Abstract

This symposium will provide a thorough introduction as to what psychologists who are treating clients/patients need to know regarding medication and medication management. We will focus on teaching practicing psychologists to educate their patients as to possible side effects of their medications and also to communicate with their physicians. We will also review the latest developments in the field of psychopharmacology. This will include a discussion of the major categories of psychotropic medications, mechanisms of drug action, approved and off label medications across the lifespan, including therapeutic dosages and range of possible side effects. This symposium would be suitable for psychologists at every level of knowledge of psychopharmacology, such as graduate students, early career psychologists, and seasoned psychologists.

Learning Objectives

- The role of successful pharmacotherapies in the derivation of neurobiological hypotheses and models of psychopathology.
- Major categories of psychotropic and psychotherapeutic medications, including structural and/or chemical, as well as functional classifications within each category, including general and trade names of drugs in each classification.
- Primary and secondary actions in each major category and classification for each drug class and respective therapeutic effects as evaluated e.g., SSRI's exert their antidepressant effects by selectively inhibiting the uptake of serotonin.
- Approved and non-approved (off-label) indications for medications in each category and classification.
- Range and degree of side effects associated with medications in each category and classification, including any serious physical as well as psychological contraindications.
- How to communicate with clients about medication and medication management, and how best to answer medicated related questions.
- How to speak to prescribing physicians concerning medication management of mutual patients.
Introduction

- **Pharmacology**: the science of how drugs affect the body.
- **Psychopharmacology**: a subdivision of pharmacology; the study of how drugs affect specifically the brain (i.e., nervous system) and behavior.

Basic Psychopharmacology Principles

- Drugs are not curative, provide symptomatic relief
- Selection of agent is based on potential for toxicity and tolerability, not efficacy
- Treat the symptoms, not the diagnosis
- Ensure adequate length of trial (6-8 weeks)
- Combine drug + non-drug therapy
- Treat acute, continuation, and maintenance phases
- Individualize treatment approach

Drug Movement

- **Absorption**: of the aspirin into the body from the swallowed tablet.
- **Distribution**: of the aspirin throughout the body, including into a fetus (should a female patient be pregnant at the time the drug is taken)
- **Metabolism (detoxification/breakdown)**: of the drug as the aspirin that has exerted its analgesic effect is broken down into metabolites (by-products or waste products) that no longer exert any effect.
- **Elimination**: of the metabolic waste products, usually in the urine.
Drug Absorption

- Drug absorption ranges (passage of the external world into the bloodstream):
  - Ineffective – where not enough drug is present to produce either sedative or antianxiety effects.
  - Therapeutic range – where we want to be!
  - Toxic range – where sedation becomes excessive.

Movement

- Knowledge of movement and time offers significant insight into the action of a drug – it helps to distinguish a particular drug from other related drugs.
  - e.g., sedative and antianxiety effects:
    - Lorazepam (Ativan, Temesta) – persists for 24 hours in the body.
    - Triazolam (Halcion, Novodorm, Songar) – persists for only about 6 to 8 hours in the body.

Action in the Bloodstream

- Every minute in an average-sized adult, the heart pumps a volume of blood – roughly equal to the amount of blood in the circulatory system.
- Entire blood circulates in the body – every minute.
- Psychoactive drugs become quickly distributed throughout the bloodstream – diluted by blood, amount of water in the body.
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- When inhaled:
  - Absorbed into lungs and carried to pulmonary veins directly to left side of heart and then directly to brain
  - Cigarettes/tobacco/marijuana are felt within 1 to 2 breaths

- When injected:
  - Bypasses intestinal absorption, rapidly enters veins, and is carried to right side of the heart and then distributed throughout the body
  - Sodium pentothal — injected general anesthetic; LOC within 30 seconds

- When a drug is taken orally:
  - It passes through cell lining of the gastrointestinal (GI) tract, then through the liver, then enters central circulation — heart and through bloodstream.

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**Drug Interactions**

- Effects of one drug can be modified by the concurrent administration of another drug
  - Some interactions are good, some are not
  - Addition mechanisms, where the effects of one drug potentiate the side effects of a second drug
    - Benzodiazepine tranquilizer/marijuana
      - Increases sedation/loss of coordination

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**Drug Toxicity**

- Drugs can produce wanted or unwanted effects
  - Expected: dry mouth from some antidepressants
  - Unexpected: allergic reactions
  - Some can be short-term and temporary inconvenience and others can lead to injury, damage, permanent disability, or even death
  - Tolerance
  - One person’s side effect may be another person’s therapeutic effect
  - Morphine/constipation
To produce an effect a drug must bind to and interact with specialized receptors, usually located on cell membranes. In psychoactive drugs, most of these receptors are located on the surface of the neurons in the brain. When a psychoactive drug binds to a receptor, it thereby alters (activates or blocks) the normal functions of that receptor, the neuronal response to the drug is one of two types:

- An immediate response to the presence of drug on a receptor
- When drug is given over a longer period of time, long-term changes in the properties of the receptors resulting in long-term changes in neuronal, brain, and behavioral functioning.
Receptors

- Hundreds of types of receptors
  - E.g., only serotonin binds to a specific protein receptor (serotonin receptor), but although the receptor is specific for serotonin, serotonin (as a NT) also binds to other, structurally different receptors.
  - 15 serotonin receptors have been described
    - Allows diversity in developing closely related drugs with a slightly different degree of affinity (i.e., strength of attachment).
      - A drug may attach to only one receptor.

Monoamines

- Effects tend to be diffuse
  - Catecholamines – synthesized from tyrosine (use of autoreceptors) – negative feedback mechanism; when stimulated they reduce the synthesis and release of transmitter
    - Dopamine (CNS)
    - Norepinephrine (CNS)
  - Epinephrine (PNS); adrenaline
  - Indolamines – synthesized from tryptophan
    - Serotonin

Depression and Anxiety
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**Depression**
- Fourth most disabling disease worldwide
- Accounts for 5.3% of the worldwide burden of disease in terms of disability-adjusted life years.
- 25% of men experience depression during lifetime
- Only about 25% are adequately treated.
- Lifetime prevalence of depression is 17%
- Average age of onset is late 20’s
- Only 40% of depressed patients receive treatment
- Only 30% of those treated receive an appropriate dose
- Childhood Risk: Males = Females
- Adolescent Risk: Females 2 X > Males

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**Long-Term Course of Depression**
- 50% of people with major depression will have one or more recurrences
- 90% of people with major depression who have had 2 previous episodes will have a 3rd recurrence
- Relapse rate is 65% within the first year if untreated

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**Similarities: Children, Adolescents, Adults**
- Sad, irritable mood
- Loss of interest in enjoyable activities
- Change in appetite or weight
- Difficulty sleeping or oversleeping
- Loss of energy
- Psychomotor agitation or retardation
- Feelings of worthlessness or inappropriate guilt
- Difficulty concentrating
- Recurrent thoughts of suicide or death

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Depression Symptoms: Children & Adolescents

- Social Withdrawal
- Frequent Somatic Complaints
- Psychomotor Agitation
- Defiance/Disturbances of Conduct (shouting, irritability)
- Talk of running away from home
- Alcohol or substance abuse
- Phobias and Separation Anxiety
- Being bored
- Not playing with friends
- Fear of death
- Rejection sensitivity
- Reckless behavior
- Poor relationship skills

Less pronounced:

- Hypersomnia
- Weight loss
- Delusions

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Suicide Risk

- Careful monitoring has always been essential
- Black box warning is not consistent with research and clinical experience
- May lead to increased underutilization and drug discontinuation
- 3rd leading cause of death in 10-24 year olds:
  - 10% of all adolescents, depressed or not, contemplate suicide
  - 40% of children with untreated depression contemplate suicide
  - 2.5% die by suicide

**Conclusion: Early diagnosis and intervention important**

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Pharmacological Intervention?

- Identification of Symptoms of Depression
- Factors to Consider
  - Severity and dysfunction of the syndrome
  - Potential benefits of drug therapy
  - Consequence of not initiating treatment
  - Willingness of patient to participate
- Don’t place pharmaceutical interventions in a vacuum

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Selection of an Antidepressant

- All are efficacious
- Patient response in the past
- Side effect profile
- Potential drug interactions
- Cost
- Concomitant conditions:
  - Pain, anxiety, OCD

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Symptom Remission

- Decreased Anxiety
- Improvement in Sleep
- Improvement in Appetite
- Increased Activity, Sex Drive, Self-care, and Memory
- Thinking and Movement Normalize
- Sleeping and Eating Patterns Normalize
- Relief of Depressed Mood
- Less Hopeless/Helpless
- Thoughts of Suicide Subside

1st Week
2-3 Weeks
4-6 Weeks
8-12 Weeks

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SSRI's
- Fluoxetine
- Sertraline
- Paroxetine
- Fluvoxamine
- Citalopram
- Escitalopram

SHTNE R
- Amoxapine
- Depoxetine
- Sramine
- Hertalatine
- Norapine
- Venlafaxine
- Quetiapine

MAOI's
- Phenoxyline
- Tranylcromine
- Isocarboxazid
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Antidepressant: Onset of Action

- Clinical effect is usually not manifest for 1-3 weeks.
- Clinical rule is to treat the patient for a minimum of 6 weeks at an adequate dosage before changing.
- Synaptic effects occur immediately (hrs).
- Adverse effects have the same time course as synaptic effects.

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First-Generation Antidepressants

- Tricyclic: Tricyclic antidepressants (imipramine) block the synaptic transporter protein receptors for the neurotransmitters norepinephrine and serotonin.
- Tricyclic: Refers to chemical structure in contrast to newer antidepressants that refer to their mechanism of action.
- Monoamine Oxide Inhibitors (MAOIs): Bound to and blocked the enzyme monoamine oxidase, this enzyme normally metabolizes and regulates the amount of biogenic amine transmitters in the presynaptic nerve terminal; the levels of neurotransmitter increase and more neurotransmitter is available for release when stimulated by an action potential reaching the nerve terminal.
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**Tricyclics Summary**

**Advantages**
- Proven to be as effective as other classes
- Inexpensive
- Useful for neuropathic and chronic pain

**Disadvantages**
- Poorly tolerated
- Require dosage titration
- Use with caution in the elderly or medically ill
- Highly fatal in overdose

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### Slide 32

**Tricyclics**

- Effectively relieves symptoms of depression and also possess significant anxiolytic and analgesic actions.
- SSRIs today are equally effective but less toxic
- Imipramine (Tofranil) is prototype TCA
- Amtriptyline (Elavil), Nortriptyline (Pamelor, Aventil)

**Mechanism of Action:**
- Block preneuronal norepinephrine reuptake transporter
- Block preneuronal serotonin reuptake transporter
- Block postsynaptic histamine receptors
- Block postsynaptic acetylcholine receptors
- Block postsynaptic norepinephrine receptors

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### Slide 33

**Tricyclics**

- Search for new antidepressants – equally effective, better tolerated, less toxic
- Second generation, or atypical, antidepressants
  - Late 1980s and 1990s – selective serotonin reuptake inhibitors (SSRIs)
- Searching for still:
  - Superior efficacy (especially in treatment of therapy-resistant depression)
  - Faster onset of action
  - Improved side effect profile
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- Blockade of histamine – result in drowsiness, sedation (similar to Benadryl)
- Blockade of acetylcholine receptors – result in confusion, memory and cognitive impairments, dry mouth, blurred vision, increased heart rate, urinary retention
- Blockade of norepinephrine receptors – affects blood pressure (“dizzy” when stand up)
- Nortriptyline & despiramine – causes less sedation and fewer anticholinergic side effects

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Pharmacokinetics of TCA

- Well absorbed – orally
- Relatively long half-lives
- Take at bedtime can reduce impact of unwanted side effects (i.e., sedation)
- Clinical effect lasting up to 4 days, even longer in elderly
- Crosses the placental barrier – to date to developmental problems noted

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Pharmacological Effects of TCA

- All TCAs attach to and inhibit the presynaptic transporter proteins for both norepinephrine and serotonin, which is thought to account for clinical limitations.
- Slow onset of action – though as fast as other antidepressants
- Do not produce euphoria – no recreational or behavior-reinforcing value
- Discontinuation not a concern
- Elevate mood, increase physical activity, improve appetite and sleep patterns, and reduce morbid preoccupation
- Useful in treating acute episodes, as well as preventing relapses. Effective analgesics in variety of clinical pain syndromes
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TCAs & Other Cyclic Antidepressants

- Tricyclic
  - Secondary (2nd)
  - Desipramine (Norpramin) 25–300mg/day
  - Treatment of depression (18 years and up)
  - Nortriptyline (Pamelor) 30–100mg/day
  - Treatment of depression (18 years and up)
  - Clomipramine (Anafranil) 25–200mg/day
  - Treatment of OCD (10 years and up)
  - Amitriptylline (Elavil) 50–300mg/day
  - Treatment of depression (9 years and up)
  - Imipramine (Tofranil) 30–300mg/day
  - Treatment of depression (6 years and up)
  - Treatment of Enuresis (6 years and up)
  - Treatment of ADHD (no official recommendations for age and dose)
  - Doxepin (Sinequan) 25–300mg/day
- Other Cyclic
  - Amoxapine (Asendin) 50–600mg/day
  - Maprotiline (Ludiomil) 50–225mg/day

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TCA - Adverse Effects

- Anticholinergic effects
  - Dry mouth, constipation, urinary retention, blurred vision, dizziness, confusion
- Sedation
- Orthostatic hypotension
- Cardiac effects (arrhythmias, ECG changes)
  - Can be life threatening
  - Give no more than one week at a time for suicidal patient
- Sexual dysfunction
- Tolerance may develop to many side effects, but some will persist
- Effects on memory and cognitive function are significant

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MAO-I Summary

Advantages
- Possibly effective in treatment resistant and atypical depression
- Minimal effect on seizure threshold

Disadvantages
- Dietary restrictions
- Significant drug interactions
- Risk of hypertensive crisis
- Frequent dosing (TID)
- Need for slow dose titration
- Last line agents
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MAOs

- MAO-A — metabolizes dopamine, noradrenaline, serotonin (including tyramine), and other substances
- MAO-B — metabolizes dopamine, tyramine and other substances

- MAO-A — antidepressant actions

- MAO-B — prevention of neurodegenerative processes

- Responsible for anti-depressant activity — blockade of metabolism causes transmitter molecules to build up in the terminal, which means more transmitter than usual is released into the synaptic cleft when the neuron fires an action potential.

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- Form a chemical bond with MAO enzyme — a bond that cannot be broken
- Potentially fatal interactions when taken with certain foods and medications:
  - Adrenalinelike drugs: nasal sprays, antiasthma medications, and cold medicines
  - Tyramine: cheeses, wines, beers, liver, and some beans
- Must follow restrictions for 10 to 14 days until new enzyme is produced
- Increases monoamine levels (NE, 5-HT, DA)
- Rarely drug of first choice
- Usually indicated for patients with atypical depression
- Patients often have mixed anxiety and depression and phobic or hypochondrial features
- Used in some patients unresponsive to other therapy

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MAOIs: Foods with Tyramine & Vasopressors

- Canned (cherry, apricot, plum, pears), fresh (grapes, figs, dates), fermented (soy sauce, sauerkraut)
- Dried: apples, dates, prunes, raisins, apricots, figs, dates, sauerkraut
- Liver (especially dark, thick)
- Bread (especially dark, thick)
- Red wine, red grape juice, red fruit juice
- Red cabbage, red wine, sauerkraut
- Tea (especially black, pu’erh)
- Foodborne: miso, tempeh
- Caffeine
- Chocolate (phenylethylamine)
- Ginseng
MAOIs: Concomitant SSRI Use

- Do not use an SSRI in combination with MAOIs or within 14 days of an MAOI
- Allow at least 2 weeks after stopping SSRI before use of MAOI
- Reports of fatal reactions including hyperthermia, rigidity, ANS instability and mental status changes which include extreme agitation, delirium and coma

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MAO-I

- Inhibits Monoamine Oxidase (enzyme responsible for neurotransmitter degradation)
  - Phenelzine (Nardil)
    - 60 – 90mg/day
  - Tranylcypromine (Parnate)
    - 30 – 60mg/day
  - Isocarboxazid (Marplan)
    - 40 – 60mg/day

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MAO-I: Adverse Effects

- Orthostatic hypotension
- Anticholinergic effects
- Sedation or insomnia
- Weight gain
- Sexual dysfunction
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**SSRI Summary**

**Advantages**
- Well tolerated
- Once Daily Dosing
- Safe in the elderly and medically ill
- Safe in overdose
- Little weight gain
- Generically available
- Gold standard antidepressant

**Disadvantages**
- High rates of sexual dysfunction
- Lack of sedative effects

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**SSRIs**

- All potent blockers of the presynaptic transporter for serotonin reuptake – make more serotonin available at the synaptic cleft, which activates all of the many postsynaptic receptors for serotonin
- 5-HT1 - associated with antidepressant and anxiolytic effects
- 5-HT2 and 5-HT3 – associated with adverse effects
  - 5-HT2 – insomnia, anxiety, agitation, sexual dysfunction, production of serotonin syndrome
  - 5-HT3 – nausea
- Few anticholinergic and antihistaminic side effects

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**Dosing**

**Starting dose**
**Time to onset**
**Titration up**
**Titration down and SSRI withdrawal**
**Switching drugs**
**Special dosing strategies**
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- Citalopram (Celexa)
  - 20mg to 60mg QD (40mg)
  - Treatment of MDD (7 years and up), Treatment of GAD (7 years and up), Treatment of OCD (7 years and up), Treatment of Intermittent Explosive Disorder (7 years and up)

- Escitalopram (Lexapro)
  - 10mg to 20mg QD (10mg)
  - Treatment of MDD (7 years and up), Treatment of Social Anxiety (10 years and up), Treatment of Autism (6 years and up)

- Paroxetine (Paxil)
  - 20mg to 50mg QD (40mg)
  - Treatment of MDD (7 years and up), Treatment of Social Anxiety (8 years and up)

- Fluvoxamine (Luvox)
  - 100mg to 300mg QD (100mg/dose)
  - Treatment of OCD (8 years and up), Treatment of MDD (7 years and up), Treatment of GAD (8 years and up), Treatment of PTSD (8 years and up)

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Serotonin Syndrome

- Cluster of responses characterized by: cognitive disturbances (disorientation, confusion, hypomnesia), behavioral agitation and restlessness, autonomic nervous system dysfunctions (fever, shivering, chills, sweating, diarrhea, hypertension, tachycardia), and neuromuscular impairment (ataxia, increased reflexes, myoclonus).

- Visual hallucinations have been reported

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Serotonin Discontinuation Syndrome

- 60% of SSSRI-treated patients following abrupt cessation:
  - Disequilibria (dizziness, vertigo, ataxia)
  - Gastrointestinal symptoms (nausea, vomiting, diarrhea)
  - Flulike symptoms (fatigue, lethargy, myalgias, chills, headache)
  - Sensory disturbances (paresthesia, sensation of electric shocks in arms, legs, or head)
  - Sleep disturbances (insomnia, vivid dreams)
  - Psychological symptoms: anxiety, agitation, uneasiness, restlessness, irritability

- Weight loss can occur initially with SSSRI but rebound weight gain can occur later in therapy

- Sexual dysfunction can occur with SSSRI

- Above do not appear to be as prominent with citalopram

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**SSRI Pharmacokinetics**

<table>
<thead>
<tr>
<th></th>
<th>Half Life</th>
<th>Active Form</th>
<th>Metabolite</th>
<th>Steady State</th>
<th>CYP 450</th>
<th>Drug Interactions</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>4-6 days</td>
<td>0-14 days</td>
<td>~ 1 month</td>
<td>nilpotent</td>
<td>2D6</td>
<td>low affinity</td>
<td>Metabolism: inhibiting 2D6, activating 3A4</td>
</tr>
<tr>
<td>Sertraline</td>
<td>26 hours</td>
<td>2-5 days</td>
<td>~ 1 week</td>
<td>nilpotent</td>
<td>2D6</td>
<td>high affinity</td>
<td>Metabolism: inhibiting 2D6, activating 3A4</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>25 hours</td>
<td>none</td>
<td>~ 1 week</td>
<td>nilpotent</td>
<td>2D6</td>
<td>high affinity</td>
<td>Metabolism: ACTIVATING 3A4</td>
</tr>
<tr>
<td>Citalopram</td>
<td>21 hours</td>
<td>nilpotent</td>
<td>~ 1 week</td>
<td>nilpotent</td>
<td>2D6</td>
<td>high affinity</td>
<td>Metabolism: weak 3A4 inhibition</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>15 hours</td>
<td>nilpotent</td>
<td>~ 1 week</td>
<td>nilpotent</td>
<td>1A2, 3A4</td>
<td>high affinity</td>
<td>Metabolism: inhibiting 1A2, 3A4</td>
</tr>
</tbody>
</table>

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**Notes**

- Long T1/2, activating
- Sedating
- Much like sertraline
- Many drug interactions

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**W. Klugh Kennedy, Pharm.D., BCPP**

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**SSRI: Adverse Effects**

- GI upset (nausea, diarrhea)
- Decreased appetite initially
- Insomnia, somnolence
- Nervousness, anxiety
- Headache
- Sexual dysfunction
- Rebound serotonergic syndrome

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### Slide 54

**Bupropion Summary**

**Advantages**

- Well tolerated
- Activating
- No cardiovascular adverse effects
- No weight gain
- No sexual dysfunction
- Useful in smoking cessation ( Zyban )

**Disadvantages**

- Mild anxiety, tremor
- BID or TID dosing may be necessary for doses > 200mg
- Expensive
- Avoid in patients with seizure or eating disorders

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**Bupropion (Wellbutrin, Zyban)**

- Inhibits the reuptake of NE and DA
- Bupropion 300 – 450 mg/day typically start at 100 mg BID
- Several sustained-release formulations
- Doses > 200 mg may be given QD after initial titration period
- Treatment of MDD (18 years and up)
- Bupropion hydrochloride SR (sustained release, Zyban) – aid to smoking cessation
- Concerns with development of newer agents is the potential for reinforcing properties which can lead to abuse
- Associated with seizures (0.4% of patients on 450 mg/d)
- Seizure incidence increases 10x in doses between 450 – 600 mg/d

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**Bupropion: Precautions**

- In substance abusers, single dose of 400 mg may produce mild amphetamine-like activity
- Does not occur if doses are divided
- Substantial number of patients experience increased restlessness, agitation, anxiety and insomnia
- Usually occurs shortly after initiation of therapy
- May require sedative-hypnotic or discontinuation of therapy
- Can precipitate mania in bipolar manic depressives

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**5-HT2a Receptor Blockers**

- Mirtazapine (Remeron)
- Nefazodone (Serzone)
- Trazodone (Desyrel)
- Antidepressant actions may be associated with both blockade of 5A and 5C receptors
- Blockade of these receptors
  - Reduce anxiety
  - Alleviates depression
  - Alleviates pain
  - May also block psychotic symptoms
  - Less likely to cause sexual dysfunction seen with SSRIs
  - Mirtazapine has histaminergic blocking activity
  - Trazodone
  - Sildenafil

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Venlafaxine (Effexor)

- Inhibits the reuptake of 5-HT and NE (at higher doses)
- Treatment of MDD, GAD, Social Anxiety Disorder (18 years and up)
- Reported as mixed NE and 5-HT transport blocker
  - Low effect on NE transporter in humans
  - Can be manifest at high dosages (375 mg/d)
- Seizures reported in patients taking doses > 150 mg/d
- May produce mania or hypomania

Venlafaxine Summary

Advantages
- Well tolerated
- Few drug interactions
- XR formulation
- Relatively safe in overdose
- 1st line like SSRIs

Disadvantages
- High rate of sexual dysfunction
- Potential to increase BP with higher doses
- Substantial dose titration required

Another second line agent.

Duloxetine (Cymbalta) Summary

Advantages
- Well tolerated
- Relatively safe in overdose
- Surprisingly little effect on CV parameters
- Works on NE as well as 5-HT

Disadvantages
- New
- Concerns over additive effects with other ADs and other drugs that increase SHT or NE
- Causes some sexual dysfunction
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Problems with Current Antidepressants

- Lack of response in 30% of patients
- Adverse effects in every class
- Inappropriate use of antidepressants based on “safety” of new agents and poor understanding of pharmacology

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Adverse Effects - General

- Cardiac:
  - Orthostasis: TCA’s, MAOI’s, and trazodone
  - Heart Block: TCA’s
  - Hypertension: venlafaxine (higher dosing)
  - Widening of QRS complex: toxicity with overdose with TCA’s
- Seizures:
  - Bupropion with dosages > 450
  - TCA’s in overdose
  - Drug interactions

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Adverse Effects - General

- Weight Changes:
  - Weight gain is most problematic with TCA’s, mirtazapine, and MAOI’s
  - SSRI’s can “normalize” weight gain from disease or drugs
  - Elderly weight loss from SSRI’s
- Sedation/insomnia:
  - Can be advantage or disadvantage depending on patient presentation
  - Tolerance usually develops
  - TCA’s, venlafaxine, mirtazapine biggest offenders
- Sexual dysfunction:
  - SSRI’s are biggest offenders
  - Can occur with all drugs
  - Disease state or drugs
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### Adverse Effects

- **SSRI's**
  - Nausea
  - Diarrhea
  - Anxiety
  - Sexual dysfunction
  - Sweating
  - Tremor
  - Hyponatremia

- **TCA's**
  - Nausea
  - Dry mouth
  - Constipation
  - Hypersalivation
  - Weight gain
  - Cardiac effects
  - Urinary retention
  - Sexual dysfunction

- **SSNRI's**
  - Nausea
  - Diarrhea
  - Nervousness
  - Insomnia
  - Sexual dysfunction
  - Sweating
  - Tremor
  - Hypotension
  - Weight gain

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### Adverse Effects

- **Mirtazapine**
  - Sedation
  - Weight gain
  - Dizziness
  - Dry mouth
  - Constipation
  - Increased chol.
  - Agranulocytosis
  - Hepatic dysfunction

- **Bupropion**
  - Insomnia
  - Seizures
  - Anxiety
  - Dry mouth
  - Constipation
  - Lightheadedness
  - Headache
  - Dry mouth
  - Nausea
  - Somnolence
  - Confusion
  - Visual changes
  - Asthenia
  - Elevated liver enzymes

- **Nefazodone**
  - Insomnia
  - Confusion

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### Serotonin Syndrome

- **Gastrointestinal**
  - Abdominal cramping
  - Bloating
  - Diarrhea

- **Neurological**
  - Tremor
  - Myclonus
  - Dystonia
  - Hypertonia
  - Restlessness

- **Cardiovascular**
  - Tachycardia
  - Hypertension

- **Psychiatric**
  - Mania-like symptoms
  - Confusion

- **Other**
  - Sweating
Withdrawal Syndrome

• Abrupt cessation of antidepressant therapy
  – Especially those with shorter half-lives
• Sertraline, paroxetine, fluvoxamine, citalopram
• Characterized by dizziness, insomnia, nervousness, nausea, agitation, diarrhea
• Distinguishing from relapse
• Tapering greatly reduces occurrence
• Educate the patient!!
Long-Term Prognosis

- Untreated, high mortality and morbidity rates
- 20-25% attempt or commit suicide
- Overall functional impairment great
- Lifetime rate substance abuse is 50-60%
- Requires identification and treatment for both disorders
- Treatable disorder for majority of patients
- Balance side effects and relief of symptoms
- Ongoing relationship with clinician vital

Treatment Goals

- Relieve acute symptoms
- Prevent suicide
- Prevent / reduce recurrences
- Improve quality of life

Common Mood Stabilizers

- Lithium
- Valproate (Depakote, Depakene)
- Carbamazepine (Tegretol)
- Oxcarbazepine (Trileptal)
- Lamotrigine (Lamictal)
Mood Stabilizers

- Reduce acute symptoms of mania and depression, including symptoms presenting in mixed states
- Not cause a switch from depression to mania or mania to depression
- Combination treatment is required, preferably with adjunctive psychosocial interventions
- First line for less severe acute manic episodes: monotherapy with lithium, valproate (divalproex), or a second-generation antipsychotic
- Same for mixed episodes: use lithium is less effective
- More severe episodes: combination of lithium or valproate and antipsychotic
- First line for less severe bipolar depression: monotherapy with lithium
- More severe bipolar depression: combination of lithium or valproate and antipsychotic
- For maintenance: can stay on acute-phase medications

Lithium Summary

Advantages
- Well established efficacy
- Use dates back 3000 years
- Proven to decrease suicide risk
- Inexpensive
- Antidepressant effects

Disadvantages
- Less effective for rapid-cycling, mixed mania, and schizoaffective disorders
- Dosage adjustment required for renal impairment
- Narrow Therapeutic Index
- Can be fatal in overdose

Lithium

- Discovered in 1817
  - Used in 19th century to treat gout, kidney stones, uremia, insomnia
  - Mechanism is still unknown
    - Membrane stabilizer
    - Alters influx of cations across membranes
- 1st line treatment for bipolar disorder type I
- 70.80% effective for treating acute mania or hypomanic episodes
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**Side Effects of Lithium Therapy**

- Tremor
  - 4% to 65%
- Hypothyroidism (more common in women)
  - Li-+ may inhibit actions of iodine
- Leukocytosis
  - 75-100% of patients will experience some increase in WBC
- Diabetes Insipidus
  - 70% of patients experience polyuria, polydipsia
  - Treat with K-sparing diuretic
- Cardiac dysrhythmia

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**Valproate**

**Summary**

**Advantages**
- Superior for rapid cyclers and mixed-mania subtypes
- Well tolerated
- Loading dose and once daily dosing are options
- Minimal interactions
- Effective for many comorbid conditions
- Becoming the Gold Standard for BPD

**Disadvantages**
- GI upset common with all formulations
- Caution in hepatic impairment
- Divalproex is moderately expensive
- Reports of drug-induced pancreatitis

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**Valproic Acid and Derivatives**

- **Mechanism of action is unknown**
- Membrane stabilizer
- ↑ GABA
- **Role in therapy**
  - Rapid cyclers
  - Mixed/Mania
  - Patients intolerant or inappropriate for lithium
  - Concomitant illnesses
  - Seizure Disorder

- **Side Effects:**
  - GI upset
  - Sedation
  - Fine Tremor
  - Lethargy
  - Var Thinning
  - Weight gain
**Carbamazepine Summary**

**Advantages**
- Superior to lithium but not to VPA for rapid cyclers and mix-mania
- Inexpensive
- Better tolerated than lithium
- Effective for seizure disorders

**Disadvantages**
- Many drug interactions
- Avoid in pregnancy
- Caution in hepatic impairment, hyponatremia, or leukopenia
- Toxic in overdose

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**Antipsychotics**
- Used for treatment of concomitant psychosis
- Can be used on an as-needed basis
- Conventional Antipsychotics
  - haloperidol, perphenazine, etc.
  - Treat positive symptoms in acute mania
  - Risk vs. benefits: EPS, TD, NMS
- Atypical Antipsychotics
  - Aripiprazole, ziprasidone, risperidone, quetiapine, clozapine, olanzapine
  - Treat positive symptoms in acute mania
  - Risk vs. benefits: safer than conventional long term

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**Adjunctive Therapy: Antidepressants**
- Useful for depressive episodes, BPD-II
- Probably will not precipitate a manic episode
- SSRIs are first line agents
- Not Fluoxetine (long half life)
- Buproprion
-recommended for rapid cycling or mixed states
- Venlafaxine or MAOI (second line)
- Avoid AD's that work on norepinephrine if possible
- Discontinue if mania presents
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**Adjunctive Therapy: Benzodiazepines**

- Useful for insomnia or initial sedation
- May prevent development of manic episode
- Short term use only with mood stabilizers
- Lorazepam (Ativan), clonazepam (Klonopin)
- *Caution: alprazolam may induce or exacerbate mania; best if avoided*
- Present or history of any substance abuse is a contraindication for long term use of benzodiazepines

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**Psychotic Disorders**

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**Antipsychotic Drugs**

- Also known as neuroleptics or major tranquilizers
- Used in adults to treat psychoses
- Phenothiazines – also used to treat nausea and vomiting, to sedate patients before anesthesia, to delay ejaculation, to relieve social anxiety, to manage the psychotic component that may accompany acute manic attacks, to treat in children also used to treat other nonpsychotic psychiatric disorders
  - First choice in childhood for schizophrenia and autistic disorder
  - However, not as effective in schizophrenia with childhood onset as compared to occurring in later adolescence and adulthood
  - Also drugs of choice in treating chronic minor and major tic and Tourette's disorder
  - Clinically effective in children with severely aggressive conduct disorders
First Generation/Typical Antipsychotics

- Chlorpromazine (Thorazine) – over 6 months
- Thioridazine (Mellaril) – 2 years
- Clozapine (Clozaril) – 18 years
- Mesoridazine (Serentil) – 12 years
- Loxapine (Loxitane) – 10 years
- Melperone (Melferone) – 12 years
- Perphenazine (Trilafon) – 12 years
- Trifluoperazine (Stelazine) – 6 years
- Thiothixene (Navane) – 12 years
- Fluphenazine (Prolixin) – 16 years
- Haloperidol (Haldol) – 3 years
- Pimozide (Orap) – 12 years

Children may metabolize and excrete antipsychotics more efficiently than adults.

- Determination of serum neuroleptic levels, if available, is recommended before a trial of an antipsychotic is deemed a failure.
- Lithium has fewer clinically significant untoward effects than neuroleptics.
  - Not approved under age 12
  - Not used as often due to necessity of monitoring serum lithium levels

Interactions of Antipsychotic Drugs with Other Medications

- CNS depressants:
  - Alcohol, sedatives, hypnotics, barbiturates, antihistamines, opiates, halothane
- Anticholinergic effects:
  - Caused by drugs that block the action of acetylcholine.
  - Acetylcholine helps with memory, learning, and concentration.
  - It also helps control the functioning of the heart, blood vessels, airways, and organs of the urinary and digestive tracts.
  - Drugs with anticholinergic effects can disrupt the normal functioning of organs.
  - Anticholinergic effects include sedation, impaired vision, constipation, dry mouth, light-headedness, difficulty starting and continuing to urinate, and loss of bladder control.
  - Can lead to confusion, disorientation, delirium, hallucinations, and worsening of preexisting psychotic symptoms
- Can be difficult to determine if inadequate treatment or worsening of symptoms.
Untoward Effects

- **Neuroleptic Malignant Syndrome:**
  - Males and younger individuals appear to be most affected.
  - Generally presents with muscle rigidity, fever, autonomic instability, and cognitive changes such as delirium, and is associated with elevated creatine phosphokinase (CPK).
  - Also altered consciousness, delirium (i.e., experience an extreme loss of mental skills or more sustained hyperactive motor activity).
- **Agranulocytosis:** Major concern of patients treated with clozapine although also noted with other antipsychotic medications (decrease in white blood counts and neutrophils).
  - Occurs typically early on in treatment such as 4th to 10th weeks.
  - Pay attention to sudden infections such as fever and sore throat.

Extrapyramidal Syndromes

- The extrapyramidal system can be affected in a number of ways.
- Akinesia (inability to initiate movement) and akathisia (inability to remain motionless).
- Tardive dyskinesia (involuntary, irregular muscle movements, usually in the face).
- Akathisia (restlessness).
- Dystonia (muscular spasms of neck – torticollis, eyes – strabismus, chin, or jaw; more frequent in children).
- Drug-induced parkinsonism (muscular lead pipe rigidity, bradykinesia/akinesia, resting tremor, and postural instability; more frequent in adults and the elderly).

Untoward Cognitive Effects:

- Higher potency antipsychotic drugs tend to cause less sedation, fewer autonomic side effects, and more extrapyramidal untoward effects.
- Lower potency antipsychotic drugs tend to cause greater sedation, more autonomic side effects, and fewer extrapyramidal effects.
  - However, often a few days/weeks tolerance often develops to the sedative effects.
- Withdrawal Dyskinesia:
  - Emerges when neuroleptic medication is withdrawn or dose is reduced.
  - Usually resolve within a few weeks to a few months of discontinuation of the neuroleptic.
- Antipsychotics, including antipsychotics, can suppress 50-90% of dopamine receptor activity.
  - "Dopamine supersensitivity" – to dopamine agents that may also occur following withdrawal of antipsychotic drugs.
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**Second Generation/Atypical Drugs**

- FDA black box warning – elderly patients with dementia-related psychotic increased risk of death 1.6 to 1.7 times that seen in placebo-treated patients.
- Differ from traditional antipsychotic drugs – in addition to being a dopamine receptor (D2) blocker, they are significant serotonin receptor (52) blockers.
- Simultaneous blocking of D2 and 52 is thought to account for increased efficacy in treating the negative symptoms of schizophrenia as well as decreased incidence of extrapyramidal-unfavorable effects.
- Also has a positive therapeutic effect when administered to some patients with preexisting tardive dyskinesia.

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**SGA/Atypical Antipsychotics**

- Risperidone (Risperdal)
- Chlorpromazine (Thorazine)
- Sertindole (Serlect)
- Quetiapine (Seroquel)
- Ziprasidone (Geodon)
- Aripiprazole (Abilify)
- Amisulpride (Solian)
- Lurasidone (Latuda)

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**SGA Common Adverse Effects**

- Daytime sedation/sleepiness
- Dizziness
- Tachycardia
- Orthostatic hypotension
- Increased salivation
- Weight gain
- Somnolence
- Insomnia
- Confusion
- Agitation
- Dry mouth
- Dyspepsia (reflux, gastritis)
Child & Adolescent Psychopharmacology

- Half of all lifetime serious adult psychiatric illnesses (including depression, anxiety, substance abuse) start by age 14 years of age, and ¾ of them are present by age 25.
- Majority of mental illness in children—go unrecognized and untreated—Problems impact emotional, social, and academic functioning.
- Median onset:
  - Anxiety: 11 years old
  - Impulse Control: 11 years old
  - Substance Abuse: 18 years old
  - Mood Disorders: 20 years old

Methylphenidate and ADHD

- 1999—Landmark studies by Multimodal Treatment Study Group of Children with ADHD (MTA) Cooperative Group—4 groups:
  - Medication
  - Intensive behavioral treatment
  - Combined medical and behavioral
  - Standard community care by local providers

- All four groups improved—but for the most part the medication and combination groups improved significantly more than those in the intensive behavior and community provider groups.

Standard Stimulant vs. Long-Acting/Sustained Release

- Sustained-release—once-daily dose
- Typically viewed as preferential—however, relative inefficacy can result from differences in pharmacokinetics or absorption or from tachyphylaxis
- Studies often refer to them as equivalent in efficacy.
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Adverse Effects of Stimulants

- Insomnia
- Anorexia
- Nausea
- Abdominal pain or cramps
- Headache
- Sweat
- Vomiting
- Loss of weight
- Stomatitis
- Numbness
- Tachycardia
- Blood pressure changes

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Rebound Effects

- May occur approximately 5 hours after the last dose of MPH
- Behavioral symptoms are identical to those of ADHD
  - May exceed baseline
  - Irritability
  - Talkativeness
  - Over activity
  - Insomnia
  - Stomachaches
  - Mild nausea

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Resources

- Epocrates (www.epocrates.com) – website, application
  - Stephen M. Stahl
- Psychotropic Drugs: Fast Facts (3rd Edition)
  - Marmor, Kennedy, & McElroy
- Quick Reference to Psychotropic Medications (Handout)
  - John Preston, Psy.D., ABPP
- Clinical Handbook of Cholinergic Psychotropic Drugs