Serotonin Toxicity
And other complications arising from psychotropic treatments
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Why Study (Psycho)Pharmacology?

- Clinical
  - ~20% of Americans are on psychotropic medications
  - 59% of patients receive psychotropic medication from PCPs not psychiatrists
  - Medications can have pronounced but predictable side-effects that affect treatment.
  - Manage medication expectations.
  - Patient see their psychologists more frequently than their prescribing clinician
  - Many patients are not educated by the prescriber about medication side-effects or risks
  - Many signs of more severe side-effects or syndromes can be missed or misinterpreted by the patient because of character disorders
  - Prescribing by proxy already happens.

- Professional
  - Incommensurability between science and psychology
    - Common language / terminology
  - Greater respect and “buy-in”
    - Getting more referrals
    - Better responses from physicians
  - More integrated / collaborative care
  - Making better referrals
Why Become A Prescribing Psychologist?

Clinical

- The power to prescribe is the power to UNprescribe!
- Patients are severely underserved and wait months to see a psychiatrist or are forced to go to a PCP for psychotropics
- Mental healthcare should be comprehensive!
- Better compliance is possible since psychologists are more aware of and better able to manage transference phenomena.

Professional

- Enhances psychology’s visibility and prestige in the public eye.
- Psychology’s scope of is being eroded by other professions (e.g., counseling, social work, “life coaches,” et cetera).
  - Many psychologists don’t do testing.
Workshop Overview

Basics of Psychopharmacology

- Neuroanatomy
- Major Neurotransmitters
- Symptoms & Neurocircuits
- Psychokinetics
- Psychodynamics
- Drug Development & Goals (agonists)
- BREAK

Medication Classes

- Anti-Depressants
- Anxiolytics
- Neuroleptics (Anti-Psychotics)
- Mood Stabilizers
- Dementia Medications

ACTIVITY & QUESTIONS
BREAK (if time)

Adverse Effects and Conditions

- Serotonin Syndrome
- Neuroleptic Malignant Syndrome
- Metabolic Syndrome
- Steven-Johnson Syndrome
Psychopharmacology Review
Neuroanatomy: Neurons

- Dendrites
- Soma (Cell Body)
- Axon
- Terminal Buttons
- Synapse
Dopamine

One of three monoamines (DA, NE, Epi)

Symptoms: Decreased positive affect, psychotic symptoms, low energy, anhedonia.
Dopamine D2 Receptor

- D2
  - Increased D2 stimulation in the mesolimbic pathway is linked with the positive symptoms of psychotic disorders.
  - All antipsychotics are D2 antagonists.
  - 80% blockade of D2 receptors in the mesolimbic pathway are required for antipsychotic effects.
Serotonin (5HT)

Origin: Raphe Nuclei

Symptoms: Increased Negative Affect and Obsessive Rumination

Several Clinically Significant Subtypes
### Serotonin Cont.

<table>
<thead>
<tr>
<th>5HT1A</th>
<th>5HT2A</th>
<th>5HT2C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autoreceptor</strong>&lt;br&gt;Stimulation of receptors in the prefrontal cortex and the raphe nuclei cause downstream release of DA in the striatum.&lt;br&gt;Potent 5HT1A partial agonists include atypical antipsychotics such as aripiprazole, clozapine, and quetiapine.</td>
<td><strong>Postsynaptic</strong>&lt;br&gt;Stimulation of receptors of cortical pyramidal neurons causes downstream decreases in DA.&lt;br&gt;Affects the production of prolactin.&lt;br&gt;Potent 5HT2A antagonists include many atypical antipsychotics.</td>
<td><strong>Postsynaptic</strong>&lt;br&gt;Regulates DA and NE release.&lt;br&gt;Antagonism of 5HT2C has pro-cognitive and strong anti-depressant effects.&lt;br&gt;Potent 5HT2C antagonists include TCAs, mirtazapine, agomelatine, olanzapine, and quetiapine.</td>
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</tbody>
</table>
Serotonin Cont.

**5HT3**

Autoreceptor

Antagonism prevents nausea. Not currently utilized in anti-depressants.

**5HT6**

Postsynaptic

Regulates release of acetylcholine.

Antagonism results in improved memory and learning.

Potent antagonists are clozapine, olanzapine, and asenapine.

**5H7**

Postsynaptic

Antagonism appears to help regulate sleep.

Potent antagonists include amoxapine, desipramine, imipramine, mianserin, fluoxetine, and vortioxetine as well as many of the atypical antipsychotics especially quetiapine but also clozapine and asenapine.
Norepinephrine (noradrenaline)

Origin: Locus Coeruleus

Subtypes: $\alpha_1$
- $\alpha_2$
- $\beta_1$
- $\beta_2$
<table>
<thead>
<tr>
<th>Alpha Receptors</th>
<th>Beta Receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>a1</strong>&lt;br&gt;(postsynaptic)</td>
<td><strong>β1</strong>&lt;br&gt;(postsynaptic)</td>
</tr>
<tr>
<td><strong>a2</strong>&lt;br&gt;(presynaptic)</td>
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</table>

<table>
<thead>
<tr>
<th>G protein coupled</th>
<th>Activates</th>
<th>Phospholipase C</th>
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<tr>
<td><strong>G protein</strong></td>
<td><strong>Gi protein</strong></td>
<td><strong>G protein</strong></td>
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<tr>
<td>coupled</td>
<td>coupled</td>
<td>coupled</td>
</tr>
<tr>
<td>Activates</td>
<td>Inhibits</td>
<td>Activates</td>
</tr>
<tr>
<td><strong>Adenyl Cyclase</strong></td>
<td><strong>Adenyl Cyclase</strong></td>
<td><strong>Adenyl Cyclase</strong></td>
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<tr>
<td><strong>ATP → cAMP</strong></td>
<td><strong>ATP → cAMP</strong></td>
<td></td>
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</tbody>
</table>


1. The heart<br>a. Heart rate (+ chronotropic)<br>b. Impulse conduction (+ dromotropic)<br>c. t contraction (+ inotropic)<br>d. ejection fraction<br>2. renin release by Juxtaglomerular cells<br>3. renin release by Juxtaglomerular cells


5. Lipolysis
6. Thickened salivary secretion
Comparison of Neurotransmitters and Psychiatric Symptoms
Medication Classes Review

ANTI-DEPRESSANTS, ANXIOLYTICS, NEUROLEPTICS, AND MOOD STABILIZERS
### Anti-Depressants

<table>
<thead>
<tr>
<th><strong>SSRIs</strong></th>
<th><strong>SNRIs</strong></th>
<th><strong>TCAs</strong></th>
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<tbody>
<tr>
<td>All six SSRIs inhibit reuptake of serotonin and are thought to be effective for anxiety disorders, when dosed at the high end: Fluoxetine (“Prozac”) Sertraline (“Zoloft”) Paroxetine (“Paxil”) Fluvoxamine (“Luvox”) Citalopram (“Celexa”) Escitalopram (“Lexapro”)</td>
<td>All SNRIs inhibit the reuptake of 5HT and NE. All are more effective for psychosomatic pain syndromes. Blocking NET also increases DA in the prefrontal cortex. Venlafaxine (“Effexor”) SERT&gt;NET Desvenlafaxine (“Pristiq”) SERT&lt;NET Duloxetine (“Cymbalta”) SERT&gt;NET Milnacipran (“Savella”) SERT&lt;NET</td>
<td>All TCAs inhibit the reuptake of 5HT and NE. Many are also effective for the psychosomatic pain syndromes. Most have 5HT2A and 2C antagonism. Amitriptyline (“Elavil”) Nortriptyline (“Pamelor”) Imipramine (“Tofranil”) Desipramine (“Norpramin”) Clomipramine (“Anafranil”) Doxepin (“Selinor”) Amoxapine (“Asendin”)</td>
</tr>
</tbody>
</table>
Anti-Depressants Cont.

Atypicals
Bupropion ("Wellbutrin") – NDRI
Trazadone ("Oleptro") – SARI
Nefazodone ("Serzone") – SARI
Mirtazapine ("Remeron") – NaSSA
*Buspirone ("Buspar") – Serotonin Stabilizer

MAOIs
All MAOI’s degrade the enzyme monoamine oxidase (A/B) which is responsible for degrading monoamine neurotransmitters leading to an increase in their availability.

Risks include:
Hypertensive crisis brought on by dangerous levels of NE due to consumption of tyramine.
Drug-drug interactions.
Serotonin Syndrome

MAOIs Cont.
AVOID: dried, aged, smoked, fermented, spoiled meats. Broad bean pods, aged cheeses, tap or unpasteurized beers, sauerkraut, soy, banana peels, and tyramine-containing nutritional supplements. Also avoid NRIs and stimulants or decongestants.

Phenelzine ("Nardil")
Tranylcypromine ("Parnate")
Isocarboxazid ("Marplan")
Selegine (Reversivle) ("Emsam")
Symptoms of Hypertensive Crisis

- Diastolic blood pressure > 120 mmHg
- Occipital headache
- Palpitation
- Nausea
- Stiff neck
- Vomiting
- Sweating
- Fever
- Dilated pupils / photophobia
- Tachycardia or bradycardia
- Constricting chest pain
Signs Unipolar Depression Is Really Bipolar Disorder

Unipolar Depression

- Typical Features
  - Early Insomnia
  - Reduced appetite / weight loss
  - Normal Activity levels / slightly increased
  - Psychomotor agitation
  - Somatic complaints
- Later age of onset
- Longer episodes (12 months)
- No family history

Bipolar Depression

- Atypical features
  - Hypersomnia
  - Hyperphagia / Weight gain
  - Psychomotor retardation
  - Psychotic features
  - Pathological Guilt
  - Mood Lability
- Early age of onset (before 25)
- Shorter Duration of Episodes (~3 months)
- Family History of Bipolar
Anxiolytics

Benzodiazepines

Symptoms: Anxiety, agitation, difficulty sleeping.

Benzos bind to a GABA\textsubscript{A} subunit to enhance GABA transmission by opening the chloride channel in GABA receptors. GABA helps alter the intensity of the fear response by toning down signals from the Amygdala.

Contraindicated in elderly due to memory problems and risk of falling.
Anxiolytics

**Short Acting ~ 1-3h**
- Midazolam ("Versed")
- Tiazolam ("Halcion")

**Intermediate Acting ~ 3-7H**
- Alprazolam ("Xanax")
- Lorazepam ("Ativan")
- Chlordiazepoxide ("Librium")

**Long Acting ~ 100h**
- Clonazepam ("Clonipin")
- Diazepam ("Valium")
Neuroleptics (Anti-Psychotics)

<table>
<thead>
<tr>
<th>Conventional (1\textsuperscript{st} Gen)</th>
<th>Atypical (2\textsuperscript{nd} Gen)</th>
<th>Atypical Atypicals (3\textsuperscript{rd} Gen)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All anti-psychotics are antagonistic to D2. Conventional antipsychotics are non-selective D2 antagonists. Effective on positive symptoms. Chlorpromazine (&quot;Thorazine&quot;) Fluphenazine (&quot;Prolixin&quot;) Haloperidol (&quot;Haldol&quot;) Mesoridazine (&quot;Serentil&quot;) Perphenazine (&quot;Trilafon&quot;) Thioridazine (&quot;Mellaril&quot;) Trifluoperazine (&quot;Stelazine&quot;)</td>
<td>Second generation neuroleptics are D2/5HT2A antagonists with greater 5HT2A antagonism than D2. Effective on positive symptoms. Mixed results on negative symptoms. Clozapine (&quot;Clozaril&quot;) Olanzapine (&quot;Zyprexa&quot;) Quetiapine (&quot;Seroquel&quot;) Asenapine (&quot;Saphris&quot;) Iloperidone (&quot;Fanapt&quot;) Lurasidone (&quot;Latuda&quot;) Risperidone (&quot;Risperdal&quot;) Paliperidone (&quot;Invega&quot;)</td>
<td>Aripiprazole* (&quot;Abilify&quot;) Brexpiprazole* (&quot;Rexulti&quot;)</td>
</tr>
</tbody>
</table>

* Atypical atypicals are not considered neuroleptics as they lack D2 antagonistic properties.
<table>
<thead>
<tr>
<th>Atypical Antipsychotics</th>
<th>Available Long-Acting Depot</th>
<th>Long-Acting Depot in Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>4 weeks</td>
<td></td>
</tr>
<tr>
<td>Iloperidone</td>
<td></td>
<td>4-week formulation in trials</td>
</tr>
<tr>
<td>Olanzapine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paliperidone</td>
<td></td>
<td>12-week formulation in trials</td>
</tr>
<tr>
<td>Risperidone</td>
<td></td>
<td>4-week formulation in trials</td>
</tr>
<tr>
<td>Conventional Antipsychotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>2-3 weeks</td>
<td></td>
</tr>
<tr>
<td>Flupenthixol</td>
<td>1-4 weeks*</td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>4 weeks</td>
<td></td>
</tr>
<tr>
<td>Pipothiazine</td>
<td>4 weeks</td>
<td></td>
</tr>
<tr>
<td>Zuclopenthixol</td>
<td>2-4 weeks*</td>
<td></td>
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</table>

Neuroleptics (Anti-Psychotics Depot versions.)
Complications of Neuroleptics

Hyperprolactinemia
Caused by blockade of D2 in the tuberoinfundibular DA pathway, which projects from the hypothalamus to the pituitary gland and causes increase in prolactin levels. Symptoms include:
- Galactorrhea
- Amenorrhea
- Fertility problems
- Demineralization of bones
- Sexual Dysfunction
- Weight Gain

Extrapyramidal Symptoms
Caused by blockade of D2 in the nigrostriatal pathway, which results in motor side effects similar to Parkinson’s Disease and therefore is often called drug-induced parkinsonism.
- Tremor
- Shuffling Gait
- Drooling
- Stooped Posture

Tardive Dyskinesia
Results from chronic blockade of D2 in the nigrostriatal pathway. Symptoms include:
- Facial and tongue movements.
- Quick jerky movements
- Chorieform movements
## What is a Mood Stabilizer?

<table>
<thead>
<tr>
<th>Strict Criteria</th>
<th>Liberal Criteria</th>
<th>Conservative</th>
</tr>
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<tbody>
<tr>
<td><em>Efficacy in acute mania, acute depression, and prophylaxis of mania and depression.</em></td>
<td><em>Efficacy in acute mania without induction of depression.</em></td>
<td><em>Efficacy in two of three phases of bipolar illness, one of which is prophylaxis.</em></td>
</tr>
<tr>
<td>Lithium (“Eskalith”)</td>
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<td>Lithium (“Eskalith”)</td>
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<tr>
<td></td>
<td>Valproate (“Depakote”)</td>
<td>Valproate (“Depakote”)</td>
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<tr>
<td></td>
<td>Carbamazepine (“Tegretol”)</td>
<td>Carbamazepine (“Tegretol”)</td>
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<td></td>
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<td>Lamotrigine (“Lamictal”)</td>
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</tbody>
</table>
Psychostimulants / ADHD Medications

- Stimulant and non-stimulant varieties.
- Stimulant varieties (methylphenidate, amphetamine salts) directly increase dopamine.
- Non-stimulant varieties boost dopamine by inhibiting the NET.
Case #1

55-year old, married, Caucasian female. Reports history of depressive episodes since early 30’s with depressed mood, crying, guilty feelings, sense of worthlessness, irritability, and constipation.
Case #2

21-old, unmarried, Hispanic male. Reports history of depressive episodes since late teens with depressed mood, low energy / fatigue, poor concentration, low self-esteem, anhedonia, and sexual dysfunction.
Case #3

29-old, unmarried, Caucasian male. Reports history of depressive episodes since early teens with depressed mood, reduced appetite, poor concentration, anhedonia, and guilty feelings. He also has experienced panic attacks and tends to ruminate obsessively on his past failures or about upcoming, anxiety producing events.
Case #4

39-old, thrice divorced, Caucasian female. Diagnosed with borderline personality disorder, suicidal behaviors, fibromyalgia, and depression. She has failed trials of several SSRIs, venlafaxine, and CBT.
49-year-old, unmarried, African-American male, with past diagnoses of depression with psychotic features, schizophrenia early onset, schizoaffective disorder bipolar type, and schizotypal personality disorder. He has been off all medications for several years and been homeless. He does not recall what medications he took previously.
Serotonin Toxicity / Syndrome

SYMPTOMS & DIAGNOSIS
Serotonin Toxicity / Syndrome

Mydriasis
Serotonin Toxicity / Syndrome

Clonus
Serotonin Toxicity / Syndrome

Diaphresis (Sweating)
Serotonin Toxicity / Syndrome

Ocular Clonus
Serotonin Toxicity / Syndrome

Pyrexia (i.e., hyperthermia or fever)
Serotonin Toxicity / Syndrome

Bilateral Babinski Sign
Serotonin Toxicity / Syndrome

Other Symptoms

- Hyperreflexia
- Agitation
- Tremor
- Akathisia
- Deep tendon hyperreflexia (common)
- Inducible or spontaneous muscle clonus (common)
- Muscle rigidity
- Dry mucus membranes
- Flushed skin
- Increased bowel sounds
Serotonin Toxicity / Syndrome

Hunter Criteria
Questions to ask yourself?

When would you refer back to the prescribing clinician?
When would you send the patient to the hospital?
What else might you do as first aid?
Serotonin Toxicity / Syndrome

Severity of Symptoms

CNS excitation
- Rigidity, Respiratory Failure

Mental state
- Coma
- Confusion

Autonomic excitation
- Severe Hyperthermia
- Mydriasis, Flushing, Diaphoresis, Low fever $\sim 101$

Severity:
- Severe (10 - 100 x)
- Moderate (5 - 10 x)
- Mild (3-5 x)
- (<3 x)

Inducible Clonus, Hyper-reflexia

Brisk reflexes

Ecstasy use

SSRI overdose

MAOI & SSRI Combination

SSRI in therapeutic use

Hypertension, Tachycardia

Insomnia

Nausea, Vomiting
Serotonin Toxicity / Syndrome Cont.

Treatment Regimens

- Anxiety
- Akathisia
- Tremors
- Tachycardia
- Sweating
- Diarrhea
- Mydriasis

Discontinuation of offending drugs, monitoring and supportive care

- Clonus
- Hyper-vigilance
- Hyperthermia
- Hypertension
- Hyperreflexia

Full-blown SEROTONIN SYNDROME

- Rigidity, hyperthermia >40°C, seizures, coma
- with fatal complications

Discontinuation of offending drugs, supportive care and intensive care

- Intubation & ventilation
- Neuromuscular paralysis
- Dialysis
- 5-Hydroxy-tryptamine antagonist, i.e. oral cyproheptadine or intravenous chlorpromazine
- Benzodiazepines
- Anticonvulsants
- Propranolol

Severe SEROTONIN TOXICITY

Mild ADVERSE REACTIONS

Discontinuation of offending drug/s
Neuroleptic Malignant Syndrome
Neuroleptic Malignant Syndrome

Pathophysiology

A continuation of sorts of EPS and TD. NMS results from chronic blockade of the D2 receptors in the nigrostriatal pathway, most commonly by 1st Gen. Anti-Psychotics.
Neuroleptic Malignant Syndrome cont.

**Symptoms**
- Severe muscular rigidity*
- Hyperthermia (temperature >101°F)*
- Autonomic instability
  - Polydipsia
  - Change in heart rate
  - Difficulty breathing
  - Dysphagia
  - Dizziness / light headedness*
  - Excessive Sweating
- Changes in the level of consciousness

**Treatment**
- Mostly Supportive
Metabolic Syndrome
Metabolic Syndrome cont.

Symptoms

- Atypical antipsychotics class warning:
  - Weight gain and risks for obesity
  - Dyslipidemia
  - Diabetes
  - Accelerated cardiovascular disease
  - Premature death.
Metabolic Syndrome
Pathophysiology
Metabolic Syndrome cont.

High metabolic risk
- Clozapine
- Olanzapine

Moderate
- Risperidone
- Paliperidone
- Quetiapine
- Iloperidone (weight)

Low
- Ziprasidone
- Aripiprazole
- Lurasidone
- Iloperidone (Dyslipidemia)
- Asenapine
- Brexpiprazole
- Cariprazine
Metabolic Syndrome

Treatment

- Mostly Supportive
- Focused on weight management strategies
- Switching antipsychotics
Steven-Johnson Syndrome

aka Toxic Epidermal Necrolysis
SJS & Lamotrigine cont.

Nonserious vs. Serious Rash
SJS and Lamotrigine

Non-Serious Rash
- Nonconfluent
- Nontender
- Doesn't involve face or neck
- Settles within a few days

Serious Rash
- Confluent
- Widespread
- Purpuric or tender
- Any prominent involvement of the neck or upper truck
- Any involvement of eyes, lips, mouth
- Any associated fever, malaise, or anorexia
SJS & Lamotrigine

Treatment

- For non-serious rashes, hold lamotrigine steady or reduce and rechallenge after rash subsides.
- For serious rashes stop lamotrigine.
- If SJS develops, hospitalization and supportive treatment similar to severe burns is initiated.
  - Push fluids / balance electrolytes
  - Corticosteroids
  - Treat infections as appropriate
  - Ensure airway remains unrestricted
- AVOID completely by titrating slowly.
Resources

- Stahl's Books
  - Essential psychopharmacology
  - Prescriber's Guide
  - Essential Evidence-Based Psychopharmacology
- Practical Guides in Psychiatry Series
  - Mood Disorders

- Electronic
  - ePocrates
  - Neuroscience Education Institute
  - Join the psychopharmacology division of TPA and follow us online.