Major Depressive Disorder (MDD)

(Prevalence almost 7% in any individual year; almost 17% lifetime prevalence, with more women affected than men)

- At least 5 of the following almost every day for at least 2 weeks:
- Persistent depressed or irritable mood
- Decreased interest or pleasure
- Significant change in appetite/weight w/o dieting
- Insomnia or hypersomnia
- May move & talk slowly, or may be restless
- Fatigue, loss of energy or motivation, apathetic
- Feel worthless; inappropriate guilt
- Can't make decisions, concentrate
- Suicidal thoughts or actions

Genetic Research: Depression shows a moderate degree of heritability

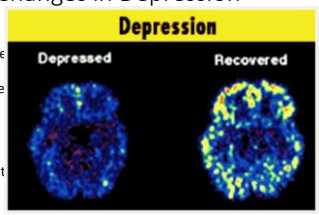
- Depression runs in families; ~10x more risk in those with affected relatives, especially female relatives who had depression early (<30 yrs)
- 25% with major depression and 50% with bipolar disorder have affected parents
- Adopted children resemble biological parents
- ~50% concordance for depression in identical twins; 15-20% in fraternal twins; 80% vs. 40% for bipolar
- Several genes seem to be linked with depression, but not all the same genes in men & women
- But remember gene-environment interactions……

An Example of Gene-Environment Interaction

- Gene for the 5HT reuptake transporter comes in 2 forms (short and long). If you have:
- 2 short genes – very likely to develop depression **if** you experience life stresses
- 2 long genes – very resistant to stress
- Heterozygous – intermediate in your likelihood to develop depression in response to life stresses
- But other genes may "protect" you – e.g. gene for one of our nerve growth factors

Brain Activity Changes in Depression

- Decreased frontal activity, especially on left (happy) side
- Drug or therapy treatment increase activity
- May be more activity on right (negative mood)
- ECT limited to right (sad) hemisphere is often effective



Circadian Changes in Depression

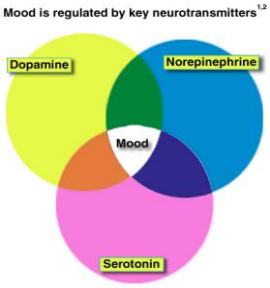
- Some genes associated with depression are circadian genes.
- Sleep & temp cycle advanced and sleep abnormal: early REM & more REM despite early morning awakening
- 70% of relatives of depressed show early REM; those with early REM 3X more likely to develo0p depression than those without.
- Either REM deprivation or total sleep deprivation can relieve depression temporarily; shifting circadian rhythm by going to bed 30 min later each day until at a normal bedtime can also help.
- (Antidepressants suppress REM sleep!)
- Another variety of depression – SAD- tied to changes in day/night cycle & abnormal melatonin secretion. BUT SAD causes a phase-*delay in rhythms*

Seasonal Affective Disorder (SAD)

- Depression typically occuring in the late fall/winter & disappearing when days get longer and brighter in the spring.
- Characterized by lack of energy, oversleeping, overeating as well as depressed, irritable mood
- Artificially lengthening the day or providing brighter light with full-spectrum lights can relieve this depression
- Growing evidence for seasonal mania symptoms in some in the spring

Incidence of SAD

- Southern Canada & US northern edge 10.2%
- OR, WY, SD, IA, WI tier 8.0%
- CA, NV, UT, CO MO, KY tier 5.8%
- AZ, NM, TX, LA, AL tier 3.6%
- Mexico, FL 1.4%



The Monoamines

Monoamine Theory of Mood

Normal mood depends on adequate monoamine activity at synapses.

↓ levels→depression
↑→euphoria/mania

Different people may have different monoamine imbalances

5HT & NE related to many depression symptoms

- 5HT is important not just to mood but also sleep & biorhythms, temp regulation, sexual function, cognition
- NE involved in energizing behavior and responsiveness to environment
- These are functions that change in depression.

Tricyclic Antidepressants

- 3 best known:
  - amitriptyline (Elavil)
  - desipramine (Norpramin)
  - imipramine (Tofranil)
- drugs which increase %HT & NE activity by blocking the reuptake from synapses (transmitters remain available to stimulate receptors for a longer period of time)
- Effective but have annoying side effects

Monoamine Oxidase Inhibitors like Nardil (phenelzine)

- drugs which inhibit the action of MAO, an enzyme that normally breaks down monoamines
- transmitters are more available because not inactivated by MAO
- Unfortunately those on MAOIs must follow an annoying diet to avoid overstimulation of their sympathetic nervous system

Selective 5HT Reuptake Inhibitors**("SSRIs")**

- fluoxetine (Prozac) (also Zoloft, Paxil, Lexepro, Celexa) are **selective 5HT reuptake inhibitors – keeps 5HT active in synapse longer**
- same effectiveness but fewer side effects and risks; patients more willing to take Prozac
- (But we now know sexual side effects and some withdrawal effects when you stop are possible)

New Drug Research

- All the major categories of antidepressants take weeks to improve the symptoms of depression.
- One surprising new finding:
  - Low dose **intravenous** ketamine can produce immediate relief of depressive or serious anxiety symptoms in some individuals. Now in Phase 3 trials – may be available in 2018. http://www.npr.org/sections/health-shots/2015/05/28/409800015/ketamine-depression-treatments-inspired-by-club-drug-move-ahead-in-tests

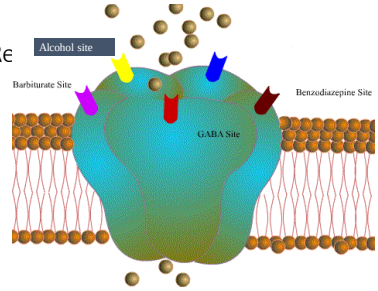
Neurogenic Theory of Depression

- Depression is associated with ⇩ size of certain brain areas (like hippocampus), ⇩ production of new neurons, ⇩ nerve growth factors.
- Hypothesis: Antidep effectiveness depends on a **slower anatomical changes in CNS:**
  - increased neuron production & anatomical "remodeling' due to increased neurotrophins like brain-derived-neurotrophic factor (BDNF) follows the rise in neurotransmitter
  - Preventing neuron production blocks the effectiveness of antidepressants

Neurochemistry of Anxiety

- Inhibitory transmitter GABA as well as 5HT
- Increased GABA action → decreased anxiety
- Benzodiazepines like Xanax or Valium and alcohol do this by enhancing the sensitivity of GABA receptors
- Many GABA receptors in limbic areas like amygdala
- More recent approach – antidepressants which increase 5HT activity

GABA Re



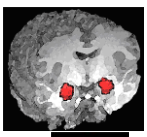
Blockers of these sites increase anxiety and decrease the relaxing effects
RO15-4513 – blocks most effects of alcohol

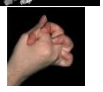
Brain Benzodiazepines?

- Brain did not develop receptors to receive outside drugs – must be for body chemicals
- Body has its own chemicals which fit the "benzo. receptors" called"endozepines" (means "endogenous benzodiazepines")
- The first one discovered blocks the calming effects of benzos & increases fear/anxiety: i.e. it has effects opposite to those of benzodiazepines.

Amygdala Reactivity Partly Determined by Genes

- Twin studies suggest genetics play a role in anxiety disorders, shyness although not as strongly as with mood disorders
- Had trouble localizing anxiety related genes until they noticed many with panic disorder and other anxiety disorders also showed "joint laxity"
- This allowed researchers to track the genes to a region of chromosome 15 .
- Many with anxiety seem to have a genetic "repeat" (multiples of a segment of code where normals only have one)





Obsessive-Compulsive Disorder

- Often occurs in conjunction with Tourette Syndrome – some of the genes involved may be the same