PSYCHOTROPICS MADE SIMPLE

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Objectives

• Review basic pharmacological and pharmacokinetic principles as applies to the major classes of psychotropic medication.
• Identify the basic issues in selecting medication for psychiatric illnesses.
• Discuss medication nonadherence and how to approach client medication education
• Recognize indications and types of side effects for the major classes of psychiatric medications, and discuss ways of managing and preventing the effect.

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**NEUROPHYSIOLOGY 101**

- Common Neurotransmitters
  - Acetylcholine (ACh)
  - Norepinephrine (NE)
  - Epinephrine (Epi)
  - Dopamine (DA)
  - Serotonin (5HT)
  - Histamine
  - GABA
  - Glutamate
  - Endorphin
  - Nitric oxide
  - Enkephalin
  - Neuropeptides
  - Neurokinins

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**SYNAPSE**

- Presynaptic Neuron
- Postsynaptic Neuron

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**SYNAPSE**

- Presynaptic Neuron
- Postsynaptic Neuron

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**SYNAPSE**

- Presynaptic Neuron
- Postsynaptic Neuron

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RECEPTOR PHARMACOLOGY

- **AGONIST** - drug that MIMICS the effects of the neurotransmitter at the receptor

- **ANTAGONIST** - drug that BLOCKS the effects of the neurotransmitter at the receptor - also known as the anti- or blocker drugs - such as antihistamines

- EFFECT is dependent on what the neurotransmitter does

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Definitions

- **Pharmacodynamic**
  - Effects drug has on body
  - Pharmacologic effect

- **Pharmacokinetic**
  - Effects body has on drug

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Pharmacokinetics

- Absorption
- Distribution
- Metabolism
- Excretion

What’s really happening...

Concentration Versus Time – Oral Dosing
Definitions

- **Half-life (t½)**
  - Time needed for serum concentration of drug to decline by 50%

- **Steady-state (SS)**
  - Plasma concentration at which drug absorption is equal to drug elimination

- **Therapeutic Range**
  - Concentration between which activity is thought to be maximized, toxicity limited

Formulations

- **Parenteral** - intravenous, intramuscular
- **Inhalation** - inhaler, smoked
- **Oral** - solution, suspension, tablets, capsule
- **Extended Release**
- **Enteric Coated**
- **Topical**

![Concentration Versus Time – Parenteral v. Oral](image)
Therapeutic Effects of Psychotropic Medication

Curative versus preventative effects

- psychotropic medications relieve symptoms
- help prevent the return of symptoms
- longer symptom free intervals between episodes
- fewer symptoms during future episodes
- relief of symptoms between episodes
- adjunctive therapy in the treatment of mental disorders
- not to be relied upon as sole treatment

Mental Illness

Genetics

Environment ← Neuropathology

Therapeutic Effects of Psychotropic Medication

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- not to be relied upon as sole treatment
Psychotherapy

- Useful in nearly every psychiatric disorder
- Different changes in brain function
- May be imperative for response in patients with trauma history
- Generally synergistic with meds
- CBT most studied

Therapeutic Effects of Psychotropic Medication

Onset of Effect

- Early - generally due to side effects
- Specific Effects - weeks to months

Long-term Maintenance Treatment

1. Not necessary for all patients
2. Not predictable which patients require long-term therapy
3. Long-term therapy is used for those patients who respond and have recurrent episodes
4. First episode - 6 months
5. Consider long-term side effects in decision
6. Taper the dose to the minimal therapeutic dose
7. Consolidate of doses to improve compliance
8. Routine follow up is imperative
### Determining Need for Medication

- Based on:
  - Treatment responsive symptoms
  - Dangerousness
  - Patient preference

### Patient Education

- 70-80% of patients readmitted stopped taking their medication
- Medication adherence is generally poor in psychiatric patients
- Low levels of knowledge, side effects, cultural influences, high levels of knowledge, and false beliefs are some of the most popular hypotheses for nonadherence
- Inform rather than give information
- Include the family/caregiver

### PATIENT EDUCATION

MEDICATION NONADHERENCE LEADS TO:

- High rate of recidivism
- Higher cost of treatment
- May potentially lead to poor prognosis
- Overall loss of functioning
COMMON QUESTIONS FROM PATIENTS
• How was the drug selected?
• How did the physician arrive at the dose I am receiving?
• How was the regimen decided?
• What are the expected effects from medication?
• When will changes be made in my medication?

COMMON QUESTIONS FROM PATIENTS
• What would happen if I took an overdose of medication?
• How long will I be treated?
• How will progress be assessed?
• What will happen if medications fail or progress is slow?
• How will I be followed for my medications? (how often, by whom, etc)
COMMON QUESTIONS FROM PATIENTS
- When and how will the decision be made to discontinue treatment?
- How will the medication be stopped?
- What will happen after the medication is discontinued?
- Are there any things I can do other than medications to improve the outcome of treatment?
- Can I learn not to get sick again?

IMPLICATIONS FOR MEDICATION EDUCATION
- Be aware of the common questions
- Make the patient aware of these questions
- Think about what your answers will be
- Encourage the patient to find the answers themselves
- Refer patient to another source if you cannot answer the question

BASIC POINTS OF INFORMATION
- type(s) of psychotropic medication(s)
- name(s) of psychotropic medication(s)
- dose patient is receiving
- purpose of medication
- common side effects of medication(s)
- what to do if side effects should happen
- signs of severe toxicity
- drug-drug and drug-food interactions
- appropriate administration
AN ANALOGY FOR TEACHING

MENTAL ILLNESS

PROBLEM:
1) Environment
2) Heredity
3) Neurochemical Changes

SYMPTOMS:
anxiety, insomnia, mood swings, agitation, delusions, hallucinations, etc

TREATMENT:
1) Rest
2) Therapy
3) Medication

COMMON COLD/FLU

PROBLEM:
1) Virus

SYMPTOMS:
cough, headache, sore throat, sneezing, etc

TREATMENT:
1) Rest
2) Fluids
3) Medication

USING THE COLD ANALOGY

SIMILARITIES:

- No "cure" for either illness.
- Symptoms of either illness are dysfunctional.
- Medications used in both illnesses only relieve symptoms.
- If the medication is stopped during treatment, the symptoms will recur because the problem is still present.
- Just as no two persons have the same cold/flu symptoms, no two have similar symptoms with mental illness.

- Medications for both illnesses have side effects.
- Both illnesses require rest; bed rest for a cold/flu, and a rest from the stressful environment for mental illness.
- There are many different medications for treatment of either illness.
- Sometimes, even with treatment there is a recurrence of the illness.
USING THE COLD ANALOGY

DIFFERENCES:

• Medications used for mental illness need to be continued for a longer period of time to prevent the recurrence of symptoms.

• CAUTION - acknowledge the differences in severity and importance of colds vs. mental illness

Response Model

First Week
• Decreased Anxiety
• Improvement in Sleep
• Improvement in Appetite

1-3 Weeks
• Increased Activity, Sex Drive, Self-care, and Memory
• Thinking and Movements Normalize
• Sleeping and Eating Patterns Normalize

2-4 Weeks
• Relief of Depressed Mood
• Less Hopeless/Helpless
• Thoughts of Suicide Subside

SIDE EFFECTS

• Limit discussion to common side effects

• Discuss patients’ experience

• Discuss seeking help for side effects

• Suggestions for minimizing side effects
Some people talk in their sleep. Lecturers talk while other people sleep.

- Albert Camus

Medication Selection

- Drug-Interactions
- Family History of Response
- Past drug trials and response
- Presenting symptoms/ Diagnosis
- Age
- Medical/Psychiatric Comorbidities
- Side Effects
- Cost/Formulary
- Drug Selection (All equally effective)

Treatment Algorithms

- Texas Medication Algorithm Project (TMAP)
- Texas Implementation of Medication Algorithm Project (TIMA)
- American Psychiatric Association (APA)
- Canadian Network for Mood and Anxiety Treatments (CANMAT)
- Expert Consensus Guidelines
- National Institute for Health and Care Excellence (NICE)
Risk: Benefit for Drug Therapy

- Adverse Effects
- Toxicity
- Exacerbation of other problems

- Improved Functioning
- Improved Quality of Life
- Reduced Symptoms
- Decreased Mortality

Generic vs. Trade Name Drugs

- Generally not a problem
- Many newer agents not yet available as generics
- Problems come when patient is switched from one to another – watch for changes in color, shape, size
- Watch for loss of therapeutic effect or emergence of side effects

Schizophrenia

- 1% of the population worldwide
- Symptomatic in early adulthood
- Course of illness is highly variable
- Among the most disabling illnesses

American Psychiatric Association Work Group on Schizophrenia, 2004; Wyatt RJ et al, Schizophr Res 1988
Clinical and Pathophysiological Course of Schizophrenia

Age: Neonatal, infancy, and childhood (0-20)  | Premorbid

Neurodevelopmental | Progressive | Residual/Chronic

FUNCTION: Normal

Neurodegeneration

Schizophrenia: Core Symptom Clusters

Positive Symptoms
- delusions/illusions
- hallucinations
- disorganized speech
- catatonia
- bizarre behavior
- aggression

Negative Symptoms
- blunted affect
- alogia
- avolition
-anhedonia
- withdrawal
- amotivation

Social and Occupational Dysfunction
- employment
- interpersonal relationships
- self-care

Cognitive Symptoms
- attention/concentration
- memory
- executive functions = decision making
- abstraction

Mood Symptoms
- dysphoria
- suicidality
- hopelessness

Dopamine Hypothesis
- Clinical efficacy of antipsychotics correlates with dopamine D2 blockade
- Psychotic symptoms can be induced by dopamine agonists
- Hypofrontality - Reduced activation of the dorsolateral prefrontal cortex contributes to negative symptoms and cognitive deficits

Tuberoinfundibular Pathway (regulates prolactin release)

Mesocortical Pathway
Hypoactivity results in negative symptoms and cognitive symptoms

Nigrostriatal Pathway
(part of extrapyramidal system)

Mesolimbic Pathway
Hyperactivity results in positive symptoms

Dopaminergic Pathways: Symptoms of Schizophrenia

Antipsychotic Effects on Neuronal Pathways in Schizophrenia

<table>
<thead>
<tr>
<th>DA Pathway</th>
<th>Function</th>
<th>FGA Effect</th>
<th>SGA Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nigrostriatal</td>
<td>EPS (movement)</td>
<td>Movement disorders</td>
<td>Less potential for movement disorders</td>
</tr>
<tr>
<td>Mesolimbic</td>
<td>Arousal, memory, motivation</td>
<td>Psychosis relief</td>
<td>Psychosis relief</td>
</tr>
<tr>
<td>Mesocortical</td>
<td>Cognition, communication, social function, response to stress</td>
<td>Increases negative symptoms</td>
<td>Controversial (no effect or some improvement)</td>
</tr>
<tr>
<td>Tuberoinfundibular</td>
<td>Regulates prolactin release</td>
<td>Proloactin increases</td>
<td>Less potential for prolactin increases</td>
</tr>
</tbody>
</table>

FGA = first generation antipsychotic; SGA = second generation antipsychotic

Serotonin

- Major monoamine neurotransmitter
- More ubiquitous than dopamine
- Postmortem Studies in Schizophrenics
  - Increase in 5-HT transmission and 5-HT-transporter density in subcortical regions, but no change or decrease in cortical regions
  - Decrease or no change in 5-HT2-receptor density in prefrontal cortex
- Cerebrospinal Fluid (CSF) Studies of 5-HT Metabolites
  - Inconsistent results between studies
- Agonist-Challenge Studies
  - Administration of m-chlorophenylpiperazine (mCPP) a partial 5-HT agonist:
  - Exacerbates symptoms in unmedicated schizophrenics
  - Has no effect in healthy volunteers
Glutamate

- Major excitatory neurotransmitter 60% of all neurons are glutamate, widely distributed in the brain
- Plays a role in many brain functions including memory and learning
- Two basic kinds of receptors: Ionotropic (AMPA, NMDA) and Metabotropic (mGlu)
- NMDA receptor hypofunction implicated in schizophrenia
  - PCP model for schizophrenia
  - Ketamine infusions in patients induce exacerbation
  - Drug therapy protects against PCP/ketamine worsening
  - Several genes associated with schizophrenia code for glutamate functions/receptors

Glutamate pathways are descending pathways

- Major Glutamate pathway to consider in Schizophrenia is the cortico-brainstem pathway that works to inhibit the ventral tegmental area through interneuronal connections via GABA pathways
- Hypofunctioning in this pathway would lead to hyperactivity in the mesolimbic area

Comparative Efficacy Of Oral Antipsychotics

- CATIE – no drug superior in Phase I comparison all cause d/c
- EUFEST – no drug superior on efficacy
- CUTLASS – no drug superior
- CAFÉ – no drug superior
- Clozapine shows superiority in most studies
- No studies comparing LAIs head to head

### Characteristics of Second Generation Antipsychotics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CLZ</th>
<th>RIS</th>
<th>OLZ</th>
<th>QUE</th>
<th>ZIP</th>
<th>ARI</th>
<th>PALI</th>
<th>ILO</th>
<th>ASE</th>
<th>LUR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Little or no EPS</td>
<td>Y</td>
<td>Y/N</td>
<td>Y/N</td>
<td>Y/N</td>
<td>Y/N</td>
<td>Y/N</td>
<td>Y/N</td>
<td>Y/N</td>
<td>Y/N</td>
<td>Y/N</td>
</tr>
<tr>
<td>Efficacy for negative symptoms</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Absence of TD</td>
<td>Y</td>
<td>Y/N</td>
<td>Y/N</td>
<td>Y/N</td>
<td>Y/N</td>
<td>Y/N</td>
<td>Y/N</td>
<td>Y/N</td>
<td>Y/N</td>
<td>Y/N</td>
</tr>
<tr>
<td>Lack of effect on prolactin levels</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>DA/5HT mechanism</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Superior efficacy</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>
Adverse Effects of Antipsychotics

Sedation – tolerance usually develops in 2 weeks

Anticholinergic side effects: tolerance usually develops to these side effects over 1-2 months.
- dry mouth
- blurred vision
- constipation
- urinary retention
- nasal congestion
- increase in heart rate
- decreased sweating

Cardiovascular side effects
- postural hypotension
- arrhythmias/palpitations

Extrapyramidal Side Effects

- Neurological side effects most troublesome
- Risk greater with first generation antipsychotics
- Can contribute to non-compliance
- Four major classifications
  - Pseudoparkinsonism
  - Dystonia
  - Akathisia
  - Tardive Dyskinesia

ANTIPSYCHOTIC SIDE EFFECT PROFILE

<table>
<thead>
<tr>
<th>DRUG</th>
<th>SEDATION</th>
<th>E.P.S.</th>
<th>ANTICHOL.</th>
<th>CARDIOV.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abilify</td>
<td>Very Low</td>
<td>Very Low</td>
<td>Very Low</td>
<td>Very Low</td>
</tr>
<tr>
<td>Clozaril</td>
<td>High initially</td>
<td>Very Low</td>
<td>High</td>
<td>Very Low</td>
</tr>
<tr>
<td>Fanapt</td>
<td>Moderate</td>
<td>Very Low</td>
<td>Very Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>Geodon</td>
<td>Very Low</td>
<td>Very Low</td>
<td>Low</td>
<td>Low*</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Moderate</td>
<td>Very High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Invega</td>
<td>Moderate</td>
<td>Low</td>
<td>Very low</td>
<td>Low</td>
</tr>
<tr>
<td>Latuda</td>
<td>Low</td>
<td>Low</td>
<td>Very Low</td>
<td>Low</td>
</tr>
<tr>
<td>Loxitane</td>
<td>Moderate</td>
<td>High</td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>Mellaril</td>
<td>High</td>
<td>Moderate</td>
<td>High</td>
<td>High*</td>
</tr>
<tr>
<td>Moban</td>
<td>Very Low</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Navane</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Prolixin</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Serentil</td>
<td>Moderate</td>
<td>Low-Med.</td>
<td>Very Low</td>
<td>Very Low</td>
</tr>
<tr>
<td>Saphris</td>
<td>Very Low</td>
<td>Very Low</td>
<td>Very Low</td>
<td>Very Low</td>
</tr>
<tr>
<td>Seroquel</td>
<td>Moderate</td>
<td>High</td>
<td>Med</td>
<td>Moderate</td>
</tr>
<tr>
<td>Stelazine</td>
<td>Low</td>
<td>High</td>
<td>Mod</td>
<td>Moderate</td>
</tr>
<tr>
<td>Symbyax</td>
<td>Very Low</td>
<td>Very Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Ticarnil</td>
<td>High</td>
<td>Moderate</td>
<td>Mod</td>
<td>High</td>
</tr>
<tr>
<td>Zyprexa</td>
<td>Moderate</td>
<td>High</td>
<td>Med</td>
<td>Moderate</td>
</tr>
</tbody>
</table>


### Acute Dystonia

<table>
<thead>
<tr>
<th>Onset</th>
<th>≤5 days of treatment initiation or dose increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Severe muscle spasm of eyes, tongue, pharynx or larynx, back, neck</td>
</tr>
<tr>
<td>Risk Factors</td>
<td>Young, African American males, High AP potency/doses, IM administration</td>
</tr>
<tr>
<td>Treatment</td>
<td>Acute treatment → Anti-ACh agent or BZD, Chronic treatment → Decrease dose, change AP, Anticholinergic agent</td>
</tr>
</tbody>
</table>

### Pseudoparkinsonism

<table>
<thead>
<tr>
<th>Onset</th>
<th>≤1–3 months of treatment initiation or dose increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Bradykinesia, tremor, drooling, cogwheel rigidity, postural abnormalities</td>
</tr>
<tr>
<td>Risk Factors</td>
<td>≥40 yo, female, high AP potency/doses</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Modified Simpson Angus Scale (MSAS)</td>
</tr>
<tr>
<td>Treatment</td>
<td>Decrease dose, change AP, Anticholinergic agent, DA agonist</td>
</tr>
</tbody>
</table>

### Akathisia

<table>
<thead>
<tr>
<th>Onset</th>
<th>≤1–4 weeks of treatment initiation or dose increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Extreme motor restlessness/inability to sit still, Difficult to distinguish from anxiety/agitation/psychosis</td>
</tr>
<tr>
<td>Risk Factors</td>
<td>Young, high AP doses, other meds, Up to 30% incidence with high potency FGAs</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Barnes Akathisia Scale (BAS)</td>
</tr>
<tr>
<td>Treatment</td>
<td>Decrease dose, change AP, beta-blocker, BZD, Anticholinergic agents are ineffective!</td>
</tr>
</tbody>
</table>
Tardive Dyskinesia

Onset
• Typically later in treatment (months-years)

Symptoms
• Buccal-lingual-masticatory (BLM) syndrome, orofacial movements, writhing movements of face, neck, back, trunk and extremities

Risk Factors
• Increased age, female, concurrent diagnosis of mood disorder, long duration of AP use

Monitoring
• AIMS or DISCUS every 6-12 months

Treatment
• Prevention
• Decrease dose of AP or switch from FGA → SGA/clozapine

Medications Used to Treat EPS and Dosage Ranges

<table>
<thead>
<tr>
<th>TRADE NAME</th>
<th>GENERIC NAME</th>
<th>DOSE (mg)</th>
<th>T1/2</th>
<th>DYSTONIA</th>
<th>PSEUDO</th>
<th>AKATHISIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akineton®</td>
<td>biperiden</td>
<td>-</td>
<td>3-4</td>
<td>-</td>
<td>4-20</td>
<td>-</td>
</tr>
<tr>
<td>Artane®</td>
<td>trihexyphenidyl</td>
<td>0.5-2 IM</td>
<td>25-50 IM</td>
<td>0.5-10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ativan®</td>
<td>lorazepam*</td>
<td>10-20</td>
<td>-</td>
<td>4-20</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Benadryl®</td>
<td>diphenhydramine*</td>
<td>2-8</td>
<td>1-2 IM</td>
<td>4-10</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Cogentin®</td>
<td>benztropine*</td>
<td>6-48</td>
<td>-</td>
<td>-</td>
<td>90-160</td>
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<tr>
<td>Inderal®</td>
<td>propranolol</td>
<td>4-6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Symmetrel®</td>
<td>amantadine</td>
<td>10-28</td>
<td>100-400</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* - available in intramuscular dosage form

Metabolic Side Effects of SGAs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight Gain</th>
<th>Risk for Diabetes</th>
<th>Worsening of Lipid Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Risperidone</td>
<td>++</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Paliperidone*</td>
<td>++</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Asenapine*</td>
<td>++</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Iloperidone*</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Lurasidone*</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
</tr>
</tbody>
</table>

(*) = increase effect; (;) = no effect; *Newer drugs with limited long-term data
### Atypicals - Adverse Effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine (Clozaril)</td>
<td>Weight Gain, Sedation, Orthostasis, Hypersalivation, Constipation, Seizures, WBC</td>
</tr>
<tr>
<td>Risperidone (Risperdal)</td>
<td>EPS, Sedation, Akathisia</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa)</td>
<td>Weight Gain, Sedation, Akathisia, Orthostasis, Akathisia</td>
</tr>
<tr>
<td>Quetiapine (Seroquel)</td>
<td>Anticholinergic, Sedation, Orthostasis</td>
</tr>
<tr>
<td>Ziprasidone (Geodon)</td>
<td>Insomnia, Sedation</td>
</tr>
<tr>
<td>Aripiprazole (Abilify)</td>
<td>Insomnia, Nausea, Akathisia</td>
</tr>
<tr>
<td>Paliperidone (Invega)</td>
<td>Sedation, EPS, Akathisia</td>
</tr>
<tr>
<td>Lurasidone (Latuda)</td>
<td>Insomnia, Nausea, Akathisia</td>
</tr>
</tbody>
</table>

### Clozapine: Black Box Warnings

- **Agranulocytosis**
  - CBC monitoring (weekly – monthly)
  - Goal WBC > 3.5 and ANC > 2

- **Orthostatic Hypotension, Syncope, Bradycardia**
  - Slow dose titration
  - Restart titration if > 2 days missed

- **Seizures**
  - Dose related (>600 mg/d)

- **Myocarditis**
  - Especially within first 8 weeks
  - Assess for dyspnea, fatigue, palpitations, fever, chest pain, heart failure, ECG findings, tachypnea

### Effect of Medication Gap on Subsequent Rate of Rehospitalization in Predominantly Adherent Patients

![Graph showing the effect of medication gap on subsequent rate of rehospitalization](Image)
The Nonadherence-Relapse Cycle

**Potential Advantages of Long-Acting Injectable Antipsychotics**

- Predictable and consistent drug delivery
- Eliminates first pass and bioavailability differences
- Better dose to concentration predictability
- Easier to assess adherence/nonadherence
- Covert nonadherence is avoided
- Reduce risk of overdose by patient
- More convenient to patient – may be preferable to patient


**Formulation of LAI Antipsychotics**

<table>
<thead>
<tr>
<th>Time Period</th>
<th>1st Generation Antipsychotics</th>
<th>2nd Generation Antipsychotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960's</td>
<td>Fluphenazine Enanthate</td>
<td>Risperidone Microspheres</td>
</tr>
<tr>
<td>1970's</td>
<td>Haloperidol Decanoate</td>
<td></td>
</tr>
<tr>
<td>1980's</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1990's</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000's</td>
<td></td>
<td>Olanzapine Pamoate</td>
</tr>
<tr>
<td>2010's</td>
<td></td>
<td>Aripiprazole Monohydrate</td>
</tr>
</tbody>
</table>

Product Package Insert
**Formulation of LAI Antipsychotics**

**1960's**
- 1st Generation Antipsychotics
  - Fluphenazine Enanthate
  - Fluphenazine Decanoate
- Haloperidol Decanoate

**1970's**
- Esterified Drug in Sesame Oil

**1980's**
- **CLINICAL POINTS - 1st Generation Antipsychotics**
  - Requires Z-track administration
  - Gluteal or Deltoid injection sites
  - 2 or 4 week dosing – Fluphenazine
  - 4 week dosing – Haloperidol
  - Loading dose +/- Haloperidol
  - Oral overlap – Haloperidol
  - No refrigeration or mixing required

**1990's**
- **2nd Generation Antipsychotics**
  - Risperidone Microspheres
  - Olanzapine Pamoate
  - Paliperidone Palmitate
  - Aripiprazole Monohydrate

**2000's**
- **CLINICAL POINTS - 2nd Generation Antipsychotics**
  - No Z-track administration
  - Gluteal or Deltoid injection sites – Risperidone and Paliperidone only
  - 2 week dosing - Risperidone
  - 2 or 4 week dosing – Olanzapine
  - 4 week dosing – Olanzapine, Paliperidone, Aripiprazole (qmo)
  - Loading dose strategy – Paliperidone and Olanzapine
  - Oral overlap – Risperidone - 3 wks, Aripiprazole – 2 wks
  - Refrigeration – only Risperidone
  - Mixing – all except Paliperidone

**2010's**
- **Formulation of LAI Antipsychotics**
  - Aqueous Suspension of copolymer matrix
  - Aqueous Suspension of Drug Nanoparticles

**Z-Track Administration Technique**

(A) (B) (C)

- Subcutaneous
- Total
- Nucleus
- Nucleus

Product Package Inserts
**US FDA-Approved Depot Antipsychotics**

<table>
<thead>
<tr>
<th>Type</th>
<th>First generation</th>
<th>Second generation</th>
<th>First generation</th>
<th>Second generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection Interval</td>
<td>1-4 weeks</td>
<td>2 weeks</td>
<td>4 weeks</td>
<td>2, 4 weeks</td>
</tr>
<tr>
<td>Tmax</td>
<td>~24 hr</td>
<td>~6 days</td>
<td>4-6 weeks</td>
<td>1 week</td>
</tr>
<tr>
<td>Dosing</td>
<td>Flexible</td>
<td>Fixed Unit</td>
<td>Fixed Unit</td>
<td>Fixed Unit</td>
</tr>
<tr>
<td>Vehicle</td>
<td>Sesame oil</td>
<td>Microspheres</td>
<td>Aqueous Suspension</td>
<td>Aqueous Suspension</td>
</tr>
<tr>
<td>Injection Site</td>
<td>Deltoid &amp; gluteal</td>
<td>Deltoid &amp; gluteal</td>
<td>Deltoid &amp; gluteal</td>
<td>Deltoid &amp; gluteal</td>
</tr>
<tr>
<td>EPS/TD Relative Risk</td>
<td>Higher</td>
<td>Lower</td>
<td>Lower</td>
<td>Lower</td>
</tr>
<tr>
<td>Storage</td>
<td>Room temp.</td>
<td>Room temp.</td>
<td>Room temp.</td>
<td>Room temp.</td>
</tr>
</tbody>
</table>

**Long-acting Injectable Antipsychotic Dosing**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>INITIAL DOSE</th>
<th>MAINTENANCE DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluphenazine Decanoate</td>
<td>12.5-25 mg IM</td>
<td>12.5-60 mg IM</td>
</tr>
<tr>
<td>Haloperidol Decanoate</td>
<td>10-20 mg daily PO dose IM</td>
<td>15-15 mg daily PO dose IM</td>
</tr>
<tr>
<td>Risperidone Microspheres</td>
<td>25 mg IM q 2 weeks + PO dose IM for 3 weeks</td>
<td>25-50 mg IM q 2 weeks (range: 25-50 mg)</td>
</tr>
<tr>
<td>Olanzapine Pamoate</td>
<td>250-300 mg IM q 2 weeks or 405 mg IM q 4 weeks (range: 250-300 mg IM q 2 weeks or 405 mg IM q 4 weeks)</td>
<td></td>
</tr>
<tr>
<td>Paliperidone Palmitate</td>
<td>150-300 mg IM q 2 weeks or 405 mg IM q 4 weeks (range: 150-300 mg IM q 2 weeks or 405 mg IM q 4 weeks)</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole Monohydrate</td>
<td>400 mg IM q month</td>
<td>400 mg IM q month can reduce to 300 mg or 200 mg for tolerability or drug interactions</td>
</tr>
</tbody>
</table>

**Antipsychotic Treatment Guidelines**

<table>
<thead>
<tr>
<th>Treatment for First Episode Schizophrenia</th>
<th>APA 2004</th>
<th>TMAP 2006</th>
<th>PORT 2009</th>
<th>NICE 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORAL SGA</td>
<td>ORAL SGA</td>
<td>ORAL SGA or FGA (not olanzapine or clozapine)</td>
<td>ORAL SGA or FGA</td>
<td></td>
</tr>
</tbody>
</table>

**Long-term Maintenance/Nonadherence**

<table>
<thead>
<tr>
<th>LAI</th>
</tr>
</thead>
</table>

Multi-Drug Therapy

- 2 or more concurrent antipsychotics
- Not cross-taper
- Few case reports
- Very expensive
- Similar mechanisms of action
- Increases risk for side effects

Brain Areas that Regulate Mood

- FC: Frontal cortex (esp. prefrontal and cingulate) - cognitive function, attention
- HP: Ventral Hippocampus - cognitive function, memory
- NAc: Nucleus Accumbens (ventral striatum) - reward and aversion
- Amy: Amygdala - mediates responses to emotional stimuli
- HYP: Hypothalamus regulates sleep, appetite, energy, sex
- VTA: Ventral Tegmental Area - Sends dopaminergic projections to other areas
- DR: Dorsal Raphe nuclei - send serotonergic input to other areas
- LC: Locus Coeruleus - sends noradrenergic input to other areas

Functional Domains of Serotonin and Norepinephrine

Serotonin (5-HT)
- Sex
- Appetite
- Aggression
- Depressed Mood
- Anxiety
- Vague Aches and pain
- Irritability
- Thought processes

Norepinephrine (NE)
- Concentration
- Interest
- Motivation

References:
Phases of Treatment for Depression

Severity

Symptoms

“Normalcy”

Response

Remission

Recovery

Symptom Syndrome

Acute Treatment (6-12 wks)

Continuation Treatment (4-9 months)

Maintenance Treatment (≥ 1yr)

Adapted from: Depression Guideline Panel, Depression in Primary Care, AHCPR, April 1993.

Target Symptoms for Antidepressant Treatment

- mood/feeling
  - sadness
  - irritability
  - pessimism
  - self-reproach
  - anxiety
  - suicidal thoughts
  - hopelessness
  - guilt
  - no enjoyment

- vegetative signs
  - slowed movement
  - slowed thinking
  - poor memory and concentration
  - fatigue
  - constipation
  - decreased sex drive
  - anorexia
  - weight change
  - insomnia

Symptom Remission

2-4 Weeks

- Relief of Depressed Mood
- Less Hopeless/Helpless
- Thoughts of Suicide Subside

1-3 Weeks

- Increased Activity, Sex Drive, Self-care, and Memory
- Thinking and Movements Normalize
- Sleeping and Eating Patterns Normalize

First Week

- Decreased Anxiety
- Improvement in Sleep
- Improvement in Appetite
Survival

Recurrence rate of 30% in 3 years at full dose, 70% at half dose
50-70% of patients will relapse over 1 year period without maintenance treatment
Risk of relapse continues to increase over time
Risk of relapse significantly reduced with maintenance therapy - 80-90% remain well during first year of maintenance therapy
Psychotherapy does not improve survival significantly over medication management

Frank, et al., Arch Gen Psychiatry 1990;47:1063.

Treatment Options for Depression

Cyclic Antidepressants
Noradrenergic and Specific Serotonin Antidepressants
Monoamine Oxidase Inhibitors
Serotonin Receptor Modulators
Selective Serotonin Reuptake Inhibitors
Selective Serotonin Norepinephrine Reuptake Inhibitors
S2 Antagonists
Benzodiazepines
Alprazolam
Other
Lithium
Thyroid
Stimulants
Combination

Comparative Antidepressant Pharmacology

Tricyclics
SSRIs
SNRIs
Bupropion
Mirtazapine
Levomilnacipran
Vilazodone
Vortioxetine
Antidepressant Side Effects

**SSRIs**
- Prozac
- Zoloft
- Paxil
- Celexa
- Lexapro

**TCAs**
- Elavil
- Tofranil

**MAOIs**
- Hypertension
- Dryness
- Iritis
- Sexual Dysfunction
- Memory Impairment

**SSNRI**
- Effexor
- Cymbalta
- Pristiq
- Fetzima

Bupropion
- Insomnia
- Seizures
- Weight Gain
- Cardiac Effects

Trazodone
- Hypertension
- Dizziness
- Weight Gain
- Constipation
- Sexual Dysfunction
- Memory Impairment

Remeron
- Sedation
- Nausea
- Vomiting
- Dizziness
- Constipation
- Visual Changes
- Sexual Dysfunction
- agranulocytosis

Viibryd
- Nausea
- Vomiting
- Dizziness
- Dry mouth
- Constipation
- Memory Impairment
Discontinuation Syndrome

- TCA withdrawal syndrome: cholinergic and/or adrenergic rebound (sweating, N/V/D)
- Serotonin withdrawal syndrome: agitation, nightmares, anxiety, dizziness, paresthesias
- Antihistaminergic withdrawal – irritability, insomnia
- Onset: 1 – 2 days after discontinuation
- Duration: 4 – 5 days
- Prevention: taper antidepressants over 2 weeks

Male and Female Sexual Phases

<table>
<thead>
<tr>
<th>Functions</th>
<th>Libido</th>
<th>Swelling and Lubrication</th>
<th>Genital Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phases</td>
<td>DESIRE</td>
<td>EXCITEMENT (arousal)</td>
<td>ORGASM</td>
</tr>
</tbody>
</table>

Comparative Incidence of SSRI-induced Sexual Dysfunction

Sexual Dysfunction

- Also think about:
  - Depression
  - Primary Sexual Dysfunction
  - Drug/Alcohol Abuse
  - Side Effects of Medical Drugs
  - Combinations of Above

Assessing Sexual Dysfunction

ASEX - Arizona Sexual Experience Scale
1. How strong is your sex drive?
2. How easily are you aroused (turned on)?
3. M - Can you easily keep and erection?/F - How easily does your vagina become moist or wet during sex?
4. How easily can you reach orgasm?
5. Are your orgasms satisfying?

Managing AD-Induced Sexual Dysfunction

- Wait and see if it resolves
- Drug Holiday
- Dose Reduction
- Augmentation with nefazodone, bupropion or buspirone
- Switch Drugs
- Add an “antidote”
Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increased risk of suicidality in adults beyond age 24. Depression is associated with an increased risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior, especially during the initial few months of therapy, or at times of dose changes. Families and caregivers should be advised for the need for close observation and communication with the prescriber.

**Suicidality Warning**

**ANTIDEPRESSANT SIDE EFFECT PROFILE**

- GASTROINTESTINAL SIDE EFFECTS
- SEXUAL DYSFUNCTION
- OVERDOSE

Have you ever noticed?
Anybody going slower than you is an idiot, and anyone going faster than you is a maniac.

*George Carlen*
Longitudinal Assessment of Bipolar Disorder Is Critical

Bipolar I Patients Are Symptomatic Almost Half Their Lives

BIPOLAR Disorders

A. Agents and Actions

- Lithium
- Valproic acid (Depakene, Depakote)
- Carbamazepine (Tegretol, Equetro)
- Lamotrigine (Lamictal)
- Antidepressants
- Atypical Antipsychotics
Target Symptoms for Mania

- mood disorder
- irritability
- expansive
- manipulative
- labile
- delusions
- sexual
- persecutory
- religious
- grandiose
- hyperactivity
- sleep disturbance
- pressured speech
- increased motor activity
- assaultive/threatening
- distractibility
- labile
- grandiose
- hyperactivity
- schizophreniform
- loose associations
- hallucinations

Cycling

Manic Symptoms

Untreated
Treated

Depressive Symptoms

Differential Diagnosis: Unipolar or Bipolar?

Mania Symptoms
- Distraction, irritability, grandiosity, Flight of ideas, Activities, Pressured speech, Thoughtlessness

Associated Features
- Unwillingness in intimate relationships?

Course of Illness
- Age of first mania/depression
- Time between episodes
- Length of episodes

Family History
- Higher rate of mood disorder impairment?

Treatment Response
- History of treatment
- Multiple treatment failures?
- Non-response to antidepressants?
- Low response to antidepressants?
Second Generation Antipsychotics: FDA Approvals in Bipolar Disorder

<table>
<thead>
<tr>
<th>Acute manic or mixed episode</th>
<th>Acute depressive episode</th>
<th>Maintenance therapy</th>
<th>Agitation (IM short-acting formulations only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine</td>
<td>Quetiapine</td>
<td>Olanzapine</td>
<td>Olanzapine</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Risperidone</td>
<td>Quetiapine, adjunct</td>
<td>Quetiapine, adjunct Risperidone(LAI)</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Ziprasidone</td>
<td>Ziprasidone, adjunct</td>
<td>Risperidone, adjunct Ziprasidone, adjunct</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Aripiprazole</td>
<td>Aripiprazole, adjunct</td>
<td>Aripiprazole</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Asenapine</td>
<td>Asenapine</td>
<td>Asenapine</td>
</tr>
</tbody>
</table>

• Efficacy
  – Effective in up to 70% of patients with acute mania
  – Onset of effect: 3-5 days

Lithium Toxicity and Symptoms

<table>
<thead>
<tr>
<th>Mild/Moderate: 1.5-2 mEq/L</th>
<th>Moderate/Severe: 2-2.5 mEq/L</th>
<th>Severe: 2.5 mEq/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/V/D</td>
<td>Anorexia</td>
<td>Seizures</td>
</tr>
<tr>
<td>Ataxia</td>
<td>Delirium</td>
<td>Renal failure</td>
</tr>
<tr>
<td>Dystonia</td>
<td>Persistent N/V/D</td>
<td>Oliguria</td>
</tr>
<tr>
<td>Lethargy</td>
<td>ECG changes</td>
<td>Death</td>
</tr>
<tr>
<td>Coarse tremor</td>
<td>Stupor</td>
<td></td>
</tr>
<tr>
<td>Nystagmus</td>
<td>Syncope</td>
<td></td>
</tr>
<tr>
<td>Drowsiness</td>
<td>Myoclonus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperreflexia</td>
<td></td>
</tr>
</tbody>
</table>

Most Common Adverse Effects

Lithium
CNS: Tremor, Sedation, Cognitive impairment
GI: Abdominal pain, Diarrhea
Other: Thirst, Polyuria, weight gain, acne

Divalproex
CNS: Tremor, Dizziness, Sedation, Headache
GI: Nausea, Abdominal pain/indigestion
Other: Weight gain

Carbamazepine
CNS: Sedation, Dizziness, Unsteady Gait, Incoordination,
     Blurred vision, Diplopia, Cognitive impairment
GI: Abdominal pain, Diarrhea
Other: Thirst, Polyuria, weight gain, acne
### Summary Lithium

#### Advantages
- 80% effective for acute mania
- Most effective MS for bipolar depression
- Reduces frequency, duration and severity of future episodes

#### Disadvantages
- Less effective in severe mania with psychotic features, mixed, rapid-cycling, organic mania, comorbid substance abuse
- Adverse effects
- Multiple drug-drug interactions
- Level monitoring
- Teratogenicity

### Summary Valproic acid

#### Advantages
- Similar efficacy to lithium for classic manic episodes
- May be more effective than lithium for mixed episodes
- May be beneficial in rapid-cycling
  - *Anti-kindling*

#### Disadvantages
- Adverse effects
- Multiple drug-drug interactions
- Level monitoring
- Teratogenicity

### Summary Carbamazepine

#### Advantages
- Similar efficacy for classic manic episodes
- May be more effective in lithium non-responders
- May be beneficial in mixed episodes, organic mania, and rapid-cycling
  - *Anti-kindling*

#### Disadvantages
- Adverse effects
- Multiple drug-drug interactions
  - Auto-inducer
- Level monitoring
- Teratogenicity
Lamotrigine- Lamictal
Approved for maintenance
Not effective for acute manic episodes
Delayed time to intervention for depression
Less delay in time to intervention for mania
Side effects
Headache
Nausea
Insomnia
Rare 0.1% severe rash

Miscellaneous Mood Stabilizers
- Clozapine
  - Generally 4th line agent secondary to both safety and lack of efficacy data
- Oxcarbazepine
  - Case series and a few small controlled studies suggest efficacy in bipolar disorder
- Omega III Fatty Acids
  - One RCT has found useful for preventing the reoccurrence of symptoms
- Topiramate or Gabapentin
  - Lack of evidence supporting use in this area

Treatment Options for Anxiety Disorders
- Tricyclic Antidepressants
  - Imipramine
  - Desipramine
  - Nortriptyline
- Monoamine Oxidase Inhibitors
  - Phenelzine
- Benzodiazepines
  - Alprazolam
  - Clonazepam
  - Diazepam
- SSRIs/SNRIs
  - Fluoxetine
  - Paroxetine
  - Fluvoxamine
  - Venlafaxine
  - Duloxetine
- Other
  - Propranolol
  - Combination
  - Valproate
  - Buspirone
Antianxiety Agents

A. Agents and Actions

Benzodiazepines
- long-acting (t1/2 > 40 hours)
- medium-acting (t1/2 10-40 hours)

Non-benzodiazepine
- buspirone (BuSpar)
- meprobamate (Miltown, Equanil)

Benzodiazepines (BZDs)

- Indications
  - Panic attacks, not panic disorder
  - Anxiety
  - Seizures
  - Sedatives
  - Muscle relaxants
  - Acute alcohol withdrawal
  - Acute mania
  - Acute agitation

<table>
<thead>
<tr>
<th>BZDP Agent</th>
<th>Dose Range(mg/d)</th>
<th>T1/2 (hrs)/metab</th>
<th>Active Metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>alprazolam</td>
<td>0.5-10</td>
<td>9-20</td>
<td>OH-alprazolam</td>
</tr>
<tr>
<td>chlordiazepoxide</td>
<td>5-200</td>
<td>4-29/28-100</td>
<td>DMD, oxazepam, DMC</td>
</tr>
<tr>
<td>clonazepam</td>
<td>0.5-6</td>
<td>9-60</td>
<td></td>
</tr>
<tr>
<td>chlordiazepate</td>
<td>15-60</td>
<td>1-120</td>
<td>DMD</td>
</tr>
<tr>
<td>diazepam</td>
<td>2-40</td>
<td>14-70/30-200</td>
<td>DMD, oxazepam, temazepam</td>
</tr>
<tr>
<td>estazolam</td>
<td>0.5-2.0</td>
<td>8-24</td>
<td></td>
</tr>
<tr>
<td>flurazepam</td>
<td>15-30</td>
<td>3/40-250</td>
<td>N-desalkylflurazepam, OH-ethylflurazepam</td>
</tr>
<tr>
<td>halazepam</td>
<td>80-160</td>
<td>14/30-96</td>
<td>DMD, 3-OH-halazepam</td>
</tr>
<tr>
<td>lorazepam</td>
<td>2-4</td>
<td>8-24</td>
<td></td>
</tr>
<tr>
<td>oxazepam</td>
<td>30-120</td>
<td>3-25</td>
<td></td>
</tr>
<tr>
<td>prazepam</td>
<td>20-60</td>
<td>30-100</td>
<td>DMD, oxazepam, desalkyllorazepam</td>
</tr>
<tr>
<td>quazepam</td>
<td>7.5-30</td>
<td>15-40/39-120</td>
<td>2-oxoquazepam, desalkylflurazepam</td>
</tr>
<tr>
<td>temazepam</td>
<td>15-30</td>
<td>3-25</td>
<td></td>
</tr>
<tr>
<td>triazolam</td>
<td>0.125-0.5</td>
<td>1-5</td>
<td>7-alpha-OH metabolite</td>
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</tbody>
</table>
### Target Symptoms for Anxiety

<table>
<thead>
<tr>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Motor Tension</strong></td>
</tr>
<tr>
<td>Trembling, twitching or feeling shaky</td>
</tr>
<tr>
<td>Restlessness</td>
</tr>
<tr>
<td>Muscle Tension, aches or soreness</td>
</tr>
<tr>
<td>Easy fatigability</td>
</tr>
<tr>
<td><strong>Autonomic Hyperactivity</strong></td>
</tr>
<tr>
<td>Shortness of breath</td>
</tr>
<tr>
<td>Sweating, cold clammy hands</td>
</tr>
<tr>
<td>Palpitations or tachycardia</td>
</tr>
<tr>
<td>Dry mouth</td>
</tr>
<tr>
<td>Dizziness or lightheadedness</td>
</tr>
<tr>
<td>Frequent urination/urgency</td>
</tr>
<tr>
<td>Nausea, diarrhea, GI distress</td>
</tr>
<tr>
<td>&quot;Lump in throat&quot;</td>
</tr>
<tr>
<td><strong>Vigilance and Scanning</strong></td>
</tr>
<tr>
<td>Feeling keyed up or on edge</td>
</tr>
<tr>
<td>Easy to startle</td>
</tr>
<tr>
<td>Irritability</td>
</tr>
<tr>
<td><strong>Panic (in addition to above)</strong></td>
</tr>
<tr>
<td>Choking - Fear of going crazy</td>
</tr>
<tr>
<td>Paresthesias - Chest pain/discomfort</td>
</tr>
<tr>
<td>Fear of dying</td>
</tr>
</tbody>
</table>

### Target Symptoms in Anxiety (continued)

<table>
<thead>
<tr>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vigilance and Scanning</td>
</tr>
<tr>
<td>Feeling keyed up or on edge</td>
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<tr>
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<tr>
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<tr>
<td>Paresthesias - Chest pain/discomfort</td>
</tr>
<tr>
<td>Fear of dying</td>
</tr>
</tbody>
</table>

### SIDE EFFECTS

**Benzodiazepine agents**
- long-acting versus short-acting
- common effects
drowsiness - sedation
blurred vision - ataxia
psychomotor impairment - disorientation
aggression - confusion
excitement
- discontinuation: rebound, relapse, recurrence and withdrawal
- abuse, dependence, addiction
Treatment: PTSD

• Initially, trauma focused CBT and non-BZD sleep agent
• After 3-4 weeks of CBT and continued moderate severity of symptoms start pharmacotherapy
  • SSRI, SNRI first line
  • Start at lower dose to avoid increase in anxiety

Treatment Considerations: PTSD

• Partial responders
  • Antipsychotic augmentation of SSRI w/ or w/o psychotic features
• Adjunct as needed for sleep, nightmares or psychotic symptoms
• Nightmares
  • Prazosin 6-10mg
  • Combat veterans may need higher doses
  • Start at 1mg, monitor BP

Treatment Considerations: PTSD

• Propranolol, a β-adrenergic antagonist, had beneficial effects on PTSD of intrusive recollections and reactivity to traumatic stimuli
• BZDs are not effective and should be avoided due to risk of substance abuse
Treatment: Generalized Anxiety Disorder

- SSRIs or SNRIs first-line
  - Paroxetine, escitalopram, venlafaxine XR, duloxetine have FDA approval
- Other ADs work
- Benzodiazepines
  - Not reliable antidepressant
- Buspirone

Treatment: Panic Disorder

- SSRIs or SNRIs first-line
- Other ADs work
- MAOIs
- Benzodiazepines
  - Not reliable antidepressant
  - Beta-blockers useful adjunctive therapy
  - Not adequate as monotherapy

*SNRIs are more expensive and less-well studied in PD

Treatment: OCD

- SSRI (or TCA) for 10-12 weeks ± CBT
  - If inadequate response
    - Taper
    - Second agent for 10-12 weeks
  - If inadequate response
    - Taper
    - Third agent for 10-12 weeks
    - Consider adding an augmenting agent
  - Treat for 1-2 years
ADHD

3 Basic Issues in Diagnosis
- **Inattention** - lack of detail orientation, makes mistakes, cannot sustain activity, difficulty listening, organizing, forgetful, loses things
- **Hyperactivity** - fidgets, moves around, difficulty being quiet, on the go, talks excessively
- **Impulsivity** - difficulty waiting turns, blurts out answers, interrupts/intrudes

ADHD

ISSUES IN TREATMENT
- Education - family, child, teacher
- Parent Management Training
- School Training
- Pharmacotherapy

Treatment Options for ADHD

- **Tricyclic Antidepressants**
  - Tofranil
  - Norpramin
- **Selective Serotonin Reuptake Inhibitors**
  - Prozac
  - Paxil
  - Zoloft
- **Atomoxetine (Strattera)**
- **Bupropion (Wellbutrin)**
- **Venlafaxine (Effexor)**
Target Symptoms for ADHD

- Motor hyperactivity
- Attention Span
- Ability to complete tasks
- Impulsivity
- Frustration Tolerance
- Distractibility
- Socialization-Relationships w/Peers
- Ability to accept limit setting

ADHD Medications

<table>
<thead>
<tr>
<th>TRADE NAME</th>
<th>GENERIC NAME</th>
<th>DOSAGE RANGE</th>
<th>MAX DOSE</th>
<th>DOSAGE INTERVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catapress</td>
<td>Clonidine</td>
<td>0.2-2.4 mg/day</td>
<td>2.4</td>
<td>BID-TID</td>
</tr>
<tr>
<td>Tenex</td>
<td>Guanfacine</td>
<td>0.5-3.0 mg/day</td>
<td>3.0</td>
<td>qd-BID</td>
</tr>
<tr>
<td>Adderall</td>
<td>Dextroamphetamine</td>
<td>2.5-40 mg/day</td>
<td>40</td>
<td>BID-QAM</td>
</tr>
<tr>
<td>AdderalXR</td>
<td>1/2 dose of Adderall</td>
<td></td>
<td></td>
<td>qd/BID</td>
</tr>
<tr>
<td>Cytel</td>
<td>Pemoline</td>
<td>0.5-3.0 mg/kg/day</td>
<td>112.5</td>
<td>Q AM</td>
</tr>
<tr>
<td>Dexedrine</td>
<td>Dextroamphetamine</td>
<td>0.15-0.3 mg/kg/day</td>
<td>40</td>
<td>BID-TID</td>
</tr>
</tbody>
</table>

(Not after 4pm)

| Ritalin     | Methylphenidate | 0.3-0.6 mg/kg/day | 60 | BID-TID |
| Ritalin LA  | Concerta        | (not after 4pm)   |    |         |
| Metadate CD | Daytrana Patch |                  |    |         |
| Focalin     | Desmethylphenidate | 1/2 Ritalin dose | 20 | BID    |
| Focalin XR  |                |                  |    |         |
| Strattera   | Atomoxetine    | 80 mg/day         | 100 | qd/BID |
| Tofranil    | Imipramine     | 25-300 mg/day     | 300 | BID-TID |
| Wellbutrin  | Bupropion      | 150-450 mg/day    | 450 | BID-TID |
| Effexor     | Venlafaxine    | 75-225 mg/day     | 225 | BID or qd |

SIDE EFFECTS

Stimulant Medications

- Insomnia
- Anorexia
- Weight loss
- Nausea
- Tachycardia
- Growth suppression
- Exacerbation of psychosis / mania

Clonidine/Guanfacine

- dry mouth
- Nausea

Dextroamphetamine

- Dizziness
- Abdominal pain
Insomnia Definition, DSM-5

A. A predominant complaint of dissatisfaction with sleep quantity or quality, associated with one (or more) of the following symptoms:
   1. Difficulty initiating sleep.
   2. Difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakenings.
   3. Early-morning awakening with inability to return to sleep.
B. The sleep disturbance causes clinically significant distress or impairments in social, occupational, educational, academic, behavioral, or other important areas of functioning.
C. The sleep difficulty occurs at least 3 nights per week.
D. The sleep difficulty is present for at least 3 months.
E. The sleep difficulty occurs despite adequate opportunity for sleep.

APA. Diagnostic and Statistical Manual of Mental Disorders. 2013.11

Causative or Contributory Factors in Secondary Insomnia

- Dietary
  - Excessive fluid intake
  - Caffeine, nicotine, etoh
- Medical conditions
  - Cancer
  - Chronic pain
  - Diabetes
  - GERD
  - Heart disease
  - Menopause
  - MS
  - RLS
  - Urinary incontinence
  - Sleep disordered breathing
- Psychiatric Disorders
  - Anxiety
  - Bipolar
  - Delirium
  - Dementia
  - Depression
  - Schizophrenia
  - Substance abuse
- Nonprescription Medications
  - Ginseng
  - Ephedrine
  - Phenytoin
  - Pseudoephedrine

Causative or Contributory Factors in Secondary Insomnia

Prescription medications

- Amphetamines
- Atomoxetine
- Bupropion
- Corticosteroids
- Diazepam
- Diuretics
- Methyldopa
- Modafinil
- MAOI
- Nadolol
- Phentermine
- Phenytoin
- Propranolol
- SSRls
- Theophylline
- Thyroid supplements
- Verapamil
Physiological Control of Sleep: Two-Process Model

Homeostatic Factor (Duration of Prior Wakefulness)

Circadian Factor (Biological Clock)

Neurochemical Control of Sleep-Wake States

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Location</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>Substantia nigra, VTA</td>
<td>Wake</td>
</tr>
<tr>
<td>Histamine</td>
<td>TMN (posterior hypothalamus)</td>
<td>Wake</td>
</tr>
<tr>
<td>Hypocretin</td>
<td>Later hypothal</td>
<td>Wake</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Locus coeruleus</td>
<td>Wake</td>
</tr>
<tr>
<td>Serotonin</td>
<td>Raphe nuclei</td>
<td>Wake, NREM</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>LDT, PPT (pons)</td>
<td>REM, wake</td>
</tr>
<tr>
<td>Adenosine</td>
<td>Basal forebrain</td>
<td>NREM sleep</td>
</tr>
<tr>
<td>GABA, galanin</td>
<td>VLPO</td>
<td>NREM sleep</td>
</tr>
</tbody>
</table>

Sleep/Wake Reflects Balance Between Opposing Systems

Adenosine GABA Galanin Melatonin

Hypocretin/Orexin Norepinephrine Histamine Serotonin

Walking: Balance is shifted toward greater activity in wake-promoting systems

Sleep: Balance is shifted toward greater activity in sleep-promoting systems

SLEEP HYGIENE
- Avoid alcohol, nicotine, caffeine, chocolate, fluids
  - For several hours before bedtime
- Cut down on non-sleeping time in bed
  - Bed only for sleep and satisfying sex
  - do not read, watch tv, or study in bed - learn to associate your bed with relaxation
- Avoid trying to sleep
  - You can’t make yourself sleep, but you can set the stage for sleep to occur naturally
- Avoid a visible bedroom clock with a lighted dial
  - Don’t let yourself repeatedly check the time!
  - Can turn the clock around or put it under the bed

SLEEP HYGIENE
- Avoid vigorous exercise before sleep
- Avoid late afternoon or evening naps
- Avoid eating large meals before bed
- Do not allow yourself to lie in bed and worry
  - get up and do something to alleviate the worry (like journaling)
  - Take a warm bath before bed if you have a particularly difficult time getting to sleep

SLEEP HYGIENE
- Establish a regular sleep schedule
  - Get up at the same time 7 days a week
  - Go to bed at the same time each night
- Exercise every day - exercise improves sleep!
- Deal with your worries before bedtime
  - Plan for the next day before bedtime
  - Set a worry time earlier in the evening
- Avoid oversleeping or lying in bed for prolonged periods of time after your sleep is completed
SLEEP HYGIENE

- Adjust the bedroom environment
  - Sleep is better in a cool room, around 65 F.
  - Darker is better
- If you get up during the night to use the bathroom, use minimum light
- Use a white noise machine or a fan to drown out other sounds
- Make sure your bed and pillow are comfortable
- If you have a partner who snores, kicks, etc., you may have to move to another bed (try white noise first)

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Generic Name</th>
<th>Control Drug Sched.</th>
<th>1/2 hr Dose</th>
<th>Sedative Length of Txt.</th>
<th>Metab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benadryl®</td>
<td>diphenhydramine</td>
<td>No 2-8 25-50</td>
<td>n/a -</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Desyrel®</td>
<td>trazodone</td>
<td>No 8 25-100</td>
<td>n/a Yes</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Sinequan®</td>
<td>doxepin</td>
<td>No 6-8 10-25</td>
<td>n/a Yes</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Slenor®</td>
<td>doxepin</td>
<td>No 6-8 3-6</td>
<td>up to 4wk Yes</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Noctizol®</td>
<td>chloral hydrate</td>
<td>C-IV 8-11 250-2000</td>
<td>2-3d Yes</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Dalmane®</td>
<td>flurazepam</td>
<td>C-IV &gt;100 15-60</td>
<td>n/a Yes</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Doral®</td>
<td>quazepam</td>
<td>C-IV &gt;100 7.5-015</td>
<td>n/a Yes</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Halcion®</td>
<td>triazolam</td>
<td>C-IV 8 0.125-0.5</td>
<td>n/a No</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Restoril®</td>
<td>temazepam</td>
<td>C-IV 10-40 15-30</td>
<td>n/a No</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Belsomra®</td>
<td>ramelteon</td>
<td>C-IV 8 mg 21</td>
<td>No</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Rozerem®</td>
<td>zolpidem</td>
<td>C-IV 2-2.6 5-20</td>
<td>5-10d No</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Sonata®</td>
<td>zaleplon</td>
<td>C-IV 1-2 5-20</td>
<td>5-10d No</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Lunesta®</td>
<td>eszopiclone</td>
<td>C-IV 6 1-3 mg</td>
<td>up to 6 mo Yes</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Classes of Pharmacologic Agents Used to Treat Insomnia

- Benzodiazepine receptor agonists
  - True benzodiazepines
  - "Nonbenzodiazepines"
- Melatonin and melatonin receptor agonists
- Sedating “antidepressants”
- Antihistamines
- Natural agents
- Sedating second-generation antipsychotics
- Miscellaneous

### Pharmacologic/Clinical Effects

- **BZDP receptor agonists:** sleep induction, sleep maintenance, muscle relaxation, slow reaction times, anticonvulsant, antianxiety, amnesia, mood changes, rebound, withdrawal, addiction, dependence, abuse
- **Antihistamine:** sedative and hypnotic, tolerance, anticholinergic effects
- **Melatonin Agonists:**
  - M1 – sleepiness
  - M2 – circadian cycles

### Non-benzodiazepine Hypnotics

- **Melatonin - non specific melatonin receptor effects – 0.3-3 mg**
- **Ramelteon (Rozerem):**
  - M1 specific agonist – sleepiness
  - M2 specific agonist – circadian rhythm
  - M1>>M2
  - 8 mg/day
  - Approved for longer term treatment
  - May not see initial sedative effects

### Non-benzodiazepine Hypnotics

- **Suvorexant (Belsomra):**
  - Orexin non selective receptor antagonist
  - 10 mg starting dose (5 mg if on 3A4 inhibitor)
  - 20 mg Max dose (10 mg if on 3A4 inhibitor)
Update on Zolpidem

• Max starting 5 mg dose in females
• Available as sublingual ODT
  • 5 & 10 mg – Edular
  • 1.75 and 3.5 mg – Intermezzo
  • Middle of the night insomnia
• Available as ER tablet
  • 6.25 & 12.5 mg – Ambien CR
• Zolpimist – 5 and 10 mg
  • Middle of the night insomnia?

Alcohol Abuse

• Disulfiram - inhibits the metabolism of alcohol resulting in an aversive reaction when a person drinks
• Available as Antabuse - dosed 125 - 500 mg/day given q AM

ALCOHOL ABUSE

• Naltrexone - an opiate antagonist which when taken is reported to decrease craving and reduce the reinforcing effects of alcohol
• Available as - ReVia - dosed 50 mg/d
• Use caution in people with hepatic disease
**Acamprosate (Campral®)**

- Primary action at the NMDA type glutamate receptors
- Maintenance of abstinence from alcohol
- Campral does not prevent withdrawal effects from alcohol
- Supplied as 333 mg tablets
- Usual dosage is two tablets (666 mg) three times daily

---

**Nicotine Replacement**

- Based on the principle that it would be easier to stop smoking with a tapered system
- Individualize usage depending on how many cigarettes/d the person is smoking
  - 1 cig = 1-3 mg of absorbed nicotine
- Patients should be cautioned not to smoke during replacement therapy

---

**NICOTINE**

Nicotine replacement therapy

- Nicotine Gum (Nicorette, 2 and 4 mg pieces) - chewed 9-12 times a day - not to exceed 80 mg total
- Transdermal Patches - 4 currently on the market - have to be used in accordance with package instructions
- Nasal Spray - (Nicotrol NS) - each spray is 0.5 mg of nicotine - max of 5 doses per hour, or 40 doses per day
NICOTINE

- Nicotine Inhaler (Nicotrol Inhaler) - 10 mg/cartridge inhaler
- Nicotine Lozenge (Commit Lozenge) - 2mg and 4 mg - uses lozenges every 1-8 hours on a tapering schedule

NICOTINE

Bupropion – Zyban

- used at antidepressant doses will help curb craving for nicotine
- side effects similar to those seen when used as an antidepressant
- have to be careful in patients receiving Wellbutrin (bupropion)

Nicotine

- Chantix (Varenicline®) – partial agonist selective for alpha-4, beta-2 nicotinic acetylcholine receptor subtypes
- Initiated 7 days prior to smoking cessation as follows:
  - Days 1-3 - 0.5 mg daily
  - Days 4-7 - 0.5 mg twice daily
  - Day 8 - 84 - 1 mg twice daily, stop smoking
- Initial 12 week course of treatment, can repeat
- Side effects - nausea, sleep disturbances, abnormal dreams, flatulence and constipation