Drugs for Affective Disorders:
Antidepressants

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Depression is characterized by
- Relentless feeling of sadness
- Decrease in sex drive
- Weight changes
- Anhedonia
- Confusion
- Inability to complete tasks
- Suicide

Types of Depression
- Reactive or exogenous depression
  - Response to specific situation in one's life
  - Short in duration - usually no pharmacological treatment
- Endogenous "from within" depression
  - Unrelated to events in life
  - Will go in & out of depressed state - can last weeks to months
  - "spontaneous remission"
  - Genetic - an underlying biochemical abnormality that is inherited

Depression
Facts:
- 19% lifetime prevalence (2x more likely in women)
- Only 33% seek help
- Suicide rate is 15%
- Costs U.S. $44 billion/year

Famous Persons with Major Mood Disorders
- Unipolar
  - Abraham Lincoln
  - Winston Churchill
  - Martin Luther
  - Robert Burns
  - Leo Tolstoy
  - Sylvia Plath
  - William Styron
  - Dan Rather
  - Alfred Lord Tennyson
  - Henry James

- Bipolar
  - Robert Lowell
  - Hector Berlioz
  - Virginia Woolf
  - Eugene O'Neill
  - Ernest Hemingway
  - Hermann Hesse
  - Delmore Schwartz
  - Edgar Allen Poe
  - Graham Greene
  - Robert Schumann
  - Vincent van Gogh

Proposed Physiological Basis of Depression:
Low norepinephrine and/or serotonin signaling in the brain
Reserpine depletes serotonin and catecholamines
Decreased levels of MOPEG in urine of depressed people
Decreased levels of 5-HIAA in CSF in a subset of depressed people
Furthermore,
Antidepressant drugs increase synaptic concentration of NE and/or 5-HT in the synaptic cleft
Inhibit monoamine oxidase (MAO)

However,
• Antidepressants raise NE and/or 5-HT concentration immediately, but there is always a delay in the onset of antidepressant action.
• Not all treatments for depression increase NE and/or 5-HT in the synapse.
• Cocaine and amphetamine are not effective antidepressants.

Most antidepressants (and ECT) cause down-regulation of β-adrenergic receptor function.
This effect occurs only after extended exposure to the antidepressant agent.

Treatment
• Pharmacotherapy
• Psychotherapy
• ECT

Antidepressants
• MAO inhibitors
• tricyclic antidepressants
• selective serotonin reuptake inhibitors (SSRI)

Actions of Antidepressants
• Inhibit MAO
• Inhibit NE reuptake
• Inhibit 5-HT reuptake
**Monoamine Oxidase Inhibitors (MAOIs)**

- Inhibit MAO irreversibly
- Isoxcarboxazid, phenelzine, tranylcypromine
- Used for depression
- Suppress REM sleep - used for narcolepsy

**MAOIs interact with other drugs**

- Also inhibit liver microsomal enzymes (irreversibly)
- Hyperpyrexia interaction with meperidine
- Life-threatening interaction with indirect-acting sympathomimetics e.g., ephedrine, dietary tyramine

**Combination of MAOIs with indirect-acting sympathomimetics can produce hypertensive crisis**

- Release of massive amounts of NE and/or 5HT

**Tricyclic Antidepressants**

- **Tertiary Amine**: Imipramine, trimipramine, amitriptyline, doxepin
- **Secondary Amine**: Desipramine, protriptyline, nortriptyline

- Side chain ending in tertiary or secondary amine

**Tricyclic Antidepressants**

- Tertiary amine: Block 5HT and NE reuptake
- Block postsynaptic receptors

- Imipramine
Tricyclic Antidepressants

- Used for depression
- Do not elevate the mood of euthymic individuals
- Suppress REM sleep - useful for enuresis

Tricyclic Antidepressants

- Enhance actions of direct-acting sympathomimetics
- Block the action of indirect-acting sympathomimetics
- Enhance the action of CNS depressants
- Dangerous in overdose

MAOIs and Tricyclics...

- Delay in onset of therapeutic actions
- Drug interactions
- Delay in onset of antidepressant actions
- Not everyone responds