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 develop 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 occurring 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%

5HT & NE related to many depression symptoms

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

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.

Tricyclic Antidepressants

- 3 best known:
  - amitriptyline (Elavil)
  - desipramine (Norpramin)
  - imipramine (Tofranil)
- Drugs which increase 5HT & 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.

Selective 5HT Reuptake Inhibitors (“SSRIs”)

- Fluoxetine (Prozac) (also Zoloft, Paxil, Lexapro, 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.

Neurogenic Theory of Depression

- Depression is associated with size of certain brain areas (like hippocampus), production of new neurons, nerve growth factors.
- Hypothesis: Antidepressant 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

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