Pharmacology of Serotonin Reuptake Inhibitors (SRIs): Clinical Uses, Adverse Effects, and Comparison of Agents

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Psychotropic Medications

- Drug classes
  - CNS stimulants/ psychostimulants
    - Most prescribed class in children
  - Antidepressants
    - Most prescribed class in adults
  - Antianxiety agents/ sedative-hypnotics
  - Antipsychotics
  - Mood stabilizers

- Many psychiatric disorders are life-long and require long-term (maintenance) drug treatment
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Importance of Diet/Nutrition

- L-tryptophan (essential amino acid) to serotonin → melatonin (with darkness)
  - Dairy products, eggs, poultry, meat, fish, soy products, nuts/legumes, grains, rice

- Tyrosine and phenylalanine (amino acid precursors) to dopamine
  - Kidney beans, beets, peas, soybeans, almonds, barley, oats, grains, eggs, dairy products, meats

- Glutamate/glutamic acid (amino acid precursors) to GABA
  - White bread, flour, potatoes
  - Glucose (Krebs cycle)
Other Factors

- Nutrition
  - Regular and well balanced meals with protein; don’t skip breakfast

- Sleep
  - REM sleep – manufacturing of neurotransmitters

- Exercise – releases neurotransmitters

- Stress – depletes neurotransmitters

- Hormone – menstrual cycle changes, deficiency states (estradiol and testosterone)
Other Factors

- **Alcohol** – sedation and depression
- **Caffeine** – anxiety, insomnia, irritability, tremors, withdrawal headaches
- **Nicotine** – anxiety, insomnia, dizziness, headache, nausea, increased heart rate, withdrawal reactions (irritability, depression)
  - smoking increases liver enzymes and lowers blood levels of many medications (e.g., antipsychotics)
Other Factors

- Cocaine, amphetamines
- Methamphetamine
- Cannabis
- Hallucinogens
  - LSD, mescaline, peyote, psilocybin, MDT, DOM, nutmeg, jimsonweed
- Phencyclidine (PCP) – angel dust
- MDA (structurally related to mescaline and amphetamine) and MDMA (modification of MDA – “Ecstasy”)
- Inhalants
  - Volatile solvents, nitrous oxide, nitrites
Mood Disorders: Use of Antidepressants
Mood or Affective Disorders

- Incidence of depression is ~ 5%
- Lifetime prevalence: 5-11%
  - Only 1/3 are in treatment
  - 15% of severely depressed patients commit suicide
- Morbidity comparable to advanced heart disease
- Episodes can last a long time (years)
- Incidence of bipolar disorder is ~1%
Depression: Diagnostic Criteria

- Key features: quality of mood, degree of mood change, and duration of abnormal mood
- Vegetative features: sleep, appetite, weight, sex drive
- Cognitive features: attention span, frustration tolerance, memory, negative distortions
Depression: Diagnostic Criteria

- Impulse control: suicide and homicide
- Behavioral features: motivation, pleasure, interests, fatigability
- Physical (somatic) features: headache, stomach aches, muscle tension

- "Somatization" used for physical symptoms that express emotional distress
Untreated episodes of depression last 6-24 months
- 50% recover within 6 months and 75% recover within 2 years
- 5-10% have episodes lasting > 2 yrs
- Nature of illness includes recurrent episodes
- Patients presenting for the 1st time usually have a history of prior unrecognized or untreated illness
Five R’s of Antidepressant Therapy

- **Response**: 50% reduction in symptoms
- **Remission**: all symptoms go away
- **Recovery**: if remission lasts 6-12 months
- **Relapse**: worsening before complete remission or recovery
- **Recurrent**: worsening after complete recovery
Relapse Predictors for Recurrent Depression

- Multiple prior episodes
- Severe episodes
- Long-lasting episodes
- Episodes with bipolar or psychotic features
- Incomplete recovery between 2 consecutive episodes (poor interepisode recovery)
- Dysthymia: chronic depression that lasts > 2 years
Bipolar Disorder

- Characterized by many recurrent episodes
  - Mania or hypomania
  - Depression
  - Mixed (both mania and depression)
  - Rapid cycling: at least 4 up and/or downs in 12 months
- May be more progressive is uncontrolled
  - Mood swings more frequent, more severe, less responsive to medications
Predicting Response to Antidepressants

- 2 out of 3 will respond to any given antidepressant (67% response rate)
  - ~90% respond to one or more treatments (e.g., combination therapies, drug + therapy)
- Not possible to predict who will respond in general to a specific agent
- May responders still have residual symptoms
Predicting Response to Antidepressants

- Other factors
  - Diet/nutrition
  - Exercise
  - Co-morbid medical disorders
  - Co-morbid medications/OTCs
  - Hormone and endocrine status
  - Substance use/abuse
Maintenance Therapy Recommended

- Two or more prior episodes
- One prior episode (elderly or youth)
- Chronic episodes
- Incomplete remission
Bad News in the Treatment of Depression

- Many patients are “treatment refractory”
  - Poor nutrition and intake of protein (amino acids)
  - Substance and alcohol abuse
- Up to 20% are nonresponders and have poor outcome
- Up to 50% of patients fail to attain remission (e.g., “apathetic” and “anxious”)
Course of Recurrent Episodes

- Seasonal Pattern
  - Phototherapy
- Rapid Cycling
  - Hormonal or endocrine disturbances
  - Antidepressant-induced
Partial Response

- **Possible Causes**
  - Continuing of the illness in a milder form
  - Underlying dysthymia or personality disorder
  - Inadequate early treatment
  - Noncompliance
  - Co-morbid medical conditions
  - Medications/substance-induced mood/anxiety symptoms

- **Outcomes**
  - Increased relapse rates
  - Functional impairment
  - Increased suicide rate
“Pooping Out”

- Primarily middle-aged females
  - Hormonal influences
  - DHEA $\rightarrow$ testosterone $\rightarrow$ estradiol
- Concomitant medications
  - SRIs + trazodone
    - Serotonin augmenting + serotonin antagonist
- Use of benzodiazepines
- Diet/nutrition
- Exercise
- Compliance
Treatment of Depression

- Treat symptoms until they are gone
- Outcomes may be worse if left untreated
- Depression begets depression
- May have long-lasting or irreversible effects if depression progresses
- Live-long illness
- Prone to multiple recurrences
Treatment of Depression

- May relapse within several months if untreated or undertreated or if antidepressants are stopped
- Response rates are generally high, but remission rates are low
- Remission rates are higher with antidepressants
  - Dual serotonin and norepinephrine actions
  - Combination therapies
Course of Bipolar Disorder

- Many recurrent episodes
- Some predominantly depressive and some predominantly manic
- Some mixed with features of both mania and depression
- Rapid cycling: at least 4 episodes in 12 months
- Progressive if untreated
Untreated Bipolar Disorder

- Very disruptive to patient’s life
- Chronic and chaotic course
- Multiple hospitalizations
- Psychotic episodes
- Relapses
  - Intermittent use of mood stabilizers
  - Poor compliance
  - Increased number of episodes may be less responsive to lithium
Treatment of Bipolar Disorder

- Lithium: first marketed treatment for acute mania and has prophylactic effects as well as antidepressant effects
- Anticonvulsants now considered mood stabilizers
- Antipsychotics can be helpful for mania
- Antidepressants can be given with mood stabilizers, but may increase risk of mania or mixed states
Mood Disorders in Children and Adolescents

- Little research for use of antidepressants in children/adolescents with depression
  - Clomipramine and sertraline for OCD
  - High risk for discontinuation syndrome/withdrawal
  - Increased suicidal thoughts/behaviors if short acting SRIs are abruptly stopped (Effexor®, Luvox®, Paxil®)

- Safety is well-established in adults only

- Mania and mixed mania often misdiagnosed as ADHD

- Stimulants and antidepressants can induce bipolar disorder, rapid cycling, and chaotic behaviors (e.g., aggression, irritability)
Biological Basis of Mood Disorders and Treatment
Biological Basis of Depression

- Monoamine hypothesis
- Monoaminergic neurons
- Antidepressants and monoamine hypothesis
- Neurotransmitter receptor hypothesis
Monoamine Hypothesis

- Depression is due to a deficiency of monoamine neurotransmitters
  - Serotonin (5-HT)
  - Norepinephrine (NE)
  - Dopamine (DA)
- Monoamines are made from dietary amino acids
- Drugs that deplete the neurotransmitters induce depression
- Drugs that boost their activity decrease depression
Norepinephrine (NE)

- Tyrosine (and phenylalanine) is amino acid precursor
- Broken down by enzymes COMT (synaptic cleft) and MAO (presynaptic neuron in mitochondria)
- NE Reuptake Pump – a transporter pump prevents its actions by taking up NE into the presynaptic neuron for restorage in vesicles without destroying it
Norepinephrine (NE)

- Receptors
  - Subclassified as
    - Alpha 1 and alpha 2
    - Beta 1 and beta 2
  - NE can shut itself off once the firing rate gets too high: “autoreceptors”
    - Presynaptic alpha 2 agonist: ↓ NE release
    - Presynaptic alpha 2 antagonist: ↑ NE release
Norepinephrine (NE)

- Important Role
  - Cognition
  - Mood and emotions
  - Movement
  - Blood pressure
Locus Coeruleus

- Located in the brainstem
- Contains most of the cell bodies for noradrenergic neurons in the brain
- Determines whether attention is being focused on the “external” environment or on monitoring the internal milieu of the body
  - Reacts to threats in the environment (pain)
  - Important for attention, learning, and memory
Locus Coeruleus

- NE projection from locus coeruleus
  - Limbic cortex controls emotions, energy, fatigue, and psychomotor agitation and retardation
  - Frontal cortex regulates mood (beta 1 postsynaptic)
  - Prefrontal cortex mediates the effects of NE on attention, concentration, and cognition (alpha 2 postsynaptic)
    - Cerebellum regulates motor movement and tremors
    - Cardiovascular centers regulate blood pressure
    - Spinal cord to peripheral tissues controls heart rate (beta 1) and bladder emptying (alpha 1)
Norepinephrine Deficiency

- Impaired attention
- Problems in concentrating
- Difficulties with memory and speed of information processing
- Psychomotor retardation and fatigue
- Apathy and decreased motivation
Norepinephrine Deficiency

- Depression
- Attention deficient disorder
- Schizophrenia (negative symptoms)
- Alzheimer’s disease
- Parkinson’s disease
Dopamine (DA)

- Tyrosine (and phenylalanine) is amino acid precursor
- MAO and COMT destroy DA
- DA Reuptake Pump
- Presynaptic DA autoreceptors: negative feedback on the release of DA

- 5-HT (serotonin) $\text{_{2A}}$ receptors affect DA release
  - 5-HT will decrease DA release
  - 5-HT$\text{_{2A}}$ antagonist will increase DA release
Dopamine (DA)

- DA postsynaptic receptors
  - 1, 2, 3, 4, 5
- Antipsychotics
  - $DA_2$ receptor antagonist (typical)
  - $DA_2$ and 5-HT$_{2A}$ antagonist (atypical)
- Antiparkinson agents
  - DA precursor (levodopa + carbidopa)
  - $DA_2$-3 agonist
  - COMT inhibitor
  - MAO inhibitor
Dopamine Pathways in the Brain

Diagram showing the dopamine pathways in the brain, including the Cingulate gyrus, Striatum, Substantia nigra, Ventral tegmental area, Nucleus accumbens, Pituitary, Arcuate nucleus, and Hippocampus.
Serotonin (5-HT)

- L-tryptophan (essential amino acid) precursor
- MAO and COMT destroy 5-HT
- Cell bodies for 5-HT in the raphe nucleus in the brainsteam
- Alpha 2 adrenergic receptors are on the 5-HT presynaptic neurons (heteroreceptors) and turn off 5-HT release: “brake”
- Alpha 1 adrenergic receptors are on the 5-HT cell bodies and dendrites and enhance 5-HT release: “accelerator”
**Serotonin (5-HT)**

- **1A:** anxiety
- **2A:** depression, sleep, anxiety, panic, OCD, movements, sexual responses
- **2C:** appetite and food cravings
- **3:** brainstem chemoreceptor trigger zone: nausea and vomiting
- **4:** GI motility
Serotonin Pathways in the Brain
<table>
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<tr>
<th>Serotonin/L-tryptophan Deficiency</th>
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<tr>
<td>- Anxiety, panic attacks, obsessive-compulsive behaviors</td>
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<tr>
<td>- Irritability, agitation, impulsivity, aggression</td>
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<tr>
<td>- Insomnia and sleep disruption</td>
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<tr>
<td>- Depression</td>
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<tr>
<td>- Increased appetite</td>
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<tr>
<td>- Aggression to kill animals for food</td>
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<td>- Decreased pain threshold</td>
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**5-Hydroxy-indole acetic acid (5-HIAA)**

- Reduced CSF 5-HIAA = decreased serotonin
  - Depressed patients (only some patients)
  - Impulsive behaviors
  - Suicide
  - Violent/aggression
  - Antisocial personality disorder with self-destructive behaviors

- Postmortem studies show increased numbers of 5-HT 2 receptors in the frontal cortex of patients who commit suicide (up-regulation)
Serotonin Deficiency Syndrome

- Depressed mood
- Anxiety
- Panic
- Phobia
- Obsessive and compulsive behaviors
- Food cravings; bulimia
- Tourette’s syndrome
- Impulsive behaviors
- Aggression
Classical Antidepressants and the Monoamine Hypothesis

- Depression related to deficiencies of monoamine neurotransmitters, altered neurotransmissions, changes in receptor sensitivity (up-regulation or postsynaptic receptor)
- All antidepressants increase either/or/and NE, DA, and 5-HT activity

- Tricyclic antidepressants
  - Block reuptake of NE >> 5-HT and DA
- Monoamine oxidase inhibitors
  - Inhibit metabolism of NE, DA, 5-HT
Antidepressants increase neurotransmitter activity immediately, but there is a delay in antidepressant effects.

Increased neurotransmitters cause a down-regulation of postsynaptic receptors (delayed response).

Abnormality in postsynaptic receptors may be the cause of depression (and secondary messenger systems).
Classical Antidepressants, Serotonin Selective and Noradrenergic Reuptake Inhibitors
Theories of Antidepressant Drug Action

- Depletion Theory
  - Neurotransmitters are depleted
  - Up-regulation of post-synaptic receptors
  - Antidepressants increase neurotransmitter activity
  - Post-synaptic receptors down-regulate (desensitization) $\rightarrow$ tolerance of side effects

- Receptor Theory
  - Abnormal functioning of neurotransmitter receptors (pre- and post-)

- Neurotransmitter-induced Gene Expression Theory
# Depression & Neurotransmitters

- Deficiency of monoamine neurotransmitters cause up-regulation of postsynaptic receptors
  - Dopamine (DA) – excitatory
  - Norepinephrine (NE) – excitatory
  - Serotonin (5-HT) – inhibitory and modulator of DA
Anxiety & Neurotransmitters

- Over activity of excitatory monoamine neurotransmitters
  - Dopamine (DA)
  - Norepinephrine (NE)
- Deficiency of inhibitory neurotransmitters
  - Serotonin (5-HT)
  - Gamma-aminobutyric acid (GABA)
Depression & Antidepressants

- Decreased neurotransmitter activity causes up-regulation of post-synaptic receptors
  - e.g., neurotransmitter depletion up-regulates post-synaptic receptors (depression)
Principles of Pharmacology

- The ability of a drug to produce an effect is dependent on:
  - Route of administration
  - Bioavailability
  - Pharmacokinetics
  - Absorption
  - Distribution
  - Elimination
  - Pharmacodynamics
Pharmacokinetics

- Study of how the drugs act in the body
  - Absorption
  - Distribution
  - Metabolism
    - Cytochrome P450 (CYP 450) enzymes in gut wall (some) and liver (most)
  - Elimination/Excretion
Pharmacokinetics

- Five CYP450 enzymes most important for antidepressant drug metabolism
  - 1A2
  - 2D6
  - 2C9
  - 2C19
  - 3A4

- Substrate/Inhibitor/Inducer
- Not everyone has the same array of enzymes
- Not everyone metabolizes drugs in the same way
**Route of Administration**

- Determines how fast a drug reaches its target organ and which organ it affects
  - Oral or sublingual
  - Parenteral
    - Subcutaneous
    - Intravenous
    - Intramuscular
  - Transdermal
  - Inhalation
Bioavailability

- Determines how much of the drug that is administrated actually reaches its target
  - Absorption
  - Binding to plasma proteins
    - ↓ albumin/protein → ↑ free drug
  - Ability to cross the blood brain barrier
  - Ability to permeate cell membranes
  - Elimination and metabolism
Pharmacodynamics

- The process by which a drug interacts with its initial protein target
  - Drug binding to a neurotransmitter receptor or protein
    - e.g., binding capacity, dissociation, competition
  - Drug efficacy
    - Potency – describes the strength of the binding between a drug and its target
    - Efficacy – describes the biologic effect exerted on the target by virtue of the drug binding
Increased neurotransmitter activity causes down-regulation of post-synaptic receptors

- e.g., antidepressants increase neurotransmitter activity that down-regulates post-synaptic receptors (antidepressant)
  - TCAs (tricyclic antidepressants)
    - MAOIs (monoamine oxidase inhibitors)
    - SRIs (serotonin reuptake inhibitors)
    - NSRIs (norepinephrine/serotonin reuptake inhibitors)
Pharmacology of Antidepressants
Antidepressants

- Side effects and toxicity
  - Weight gain/loss
  - Sedation/stimulation
  - Anticholinergic/antihistamine
  - Sexual dysfunction/stimulation
  - Cardiac changes
    - GI side effects
    - Seizures
- Drug interactions
Pharmacology of Antidepressants

- **↑ 5-HT**
  - Citalopram (Celexa®)
  - Escitalopram (Lexapro®) – most selective

- **↑ 5-HT >> NE**
  - Fluoxetine (Prozac®)
  - Paroxetine (Paxil®)
  - Duloxetine (Cymbalta®)
  - Venlafaxine (Effexor®)

- **↑ 5-HT >> DA**
  - Sertraline (Zoloft®)

- **↑ NE**
  - Desipramine (Norpramin®)
  - Reboxetine – investigational
  - Atomoxetine (Strattera®)

- **↑ NE + DA**
  - Bupropion (Wellbutrin®, Zyban®)
Pharmacology of Antidepressants

- ↑ NE >> 5-HT, antihistamine, anticholinergic, α adrenergic antagonist
  - Amitriptyline (Elavil®)
  - Nortriptyline (Pamelor®)
  - Imipramine (Tofranil®)
  - Doxepin (Sinequan®)
- ↑ 5-HT >> NE
  - Clomipramine (Anafranil®)
- ↑ 5-HT, NE, DA
  - MAOIs
    - Phenelzine (Nardil®)
    - Tranylcypromine (Parnate®)
    - Isocarboxazid (Marplan®)
- Venlafaxine (Effexor®) at higher doses
Pharmacology of Antidepressants

- 5-HT$_{2A}$ antagonist + 5-HT & NE reuptake inhibitor + alpha$_1$ adrenergic antagonist
  - Nefazodone (Serzone®)
  - Trazodone (Desyrel®)

- 5-HT$_{2A/2C/3}$ antagonist + antihistamine (H$_1$) + alpha$_{1-2}$ adrenergic antagonist + muscarinic antagonist
  - Mirtazapine (Remeron®)
Serotonin Reuptake Inhibitors

- citalopram (Celexa®)
- escitalopram (Lexapro®)
- duloxetine (Cymbalta®)
- fluoxetine (generic, Prozac®, Sarafem®)
- fluvoxamine (generic, Luvox®)
- paroxetine (Paxil®)
- sertraline (Zoloft®)
## Serotonin Reuptake Inhibitors

### Clinical Uses
- Major depression
- Menstrual – related depression
  - Premenstrual dysphoric disorder (PMDD)
  - Postpartum depression
- Perimenopausal depression
  - Decreased estradiol $\rightarrow \downarrow$ serotonin activity
Serotonin Reuptake Inhibitors

Clinical Uses

- Obsessive-compulsive spectrum disorders
  - Autistic disorder / Asperger’s disorder
  - Body dysmorphic disorder
- Eating disorders
  - Bulimia, binge-eating, anorexia, obesity
- Tourette’s disorder
Serotonin Reuptake Inhibitors

Clinical Uses

Anxiety disorders
- Generalized anxiety disorders
- Obsessive-compulsive disorder
- Panic disorder
- Posttraumatic stress disorder
- Social phobia
- Mixed anxiety/depression
Serotonin Reuptake Inhibitors

- Clinical Uses
  - Impulse control disorders
    - Alcohol dependence
    - Trichotillomania
    - Paraphilias/hypersexual
  - Tourette’s disorder
  - Pathological gambling
  - Compulsive shopping
Side Effects of SRIs

- **Acute:**
  - 2A and 2C stimulation causes mental agitation and anxiety (akathisia)
  - 2A stimulation in basal ganglia causes akathisia, tremors, psychomotor retardation, and dystonic movements
  - 2A stimulation in brain stem sleep center interrupts sleep patterns (decreases REM)
  - 2A stimulation in spinal cord results in sexual dysfunction
  - 5-HT3 stimulation causes nausea and vomiting
- **Chronic:** down-regulation of receptors and decreases severity of side effects over time
Serotonin Reuptake Inhibitors

- Common Side Effects
  - Gastrointestinal
    - nausea, dyspepsia, diarrhea, emesis, cramping
  - CNS: $\uparrow$ 5-HT $\rightarrow$ $\downarrow$ DA and $\uparrow$ NE
    - insomnia, jitteriness, agitation, restlessness
  - Neurological - headache, tremor
  - Autonomic - excessive perspiration
  - Sexual dysfunction
    - decreased libido, delayed ejaculation and orgasm
Serotonin Reuptake Inhibitors

- Other Side Effects
  - Extrapiramidal reactions
    - Dystonia, akathisia, pseudoparkinsonism
  - Jaw and neck tightness
    - Worsening of TMJ and bruxism
  - Hyponatremia
    - Monitor with volume depletion or with diuretics
  - Vasoconstriction
    - Migraine headache and stroke
Serotonin Reuptake Inhibitors

May make the following conditions worse:

- Migraine headaches
- EPS (dystonia, akathisia, pseudoparkinsonism)
- Parkinson’s disease
- Temporal mandibular joint disease, bruxism, neck and shoulder muscle tension
  - Attention-deficit disorder
  - Nicotine and cocaine dependence
Discontinuation Syndrome

- Serotonin Agents
  - Paroxetine (Paxil®)
  - Fluvoxamine (Luvox®)
  - Venlafaxine (Effexor®)
  - Flu-like syndrome
  - Dizziness, lightheadedness
  - GI symptoms, nausea, loose stools
  - Paresthesia, electrical shock feelings
  - Headache
  - Changes in mood, appetite, and sleep

- Anticholinergic Agents
  - Paroxetine (Paxil®)
  - TCAs
  - Increased gut motility, loose stools, urinary frequency, hypersalivation
  - Anxiety
  - Irritability
  - Flu-like symptoms
  - Myalgias
  - Headache
Discontinuation Syndrome

- Increased risk if abruptly stopped or doses missed
  - Shorter-acting agents >>> longer-acting agents
- Suicidal thoughts and behaviors
- Children/adolescents at higher risk because of non-compliance with dosing
Serotonin Syndrome

- Caused by mixing two or more agents that augment serotonin activity
  - SRIs
  - MAOIs
  - TCAs
  - Buspirone

- ↑ 5-HT → ↓ DA (like a neuroleptic malignant syndrome) + ↑ NE activity
**Serotonin Syndrome**

- **Symptoms:**
  - altered mental status (confusion or hypomania)
  - agitation, restlessness
  - tremors, shivering, hyperreflexia, myoclonus
  - ataxia, incoordination
  - fever, diaphoresis, flushing

- **Avoid combining:** SRIs, NSRIs, MAOIs, TCAs, L-tryptophan, buspirone, lithium, melatonin, meperidine, triptans, St. Johns wort, sibutramine
Comparison of Antidepressants
Citalopram (Celexa®)

- Selective for inhibiting serotonin (5-HT) reuptake
  - “S” and “R” isomers (racemic mixture)
  - “S” isomer is more selective and potent
- Less activating or sedating
- Weight neutral
- Half-life = 33-35 hrs
- Less withdrawal reactions
Citalopram (Celexa®)

- Minimal effect on cytochrome P450 isoenzymes
  - Substrate: CYP2C19, 2D6, 3A4
  - Inhibitor: CYP1A2, 2B6, 2C19, and 2D6 (weak)
Duloxetineine (Cymbalta®)

- Selective 5-HT and NE RI = SSNRI
- 5-HT = NE Reuptake Inhibition
  - Binding studies suggest 5-HT >> NE
- Marketed for Major Depressive Disorder
  - Investigational for pain syndromes
- Elimination t½ = 12 hrs (8-17 hrs)
  - Possible withdrawal reactions
  - Dosing: 20 mg BID to 30 mg BID
- Highly protein bound
Duloxetineine (Cymbalta®)

- Substrate: CYP2D6 and 1A2
  - Bioavailability reduced by 1/3 in smokers
- Inhibitor: CYP2D6 (moderate)
Escitalopram (Lexapro®)

- Most selective for inhibiting serotonin (5-HT) reuptake
  - “S” isomer (active product of citalopram)
  - No antihistamine effects
  - Binds at 5-HT reuptake transporter pump > citalopram
  - 10 mg = 20-40 mg citalopram
- Less activating or sedating
- Weight neutral
- Less withdrawal reactions
Escitalopram (Lexapro®)

- Minimal effect on cytochrome P450 isoenzymes
  - Substrate: CYP2C19, 3A4
  - Inhibitor: CYP 2D6 (weak)
Fluoxetine (Prozac®, Sarafem®)

- 5-HT >> NE Reuptake Inhibition; 5-HT2C agonist
- More activating/stimulating
- Weight neutral or mild loss
- Half-life: 2-3 days for parent and 4-16 days for norfluoxetine
- Less withdrawal reactions
Fluoxetine (Prozac®, Sarafem®)

- Moderate-Severe effect on cytochrome P450 isoenzymes
  - Substrate: CYP1A2, 2B6, 2C8/9, 2C19, 2D6, 2E1, 3A4
  - Inhibitor: CYP1A2, 2B6, 2C8/9, 2C19, 2D6, 3A/4
  - Norfluoxetine: Inhibitor of 3A3/4 (potent)
Fluvoxamine (Luvox®)

- 5-HT Reuptake Inhibition >> DA antagonist
- More sedating
- Weight gain
- Half-life = 16 hrs
- Withdrawal reactions (severe)
Fluvoxamine (Luvox®)

- Moderate-Severe effect on cytochrome P450 isoenzymes
  - Substrate: CYP1A2, 2D6
  - Inhibitor: CYP1A2, 2B6, 2C8/9, 2C19, 2D6, 3A/4
Paroxetine (Paxil®®, Paxil CR®)

- 5-HT >> NE Reuptake Inhibition
- Anticholinergic effects
- More sedating
- Weight gain
- Half-life = 21 hours
- Withdrawal reactions (severe)
Paroxetine (Paxil®, Paxil CR®)

- Moderate-Severe effect on cytochrome P450 isoenzymes
  - Substrate: CYP2D6
  - Inhibitor: CYP1A2, 2B6, 2C8/9, 2C19, 2D6, 3A/4
Sertraline (Zoloft®)

- 5-HT > > DA Reuptake Inhibition
- More activating than sedating; weight neutral
- Half-life = 24 hrs (parent) and 66 hrs (metabolite)
- Less withdrawal reactions
- Drug interactions: inhibits liver enzymes
  - CYP 1A2 and 2D6 (minor)
  - CYP 2C19 and 3A3/4 (moderate at higher doses)
Sertraline (Zoloft®)

- Moderate effect on cytochrome P450 isoenzymes at higher doses
  - Substrate: CYP2B6, 2C8/9, 2C19, 2D6, 3A/4
  - Inhibitor: CYP1A2, 2B6, 2C8/9, 2C19, 2D6, 3A/4
Venlafaxine (Effexor®)

- 5-HT/NE/DA Reuptake Inhibitor
  - 5-HT > NE > DA (at higher doses)
- Sedating at lower doses; activating at higher doses (increased blood pressure > 300 mg/d)
- Withdrawal reactions (severe)
- Few drug interactions
- Common Side Effects
  - headache, dizziness, insomnia, nervousness, nausea, constipation, sweating, palpitations, GI upset, tremor, sexual dysfunction
Venlafaxine (Effexor®)

- Minimal effect on cytochrome P450 isoenzymes
  - Substrate: CYP2C8/9, 2C19, 2D6, 3A/4
  - Inhibitor: CYP2B6, 2D6, 3A/4
Serotonin Drug Interactions

- **Increase serotonin**
  - clomipramine
  - SRIs
    - citalopram
    - duloxetine
    - escitalopram
    - fluoxetine
    - fluvoxamine
  - paroxetine
  - sertraline
  - venlafaxine
  - buspirone
  - MAOIs
- **Decrease serotonin (5-HT$_{2A}$ antagonist)**
  - mirtazapine
  - nefazodone
  - trazodone
  - atypical antipsychotics
    - aripiprazole
    - clozapine
    - olanzapine
    - risperidone
    - quetiapine
    - phenothiazines
    - ziprasidone
- cyproheptadine
**NE and 5-HT Reuptake Inhibitors**

- **Tricyclic Antidepressants (TCAs)**
  - Clomipramine - 5-HT > NE
  - Desipramine - NE >>> 5-HT
  - Side effects: anticholinergic, antihistamine, alpha-1 antagonists, cardiac changes, lowers seizure threshold, toxicity with overdoses

- Use: anxiety disorders, depression, migraine prophylaxis, pain syndromes, insomnia, enuresis (imipramine)
## Tricyclic Antidepressants

- Clomipramine (Anafranil)
- Imipramine (Tofranil)
- Amitriptyline (Elavil, Endep)
- Nortriptyline (Pamelor)
- Protriptyline (Vivactil)
- Maprotiline (Ludiomil)
- Amoxapine (Asendin)
- Doxepin (Sinequan, Adapin)
- Desipramine (Norpramin, Pertofran)
- Trimipramine (Surmontil)
Inhibits Metabolism of 5-HT, DA and NE

- Monoamine Oxidase Inhibitors (MAOIs)
  - isocarboxazid (Marplan®)
  - phenelzine (Nardil®)
  - tranylcypromine (Parnate®)
- Irreversible and nonselective
  - drug-food interactions (tyramine)
- Use: anxiety disorders, atypical depression
Monoamine Oxidase Inhibitors (MAOIs)

- **MAO A**
  - Irreversible (suicide inhibitors)
    - Tyramine (releases NE and sympathomimetic amines)
  - Reversible (RIMAs) – safer
    - Moclobemide (Aurorix)
    - Brofaramine
    - Befloratone

- **MAO B**
  - Inhibitors: used for Parkinson’s disease
    - Selegiline (Eldepryl)
  - Don’t require any special diet
  - Not effective antidepressants
# NE and DA Reuptake Inhibitors

## Clinical Uses
- Nicotine cessation
- ADHD/ADD
- Seasonal affective disorder
- Chronic pain syndrome/fibromyalgia
- Parkinson’s disease (depression)
- Bipolar disorder (depression)
- Appetite suppression/weight reduction
- Sexual dysfunction/decreased libido
- Low energy/fatigue (chronic fatigue)
Bupropion (Wellbutrin®, Zyban®)

- NE > DA Reuptake Inhibitor
- Active metabolite
- Clinical Uses
  - Major depression, ADHD, smoking cessation, chronic pain, bipolar depression
- Common Side Effects
  - Nausea, agitation, insomnia, tremor, tachycardia, headache, dizziness, constipation, blurred vision, rash
  - > 450 mg/d - increased seizure risk
- Weight Neutral
Bupropion (Wellbutrin®, Zyban®)

- Moderate effect on cytochrome P450 isoenzymes
  - Substrate: CYP1A2, 2A6, 2B6, 2C8/9, 2D6, 2E1, 3A/4
  - Inhibitor: CYP2D6
Atomoxetine (Strattera®)

- NE Reuptake Inhibitor
- Clinical Uses
  - ADHD, depression, chronic pain syndromes
- Common Side Effects
  - Increased heart rate and blood pressure, appetite suppression, weight loss, headache, dizziness, GI symptoms, insomnia, fatigue, dry mouth, nervousness, nightmares
- Drug Interactions
  - Substrate: CYP2C19 and 2D6
Serotonin Antagonists

- $5\text{-HT}_2\text{A}$ antagonists may worsen depression, anxiety, and OCD
- $5\text{-HT}_2\text{C}$ antagonist – increases appetite and weight gain (olanzapine, mirtazapine)
  - Obesity
  - Diabetes (Type II)
  - Hyperlipidemia
  - Hypertension
## Serotonin Antagonists

### 5-HT<sub>2A</sub> antagonists
- Cyproheptadine (Periactan®)
- Aripiprazole (Abilify®)
- Clozapine (Clozaril®)
- Quetiapine (Seroquel®)
- Risperidone (Risperdal®)
- Trazodone (Desyrel®)
- Nefazodone (Serzone®)

### 5-HT<sub>2A-2C</sub> antagonists
- Olanzapine (Zyprexa®) + antihistamine
- Ziprasidone (Geodon®)

### 5-HT<sub>2A-2C-3</sub> antagonist
- Mirtazapine (Remeron®) + antihistamine
Nefazodone (Serzone®)

- Serotonin (5-HT$_{2A}$) Antagonists
  - chemically related to trazodone
  - inhibits 5-HT/NE reuptake; 5-HT$_{2A}$ receptor antagonist; alpha$_1$ adrenergic antagonist

- Common Side Effects
  - GI upset, nausea, dry mouth, constipation, dizziness, headache, drowsiness, agitation, weakness, visual trails, liver failure (rare)
  - Minimal effect on sleep stages and sexual functioning

- Drug Interactions
  - CYP 3A4 inhibitor (potent)
Nefazodone (Serzone®)

- Severe effect on cytochrome P450 isoenzymes
  - Substrate: CYP2D6, 3A/4
  - Inhibitor: CYP1A2, 2B6, 2D6, 3A/4
Trazodone (Desyrel®)

- Sedating antidepressant
  - 5-HT$_{2A}$ antagonist; 5-HT reuptake inhibitor; alpha$_{1-2}$ adrenergic antagonist, histamine$_1$ antagonist; mCPP (metabolite) – potent 5-HT agonist; low anticholinergic effects
- Minimal effect of sleep stages and sexual functioning
- May reverse 5-HT effects of SRIs
- Common Side Effects
  - Dizziness, headache, sedation, nausea, hypotension, confusion, fatigue, nasal congestion, edema, blurred vision, myalgia
Trazodone (Desyrel®)

- Minimal effect on cytochrome P450 isoenzymes
  - Substrate: CYP2D6, 3A/4
  - Inhibitor: CYP2D6
Mirtazapine (Remeron®)

- 5-HT$_{2A/2C/3}$ receptor antagonist; alpha$_{1-2}$ adrenergic receptor antagonist; muscarinic antagonist, histamine$_{1}$ antagonist
- Minimal effect on sexual functioning
- Common Side Effects
  - Sedation, dizziness, dry mouth, constipation, increased appetite, weight gain, increased triglycerides, peripheral edema, edema, hypertension, tremor, weakness, myalgia, abnormal dreams, agranulocytosis (rare)
Mirtazapine (Remeron®)

- Minimal effect on cytochrome P450 isoenzymes
  - Substrate: CYP1A2, 2C8/9, 2D6, 3A/4
  - Inhibitor: CYP1A2, 3A/4
Drug-Drug Interactions

- CYP 1A2, 2C9/19
  - fluvoxamine
  - fluoxetine (high dose)
- CYP 2B6
  - fluoxetine
  - fluvoxamine
  - faroxetine
  - sertraline
- CYP 2C19
  - fluvoxamine
  - sertraline
- CYP 2D6
  - bupropion
  - duloxetine
  - fluoxetine
  - paroxetine
- CYP 3A3/4
  - fluvoxamine
  - nefazodone
  - norfluoxetine
Drug Interactions

- CYP 1A2 Substrates
  - Acetaminophen
  - Aminophylline
  - TCAs
  - Caffeine
  - Duloxetine
  - Phenothiazines
  - Clozapine
  - Diazepam
  - Estradiol
  - Haloperidol
  - Methadone
  - Metoclopramide
  - Mirtazapine
  - Olanzapine
  - Phenacetine
  - Propranolol
  - Tamoxifen
  - Theophylline
  - Verapamil
  - Warfarin
Drug Interactions

- **CYP 2D6 Substrates**
  - TCAs
  - Amphetamines
  - Antipsychotics
  - Codeine, hydrocodone, oxycodone, meperidine, methadone, morphine, pentazocine
  - Metoclopramide
  - ACE inhibitors
  - Beta-blockers
  - Tramadol

- **CYP 3A4 Substrates**
  - TCAs
  - Antipsychotics
  - Benzodiazepines
  - Glyburide
  - Steroids, hormones
  - Statins
  - Quinidine, quinine
  - Calcium channel blockers
  - Theophylline, caffeine
  - Antibiotics
  - Anticancer agents
  - Warfarin
Selection of Antidepressants Based on Pharmacology, Adverse Effects, Drug Interactions and Special Populations
Mixed Anxiety-Depression

1st choice: SRIs
- Escitalopram (Lexapro®) and citalopram (Celexa®) - less drug interactions
- Duloxetine (Cymbalta®) – 5-HT/NE RI
- Sertraline (Zoloft®) – 5-HT/DA RI

2nd choice: venlafaxine (Effexor®)
- Monitor for blood pressure > 225 mg/d

3rd choice: nortriptyline (Pamelor®)
- Monitor for ECG changes and hypotension
Depression with Anergy, Fatigue, Chronic Pain

- Atomoxetine (Strattera®)
- Bupropion (Wellbutrin®)
- Despiramine (Norpramin®)
- Duloxetine (Cymbalta®)
- Venlafaxine (Effexor®)
- CNS Stimulants
Delusional Depression

- Postpartum
  - SRIs (citalopram or escitalopram)
    - Most studies with sertraline
    - Transdermal estradiol
- Antidepressant + Antipsychotic
- Atypical antipsychotic
- ECT
Bipolar Depression

- Bupropion (Wellbutrin®)
- SRIs
  - Citalopram, escitalopram and sertraline – fewer drug interactions and withdrawal reactions
  - Drug interactions with duloxetine, fluoxetine, fluvoxamine, and paroxetine
- Lithium
- Lamotrigine (Lamictal®)
- Monitor for perimenopausal recurrent depression (Bipolar Type II) that may respond to transdermal estradiol replacement
Depression in Women

- **PMS/PMDD**
  - SRIs
    - Citalopram, escitalopram, and sertraline have fewer drug interactions and withdrawal reactions; can be given luteal phase only
    - venlafaxine
    - nortriptyline

- **Postpartum**
  - SRIs
  - venlafaxine
  - TCAs

- **Perimenopausal (late-30’s to 50’s)**
  - estradiol (transdermal)
    - + progesterone
    - + testosterone
  - SRIs
    - Citalopram, escitalopram or sertraline
  - venlafaxine
Geriatric Depression

- Preferred Agents
  - SRIs
    - avoid in Parkinson’s and chronic pain
    - Citalopram, escitalopram and sertraline have fewer drug interactions
  - Bupropion
    - avoid in epilepsy
    - good for nicotine cessation and Parkinsons
  - TCAs (nortriptyline, desipramine)

- Increased Side Effects
  - MAOIs
  - Tertiary TCAs
  - Nefazodone
  - Trazodone
  - Mirtazapine
  - Venlafaxine
Depression with Comorbid Diabetes or Obesity

- **Weight Neutral**
  - SRIs (except paroxetine)
    - Citalopram, escitalopram, and sertraline have fewer drug interactions
    - Fluoxetine may cause weight loss but has drug interactions
  - Bupropion – may cause weight loss
  - Venlafaxine

- **Weight Gain**
  - TCAs
  - MAOIs
  - Nefazodone
  - Mirtazapine
  - Paroxetine


**Depression with Cardiovascular Disorders**

- Congestive heart failure or ischemic heart disease, conduction disturbance, tachycardia, or orthostatic hypotension
  - SRIs (citalopram, escitalopram or sertraline) > > > fluoxetine, fluvoxamine, and paroxetine (drug interactions)
    - Bupropion
    - TCAs (nortriptyline, desipramine)
Depression with Cardiovascular Disorders

- High blood pressure
  - SRIs – citalopram, escitalopram or sertraline
  - TCAs, nefazodone, trazodone
    - Monitor for orthostatic hypotension
  - Must monitor BP with venlafaxine > 225 mg/d

- Orthostatic hypotension
  - SRIs – citalopram, escitalopram or sertraline
  - Bupropion
  - Avoid: TCAs, mirtazapine, nefazodone, trazodone
**Depression with Neurological Disorders**

- **Seizure disorder**
  - SRIs – citalopram, escitalopram or sertraline
  - Venlafaxine, mirtazapine, nefazodone
  - Avoid: bupropion, clomipramine, maprotiline

- **Migraine**
  - TCAs, nefazodone, trazodone

- **Stroke**
  - SRIs – citalopram, escitalopram or sertraline (caution with high doses due to vasoconstriction effects)
Depression with Neurological Disorders

- Parkinson’s disease
  - Bupropion, TCAs
  - Avoid SRIs (down-regulation of DA), and amoxapine (dopamine antagonist)
- Chronic pain
  - Bupropion, TCAs (amitriptyline, doxepin, nortriptyline), venlafaxine
  - SRIs - citalopram, escitalopram or sertraline (duloxetine, paroxetine and fluoxetine inhibit metabolism of codeine to morphine)
<table>
<thead>
<tr>
<th>Depression with GI Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peptic ulcer disease</strong></td>
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<tr>
<td>- TCAs (amitriptyline, doxepin, imipramine)</td>
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<tr>
<td><strong>Chronic diarrhea</strong></td>
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<tr>
<td>- TCAs (amitriptyline, doxepin, imipramine)</td>
</tr>
<tr>
<td>- Avoid: sertraline</td>
</tr>
<tr>
<td><strong>Chronic constipation</strong></td>
</tr>
<tr>
<td>- SRIs &gt; &gt; venlafaxine, bupropion, nefazodone, trazodone</td>
</tr>
<tr>
<td>- Avoid: TCAs, mirtazapine</td>
</tr>
</tbody>
</table>
Depression with Sexual Dysfunction

- Erectile failure
  - Bupropion, nefazodone, trazodone, mirtazapine
  - Avoid: SRIs, venlafaxine, TCAs, MAOIs

- Priapism: nefazodone, trazodone

- Anorgasmia
  - Bupropion, desipramine, nefazodone, trazodone
  - Avoid: SRIs, venlafaxine, TCAs, MAOIs
Depression with Ophthalmological Problems

- Angle-closure glaucoma
  - SRIs – citalopram, escitalopram or sertraline
  - Bupropion, nefazodone, trazodone, venlafaxine
  - Avoid: TCAs, mirtazapine
## Use of Serotonin Antidepressants

- Generalized Anxiety Disorder (GAD)
- Panic Disorder (PD)
- Posttraumatic Stress Disorder (PTSD)
- Obsessive-Compulsive Disorder (OCD)
- Agoraphobia
- Social Phobia
- Specific Phobia
Use of Serotonin Antidepressants

- Bulimia, binge-eating, obesity
  - SRIs – citalopram, escitalopram, sertraline > fluoxetine
  - Venlafaxine
  - Avoid: mirtazapine, paroxetine, TCAs, MAOIs, bupropion (binge/purge behavior)
Use of Serotonin Antidepressants

- Impulse Control Disorders
  - Alcohol dependence
  - Trichotillomania
  - Paraphilias/hypersexual
  - Tourette’s disorder
- Pathological gambling
- Compulsive shopping
Use of NE/DA Antidepressants

- ADHD/ADD
  - bupropion, venlafaxine, desipramine
  - atomoxetine
- Nicotine Dependence
  - bupropion
- Cocaine Dependence
  - bupropion, desipramine
Augmentation or Refractory Depression
**Serotonin Augmenting Agents**

- **5-HT Reuptake Inhibitors**
  - SRIs (citalopram and escitalopram the most selective)
- **5-HT$_{1A}$ Agonist**
  - Buspirone (BuSpar®)
- **5-HT Metabolite**
  - melatonin
- **5-HT Precursor**
  - L-tryptophan
  - 5-hydroxytryptophan
- **Dietary Protein**
  - L-tryptophan containing foods
Norepinephrine Augmenting Agents

- NE Reuptake Inhibitors
  - Desipramine (Norpramin®)
  - Bupropion (Wellbutrin®, Zyban®)
  - Sibutramine (Meridia®) – NE >>>5-HT & DA
  - Atomoxetine (Strattera®)

- Alpha-2 Adrenergic Antagonist
  - Yohimbine (Yocon®, Yohimex®)

- NE Precursor
  - L-tyrosine
# Dopamine Augmenting Agents

- **DA Precursor**
  - levodopa
- **DA Agonist**
  - bromocriptine
  - pergolide
  - pramipexole
    - ropinirole
- **DA Releasing Agent**
  - amphetamines
- **DA Augmenting**
  - nicotine
- **MAOI-Type B**
  - selegiline
- **COMT Inhibitor**
  - entacapone
  - tolcapone – liver toxicity
## Treatment-Refractory Depression

- Lithium augmentation of antidepressants
- Thyroid (T3) augmentation of antidepressants
- Stimulant augmentation of antidepressants
- TCA + MAOI
- Estrogen (estradiol transdermal)
- SRI + NRI (e.g., atomoxetine, bupropion or desipramine)
Treatment-Refractory Depression

- Electroconvulsive therapy
- Repetitive transcranial magnetic stimulation (rTMS)
- Vagus nerve stimulation
Mood Stabilizers
Clinical Uses of Anticonvulsants

- Mood disorders
  - Bipolar mania (rapid cycling, mixed)
  - Recurrent major depression
- Anxiety disorders
  - Panic disorder
  - Social phobia
  - Posttraumatic stress disorder
- Psychotic disorders
  - Schizoaffective disorder
  - Recurrent auditory hallucinations
Clinical Uses of Anticonvulsants

- Aggression
  - Intermittent explosive disorder
- Impulse-control disorder
- Sleep disorders
  - Nocturnal myoclonus
    - Restless legs syndrome
- Tremors
- Alcohol withdrawal
GABA Augmenting Agents

- **Anticonvulsants**
  - Clonazepam (Klonopin®) - $\text{GABA}_A$
  - Diazepam (Valium®) - $\text{GABA}_A$
  - Gabapentin (Neurontin®) – GABA analogue
  - Lorazepam (Ativan®) - $\text{GABA}_A$
  - Tiagabine (Gabatril®) – blocks GABA uptake
  - Topiramate (Topamax®) – blocks glutamate
  - Valproate (Depakote®) – increases GABA activity
Inhibits Sodium Channels

- Carbamazepine (Carbitrol®, Tegretol®)
- Gabapentin (Neurontin®)
- Lamotrigine (Lamictal®)
- Oxcarbazepine (Trileptal®)
- Topiramate (Topamax®)
Inhibits Calcium Channels

- Gabapentin (Neurontin®)
- Nifedipine (Adalat®, Procardia®)
- Verapamil (Calan®, Isoptin®, Verelan®)
Other Mechanisms

- Increases potassium conductance and modulates activity of high-voltage activated calcium channels
  - Oxcarbazepine (Trileptal®)
- Inhibits release of glutamate (excitatory amino acid)
  - Lamotrigine (Lamictal®)
- Blocks glutamate activity
  - Topiramate (Topamax®)
Mood Stabilizers

- Common Side Effects
  - Weight gain
  - Upset stomach, nausea, vomiting, diarrhea
  - Blurred vision
  - Tremor
  - Sedation, drowsiness
  - Dizziness, clumsiness, unsteadiness
  - Confusion
Anxiolytics and Hypnotics
GABA Augmenting Agents

- Benzodiazepines Anxiolytics
  - Alprazolam (Xanax®)
  - Clonazepam (Klonopin®)
  - Diazepam (Valium®)
  - Lorazepam (Ativan®)
  - Oxazepam (Serax®)

- Benzodiazepine Hypnotics
  - Flurazepam (Dalmane®)
  - Temazepam (Restori®)
  - Triazolam (Halcion®)
GABA Augmenting Agents

- Non-Benzodiazepine (omega-1) Hypnotics
  - Zaleplon (Sonata®)
  - Zolpidem (Ambien®)
<table>
<thead>
<tr>
<th>Other Antianxiety Agents</th>
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<tbody>
<tr>
<td><strong>Buspirone</strong> (BuSpar®) – 5-HT$_{1A}$ partial agonist</td>
</tr>
<tr>
<td><strong>Propranolol</strong> (Inderal®) – beta-blockers</td>
</tr>
<tr>
<td><strong>Clonidine</strong> (Catapres®) and <strong>guanfacine</strong> (Tenex®) – alpha-2 agonists</td>
</tr>
<tr>
<td><strong>Diphenhydramine</strong> (Benadryl®) and <strong>hydroxyzine</strong> (Vistaril®, Atarax®) – antihistamines</td>
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<tr>
<td><strong>Antidepressants</strong></td>
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<tr>
<td>- TCAs and trazodone</td>
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</tbody>
</table>
Benzodiazepines

- Clinical Uses
  - Anxiety disorders (short term)
  - Insomnia (short term)
  - Acute mania
  - Drug-induced akathisia
  - Restless leg syndrome
  - Muscle relaxant
  - Anticonvulsant
  - Alcohol detoxification
Benzodiazepines

- Common Side Effects
  - Sedation, drowsiness, slurred speech
  - Decreased cognitive performance
  - Disinhibition, anger outbursts, irritability
  - Respiratory depression
- Dependence
- Withdrawal: tremors, severe anxiety, agitation, psychosis, seizures, nightmares
References

- Fuller MA, Sajatovic M. *Drug Information for Mental Health 2004 and Psychotropic Drug Information Handbook 2004*. APhA/Lexi-Comp
- *AHFS Drug Information 2004*