  - Molindone
  - Pimozide
- High potency (more EPS, less sedation)
  - Fluphenazine
  - Haloperidol (most common cause of NMS)
  - Thiothixene

Reversible EPS: Acute Dystonia

- Intermittent spasmic and involuntary contractions of face, neck, trunk
  - Facial grimacing
  - Trismus
  - Blepharospasm
  - Oculogyric crisis
- Idiosyncratic
  - Males 5-45 years
  - Depot preps
  - Resolves during sleep
Reversible EPS

- Akathesia
- Subjective unease
- Motor restlessness
- Dose related
- Women
- High potency
- Dopamine-cholinergic basal ganglia balance disrupted
  - Excess choline with dopamine depletion...

Irreversible EPS: Tardive Dyskinesia

- Involuntary movements of orofacial structures
  - Lip smacking
  - Facial grimacing
  - Eye blinking
  - Grunting
- Late onset > 2 years after therapy onset
- More common in women > 50 years

Antipsychotic Pearls

- Thioridazine
  - Peak serum level can be delayed 120 hours
  - QTc but not QRS correlates closely with peak concentration
  - Most lethal in overdose
  - Most common cause of NMS (> 90%)
  - Haloperidol
  - Agranulocytosis
  - Chlorpromazine (Thorazine)
  - Cholestatic jaundice
  - Chlorpromazine (Thorazine)
  - Acute reversible oliguria
  - Chlorprothixene (Taractan)
Atypical Antipsychotics

- Aripiprazole (Abilify)
  - Longest potential e-half-life in overdose (146 hrs)
- Clozapine (Clozaril)
  - Aplastic anemia, seizures, drug-induced DM, myocarditis, fever
- Olanzapine (Zyprexa)
  - Highest incidence of NMS
  - Highest antimuscarinic activity but salivation common
  - Drug-induced DM
  - Classically resembles opiate toxidrome

Atypical Antipsychotics

- Paliperidone (Invega)
  - Active metabolite of risperidone
- Risperidone (Risperdal)
  - Highest rate of dystonia
  - Most reported seizures
  - Potent alpha blockade
  - No antimuscarinic effects; miosis
  - Unusual dysrhythmias for class (aflutter, heart blocks)
- Ziprasidone (Geodon)
  - Highest rate of increased QT
  - Miosis common

Quetiapine Pearls

- CNS depression, prolonged QT, tachycardia
- 3 grams predicted ICU/prolonged LOS
- Cross reacts with TCA assay
- Most sedating of class
  - Highest antihistamine activity
- High alpha blockade
- Less miosis
- Half-life longer in overdose
New! Improved!

- Asenapine
  - Hypotension
  - Agitation, altered
  - QT?
- Iloperidone
  - Hypotension, antimuscarinic
  - QT prolongation
- Lurasidone
  - Hypotension, confusion, leukopenia

Mood Stabilizing Lithium

- Main therapy for bipolar disorder
- Narrow therapeutic index (0.6-1.2 mEq/L)
- Slow distribution across cell membranes
  - Delay between peak blood levels and CNS effects
- Most cases chronic due to a reduction in GFR
  - Volume loss
  - NSAIDs, diuretics, ACE inhibitors
  - Age

Acute vs Chronic Lithium

- Increased intake
- Decreased excretion
  - Serum levels lower since intercellular levels high
- Subacute/subacute neurologic symptoms
- GI symptoms less severe
- Encephalopathy, myoclonus, severe rigidity, seizures
- ECG
  - Bradycardia
  - T-wave flattening/inversion
  - QT prolongation

- Delayed toxicity due to delayed distribution
- High serum levels initially do not correlate with toxicity
- GI symptoms more severe
- Tremor, muscle weakness, ataxia, hyperreflexia
- Decreased excretion
  - Serum levels lower since intercellular levels high
- Subacute/subacute neurologic symptoms
- GI symptoms less severe
- Encephalopathy, myoclonus, severe rigidity, seizures
- ECG
  - Bradycardia
  - T-wave flattening/inversion
  - QT prolongation
Lithium Management

- D/C lithium and offending drugs
- Improve GFR
  - 20% reduction in Li over 6 hours
- Hemodialysis (guidelines vary)
  - Renal failure
  - Encephalopathy, myoclonus, severe rigidity, seizures
  - Acute > 4.0 mEq/L
  - Chronic > 2.5 mEq/L

Question

A 23-year-old woman is taking ziprasidone for her schizoaffective disorder. Her ECG reveals a QRS 86 msec, and QTc 560 msec. Her physician wants to know what medication you would recommend in place of her ziprasidone?

A. Chlorpromazine (Thorazine)
B. Haloperidol (Haldol)
C. Olanzapine (Zyprexa)
D. Quetiapine (Seroquel)
E. thioridazine (Mellaril)
Questions?

Good Luck!!
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**ANXIOLYTICS AND SEDATIVE-HYPNOTICS**

**Benzodiazepines**

- **Background**
  - Roughly 50,000 benzodiazepine OD cases reported annually
  - 65% intentional
  - Few deaths
  - Most are combination exposures
  - Mixed drug overdose or IV administration = increased morbidity
  - About 15 types marketed in the US
  - 50 types worldwide

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- **Kinetics**
  - Vary in elimination half-life and metabolism
  - All rapidly absorbed
  - CNS redistribution varies
  - Half-life ≠ duration of action
  - Conjugation only BZDs = oxazepam, lorazepam, temazepam
  - IM administration = lorazepam, midazolam
• Dynamics
  o All are indirect agonists at post-synaptic 
    \( \text{GABA}_A \) channels
    • Can’t open the channel without \( \text{GABA} \)
    • \( \text{BZD}_1 \) receptor subtype
    • Increase \emph{frequency} of chloride channel opening
  o \( \text{BZD}_2 \) receptors (HC, spinal cord) affect muscle relaxation
  o All produce tolerance with cross-reactivity
  o Predispose to physical dependence
    • \( \text{BZD}_2 \) receptor agonism

• Benzodiazepine Overdose
  o Nonspecific – sedative-hypnotic symptoms
  o CNS changes without vital sign changes: drowsiness, dizziness, slurred speech,
    nystagmus, confusion, amnesia, ataxia, coma (rare)
  o Patients look “drunk”
  o Children: 17% isolated ataxia
  o Other: respiratory depression, hypotension with IV administration

• Benzodiazepine withdrawal
  o Worse for short half-life agents
  o Agitation, tremor, headache, weight loss, seizures
  o Mild symptoms start in 1-3 days with peak in 5-9 days. Symptoms taper over 3-4 weeks
  o May be precipitated by flumazenil

• Flumazenil (Romazicon)
  o Competitive BZD antagonist
  o Reverses CNS depression but not respiratory depression
  o Withdrawal symptoms more likely in doses > 1 mg
  o Safest patient populations
    • Children with single dose ingestions
    • Reversal of iatrogenic sedation (procedural sedation)

• Benzodiazepine Pearls
  o Increase \emph{frequency} of \( \text{GABA}_A \) chloride channel opening
  o Propylene glycol: lorazepam, diazepam
  o Clonazepam: Anticonvulsant, mood stabilizer, sounds like “clonidine”
  o Flunitrazepam (RoHypnol): “Date Rape” drug
  o In-house urine qualitative EMIT toxicology screen may not detect BZDs that do
    not produce oxazepam metabolite (false negative)
    • Midazolam, alprazolam, lorazepam, triazolam, clonazepam

Barbiturates
• 4 Categories
  o Ultrashort: methohexital, thiopental
  o Short: pentobarbital, secobarbital
  o Intermediate: butalbital
  o Long-acting: Phenobarbital
  o Combination products
    • Donnatal: phenobarbital, atropine, hyoscyamine
    • Fiorinal/cet: butalbital, caffeine, ASA/APAP
• Pharmacology
  o GABA$_A$ agonist with direct increase in duration of channel opening
  o Contrast to BZD, GABA not needed with barbiturates
  o Pharmacology secondary to decrease in central sympathetic tone and direct myocardial depression
• Barbiturate Toxicity
  o Symptoms similar to other sedatives with CNS depression and cerebellum symptoms
  o More likely to see respiratory depression
    ▪ CNS tolerance ≠ Respiratory tolerance
  o Medullary effect: cardiovascular collapse, miosis
  o Hypothermia, bullae at pressure points (“barb burns”), concretions
  o Noncardiogenic pulmonary edema
• Barbiturate withdrawal
  o Life threatening
  o Agitation, tremor, seizures, insomnia, delirium
  o Occurs 3 days after cessation of drug and lasts 10-14 days
• Phenobarbital (PHB)
  o Long-acting barbiturate
  o Normal range 15-40 mg/L
  o PHB CNS tolerance does not usually involve respiratory tolerance
  o Death is uncommon with good supportive care
  o Remember primidone metabolized to PEMA and PHB
  o Treatment
    ▪ Supportive care
    ▪ Passive warming
    ▪ IVF, norepinephrine for hypotension
    ▪ Urinary alkalination
      ▪ Phenobarbital is only barbiturate effectively eliminated with urine alkalization
      ▪ Stop alkalization when PHB < 40 mg/L
    ▪ Multidose activated charcoal
      ▪ Stop MDAC when PHB < 40 mg/L
      ▪ MDC demonstrates better elimination than urine alkalization
      ▪ Listed as one of five drugs in position statement for MDAC with best data for enhanced elimination (NOT outcome data)
        o Carbamazepine, dapsone, phenobarbital, quinine, theophylline)
  o Caveat
    ▪ Positive barbiturate (qualitative) on urine drugs of abuse screen: PHB vs butalbital are typically only barbiturates available for use by general patient population. If PHB level is zero, likely butalbital overdose, which means also ordering ASA and APAP (Fiorinal/cet)
‘Z’ Drugs
• Zolpidem (Ambien, Stilnox)
• Zaleplon (Sonata)
• EcZopiclone (Lunesta, Estorra)
• Ramelteon (RoZerem)

• Non-benzodiazepine sedatives
• Selective for GABAA BZ-1 receptors
• Less physical dependence
• Flumazenil may precipitate withdrawal
• Ramelteon ay alter testosterone and prolactin levels

“Z” Drug Overdose
○ Nausea/vomiting, respiratory depression, hypotension
○ Can see both miosis and mydriasis and fixed pupils
○ CNS depression and hallucinations
○ Flumazenil reverses ‘Z agent’ effect and precipitates withdrawal with same precautions as with benzodiazepines

Sedative-Hypnotics
• Buspirone
  ○ Non-benzodiazepine, anxiolytic
    ▪ Does not stimulate GABA_A receptors
    ▪ Acts act 5-HT_1A
  ○ No reported withdrawal syndrome
  ○ CNS depression, miosis
  ○ Serotonin syndrome potential

• Chloral Hydrate
  ○ Commonly used by alcoholics in the late 19th century to induce sleep
  ○ Solutions of alcohol and chloral hydrate often called “knockout drops” or “Mickey Finn”
  ○ Sedation with minimal respiratory depression and hypotension
  ○ Used recreationally only by a small number of people
  ○ Common trade names are Noctec, Somnos and Felsules
  ○ Pharmacology
    ▪ Trichloroactic acid
      • Highly protein bound
      • May displace acidic drugs from plasma protein
    ▪ Trichloroethanol exerts barbiturate like effects on the GABA_A receptor channels
    ▪ Trichloroethanol inhibits ethanol metabolism
Chloral hydrate clinical highlights
- Hemorrhagic gastritis
- Cardiac arrhythmias
  - Sensitized myocardium to circulating catecholamines
  - Attributed largely to trichloroethanol
- Radioopaque

Sedative-Hypnotic Pearls
- Meprobamate (Miltown, Equanil, Meprospan)
  - Active metabolite of carisoprodol
  - Concretions/zoars in overdose
- Glutethimide (Doriden)
  - 2D6 inducer – codeine abuse
  - “Doors and Fours” with Tylenol#4
- Ethchlorvynol (Placidyl)
  - “Jelly-bellies”
  - Used by William Rehnquist (oversedation then withdrawal)
- Methaqualone
  - Quaaludes, Mandrax
  - Recent abuse in South Africa
  - Can see hyperreflexia, clonus
  - Residual paresthesias and polyneuropathies effects after overdose

ANTIDEPRESSANTS

Cyclic Antidepressants (CAs)
- Account for nearly 50% of all cardiovascular deaths in the U.S. CAs are widely available for medical conditions other than depression (e.g., chronic pain, pediatric enuresis)
- Usual Suspects
  - Tertiary amines
    - Amitriptyline
    - Clomipramine
    - Doxepin
    - Imipramine
    - Trimipramine
  - Secondary amines
    - Desipramine
    - Nortriptyline
    - Protriptyline
  - Tetracyclic
    - Amoxapine (high risk of intractable seizures)
    - Maprotiline (high risk of intractable seizures)
- TCA Urine Drug Screen Cross Reactivity
  - Cyclobenzaprine (Flexeril)
  - Diphenhydramine (Benadryl)
  - Cyproheptadine (Periactin)
  - Carbamazepine (Tegretol)
  - Thioridazine (Mellaril)
  - Quetiapine (Seroquel)
• Pharmacokinetics
  o Peak serum concentration 1-8 hrs (symptoms in 1-2 hours)
  o Antimuscarinic – remember delayed gastric emptying
  o Lipophilic – large Vd
  o Elimination almost entirely hepatic
  o Hepatic phase I: Demethylation (CAs remain active until hydroxylation occurs)
    ● Imipramine → desipramine
    ● Amitriptyline → nortriptyline
  o Hydroxylation of some CAs affected by genetic polymorphism at the CYP2D6 allele. For example, 90-95% of U.S. population are rapid hydroxylators producing shorter desipramine elimination half-lives 12-23 hours than slow hydroxylators (81-131 hours)
• Clinical Toxicity
  o Rapid onset of symptoms
  o Early sedation and coma
  o Early antimuscarinic symptoms
  o Cardiovascular
    ● Hypotension
    ● Dysrhythmias
      • Blockade of fast Na⁺ channels phase 0 of the action potential → QRS prolongation
      • RBB more susceptible (leads V1, V2, aVR, I)
        o Rate dependent – increase in CA binding with ↑ HR
        o pH dependent - increase in CA binding with ↓ pH
      • R axis deviation in terminal 40 msec
      • AV node blocks
      • K⁺ channel blockade (Ikr)
        o Increased QT but TdP uncommon with tachycardia
        o Can be seen with therapeutic dosing

• Treatment caveats
  o Airway management early
  o Multi-dose charcoal may be beneficial with amitriptyline
  o Levels generally not useful in acute overdose. However, levels > 1000 ng/mL will likely result in significant toxicity (remember to order both tertiary and secondary CA levels)
  o Sodium bicarbonate (no outcome data comparing infusion vs IV bolus)
  o Lidocaine most commonly advocated for VT/VFib but efficacy data is lacking
Seizures usually resolve spontaneously – but resulting lowered pH may increase risk of dysrhythmias
  • Phenytoin not to be used for seizures
    • Hypotension and dysrhythmias from rapid infusions
    • Seizure most likely due to GABA and adenosine inhibition, not sodium channel effects
    • Animal models suggest phenytoin is prodysrhythmic in CA toxicity
  • Physostigmine
    • Not currently advocated
    • Most likely risk of asystole and death is in the treatment of patients with severe toxicity with seizures and bradycardia. QRS widening has not been directly linked to asystolic risk

**Monoamine Oxidase Inhibitors**
- Isoniazid and its isopropyl derivative, iproniazid (Marsilid, no longer marketed), were used in 1951 for the treatment of tuberculosis. Patients on these drugs were noted to have elevated mood, secondary to both drugs having the ability to inhibit MAO. MAOIs were widely used for nearly a decade until a tyramine reaction (see below) resulted in a death in 1962.
- **MAOI pharmacology**
  - Intracellular enzyme found on mitochondrial membrane
  - Degrades intracellular biogenic amines with H$_2$O$_2$ as a free radical byproduct
  - Increases neurotransmitter activity in CNS, down-regulates post-synaptic serotonin and adrenergic receptors
  - Post-synaptic DA unaffected
  - Liver has highest concentration of MAO with equal amounts of each isozymes. Brain has both with MAO-B more prominent in glial cells. Selectively often lost in overdose. Serotonin primarily metabolized by MAO-A. Phenethylamines (including designer drugs) primarily metabolized by MAO-B.
  - Isocarboxazid and phenelzine derived from hydrazine and are therefore acetylated with risk of slow and rapid acetylators (NAT2 enzyme)
  - Herbals such as Ephedra (Ma Huang) and St. John’s Wart (*Hypericum perforatum*) may interact with MAOIs
  - Selegiline (MAOI) metabolized to methamphetamine and amphetamine
- **MAOI pharmacology**
  - Irreversible binding
    • Phenylzine
    • Tranylcypromine
    • Isocarboxazide
    • Selegiline
    • Pargyline
  - Selective
    • Clorgyline (A)
    • Moclobemide (A)
    • Toloxatone (A)
    • Harmaline (A)
    • Selegiline (B)
    • Pargyline (B)
  - Reversible binding
    • Moclobemide
    • Brofaromine
    • Cimoxatone
    • Toloxatone
    • Harmaline
  - Nonselective
    • Tranylcypromine
    • Phenylzine
    • Isocarboxazid
    • St. Johns Wort
• **Signs and Symptoms (MAOI Overdose)**
  - Phase I
    - Latent period: 6-12 hrs in pts on medication
    - 24-36 hrs in “naïve” patients
  - Phase II
    - Excitatory phase
      - Hyperadrenergic appearing
      - “Ping-pong” nystagmus
      - Hyperreflexive with rigidity
      - Writhing, opisthotonus, facial grimacing
    - Progression
      - CNS depression
      - Fever, diaphoresis, salivation
      - Rigidity, myoclonus, carpopedal spasm
      - Myocardial ischemia, ICH, seizures

• **MAOI Treatment**
  - Expect prolonged period of toxicity
  - ICU for 24 hrs after resolution of signs and symptoms
  - Restricted diet for 2-3 weeks
  - Check ALL medications for interactions
  - Treat as signs and symptoms appear
  - Use SHORT acting agents
  - Use DIRECT acting agents-COMT metabolism

• **MAO-Tyramine reaction**
  - Not an overdose
  - Onset within 2 hrs after eating
  - Ingested tyramine is 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

**Serotonin Reuptake Inhibitors**

- In overdose, have been less toxic in overdose than previous generation antidepressants. Death with SSRI alone is rare.
- Types include selective serotonin reuptake inhibition as well as some with norepinephrine, dopamine, and alpha-adrenergic blockade
- Current SSRIs
  - Paroxetine (Paxil) or Sertraline (Zoloft)
  - Fluoxetine (Prozac, Sarafem) or Fluvoxamine (Luvox)
  - Citalopram (Celexa) or Fluoxetine + olanzepine (Symbyax)
  - Escitalopram (Lexapro) or Dapoxetine (Priligy) - Europe

• **Pearls**
  - SSRI in overdose: CNS depression and tachycardia most common
  - Citalopram and escitalopram: reports of seizures and widened QT interval
  - Fluvoxamine inhibits CYP1A and CYP2C
  - Paroxetine, fluoxetine, and metabolites strong inhibitors of CYP2D6
• **SSNRI and Others**
  o Bupropion
    • Excitation in overdose, **seizures** common, sustained release product
  o Duloxetine (Cymbalta)
  o Mirtazepine (Remeron)
    • Sedation, mild symptoms in toxicity
  o Nefazadone (Serzone), Trazadone (Desyrel)
    • Prolonged QT, orthostatic hypotension, priapism
  o Venlafaxine (Effexor)
    • Seizures, QRS prolongation

**Serotonin Syndrome**

- Stimulation of post-synaptic 5HT$_{1A}$ and 5HT$_2$ brain receptors
- **Mechanism**
  o Two or more serotonergic agents (eg, meperidine and MAOI [Libby Zion case])
  o SSRI + neuroleptic
  o SSRI + agent with serotonergic properties
  o Change in dose of serotonergic drug
  o Metabolic inhibition of serotonergic drug
- **Modified Sternbach criteria:** A, B, C must be met:
  o A. Syndrome occurs after addition of known serotonergic agent to established regimen or increase in dose of a serotonergic agent
  o B. At least 3 of the following:
    • Uncontrollable shivering, incoordination, restlessness in feet while sitting, initial involuntary ctx followed by myoclonic-like movements in legs, hyperreflexia, frightened hyperarousal state, agitation, oculogyric crises, diarrhea, fever
    • Other causes ruled out (sympathomimetics, MAOI, lithium, ASA, anticholinergics, withdrawal, CNS infection, SIRS, NMS, etc.)
  o C. A neuroleptic has not been started or increased in dosage prior to onset of symptoms

- **NEJM M. Shannon article on serotonin syndrome**
  o Hyperthermia
  o Mental status changes
  o Autonomic instability
  o CLONUS

- **Treatment**
  o Good supportive care
  o Benzodiazepines
  o External cooling
  o Paralysis with a nondepolarizing agent
  o **Specific agents**
    • Cyproheptadine: nonspecific 5HT antagonist (4-8 mg q1h) – no trials showing cyproheptadine more efficacious than BZD
    • NTG: nitric acid mediated down regulation of 5HT (drip titrated to effect)
    • Propranolol: 5HT$_{1A}$ antagonism (1-5 mg IV)
    • Chlorpromazine: 5HT$_2$ antagonist
• **Neonatal SSRI Withdrawal**
  o Fetus exposed to an SSRI late in the third trimester
  o Symptoms
    ▪ Respiratory distress (apnea)
    ▪ Cyanosis, apnea
    ▪ Feeding difficulties
    ▪ Vomiting
    ▪ Hypoglycemia
    ▪ Tremors, jitteriness, irritability
  o Onset hours to days after delivery, which resolved in days or weeks
  o Prolonged hospitalization, respiratory support, and tube feeding

• **Serotonin syndrome vs neuroleptic malignant syndrome**

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<th>Signs/Symptoms</th>
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<th>NMS</th>
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<td><strong>Onset</strong></td>
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<tr>
<td><strong>Resolution</strong></td>
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<td>Days</td>
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<tr>
<td>Myoclonus</td>
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<td>–</td>
</tr>
<tr>
<td>Hyperreflexia</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>+/-</td>
<td>++++</td>
</tr>
<tr>
<td>Muscle rigidity</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td>Autonomic dysfunction</td>
<td>+++</td>
<td>++++</td>
</tr>
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</table>

**ANTIPSYCHOTICS**

• Traditional antipsychotics
  o D2 antagonists

• Atypical antipsychotics
  o Selective for limbic vs EP sites
  o Mixed DA receptor affinities (D1,D2 etc)
  o Looser binding to D2, less EPS
  o Mixed affinity for DA, 5HT, alpha

• **Antipsychotic Classification**
  o Low potency (sedating, antimuscarinic, miosis)
    ▪ Chlorpromazine (most sedating in overdose)
    ▪ Chlorprothixene
    ▪ Mesoridazine (very cardiotoxic in overdose)
    ▪ Thoridazine (most cardiotoxic in overdose)
  o Medium potency
    ▪ Droperidol
    ▪ Loxapine (more seizures in overdose)
    ▪ Molindone
    ▪ Perphenazine
High potency (more EPS, less sedation)
- Fluphenazine
- Haloperidol (most common cause of NMS)
- Trifluoperazine
- Thiothixene

**Reversible EPS: Acute Dystonia**
- Idiosyncratic and occurs more commonly in males 5-45 years with depot preps.
  - Increased risk with family history of AD and recent ethanol or cocaine use.
  - Dystonia is known to resolve during sleep.
- Symptoms
  - Facial grimacing
  - Trismus
  - Blepharospasm
  - Oculogyric crisis
  - Tongue protrusion
  - Torticollis
  - Opisthotonis
  - Abnormal posture, gait

**Reversible EPS**
- Akathesia
  - Subjective unease
  - Motor restlessness
  - Dose related
  - Women
  - High potency Drugs
- Parkinsonism
  - Muscle rigidity
  - Bradykinesia
  - Tremor
  - Elderly women
  - High potency

**Irreversible EPS: Tardive Dyskinesia**
- Involuntary movements of orofacial structures
- Lip smacking
- Facial grimacing
- Late onset > 2 years after therapy onset
- More common in women > 50 years who have had their long-term meds discontinued. Cessation of therapy leads to increased number of DA receptors in the nigrostriatal system (DA excess, cholinergic underactivity)

**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
- Pimozide (Orap®)
  - Akathisia most characteristic adverse effect
- Most common cause of NMS (> 90%)
  - Haloperidol
- Agranulocytosis
  - Chlorpromazine (Thorazine)
- Cholestatic jaundice
  - Chlorpromazine (Thorazine)
- Acute reversible oliguria
  - Chlorprothixene (Taractan)
• **Atypical Antipsychotic Pearls**
  o Aripiprazole (Abilify®)
    ▪ Longest half-life in overdose
    ▪ Sedation and mild antimuscarinic symptoms reported
  o Clozapine (Clozaril®)
    ▪ Prototypic atypical antipsychotic
    ▪ Long half-life in overdose
    ▪ Highest alpha-1 blockade
    ▪ Highest rate of seizures
    ▪ Central antimuscarinic (delirium) but salivation, miosis common
    ▪ Chronic therapy associated with agranulocytosis and hyperglycemia
  o Olanzapine (Zyprexa® Zydus®)
    ▪ Long half-life in overdose
    ▪ Highest anti-muscarinic, but salivation, miosis
    ▪ No reported cardiac effects
    ▪ Most cases of NMS of atypicals
    ▪ Chronic therapy associated with:
      ▪ Hyperglycemia (drug-induced diabetes)
      ▪ Waxing and waning sedation
      ▪ Overdose resembles opiate toxidrome with miotic pupils
  o Quetiapine (Seroquel®)
    ▪ Tachycardia, sedation, prolonged QT
    ▪ Highest antihistamine activity
    ▪ > 3 grams predicted ICU and prolonged length of stay
    ▪ Cross reacts with TCA drug assay
  o Risperidone (Risperdal®)
    ▪ Highest rate of dystonia
    ▪ High rate of seizures
    ▪ High rate of alpha blockade
    ▪ No antimuscarinic effects; miosis
    ▪ Electrolyte depletion
    ▪ Unusual dysrhythmias for class (a flutter, heart blocks)
  o Paliperidone (Invega®)
    ▪ Major active metabolite of risperidone
    ▪ Observed signs and symptoms included EPS and ataxia
    ▪ Other potential signs and symptoms: sedation, tachycardia, and hypotension
    ▪ QT prolongation (12.5-62 msec in pre-clinical trials)
    ▪ Overdose experience reported similar to risperidone
  o Ziprasidone (Geodon®)
    ▪ Highest rate of increased QT prolongation
    ▪ Miosis common
    ▪ Not as sedating as others (no H₁ block)
MOOD STABILIZERS - LITHIUM

- Mood Stabilizing Lithium
  - Main therapy for bipolar disorder
  - Narrow therapeutic index (0.6-1.2 mEq/L)
  - Slow distribution across cell membranes
  - Delay between peak blood levels and CNS effects
  - Most cases chronic due to a reduction in GFR
    - Volume loss
    - NSAIDs, diuretics, ACE inhibitors
    - Age

- Acute vs chronic toxicity. Most cases involve chronic poisoning due to a reduction in renal elimination of lithium. Role of hemodialysis continues to be controversial.
  - Acute
    - Increased intake
    - Delayed toxicity due to delayed distribution
    - High serum levels initially do not correlate with toxicity
    - GI symptoms more severe
    - Tremor, muscle weakness, ataxia, hyperreflexia
  - Chronic
    - Decreased excretion
    - Serum levels lower since intracellular levels high
    - Subacute/nonspecific neurologic symptoms
    - GI symptoms less severe
    - Encephalopathy, myoclonus, severe rigidity, seizures

- ECG
  - Bradycardia
  - T-wave flattening/inversion
  - QT prolongation

- Other effects of lithium
  - Nephrogenic diabetes insipidous
  - Hypothyroidism
  - Teratogenic: Ebstein’s anomaly

- Lithium Management
  - Discontinue lithium and offending drugs
  - Improve GFR – normal saline
    - 20% reduction in Li over 6 hours
  - Hemodialysis (guidelines vary)
    - Renal failure
    - Stage III neurotoxicity: encephalopathy, myoclonus, severe rigidity, seizures
    - Acute > 4.0 mEq/L?
    - Chronic > 2.5 mEq/L?
  - Kayexelate (Na polystyrene sulfonate)
    - Some newer data to suggest improved clearance
    - Theoretical risk of worsening cardiac effects due to hypokalemia
1. Acute overdose of selective serotonin reuptake inhibitor (SSRI) antidepressant medications most often result in
   A. Cardiac dysrhythmias
   B. CNS depression and tachycardia
   C. Hallucinations and delirium
   D. Profound hyperthermia and rigidity
   E. Seizures

Patients with acute exposures to SSRI medications typically due very 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 is not common after a single acute overdose of an SSRI.

2. A 14-year-old girl presents to the emergency department after two witnessed generalized, tonic-clonic seizures. In resuscitation she is comatose and requires ventilatory support. Her initial vital signs are BP 80/43 mmHg, HR 133 bpm, RR 14 (vent), temperature 99.6°F, and pulse oximetry 100% on FiO2 1.0. Her ECG is provided below.

![ECG Image]

What is the next best course of management in this patient?

   A. Octreotide
   B. Glucagon
   C. Naloxone
   D. Sodium bicarbonate
   E. Calcium chloride

The patient’s presentation is consistent with cyclic antidepressant toxicity. The antidote of choice from the above options is sodium bicarbonate. Octreotide is used in sulfonylurea exposure. Naloxone is the antidote for opiates. Calcium chloride is not expected to improve this patient’s hypotension or cardiac conduction disturbance.
3. A 23-year-old woman with schizoaffective disorder presents to the emergency department for chest pain. She is currently taking ziprasidone (Geodon) for her psychiatric disorder. In the evaluation of her complaint, a 12-lead ECG is completed. It reveals a normal sinus rhythm, normal T waves, normal ST segments, QRS 86 msec, and QTc 560 msec. You diagnose her with musculoskeletal pain, but are concerned by her ECG. What medication would you recommend in place of her ziprasidone?

A. Chlorpromazine (Thorazine)
B. Haloperidol (Haldol)
C. Olanzapine (Zyprexa)
D. Quetiapine (Seroquel)
E. Thioridazine (Mellaril)

The greatest concern in this patient is the prolonged QT interval. From the above choices, the medication with the least amount of IKr blockade and subsequent QT prolongation is olanzapine.

4. A young woman presents with chronic lithium intoxication. Which of the following clinical signs is the most likely indication for hemodialysis in this patient?

A. Ataxia
B. Diabetes insipidus
C. Hyperreflexia
D. Tremor
E. Seizures

Although uncommon, seizures represent severe lithium toxicity (Stage III neurotoxicity) and are an indication for hemodialysis. Ataxia, hyperreflexia, and tremor are common clinical manifestations that occur even at baseline in patients on chronic lithium. Diabetes insipidus is seen in both acute and chronic lithium toxicity and managed through fluid restriction and not hemodialysis.

5. Which of the following agents is the most appropriate treatment for a patient with severe hypertension due to MAO-I toxicity?

A. Clonidine
B. Diltiazem
C. Labetalol
D. Nitroprusside
E. Verapamil

Patient’s blood pressure is often unpredictable after MAO-I toxicity. Shorter acting anti-hypertensive agents are preferred in case of precipitous drops in blood pressure. Nitroprusside is the agent of choice among those listed due to its rapid onset and offset.

1B 2D 3C 4E 5D
PSYCHOTROPICS
G. Patrick Daubert, MD; Michelle Burns-Ewald, MD

CORE CONTENT

2.1.11.2 Psychotropics
  2.1.11.9.1 Anxiolytics and sedative-hypnotics
  2.1.11.9.2 Antidepressants
  2.1.11.9.3 Antipsychotics
  2.1.11.9.4 Mood stabilizers

ANXIOLYTICS AND SEDATIVE-HYPNOTICS

Benzodiazepines
  • Background
    o Roughly 50,000 benzodiazepine OD cases reported annually
    o 65% intentional
    o Few deaths
    o Most are combination exposures
    o Mixed drug overdose or IV administration = increased morbidity
    o About 15 types marketed in the US
    o 50 types worldwide

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• Kinetics
  o Vary in elimination half-life and metabolism
  o All rapidly absorbed
  o CNS redistribution varies
  o Half-life ≠ duration of action
  o Conjugation only BZDs = oxazepam, lorazepam, temazepam
  o IM administration = lorazepam, midazolam
• Dynamics
  o All are indirect agonists at post-synaptic GABA<sub>A</sub> channels
    ▪ Can’t open the channel without GABA
    ▪ BZD<sub>1</sub> receptor subtype
    ▪ Increase frequency of chloride channel opening
  o BZD<sub>2</sub> receptors (HC, spinal cord) affect muscle relaxation
  o All produce tolerance with cross-reactivity
  o Predispose to physical dependence
    ▪ BZD<sub>2</sub> receptor agonism
• Benzodiazepine Overdose
  o Nonspecific – sedative-hypnotic symptoms
  o CNS changes without vital sign changes: drowsiness, dizziness, slurred speech, nystagmus, confusion, amnesia, ataxia, coma (rare)
  o Patients look “drunk”
  o Children: 17% isolated ataxia
  o Other: respiratory depression, hypotension with IV administration
• Benzodiazepine withdrawal
  o Worse for short half-life agents
  o Agitation, tremor, headache, weight loss, seizures
  o Mild symptoms start in 1-3 days with peak in 5-9 days. Symptoms taper over 3-4 weeks
  o May be precipitated by flumazenil
• Flumazenil (Romazicon)
  o Competitive BZD antagonist
  o Reverses CNS depression but not respiratory depression
  o Withdrawal symptoms more likely in doses > 1 mg
  o Safest patient populations
    ▪ Children with single dose ingestions
    ▪ Reversal of iatrogenic sedation (procedural sedation)
• Benzodiazepine Pearls
  o Increase frequency of GABA<sub>A</sub> chloride channel opening
  o Propylene glycol: lorazepam, diazepam
  o Clonazepam: Anticonvulsant, mood stabilizer, sounds like “clonidine”
  o Flunitrazepam (RoHypnol): “Date Rape” drug
  o In-house urine qualitative EMIT toxicology screen may not detect BZDs that do not produce oxazepam metabolite (false negative)
    ▪ Midazolam, alprazolam, lorazepam, triazolam, clonazepam

Barbiturates
• 4 Categories
  o Ultrashort: methohexital, thiopental
  o Short: pentobarbital, secobarbital
  o Intermediate: butalbital
  o Long-acting: Phenobarbital
  o Combination products
    ▪ Donnatal: phenobarbital, atropine, hyoscyamine
    ▪ Fiorinal/cet: butalbital, caffeine, ASA/APAP
• Pharmacology
  o GABA<sub>A</sub> agonist with direct increase in duration of channel opening
  o Contrast to BZD, GABA not needed with barbiturates
  o Pharmacology secondary to decrease in central sympathetic tone and direct myocardial depression

• Barbiturate Toxicity
  o Symptoms similar to other sedatives with CNS depression and cerebellum symptoms
  o More likely to see respiratory depression
    ▪ CNS tolerance ≠ Respiratory tolerance
  o Medullary effect: cardiovascular collapse, miosis
  o Hypothermia, bullae at pressure points (“barb burns”), concretions
  o Noncardiogenic pulmonary edema

• Barbiturate withdrawal
  o Life threatening
  o Agitation, tremor, seizures, insomnia, delirium
  o Occurs 3 days after cessation of drug and lasts 10-14 days

• Phenobarbital (PHB)
  o Long-acting barbiturate
  o Normal range 15-40 mg/L
  o PHB CNS tolerance does not usually involve respiratory tolerance
  o Death is uncommon with good supportive care
  o Remember primidone metabolized to PEMA and PHB
  o Treatment
    ▪ Supportive care
    ▪ Passive warming
    ▪ IVF, norepinephrine for hypotension
    ▪ Urinary alkalization
      ▪ Phenobarbital is only barbiturate effectively eliminated with urine alkalization
      ▪ Stop alkalization when PHB < 40 mg/L
    ▪ Multidose activated charcoal
      ▪ Stop MDAC when PHB < 40 mg/L
      ▪ MDC demonstrates better elimination than urine alkalization
      ▪ Listed as one of five drugs in position statement for MDAC with best data for enhanced elimination (NOT outcome data)
        ▪ Carbamazepine, dapsone, phenobarbital, quinine, theophylline)
  o Caveat
    ▪ Positive barbiturate (qualitative) on urine drugs of abuse screen: PHB vs butalbital are typically only barbiturates available for use by general patient population. If PHB level is zero, likely butalbital overdose, which means also ordering ASA and APAP (Fiorinal/cet)
‘Z’ Drugs
• Zolpidem (Ambien, Stilnox)
• Zaleplon (Sonata)
• EcZopiclone (Lunesta, Estorra)
• Ramelteon (RoZerem)

• Non-benzodiazepine sedatives
• Selective for GABA AA BZ-1 receptors
• Less physical dependence
• Flumazenil may precipitate withdrawal
• Ramelteon may alter testosterone and prolactin levels

“Z” Drug Overdose
  o Nausea/vomiting, respiratory depression, hypotension
  o Can see both miosis and mydriasis and fixed pupils
  o CNS depression and hallucinations
  o Flumazenil reverses ‘Z agent’ effect and precipitates withdrawal with same precautions as with benzodiazepines

Sedative-Hypnotics
• Buspirone
  o Non-benzodiazepine, anxiolytic
    ▪ Does not stimulate GABA A receptors
    ▪ Acts act 5-HT 1A
  o No reported withdrawal syndrome
  o CNS depression, miosis
  o Serotonin syndrome potential

• Chloral Hydrate
  o Commonly used by alcoholics in the late 19th century to induce sleep
  o Solutions of alcohol and chloral hydrate often called “knockout drops” or “Mickey Finn”
  o Sedation with minimal respiratory depression and hypotension
  o Used recreationally only by a small number of people
  o Common trade names are Noctec, Somnos and Felsules
  o Pharmacology
    ▪ Trichlorocetic acid
      • Highly protein bound
      • May displace acidic drugs from plasma protein
    ▪ Trichloroethanol exerts barbiturate like effects on the GABA A receptor channels
    ▪ Trichloroethanol inhibits ethanol metabolism

![Diagram of Chloral Hydrate, ADH, P450, Trichloroethanol, and Trichloroacetic Acid]
o Chloral hydrate clinical highlights
  ▪ Hemorrhagic gastritis
  ▪ Cardiac arrhythmias
    • Sensitized myocardium to circulating catecholamines
    • Attributed largely to trichloroethanol
  ▪ Radioopaque
• Sedative-Hypnotic Pearls
  o Meprobamate (Miltown,, Equanil, Meprospan)
    ▪ Active metabolite of carisoprodol
    ▪ Concretions/bezoars in overdose
  o Glutethimide (Doriden)
    ▪ 2D6 inducer – codeine abuse
    ▪ “Doors and Fours” with Tylenol#4
  o Ethchlorvynol (Placidyl)
    ▪ “Jelly-bellies”
    ▪ Used by William Rehnquist (oversedation then withdrawal)
  o Methaqualone
    ▪ Quaaludes, Mandrax
    ▪ Recent abuse in South Africa
    ▪ Can see hyperreflexia, clonus
    ▪ Residual paresthesias and polyneuropathies effects after overdose

ANTIDEPRESSANTS

Cyclic Antidepressants (CAs)
• Account for nearly 50% of all cardiovascular deaths in the U.S. CAs are widely available for medical conditions other than depression (e.g., chronic pain, pediatric enuresis)
• Usual Suspects
  o Tertiary amines
    ▪ Amitriptyline
    ▪ Clomipramine
    ▪ Doxepin
    ▪ Imipramine
    ▪ Trimipramine
  o Secondary amines
    ▪ Desipramine
    ▪ Nortriptyline
    ▪ Protriptyline
  o Tetracyclic
    ▪ Amoxapine (high risk of intractable seizures)
    ▪ Maprotiline (high risk of intractable seizures)
• TCA Urine Drug Screen Cross Reactivity
  o Cyclobenzaprine (Flexeril)
  o Diphenhydramine (Benadryl)
  o Cyproheptadine (Periactin)
  o Carbamazepine (Tegretol)
  o Thioridazine (Mellaril)
  o Quetiapine (Seroquel)
• Pharmacokinetics
  o Peak serum concentration 1-8 hrs (symptoms in 1-2 hours)
  o Antimuscarinic – remember delayed gastric emptying
  o Lipophilic – large Vd
  o Elimination almost entirely hepatic
  o Hepatic phase I: Demethylation (CAs remain active until hydroxylation occurs)
    ▪ Imipramine → desipramine
    ▪ Amitriptyline → nortriptyline
  o Hydroxylation of some CAs affected by genetic polymorphism at the CYP2D6 allele. For example, 90-95% of U.S. population are rapid hydroxylators producing shorter desipramine elimination half-lives 12-23 hours than slow hydroxylators (81-131 hours)
• Clinical Toxicity
  o Rapid onset of symptoms
  o Early sedation and coma
  o Early antimuscarinic symptoms
  o Cardiovascular
    ▪ Hypotension
    ▪ Dysrhythmias
      • Blockade of fast Na\(^+\) channels phase 0 of the action potential → QRS prolongation
      • RBB more susceptible (leads V1, V2, aVR, I)
        o Rate dependent – increase in CA binding with ↑ HR
        o pH dependent - increase in CA binding with ↓ pH
      • R axis deviation in terminal 40 msec
      • AV node blocks
      • K\(^+\) channel blockade (Ikr)
        o Increased QT but TdP uncommon with tachycardia
        o Can be seen with therapeutic dosing

• Treatment caveats
  o Airway management early
  o Multi-dose charcoal may be beneficial with amitriptyline
  o Levels generally not useful in acute overdose. However, levels > 1000 ng/mL will likely result in significant toxicity (remember to order both tertiary and secondary CA levels)
  o Sodium bicarbonate (no outcome data comparing infusion vs IV bolus)
  o Lidocaine most commonly advocated for VT/VFib but efficacy data is lacking
Seizures usually resolve spontaneously – but resulting lowered pH may increase risk of dysrhythmias
- Phenytoin not to be used for seizures
  - Hypotension and dysrhythmias from rapid infusions
  - Seizure most likely due to GABA and adenosine inhibition, not sodium channel effects
  - Animal models suggest phenytoin is prodysrhythmic in CA toxicity
- Physostigmine
  - Not currently advocated
  - Most likely risk of asystole and death is in the treatment of patients with severe toxicity with seizures and bradycardia. QRS widening has not been directly linked to asystolic risk

Monoamine Oxidase Inhibitors
- Isoniazid and its isopropyl derivative, iproniazid (Marsilid, no longer marketed), were used in 1951 for the treatment of tuberculosis. Patients on these drugs were noted to have elevated mood, secondary to both drugs having the ability to inhibit MAO. MAOIs were widely used for nearly a decade until a tyramine reaction (see below) resulted in a death in 1962.
- MAOI pharmacology
  - Intracellular enzyme found on mitochondrial membrane
  - Degrades intracellular biogenic amines with H₂O₂ as a free radical byproduct
  - Increases neurotransmitter activity in CNS, down-regulates post-synaptic serotonin and adrenergic receptors
  - Post-synaptic DA unaffected
  - Liver has highest concentration of MAO with equal amounts of each isozymes. Brain has both with MAO-B more prominent in glial cells. Selectively often lost in overdose. Serotonin primarily metabolized by MAO-A. Phenethylamines (including designer drugs) primarily metabolized by MAO-B.
  - Isocarboxazid and phenelzine derived from hydrazine and are therefore acetylated with risk of slow and rapid acetylators (NAT2 enzyme)
  - Herbals such as Ephedra (Ma Huang) and St. John’s Wart (Hypericum perforatum) may interact with MAOIs
  - Selegiline (MAOI) metabolized to methamphetamine and amphetamine
- MAOI pharmacology
  - Irreversible binding
    - Phenylzine
    - Tranylcypromine
    - Isocarboxazide
    - Selegiline
    - Pargyline
  - Selective
    - Clorgylaine (A)
    - Moclobemide (A)
    - Toloxatone (A)
    - Harmaline (A)
    - Selegiline (B)
    - Pargyline (B)
  - Reversible binding
    - Moclobemide
    - Brofaromine
    - Cimoxatone
    - Toloxatone
    - Harmaline
  - Nonselective
    - Tranylcypromine
    - Phenylzine
    - Isocarboxazide
    - St. Johns Wort
• **Signs and Symptoms (MAOI Overdose)**
  o Phase I
    ▪ Latent period: 6-12 hrs in pts on medication
    ▪ 24-36 hrs in “naïve” patients
  o Phase II
    ▪ Excitatory phase
      • Hyperadrenergic appearing
      • “Ping-pong” nystagmus
      • Hyperrelexive with rigidity
      • Writhing, opisthotonus, facial grimacing
    ▪ Progression
      • CNS depression
      • Fever, diaphoresis, salivation
      • Rigidity, myoclonus, carpopedal spasm
      • Myocaridal ischemia, ICH, seizures

• **MAOI Treatment**
  o Expect prolonged period of toxicity
  o ICU for 24 hrs after resolution of signs and symptoms
  o Restricted diet for 2-3 weeks
  o Check ALL medications for interactions
  o Treat as signs and symptoms appear
  o Use SHORT acting agents
  o Use DIRECT acting agents-COMT metabolism

• **MAO-Tyramine reaction**
  o Not an overdose
  o Onset within 2 hrs after eating
  o Ingested tyramine is normally inactivated by gut MAO-A
  o Inhibition of gut MAO-A: absorption of dietary tyramine and byproducts
  o Tyramine releases NE formed by inhibition of neuronal MAO-A
  o Hyperadrenergic state
  o Treat symptomatically

**Serotonin Reuptake Inhibitors**
- In overdose, have been less toxic in overdose than previous generation antidepressants. Death with SSRI alone is rare.
- Types include selective serotonin reuptake inhibition as well as some with norepinephrine, dopamine, and alpha-adrenergic blockade
- Current SSRIs
  o Paroxetine (Paxil)
  o Fluoxetine (Prozac, Sarafem)
  o Citalopram (Celexa)
  o Escitalopram (Lexapro)
  o Sertraline (Zoloft)
  o Fluvoxamine (Luvox)
  o Fluoxetine + olanzepine (Symbyax)
  o Dapoxetine (Priligy) - Europe

• **Pearls**
  o SSRI in overdose: CNS depression and tachycardia most common
  o Citalopram and escitalopram: reports of seizures and widened QT interval
  o Fluvoxamine inhibits CYP1A and CYP2C
  o Paroxetine, fluoxetine, and metabolites strong inhibitors of CYP2D6
• SSNRI and Others
  o Bupropion
    ▪ Excitation in overdose, seizures common, sustained release product
  o Duloxetine (Cymbalta)
  o Mirtazepine (Remeron)
    ▪ Sedation, mild symptoms in toxicity
  o Nefazadone (Serzone), Trazadone (Desyrel)
    ▪ Prolonged QT, orthostatic hypotension, priapism
  o Venlafaxine (Effexor)
    ▪ Seizures, QRS prolongation

Serotonin Syndrome
• Stimulation of post-synaptic 5HT1\textsubscript{A} and 5HT2 brain receptors
• Mechanism
  o Two or more serotonergic agents (eg, meperidine and MAOI [Libby Zion case])
  o SSRI + neuroleptic
  o SSRI + agent with serotonergic properties
  o Change in dose of serotonergic drug
  o Metabolic inhibition of serotonergic drug
• Modified Sternbach criteria: A, B, C must be met:
  o A. Syndrome occurs after addition of known serotonergic agent to established regimen or increase in dose of a serotonergic agent
  o B. At least 3 of the following:
    ▪ Uncontrollable shivering, incoordination, restlessness in feet while sitting, initial involuntary ctx followed by myoclonic-like movements in legs, hyperreflexia, frightened hyperarousal state, agitation, oculogyric crises, diarrhea, fever
    ▪ Other causes ruled out (sympathomimetics, MAOI, lithium, ASA, anticholinergics, withdrawal, CNS infection, SIRS, NMS, etc.)
  o C. A neuroleptic has not been started or increased in dosage prior to onset of symptoms
• NEJM M. Shannon article on serotonin syndrome
  o Hyperthermia
  o Mental status changes
  o Autonomic instability
  o CLONUS
• Treatment
  o Good supportive care
  o Benzodiazepines
  o External cooling
  o Paralysis with a nondepolarizing agent
  o Specific agents
    ▪ Cyproheptadine: nonspecific 5HT antagonist (4-8 mg q1h) – no trials showing cyproheptadine more efficacious than BZD
    ▪ NTG: nitric acid mediated down regulation of 5HT (drip titrated to effect)
    ▪ Propranolol: 5HT\textsubscript{1A} antagonism (1-5 mg IV)
    ▪ Chlorpromazine: 5HT\textsubscript{2} antagonist
• **Neonatal SSRI Withdrawal**
  - Fetus exposed to an SSRI late in the third trimester
  - Symptoms
    - Respiratory distress (apnea)
    - Cyanosis, apnea
    - Feeding difficulties
    - Vomiting
    - Hypoglycemia
    - Tremors, jitteriness, irritability
  - Onset hours to days after delivery, which resolved in days or weeks
  - Prolonged hospitalization, respiratory support, and tube feeding

• **Serotonin syndrome vs neuroleptic malignant syndrome**

<table>
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<tr>
<th>Signs/Symptoms</th>
<th>SS</th>
<th>NMS</th>
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<tbody>
<tr>
<td>Onset</td>
<td>Rapid</td>
<td>Gradual</td>
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<tr>
<td>Resolution</td>
<td>&lt; 24 hour</td>
<td>Days</td>
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<tr>
<td>Myoclonus</td>
<td>++</td>
<td>—</td>
</tr>
<tr>
<td>Hyperreflexia</td>
<td>++</td>
<td>—</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>+/-</td>
<td>++++</td>
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<tr>
<td>Muscle rigidity</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Autonomic dysfunction</td>
<td>+++</td>
<td>+++</td>
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</tbody>
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**ANTIPSYCHOTICS**

• **Traditional antipsychotics**
  - D2 antagonists

• **Atypical antipsychotics**
  - Selective for limbic vs EP sites
  - Mixed DA receptor affinities (D1,D2 etc)
  - Looser binding to D2, less EPS
  - Mixed affinity for DA, 5HT, alpha

• **Antipsychotic Classification**
  - Low potency (sedating, antimuscarinic, miosis)
    - Chlorpromazine (most sedating in overdose)
    - Chlorprothixene
    - Mesoridazine (very cardiotoxic in overdose)
    - Thioridazine (most cardiotoxic in overdose)
  - Medium potency
    - Droperidol
    - Loxapine (more seizures in overdose)
    - Molindone
    - Perphenazine
High potency (more EPS, less sedation)
- Fluphenazine
- Haloperidol (most common cause of NMS)
- Trifluoperazine
- Thiothixene

**Reversible EPS: Acute Dystonia**
- Idiosyncratic and occurs more commonly in males 5-45 years with depot preps. Increased risk with family history of AD and recent ethanol or cocaine use. Dystonia is known to resolve during sleep.
- Symptoms
  - Facial grimacing
  - Trismus
  - Blepharospasm
  - Oculogyric crisis
  - Tongue protrusion
  - Torticollis
  - Opisthotonis
  - Abnormal posture, gait

**Reversible EPS**
- Akathesia
  - Subjective unease
  - Motor restlessness
  - Dose related
  - Women
  - High potency Drugs
- Parkinsonism
  - Muscle rigidity
  - Bradykinesia
  - Tremor
  - Elderly women
  - High potency

**Irreversible EPS: Tardive Dyskinesia**
- Involuntary movements of orofacial structures
- Lip smacking
- Facial grimacing
- Late onset > 2 years after therapy onset
- More common in women > 50 years who have had their long-term meds discontinued. Cessation of therapy leads to increased number of DA receptors in the nigrostriatal system (DA excess, cholinergic underactivity)

**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
- Pimozide (Orap®)
  - Akathisia most characteristic adverse effect
- Agranulocytosis
  - Chlorpromazine (Thorazine)
- Cholestatic jaundice
  - Chlorpromazine (Thorazine)
- Acute reversible oliguria
  - Chlorprothixene (Taractan)
**Atypical Antipsychotic Pearls**

- **Aripiprazole (Abilify®)**
  - Longest half-life in overdose
  - Sedation and mild antimuscarinic symptoms reported

- **Clozapine (Clozaril®)**
  - Prototypic atypical antipsychotic
  - Long half-life in overdose
  - Highest alpha-1 blockade
  - Highest rate of seizures
  - Central antimuscarinic (delirium) but salivation, miosis common
  - Chronic therapy associated with agranulocytosis and hyperglycemia

- **Olanzapine (Zyprexa® Zydus®)**
  - Long half-life in overdose
  - Highest antimuscarinic, but salivation, miosis
  - No reported cardiac effects
  - Most cases of NMS of atypicals
  - Chronic therapy associated with:
    - Hyperglycemia (drug-induced diabetes)
    - Waxing and waning sedation
    - Overdose resembles opiate toxidrome with miotic pupils

- **Quetiapine (Seroquel®)**
  - Tachycardia, sedation, prolonged QT
  - Highest antihistamine activity
  - > 3 grams predicted ICU and prolonged length of stay
  - Cross reacts with TCA drug assay

- **Risperidone (Risperdal®)**
  - Highest rate of dystonia
  - High rate of seizures
  - High rate of alpha blockade
  - No antimuscarinic effects; miosis
  - Electrolyte depletion
  - Unusual dysrhythmias for class (a flutter, heart blocks)

- **Paliperidone (Invega®)**
  - Major active metabolite of risperidone
  - Observed signs and symptoms included EPS and ataxia
  - Other potential signs and symptoms: sedation, tachycardia, and hypotension
  - QT prolongation (12.5-62 msec in pre-clinical trials)
  - Overdose experience reported similar to risperidone

- **Ziprasidone (Geodon®)**
  - Highest rate of increased QT prolongation
  - Miosis common
  - Not as sedating as others (no H1 block)
MOOD STABILIZERS - LITHIUM

- Mood Stabilizing Lithium
  - Main therapy for bipolar disorder
  - Narrow therapeutic index (0.6-1.2 mEq/L)
  - Slow distribution across cell membranes
  - Delay between peak blood levels and CNS effects
  - Most cases chronic due to a reduction in GFR
    - Volume loss
    - NSAIDs, diuretics, ACE inhibitors
    - Age
- Acute vs chronic toxicity. Most cases involve chronic poisoning due to a reduction in renal elimination of lithium. Role of hemodialysis continues to be controversial.
  - Acute
    - Increased intake
    - Delayed toxicity due to delayed distribution
    - High serum levels initially do not correlate with toxicity
    - GI symptoms more severe
    - Tremor, muscle weakness, ataxia, hyperreflexia
  - Chronic
    - Decreased excretion
    - Serum levels lower since intracellular levels high
    - Subacute/nonspecific neurologic symptoms
    - GI symptoms less severe
    - Encephalopathy, myoclonus, severe rigidity, seizures
- ECG
  - Bradycardia
  - T-wave flattening/inversion
  - QT prolongation
- Other effects of lithium
  - Nephrogenic diabetes insipidous
  - Hypothyroidism
  - Teratogenic: Ebstein’s anomaly
- Lithium Management
  - Discontinue lithium and offending drugs
  - Improve GFR – normal saline
    - 20% reduction in Li over 6 hours
  - Hemodialysis (guidelines vary)
    - Renal failure
    - Stage III neurotoxicity: encephalopathy, myoclonus, severe rigidity, seizures
    - Acute > 4.0 mEq/L?
    - Chronic > 2.5 mEq/L?
  - Kayexelate (Na polystyrene sulfonate)
    - Some newer data to suggest improved clearance
    - Theoretical risk of worsening cardiac effects due to hypokalemia
QUESTIONS

1. Acute overdose of selective serotonin reuptake inhibitor (SSRI) antidepressant medications most often result in
   
   A. Cardiac dysrhythmias
   B. CNS depression and tachycardia
   C. Hallucinations and delirium
   D. Profound hyperthermia and rigidity
   E. Seizures

   Patients with acute exposures to SSRI medications typically do very 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 part of the serotonin syndrome but is not common after a single acute overdose of an SSRI.

2. A 14-year-old girl presents to the emergency department after two witnessed generalized, tonic-clonic seizures. In resuscitation she is comatose and requires ventilatory support. Her initial vitals signs are BP 80/43 mmHg, HR 133 bpm, RR 14 (vent), temperature 99.6°F, and pulse oximetry 100% on FiO2 1.0. Her ECG is provided below.

   ![ECG Image]

   What is the next best course of management in this patient?

   A. Octreotide
   B. Glucagon
   C. Naloxone
   D. Sodium bicarbonate
   E. Calcium chloride

   The patient’s presentation is consistent with cyclic antidepressant toxicity. The antidote of choice from the above options is sodium bicarbonate. Octreotide is used in sulfonylurea exposure. Naloxone is the antidote for opiates. Calcium chloride is not expected to improve this patient’s hypotension or cardiac conduction disturbance.
3. A 23-year-old woman with schizoaffective disorder presents to the emergency department for chest pain. She is currently taking ziprasidone (Geodon) for her psychiatric disorder. In the evaluation of her complaint, a 12-lead ECG is completed. It reveals a normal sinus rhythm, normal T waves, normal ST segments, QRS 86 msec, and QTc 560 msec. You diagnose her with musculoskeletal pain, but are concerned by her ECG. What medication would you recommend in place of her ziprasidone?

A. Chlorpromazine (Thorazine)
B. Haloperidol (Haldol)
C. Olanzapine (Zyprexa)
D. Quetiapine (Seroquel)
E. Thioridazine (Mellaril)

The greatest concern in this patient is the prolonged QT interval. From the above choices, the medication with the least amount of IKr blockade and subsequent QT prolongation is olanzapine.

4. A young woman presents with chronic lithium intoxication. Which of the following clinical signs is the most likely indication for hemodialysis in this patient?

A. Ataxia
B. Diabetes insipidus
C. Hyperreflexia
D. Tremor
E. Seizures

Although uncommon, seizures represent severe lithium toxicity (Stage III neurotoxicity) and are an indication for hemodialysis. Ataxia, hyperreflexia, and tremor are common clinical manifestations that occur even at baseline in patients on chronic lithium. Diabetes insipidus is seen in both acute and chronic lithium toxicity and managed through fluid restriction and not hemodialysis.

5. Which of the following agents is the most appropriate treatment for a patient with severe hypertension due to MAO-I toxicity?

A. Clonidine
B. Diltiazem
C. Labetalol
D. Nitroprusside
E. Verapamil

Patient’s blood pressure is often unpredictable after MAO-I toxicity. Shorter acting anti-hypertensive agents are preferred in case of precipitous drops in blood pressure. Nitroprusside is the agent of choice among those listed due to its rapid onset and offset.

1B 2D 3C 4E 5D