Anxiety and Depression

Chapter 29
Introduction

- Depression and anxiety in primary care
- Pathophysiology: what do we know?
- Medications that are available
- Pharmacodynamics
- Goals of treatment
- Rational drug selection
- Non-drug approaches
- Adverse Drug Reactions
- Patient Education
- Monitoring
Pathophysiology:

- Anxiety and depression result from interaction of the central nervous, peripheral nervous, endocrine systems, genetic and environmental factors.
- Many structures of the brain are involved in depression: cerebral cortex, frontal, temporal lobes, brain stem, basal nuclei, limbic system, hippocampus, amygdala, cingulate gyrus
- Hypothalamus: maintains endocrine functions
Neurotransmitters involved

- Each Neurotransmitter has a specific neuroreceptor:
  - Serotonin (5HT)
  - Norepinephrine (NE)
  - Dopamine (DA)
  - Gamma-aminobutyric acid (GABA)
  - Acetylcholine (Ach)
Neuroconduction-neurotransmission Cascade

- Communication between neurons is accomplished through action potentials and neurochemical events:
  - Depolarization
  - Repolarization
  - Resting stage
  - Postsynaptic neuroreceptor binding
Pharmacodynamics:

- All current psychoactive drugs affect the neuroconduction-neurotransmission cascade in some way.
- Nine classes of drugs are used for anxiety and depression:
  - Nonselective Norepinephrine-Serotonin Reuptake Inhibitors
  - Serotonin-Selective Reuptake Inhibitors
  - Serotonin-Norepinephrine reuptake inhibitors
  - Norepinephrine-Dopamine Agonists
  - Serotonin Agonist Reuptake Inhibitor
  - Norepinephrine and Serotonin Specific Agonist
  - Norepinephrine-Specific Reuptake Inhibitors
  - Monoamine Oxidase Inhibitors
  - Benzodiazepines/GABAergics
Nonselective Norepinephrine-Serotonin Reuptake Inhibitors

- Referred to as Tricyclic Antidepressants (TCA’s)
- Affect the NE, 5HT, Ach and histamine receptors
- Inhibits the transport of NE, 5HT back into the presynaptic neuron
- Have high side effect profile
- Death readily occurs with overdose
- Careful with refill and amounts with new onset of depression, history of suicide, high risk populations.
Nonselective Norepinephrine-Serotonin Reuptake Inhibitors

- **Imipramine (Tofranil)**
  - FDA approved for treatment of nocturnal enuresis in children > 6 years of age

- **Desipramine (Norpramin)**
  - FDA approved for use in adolescents

- **Amitriptyline (Elavil)**
  - Causes drowsiness
  - Avoid use with alcohol
  - FDA for use in children > 12 years of age

- **Doxepin (Sinequam)**
Serotonin-Selective Reuptake Inhibitors

- Most commonly used
- Blocks transport mechanism for unbound 5HT making more available to bind to the postsynaptic 5HT receptor
- Fluoxetine (Prozac, Serafem)
  - Longest acting
- Paroxetine (Paxil, Paxil CR)
- Sertraline (Zoloft)
- Fluvoxamine (Luvox)
- Citalopram (Celexa)
- Escitalopram (Lexapro)
Serotonin-Norepinephrine Reuptake Inhibitors: SNRI’s

- Increase the levels of both serotonin and norepinephrine by inhibiting their reabsorption (reuptake) into cells in the brain.
- Precise mechanism of action isn't clear,
  - it's thought that these higher levels enhance neurotransmission — the sending of nerve impulses — and so improve and elevate mood.
- Venlafaxine (Effexor, XR)
- Duloxetine (Cymbalta)
Norepinephrine-Dopamine Reuptake Inhibitor

- Inhibitor of the neuronal uptake of NE and Dopamine
- Blocks receptor sites in reward center
  - Used to treat smoking and adjunct in drug abuse
- High risk for seizures
- Bupropion: (Wellbutrin, Wellbutrin SR, Wellbutrin XL)
- **NOT** FDA approved for children
Serotonin Agonist Reuptake Inhibitor

- Inhibit the reuptake of 5HT, and block their subtypes
- Causes drowsiness, dizziness often given at night.
- **NOT** FDA approved for use in children
- Nefazadone (Serzone)
- Trazadone (Desyrel)
  - Major CYP3A4 metabolism: decreases effects of codeine, increases effects of alcohol, St. John’s Wort
Norepinephrine and Serotonin Specific Agonist: Alpha-2 antagonist

- Effects of this drug results in increase levels of NE and 5HT.
- Because it also blocks Histamine has high drowsiness and weight gain as side effects.
- **NOT** FDA approved for use in children
Norepinephrine-Specific Reuptake Inhibitors

- Used primarily a non-stimulant treatment of ADHD
- Increases availability of NE in the frontal cortex improving executive functions.
- Increases effects of alcohol
- Careful with slow metabolizers
- Atomoxetine (Strattera)
Monoamine Oxidase Inhibitors

- Not used very often in primary care
- Become familiar with dietary restrictions when these drugs are used.
- These drugs should ONLY be prescribed by a psychiatrist specialist.
  - Potential lethal effects
- Phenelzine (Nardil)
- Tranylcypromine (Parnate)
Benzodiazepines/GABAergics

- Used to treat anxiety disorders
- Short-acting agents
  - Clorazepate (Tranxene)
  - Halazepam (Paxipam)
  - Prazepam (Centrex)
- Intermediate acting agents
  - Alprazolan (Xanax)
  - Lorazepam (Ativan)
  - Oxazepam (Serax)
  - Chlordiazepoxide (Librium)
- Long acting agents
  - Diazepam (Valium), Clonazepam (Klonopin)
Benzodiazepines/GABAergics

- All BZD’s work on chloride ion channels of GABA-A receptors. They enhance GABA neurotransmission which lengthens hyperpolarization and slow down responses.
  - Anxiolytic
  - Anticonvulsion
  - Muscle relaxation
  - Sedation
- Nonbenzodiazepine GABA agonist:
  - Buspirone (Buspar)
Goals of Treatment

- **Anxiety:**
  - Reduction of symptoms
  - Understanding etiology/contributing symptoms
  - Patient Education: understand the role of SNS
    - Provide coping skills
    - Becoming involve in altering Hypothalamus-Pituitary Axis responses

- **Depression**
  - Reduction of symptoms
  - Understanding contributing factors
  - Patient Education: understand role of adrenal, cognitive, HP axis, etc.
    - Providing counseling/coping skills
Rational Drug Selection

- Having correct diagnosis
  - Know relationship between anxiety/depression
  - Understand populations: elderly vs. children vs. adolescents
- Understanding pathophysiology:
- Look for high risk populations
- Looking for comorbidities:
  - Drug/alcohol abuse
  - Chronic illnesses
  - Learning disabilities, ADHD
  - Other psychiatric disorders: bipolar illness, OCD,
Non Drug Approaches

- Psychoneuroimmunology research
- Brain Plasticity research
- JAMA article: antidepressants= placebo affect?
- Role of counseling
- Role of relaxation techniques
- Lifestyle modifications
ADR’s

- Increase with alcohol use, with multiple drug use
  - CYP450 enzymes responsible for metabolism of many psychotropic drugs
  - Drug dependency: Benzodiazepines
- SSRI:
  - sexual dysfunction
Patient Education

- Evaluating anxiety and depression must be ongoing because so many variables contribute.
- What does it mean to have therapeutic dosing?
- When there is anxiety may need to provide anxiolytics until antidepressant can help.
- Patients need to understand the role of counseling, lifestyle modification, stress reduction.
Monitoring

- Very important to assess 2-3 weeks after starting medications for suicide ideology.
- No refills until you are comfortable with diagnosis, contributing factors, etc.
- Evaluation is essential component
  - Referral if no change even when adjusting medications
  - Minimal response
  - Need to reasses diagnosis
- After one year it is reasonable to taper off keeping in mind:
  - High risk populations
  - Factors contributing to anxiety/depression