Psychotropics

Andrew Stolbach, MD

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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 CI 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 CI channel opening
- Propylene glycol: lorazepam
- Clonazepam:
  - Anticonvulsant
  - Mood stabilizer
- Flunitrazepam (RoHypnol): “Date Rape”
- EMIT: Oxazepam false negatives
Barbiturates

- GABA
  - 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 burn”), 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 pH < 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-benzodiazepine sedatives
- Selective for GABA\textsubscript{A} 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)
- Chloral hydrate
- Meprobamate
- Methaqualone
- Glutethimide
- Ethchlorvynil

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/Esctalopram
  - Mirtazapine
  - Trazadone
  - Venlafaxine

Usual Suspects

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

TCA Screen Cross Reactivity

- Cylcobenzaprine (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 → desipramine
  - Amitriptyline → 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
- RBB more susceptible (leads V1, V2, aVR, I)
- Rate dependent
- pH dependent
- R axis deviation in terminal 40 msec
- AV node blocks
- K⁺ channel blockade (like)
- 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  \[ R \]
\[ \text{aVR} \]  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
  - Phenylzine
  - Transcytropicine
  - Isocarbocysteïde
  - Belegline
  - Pargyline
- Reversible binding
  - Moclobemide
  - Brofaromine
  - Climoxatone
  - Toloxatone
  - Harmaline
MAOI pharmacology

- Selective
  - Clorgyline (A)
  - Moclobemide (A)
  - Toloxatone (A)
  - Harmaline (A)
  - Selegiline (B)
  - Pargyline (B)

- Nonselective
  - Tranylcypromine
  - Phenelzine
  - Isoxcarbazide

Signs and Symptoms (Overdose)

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

- Phase II
  - Excitatory phase
    - Hyperadrenergic appearing
    - "Ping-pong" nystagmus
    - Hyperreflexive with rigidity
    - Wringing, 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)
**Peaks**

- 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**

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

**Serotonin Syndrome**

- Stimulation of post-synaptic 5HT_{1A} and 5HT_{2A} 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 (all 3 must be met)
  - Syndrome occurs after addition of known serotonergic agent
  - List of symptoms to be met (at least 3) and other causes ruled out
  - No neuroleptic involved
- NEJM M. Shannon article
  - Hyperthermia
  - Mental status changes
  - Autonomic instability
  - CLONUS

Serotonin Syndrome - Treatment

- Good supportive care
- Benzodiazepines
- External cooling
- Paralysis with a nondepolarizing agent
- Specific agents
  - Cyproheptadine: nonspecific SHT<sub>1-2</sub> antagonist (4-8 mg q1h)
  - NTG: nitric acid mediated downregulation of SHT (drip titrated to effect)
  - Propranolol: SHT<sub>1</sub> antagonist (1-5 mg IV)
  - Chlorpromazine: SHT<sub>2</sub> antagonist

SS vs NMS

<table>
<thead>
<tr>
<th>Signs/Symptoms</th>
<th>SS</th>
<th>NMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Rapid</td>
<td>Gradual</td>
</tr>
<tr>
<td>Resolution</td>
<td>&lt; 24 hour</td>
<td>Days</td>
</tr>
<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>
</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>
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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

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)
  - 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
  - Thioridazine (most cardiotoxic in overdose)
- Medium potency
  - Droperidol
  - Loxapine (more seizures in overdose)
  - Melperone
  - Perphenazine
- High potency (more EPS, less sedation)
  - Fluphenazine
  - Haloperidol (most common cause of NMS)
  - Trifluoperazine
  - Thiothixene

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
  - Cholestatic jaundice
  - Acute reversible oliguria
  - Chlorprothixene (Taractan)
Atypical Antipsychotics

- **Aripiprazole** (Abilify)
  - Longest elimination 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

- **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 (Saphris®)
  - Hypotension
  - Agitation, altered
  - QT?
- Iloperidone (Fanapt®)
  - Hypotension, antimuscarinic
  - QT prolongation
- Lurasidone (Latuda®)
  - 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 intracellular levels high
- Subacute/non-specific 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
- GI symptoms more severe
- Tremor, muscle weakness, ataxia, hyperreflexia
- Decreased excretion
- Serum levels lower since intracellular levels high
- Subacute/non-specific 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!!