All SSRI’s Are Not Created Equal

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Reston, VA

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This speaker has no conflicts of interest, commercial support, or off-label use to disclose.

Objectives

1. Discuss the role of serotonin and serotonin receptors in the regulation of mood
2. Describe the unique mechanisms of action, side effects, and drug interactions of the 6 FDA approved serotonin reuptake inhibitor medications: fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram.
3. Choose an SSRI for a selected patient based on scientific rationale
Brief Anatomy Review

Autonomic Nervous System

- Sympathetic (Adrenergic)
  - Monoamines
    - Catecholamines
    - Dopamine
    - Norepinephrine
    - Epinephrine
  - Serotonin

- Parasympathetic (Cholinergic)
  - Acetylcholine
    - Muscarinic
    - Nicotinic

The Neuron

Cells of the Brain

1. Neurons (150 kinds) (100 billion)
   A. Axons (association, commissural, projection)
      1. Long
      2. Short (within a given nucleus)
   B. Dendrites (extensions of the cell body)

2. Glia (100 billion x 10^{100})
   A. Oligodendrocytes (myelinate axons)
   B. Astrocytes (regulate ions, guide neurons, remove toxins, form scars)

Axons

- Axons are separate, myelinated, and connected via the axon hillock
  - Associative-communicate within hemisphere through interneurons (local communication to link sensory and motor and limited to a specific area-GABA)
  - Commisural-communicate across hemispheres
  - Projections-long-distance axons→cortex or other structures throughout the brain and to the spinal cord
Layers of the Cortex

(10-14,000,000,000 neurons)

I. Molecular layer: contains very few neurons
II. External granular layer
III. External pyramidal layer
IV. Internal granular layer: receives thalamocortical connections, especially from the specific thalamic nuclei. This is most prominent in the primary sensory cortices.
V. Internal pyramidal layer; Infragranular, gives rise to all of the principal cortical efferent projections to basal ganglia, brain stem and spinal cord.
VI. Multiform, or fusiform layer projects primarily to the thalamus.

Brief History

• Observation of depression as an effect of reserpine, led to discovery of NE/5HT depletion via ‘leaky vesicles’.

• Observation of mood elevation as an effect of iproniazide led to recognition of effects of monoamine oxidase inhibition.

• Today, available antidepressants, through many mechanisms, act primarily as NE and 5HT agonists although many also have relative DA agonist activity.
What Do We Know About the Antidepressant Drugs We Have?

• Antidepressants exert initial effects by increasing the intrasynaptic levels of serotonin and/or norepinephrine

• Clinical antidepressant effects are only observed after chronic administration
  – This suggests a cascade of downstream effects ultimately responsible for therapeutic effects

• This effect is indicative of a more primary ‘upstream’ abnormality.

Available Antidepressants

<table>
<thead>
<tr>
<th>SSRI</th>
<th>SPARI</th>
<th>SNRI</th>
<th>SARI</th>
<th>NRI</th>
<th>NDRI</th>
<th>NE/SSA</th>
<th>TCA</th>
<th>MAOI</th>
</tr>
</thead>
<tbody>
<tr>
<td>fluoxetine</td>
<td>vilaxid</td>
<td>venlafaxine</td>
<td>trazodone</td>
<td>atomoxetine</td>
<td>bupropion</td>
<td>mirtazapine</td>
<td>amitriptyline</td>
<td>phenelzine</td>
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<tr>
<td>paroxetine</td>
<td>desvenilaxid</td>
<td>nefazodone</td>
<td>nortriptyline</td>
<td>protriptyline</td>
<td>clomipramine</td>
<td>moclobemide</td>
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<td></td>
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<tr>
<td>sertralin</td>
<td>duloxetine</td>
<td>milnacipran</td>
<td>citalopram</td>
<td>escitalopram</td>
<td>fluvoxamine</td>
<td>citalopram</td>
<td>escitalopram</td>
<td>amoxapine</td>
</tr>
</tbody>
</table>

Available Antidepressants

Overall Efficacy and Acceptability

- Efficacy of antidepressants is not related to selectivity or potency for NE, DA, or 5HT uptake blockage, but their relative profiles of side-effects and individual patient tolerance.
- Meta-analysis revealed mirtazapine, escitalopram, venlafaxine, and sertraline significantly more efficacious and acceptable than duloxetine, fluoxetine, fluvoxamine, paroxetine, and reboxetine (not approved). (Cipriani et al, 2009).
- Less then 1% of trials have been done on treatment resistant patients.

Serotonin: Location

- Cell bodies in raphe nuclei of the midbrain regions and upper pons – most extensive monoaminergic – 40,000-60,000 SE neurons in the brain
- Multiple gene products for SE
- ‘Surrogates’ are alcohol, nicotine
**Synthesis of Serotonin**

Tryptophan plus Vitamin B6

\[
\text{(tryptophan hydroxylase)}
\]

5-hydroxytryptophan

\[
\text{(5HTP decarboxylase)}
\]

5HT

---

**Serotonin: Functions**

- Inhibits activity and behavior
- Increases sleep time
- Reduces aggression, play, sexual, and eating activity
- Temperature regulation
- Sleep cycle
- Pain perception
Serotonin: Functions (cont’)

• Mood states
• Precursor to melatonin which plays a role in
  – circadian rhythms
  – some depressions
  – light-dark cycle
  – jet lag
  – female reproductive cycle
  – seasonal skin pigment changes

WHAT ABOUT ALL THOSE SEROTONIN RECEPTORS?

1A, 2A, 2C, 3, 4, 5, 6, 7
### 17 Known Major 5HT Receptors

**Grouped in 7 Categories**

<table>
<thead>
<tr>
<th>5HT</th>
<th>1A</th>
<th>2A</th>
<th>3A</th>
<th>4</th>
<th>5A</th>
<th>6</th>
<th>7</th>
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<tbody>
<tr>
<td>1A</td>
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<td>2B</td>
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<tr>
<td>1D</td>
<td></td>
<td>2C</td>
<td>3C</td>
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<tr>
<td>1E</td>
<td></td>
<td></td>
<td>3D</td>
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<tr>
<td>1F</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3E</td>
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<table>
<thead>
<tr>
<th></th>
<th>SE Inhibitory</th>
<th>SE Excitatory</th>
<th>SE Inhibitory</th>
<th>SE Excitatory</th>
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<tbody>
<tr>
<td>DA</td>
<td>DA Excitatory</td>
<td>DA Inhibitory</td>
<td>DA Excitatory</td>
<td>DA Inhibitory</td>
<td>DA Excitatory</td>
<td>DA Inhibitory</td>
<td>DA Inhibitory</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE:** 1C was the first 5HT3 to be discovered, but it was later found to have the excitatory mechanism of the 2 receptor.

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### Individual Receptor Functions

**5HT 1A** *(buspirone is agonist-functions to increase inhibition of:)*

- Addiction
- Aggression
- Anxiety
- Appetite
- Blood pressure
- Cardiovascular function
- Emesis
- Heart rate
- Impulsivity
- Memory
- Mood
  - Nausea
  - Nociception
  - Penile erection
  - Pupil dilation
  - Respiration
  - Sexual behavior
  - Sleep
  - Sociability
  - Thermoregulation
  - Vasoconstriction

**5HT 1B**

- Addiction
- Aggression
- Anxiety
- Learning
- Locomotion
- Memory
- Mood
- Penile erection
- Sexual behavior
- Vasoconstriction

5HT 1 is found in raphe, hippocampus, cortex

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### Individual Receptor Functions

#### 5-HT 1D
- Anxiety
- Locomotion
- Vasoconstriction

#### 5-HT 1E
- Not sure

#### 5-HT 1F
- Migraine (Sumatriptin is antagonist)
- (Pindolol is antagonist that works faster than a triptin)

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#### 5-HT 2A
- Addiction (potential modulator)
- Anxiety
- Appetite
- Cardiovascular function
- GI motility
- Sleep
- Vasoconstriction

#### 5-HT 2B
- Anxiety
- Appetite
- Cardiovascular function
- GI motility
- Sleep
- Vasoconstriction

#### 5-HT 2C
- Addiction (potential modulator)
- Anxiety
- Appetite (obesity)
- Cognition
- GI Motility
- Locomotion
- Mood
- Penile erection
- Sexual behavior
- Sleep
- Thromoregulation

#### 5-HT 2B
- 5-HT2 Located in cortex, olfactory system, claustrum (BG)
- 5-HT2 Located in area postrema of medulla—controls vomiting, cortex—‘leaky’ blood brain barrier around posterior pituitary and supraventricular areas

#### 5-HT 3
- Addiction
- Anxiety
- Emesis
- GI motility
- Learning
- Memory
- Nausea (odansetron is an antagonist)
- Penile erection
- Sexual behavior
- Sleep
- Thromoregulation
- Vasconstriction

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### Individual Receptor Functions

<table>
<thead>
<tr>
<th>5 HT 4</th>
<th>5HT 5A</th>
<th>5HT 6</th>
<th>5HT 7</th>
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<tbody>
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<td>Anxiety</td>
<td>Locomotion</td>
<td>Anxiety</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Appetite</td>
<td>Sleep</td>
<td>Cognition</td>
<td>Memory</td>
</tr>
<tr>
<td>GI motility</td>
<td></td>
<td>Learning</td>
<td>Mood</td>
</tr>
<tr>
<td>Learning</td>
<td></td>
<td>Memory</td>
<td>May regulate BDNF</td>
</tr>
<tr>
<td>Memory</td>
<td></td>
<td>Mood</td>
<td></td>
</tr>
<tr>
<td>Mood</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiration</td>
<td></td>
<td></td>
<td>May regulate BDNF</td>
</tr>
</tbody>
</table>

5 HT 4-Superior colliculi (eye movements; gastrointestinal tract and chemoreceptor trigger zone of medulla (*metocloprimide* is anti-nausea)

### Serotonin:

**General Effects of Excess/Deficit**

#### Excess
- Sedation
- If greatly increased, the metabolites may lead to hallucinations
- Sexual dysfunction
- Weight gain
- Suppression of dopamine transmission

#### Deficit
- Irritability
- Hostility
- Depression
- Sleep disturbance
- Obsessive compulsive symptoms

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5 HT 1A-Inhibitory to SE
(Stimulation of DA)

• Strong affinity for SE
• When SE binds to a 5HT 1A receptor it alters the receptors spatial configuration which activates a G-protein
• This opens an ion channel which allows $K^{++}$ to exit the neuron
• This causes the internal charge to be more – making it harder to trigger an action potential
• Net result is inhibition of SE and increased DA

Effects of Post-Synaptic 5HT 1A Binding (Agonism)

• Anti-depressant Disinhibits SE in PFC (restores)
• Anti-obsessional Disinhibits SE in Basal Ganglia
• Anti-panic Disinhibits SE in Limbic/Hippo
• Anti-social phobia Disinhibits descending pathways
• Anti-bulemic Activates receptors in hypothalamus
• Also affects: Hormones, cognition, and inhibition of cortical pyramidal neurons
5HT 2A-Excitatory to SE- (Inhibitory to DA)

- Have a weaker affinity for serotonin and only ‘fill’ when 1A receptors are saturated
- When SE binds to a 5HT 2A receptor it alters the receptors spatial configuration which activates a G-protein
- This closes K++ ion channel causing K++ to build up which depolarizes the cell membrane
- The excitation threshold is reached more readily

Effects of Post-Synaptic 5HT 2A Binding

- Production of 2nd messenger that produces transcription factor
  - Increases or decreases expression of neuronal genes
- Inhibits DA→↑ACH=
  - Akathisia
  - Agitation
  - Anxiety
  - Panic
  - Insomnia
  - Sexual dysfunction
- Pharmacologically we want ANTAGONISM
- Targeted by psychedelics
5HT 2C-Inhibitory to DA

- ↓ DA & NE binding on GABA interneurons in brain stem
- This action causes **excitation of GABA**
- Results in ↑ effect of GABA on both NE and DA
- GABA is inhibitory, therefore decreased release of DA in pre-frontal cortex
- Exerts tonic inhibitory influence over DA
- High level expression in amygdala

Summary of Serotonin 1 and 2 Effects on DA/NE

Axon Terminal
- 5HT 1A-decreases neuronal firing (inhibitory)
- 5HT 1 B/D-autoreceptor (gatekeeper)
- 5 HT 1D-anti-migraine
- 5HT2C↓ DA & NE binding on GABA interneurons in brain stem → causing excitation → ↑ GABA on both NE and DA

Somatodendritic
- 5HT 1A-decreases neuronal electrical activity=↓ SE
- 5HT 1A binding inhibits its own release → ↑ DA
- 5HT 2A binding → ↓ DA release directly
- 5HT 2A binding → ↓ DA release indirectly via binding at GABA neurons. DA and NE inhibition of GABA
5HT-3-Excitatory

- Comprise both the binding sites and the ion channel
- When SE binds to a 5HT 3 receptor it alters the G-protein causing the central channel to allow sodium ions to ENTER the post-synaptic neuron
- Positively charged ions cause cell depolarization and number of nerve impulses discharged
- Agonism causes:
  - Nausea
  - GI distress
  - Diarrhea
  - Headache
- Odansetron is antagonist (used in chemotherapy to combat nausea)

General Action of an SSRI

- Selective for SE only (removes side effects from tricyclics)
- Block reuptake at both axon terminal and somatodendrite (down-regulates both)
- No longer inhibited=↑ SE
- Delay caused by time it takes to downregulate 5HT 1 autoreceptors and turn on flow in SE
  - Has to fill the vesicles in axon terminal
5 Steps to the Action of SSRI

1. Block reuptake pump at both the axon terminal and somatodendrite
   ✓ Results in initial ↑ in somatodendrite SE levels
2. Results in down-regulating somatodendritic 5HT 1A autoreceptor
3. This turns on neuronal electrical impulse flow
4. Ultimately ↑ release of SE from axon terminal
5. Eventually down regulates post-synaptic SE receptors

General Efficacy

• If any of the currently available antidepressants are administered for 6-8 weeks in therapeutic doses to patients with DSM IVTR depression, 5-75% will exhibit a significant response
• Only 30% exhibit full remission
• 10-20% cannot tolerate needed doses
• 25-35% do not respond to available agents
Effects on Existing Anxiety

- High baseline levels of anxiety predictive of greater depression severity and **poorer treatment response**.

  (2012-Gollan, Fava, Kurian, Wisniewski)

Pathway for Neurogenesis

- Fluoxetine activates raphe
  - Decreases raphe levels of the SERT
- This causes BDNF to act on the hippocampus
- This stimulates the locus coeruleus to induce SERT and secrete serotonin.
- Leads to increase in both hippocampal SERT and bcl-2 protein

Launay, et al, 2011
Considerations in Medication Selection

- Prior positive response
- Response in other family members
- Short-term side effects
- Long-term side effects
- Interaction with nonpsychiatric medication
- Patient preference
- Patient age
- Cost of medication
- Concurrent medical disorder
- Concurrent psychiatric disorder
### The Impact of Medication on Target Depressive Symptoms

#### Approximate Onset of Drug Effect
- **Week 2**

#### Target Symptoms Improved
- Fatigue
- Poor motivation
- Somatic complains
- Agitation/retardation

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#### The Impact of Medication on Target Depressive Symptoms

#### Approximate Onset of Drug Effect
- **Week 3**

#### Target Symptoms Improved
- Dysphoric mood
- Subjective depressive feelings
- Suicidal thoughts
FDA Approvals for SSRIs

<table>
<thead>
<tr>
<th></th>
<th>Fluoxetine</th>
<th>Sertraline</th>
<th>Paroxetine</th>
<th>Fluvoxamine</th>
<th>Citalopram</th>
<th>Escitalopram</th>
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<tbody>
<tr>
<td>MDD</td>
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<td>X</td>
<td>X</td>
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<td>Social phobia</td>
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<td>X</td>
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<tr>
<td>GAD</td>
<td>X</td>
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Review of Antagonist Properties

- Histamine 1 (drowsiness, sedation, weight gain)
- Alpha 1 adrenergic (tachycardia, orthostatic hypotension, dizziness, sexual dysfunction)
- Alpha 2: sweating, dilated pupils, tachy
- Muscarinic cholinergic (dry mouth, blurred vision, urinary retention, constipation, tachycardia, memory problems)
- Muscarinic 3 cholinergic on pancreatic beta cells (interferes with insulin)
**What Does an SSRI Look Like?**

SRI = Serotonin Reuptake inhibitor  
NRI = Norepinephrine Reuptake Inhibitor  
DRI = Dopamine Reuptake Inhibitor  
5HT2C = antagonist  
Muscarinic = antagonist  
Sigma 1 receptor = agonist  
(endoplasmic reticulum affects CA++, may affect NMDA receptor)  
Nitric Oxide Synthetase = inhibitor  
CYP = 2D6, 3A4, 1A2 inhibitor

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**Comparison of Action at Major Receptors**

<table>
<thead>
<tr>
<th>Drug</th>
<th>NE (Ki)</th>
<th>SE (Ki)</th>
<th>NE/SE (Ki)</th>
</tr>
</thead>
<tbody>
<tr>
<td>desipramine</td>
<td>180</td>
<td>0.6</td>
<td>0.003</td>
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<tr>
<td>doxepin</td>
<td>220</td>
<td>18</td>
<td>0.08</td>
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<tr>
<td>amitriptyline</td>
<td>84</td>
<td>14</td>
<td>0.2</td>
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<tr>
<td>imipramine</td>
<td>41</td>
<td>14</td>
<td>0.3</td>
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<tr>
<td>venlafaxine</td>
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<td>25</td>
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<tr>
<td>sertraline</td>
<td>3</td>
<td>220</td>
<td>64</td>
</tr>
</tbody>
</table>

Fluoxetine Prozac-1988

- Dosage range 10-80mg
- 5HT2C antagonist
- Serotonin reuptake inhibitor
- Norepinephrine reuptake inhibitor
- Has active metabolite-norfluoxetine that takes 5 weeks to reach steady state
- Minimal problems with withdrawal because of long half-life
- Available in weekly dose of 90mg

Fluoxetine Side Effects

<table>
<thead>
<tr>
<th>COMMON</th>
<th>OCCASIONAL</th>
<th>RARE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Restlessness</td>
<td>EPS</td>
</tr>
<tr>
<td>Headache</td>
<td>Rash</td>
<td>Lowers seizure threshold</td>
</tr>
<tr>
<td>Nervousness</td>
<td>Fever</td>
<td>High WBCs</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Joint pain</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>Sexual</td>
<td>Mania</td>
<td>Fainting</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Aminotransferase elevations</td>
<td>Respiratory distress</td>
</tr>
<tr>
<td></td>
<td>Inability to make decisions</td>
<td>Anorexia</td>
</tr>
<tr>
<td></td>
<td>Hair loss</td>
<td></td>
</tr>
</tbody>
</table>

Graphic: Stahl, 2008, p.533-Used With Permission
Sertraline *Zoloft*-1991

- Dosage: 50-200mg
- Dopamine reuptake inhibitor
- Serotonin reuptake inhibitor-desensitizes 1A
- Sigma antagonism may assist with calming
- Higher incidence of diarrhea
- Approved for PTSD (start at 25mg)
- Moderate withdrawal syndrome
- Absorption increased by 40% when taken with food
- Raises level of hydroxybupropion

**Sertraline Side Effects**

**COMMON**
- Nausea
- Headache
- Diarrhea
- Insomnia
- Dry mouth
- Sexual
- Dizziness
- Tremor
- Fatigue
- Increased sweating

**OCCASIONAL**
- Agitation/anxiety
- Pricking/tingling sensations
- Appetite loss
- Palpitations
- Frequent urination
- Hot flushes
- Weakness

**RARE**
- ↓ Concentration
- Yawning
- Muscle pain,
- Abnormal taste
- Ringing in ears
- ↑ Appetite / thirst
- EPS
- Lactation
- Platelet dysfunction

Graphic: Stahl, 2008, p. 536-Used with permission
**Paroxetine** *Paxil-1992*

- Serotonin reuptake inhibitor
- Norepinephrine reuptake inhibitor
- Muscarinic antagonist
- Nitrous oxide synthetase antagonist
- Dosage range: 20-50mg
- Very sedating—take at night
- Potent 2D6 blocker
- Greatest risk for withdrawal syndrome
- Approved for GAD
- Initially causes agitation
- Cardiac risks over 40mg

**Paroxetine Side Effects**

**COMMON**
- Nausea
- Somnolence
- Headache
- Asthenia
- Sweating
- Cough

**OCCASIONAL**
- Decreased appetite
- Sexual dysfunction
- Dry mouth
- Constipation
- Diarrhea
- Vomiting
- Indigestion
- Muscle twitching
- Confusion
- Yawning
- Blurred vision
- Taste disturbance

**RARE**
- Bradycardia
- Delirium
- Psychosis
- EPS
- Platelet dysfunction and bleeding

Graphic: Stahl, 2008-p. 537-Used with Permission
Fluvoxamine *Luvox-1993*

- Desensitizes Serotonin 1A
- Serotonin reuptake inhibitor
- Sigma 1 agonist (energizing)
- Dosage range of 50-300mg in divided doses
- Approved for obsessive-compulsive disorder
- Short half-life
- Contraindicated with Hismanal, Seldane
- Use lithium with caution
- Nausea, sedation, insomnia, nervousness
- General side effects similar to Prozac

Graphic-Stahl, 2008, p. 538 – Used with Permission

Fluvoxamine Side Effects

<table>
<thead>
<tr>
<th>COMMON</th>
<th>OCCASIONAL</th>
<th>RARE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Weight gain</td>
<td>Bruising</td>
</tr>
<tr>
<td>Headache</td>
<td>Weight loss</td>
<td>Bleeding</td>
</tr>
<tr>
<td>Insomnia or</td>
<td>Emotional flattening</td>
<td>Hyponatremia</td>
</tr>
<tr>
<td>Sedation</td>
<td>Cognitive slowing</td>
<td>Induction of mania</td>
</tr>
<tr>
<td>Sexual</td>
<td></td>
<td>Seizures</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td>Activation of suicidal ideation</td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agitation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Fluvoxamine: Common Drug Interactions

- Cytochrome P450-decrease
  - TCA dose by 2/3
  - Theophylline by 1/3
- Benzodiazepines:
  - Alprazolam dose must be halved
  - Diazepam should not be used
  - Triazolam dose reduced
  - Lorazepam not effected

- Use lithium with caution
- Reduce dose of warfarin and monitor PT
- Reduce dose of carbamezapine and monitor levels
- No problems with digoxin, beta blockers

Citalopram Celexa-1998

- Serotonin reuptake inhibitor
- Desensitizes SE 1A autoreceptor
- Dosage is 20-60mg
- Mild H1 antagonist
- The R (rectus=right) molecule may interfere with the S (sinister=left) the ACTIVE molecule
- Acts by enhancing postsynaptic 5HT
- Low toxicity and few P450 interactions

Graphic: Stahl, 20008-p. 538-Used With Permission
**Citalopram- Side Effects**

**(Dose-related)**

<table>
<thead>
<tr>
<th>COMMON</th>
<th>OCCASIONAL</th>
<th>RARE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>Aesthenia</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Impotence</td>
<td>Tachycardia</td>
<td>Edema</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Postural hypotension</td>
<td>Phlebitis</td>
</tr>
<tr>
<td>Increased sweating</td>
<td>Migraine</td>
<td>Leg cramps</td>
</tr>
<tr>
<td>Somnolence</td>
<td>Flatulence</td>
<td>Dysphagia</td>
</tr>
<tr>
<td>Yawning</td>
<td>Amenorrhea</td>
<td>Teeth grinding</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>Anemia</td>
<td>Colitis</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>Coughing</td>
<td>Hiccups</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Rash, itching</td>
<td>Tinnitus</td>
</tr>
<tr>
<td>Weight loss or gain</td>
<td>concentration</td>
<td>Loss of taste</td>
</tr>
<tr>
<td>Agitation</td>
<td>Apathy</td>
<td>Psychosis</td>
</tr>
</tbody>
</table>

**Escitalopram Lexapro-2002**

- The purest SSRI we have
- Desensitizes the 1A autoreceptor
- Dosage: 10-20mg
- Escitalopram is the single isomer active ingredient of (S&R = assigning priority to the atoms attached to the chiral center. )
- Elimination of the “R” (rectus=right) isomer may increase potency so dose lower to start
- Side effects similar to citalopram

**Graphic:** Stahl (2008), p. 541- Used With Permission
Estrogen and Antidepressants

• Estradiol inhibits 1A2 and 2C19 enzymes which are responsible for metabolism of many SSRIs including sertraline
  – leads to increased availability of SSRIs in women compared to men

• Inhibits reuptake of NE
  – Decreases effects of TCAs in women

• Males respond better to TCAs than women

General CYP 450 Actions of Antidepressants

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 A2</td>
<td>amitriptyline, citalopram, fluoxetine, fluvoxamine, imipramine, mirtazapine, nefazodone, paroxetine, sertraline, tranylcypromine</td>
</tr>
<tr>
<td>2C9</td>
<td>amitriptyline, buproprion, clomipramine, fluoxetine, imipramine, mirtazapine, venlafaxine</td>
</tr>
<tr>
<td>2C19</td>
<td>amitriptyline, citalopram, clomipramine, escitalopram, fluoxetine, imipramine, nortriptyline, trimipramine, sertraline, venlafaxine</td>
</tr>
<tr>
<td>3A4</td>
<td>Amitriptyline, citalopram, escitalopram, clomipramine, desipramine, doxepine, duloxetine, fluoxetine, imipramine, mirtazapine, nefazodone, nortriptyline, sertraline, trazodone, trimipramine, venlafaxine</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, tranylcypromine, venlafaxine</td>
</tr>
</tbody>
</table>
General CYP 2D6 P450 Actions of Antidepressants

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Substrate</th>
<th>Inhibitors</th>
</tr>
</thead>
</table>
| 2D6    | **TCAs:** Amitriptyline, amoxapine, clomipramine, desipramine, doxepine, imipramine, nortriptyline, trimipramine  
SSRIs: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline  
Other: buproprion, duloxetine, mirtazapine, nefazodone, trazodone, venlafaxine | **TCAs:** Amitriptyline, clomipramine, desipramine, imipramine, nortriptyline, SSRIs: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, Other: buproprion, duloxetine, mirtazapine, nefazodone, tranylcypromine, trazodone, venlafaxine |

Mathys, 2007

Clinically Significant Interactions with SSRIs

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Substrate</th>
<th>Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A2</td>
<td>clozapine, haloperidol theophylline, caffeine, diazepam, thiothixene, trifluoperazine, cyclobenzapine, propranolol</td>
<td>ciprofloxacin</td>
<td>cigarette smoker rifampin, phenytoin, phenobarbital, carbamazepine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cimetadine</td>
<td></td>
</tr>
<tr>
<td>2C9</td>
<td>Amiodarone, carvedilol, glipizide, losartan, phenytoin, rifampin, warfarin</td>
<td>Amiodarone, fluconazole, fluvastatin</td>
<td>Carbamazepine, phenobarbital, phenytoin, rifampin</td>
</tr>
<tr>
<td>2C19</td>
<td>Carisprudol, diazepam, phenobarbital, phenytoin, propranolol</td>
<td>Omeprazole, fluconazole, omeprazole</td>
<td>Carbamazepine, phenytoin, rifampin</td>
</tr>
</tbody>
</table>

Mathys, 2007
# Clinically Significant Interactions with SSRIs

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Substrate</th>
<th>Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2D6</strong></td>
<td>Aripiprazole, carvedilol, chlorpromazine, codeine, dextromethorphan, flecainide, fluphenazine, haloperidol, labetalol, lidocaine, metoprolol, mexiletine, oxycodone, perphenazine, procainamide, propafenone, propranolol, risperidone, thioridazine, warfarin</td>
<td>Quinidine, propafenone, amiodarone, cimetidine, haloperidol, perphenazine, tironavie, thioridazine, valproate</td>
<td><em>Paroxetine, Fluoxetine, Fluvoxamine, Sertraline</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Buproprion mirtazapine</td>
</tr>
</tbody>
</table>

Mathys, 2007

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<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Substrate</th>
<th>Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3A4</strong></td>
<td>Alprazolam, amitriptyline, amlodipine, aripiprazole, atorvastatin, bisoprolol, bupropine, carbamazepine, clarithromycin, clonazepam, clorazepate, cyclosporine, diazepam, diltiazem, disopyramide, erythromycin, felodipine, fentanyl, flurazepam, haloperidol, itraconazole, ketoconazole, lidocaine, lovastatin, methadone, nifedipine, phenytoin, quetiapine, quinidine, rifampin, sildenaflil, simvastatin, theophylline, triazolam, verapamil, zolpidem</td>
<td>Amiodarone, cimetidine, ciprofloxacin, clarithromycin, diltiazem, erythromycin, fluconazole, grapefruit juice, indinavir, iraconazole, ketoconazole, nefinavir, omeprazole, ritonavir, squinnavir, verapamil</td>
<td><em>Carbamazepine Oxcarbazepine</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Phenobarbital, phenytoin, rifampin</td>
</tr>
</tbody>
</table>

Mathys, 2007
2D6 and Serotonin Syndrome

- Occurs when central and peripheral serotonin receptors are overstimulated
- *Usually within 6 hours of ingestion of the offending substance*


What is Serotonin Syndrome?

- **Autonomic changes**: diarrhea, fever, flushing, hypo/hypertension, sweating
- **Neuromuscular changes**: hyperreflexia, increased muscle tone, restlessness, rigidity, tremor, shivering
- **Central nervous system**: agitation confusion, delirium, hallucinations
References
References


