Background Information for Psychiatry Rotation

A Brief History of Psychiatric Medicine

Anxiety Disorders

Attention Deficit Hyperactivity Disorder

Bipolar Disorder

Depressive (Affective) Disorders

Drug Interactions

Neuroleptic Malignant Syndrome (NMS)

Obsessive-Compulsive Disorder (OCD)

Parkinson's Disease

Seizure Disorders / Anticonvulsants

Schizophrenia / Psychosis

Sleep Disorders

Substance-Related Disorders

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TABLE OF CONTENTS

BACKGROUND INFORMATION FOR PSYCHIATRY ROTATION

A. DSM-IV

B. MULTI-AXIAL DIAGNOSIS

1. Axis I: Main psychiatric diagnosis
2. Axis II: Personality disorders or Mental Retardation
3. Axis III: Co-morbid medical disorders (supposedly related to psychiatric diagnosis)
4. Axis IV: Psychosocial stressors (listed)
    a. i.e. Divorce, school issues, job-related stress
5. Axis V: Global Assessment of Functioning (GAF)
    a. Scale of function from 0 to 100 (0=lowest / 100=highest)
    b. See DSM-IV book for more information

C. BAKER ACT INFORMATION

1. Definition: A law that protects the patient's rights while in a psychiatric hospital
2. Terminology:
    A. **Consent to treatment** – Patient agrees to be in the hospital
        1. The capacity of a patient to understand and agree is up to psychiatrist
        2. If psychiatrist deems patient not able to give expressed and informed consent, a Proxy or Guardian Advocate must be found
    B. **Consent for medication**
        1. Patient is informed of purposes of prescribed medication, common side effects, risks, and alternatives to medication
        2. Even if patients is admitted involuntarily, he/she can consent or not consent to medications
        3. A patient is never force-medicated if no consent is given, unless in the event of an emergency or a guardian or judge gives permission
    C. **BA-52** – Involuntary admission for up to a 72 hour period of time
    D. **Voluntary Admission** – patient consents to treatment or admits self
        1. BA-51 – request for discharge that must be addressed in 24 hours
    E. **Marchman Act**: An involuntary admission due to substance abuse
    F. **Emergency Treatment Orders (ETOs)**
        1. If a patient is deemed by their psychiatrist to be unable to consent to treatment or medications, and a guardian or proxy cannot be obtained in a timely manner, the physician treats the patient based on these ETOs
    G. **Guardian Advocate or Proxy**
        1. Assigned when a patient is deemed unable to consent to treatment to protect the patient's rights and consent for medications
    H. **Court-ordered detainment**
        1. After the 72hr period of the BA-52 is up, a psychiatrist must either let the patient go or petition the court for more time to treat the patient (involuntarily) – Petition must be filed before the BA expires (w/in 72hrs)
        2. The court can decide to let the patient go, or decide to retain them for an indeterminate amount of time for treatment
        3. The patient can still refuse medication if capable of consenting unless court-ordered to be force-medicated

COMMON DSM-IV PERSONALITY DISORDERS

ANTISOCIAL PERSONALITY DISORDER

A. There is a pervasive pattern of disregard for and violation of the rights of others occurring since age 15 years, as indicated by three (or more) of the following:
   (1) failure to conform to social norms with respect to lawful behaviors as indicated by repeatedly performing acts that are grounds for arrest
   (2) deceitfulness, as indicated by repeated lying, use of aliases, or conning others for personal profit or pleasure
   (3) impulsivity or failure to plan ahead
   (4) irritability and aggressiveness, as indicated by repeated physical fights or assaults
   (5) reckless disregard for safety of self or others
   (6) consistent irresponsibility, as indicated by repeated failure to sustain consistent work behavior or honor financial obligations
   (7) lack of remorse, as indicated by being indifferent to or rationalizing having hurt, mistreated, or stolen from another

B. The individual is at least age 18 years.

C. There is evidence of Conduct Disorder with onset before age 15 years.

D. The occurrence of antisocial behavior is not exclusively during the course of Schizophrenia or a Manic Episode.

BORDERLINE PERSONALITY DISORDER

A. A pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:
   (1) frantic efforts to avoid real or imagined abandonment. Note: Do not include suicidal or self-mutilating behavior covered in Criterion 5.
   (2) a pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation
   (3) identity disturbance: markedly and persistently unstable self-image or sense of self
   (4) impulsivity in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating). Note: Do not include suicidal or self-mutilating behavior covered in Criterion 5.
   (5) recurrent suicidal behavior, gestures, or threats, or self-mutilating behavior
   (6) affective instability due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days)
   (7) chronic feelings of emptiness
   (8) inappropriate, intense anger or difficulty controlling anger (e.g., frequent displays of temper, constant anger, recurrent physical fights)
   (9) transient, stress-related paranoid ideation or severe dissociative symptoms

DEPENDENT PERSONALITY DISORDER

A. A pervasive and excessive need to be taken care of that leads to submissive and clinging behavior and fears of separation, beginning by early adulthood and present in a variety of contexts as indicated by five (or more) of the following:
   (1) has difficulty making everyday decisions without an excessive amount of advice and reassurance from others
   (2) needs others to assume responsibility for most major areas of his or her life
   (3) has difficulty expressing disagreement with others because of fear of loss of support or approval. Note: Do not include realistic fears of retribution.
   (4) has difficulty initiating projects or doing things on his or her own (because of a lack of self-confidence in judgment or abilities rather than a lack of motivation or energy)
   (5) goes to excessive lengths to obtain nurturance and support from others, to the point of volunteering to do things that are unpleasant
   (6) feels uncomfortable or helpless when alone because of exaggerated fears of being unable to care for himself or herself
   (7) urgently seeks another relationship as a source of care and support when a close relationship ends
   (8) is unrealistically preoccupied with fears of being left to take care of himself or herself

A BRIEF HISTORY OF PSYCHIATRIC MEDICINE

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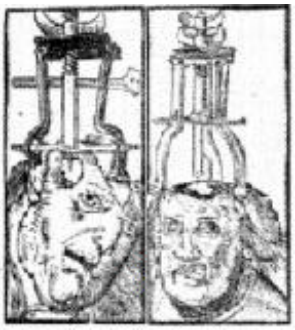
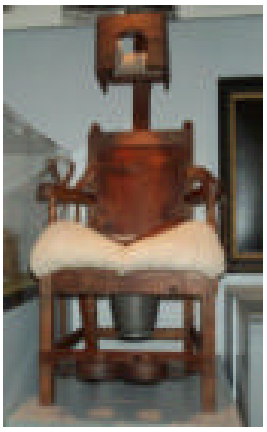
- **FIRST PSYCHIATRIC MEDICATION IN EXISTENCE**
  - Lithium
    - Monovalent alkali metal
    - #3 on Periodic Table of Elements
    - Used thousands of years ago for mania
      - Soranus of Ephesus, in the second century A.D. recommended alkaline waters which contained lithium for various ailments

- **PSYCHIATRIC TREATMENT SEVERAL HUNDRED YEARS AGO**
  - No medications existed (except lithium)
  - Mentally ill were removed from society
    - Asylums, basements, prisons, etc.
    - Lobotomies, *trephining*, electroshock, restraints, chains, hydrotherapy, insulin shock



- **PSYCHIATRIC TREATMENTS OF DAYS PAST**

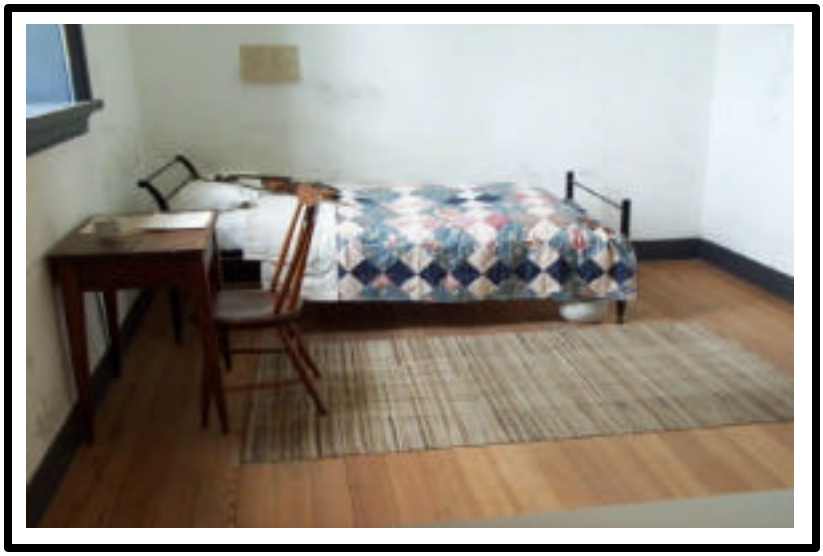


- **18th CENTURY CELL**

- **PSYCHIATRIC TREATMENTS IN THE EARLY 1800s**
  - Morphine was isolated from crude opium
  - Codeine was isolated in 1832
  - Cocaine
    - Widespread use for stimulant effects
    - Adapted from use in native South Americans
  - *Laudanum* used in mental illness

- **PSYCHIATRIC TREATMENT IN THE LATE 1800s**
  - 1887
    - First amphetamine developed
    - Benzedrine Sulfate
    - Used as a bronchodilator
  - 1898
    - Heroin was created
    - From the acetylation of morphine
    - Used as a cough suppressant

- **19th CENTURY CELL**



- **PSYCHIATRIC TREATMENT IN THE EARLY 1900s**
  - 1930s
    - Amphetamines recognized for CNS activity
      - Found to "produce feelings of euphoria and relief from fatigue" and "improve performance on some simple tasks, increase activity levels, and produce anorexia"
    - 1936 medical journal contains case reports of usefulness in depression, manic-depression, and "dementia praecox"
      - Effects were temporary
    - Benzodiazepine compounds discovered
      - Not used for anxiety until 1960s

- **LITHIUM**
  - Until the 1940's, had been used for:
    - Gout
    - Arthritis
    - Mild tonic
    - Sedative
    - Anticonvulsant
    - Diuretic
    - Salt substitute in cardiac patients
    - Soft drink additive
      - 7-UP®
  - Removed from the US market after several deaths from toxicity

- **PSYCHIATRIC TREATMENT IN THE EARLY 1900s (cont.)**
  - Antidepressants tried
    - Thyroid & Adrenal hormones
    - Strychnine
    - Various narcotics
      - Tried with little success long-term
      - Short-term has some effects
  - Barbiturate use for seizures, anxiety, and sleep growing
    - Phenobarbital and derivatives cause fatalities in overdose

- **IN THE 1950s AND 1960s**
  - Chlordiazepoxide (Librium®) was the first benzodiazepine marketed in the US
    - Many benzodiazepines followed
      - Originally thought to help with depression and anxiety
      - Now we know that they can <u>cause</u> depression
  - Chlorpromazine (Thorazine®)
    - First antipsychotic
    - Discovered by accident
      - Chemists were looking for better antihistamines for sedation in surgeries
- **ANTIDEPRESSANTS IN THE 1960s**
  - Tricyclic Antidepressants
    - Discovered in the late 1940's by 2 chemists
    - Derived from antipsychotics
      - Looking for antihistamines, analgesics, sedatives, and antiparkinson drugs
  - Monoamine Oxidase inhibitors

- Derived from iproniazid and isoniazid
  - Used to treat tuberculosis in 1950's
- Risk of toxicity and dangerous drug interactions

- **PSYCHIATRIC MEDICATIONS BOOM IN THE 1960s AND 1970s**
  - Numerous antipsychotics and antidepressants developed from original drugs discovered
  - Many have unpleasant side effects and are toxic in overdose
  - Clozapine (Clozaril®) found to be a miracle drug for schizophrenia
    - Later recalled due to agranulocytosis

- **LITHIUM (cont.)**
  - Extensively studied in the 1950's and 1960's for sedative properties
  - Not approved for mania in the U.S. until 1970 (and for maintenance of Bipolar until 1974)
  - Today is still one of the most effective treatments for acute mania

- **MEDICATIONS IN THE 1980s**
  - First non-addicting anxiolytic developed
    - Buspirone (Buspar®)
  - First Selective Serotonin Reuptake Inhibitor (SSRI) marketed in U.S.
    - Fluoxetine (Prozac®)
  - Barbiturates losing favor due to fatalities in overdose
  - Clozaril® re-marketed with strict guidelines

- **MEDICATIONS IN THE LAST 10 YEARS**
  - Several more antidepressants developed
    - New indications given also (OCD, anxiety)
  - New theories about mental illness arise
    - Reintegration of ill person into society
    - Treatment with non-addictive medications
  - New atypical antipsychotics developed
    - Some based on clozapine structure

- **INTO THE 21st CENTURY**
  - Beginning to understand mental illness as a fully treatable disease state
  - New medications will be developed based on brain's malfunction
    - The ideal medication:
      - Works quickly with no side effects
      - Non-addictive and Inexpensive
      - Effective on all symptoms and does not "wear off"
      - No drug interactions
  - Search for a cure

ANXIETY DISORDERS

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I. Introduction / Definition:

- Anxiety is an unpleasant emotion commonly caused by the perception of actual or potential (anticipatory) danger that threatens the security of the individual.
- Anxiety is normal in life
- Becomes a disorder when it is excessive and interferes with normal daily life

II. Epidemiology:

- estimated at approx. 25%* (lifetime prevalence) [*or greater]
  - approx. 13.3% are Social phobias
  - approx. 11.3% are Simple phobias
  - approx. 3.5% are Panic disorder
  - approx. 2.5% are OCD
  - approx. 5.1% are GAD
- Women > Men
- Mostly untreated → leads to high utilization of the health care system

III. Differential Diagnosis:

Common Medical Disorders Associated with Anxiety Symptoms:

Cardiovascular/respiratory system
- Arrhythmias
- Chronic obstructive lung disease
- Hyperdynamic *b* -adrenergic state
- Hypertension
- Hyperventilation
- *Mitral valve prolapse*
- Myocardial infarction
- Angina
- Pulmonary embolus

Endocrine system
- Cushing's disease
- Hyperthyroidism
- Hypothyroidism
- Hypoglycemia
- Pheochromocytoma

Gastrointestinal system
- Colitis
- Irritable bowel syndrome
- Peptic ulcer
- Ulcerative colitis

Miscellaneous
- Epilepsy
- Migraine
- Pain
- Pernicious anemia
- Porphyria

Drugs Associated with Anxiety Symptoms:

CNS depressants
- Anxiolytics/sedatives
- Ethanol
- Narcotic agonists (withdrawal)

CNS stimulants:

Prescription products
- Albuterol (Proventil, Ventolin)
- Amphetamines (Dexedrine)
- Cocaine
- Diethylpropion (Tenuate)
- Fenfluramine (Pondimin)
- Isoproterenol (Isuprel, Medihaler Iso)
- Methylphenidate (Ritalin)

Nonprescription products
- Caffeine (NoDoz, Vivarin)
- Ephedrine (Ephedrine Nasal)
- Naphazoline (Privine, Allerest Eye drop)
- Oxymetazoline (Afrin, Dristan)
- Phenylephrine (Neo-Synephrine, Allerest)
- Phenylpropanolamine (Dexatrim, Acutrim)
- Pseudoephedrine (Sudafed, Novafed)

Miscellaneous
- Anticholinergic toxicity
- Baclofen (Lioresal)
- Digitalis toxicity
- Dapsone
- Cycloserine (Seromycin)
- Quinacrine (Atabrine)

- Anxiety symptoms are common with other psychiatric disorders, such as Mood Disorders, Schizophrenia, Substance abuse, and other anxiety disorders.

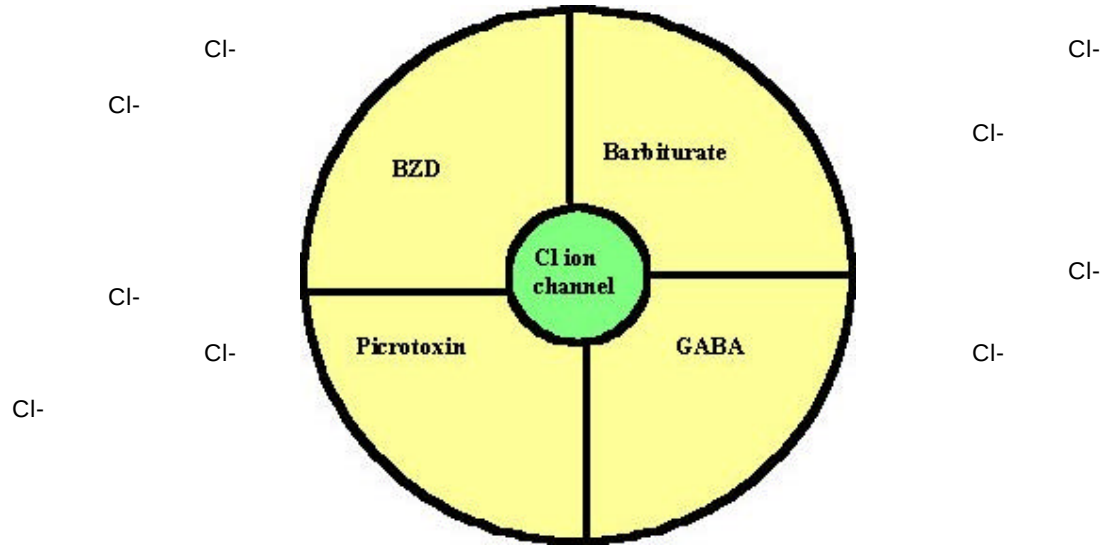
IV. Pathophysiology of anxiety

1. Noradrenergic Model
   - Hypersensitive autonomic nervous system
   - Dysregulation in the locus coeruleus (LC) in the midbrain
     - Neurons within supply 50-70% of brain NE by projecting into other areas
     - May be related to abnormal presynaptic α_2 receptors
2. Benzodiazepine receptor Model (see Figure 1 below)
   - Benzodiazepine receptor is linked to the GABA (*gamma* aminobutyric acid) receptor
   - GABA receptor + a chloride ion channel is a "supramolecular receptor complex"
     - GABA opens the Cl^- channel letting negative Cl^- ions into neuron
     - Causes a ↓ in nerve cell excitability (inhibition)
3. Serotonin (5HT) Model
     - 5HT is predominately supplied through neurons from the raphe nuclei of the brainstem
     - Drugs that are partial agonists on $5HT1_a$ receptors are effective on general anxiety
       - Not for Panic though
       - Buspirone, azapirone, gepirone, ipsapirone, and tandospirone have been studied

V. Guidelines for Anti-Anxiety Treatment:

1. Treatment should be based on level of severity.
2. Drugs treat symptoms, should be used as adjunct to therapy / counseling.
3. Begin with low doses and continue with lowest effective doses.
4. Inform patients of sedation, potentiation with other CNS agents, and dependence potential
5. Patients must avoid alcohol!!!!!! (makes symptoms worse)

Figure 1



VI. DSM-IV Classifications of Anxiety Disorders:

A. Phobic disorders
   Social phobia or Simple phobia
B. Generalized anxiety disorder (GAD)
C. Panic Disorder
   With agoraphobia or Without agoraphobia
D. Obsessive Compulsive Disorder (OCD)
E. Post-traumatic stress disorder (PTSD)
F. Atypical anxiety disorder

A. Phobias

Social Phobia:

- A persistent fear of one or more situations. The person fears they may act in a way or do something that will be humiliating or embarrassing in public, when the individual is the focus of others' attention. Avoidance behavior interferes with life.
    - Examples: Using a public restroom, speaking in public, signing name in public, eating in restaurants…
    - A variation of social phobia is "performance anxiety" (i.e. musician, actor)

Treatment of Social Phobias:

- Paxil® (Paroxetine) is currently the only FDA approved medication for this diagnosis
- Beta-blockers: Propranolol 10-40mg before performance.
  Atenolol: 50-10mg qd for more generalized fears.
- MAOIs: Phenelzine up to 90mg/day in divided doses. May take a few weeks for effect. Diet restrictions, drug interactions, SE's.
- Benzodiazepines: prn or regular dose (depends on pt.) use lowest effective dose.

Specific* (Simple) Phobias *******Newly redesignated in DSM-IV-TR*

- An irrational fear of a specific object or situation. (snakes, heights, insects, flying, etc.)
- Considered non-responsive to pharmacotherapy. Very responsive to behavioral therapy.
- Specific phobias usually do not interfere with daily functioning and few people seek help.

B. (GAD) – Generalized Anxiety Disorder

Unrealistic or excessive anxiety or worry about 2 or more life circumstances for a period of six months or longer. Absence of any organic factors. At least six of the following 18 symptoms:

Motor tension:

1. Trembling, twitching, or feeling shaky
2. Muscle tension, aches, or soreness
3. Restlessness
4. Easily fatigued

Autonomic hyperactivity:

5. Shortness of breath or smothering sensation
6. Palpitations or tachycardia
7. Sweating or cold clammy hands
8. Dry mouth
9. Dizziness or lightheadedness
10. Nausea, diarrhea, or other abdominal distress
11. Hot or cold flashes or chills
12. Frequent urination
13. Trouble swallowing or "lump in the throat"

Vigilance or scanning

14. Feeling keyed up or on edge
15. Startling easy
16. Difficulty concentrating
17. Trouble falling or staying asleep
18. Irritability

1. Treatment of GAD

- Non-pharmacologic tx. is primary
  - behavioral, supportive psychotherapy, group therapy, biofeedback, and other relaxation training, etc.
- SSRIs, TCAs, buspirone, and MAOIs are now DRUGS OF CHOICE due to addictive nature of the benzodiazepines
  - Benzo's used to be drugs of choice (now only use prn or short-term)
  - Of the newer drugs: Effexor and BuSpar are FDA approved for GAD
    - Serzone, Paxil, Zoloft, Prozac, Celexa, and Luvox are acceptable alternatives
- Begin antidepressant therapy with the lowest possible dose
  - ie. 5mg of Paxil QD or 12.5mg of Zoloft QD
    - Increase dose every 3-7 days as tolerated so as not to induce anxiety
    - Many newer antidepressants can initially cause anxiety at "antidepressant doses"
  - Can use benzodiazepines prn for first 2 weeks until antidepressants take effect
  - Benzodiazepines should not be used continuously for > 4-8 weeks due to tolerance and addiction
  - Non-benzodiazepine alternatives should be considered for prn use also
- Clinical drug trials reveal a 50-60% placebo response against any medication

2. SPECIFIC AGENTS

Benzodiazepines: (Drugs of choice for prn tx of GAD)

- Discovered in the 1930's, but not used until 1960
- All BZD's are similar in sedative, hypnotic, anxiolytic, muscle relaxation, and anti-convulsant activity.
- Differ in pharmacokinetics
  - Absorption: determines onset of action
    - Rapid: Diazepam, clorazepate, alprazolam (onset in 15-60 minutes)
    - Intermediate: chlordiazepoxide, lorazepam
    - Slow: lorazepam, prazepam, oxazepam, temazepam, clonazepam
  - Lipophilicity of drug causes redistribution into the periphery (ie. adipose tissue)
    - Large Vd
    - Results in a shorter duration of effect than t ½ after a single dose
    - Lorazepam, oxazepam, and prazepam have small Vd (longer duration of action)
  - Distribution: determines duration of action (along with elimination, and lipid solubility)
    - Rapid: diazepam = short effect despite long t ½
    - Slow: lorazepam = long effect despite short t ½
  - Multiple Dose Kinetics

	Elimination half-life	
	Short	Long
Rate of accumulation	rapid	slow
Post-drug washout	rapid	slow

  - Metabolism
    - Most BZD's are metabolized to active metabolites except:
      - ***Lorazepam, Oxazepam, Temazepam***
        - Can be used in individuals with severe liver disease
        - These are conjugated to inactive metabolites, therefore no interactions

- **Prodrugs:**
  - Clorazepate (needs acidic stomach pH to be metabolized)
  - Prazepam (requires first pass metabolism by hepatic oxidation in liver)
  - Flurazepam
  - Active antianxiety agent is *N*-DMDZ

- IM administration: diazepam (gluteal muscle) and chlordiazepoxide is variable

- IM administration of Lorazepam is rapid and has faster onset than oral

- Not all BZDs are indicated for anxiety
  - Estazolam, flurazepam, temazepam, quazepam, and triazolam → hypnotics
  - Clonazepam → seizures, Midazolam → preoperative sedation

- **Drug Interactions (see Table in Dipiro):**
  - Pharmacodynamic or Pharmacokinetic in nature
    - ie. CNS Depressants, Alcohol
    - ie. cimetidine – except "LOT"
    - ie. Nefazodone and fluvoxamine drastically ↑ alprazolam / triazolam levels

- **Adverse Drug Reactions**
  - CNS- sedation, fatigue, depression, dizziness, ataxia
  - Paradoxical excitement, agitation, confusion, disorientation
  - Anterograde amnesia – lorazepam and others used as premedication, most common in the high potency BZD's
  - Respiratory depression – COPD (additive effects with other resp. depressants)
  - Abuse potential, dependence, withdrawal, tolerance
    - Occurs after long-term use **(Use should not exceed 4 months)**
    - Psychologically and physically reinforcement of use
    - Rebound anxiety results after discontinuation
    - Seizures are possible with acute withdrawal (must taper!!!)

Drug	**Usual Daily Max.**
Librium (Chlordiazepoxide)	100mg
Valium (Diazepam)	40mg
Dalmane (Flurazepam)	30mg
Ativan (lorazepam)	8mg
Serax (Oxazepam)	120mg
Restoril (Temazepam)	30mg
Halcion (Triazolam)	0.25mg
Xanax (Alprazolam)	4mg
Quazepam (Doral)	15mg
Tranxene (Clorazepate)	60mg
Centrax (Prazepam)	60mg
Prosom (Estazolam)	2mg

Buspirone (BuSpar®)

- MOA- 5HT-1_a partial agonist
  - Binds pre-synaptically to receptors in the dorsal raphe
  - Binds post-synaptically to receptors in the hippocampus and cortical brain areas

- Possesses no BZD or GABA complex activity

- Has some dopaminergic activity (agonist and indirect antagonist)
- No anti-convulsant activity
- Minimal sedative / euphoric effects
- No muscle relaxation

- Onset of action 2-4 weeks

- Not for prn therapy!!!

- More effective if used prior to BZDs (BZD naï ve pts.)

  - Due to lack of euphoriant or immediate effects
  - Does not have cross tolerance with BZDs (will not prevent BZD withdrawal)
  - No addiction / dependence potential

- Pharmacokinetics:

  - 4% bioavailable
  - 95% protein bound
  - t ½= 2.5 hrs.
  - metabolized by P450IID6 (active metabolites)
  - ↓↓clearance with cirrhosis, ↓clearance with renal impairment

- Dosing: due to short t ½use multiple dosing (BID to TID)
  - Start at 5mg po TID and increase by 5mg/day every 2-3 days as tolerated
  - Average dose is 20-30mg/d divided
  - Anxiolytic effects at 10-60mg/day

- Adverse reactions: nausea, dysphoria (with large single doses), headache, weakness, dizziness, nervousness

  - Minimal sedation
  - Potential SE's (≤1%) - gynecomastia, galactorrhea, EPS

- Drug interactions:
  - Haloperidol (may ↑ haloperidol levels)
  - MAOIs (contraindicated!)
  - Fluoxetine & paroxetine (↑ buspirone levels) due to metabolic inhibition
  - Supposedly no interaction with EtOH

Tables adapted from Pharmacotherapy, 3rd edition.

OTHER NON-BENZODIAZEPINE ANTIANXIETY AGENTS USED IN GAD:

Generic name	*Brand name*	*Manufacturer*	*Approved for anxiety*	*Usual dosage range (mg/d)*[a]
Venlafaxine	Effexor	Wyeth-Ayerst	Yes	25-375
Diphenhydramine	Benadryl	Parke-Davis	No	25-200
	Generics	Various		
Hydroxyzine	Vistaril	Pfizer	Yes	50-400
	Atarax	Roerig		
	Generics	Various		
Meprobamate	Equanil	Wyeth-Ayerst	Yes	400-1600
	Miltown	Wallace		
	Generics			
B-Blockers:				
Propranolol	Inderal	Wyeth-Ayerst	No	80-160 (start at 10mg bid)
	Generics	Various		
Buspirone	BuSpar	Mead Johnson	Yes	15-60[b]

a. Elderly patients are usually treated with approximately one half of the dose listed.
b. The dosage range in elderly patients appears to be the same. But is not established.

FDA-APPROVED BENZODIAZEPINE AGENT COMPARISONS:

Generic name	***Brand name***	***Manufacturer***	***Approved indications***	***Approved dosage range (Mg/d)***[a]	***Approved equivalent dose (mg)***
Alprazolam	Xanax	Upjohn	Anxiety	0.75-4	*0.5*
			Anxiety-depression		
			Panic disorder	1.5-10	
Chlordiazepoxide	Librium	Roche	Anxiety	25-200	10
	Generics	Various	Alcohol withdrawal		
			Pre-op sedation		
Clorazepate	Tranxene	Abbott	Anxiety	7.5-90	75
	Generics	Various	Seizure disorders		
Diazepam	Valium	Roche	Anxiety	2-40	5
	Generics	Various	Alcohol withdrawal		
			Muscle spasm		
			Pre-op sedation		
			Status epilepticus		
Halazepam	Paxipam	Schering	Anxiety	20-160	20
Lorazepam	Ativan	Wyeth-Ayerst	Anxiety	0.5-10	1
	Generics	Various	Pre-op sedation		
Oxazepam	Serax	Wyeth-Ayerst	Anxiety	30-120	15
	Generics	Various	Anxiety-depression		
			Alcohol withdrawal		
Prazepam	Centrax	Parke-Davis	Anxiety	20-60	10

[a] Elderly patients are usually treated with approximately one half of the dose listed.

PHARMACOKINETICS OF BENZODIAZEPINE ANTIANXIETY AGENTS

Generic name	*Peak plasma level (h)*	*Elimination half-life parent (h)*	*Metabolic pathway*	*Clinically significant metabolites*	*Protein binding (%)*
Alprazolam	1-2	12-15	Oxidation	None	80
Chlordiazepoxide	1-4	5-30	N-Dealkylation Oxidation	Desmethylchlordiazepoxide Demoxepam N-DMDZ[a]	96
Clorazepate	1-2	Pro-drug	Oxidation	N-DMDZ	97
Diazepam	0.5-2	20-80	Oxidation	N-DMDZ	98
Halazepam	1-3	14	Oxidation	N-DMDZ	97
Lorazepam	2-4	10-20	Conjugation	None	85
Oxazepam	2-4	5-20	Conjugation	None	97
Prazepam	6	Pro-drug	Oxidation	N-DMDZ	97

[a] N-Desmethyldiazepam, half-life 36-200 h.

DRUG INTERACTIONS WITH BENZODIAZEPINES

Drug	*Effect*
Alcohol	Decreased clearance of chlordiazepoxide and diazepam; additive psychomotor impairment
Antacids	Decreased rate and extent of clorazepate absorption; decreased rate of diazepam and chlordiazepoxide absorption
Cimetidine	Decreased clearance of alprazolam, diazepam, and chlordiazepoxide, clorazepate and increased elimination half-life
Disulfiram	Decreased clearance of chlordiazepoxide and diazepam by 40% to 50%, and probably alprazolam, clorazepate, halazepam, and prazepam
Fluoxetine	Decreased clearance of diazepam
Isoniazid	Decreased metabolism of diazepam
Omeprazole	Decreased clearance of diazepam
Oral contraceptives	Increased free concentration of chlordiazepoxide and slightly decreased clearance; decreased clearance and increased half-life of diazepam and alprazolam
Rifampin	Increased metabolism of diazepam

DRUGS USED IN THE TREATMENT OF PANIC DISORDER

Class I generic name	*Brand name*	*Manufacturer*	*Antipanic dosage range [a](mg/d)*	*Comments*
Tricyclic antidepressants				
Imipramine	Tofranil	Ciba-Geigy	150-300	Effective
Generics	Various			Problems: lag time, side effects
Monoamine oxidase inhibitors				
Phenelzine	Nardil	Parke-Davis	45-90	Effective Problems: patient acceptance, dietary restrictions, side effects
Benzodiazepines				
Alprazolam	Xanax	Upjohn	4-10[b]	Effective in high doses Problems: ADR's, withdrawal
Diazepam	Valium	Roche	30-40	Possibly effective, needs more study
	Generics	Various		
Clonazepam	Klonopin	Roche	3-6	Possibly effective, needs more study
Miscellaneous agents				
Clonidine	Catapres	Boehringer Ingelheim	0.5	Tolerance develops to antipanic effects
	Generics	Various		

[a] Dosage used in clinical trials but not FDA approved.
[b] Dosage is FDA approved.

C. PANIC DISORDER

Introduction:

- Usually begins in late adolescence to mid-thirties
- Higher probability if have a first-degree relative
- Twin studies show a genetic component

With or without agoraphobia:

Agoraphobia is "anxiety about being in places or situations where escape might be difficult (or embarrassing) or where help might not be available in the event of having a panic attack or panic-like symptoms". Agoraphobia develops secondary to panic disorder in some patients.

DSM-IV DIAGNOSTIC CRITERIA FOR PANIC ATTACKS:

- At least 4 attacks occurred in a four week period.
- At least one attack has occurred totally "out of the blue".
- A fear of having another attack that has lasted at least one month.
- At least 4 of the following symptoms developed during at least one of the attacks:
  1. Dyspnea
  2. Dizziness / faintness
  3. Palpitations or tachycardia
  4. Trembling or shaking
  5. Sweating
  6. Choking
  7. Nausea or abdominal distress
  8. Depersonalization or Derealization
  9. Parasthesias
  10. Hot / cold flashes
  11. Chest pain
  12. Fear of dying
  13. Fear of going crazy or doing something uncontrolled

***must develop within 10 minutes of first symptom; caution of organic factors.
(generally resolves within 20-30 minutes, high use of healthcare system.)

Treatment:

- Cognitive-behavioral therapy is effective in reducing attacks in >80% of patients
  - Especially with agoraphobia
- Medications:
  1) Paxil or Zoloft (start very low and ↑ slowly) – FDA approved
     - Other SSRIs / newer antidepressants may work (except bupropion)
     - Prozac is now available in 10mg scored tablets
  2) Tricyclics: Imipramine; start low / go slow, takes 4-6 weeks.
     - Desipramine is used also.
  3) Benzodiazepines: Alprazolam (hi dose), diazepam, clonazepam
  4) MAOIs: Phenelzine 45-90mg/day, may take 6+ weeks.
- Should start antidepressant and prn BZD at same time
  - Watch for stimulating effects from antidepressants (both TCAs and SSRIs)
  - Taper off BZD after 1-2 weeks as ↑'ing antidepressant dosage
- **Current treatments should not employ BZDs as sole therapy!!!!!**

D. OBSESSIVE - COMPULSIVE DISORDER (OCD)
(see complete lecture for full information)

Obsessions: Recurrent and persistent thoughts, ideas, impulses, or images, initially considered intrusive and senseless. Person attempts to ignore / suppress, which causes marked distress. Person recognizes as unreasonable.

Compulsions: Repetitive, purposeful, intentional behaviors, performed in response to an obsession. Performed according to certain rules or in a stereotyped fashion. This behavior is designed to neutralize or to prevent discomfort. Person recognizes behavior as excessive and unreasonable.

The obsessions and compulsions cause the person marked distress, are time-consuming (more than an hour / day), or significantly interfere with the person's normal routine, occupational functioning, or usual social activities or relationships.

-Pathophysiology:
- -unknown origin
- -serotonin mediated 2° to tx's used
  - -5HT agonist, m-CPP, ↑ OCD symptoms
  - -clomipramine ↓'ed symptoms
  - -5HT antagonists worsened symptoms after clomipramine
- -? abnormal pathways b/t frontal lobes and basal ganglia (PET scan)
- -PET studies suggest a hyperfunctioning "loop" in the brain

-Treatment (Pharmacological) - (assumed behavioral tx is also done)
- -About 20% have significant recovery, about 50% have partial recovery (improved quality of life).

1) Fluoxetine: 20-80 mg/day (doses tend to avg. at 60-80mg/day)
2) Clomipramine: up to 250mg/day, seizures (0.5%), anticholinergic, sedation, orthostasis, sexual dysfunction (up to 70%), typical TCA(caution in pts. with hx. of seizures, alcoholism, brain liver disease.
3) Benzodiazepines: during periods of intense anxiety. (rarely used)
4) MAOIs/Tricyclics: generally 2nd & 3rd line agents (use after FLX, CLO)

E. POST-TRAUMATIC STRESS DISORDER (PTSD)

- Acute or delayed symptoms. When an out of normal experience is witnessed or experienced.
- Nightmares and flashbacks. Re-experiencing of the event!
- Avoidance behavior of triggers of the event. Autonomic hyperactivity and outbursts occur.
- Every drug has been tried. Can only reduce or try to manage the symptoms.
- Sertraline (Zoloft®) is the first FDA approved drug to treat this disorder.

ATTENTION DEFICIT HYPERACTIVITY DISORDER

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A. Epidemiology
    1. Onset is typically by age 3 and must be by age 7
    2. Approx. 10% of boys and 2% of girls
    3. General prevalence is 6%
    4. Frequently comorbid with anxiety, depression, learning deficiencies, and conduct / oppositional disorder
B. Etiology / Pathophysiology
    1. May be genetic
    2. May be due to Fetal Alcohol Syndrome, lead poisoning, and meningitis
C. Clinical Presentation - target symptoms of ADHD
    1. Inappropriate inattention
        a. Failing to finish tasks
        b. Not seeming to listen
        c. Easily distracted
    2. Impulsivity
        a. Acting before thinking
        b. Difficulty awaiting turn
        c. Needing much supervision
    3. Hyperactivity
        a. Excessive movement (ie. running, climbing)
D. Diagnostic Criteria

Attention-Deficit/Hyperactivity Disorder

A. Either (1) or (2):

(1) Six (or more) of the following symptoms of **inattention** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Inattention

(a) Often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
(b) Often has difficulty sustaining attention in tasks or play activities
(c) Often does not seem to listen when spoken to directly
(d) Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
(e) Often has difficulty organizing tasks and activities
(f) Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
(g) Often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)
(h) Is often easily distracted by extraneous stimuli
(i) Is often forgetful in daily activities

(2) Six (or more) of the following symptoms of **hyperactivity-impulsivity** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Hyperactivity

(a) Often fidgets with hands or feet or squirms in seat
(b) Often leaves seat in classroom or in other situations in which remaining seated is expected
(c) Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
(d) Often has difficulty playing or engaging in leisure activities quietly
(e) Is often "on the go" or often acts as if "driven by a motor"
(f) Often talks excessively

Impulsivity

(g) Often blurts out answers before questions have been completed
(h) Often has difficulty awaiting turn
(i) Often interrupts or intrudes on others (e.g., butts into conversations or games)

B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.
C. Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home).
D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.
E. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).

E. Course of Illness
    1. Symptoms usually decrease by adolescence
    2. May persist into adulthood (30-70%)
    3. Hyperactivity doesn't usually persist

F. Considerations in the Pharmacotherapy of ADHD
    1. Mild cases
        a. Environmental manipulation
        b. Educational and behavioral interventions
    2. Moderate to severe cases
        a. Medication intervention may be needed in addition to the above
        b. Stimulants are the most effective treatment for severe disorder
    3. Caution of cardiovascular complications with TCAs

G. Review of the Pharmacotherapeutic Agents Used in the Management of ADHD
    1. Medications used in ADHD
        a. Psychostimulants
            1. Methylphenidate (Ritalin®)
            2. Dextroamphetamine (Dexedrine®)
            3. Pemoline (Cylert®)
            4. Amphetamine/Dextroamphetamine (Adderall®)
        b. Bupropion (Wellbutrin®)
        c. *Alpha*$_2$ agonists
            1. Clonidine (Catapres®)
            2. Guanfacine (Tenex®)
        d. Antidepressants
            1. Tricyclic Antidepressants (TCAs)
            2. Monoamine Oxidase Inhibitors (MAOIs)
            3. Selective Serotonin Reuptake Inhibitors (SSRIs)
    2. Psychostimulants in ADHD
        a. Approximately 60-75% effective on symptoms
        b. Effects rapidly evident
        c. Cylert® less effective (50%)
        d. Inhibit the reuptake of dopamine and norepinephrine
        e. Also release DA, NE, and 5HT from presynaptic neurons
        f. May inhibit the enzyme Monoamine Oxidase
        g. "May serve as a homeostat to stabilize arousal and thereby temper the spontaneous fluctuations of behavior."[1]
        h. Reaction is not paradoxical and not specific for ADHD
        i. Non-ADHD children will also experience increased attention, decreased motor activity, and improvement on learning tasks[2]
        j. Low abuse potential in children
        k. Possible abuse by family, friends, etc.
        l. May cause motor or vocal tics and ↑BP
        m. May inhibit growth, sleep, and appetite
        n. Should not be given late in day unless absolutely needed due to insomnia
    3. Specific Psychostimulants
        a. Methylphenidate (Ritalin®)
            1. Dosing begins at 5mg a day and can be adjusted by 5-10mg a week
            2. Can be dosed up to 60mg a day (or 2mg/kg/day)
            3. Doses can be divided and given 2-3 times a day
            4. Response is seen in 15-30 minutes
            5. Effects last approx. 2-4 hours
            6. Available in 5mg, 10mg, and 20mg tablets

[1] Theesen KA and Dopheide JA. Disorders of Childhood. Pharmacotherapy: A Pathophysiologic Approach 3rd Ed. Stanford, Appleton & Lange, 1997,1301-10.
[2] Rapoport JL *et al*. Archives of General Psychiatry 1980;37:933-943

7. Doses should be given 30-45 min before meals to reduce anorexia
8. Contraindicated with severe depression, *Gilles de la Tourette's* syndrome, motor tics
9. Side effects:
    a. abdominal pain
    b. weight loss
    c. insomnia
    d. agitation
    e. tachycardia

b. Ritalin SR® (Sustained-Release)
1. Longer duration of action (8 hours)
2. Peak effects in 4-5 hours
3. Same dose, but lower plasma levels
4. Equally or less effective than regular release
5. Should not be chewed or crushed
6. Available in 20mg tablets

c. Dextroamphetamine (Dexedrine®)
1. Dosing begins at 2.5mg a day
2. Adjust by 2.5mg a day at weekly intervals
3. Can be dosed up to 40mg
4. Doses can be divided and given 2-3 times a day
5. Response is seen in 15-30 minutes
6. Effects last 3-8 hours
7. Available in 5mg and 10mg tablets

d. Dexedrine Spansules®
1. Sustained-release formulation
2. Available in 5mg, 10mg, and 15mg capsules

e. Pemoline (Cylert®)
1. Not an amphetamine
2. Dosing begins at 18.75mg once a day
3. Adjust by 18.75mg a week
4. Can be dosed up to a maximum of 112.5mg/d
5. Response may take a few weeks
6. May be faster if higher doses are used
7. 2-3mg/kg/day
8. Less effective in ADHD (only 50%)
9. Several children have died from acute, unpredictable hepatic failure
10. Less peripheral side effects (ie. blood pressure)
11. Available in 18.75mg, 37.5mg, and 75mg tablets
12. Also available as a 37.5mg chewable tablet

f. Adderall®
1. Contains an equally proportioned mixture of 4 amphetamine salts
    a. Dextroamphetamine saccharate
    b. Dextroamphetamine sulfate
    c. Amphetamine aspartate
    d. Amphetamine sulfate
2. Approved for children 3yrs of age and older
3. Dosing begins at 2.5-5mg a day
    -- 1/4 to 1/2 tablet in the morning
4. Maximum of 40mg a day

5. Most patients respond to 10-20mg a day given QD or divided BID
6. Duration of action is approx. 8 hours

4. Bupropion (Wellbutrin®)
    a. Antidepressant with stimulant-related properties
    b. Mechanism of action possibly related to DA and NE reuptake inhibition
    c. Shown effective in both childhood and adult ADHD in several studies over placebo
    d. Shown in one study to be comparable to methylphenidate[1]
        [1]Barrickman *et al.* J Am Acad Child Adolesc Psychiatry 1995; 34:649-57.
    e. Begin with 50mg a day
    f. Average dose in children is 3-6mg/kg/day
    g. Can be dosed up to 450mg/d in adults
    h. Should be divided at a maximum of 150mg/dose
    i. No dosing maximum is set for children
    j. Onset of effect may take 3-4 weeks
    k. May exacerbate tics in *Tourette's* Syndrome
    l. Second-line to stimulants due to time of onset
    m. Adverse effects (very mild, well tolerated)
        1. Nausea / vomiting, constipation, dry mouth
        2. Headache, nervousness, skin rash
        3. Seizures with regular release (0.3-0.4%)
    n. New Sustained Release formulation
        1. Advantage of less side effects due to decreased plasma levels
        2. Lower seizure incidence (0.1%)
    o. Contraindicated in patients with seizure disorders and eating disorders!
5. Clonidine (Catapres®)
    a. Decreases <u>hyperactivity</u> and aggressiveness
    b. Mechanism of action may be the result of a reduction in the firing rate of the locus coeruleus
    c. Decreases excessive arousal
    d. Reduces noradrenergic activity
    e. Dosing begins at 0.05mg a day
    f. 0.004-0.005mg/kg/day
    g. May be increased by 0.05mg every few days up to 25mcg/kg/day
    h. Peak effects 3-5 hours after dosing
    i. Improvement may take weeks
    j. Taper before discontinuation to prevent rebound hypertension
    k. Transdermal patch available
    l. Only lasts 5 days in children compared to 7 days in adults
    m. May be useful in comorbid *Tourette's* Syndrome
    n. Adverse effects
        1. Dry mouth (40%), drowsiness (33%), fatigue
        2. Dizziness (16%), constipation (10%), depression
        3. Side effects may diminish within 4-6 weeks
        4. Drowsiness may be useful with insomnia from stimulants
6. Guanfacine (Tenex®)
    a. Mechanism similar to clonidine
    b. Action may be specific for cerebral cortex
    c. Clinical advantages:
        1. Longer half-life

2. Less sedation
3. Less risk of rebound hypertension if abruptly discontinued

d. Dosing begins at 0.5mg a day
e. Average is 0.5mg twice daily
f. Doses should not exceed 4mg/day divided
g. Adverse effects seen are also similar to clonidine, but to a lesser extent
h. Dose-related decreases in blood pressure seen above 2mg a day
i. There are only a few studies with few patients

7. Tricyclic Antidepressants (TCAs)
   a. Imipramine (Tofranil®) and Desipramine (Norpramin®) studied most
   b. Nortriptyline (Pamelor®) also effective
   c. Onset of effect is 2 - 4 weeks
   d. Effect may wear off after several months
   e. Dosing begins at 10mg twice daily or 25mg/d
   f. Therapeutic range is 1-5mg/kg/day divided
   g. Advantages over stimulants:
      1. Longer duration of action
      2. Less sleep disturbance
      3. Reduced risk of abuse
      4. Lack of growth suppression
      5. Reduced likelihood of exacerbating tics
   h. Disadvantages over stimulants:
      1. Decreased efficacy
      2. Risk of death in overdose (cardiac toxicity)
      3. More adverse effects
   i. Side effects
      1. CNS effects: sedation or stimulation
      2. Dry mouth, blurred vision, urinary retention
      3. Cardiac effects and toxicity
      4. Weight gain
      5. Allergic reactions

8. Monoamine Oxidase Inhibitors (MAOIs)
   a. Efficacy similar to Dextroamphetamine
   b. Phenelzine (Nardil®)
   c. Tranylcypromine (Parnate®)
   d. Mechanism of action
      1. Irreversibly inhibit enzyme MAO
      2. 2 week duration of action
      3. Result is more dopamine, norepinephrine, and serotonin in synaptic cleft of neurons
   e. Adverse Effects of MAOIs
      1. Postural hypotension
      2. Hepatic complications
      3. Dry mouth, blurred vision, urinary retention
      4. Sedation (mostly with Nardil®)
      5. Stimulation (mostly with Parnate®)
      6. Hypertensive Crisis

9. Selective Serotonin Reuptake Inhibitors (SSRIs)
    a. Use in ADHD needs further study
    b. Fluoxetine (Prozac®)[1]
    c. Sertraline (Zoloft®)
    d. Paroxetine (Paxil®)
    e. Fluvoxamine (Luvox®)
    f. Preliminary trial showed 11 of 19 treatment-refractory children improved.
       --Barrickman L *et al.* J Am Acad Child Adolesc Psychiatry 1991;30:762-7.
    g. SSRI Adverse Reactions
        1. Weight loss / anorexia
        2. Anxiety
        3. Insomnia
        4. More with Prozac® and Zoloft®
        5. Some drowsiness with Paxil® and Luvox®
        6. Headache, sweating
        7. Nausea, and diarrhea

PHARMACOTHERAPY OF BIPOLAR DISORDER

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Learning objectives:

1. Be familiar with the general epidemiology, possible pathophysiology, and course of Bipolar disorder.

2. Be able to identify the target symptoms of mania (mood, cognitive, behavioral).

3. List the indications, clinical efficacy, pharmacokinetic characteristics, dosing, and monitoring parameters for Lithium.

4. Be able to list the side effects of Lithium (dose related and non-dose related) and be able to identify Lithium toxicity and its treatment.

5. Describe what tests are done for the initial work-up for Lithium tx. and why they are done and then what monitoring parameters are used for Lithium maintenance.

6. Be familiar with the DSM-IV criteria for Bipolar disorder (Mania)

7. Be able to identify possible organic causes of manic or hypomanic-like symptoms.

8. Describe the rational for the use of concomitant antipsychotic and/or benzodiazepine drug therapy with Lithium in the treatment of mania.

9. Identify potentially significant drug interactions with Lithium and also possible situations that may affect Li+ levels.

10. Identify and describe alternative Pharmacotherapy for bipolar disorder. in Li+ intolerant or refractory patients (i.e. Carbamazepine and Valproic acid); including (drug, doses, monitoring, SE's, drug interactions, efficacy).

PHARMACOTHERAPY OF BIPOLAR DISORDER

I. Introduction / Epidemiology / Course of Illness

A. Cyclic disorder -- fluctuations in mood, energy, behavior
B. Genetically based, environmentally influenced, and clinical presentation varies from person to person
C. Lifetime prevalence = 0.6-1.2%
   1. women = men
   2. onset usually between 18-44 (late adolescence / middle age)
D. Subtypes of bipolar disorder[1]
   1. 40% only manic
   2. 40-50% mixed mania
   3. Mania with ANY depression
   4. 12-20% rapid cyclers
   5. 8-10% Bipolar II

II. Pathophysiology – all theoretical, nothing is certain

A. Genetics -- 80-90% have a relative with Bipolar Disorder
   1. Twins -- 80% concordance
   2. Child of 1 parent ≅ 40% chance
B. Neurotransmitter theories -- ↓ in depression / ↑ in mania
   1. ? dysregulation with DA and NE balance
      -↓ NE or ↑ DA = mania
   2. Maybe a GABA deficiency [inh. NE / DA]
      -most of our drugs ↑ GABA activity
C. Receptor Functioning theories -- due to fact that Li+ affects N.T.'s from production to release
   - Also affects B-receptor and DA receptor sensitization (↓)
D. Sensitization-Kindling theories -- useful to explain rapid cyclers
   - Similar to anticonvulsant seizure model -- kindling→mania
E. Neuroendocrine theories -- HPA / thyroid dysfx.
   -Li+ can cause ↓ thyroid fx.
F. Electrolyte and Membrane theories -- ↑Ca^{++} CSF conc's
   -? 2nd messenger systems ⇒Li^{+} interferes
G. Environmental, Seasonal, Circadian rhythm theories -- DIAGRAM
   -Night -- melatonin released
   -Changes in sleep cycles⇒mania - insomnia
   ⇒depression - hypersomnia

III. Target Symptoms for Bipolar Disorder (MANIA)

A. Mood-
   1. Euphoric
   2. Elated
   3. Happy

[1] Goodwin and Jamison, 1990

B. Cognitive and perceptual-
   1. Grandiose
   2. Flight of ideas / racing thoughts
   3. Hallucinations & delusions (paranoid / grandiose --2/3)
   4. Ideas of reference

C. Activity and behavior-
   1. Aggressiveness / violence / outbursts
   2. Insomnia / constant motion
   3. Impulsiveness -- i.e. buying sprees
   4. Pressured speech
   5. ↑ sexual activity
   6. ↑ artistic abilities

DSM-IV Diagnostic Criteria for a Manic Episode

A) One or more distinct periods when mood was abnormally and persistently elevated, expansive, or irritable for at least 1 week.
B) During the period of mood disturbance, at least three of the following symptoms persisted (four if the mood was only irritable) and were present to a significant degree:
   1. Inflated self-esteem (grandiosity, which may be delusional)
   2. Decreased need for sleep (e.g. feels rested after only 3 hours of sleep)
   3. More talkative than usual or pressure to keep talking
   4. Flight of ideas or subjective experience that thoughts are racing
   5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
   6. Increase in activity (either socially, at work, or sexually) or psychomotor agitation
   7. Excessive involvement in pleasurable activities that have a high potential for painful consequences that is not recognized, (for example, buying sprees, sexual indiscretions, foolish business investments, reckless driving)
C) Episode of mood disturbance sufficiently severe to cause marked impairment in social or occupational functioning, or hospitalization was necessary.
D) At no time during the illness were delusions or hallucinations present at least 2 weeks in the absence of prominent mood symptoms, that is, before the mood symptoms developed or after they remitted.
E) Not superimposed on either schizophrenia, schizophreniform disorder, or a delusional disorder.
F) Not sustained by a specific organic factor or substance (although there may be an organic precipitant).

--Manic episode is defined as meeting criteria A, B, and C. A hypomanic episode meets only criteria A and B (no marked impairment).

Organic causes of manic and hypomanic symptoms:

Medications

Alcohol	Amantadine	Disulfiram
Amphetamines	Ephedrine	Anabolic steroids
Antidepressants	Monoamine oxidase inhibitors	Baclofen
Bromides	Niridazole	Bronchodilators
Calcium replacement	Procarbazine	Captopril
Cocaine	Theophylline	Corticosteroids (ACTH)
Hallucinogens	Indomethacin	Anticholinergics
Isoniazid	Anticonvulsants	Levodopa
Methylphenidate	Benzodiazepines	Metoclopramide
Phenylpropanolamine	Caffeine	Procainamide
Quinacrine	Cimetidine	Sympathomimetics
Thyroid supplements	Tolmetin	Decongestants
Yohimbine	Diltiazem	

Medical conditions

AIDS	Neoplasm	Addison's disease
Cushing's disease	Post concussion	Encephalitis (herpes simplex, HIV)
Epilepsy	Right-temporal lobe seizures	Post-infection (viral, encephalitis, influenza)
Hemodialysis	Postcerebrovascular accident	Multiple sclerosis
Hyperthyroidism	Huntington's disease	Surgical trauma with subsequent epileptic focus
Neurosyphilis	Carcinoid tumors	Post-electroconvulsive therapy
Subarachnoid hemorrhage		

Drug withdrawal syndromes

Baclofen	Tricyclic antidepressants	Clonidine
Corticosteroids	Methyldopa	

IV. Medications

Lithium (Eskalith®, Lithobid®, others)

A. Efficacy / Mechanism of Action
   1. 60-80% effective for acute manic episode / 80-90% effective for prophylaxis
   2. Affects all neurotransmitters from production to release
   3. Has some calcium blocking activity

B. Pharmacokinetics
   1. Absorption
      a. Readily absorbed from the GI tract (95-100%)
      b. Peak serum levels occur in 2-4 hours
      c. Complete within 8 hours
      d. Slow release formulations have a slower and more variable absorption rate
   2. Distribution
      a. Approximates total body water (0.5-1.2 L/kg)
      b. Not protein bound!
      c. CSF concentration 40-50% that of plasma
      d. Brain concentrations 50% than that of plasma
   3. Elimination
      a. >95% renally excreted
      b. 80% is reabsorbed at proximal tubule
      c. 20% is excreted in urine
      d. $T_{1/2}$ ranges from 18 to 36 hours depending on age, renal fxn., disease state, and concomitant drug use. (avg.=24 hours)

C. Pre-treatment work-up
   1. Serum creatinine (24 hr CrCl if needed)
   2. Urinalysis / osmolality / specific gravity
   3. CBC w/ diff.
   4. Serum electrolytes / glucose
   5. Weight
   6. EKG, Pulse/BP
   7. Thyroid function tests
   8. History and Physical (of course)

D. Administration and dosage
   1. Initiation
      a. Start low and titrate upward slowly
      b. Usually start at 300 mg bid, then titrate upwards 600 - 900 bid to tid according to serum levels and clinical response.
      c. Observe for clinical improvement
      d. Serum level range:
         - Acute phase = 0.8 - 1.2 mEq/L (up to 1.4 severe)
         - Maintenance phase = 0.4 - 1.0 mEq/L
   2. Steady-state serum level determination
      a. Steady-state should be reached after 4-5 days of each dosage change
      b. Draw levels 12 hours post dose
   3. Once maintenance therapy is achieved, monitor every 2 to 3 months.

E. Side effects

1. **Early**

-GI disturbances (N/V, diarrhea, anorexia)
-Muscle weakness, lethargy
-Sedation
-Headache, ↓ memory, confusion, ↓ concentration
-Polyuria/polydipsia
-Tremor
-Dry mouth
-Leukocytosis

2. **Maintenance**

-Fine hand tremor
-Polyuria / polydipsia
-Weight gain
-Goiter / hypothyroidism
-Leukocytosis
-EKG changes
-Neurologic (cogwheel rigidity, concentration, ↓ memory)- rare
-Dermatologic (psoriasis, alopecia, rash, acne)
-↓ libido
-Altered taste (metallic)

3. **Late**

-Nephrogenic diabetes insipidus
-Hypothyroidism

4. **Toxicity** - related to serum levels

-Diarrhea
-Severe Nausea and Vomiting
-Coarse hand tremor
-Hyperreflexia
-Drowsiness, lethargy
-Muscular weakness, lack of coordination, ataxia
-Blurred vision, dry mouth
-Large output of dilute urine
-Confusion, CNS irritability
-Slurred speech
-Cardiovascular (arrhythmias, hypotension)
-Seizures, Coma, Death

5. **Treatment of extreme lithium toxicity**

a. Lavage (for acute ingestion)
b. Correct / Maintain fluid and electrolyte balance
c. Monitor cardiac and respiratory fxn.
d. Seizure precautions
e. Monitor Lithium concentrations (q 3-4 hours)
f. Dialysis! [NOTE: Lithium is the only psychotropic that is dialyzable!]

F. Drug Interactions
1. NSAID's
2. Diuretics
3. Neuroleptics
4. Xanthines
5. Cardiovasculars
6. Others

G. Contraindications
1. Significant renal, cardiovascular, thyroid disease
2. Pregnancy, caution w/ breast-feeding
3. Dehydration syndromes

H. Patient information
1. Take with food or milk.
2. Discontinue medication and notify physician if signs of toxicity occur.
3. May cause drowsiness, caution while driving
4. Maintain adequate fluid and salt intake, especially in situations of dehydration.

I. Follow-up
1. Record weight every 3-6 months
2. Check lithium levels monthly, then q 3-4 MOS.
3. Serum creatinine every 3 months
4. Yearly physical exam and routine lab tests for work-up including thyroid function tests.

J. Situations which may ↑ Lithium levels
1. Low sodium diet (↑Na^+ = ↓Li^+)
2. Diuretics (Thiazides) - up to 1/3 more
3. Excess sweating and exercise
4. Protracted diarrhea or vomiting
5. Renal disease
6. Post-partum fluid changes
7. NSAIDs - due to ↓'ing renal function
8. Dehydration

<u>Valproic Acid (Depakote®, Depakene®)</u> -- FDA approved for Bipolar

A. Efficacy:
-May be >50-90% effective for acute mania and maintenance therapy

B. Mechanism of Action:
1. Inhibits GABA metabolism
2. ↑ synthesis and release of GABA

C. Baseline assessment:
1. Less toxicity with this agent
2. Use same tests as for CBZ (LFT's, CBC w/diff., platelets, etc.)

D. Dosing:
    1. Start at 250-500 mg/day in divided doses
    2. ↑ by 250 mg/day every 3 to 4 days as tolerated and necessary
    3. Dose range is approx. 500 to 3000 mg/day in divided doses (Max. = 60mg/kg/d)
    4. Fast crisis stabilization regimen
        a. New literature says load at 20mg/kg/d, divided
        b. Draw level in 24hrs and adjust dose
        c. Final dose should be ten times wt. in lbs. (i.e. 150lbs=1500mg/d)
    5. Give with food to minimize GI SE's.

E. Plasma concentrations and routine monitoring:
    1. 50-125mcg/ml for acute bipolar treatment (80mcg/ml is target)
    2. 50-100mcg/ml for maintenance therapy

F. Adverse effects:
    1. Neurologic-
    2. Gastrointestinal-
    3. Hematologic-
    4. Hepatotoxic-
    5. Dermatologic-
    6. Tremor-
    7. Caution with pregnancy and breast-feeding

G. Drug Interactions:
    1. Enzyme inhibitor of metabolism
    2. Protein bound drugs (e.g. warfarin / aspirin)
    3. Lithium may ↑ Depakote concentrations

Carbamazepine (Tegretol®, others)

A. Efficacy:
    1. 60% for acute mania
    2. 60-75% for prophylaxis

B. Mechanism of Action:
    1. Structurally like a TCA
    2. ↓'s kindling (i.e. rapid cycling)
    3. ↓'s Dopamine and GABA turnover

C. Baseline assessment:
    1. CBC w/diff, Platelet count
    2. LFT's
    3. TFT's
    4. Electrolytes
    5. SrCr, BUN, Urinalysis
    6. History and Physical
    7. Neurological assessment
    8. EKG (if necessary)

D. Dosing:
   1. Initiate at 200 to 400mg/d
   2. Increase by 200mg every 3-5 days up to 600mg to 1200mg/day in divided doses (use higher doses if necessary)

E. Plasma concentrations and routine monitoring:
   1. Draw levels at steady state (1-2 wks after initiation)
   2. Then biweekly x 2 months → [NOTE: autoinduction occurs in ≈4-5 weeks]
   3. Then every 2-4 months if necessary

F. Adverse effects:
   a. Neurologic-
   b. Gastrointestinal-
   c. Dermatologic-
   d. Hematologic-
   e. Hyponatremia-
   f. Hepatic-
   g. Caution in pregnancy and breast-feeding

G. Potential Drug-Drug interactions:
   1. Metabolic
      a) Enzyme inducer of all drugs metabolized
      b) Enzyme inhibitors will ↑ CBZ levels (e.g. Cimetidine, Fluoxetine)
   2. Protein Binding

IV. OTHER TREATMENT MODALITIES (TO BE USED AS ADJUNCTIVE THERAPY ONLY)

1. Benzodiazepines:
   A. Lorazepam
   B. Clonazepam
   C. Benzodiazepines usually control manic symptoms faster, are safer, and may allow for lower doses of Antipsychotics to be used if their use is required.

2. Antipsychotics:
   A. **All** antipsychotics can be used (depends on specific pt. presentation)
   B. Antipsychotics usually control manic symptoms faster than Li+.
   C. Not to be used chronically for bipolar disorder
   D. May be the safest option for a bipolar female who is pregnant

3. ECT (Electroconvulsive Therapy)

4. Other potential therapies:
   A. Calcium channel blockers (Verapamil, Nimodipine)
   B. Clonidine
   C. Propranolol
   D. *Combinations with TCAs **or** MAOIs - Be careful not to induce mania.
   E. Lamotrigine (Lamictal®) - in study (may also have antidepressant effects)
   F. Gabapentin (Neurontin®) - in study (may be used as an adjunct to other anti-manics)

PHARMACOTHERAPY OF MAJOR DEPRESSION

Leonard Rappa, Pharm.D., BCPP
Assistant Professor, Florida A&M University

Learning objectives:

1. Be familiar with the general epidemiology, possible pathophysiology (theories), and course of Major depression.

2. Be able to list the target symptoms of depression and the DSM-IV criteria for Major depression.

3. Discuss the role of medications (i.e. efficacy) in the treatment of depression.

4. Know the basic mechanisms of action for the various antidepressants.

S. Be able to identify possible non-psychiatric and psychiatric disorders or possible organic causes of depression. (i.e. medical conditions, drugs).

6. Be able to list the various categories or classes of antidepressants and identify which drug belongs to which class. (i.e. MAOIs, TCAs: secondary and tertiary amines, non-TCAs, SSRIs, etc.)

7. Be able to list the drug selection criteria for antidepressant therapy.

8. Know the doses, adverse effects, possible drug-drug or drug-food interactions, and clinical considerations that effect drug therapy with antidepressants for all antidepressants.

AFFECTIVE DISORDERS

I. Classification of Affective (Mood) Disorders

A. Depressive Disorders 1. Major Depression (>2 wks) a. Single Episode b. Recurrent 2. Dysthymia (>2 yrs) 3. Double Depression	B. Bipolar Disorders 1. Bipolar a. Mixed b. Manic c. Depressed d. Type I or Type II 2. Cyclothymia 3. Seasonal Affective Disorder (SAD)

II. Major Depression

A. Epidemiology

B. Proposed etiologies

1. Biogenic-amine Theory
   -deficit of NE &/or 5HT in synaptic cleft

2. Receptor-sensitivity theory (Modified biogenic-amine theory)
   -alterations in sensitivity of receptor systems (dysregulation)

3. Cortisol theory
   -overstimulation of cortisol on its receptor leads to down-regulation of receptor which leads to depression

C. Signs / Symptoms **-- S.I.G.E.C.A.P.S.**

1. depressed mood
2. change in **S**leep habits
3. loss of pleasure / **I**nterest in usual activities (anhedonia)
4. feelings of worthlessness or **G**uilt
5. loss of **E**nergy
6. difficulties in thinking / **C**oncentration
7. change in **A**ppetite
8. **P**sychomotor retardation or agitation
9. recurrent thoughts of death and **S**uicide
10. DSM-IV criteria

III. Dexamethasone suppression test (DST)

IV. Thyrotropin Releasing Hormone Test (TRHT)

COMMON DISEASES AND DRUGS ASSOCIATED WITH DEPRESSION

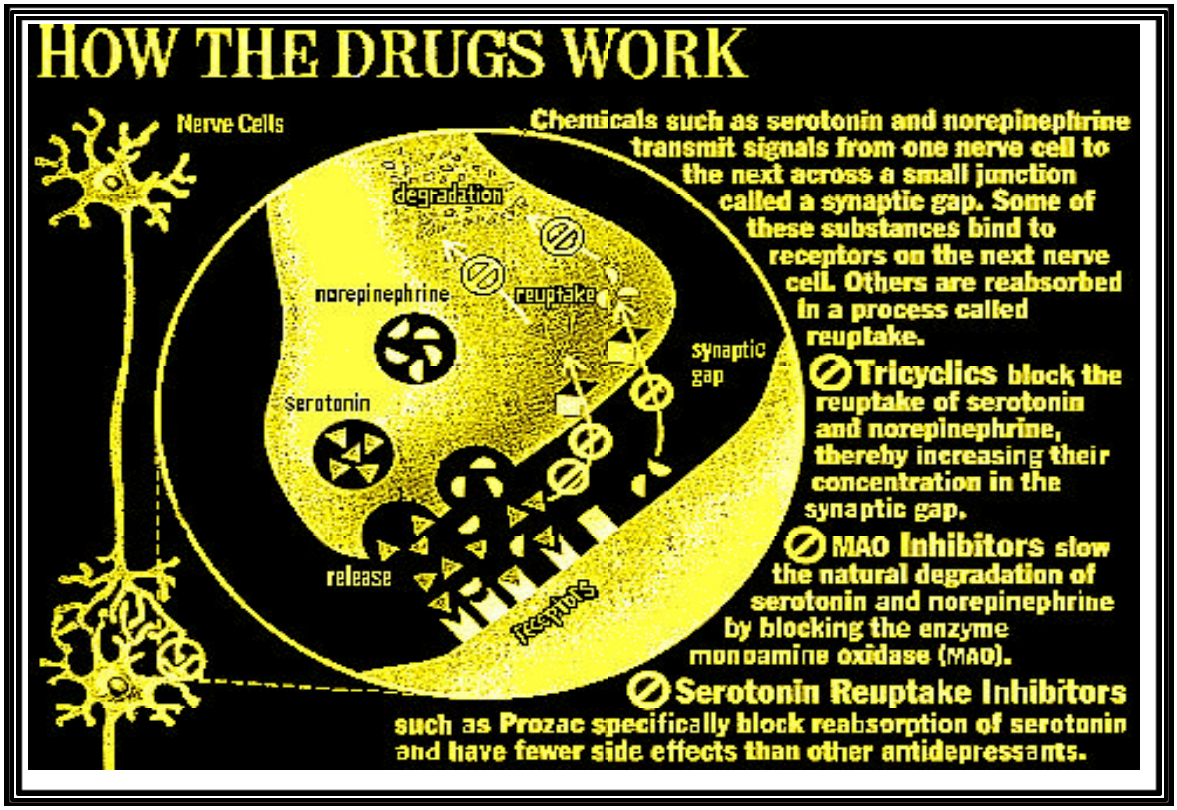
Medical Disorders		***Psychiatric Disorders***	***Drugs***
Endocrine Disorders	Collagen disorders	Anxiety disorders	Alcohol
Hypothyroidism	Metabolic disorders	Generalized Anxiety disorder	Anabolic steroids
Addison's disease	Hypokalemia	Panic disorder	Antihypertensives
Cushing's disease	Hyponatremia	Phobic disorders	*Alpha*-Methyldopa
Deficiency states	Hepatic encephalopathy	Post-traumatic stress disorder	*Beta*-blockers
Pernicious anemia	Cardiovascular disease	Eating disorders	Calcium channel blockers
Wernicke's encephalopathy	Neurological disorders	Anorexia nervosa	Clonidine
Severe anemia	Alzheimer's disease	Bulimia	Guanethidine
Infections	Huntington's disease	Obsessive-compulsive disorder	Reserpine
Encephalitis	Multiple sclerosis	Personality disorders	Barbiturates
Hepatitis	Parkinson's disease	Schizophrenia	Benzodiazepines
Influenza	Stroke (CVA)	Somatization disorder	Corticosteroids
Mononucleosis	Malignancies / cancer	Substance abuse	Diuretics
Tuberculosis	Wilson's disease	Alcoholism	H_2-antagonists
AIDS			Isoniazid
Systemic Lupus erythematosus (SLE)			Isotretinoin
			Opiate analgesics
			Oral contraceptives
			NSAIDs

V. Pharmacologic Treatment of Depression:

A. Efficacy – Each is 60 to 80% effective

B. Drug Selection Criteria (a PROCESS OF ELIMINATION):

1. Patient's history of response
2. Family History
3. Patient's Medical Status
4. Side effect profile
5. Patient's clinical presentation (severity/suicidality)
6. Subtype of Depression
7. Drug-Drug interaction potential
8. Drug cost to patient
9. Previous compliance issues



VI. Heterocyclic / TCA Agents:

A. Mechanism of Action:

1. inhibition of pre-synaptic reuptake mechanisms
2. changes in receptor sensitivity

B. Administration and Dosage:

DRUG	USUAL DOSAGE RANGE	
Amitriptyline (Elavil®)*	25-300 mg/d in single / divided doses	3° amines
Imipramine (Tofranil®)**	25-300 mg/d in single / divided doses	
Doxepin (Sinequan®, Adapin®)	25-300 mg/d in single / divided doses	
Trimipramine (Surmontil®)	25-300 mg/d in single / divided doses	
Nortriptyline (Pamelor®)*	25-200 mg/d in single / divided doses	2° amines
Desipramine (Norpramin®)**	25-300 mg/d in single / divided doses	
Protriptyline (Vivactil®)	15-60 mg/d in single / divided doses	
Clomipramine (Anafranil®)	25-250mg/d in single / divided doses	
Amoxapine (Asendin®)	50-600 mg/d in single / divided doses	
Maprotiline (Ludiomil®)	50-225 mg/d in single / divided doses	

VII. Adverse effects:

A. Adverse behavioral effects

1. Drowsiness / sedation (very common)
2. CNS stimulation (more with 2° amines)
3. Toxic Psychosis

B. Anticholinergic side effects

1. Blurred vision
2. Constipation
3. Dry mouth
4. Tachycardia
5. Urinary retention
6. Decreased memory, delirium
7. Cholinergic rebound upon abrupt withdrawal -- **taper off!**

C. Seizures

1. Highest with Bupropion (non-TCA), Amoxapine, and Maprotiline **[BAM]**
2. **All antidepressants lower seizure threshold!!!**

D. Autonomic side effects
    1. Nasal congestion
    2. Tremors
    3. Sexual dysfunction (not as high as with SSRIs)

E. Cardiac Side effects
    1. Heart Block - 1° or 2° is contraindicated
    2. Arrhythmias (Quinidine-like effects) - prolong Q-T interval
    3. Hypotension / orthostasis
    4. Tachycardia (direct, anticholinergic, and reflex)

F. Other:
    1. weight gain
    2. allergic rxn's (rash, urticaria, photosensitivity, drug fever)
    3. agranulocytosis (rare)
    4. hepatic obstructive jaundice (very rare)
    5. endocrinologic (i.e. SIADH)
    6. Caution in pregnancy and breastfeeding!
        a. Most are Category C or B (fairly safe)

VIII. Clinical considerations

A. May take from 4 to 6 weeks before maximum clinical improvement is seen. (Some improvement may be seen in 1 to 3 weeks.)

B. Evaluate suicide potential - dispensing small quantities of TCAs
    1. Toxic doses (750mg to 1500mg can kill)
    2. May consider SSRIs, trazodone, or newer agents (e.g. Mirtazapine, Venlafaxine, Nefazodone)

C. Combination with other medications (augmentation)
    1. Lithium
    2. MAOIs **(caution)**
    3. ECT - Electroconvulsant therapy
    4. Thyroid replacement

D. Therapeutic window for Nortriptyline **(50-150 ng/ ml)**

E. On maintenance therapy, can usually give total daily dose at bedtime
    1. Begin with divided doses
    2. will decrease daytime sedation

F. May precipitate mania or hypomania (less potential with bupropion (?))

G. Length of antidepressant treatment
    1. 1st time depressed → 9 months to 1 year
    2. 2nd time depressed → 2 years
    3. 3rd or more time depressed → lifetime therapy (chronic illness)

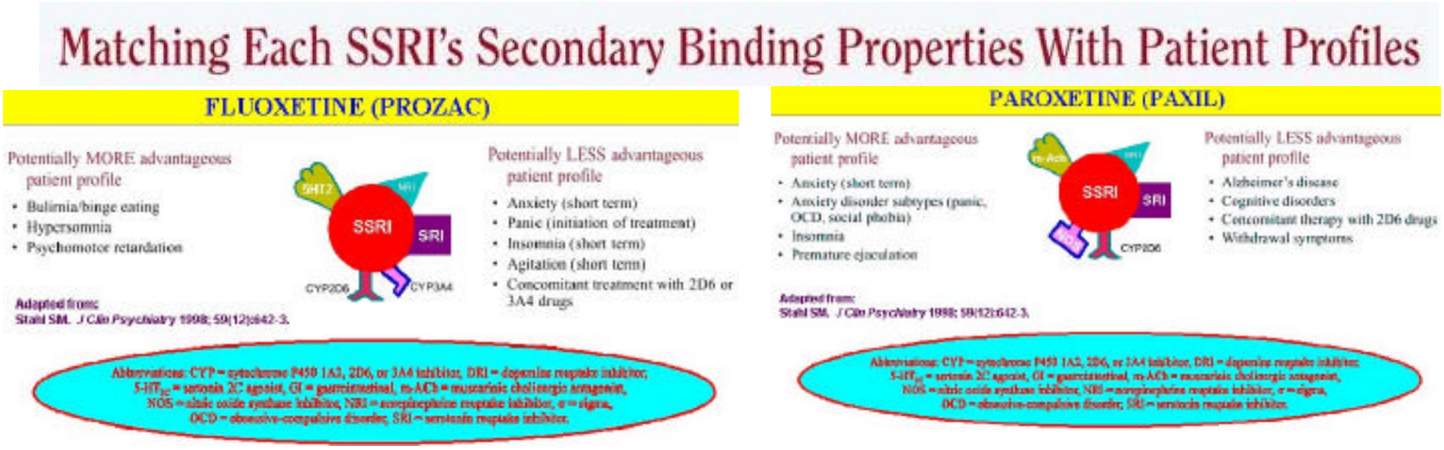
IX. MONOAMINE OXIDASE INHIBITORS

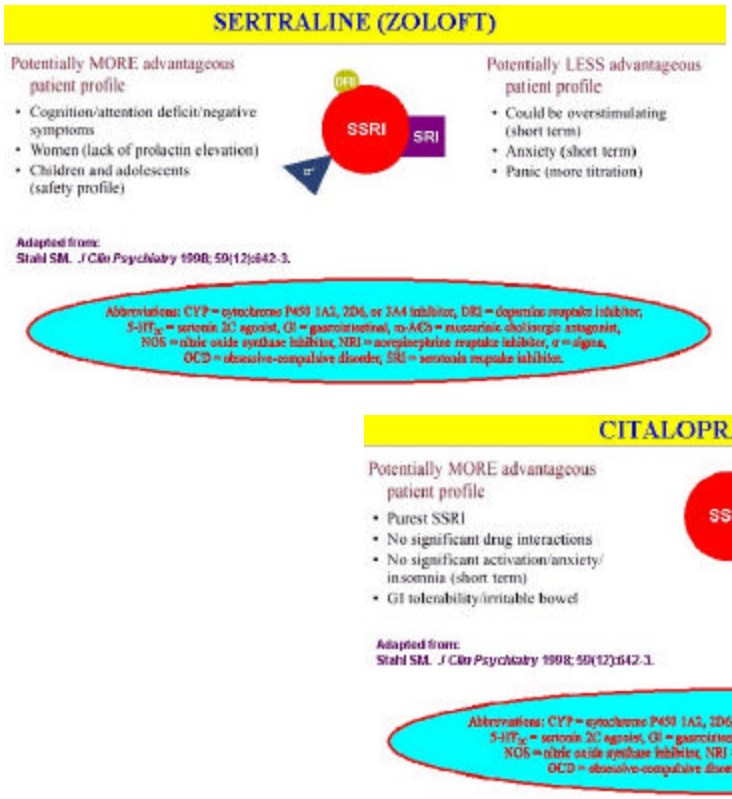
A. Types
   1. **Phenelzine (Nardil®)**
      a. Initiate at 15 mg/d, increase by 15mg at 2-day intervals to reach 45 mg/d in divided doses by end of 1st week.
      b. Continue titration upwards to at least 60 mg/d until clinical improvement is seen or limiting SE's occur.
      c. Do not exceed 90 mg/d.
      d. Maintenance: May be as low as 15 mg/d.
   2. **Tranylcypromine (Parnate®)**
      a. Initiate at 10 mg BID. If no response after 2 weeks, increase to 30 mg/d (20mg in AM, 10mg in afternoon).
      b. Maintenance: May be as low as 10 mg/d.

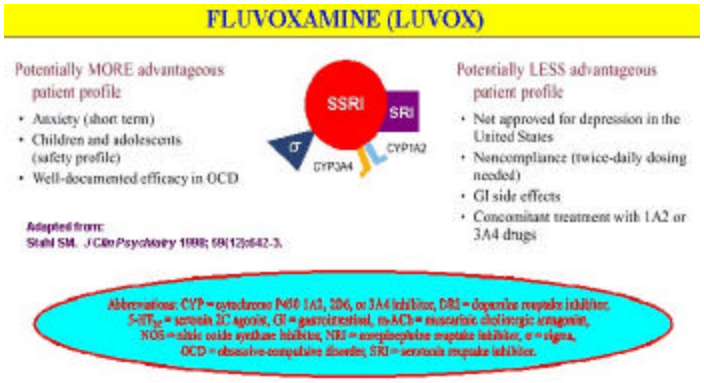
B. Mechanism of action
   1. Irreversibly inhibit MAO
   2. Two week duration of effect

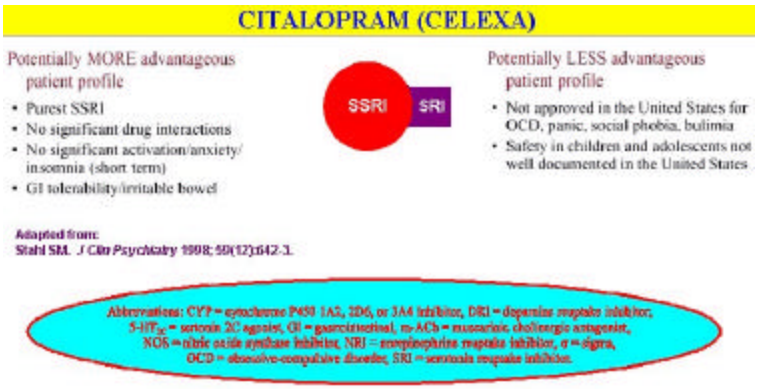
C. Adverse Effects
   1. Postural hypotension
   2. Hepatic complications (hydrazine > non-hydrazine)
   3. Anticholinergic (less than TCAs)
   4. Sedation (most with phenelzine)
   5. Stimulation (most with tranylcypromine)
   6. Sexual dysfunction
   7. **<u>Hypertensive crisis</u>**:
      a. ***Tyramine*-containing foods:**
         a. cheeses, yeast products, pickled herring, liver, aged meats
         b. alcoholic beverages (esp. red / Chianti wines),
      b. ***Sympathomimetic*-containing drugs**
         a. OTC decongestants, TCAs, SSRIs, cocaine, etc.
         b. **Serotonin syndrome:** n/v, tremors, seizures, mental status changes, hypo-/hypertension, ataxia, sweating, cardiovascular changes

X. SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)









A. **Fluoxetine (Prozac®)**

1. M.O.A. - Specific for serotonin reuptake inhibition
2. Pharmacokinetics
   a. Active metabolite - norfluoxetine
   b. $T_{1/2}$ - parent = 2-3 days
      metabolite = 7-9 days
   c. Highly protein bound (95%)
   d. Metabolized by Cytochrome P450IID$_6$ isoenzyme
3. Drug interactions
   a. MAOIs or Tryptophan (SEROTONIN SYNDROME)
   b. Other highly protein bound drugs
   c. **Other drugs metabolized by P450IID$_6$**
      -TCAs, neuroleptics, some antiarrythmics, etc.
4. Adverse reactions
   a. weight loss / anorexia
   b. anxiety
   c. insomnia
   d. headache
   e. sweating
   f. nausea and diarrhea
   g. ***sexual dysfunction (very common)***
   h. hyponatremia/SIADH – rare (more in elderly)
5. Dosage
   a. 5mg up to 20mg in AM (may ↑ if no improvement after a few weeks)
      -range is 20 to 80 mg/d
   b. Initiate at lower doses for elderly and pts who are sensitive to side effects
   c. Available in 10mg scored tablets, 10mg, 20mg, & 40mg capsules (pulvules)
      -Mint liquid available (20mg/5ml)
6. Indications
   a. Depression
   b. Obsessive-Compulsive Disorder (OCD)
   c. Bulimia / Eating Disorders

B. **Sertraline (Zoloft®)**

1. M.O.A. -- Specific for serotonin reuptake inhibition (same as Prozac)
2. Pharmacokinetics:
    a. $T_{1/2}$ = 26 hours
    b. active metabolite - desmethylsertraline - 1/10th potency
    c. ≥97% protein bound (? possible interactions)
    d. less metabolic inhibition than fluoxetine
3. Dosage
    a. 50 mg/d initially (usually in AM) - half for elderly
    b. may increase in a few weeks if no improvement seen
    c. range = 50mg - 200 mg/d
    d. Available in 25, 50, and 100mg tablets (scored), Liquid concentrate (20mg/ml)
4. Adverse effects
    -same as fluoxetine (slightly more GI SE's)
5. Drug Interactions
    -minor inhibitor of $P450IID_6$ and $P450IIIA_4$
6. Indications
    a. Depression
    b. Obsessive-Compulsive Disorder (OCD)
    c. Panic Disorder
    d. Post-Traumatic Stress Disorder (PTSD)

C. **Paroxetine (Paxil®)**

1. M.O.A. -- Specific for serotonin reuptake inhibition (same as Prozac)
2. Pharmacokinetics
    a. $T_{1/2}$ = 21 hours
    b. NO active metabolites
    c. 95% protein bound (? drug interactions)
    d. **metabolic enzyme inhibitor of $P450IID_6$ (> fluoxetine)**
3. Dosage
    a. 20 mg/d initially **(PM>AM)** - half in elderly
    b. may increase in a few weeks if no improvement seen
    c. range = 20 to 50 mg/d
    d. Available in 10, 20, 30, and 40mg tablets, Liquid suspension (10mg/5ml)
4. Adverse effects
    -similar to fluoxetine (reports to be more sedating)
5. Indications
    a. Depression
    b. Obsessive-Compulsive Disorder (OCD)
    c. Panic Disorder
    d. Social Anxiety Disorder
    e. Generalized Anxiety Disorder (GAD)
    f. Post-Traumatic Stress Disorder (PTSD)

D. **Fluvoxamine (Luvox®)** -- FDA approved for OCD only

1. M.O.A.
2. Pharmacokinetics:
    a. Metab. by $P450IA_2$ and $IIIA_4$ to >9 metabolites
        -most metabolites are inactive
    b. protein binding = 80%
    c. average $T_{1/2}$ is 15.6 hours
    c. clearance is decreased in hepatic impairment

3. Dosage**:**
    a. start at 50mg/d at HS (AM if insomnia occurs)
    b. increase 50mg/d every 4-7 days up to a max. of 300mg/d
    c. doses >100mg should be given BID (larger dose in PM)
    d. lowest effective dose is the best dose
    e. should be taken with FOOD to decrease nausea
4. Adverse Reactions:
    -most common: Headache (22%), asthenia (14%),
    nausea (40%), diarrhea / constipation (11%), somnolence / insomnia (22%),
    dry mouth (14%), nervousness (12%), sexual dysfunction (>8%)
5. Drug interactions:
    a. MAOIs - need 2 week washout
    b. Inhibits $P450IA_2$ and $P450IIIA_4$
    c. Propranolol and metoprolol (bradycardia & hypotension)
    d. triazolo-BZD's (triazolam & alprazolam) - ↑ levels
    e. digoxin and warfarin may show ↑ levels
    f. smoking increases fluvoxamine's clearance by 25%
    g. Li^+ and Tryptophan -- seizures and vomiting, respectively
    h. protein binding interactions are <u>insignificant</u>
6. Availability: 25, 50, and 100mg tablets (scored)

E. **Citalopram (Celexa®)**

1. Used in Europe for over a decade
2. Pharmacokinetics
    a. Metabolized by Cytochrome $P450IIIA_4$ and $P450IIC_{19}$
    b. $T_{1/2}$ is 35 hours (Half-life increases by 30-50% in the elderly)
    c. Protein binding = 80%
3. Drug interactions
    a. Weak inhibitor of $P450IIIA_4$, $P450IIC_{19}$, and $P450IID_6$
    b. No significant drug interactions
4. Dosage
    a. 20mg - 60mg QD with or without food
    b. 20mg/d is recommended dose for the elderly
    c. Adjust dose up by 20mg at intervals of no less than 1 week
    d. Available in 10, 20, & 40mg tablets (scored), peppermint liquid (10mg/5ml)
5. Adverse Reactions
    a. Less activating than other SSRIs
6. Advantages
    a. May have a quicker onset of action compared to other antidepressants[1]
    b. Improvement may be seen in 1-2 weeks
    c. In comparison to fluoxetine, improvement from baseline at 2 weeks was statistically superior with citalopram
    d. Greater significance in those not receiving concomitant benzodiazepines[2]

[1]Clin. Drug Invest. 1997; 14(2):77-89.
[2]International Clinical Psychopharmacology 1996;11:129-36.

XI. Other Antidepressants:

A. Bupropion (Wellbutrin®)

1. M.O.A. - weak DA and NE reuptake inhibition (???)
2. Administration and dosage
   a. 100mg BID initially, ↑ to 100mg TID after 3-4 days
   b. *N.T.E.* ***450 mg/d*** *(150mg/dose) due to seizure risk*
   c. S.R. available in 100mg and 150mg tablets
      - Seizure incidence <0.1%
   d. *N.T.E.* ***400mg/d of S.R.*** *divided BID*
   e. Available in 75mg and 100mg (immediate release - RR) tablets
3. Adverse effects (very mild, well tolerated)
   a. Nausea / vomiting, constipation, dry mouth
   b. HA, nervousness, dermatologic reactions
   c. **Seizures** (0.3-0.4% with RR)
      **NOT FOR THOSE WITH SEIZURES OR EATING DISORDERS!
   d. Little sexual dysfunction
4. May be as effective as Ritalin® for ADD/ADHD in adults

B. Venlafaxine (Effexor®)

1. Mechanism of Action
   -5HT > NE (and weak DA) reuptake inhibitor
2. Pharmacokinetics:
   a. 27% protein bound
   b. Metabolized by $P450IID_6$ to 3 active metabolites
      1. O-desmethyl-venlafaxine
      2. N-desmethyl-venlafaxine
      3. N,O-didesmethyl-venlafaxine
   c. $T_{1/2}$ is 5-11 hours (s.s. in 3 days)
3. Dosage**:**
   a. Starting dose is 75m/d (divided BID)
   b. Maximum recommended dose is 375mg/d (BID or TID)
   c. Reduce dose in hepatic or renal impairment
   d. No dose reduction is suggested in elderly patients
   e. **XR** formulation is **QD** dosing
4. Adverse Reactions:
   a. Similar to SSRIs
   b. Nausea(35%), somnolence(24%), dry mouth(22%), dizziness(18%), nervousness(17%), vomiting, hypertension, orthostasis, EKG changes, wt. loss, mania/hypomania, seizures (0.26%)
   c. N/V can be minimized by giving with FOOD
   d. Increases in BP of 5-6mmHg have been seen at 375mg/d
5. Drug interactions
   a. Drugs that inhibit $P450IID_6$ should ↑ Venlafaxine levels
   b. MAOIs-possible hypertensive crisis / serotonin syndrome
6. May be beneficial to those with *neuropathic pain* syndromes (like TCAs)
7. Availability**:**
   a. RR: 25mg, 37.5mg, 50mg, 75mg, and 100mg <u>tablets</u>
   b. XR: 37.5mg, 75mg, and 150mg <u>capsules</u>
8. Other indications:
   a. Generalized Anxiety Disorder (GAD)

C. **Trazodone (Desyrel®)**

1. M.O.A. - less potent SSRI + 5HT agonist
2. Pharmacokinetics
    a. Short $t_{1/2}$ (approx. 6-11 hours)
    b. Active metabolite (mCPP) – 5HT agonist
        1. Causes vasoconstriction
        2. When wears off, vasodilation occurs → migraine headache
    c. 92% protein bound (? Drug interactions)
3. Adverse effects
    a. Priapism (very rare) - 1/6000 to 1/10000
    b. **Drowsiness** (some anticholinergic potential)
    c. Orthostasis
    d. Less cardiac conduction effects than TCAs
4. Dosage is from 25mg HS up to 600 mg/d in divided doses

D. **Nefazodone (Serzone®)**

1. M.O.A.
    a. NE and 5HT reuptake inhibitor and *$5HT_2$ blocker*
        1. NE reuptake very weak
        2. 5HT > Trazodone but < SSRIs
        3. Blocking $5HT_2$ receptors blocks sexual dysfuntion and ↓'s anxiety
    b. Chemical Class: Phenylpiperazine (analog of Trazodone)
2. Pharmacokinetics**:**
    a. Absorbed rapidly and completely with high first pass metabolism
        1. Food delays and decreases by about 20%
    b. >99% protein bound
    c. Metabolized by $P450IIIA_4$ to 2 active metabolites
        1. hydroxy-nefazodone
        2. mCPP (see above information)
    d. $T_{1/2}$ is 2-4 hours
    e. Kinetics are non-linear
3. Dosage**:**
    a. Start at 50mg bid
    b. Increase 100mg or 200mg/d every week
    c. Usual dose is 300-600mg/d divided bid
    d. Reduce dose in renal/hepatic impairment and elderly
        1. Geriatric max. dose is 400mg/d
4. Adverse Reactions - reportedly well tolerated
    a. Headache (migraine-like), anticholinergic, nausea, drowsiness, weakness
    b. Rare: dizziness, confusion, blurred vision, sexual dysfunction
        ***Liver failure (1 case per 250,000 patient-years exposure)*
5. Drug interactions
    a. Other drugs metabolized by $P450IIIA_4$ - will ↑ their conc.'s
        1. Triazolobenzodiazepines - **triazolam / alprazolam**
            a. Should reduce BZD dose by 50-75%
        2. Theophylline
    b. MAOIs - 2 week washout each way is desired
    c. Other protein bound drugs
6. Availability**:** 50mg, 100mg & 150mg (scored), 200mg, 250mg tablets

E. **Mirtazapine (Remeron®)**

1. Mechanism of Action
    a. *Alpha*$_2$ antagonist (autoreceptors and heteroreceptors)
    b. Blocks post-synaptic 5HT$_2$ and 5HT$_3$ receptors
        1. Blocking 5HT$_2$ receptors blocks sexual dysfunction and ↓'s anxiety
        2. Blocking 5HT$_3$ receptors blocks nausea and vomiting
    c. 5HT$_1$ receptors enhance serotonin transmission
2. Other actions
    a. High H$_1$ blockade
    b. Weak antagonism of muscarinic and *alpha*$_1$ receptors
3. Pharmacokinetics
    a. Rapid and complete absorption
        1. Peak in 2 hours
        2. Not affected by food
        3. 50% bioavailable
    b. 85% protein bound
    c. Half-life of 20-40 hours
    d. Cytochrome P450 2D$_6$, 1A$_2$, and 3A involved
4. Dosage
    a. Start at 15mg at hs
    b. Increase by 15mg Qhs every 1- 2 weeks up to a max. of 45mg/d
    c. Lower doses may be necessary in the elderly and in hepatic / renal impairment
5. Adverse effects
    a. Most common: somnolence (54%), increased appetite (17%), weight gain (12%), and dizziness (7%)
    b. Less common: ↑ cholesterol, ↑ triglycerides, dry mouth, asthenia, abnormal dreams, constipation, hypertension
    c. Rare: 2 or 2796 patients in clinical trials developed *agranulocytosis (1.1 per 1000 patients)*
    d. Less nausea, nervousness, insomnia, diarrhea, and sexual dysfunction than with SSRIs
    e. Side effects may ↓ with ↑'ing doses due to specificity of receptor blockades (ie. Higher doses = blocking more receptors that block side effects)
6. Drug interactions
    a. MAOIs
    b. No others reported
    c. Possibly clonidine and guanfacine, but not studied
7. Availability
    a. Scored 15mg, 30mg, and 45mg tablets
    b. Remeron SolTabs™ – orally disintegrating tablets now available
8. Recent studies show that onset of action is faster for Remeron than SSRIs
    a. April 2001 – information from the Netherlands – http://212.206.26.201/front-end/public/news/news_display.asp?nws_id=80

F. **Reboxetine (Vestra®)**

1. Mechanism of Action
    a. A highly selective norepinephrine reuptake inhibitor, with no affinity for serotonin or dopamine receptors, and little affinity for muscarinic or adrenergic receptors.
2. Pharmacokinetics
    a. Rapidly absorbed orally with a bioavailability of >60%
    b. 97% plasma protein binding
    c. Volume of distribution 0.5L/kg
    d. Elimination half-life of 12-16 hours
    e. Does not inhibit hepatic enzymes involved in drug metabolism
3. Usual Dosage
    a. In clinical trials, twice daily dosing has been tested ranging from 2mg-12mg
    b. Currently, there is no set standard of dosing
4. Adverse reactions reported in studies
    a. Dry mouth
    b. Blurred vision
    c. Increased sweating
    d. Tachycardia
    e. Insomnia
    f. Urinary hesitancy/retention
    g. Decreased libido
5. Status:
    a. Reboxetine is currently available in the United Kingdom under the trade name Edronax.[1]
    b. Reboxetine was submitted for new drug application (NDA) on 4/29/98; the Pharmacia & Upjohn expect a decision from the FDA by mid-1999.[1]

[1] www.cponline.gsm.com – Clinical Pharmacology Online "Reboxetine", Nov. 23,1998.

Standard Augmentation Techniques:

- Lithium
- Cytomel® 25-50 ì g/day
- Carbamazepine (Tegretol®)
- Buspirone (BuSpar®)
- Monoamine Oxidase Inhibitor + other Antidepresssant **[Caution!]**
- Electroconvulsive Therapy (ECT) - (6 to12 exposures)

Treatments with positive results in some studies:

- Olanzapine (Zyprexa®)
- Pindolol (Visken®)
- Lamotrigine (Lamictal®)
- Dexamenthasone [3mg a day for 4 days]
- Clomipramine (Anafranil®)
- Amphetamine/Psychostimulant short-term (i.e. Ritalin®/Dexedrine®)
- 24-36 hour sleep deprivation
- Bright Light exposure therapy
- Vagal nerve stimulation
- Dopaminergic agents (i.e. Symmetrel®, Parlodel®, others)

Non-effective studied therapies:

- Melatonin S.R.
- Repetative Transcranial Magnetic Stimulation (rTMS)

PREDICTING DRUG INTERACTIONS

Leonard Rappa, Pharm.D., BCPP
Assistant Professor, Florida A&M University

TYPES OF DRUG INTERACTIONS:

A. Pharmacodynamic
B. Protein binding
C. High extraction drugs
D. Renal clearance rate
E. Inhibitors / inducers of absorption
F. Combination factors
G. Metabolic

A. PHARMACODYNAMIC

1. Competing mechanisms
2. ie. agonists + antagonists
3. Symmetrel® + antipsychotics
4. May worsen a disease state (ie. depression, psychoses, CV, HTN)
5. Additive or synergistic effects
   a. ie. TCA + anticholinergic = delirium / euphoria
   b. MAOI + Sympathomimetics = hypertensive crisis
   c. SSRI + antipsychotics = tremor / EPS

B. PROTEIN BINDING

1. Highly protein bound drugs compete for binding sites on albumin & α_1-glycoprotein
2. Unbound drug is pharmacologically active
3. Only significant when > 90% bound
   a. Warfarin, digoxin, theophylline, phenytoin, barbiturates
   b. Serzone® and aspirin are >99% protein bound

C. HIGH EXTRACTION DRUGS

1. Drugs that affect liver blood flow will affect first pass metabolism
   a. ie. propranolol (Inderal®)
2. Can ↓ metabolism of antipsychotics
3. Slows liver blood flow

D. RENAL CLEARANCE RATE

1. Drugs that affect GFR (Glomerular Filtration Rate) will change renal elimination rates
   a. Can affect parent compound or metabolite excretion
2. Most significant with drugs that are <u>only</u> renally eliminated
   a. ie. NSAIDs can cause ↓ lithium elimination
   b. ie. Lithium itself inhibits its own clearance
   c. concentration dependent
   d. Non-linear kinetics

E. INHIBITORS / INDUCERS OF ABSORPTION

1. Prevent / reduce OR increase amount of drug absorbed in the gut
    a. ie. Food ↑'s Zoloft®'s absorption by 40%
    b. Depakote® + lithium can ↑ Depakote® levels
        1. Lithium is not metabolized or protein bound
        2. Carbonate salt dissolves Depakote® in stomach
    c. Lithium citrate (liquid) can form an insoluble complex with antipsychotic concentrates

F. COMBINATION FACTORS

1. ie. Coumadin® and Prozac®
    a. Both highly protein bound
    b. Prozac® is a metabolic inhibitor
    c. SSRIs in general may increase bleeding time by diminishing granular storage of serotonin in platelets[1]

[1]Stoudemire A. Psychosomatics 1995;36:19-26.

G. METABOLIC

1. Inhibitors and Inducers of metabolism can ↑ or ↓ levels of other drugs, respectively
2. Inhibitors
    a. Cimetidine (Tagamet®)
    b. Acute EtOH ingestion
3. Inducers
    a. Carbamazepine (Tegretol®)
    b. Chronic EtOH ingestion
    c. Smoking cigarettes

H. CYTOCHROME P450 ENZYME SYSTEM (CYP-450)

1. >70% of total content of liver
2. CYP-450 enzymes are over 100 million yrs old
3. All living organisms contain CYP-450 enzymes
4. In humans, most are distributed in the liver, brain, lung, and intestine
5. CYP-450 is responsible for most Phase 1 oxidative reactions
6. The name CYP-450 is derived from the light absorbance characteristics of the reduced enzymes of 450 nanometers

7. P450 ENZYME SYSTEM (See TABLE 1 after APPENDIX A)

a. Arabic numerals indicate the family
    1. Categorized by amino acid sequences
    2. ie. CYPI, CYPII, CYPIII
    3. 12 families identified
    4. only 3 important
    5. Family members have >40% similarity in amino acid sequences
b. Upper case letter indicates the subfamily
    1. Subfamily members have >55% similarity in amino acid sequences
c. Last Arabic numeral indicates the individual enzyme
    1. ie. P450IIIA$_{3/4}$ have 97% similarity in amino acid sequences

I. DEADLY COMPLICATIONS

1. Occur when a PRODRUG is not converted to a non-toxic active metabolite
2. Parent compound is cardiotoxic
3. Terfenadine (Seldane®), Astemizole (Hismanal®), and Cisapride (Propulsid®) were removed from the market for this reason

J. DRUG CONTRAINDICATIONS

Triazolam (Halcion®) WITH
- Ketoconazole (Nizoral®)

K. CONCLUSION

1. Predict future interactions by knowing:
    a. Pharmacodynamic action of the drugs you order
    b. Protein binding of prescription and OTC drugs
    c. Which drugs are high extraction drugs
    d. Which drugs are inhibitors / inducers of absorption
    e. Which drugs interact metabolically

NEUROLEPTIC MALIGNANT SYNDROME (NMS)

Prepared by Leonard Rappa, Pharm.D., BCPP
Assistant Professor, Florida A&M University

DEFINITION: A rare, idiosyncratic reaction to typical neuroleptic agents that is characterized by severe muscle rigidity, hyperthermia, autonomic dysfunction, and stupor

ETIOLOGY:

1. Originally identified in Europe in the 1960's
2. First recognized case in the USA was confirmed in the early 1980's
3. Pathoetiology is poorly understood
4. May develop over 24 to 72 hours
5. Muscle rigidity may result from decreased transmission in the nigrostriatal pathway from blockade of D_2 receptors
6. Hyperthermia may result from altered D_1 transmission, anticholinergic activity, and muscle rigidity
7. Autonomic dysregulation may result from increased sympathetic outflow secondary to decreased dopamine inhibition
8. Mental Status changes may result from hyperthermia, anticholinergic effects, or hypoactivity of the dopaminergic system in the mesocortical area

INCIDENCE:

1. NMS occurs in 0.5% to 1.0% of patients receiving neuroleptics
2. Affects twice as many men as women
3. Usually occurs in younger patients
4. Can occur at any point in neuroleptic drug therapy but usually within the first 2 weeks of initiation, dose change, or drug therapy change
5. Highest occurrence with chlorpromazine and high-potency neuroleptics (ie. haloperidol)
6. Lowest occurrence with the long-acting depot formulations
7. Rare occurrence with thioridazine (MELLARIL)
8. Sudden withdrawal of a dopamine agonist (ie. for Parkinson's disease) can cause NMS
9. Inhaled operating-room anesthetics have been reported causing NMS.

SIGNS AND SYMPTOMS:

1. Usually develop over 24 to 72 hours
2. Extrapyramidal Symptoms:
    a. Muscle rigidity
        1. May be so intense that it leads to rhabdomyolysis and necrolysis
    b. Diffuse tremors
    c. Dystonic reactions in upper extremities (ie. trismus)
    d. Agitation
    e. Catatonia
    f. Akinesia
    g. Hands and feet become fixed in spasm
    h. Hypertonicity in oropharyngeal areas, dysphagia, mutism
    i. Sialorrhea
    j. Dysarthria
3. Altered Consciousness / Stupor
    a. Characterized by coma or near-unconsciousness
    b. Patient is unable to communicate because of mutism
    c. Mental status extremely difficult to assess
4. Autonomic disturbances
    a. Malignant hyperthermia (>104^{o}F)
    b. Diaphoresis
    c. Tachycardia

d. Fluctuations in BP
e. Tachypnea
f. Urinary retention
g. Severe cases may be complicated by dehydration and renal failure from myoglobinuria secondary to rhabdomyolysis
h. Late Stage: may develop dyspnea, tachypnea, and respiratory failure (may be due to pulmonary emboli or pneumonia)

DIAGNOSIS:

1. Widespread muscle rigidity, tremors, severe EPS and dystonias
2. Temperature elevation (100 to 108^{o}F)
3. Altered level of consciousness and/or autonomic dysfunction
4. R/o allergic, infectious, neurologic, metabolic, and toxic etiologies
5. Hypertension or fluctuations in BP

LABS:

1. Elevated WBC/ CBC with or without left shift
2. Elevated CPK (creatinine phosphokinase) from muscle rigidity
    a. Can lead to myoglobinuria and acute renal failure
    b. Increases in CPK and potassium indicates skeletal muscle necrosis (rhabdomyolysis)
3. Increased liver enzymes (ALT and AST)

TREATMENT / GOALS:

<u>Generally Supportive</u>

1. Discontinue neuroleptic immediately
2. Decrease hyperthermia
    a. Cooling blanket
    b. Drug therapy
3. Maintain renal function
4. Intensive Care Unit (ICU) for cardiopulmonary support
5. Treat any concurrent infections
6. Correct electrolyte abnormalities
7. Use Dantrolene (DANTRIUM) to relax skeletal muscles
    a. Dose: 1mg/kg IV initially
        1. Repeat dose prn until symptoms subside
        2. Up to a total of 10mg/kg
    b. Oral dose is 100-200mg/d
    c. May reverse muscle rigidity / rhabdomyolysis
    d. May decrease temperature
8. Use Bromocriptine (PARLODEL) 2.5-5mg two to six times a day
    a. May reverse EPS and autonomic symptoms
9. Amantadine (SYMMATREL) may also be used (100mg po BID)

TREATMENT COURSE:

1. Treatment and monitoring usually requires 1-3 weeks
2. NMS will subside in 5-10 days if oral neuroleptics were the causative agents and 10-21 days if depot medications were the causative agents

MORTALITY RATE:

1. NMS has a 20-30% mortality rate
2. Decreases with awareness and modern care
3. Usually die from respiratory failure from pulmonary emboli, cardiovascular collapse, or acute renal failure

PHARMACOTHERAPY OF OBSESSIVE-COMPULSIVE DISORDER

Leonard Rappa, Pharm.D., BCPP
Assistant Professor, Florida A&M University

LEARNING OBJECTIVES:

Upon completion of this lecture, you should be able to:

1. Be familiar with the general epidemiology and diagnosis of OCD.
2. Recognize disorders resembling OCD.
3. Identify the neurotransmitter implicated in OCD.
4. Describe the general course of treated and untreated OCD.
5. Identify proper management and augmentation strategies in treating OCD.
6. Monitor the patient's target symptoms of OCD.

PHARMACOTHERAPY OF OBSESSIVE-COMPULSIVE DISORDER

Leonard Rappa, Pharm.D., BCPP
Assistant Professor, Florida A&M University

BACKGROUND

1. OCD classified as an anxiety disorder
2. Rarely remits without treatment
3. Patients may suffer lifelong disability

EPIDEMIOLOGY

1. Lifetime prevalence of 1.9 - 3.3% for adults
    A. > 6 million people
    B. 1% in children
2. 4th most common psychiatric disorder
3. Prevalence is 2 X that of schizophrenia and panic disorder
4. Large % do not seek treatment
5. Average age of onset**:** late adolescence or early 20's
6. Males = females
7. ? genetics
    A. 20% of pts. have 1° degree relatives
    B. 15% of 1° relatives may be subclinical
    C. More common in monozygotic twins
    D. Connection with Tourette's Syndrome

DSM-IV CRITERIA FOR DIAGNOSIS:

A) Either obsessions or compulsions
B) Obsessions as defined by:
    1) Recurrent and persistent thoughts, impulses, or images that are experienced as intrusive and inappropriate and that cause marked anxiety or distress
    2) The thoughts, impulses, or images are not simply excessive worries about real-life problems
    3) The person attempts to ignore or suppress such thoughts, impulses, or images, or to neutralize them with some other thought or action
    4) The person recognizes that the obsessional thoughts, impulses, or images are a product of his or her own mind
C) Compulsions are defined by:
    1) Repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting) that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly
    2) The behaviors or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation; however, these behaviors or mental acts are not connected in a realistic way with what they are designed to neutralize or prevent or are clearly excessive
D) At some point, person recognizes these are excessive or unreasonable
E) Symptoms cause marked distress, are time consuming (>1 hr/d), or significantly interfere with the person's normal routine

DIFFERENTIAL DIAGNOSIS

1. Disorders resembling OCD:
    A. Trichotillomania, Tourette's, bowel obsessions, eating disorders (15% of adult women with OCD had anorexia in adolescence), compulsive gambling, compulsive sexual behaviors, monosymptomatic hypochondriasis
    B. Not to be confused with obsessive-compulsive personality disorder
        1. Perfectionists; rigidly inflexible; preoccupied with rules, details, procedures

CLINICAL PRESENTATION

1. 20% of patients have involuntary neurologic movements (ie. tics, grimace)
2. Typically, 7.5 yrs elapses between onset and 1st psychiatric visit
3. 50% have another psych disorder

PATHOPHYSIOLOGY -- Unknown

1. Serotonin mediated 2° to tx's used
   A. 5HT agonist, m-CPP, ↑ OCD symptoms
   B. Clomipramine ↓'ed symptoms
   C. 5HT antagonists worsened symptoms after clomipramine
2. ? abnormal pathways b/t frontal lobes and basal ganglia (PET scan)
   A. PET studies suggest a hyperfunctioning "loop" in the brain

TREATMENT

1. Clomipramine (Anafranil®)

A. TCA approved for OCD in 1989
B. 97% protein bound
C. $t_{1/2}$ = 31 - 37 hrs
D. DI's similar to other TCAs
E. Clomipramine is superior to SSRI, which are superior to others antidepressants
F. Side Effects:
   1. dry mouth (80%)
   2. dizziness and tremor (>50%)
   3. fatigue (38%)
   4. sexual dysfx. (up to 70%)
   5. seizures (0.5 - 2.2%) -- dose related
      a. Max. dose N.T.E. 250mg/d (exponential ↑ in seizures)

2. SSRIs all FDA approved (except citalopram yet) – see Antidepressant lecture
   A. Fluoxetine (Prozac®)
   B. Sertraline (Zoloft®) – approved for pediatric OCD also
   C. Paroxetine (Paxil®)
   D. Fluvoxamine (Luvox®) -only FDA approved indication

AUGMENTATION STRATEGIES:

1. Lithium (300-1800mg/d) + clomipramine (25-250mg/d)
2. Buspirone (20-60mg/d) + fluoxetine (20-80mg/d)
3. Fenfluramine (30-60mg/d) + fluoxetine / fluvoxamine (50-300mg/d) / clomipramine
4. Haloperidol (1-20mg/d) or pimozide (1-2mg/d) + SSRI + lithium
5. ADD carbamazepine (400-1200mg/d), clonazepam (2-4mg/d), desipramine (10-300mg/d), valproic acid (500-3000mg/d), or verapamil (240-480mg/d)
6. OTHERS: MAOIs, antiandrogens
   1. Behavioral therapy
   2. Psychosurgery (capsulotomy or cingulotomy)

RESPONSE

1. Rarely complete
2. Reduction of symptoms is target
3. May take at least 6-8 weeks (sometimes up to 3 months)

CONCLUSION

1. OCD is an under-recognized and under-treated disorder
2. SSRIs and clomipramine are FDA approved
3. Theoretically all drugs that affect serotonin will be somewhat effective
4. No drug is perfect
5. Must measure SE profile and DI's against efficacy

PARKINSON'S DISEASE

Leonard Rappa, Pharm.D., BCPP
Assistant Professor, Florida A&M University

Introduction / Definition:

-PD was first described in 1817 as "paralysis agitans"
-characterized by tremor, muscular difficulties, and postural abnormalities
-progressive, degenerative, neurologic motor disorder

Epidemiology:

-results from the degeneration of dopaminergic neurons, or depletion of DA from within the extrapyramidal system
-a disorder of the middle-aged and elderly (mostly)
-incidence is 20 cases per 100,000 people

Differential Diagnosis:

-parkinsonian-like syndromes:
  -neurotoxins
  -trauma
  -progressive supranuclear palsy
  -Shy-Drager syndrome
  -drugs (ie. MPTP -- meperidine analog 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine -- converted to MPP^+ by MAO_b)

Etiology:

-unknown -- may be due to genetics, acceleration of the normal aging process, or normal aging plus an environmental insult
-80% of total brain dopamine is located in the corpus striatum (part of the EPS)
  -major DA neuron system is the nigrostriatal tract that originates in the substantia nigra
  -stimulation or destruction of these areas results abnormalities of movement
-Ach is thought to balance the actions of DA within the EPS
-hallmark finding is loss of melanin-containing neurons within the substantia nigra
  -at autopsy, only 10% of normal dopamine conc. is found in the basal ganglia

Clinical Features:

-initial: aching pains, parathesias, numbness, and coldness
-later: tremor, rigidity, akinesia or bradykinesia, and postural difficulties, "pill-rolling", shuffling gait, cog-wheel rigidity, drooling

Treatment:

-drug therapy involves the enhancement of dopaminergic function within the CNS via several mechanisms:

-Specific Drug Therapy:

1) anticholinergic drugs - see table below
   -better for tremor and rigidity, not bradykinesia
   -watch SE's: delirium, disorientation, ↓ memory function, urinary retention, blurred vision, dry mouth, tachycardia
   -effective adjunct therapy to L-dopa
   -taper before d/c'ing (rebound cholinergic symptoms)
2) amantadine (Symmetrel®) -- pre-synaptic
   -100mg po BID
   -SE's: depression, hallucinations, psychosis, confusion, *livedo*

reticularis (diffuse rose color mottling of the skin that is reversible)
-tolerance develops in 4-12 weeks

3) selegiline (L-Deprenyl, Eldepryl®) -- MAO_b inhibitor / antioxidant
-approved as adjunct therapy to L-dopa -- prolongs efficacy
-prevents neurotoxicity of MPTP
-5mg BID (breakfast and lunch) -- insomnia if later
-at doses > 20mg/d = same DI's as other MAOIs
-DATATOP study group *(Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism)*
-concluded that selegiline may delay progression of PD up to 1 yr

4) levodopa (Larodopa®, Dopar®, Sinemet® [with carbidopa])
-most effective drug in PD
-L-dopa, a dopamine precursor, crosses the BBB and is converted to DA by dopa decarboxylase
-peripheral conversion to DA causes n / v, arrhythmias, postural hypotention
-carbidopa (peripheral dopa decarboxylase inhibitor) -- prevents this
-start at 100mg po TID of levodopa or 25/100mg po BID (max. 8 tabs/d)
-DI with pyridoxine (levodopa alone)
-long term use may lead to loss of efficacy over time
-"on-off" phenomenon - occurs in as many as 2/3 of pts after 5 yrs
-may occur several times a day
-may try to divide doses to give every 2 hrs instead of every 4-6 hrs
-drug holidays (taper over 1-2 wks and d/c)
-other long term effects:
-akathisia, depression, delirium, agitation, paranoia, delusions, hallucinations, dementia
-when to start:
-delay until benefits outweigh disadvantages (SE's / ↓ efficacy over time)

5) Dopamine agonists -- post-synaptic
-pergolide (Permax®), bromocriptine (Parlodel®)
-pergolide 0.05mg/d up to a mean of 3mg/d over 2 weeks (↑ every 2-3 days)
-bromocriptine 1.25mg QD-BID up to 10-30mg/d
-adjunctive to levodopa
-decrease frequency of "off" periods
-effective as monotherapy initially
-SE's: nausea (50%), CNS (33%) - confusion, hallucinations, sedation, and postural hypotension
-increased in combination with levodopa

Other Therapeutic Options:

1) Surgical Transplantation of:
a) autologous medulla tissue
b) dopamine-rich dissociated mesencephalic fetal tissue in to the caudate nucleus (not in US)

2) Surgical Pallidotomy
-immediate results
-hi risks

SEIZURE DISORDERS / ANTICONVULSANTS

Leonard Rappa, Pharm.D.
Assistant Professor, Florida A&M University

Background:

-epilepsy recognized for >2400 yrs -- "falling sickness"

-*epilepsia* (Greek) - means "to come upon, to be grabbed hold of or thrown down, to attack, to seize hold of"

Epidemiology:

-5-10% of population will experience a seizure sometime in life

-Prevalence -- 1-2% have chronic epilepsy

International Classification of Seizures:

Traditional terminology	*New nomenclature*
Focal motor; Jacksonian seizures	I. Partial seizures (seizures begin locally)
	A. Simple (without impairment of consciousness)
	1. With motor symptoms
	2. With special sensory or somatosensory symptoms
	3. With autonomic symptoms
Temporal lobe or psychomotor seizures	4. With psychic symptoms
	B. Complex (with impairment of consciousness)
	1. Simple partial onset followed by impairment of consciousness —with or without automatisms
	2. Impaired consciousness at onset—with or without automatisms
	C. Secondarily generalized (partial onset evolving to generalized tonic-clonic seizures)
Petit mal	II. Generalized seizures (bilaterally symmetrical and without local onset)
Minor motor	A. Absence
	B. Myoclonic
Limited grand mal	C. Clonic
	D. Tonic
Grand mal	E. Tonic-clonic
Drop attacks	F. Atonic
	G. Infantile spasms
	III. Unclassified seizures
	IV. Status epilepticus (prolonged partial or generalized seizures without recovery between attacks)

Pharmacotherapy:

-Goal -- to allow the pt. to be seizure-free or reduce seizure frequency with minimal adverse effects and toxicities

-Agent Selection

-depends on proper diagnosis of seizure type, incl. underlying cause

-consider potential ADR's, DI's, and pt. specific factors

-consider laboratory parameters and monitoring

-begin with monotherapy and slow dosage titration

-allow adequate time to reach steady state serum concentrations (5-$t_{1/2}$'s)

-try to avoid in pregnancy - try $MgSO_4$ or CBZ maybe

-Polytherapy

-avoid combining agents with similar SE's (i.e. sedation)

-avoid combining agents from the same chemical family (i.e. phenobarbital and primidone)

-use agents with different mechanisms of action

-Clinical monitoring parameters

-seizures
-neurological findings 2° to ADR's (i.e. nystagmus)
-laboratory tests (baseline LFT's, serum albumin, CBC / Diff, UA, P7, serum ammonia [VPA])

-Serum concentrations of AED's
-may change if: 1) change in protein binding (i.e. liver disease, age)
2) drug-drug interaction
-monitor after reaching s.s., or following a change in dose, or new AED
-used to assess compliance and toxicity
-obtain free drug concentrations whenever possible (i.e. with phenytoin)

SPECIFIC AGENTS:

A) **Phenytoin (Dilantin, Di-Phen, Diphenylan)**

1) MOA -
1) absorption- dependent on dose, GI motility, and particle size
-Capsules -- Na^+ salt (92% phenytoin acid)
-QD dosing -- extended release
-Chewable tablets (100% phenytoin acid) -- immediate release
-Suspension (100% acid) and IV soln. (92% acid) available also
2) distribution- highly protein bound (90-95%)
3) metabolism- enzyme inducer, saturable metabolism
4) elimination- non-linear
5) therapeutic conc's:
-total: 10-20 mcg/ml
-free: 1-2 mcg/ml
6) ADR's
-** osteomalacia
7) DI's
8) Therapeutic monitoring
-phenytoin trough levels
-CBC/diff
-periodic dental exam
- serum Ca^{++} levels
9) dosing

B) **Carbamazepine (Tegretol, Epitol, Mazepine)**

1) MOA -
1) absorption - slow and erratic
2) distribution - peak conc. in 6-24 hrs.
3) metabolism - active metabolite (10,11-epoxy-carbamazepine) -- ring
-metabolite is neurotoxic / allergenic (good antiepileptic, though)
-inducer of own metabolism and of other drugs' metabolism
4) maintenance doses - must give BID-QID
-adults - 7-15 mg/kg/day
-children (<15 y.o.) - 11-40 mg/kg/day
5) other uses - bipolar disorder, trigeminal neuralgia
6) ADR's -** agranulocytosis, hyponatremia
7) DI's

-** chronic hi dose acetaminophen ⇒ acetaminophenol (toxic)

8) therapeutic monitoring
-serum trough levels
-serum sodium
-CBC / diff at baseline, Q2wks, then Q3months X 1yr

C) **Valproic acid / Valproate (Depakene, Dalpro, Depakote, Myproic Acid)**

1) MOA -
1) availability
-valproate sodium syrup (250mg/5ml)
-divalproex sodium capsules (125mg of VPA)
-liquid filled capsules (250mg of VPA)
-enteric coated tablets
2) metabolism - Enzyme inhibitor
3) half-life 8-20 hours
4) doses (VPA)
-adults - start at 10-15mg/kg/d in divided doses
- increase by 5-10mg/kg/d each week
-children - 7.5-60mg/kg/day
5) other uses - bipolar disorder
-first-line therapy in absence, myoclonic, clonic/tonic, GTC, and febrile sz's
6) ADR's
-neural tube defects in pregnancy (2%) - give folic acid - may reduce
7) DI's
-↑ NH_3 levels, ↓ platelet aggregation
8) therapeutic monitoring
-trough levels
-serum ammonia levels
-CBC/diff, platelets, bleed times
-LFT's, pancreatic enzymes

D) **Phenobarbital / Primidone (Luminal, Barbita / Mysoline, Sertan)**

1) MOA -
1) very lipophilic drugs
2) metabolism - Enzyme inducer
-Primidone is metabolized to phenobarbital (PB - 5%) and PEMA (40%)
-half-life = 100hrs (s.s. in weeks)
3) doses
a) PB: adults - 1.5-3.5mg/kg/d (120-250mg) as single daily dose
children - 2-6mg/kg/d
b) Primidone: adults - 750-1000mg/d in divided doses
children - 5-20mg/kg/d
4) other uses - sedative hypnotic, anxiolytic, drug of abuse
5) ADR's
-osteomalacia (monitor Ca^{++})
6) DI's

E) **Ethosuximide (Zarontin)**

1) MOA - may inhibit the Na^+/K^+ ATPase system and inhibits the NADPH-linked aldehyde reductase necessary for the formation of γ-hydroxybutyrate
2) available as capsules (250mg) and syrup (250mg/5ml)
3) little to no protein binding
4) metabolized - to several inactive metabolites
5) ADR's (see table 51.9)
6) DI's - with other CNS depressants
   - metabolism may be induced by CBZ or inhibited by VPA

F) **Felbamate (Felbatol)**

1) structurally similar to meprobamate (Equanil, Miltown)
2) MOA -
3) absorbed rapidly, with peak in 1-4 hrs.
4) s.s. in 5 days
5) DI's - induces the metabolism of CBZ
   - inhibits the metabolism of phenytoin and VPA
6) SE's - dose-related GI upset, n/v/HA, insomnia
   - non-dose related blurred vision, diplopia, tremors, ataxia
   - rare aplastic anemia and acute hepatic failure
7) dose - 1200-3600mg/d in 3-4 divided doses
8) indicated for partial and secondarily generalized seizures, and for Lennox-Gastaut syndrome in adults and children

G) **Gabapentin (Neurontin)**

1) MOA - a gamma-aminobutyric acid (GABA) analog
2) partially absorbed with peak levels in 1-3 hrs.
3) no protein binding
4) not metabolized - excreted unchanged in urine
5) half-life is 5-7 hours
6) SE's - somnolence, dizziness, ataxia, nystagmus, weight gain, skin rash, n/v, blurred vision, tremor, slurred speech (mild and often transient)
7) dose - 900-1800mg/d divided TID
8) indicated as adjunct therapy in adults and children > 12 y.o. with refractory partial and secondarily generalized seizures

H) **Clobazam**

1) MOA - a 1,5-benzodiazepine derivative used as an anxiolytic
2) rapidly absorbed with peak levels in 1-3 hrs.
3) 90% protein binding
4) metabolized to 14 metabolites, incl. desmethylclobazam (active)
5) half-live is 11-77 hrs.
6) SE's - sedation, hangover effects, rare orthostasis and syncope, confusion, HA, dry mouth, n/v, and weight gain have been reported
7) dose - 20-80mg/d divided or as a single dose
8) used in uncontrolled or refractory epilepsy, catamenial epilepsy, and EtOH withdrawal, as well as for anxiety

I) **Lamotrigine (Lamictal)**

1) MOA - Na^+ channel blocker
2) absorption is almost complete with peak levels in 1-4 hrs
3) 55% protein bound
4) conjugated, not metabolized, and excreted in urine and feces
5) half-live is 25-30 hrs if taken alone
6) SE's - fatigue, drowsiness, ataxia, dizziness, headache, blurred vision, diplopia, n/v, and rash (10% - usually within first 2 weeks), Stevens-Johnson's (0.3%)
7) dose:
   a) <u>If no VPA</u>, begin at 50mg/d x 2wks, then 50mg BID X 2wks, then 100mg BID X 1 wk, then 150mg BID thereafter
   b) <u>If VPA</u>, begin at 25mg QOD X 2wks, then 25mg QD X 2wks, then 25mg BID X 1wk, then 50mg BID thereafter
8) Approved as adjunct therapy for adults with uncontrolled partial seizures
9) also used in idiopathic generalized seizures, incl. tonic/clonic and absence seizures, and those associated with Lennox-Gastaut syndrome

J) **Vigabatrin**

1) MOA - a synthetic derivative of GABA
2) only the S(+) enantiomer is biologically and pharmacologically active
3) peak levels in 1/2 to 2 hrs.
4) eliminated via renal excretion
5) half-life is 7 hrs. (for both enantiomers)
6) SE's - drowsiness, fatigue
   - reported: dizziness, HA, ataxia, irritability, behavior changes, anxiety, GI upset, and weight gain
7) dose - adults: 2000-3000mg/d, increasing to 4g/d if necessary
   children: 1000-2000mg/d
   reduce dose in renal impairment
8) used as add-on therapy in patients with multidrug-refractory complex partial seizures in adults, as well as infantile spasms in children and adolescents

K) **Oxcarbazepine (Trileptil®)**

1) MOA - an analog of carbamazepine
2) Prodrug with active compound 10-hydroxy-carbazepine
3) peak in 5-8 hrs of metabolite
4) half-life is 8-11 hours for metabolite
5) SE's - CNS (HA, ataxia, dizziness), GI upset, hyponatremia (> CBZ)
   - reported: memory impairment, anorexia / wt. gain, difficulty concentrating
6) optimal dose -1000-2500mg/d in clinical trials (range = 300-5400mg/d)
7) trigeminal neuralgia dose - 1200-2400mg/d
8) uses include epilepsy, trigeminal neuralgia, and possibly spasticity related to cerebral epileptogenic lesions
9) drug should be considered an alternative to CBZ in intolerant / unresponsive patients

L) **Others:**

1) **ACTH (Acthar, ACTHGel)** (Adrenocorticotropin hormone / corticotropin)
   - used in infantile spasms since 1951
   - IM gel injection given QD-QOD at 40-120 IU/d

2) **Magnesium Sulfate**
   - used as an anticonvulsant for prevention and control of seizures in severe preeclampsia or in eclampsia, and management of convulsive toxemia of pregnancy (IV only)
   - dose - 4g IV L.D., then 1-4g hourly as IV infusion
     -infuse no > 150mg/min due to feelings of heat
     - can give deep IM into each buttock (Painful!)
   - may cause neuromuscular and respiratory depression
   - therapeutic range is 2.5-7.5mEq/L

3) **Benzodiazepines**
   - all can be used, but tolerance to anticonvulsant effect occurs in 80% of patients in a few months
   - save for *Status Epilepticus*

4) **Acetazolamide (Diamox)**
   - Carbonic anhydrase inhibitor used in glaucoma
     - ↑'s CO_2 and cause acidosis
   - useful in catamenial and intractable epilepsy
   - recommended as monotherapy for juvenile myoclonic epilepsy
   - dose - adults: 375mg QD up to 250mg QID (if other AED's - 250mg/d)
     - children: 8-30mg/kg divided TID-QID up to 1.5gm/d

5) **Bromides (triple)**
   - the first effective AED's
   - not well tolerated due to SE's such as skin eruptions, sedation, and psychosis
   -reserved for pts with myoclonic seizures who are refractory to AED's

6) **Amantadine (Symmetrel)**
   - used for intractable epilepsy

7) **Intravenous IGG (Gamma Globulin)**
   - used in IGG_2 deficient epilepsy

PHARMACOTHERAPY OF SCHIZOPHRENIA

Leonard Rappa, Pharm.D., BCPP
Psychiatric Pharmacy Specialist
Assistant Professor, Florida A&M University

Learning Objectives:

1. List the target symptoms of schizophrenia and know the DSM-IV diagnostic criteria for this disorder.

2. Discuss mechanism of action and rationale of pharmacotherapy in the treatment of psychosis with antipsychotics.

3. Identify low potency vs. high potency antipsychotic agents.

4. Know the relative incidence of antipsychotic adverse effects (i.e. sedation, EPS, anticholinergic and cardiovascular) for high vs. low potency agents.

5. In addition to the above SE profiles, be able to identify other side effects associated with antipsychotic agents and potential drug interactions.

6. Given specific patient information, be able to make a rational drug selection based on criteria for selection.

7. List the different types of EPS and the characteristics of each.

8. Be familiar with the practical guidelines for the treatment of EPS. (Drug regimen modification and anti-EPS drugs)

9. Be familiar with the atypical antipsychotics. (Monitoring parameters, doses, adverse effects, place in therapy for tx. of schizophrenia.)

10. Be familiar with basic pathophysiology of psychosis.

11. Know the equivalent doses of the antipsychotics (chlorpromazine-equivalents) and the dosage ranges for each.

PHARMACOTHERAPY OF SCHIZOPHRENIA

Leonard Rappa, Pharm.D., BCPP
Assistant Professor, Florida A&M University

I. DEFINITION OF SCHIZOPHRENIA / PSYCHOSIS:

A. Inability to function in society based on a loss of reality testing.
B. May never again regain ability to cope and function.

II. EPIDEMIOLOGY / CHARACTERISTICS:

A. General population incidence - approx. 0.2 - 2%
B. Genetics
    1. Identical twins - 40-50%
    2. Fraternal twins / siblings - 10%
    3. Child of 1 parent - 10-15%
    4. Child of 2 parents - 30-40%
C. Age of onset - usually 15-34 yrs old
D. Course - generally chronic

III. Types of Schizophrenia (from DSM-IV)

A. Paranoid (Chronic of the Paranoid Type – SCPT)
B. Undifferentiated (Chronic of the Undifferentiated Type – SCUT)
C. Catatonic (Chronic of the Catatonic Type – SCCT)
D. Residual
E. Disorganized

IV. PATHOPHYSIOLOGY OF SCHIZOPHRENIA: (proposed theories)

A. Old theory -- too much dopamine (but doesn't explain negative symptoms)
    1. Mesolimbic system - ↑ DA (too much ?)
    2. Mesocortical system - ↓ DA (too little ?? negative symptoms)
    3. Nigrostriatal system - EPS from DA block (?D_2)
    4. Tuberoinfundibular system - if blocked will ↑ prolactin (pituitary gland)

V. TARGET SYMPTOMS OF SCHIZOPHRENIA: (POSITIVE & NEGATIVE)

POSITIVE SYMPTOMS: → Typical & Atypical Neuroleptics

delusions	grandiosity
conceptual disorganization	hostility
excitement	hallucinations
suspiciousness / persecution	

NEGATIVE SYMPTOMS: → Atypical Neuroleptics

difficulty in abstract thinking	blunted mood
lack of spontaneity	emotional withdrawal
flow of conversation	poor rapport
apathetic social withdrawal	stereotyped thinking

VI. RELATIVE RESPONSIVENESS OF TARGET SYMPTOMS TO DRUG THERAPY:

A. 1-2 days: hyperactivity, combativeness, hostility
B. 1-2 weeks: hallucinations, sleep, appetite, hygiene, delusions, social skills
C. 1-2 months: judgment, insight
D. 20% relapse rate per year

VII. DRUG THERAPY:

A. Indications - psychosis (regardless of etiology) - [see DSM-IV criteria]
B. Efficacy - all equal (Except for Clozapine)
C. Similarities - half-lives, kinetics, mechanism of action, poorly absorbed
D. Differences - potency, SE profile
E. Dosing - single vs. multiple, compliance, SE's
F. Cigarette smoking may increase clearance by 50%

VIII. CRITERIA FOR ANTIPSYCHOTIC (AP) SELECTION:

A. Previous history of response
B. Family history of response
C. Patient's medical status
D. SE profile - high vs. low potency
E. Complexity of dosing (Compliance issues)
F. Medication Cost to patient

IX. SIDE EFFECTS OF ANTIPSYCHOTICS:

A. Extrapyramidal Side effects (EPS).

1. *Acute Dystonias*
    a. Treat with an I.M. medication, like Cogentin or Lorazepam
    b. Laryngospasm can asphyxiate
2. *Pseudoparkinsonism*
    a. Treat with p.o. anticholinergics or amantadine
    b. Test for this with an AIMS test (Abnormal Involuntary Movement Scale)
3. *Akathisias* -- 25-36% of patients on high potency agents
    a. Treat with propranolol or benzodiazepines
4. *Tardive Dyskinesia* -- (from DA up-regulation -- generally irreversible)
    a. Mean incidence is approx. 20%
    b. May be 4% per year for first 4 yrs of tx.

B. Treatment of EPS:

1. Benztropine (Cogentin) - 1-8mg/d
2. Trihexyphenidyl (Artane) - 2-15mg/d
3. Biperiden (Akineton) - 2-8mg/d
4. Diphenhydramine - up to 400mg/d (range 50-300)
5. Amantadine - presynaptic DA agonist - 100-300mg/d
6. Lorazepam or Diazepam for acute tx.
7. Propranolol - 20-60mg/d or more (D.O.C. for akathisia)

C. Sedation - mostly with low potency (histamine blockade)
D. Anticholinergic effects - mostly with low potency
E. Orthostatic Hypotension - mostly with low potency (alpha blockade)

F. Tachycardia /Arrhythmias - mostly with low potency due to: a) vagal inhibition
b) reflex tachycardia
c) quinidine-like effects

G. Seizures

1. Lowest with molindone
2. Decreased with thioridazine, haloperidol, and fluphenazine

H. Retinitis Pigmentosis - (Thioridazine max. dose = 800mg/d)

1. Melanin deposits in the cornea and lens from phenothiazines

J. Dermatological effects

1. Contact dermatitis
2. Photo sensitivity / allergy - Use Sunscreen!

K. Hepatotoxicity- cholestatic jaundice (monitor LFT's)

L. Hematologic

1. Agranulocytosis with clozapine (1-2%), others (0.01%)
2. Transient leukopenia

M. Hormonal / Endocrine

1. Galactorrhea (57%)
2. Gynecomastia & amenorrhea (up to 97%)

N. Genitourinary and Sexual dysfunction

1. Erectile dysfunction & impotence (25-60%) - anticholinergic effect
    a. Anorgasmia
    b. Decreased libido
2. Urinary incontinence

O. Thermoregulation - Poikilothermia

P. Sudden Death - (extremely rare- unknown etiology – probably from CV involvement)

Q. NEUROLEPTIC MALIGNANT SYNDROME (NMS):

1. Rare-(O.5-1.0%), but potentially lethal, most common from high potency
2. Symptoms usually develop 24-72 hours
3. Mortality rate 20-30%

4. Symptoms:

hyperpyrexia (up to 41°C)	diaphoresis
confusion	incontinence
↑ muscle tone	↑ WBC
tachycardia	↑ LFT's
dysarthria	urinary myoglobin
labile BP	muscle rigidity
dysarthria	↑ CPK

5. Treatment:

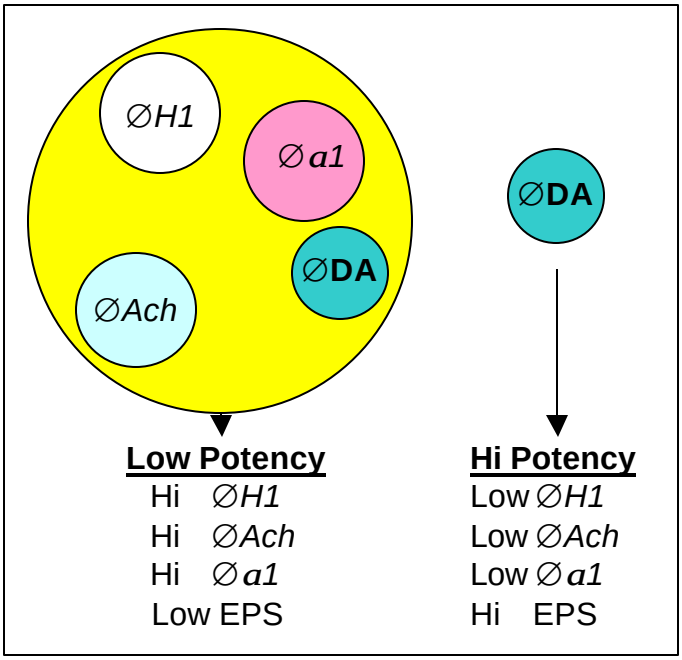
D/C neuroleptics
Dopamine agonists
Dantrolene or Benzodiazepines

6. Respiratory and CV complications are main cause of death.

X. RELATIVE POTENCIES:

100mg Chlorpromazine (Thorazine) =

100mg Thioridazine (Mellaril)
50mg Mesoridazine (Serentil)
10mg Molindone (Moban)
10mg Loxapine (Loxitane)
8-10mg Perphenazine (Trilafon)
5mg Trifluoperazine (Stelazine)
4-5mg Thiothixene (Navane)
2mg Haloperidol (Haldol)
2mg Fluphenazine (Prolixin)



XI. TYPICAL NEUROLEPTICS:

1. CHLORPROMAZINE (THORAZINE®) - developed in early 1950's -- Gold Standard

A. Protein binding 92-97%, $t_{1/2}$=avg.30 hours, over 100 metabolites, IM dosage gives plasma level 4-10 times po
B. M.O.A. - DA antagonist
C. Max. benefit about 1gm po/day
D. Interactions - antacids decrease absorption, CNS depressants, guanethidine

2. THIORIDAZINE (MELLARIL®) - interpatient variability of plasma levels may be 10 fold

A. Highest of all neuroleptics in anticholinergic side effects.
B. Lowest of all neuroleptics in EPS.
C. Pigmentary retinopathy **(max. dose 800mg/day)**
D. Retrograde ejaculation and other sexual dysfunction (up to 60%).
E. Photosensitivity extremely rare
F. No parenteral form available!
G. The usual starting dose in adults is 50-100mg three times a day
H. Not indicated for children under the age of 2 years
I. Contraindicated in severe CNS depression or comatose states from any cause.
*It should also be noted that hypertensive or hypotensive heart disease of extreme degree is a contraindication of phenothiazine administration.
J. Cardiovascular effects have included prolongation of the Q-T interval, lowering and inversion of the T wave and appearance of a wave tentatively identified as a bifid T or U wave have been observed.

3. MESORIDAZINE (SERENTIL®) - a metabolite of thioridazine

A. Potent antiemetic
B. Available as injection also
C. Low EPS, High Sedative, and High Anticholinergic Effects
D. Indications also include alcoholism, anxiety, and ADHD
E. Interaction
1. Aminoglycosides, Anticonvulsants, Anticholinergics -- decrease effect
2. CNS depressants, propranolol -- increase toxicity
F. Avoid excessive sunlight

4. MOLINDONE (MOBAN®)

A. High EPS, Low sedative, Low anticholinergic effects
B. Half-life: 1.5 hours, therefore TID-QID dosing may be needed
C. Less effect on lowering seizure threshold
D. Only agent reported not causing weight gain (or very little)
E. Skin pigmentation not reported.
F. Sedation subsides after continued use
G. Contraindications - severe cardiovascular disorders
H. Available as an oral concentrate, and tablet

5. LOXAPINE (LOXITANE®)

A. Active metabolite is amoxapine (Asendin) an antidepressant with EPS SE's.
B. Moderate EPS/anticholinergic
C. Supposedly little wt. gain
D. Usually administered in divided doses two to four times a day
E. Initial dosage of 10mg twice daily is recommended, although in severely disturbed patients initial dosage up to a total of 50mg daily may be desirable.
F. Signs of sedation were seen in clinical trials within 20-30 minutes.
G. Contraindicated in comatose or severe drug-induced depressed states

6. PERPHENAZINE (TRILAFON®) -- *Mid-potency*

A. Also used to treat intractable hiccups and nausea/vomiting
B. Max. dose 64mg/day
C. Half-life: 9 hours
D. Initial dose 12-24mg/day in 2 to 3 divided doses
    a. Elderly patients: initial doses over 75% lower are generally used
E. Contraindications – If receiving large doses of CNS depressants, existing blood dyscrasias, bone marrow suppression, or liver damage.
F. Cautions -- hyperthyroidism, GI obstruction, hypocalcemia, and cardiac disease.

7. TRIFLUOPERAZINE (STELAZINE®)

A. Doses
    a. Children 6-12: initial dose 1mg 1-2 times/day; maximum:15mg/day
    b. Adults: initial 2-5mg/day; maximum 40mg/day
B. Also has anxiolytic indication
    a. Non-psychotic anxiety: 1-2mg/day; maximum 6mg/day
    b. THERAPY FOR ANXIETY SHOULD NOT EXCEED 12 WEEKS
C. Half-life: >24hours with chronic use.
D. Contraindications: blood dyscrasias, bone marrow depression, or liver damage.
E. Precautions: CV disease, myasthenia gravis, seizures, or narrow-angle glaucoma.

8. THIOTHIXENE (NAVANE®)

A. High-potency antipsychotic; associated with high EPS
B. moderate anticholinergic effects
C. Half-life: >24 hours with chronic use
D. Dosing
    a. Children >12 and adults: begin with 2-3mg po tid up to 5mg bid
    b. Maximum 60mg/day.
E. Contraindications: circulatory collapse, CNS depression, and blood dyscrasias.

F. Precautions: Narrow-angle glaucoma, bone marrow suppression, severe liver or cardiac disease, or seizures.

9. HALOPERIDOL (HALDOL®)

A. Very little anticholinergic side effects, high EPS, less sedation, little CV effects
B. Indications: Tourette's (syndrome (to control of tics and vocal utterances), severe behavioral problems in children (unresponsive to behavioral or counseling therapy), emergency sedation of severely agitated or delirious patients, infantile autism, Huntington's disease, chemotherapy induced nausea and vomiting
C. Available as decanoate **dosed 15-20 times total daily dose q 4 weeks**
   1. give no more than 100mg on first dose (Z-track method)
   2. remainder of first dose can be given in 3-7 days
   3. reduce dose by 25% on month 2 and 25% again on month 3
   4. maintain on dose from month 3 or adjust based on clinical response
   5. average dose is approximately 200mg per month
   6. half-life is approximately 3-4 weeks
D. No pigmentation effects
E. Protect oral dosage forms from light

10. FLUPHENAZINE (PROLIXIN)

A. Available as a decanoate / enanthate IM depot formulations
   1. Decanoate - **1.25 times total daily dose given Q 2-3 weeks**
   2. Effects of decanoate last 2-3 weeks
B. IM steady state of decanoate may be several weeks.
C. High incidence of EPS, up to 90%
D. Total daily dosage may range initially from 2.5-10mg and should be divided and given in 6-8 hour intervals
E. Fluphenazine is contraindicated in patients with suspected or established sub cortical brain damage, in patients receiving large doses of hypnotics, and in comatose or severely depressed states
F. Routine blood counts are advisable since blood dyscrasias including leukopenia, agranulocytosis, thrombocytopenia, eosinophilia, and pancytopenia have been observed.

XII. ATYPICAL AGENTS

1. CLOZAPINE (CLOZARIL®)

A. Structural analogue of Loxapine
B. Useful in treatment resistant schizophrenia
C. **D_1** > D_2, **D_4**, $5HT_2$, $5HT_3$, $5HT_6$, and $5HT_7$ antagonist
D. Also blocks adrenergic (*alpha2)*, cholinergic, and histaminic receptors as well
E. Dosing
   1. 25mg BID + 25-50mg/d up to 300 to 900mg/d
   2. Available as 25mg and 100mg tablets
F. Side effects
   1. Most common
      a. Drowsiness
      b. Dizziness
      c. Tachycardia (reflex)
      d. Orthostatic hypotension
      e. N/V
      f. Fever
      g. Visual disturbances
      h. Constipation
      i. Weight gain
      j. Salivation (glycopyrrolate / Robinul®)

2. Rare
    a. Agranulocytosis (1-2%)
    b. G-CSF not effective
    c. Seizures
        1. <300mg=1-2%
        2. 300-600mg=3-4%
        3. 600-900mg=5-14%

G. Clozapine Patient Monitoring System / $ cost / labs
    1. No more than a 1 wk. supply can be dispensed at any one time
    2. Unless patient has been on therapy for > 6 months with no problems
        --Then Q 2 week WBC's can be monitored

H. Very little EPS

I. Plasma levels greater than 350 ng/ml show better efficacy -- [watch seizures!]

2. RISPERIDONE (RISPERDAL®)

A. M.O.A.
    1. D_2 antagonist (affects positive symptoms)
    2. $5HT_{2a}$ antagonist (affects negative symptoms)
        a. 10-20 times more than D_2 antagonism
    3. *alpha*$_1$ and *alpha*$_2$ blockade (see Remeron info)

B. Half-life is approx. 20 hours

C. Side effects
    1. Sedation, orthostatic hypotension, dose-related EPS
    2. No anticholinergic effects!

D. Dose must be titrated slowly to minimize orthostatic hypotension and sedation
    1. Begin with 0.25mg to 1mg given QHS or BID
    2. Reduce dose in the elderly
    3. Average dose is 4mg/d (National average)

E. Dosing may be up to 16mg/d divided

F. Available as
    1. 0.25mg, 0.5mg, 1mg, 2mg, 3mg, & 4mg tablets
    2. New liquid formulation available in 30ml bottles (1mg/ml)

3. OLANZAPINE (ZYPREXA® / ZYDIS®)

A. Antagonist of $5HT_{2a/2c}$, D_{1-4}, M_{1-5}, H_1, and *alpha*$_1$ receptors

B. Weakly binds to $GABA_a$, BZD, and *Beta*-adrenergic receptors

C. Half-life of 21-54 hours (mean 30 hours)

D. QD dosing

E. 93% protein bound

F. Absorption and onset of action is similar for both tablet types

G. Buccal absorption of Zydis is not significant

H. Metabolized by glucuronidation and P450 enzymes

I. Dosing
    1. 2.5 to 20mg QD
    2. Higher doses have been used successfully, but is very expensive
    3. Average dose is 15-20mg/d

J. Side Effects :
    1. Most common (<10%)
        a. Drowsiness
        b Dizziness
        c. Akathisia
        d. Weight gain

K. Zyprexa tabs available in 2.5mg, 5mg, 7.5mg, 10mg, 15mg, and 20mg tablets
    1. Cannot break oral tablets, because medication oxidized quickly
L. Zyprexa Zydis® is available as a rapidly dissolving oral tablet in 5mg and 10mg dosages
    1. Advantages:
        a. Increased compliance for those with difficulty swallowing or those who "cheek" their meds
        b. Analogous to a liquid formulation
M. Soon to be available in a rapidly acting IM injection
N. See Tables 1 and 2 for cost comparisons

4. QUETIAPINE (SEROQUEL®)

A. Zeneca Labs
B. Mechanism of action
    a. $5HT_2$ and $5HT_{1a}$ antagonism > D_1 and D_2 > Ach
    b. *alpha$_1$ / alpha$_2$* antagonism
    c. Also blocks histamine receptors
C. Structurally similar to clozapine (analogue)
D. Pharmacokinetics:
    1. 83% bound to plasma proteins
    2. Half-life = 6hrs (longer in some elderly pts.)
    3. Metabolized partially by $P450IIIA_4$
E. Drug Interactions
    1. Phenytoin increases clearance up to 500%
    2. Thioridazine increases clearance up to 65%
    3. May need to ↑ dose of quetiapine
F. Side Effects
    1. Precaution of cataract formation --Seen in beagle dogs in study, not in primates
        --Slit lamp eye exam or other suitable exam should be performed at initiation of therapy or shortly thereafter and every 6 months during treatment. (from P.I.)
    2. Dizziness (10% vs. 4% with placebo)
    3. Postural hypotension (7% vs. 2% with placebo)
    4. Somnolence (18% vs. 11% with placebo)
    5. Dry mouth (7% vs. 3% with placebo)
    6. Dyspepsia (6% vs. 2% with placebo)
    7. Transient - ALT (6% vs. 1% with placebo)
    8. No EPS or prolactin elevations seen at any dose
G. Dosing
    1. Initiate at 25mg BID
    2. Increase as tolerated by 25-50mg/d up to 300-400mg/d
    3. Elderly should not receive more than 100mg/d
    4. Dose range is 150mg/d to 800mg/d
    5. Average dose is 300-400mg/d divided
H. Available as: 25mg, 100mg, 200mg and 300mg tablets

5. ZIPRASIDONE (GEODON™) - Pfizer Laboratories

A. Structurally resembles risperidone

B. Mechanism of action
1. $5HT2_A$, $5HT2_C$, and $5HT1_D$ Antagonist / $5HT1_A$ agonist
2. D_2 and D_3 antagonist (weaker than serotonin antagonism) – like risperidone
3. Moderate *alpha*$_1$ and histamine$_1$ blockade
4. Moderate 5HT and NE reuptake inhibition (? antidepressant effects)
5 Negligible anticholinergic effects

C. Pharmacokinetics
1. Absorption is increased with food – Peak in 3 to 5 hours
2. Half-life is 3.2 to 10 hours (avg. 7 hrs.)
3. >99% protein bound
4. Metabolized by $P4503A_4$
5. Weak inhibitor of $P4502D_6$ (hi dose)

D. Side Effects
1. ↑ in QTC interval *(avg. of 10-20 msec)*
2. Akathisia (10%)
3. Anorexia
4. Anxiety
5. Arthralgia
6. Asthenia (5.5%)
7. Depression (8%)
8. Diarrhea (7%)
9. Dizziness
10. Dry mouth
11. Dyspepsia
12. EPS
13. Hallucinations (9%)
14. Headache (7%)
15. Hostility (7%)
16. Insomnia (35%)
17. Nausea & vomiting (5%)
18. Orthostatic hypotension
19. Rash (6%)
20. Seizures (0.4%) – *compounding factors*
21. Somnolence
22. Tremor
23. Upper respiratory tract symptoms

E. Drug Interactions
1. Drugs that prolong the QT interval (partial list)
   a. Quinidine
   b. Dofetilide
   c. Pimozide
   d. Sotalol
   e. Thioridazine
   f. Moxifloxacin & Sparfloxacin
2. Other interactions
   a. Carbamazepine – Can ↓ ziprasidone by 36% (need more Geodon)
   b. Ketoconazole – Can ↑ ziprasidone by 33% (need less Geodon)

F. Dosing
1. Begin with 20mg BID (with food)
2. Adjust dose up to 80mg BID every few days to weeks
3. Average is 120mg/d to 160mg/d divided BID with food
4. No dosage change recommended for elderly or renal/hepatic impairment

G. Differs from other antipsychotics
1. Less weight gain (avg. 1kg)
2. Low risk of EPS
3. Lower degree of prolactin elevation (mostly transient)

H. Warning
1. **May cause QT prolongation and risk of sudden death**
2. EKG is recommended in those patients at high risk for cardiac complications
   a. ie. Those > 40 or <18 years old
   b. Recent acute MI or uncompensated heart failure

I. Availability
1. Capsules – 20mg, 40mg, 60mg and 80mg
2. Immediate acting Intramuscular injection soon to be available
3. See Tables 1 and 2 for cost comparisons

XIII. OTHER ATYPICAL ANTIPSYCHOTICS BEING STUDIED

A. Iloperidone / HP 873 by Titan Pharmaceuticals
B. Aripiprazole (Abilitat®) by Bristol-Myers Squibb Co.
C. Mazapertine by Janssen
D. Zotepine by Knoll

XIV. ADDITIONAL INFORMATION

TABLE 1. ATYPICAL ANTIPSYCHOTIC RETAIL COST COMPARISON

DRUG	DOSE	QUANTITY (1 MONTH SUPPLY)	AVERAGE RETAIL COST* *As of 5/2001
Geodon™	20mg	60	$263.95
	80mg	60 (max. dose)	$263.95
Risperdal®	1mg	30	$88.95
	4mg	60	$441.95
Seroquel®	25mg	60	$94.95
	200mg	120 (max. dose)	$616.95
Zyprexa®	5mg	30	$192.95
	10mg	60 (max. dose)	$570.95

TABLE 2. MRH COST COMPARISON (HOSPITAL CONTRACTED COST)

DRUG	DOSE	MRH COST OF 1 DAY'S THERAPY	MRH COST FOR 1 MONTH SUPPLY
Geodon™	20mg	$6.38	$191.40
	80mg	$6.38	$191.40
Zyprexa®	5mg	$4.82	$144.60
	20mg	$14.66	$439.80
Zyprexa Zydis®	5mg	$5.74	$172.20
	10mg	$8.23	$246.90
Tenex® (guanfacine)	1mg	$0.13	$3.90
	2mg	$0.18	$5.40

PHARMACOTHERAPY OF SLEEP DISORDERS

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I. BACKGROUND

- 1/3 of life is spent asleep (3 to 10 hours a night)
- No ideal duration of sleep
  - Adequacy is best determined by feelings of restfulness, mental acuity, and alertness
- Disorders of sleep related to:
  - Too little or too much
  - Inconsistent sleep patterns
- Lack of sleep
  - Causes irritability and impaired functioning

II. EPIDEMIOLOGY

- Magnitude of the Problem
  - 25-35% have some sleep complaint at any given time
  - 2-4% use prescription hypnotics
  - 40% use non-prescription sleeping aids or alcohol
  - Only 5% seek help and receive treatment
- Costs
  - Direct costs = $11 billion in 1991
  - Indirect costs = > 100 billion today

III. CLASSIFICATIONS

- Dyssomnias
  - Insomnia
  - Sleep apnea
  - Narcolepsy
  - Restless leg syndrome (RLS)
  - Nocturnal myoclonus
    - Periodic limb movements (PLM)
- Parasomnias (common in children)
  - Sleepwalking (somnambulism)
  - Night terrors
- Medical or Psychiatrically-related

IV. SLEEP STAGES

- Non-REM sleep:
  - Stage 1
    - Transition between sleep and wakefulness
  - Stage 2
    - Light sleep
  - Stage 3 / 4
    - Deep, restorative sleep (delta sleep)
- REM sleep
  - Similar to Stage 1

V. PHYSIOLOGICAL CHANGES DURING SLEEP

- In REM sleep:
  - Rapid Eye Movements
  - ↑HR, ↑RR, ↑BP
- In Non-REM sleep:
  - ↓HR, ↓RR
- Also:
  - ↑ Cortisol levels
  - ↑ Growth hormone
  - ↑ Protein synthesis
  - ↑ Melatonin secretion
  - ↑ Immune function
  - ↑ Tissue repair
  - ↓ Body temperature
  - ↓ Metabolic rate
  - ↓ Glucose consumption
  - ↓ Catabolic hormones

VI. INSOMNIA

- Most common sleep disorder
  - 95% incidence in a lifetime
  - 1.5 times more in elderly vs. young
  - 1.3 times more in women vs. men
- Diagnosis
  - Relative lack of sleep
  - Subjective complaint
  - Sleep diary
  - Sleep disorder center

A. TYPES OF INSOMNIA

- Transient
  - Lasts only a few days
- Short-term
  - Lasts days to weeks
- Chronic
  - Lasts months to years
  - 10% of the population

B. PATTERNS OF INSOMNIA

- Difficulty falling asleep
  - Correlated with anxiety
- Mid-sleep awakenings
- Early morning awakenings
  - Can’t fall back asleep
  - Correlated with depression
- Non-restorative sleep

C. CAUSES OF INSOMNIA

- Psychiatric Disorders - 50%
  - Mood disorders
    - Major depression, dysthymic disorder, mania, anxiety, obsessive-compulsive disorder (OCD)
    - 40% of insomniacs have depression or anxiety
      - 70% of depressed patients have insomnia
      - 25% of anxious patients have insomnia
  - Character (personality) disorders
    - Borderline, narcissistic, dependent
  - Psychosis
    - Schizophrenia, other
- Drug and Alcohol Use / Abuse - 10% to 15%
  - Sedatives
    - Alcohol, benzodiazepines, barbiturates, narcotics
  - Stimulants
    - Amphetamines, cocaine, methylphenidate, pemoline, decongestants (ie. phenylpropanolamine), stimulating antidepressants (bupropion, SSRIs, protriptyline), caffeine (xanthines), antipsychotics (? akathisia)
  - Anti-asthmatics
    - Terbutaline, aminophylline, *Beta* agonists
  - Nicotine-containing products (cigarettes)
  - Antihypertensives & Diuretics
- Medical / Surgical Problems - 10%
  - Cardiovascular: Nocturnal angina, orthopnea
  - Respiratory: COPD
  - Renal: UTI, urinary frequency
  - Endocrine: Hyper- or hypothyroidism
  - Pain of any source
  - Delirium
    - Dementia, infection, metabolic derangement, medication toxicity (ie. anticholinergic delirium)
  - Sleep apnea
- Primary Sleep Disorder - 10% to 20%
  - Idiopathic insomnia
  - Psychophysiologic or conditioned insomnia
  - Phase shift (Delayed Sleep Phase Syndrome)
  - Nocturnal myoclonus (Restless legs / limbs)
  - Persistent complaint without objective evidence
  - Unusual polysomnographic patterns
    - Alpha-delta sleep

D. PATIENT ASSESSMENT OF INSOMNIA

- History
  - Onset of disturbance
    - In relation to:
      - New life events
      - New medications, drugs, or alcohol
      - Recent changes in diet and/or exercise

- ▲ Sleep characteristics
  - ● Total time perceived asleep
  - ● Sleep latency
  - ● Number of awakenings
- ▲ Daytime functioning

E. TREATMENT OF INSOMNIA

- ■ Depends on duration and severity
- ■ Non-pharmacologic therapy
  - ▲ ie. behavioral interventions and sleep hygiene
- ■ Medication therapy
  - ▲ Over-the-counter sleep aids
  - ▲ Prescription medications
  - ▲ Controlled-substances

F. NON-PHARMACOLOGIC TREATMENT OF INSOMNIA

- ■ Sleep hygiene
  - ▲ Schedule regular sleep times
  - ▲ No daytime napping
  - ▲ Regular exercise early in the day
  - ▲ Avoid big evening meals, fluids, and caffeine
    - ● Light snack preferred
  - ▲ Use bedroom only for sleep & sex
  - ▲ Take a hot bath about 1-1/2 hrs before bedtime
  - ▲ If sleep does not occur in 30 min. get up
    - ● Do a quiet activity or read (Do not exercise!)
  - ▲ Eliminate the bedroom clock (or face it away)

G. OTHER NON-PHARMACOLOGIC TREATMENTS OF INSOMNIA

- ■ Elimination of exogenous factors
  - ▲ Caffeine, drugs, excess stimulus & stress
- ■ Deep breathing & muscle relaxation
- ■ Chronotherapy (Sleep restriction therapy)
- ■ Total sleep deprivation
- ■ Light therapy in daytime (Will ↑ melatonin at night)
- ■ Lavender

H. MEDICATIONS (HYPNOTICS)

- ■ Intended for short-term (prn) use
- ■ Not effective or less effective if used chronically
- ■ 40% of sleeping pills taken by the elderly

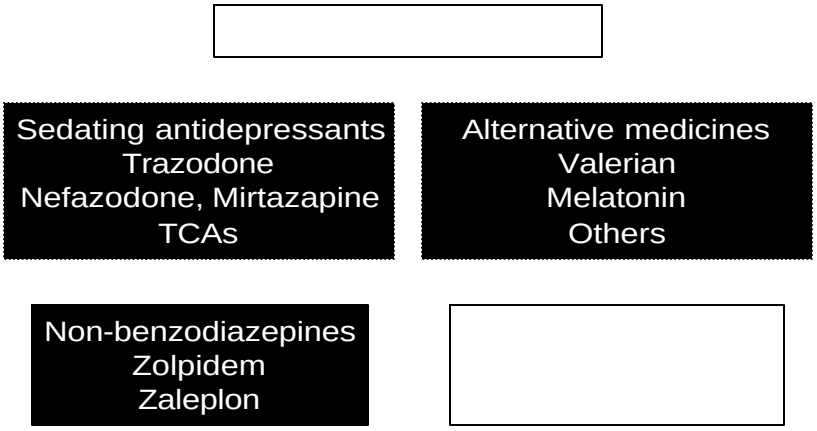
I. PROPERTIES OF AN IDEAL HYPNOTIC

- Rapid onset of action
- Duration of action allows 6-8 hours of sleep
- Sleep mimics normal sleep
- Patient functions well if awakened
- No hangover symptoms
- No tolerance (does not "wear off")
- No abuse or addiction potential
- No withdrawal symptoms
- No side effects
- No drug interactions

J. CLASSIFICATION OF HYPNOTIC AGENTS

- Barbiturates
- Older non-barbiturate hypnotics
- Antihistamines
- Benzodiazepines
- Non-benzodiazepines
- Sedating antidepressants
- Others / alternative medicine
  - Melatonin
  - Valerian

K. ORDER OF HYPNOTIC USE



1. BARBITURATES AND NON- BARBITURATES

- Pentobarbital (Nembutal®)
- Secobarbital (Seconal®)
- Amobarbital (Amytal®)
- Ethchlorvynol (Placidyl®)
- Methyprylon (Noludar®)
- Glutethimide (Doriden®)
- Chloral hydrate (Noctec®)

2. BARBITURATES

- Not recommended due to the following disadvantages:
  - Narrow therapeutic index
  - Abuse potential
  - Potential drug-drug interactions
  - REM rebound after abrupt discontinuation
  - Tolerance
    - Loss of efficacy in < 2 weeks

3. NON-BARBITURATES

- These agents share the same disadvantages as the barbiturates
- Chloral hydrate
  - Drug interaction with alcohol
    - Mickey Finn effect

4. ANTIHISTAMINES

- Diphenhydramine
  - Benadryl, Sominex, Nytol, Sleep-EEZ, Compoz, Tylenol PM
- Doxylamine
  - Unisom
- Pyrilamine
  - Nervine, Quiet World
- Subjective reports suggest they are effective and well tolerated
- Not overly toxic in overdose
- Safe in pregnancy
- Not for patients with glaucoma, prostate problems, or cardiac arrythmias

a. ANTICHOLINERGIC SIDE EFFECTS

- Dry mouth
- Constipation
- Blurred vision
- Tachycardia
- Urinary retention
- Anticholinergic psychosis
- Memory deficits in the elderly

5. ANTIDEPRESSANTS USED IN SLEEP

- Can be used in the absence of depression and anxiety
  - SSRIs can also be used if etiology of insomnia is depression, anxiety, or Panic disorder
- Non-addicting
- TCAs should not be used in:
  - Elderly
  - Cardiac arrythmias
  - Restless leg syndrome (RLS)
  - Periodic limb movements (PLM)

a. TRAZODONE (DESYREL)

- Not well studied, but used often
- Dose is 25 to 50mg an hour before bedtime
- Little anticholinergic effects
- Minimal to no hangover effect
- Side effects
  - ▲ Orthostatic hypotension
  - ▲ Priapism (very rare)
- Non-addicting, so may be useful in recovering addicts
- Increases delta wave sleep (Stage 3/4)

b. NEFAZODONE (SERZONE) AND MIRTAZAPINE (REMERON)

- Improve sleep architecture and efficiency
- Significantly shortens sleep-onset latency
- Increases total sleep time
- Reduces the number of awakenings over time
- Does not cause REM suppression
  - ▲ Increases total REM sleep time
- Not associated with sexual dysfunction

6. BENZODIAZEPINES APPROVED AS HYPNOTICS

Flurazepam (Dalmane)	15 - 30mg
Temazepam (Restoril)	15 - 30mg
Triazolam (Halcion)	0.125 - 0.25mg
Quazepam (Doral)	7.5 - 15mg
Estazolam (Prosom)	1 - 2mg

a. BENZODIAZEPINES (BZDs)

- All BZDs cause sedation
  - ▲ Tolerance develops over weeks
  - ▲ 30% are prescribed for > 1 month
- Many of the BZDs marketed as anxiolytics can be effective hypnotics
- ↑ Stage 2 sleep
- ↓ Stage 1 and 4 sleep
- Suppress REM sleep
- Pharmacokinetic differences determine their usefulness in insomnia

b. WHEN TO USE WHAT

- Short-acting BZDs
  - ▲ Difficulty falling asleep
  - ▲ Triazolam / estazolam
- Intermediate-acting BZDs
  - ▲ Difficulty staying asleep
  - ▲ Temazepam / quazepam
- Long-acting BZDs
  - ▲ Useful in daytime anxiety with insomnia
  - ▲ Flurazepam / clonazepam

c. SIDE EFFECTS OF BZDs

- Rebound insomnia
  - Recrudescence
  - Early morning awakening / morning anxiety
  - Worsening of sleep beyond baseline
  - Most common with short-acting BZDs
  - Dose-related
  - Can be avoided if dose is tapered
- Hangover
  - Impaired daytime performance due to sedation, motor incoordination and cognitive impairment
  - More common with the long-acting BZDs
  - Dose-related
  - Elderly patients are more susceptible
    - Risk of motor vehicle accidents and falls with hip fractures
- Anterograde amnesia
  - Inability to remember events following BZD administration
  - All BZDs can cause amnesia
  - Mostly from high potency BZDs
  - Severity is a function of route, dose, and half-life
  - Useful effect with midazolam I.V.
- Adverse behavioral effects
  - Paradoxical excitation
    - Disinhibition
    - Hyperactivity, rage, anxiety, agitation, paranoia, hallucinations, confusion, etc.
    - More common with high potency BZDs
    - Common in elderly and very young
- Respiratory depression

d. ABUSE POTENTIAL OF BZDs

- Should be minimal when used appropriately for transient or short-term insomnia
  - Use the lowest possible dose
  - Use no more than 3 weeks
  - Use no more than 3 or 4 days a week if used chronically
    - Chronic use increases risk of:
      - ★ Tolerance with resulting escalation of dose
      - ★ Physical and psychological dependence
      - ★ Difficulty in attempted withdrawals

e. GENERAL PRINCIPLES FOR CLINICAL USE OF BZDs

- Avoid in:
  - Sleep apnea
  - Alcoholics / Substance abusers
  - Pregnancy
  - Depression
- Monitor effect and daytime sequelae
- Educate patient of possible temporary withdrawal effects upon D/C
- Never use > 2 BZDs together
  - Not justified

7. NON-BENZODIAZEPINES

- Zolpidem (Ambien)
- Zaleplon (Sonata)

- Do not suppress delta wave sleep
  - Restful sleep
- Little or no hangover next day
- Minimal or no rebound after chronic use
  - >30 days
- No important drug interactions

a. Zolpidem (Ambien)

- An imidazopyridine
  - BZD omega$_1$ (ω1) receptor agonist
- Half-life of 1.7 to 2.5 hours
  - Onset of action in 15 to 30 minutes
  - Duration of effect is 6 to 8 hours
- Side effects
  - Amnesia, dizziness, headache, GI upset, psychosis (rare)
- Average dosage
  - Adult = 10mg
  - Elderly = 5 mg
    - ★ Receptor selectivity decreases as dose is increased

b. Zaleplon (Sonata)

- Pyrazolopyrimidine compound
  - GABA$_A$ benzodiazepine receptor agonist
- Half-life = 1 hour
  - Onset of action in 15 to 30 minutes
  - Duration of effect is 2 to 3 hours
- Side effects
  - Headache, drowsiness, dizziness, and weakness
- Dosage
  - Adult = 10 mg
  - Elderly = 5 mg
- Not associated with rebound insomnia

8. ALTERNATIVE MEDICINES

- Herbs, etc.
  - Valerian
  - Melatonin
  - Hops
  - Chamomile
  - Lemon balm
  - Kava
  - Sleeping Buddha (contains a BZD)
- Estrogen replacement after menopause
- Low energy emission therapy (LEET)
- Warm milk / Graham crackers

a. VALERIAN

- Not FDA-approved or regulated
- Increases delta sleep and sleep quality
  - Minimal hangover effects
- 400 - 900mg studied
- May work on $GABA_A$ receptors
  - Not a BZD
- Has a bad taste and smell

b. MELATONIN

- Naturally occurring hormone released by the pineal gland in response to darkness at night
  - Increased secretion during sleep
- Dose of 3mg produces blood levels 10 times normally secreted
- Not FDA-approved or regulated
- Use for insomnia minimally effective
- Best for jet lag / phase shift sleep

VII. SLEEP APNEA

- Episodes of cessation of breathing with sleep disturbance, gasping, heavy snoring, and daytime sleepiness
- Three types:
  - Obstructive
    - 1 to 9% of population
    - Mostly males
  - Central
    - < 10% of apneas
  - Mixed

A. TREATMENT OF SLEEP APNEA

- Obstructive apnea
  - Removal of causative factor
    - Enlarged tonsils
    - Weight loss
  - UPPP (uvulopalatopharyngoplasty)
    - ↓ apnea by 50%
    - ↓ snoring by 90%
  - Nasal CPAP (continuous positive airway pressure)
  - Tracheotomy (if severe)
- Obstructive apnea medications used
  - Non-sedating antihistamines
  - Protriptyline or Fluoxetine
  - Medroxyprogesterone 60mg/d
  - Theophylline and clonidine tried
  - Avoid CNS depressants and alcohol

- Central apnea
  - Hypercapnic ($\uparrow CO_2$)
    - Ventilation support with O_2 and CPAP
    - Theophylline, acetazolamide, medroxyprogesterone
      - Mixed results
  - Non-hypercapnic patients
    - Benzodiazepines (to $\downarrow$ arousals)
- Mixed apnea
  - Combination of previous treatments

VIII. NARCOLEPSY

- 0.5% of population
- May be genetically related
- Clinical Presentation
  - Daytime sleeping attacks (up to 30 minutes)
  - Cataplexy
    - In 70 - 80% of narcoleptics
    - Acute muscle weakness and collapse
      - Exacerbated by laughter, anger, excitement, etc.
  - Sleep paralysis
  - Hypnogogic hallucinations (upon sleep)
  - Hypnopompic hallucinations (upon wakening)

A. TREATMENT OF NARCOLEPSY

- For the daytime sleeping attacks
  - Stimulants
    - Methylphenidate
    - Dextroamphetamine
      - FDA approved
      - 3 to 10 hour duration of effect
      - 5 - 60mg divided daily
    - Pemoline also used
      - 18.75 - 112.5mg divided daily
- For the cataplexy
  - TCAs
    - 80% effective
    - Imipramine
    - Protriptyline (Vivactil)
    - Nortriptyline
  - Selegiline
  - Wellbutrin (?)

IX. DYSSOMNIAS NOT OTHERWISE SPECIFIED

- Restless leg syndrome (RLS)
  - Ekbom's Syndrome
- Periodic limb movements (PLM)
  - 1/3 have RLS
  - Usually only lower extremities involved
  - Usually starts after age 40
  - Irresistible urge to repetitively move legs to achieve comfort

- ▲ RLS is more severe than PLM
  - ● Higher risk of suicide

A. RLS / PLM

- ■ Medications that can aggravate disease
  - ▲ Diuretics
  - ▲ Bronchodilators
  - ▲ Antihistamines
  - ▲ Decongestants
  - ▲ Antipsychotics (? Akathisia)
  - ▲ Antidepressants
  - ▲ Caffeine
  - ▲ Alcohol

B. TREATMENT OF RLS / PLM

- ■ Drugs that affect Dopamine systems
  - ▲ Sinemet 25/100 at bedtime
  - ▲ Pergolide (Permax)
    - ● Start at 0.05mg and increase slowly
  - ▲ Bromocriptine (Parlodel)
- ■ Others tried:
  - ▲ Clonazepam and other BZDs
    - ● Less severe cases
  - ▲ Propoxyphene and oxycodone
  - ▲ Vitamin E (1000 IU/d)
  - ▲ NSAIDS / acetaminophen
  - ▲ Quinine, clonidine, carbamazepine, trazodone, baclofen (Lioresal), cyclobenzaprine, SSRIs, TCAs, lamotrigine (Lamictal)

X. PARASOMNIAS

- ■ Types
  - ▲ Sleepwalking (somnambulism)
  - ▲ Night terrors
- ■ Not usually medication treatable in childhood
  - ▲ Psychotherapy is treatment of choice
- ■ In adults, may try to medicate
  - ▲ Benzodiazepines suppress REM & delta sleep
  - ▲ SSRIs and TCAs tried
  - ▲ Cyproheptadine (Periactin) may help nightmares

XI. CONCLUSION

- ■ Sleep disorders can be a significant and costly public health problem
- ■ Proper diagnosis is necessary for appropriate treatment
  - ▲ Use least detrimental treatment possible
- ■ Hypnotics recommended only for short-term use
  - ▲ Can be harmful in some types of insomnia

SUBSTANCE-RELATED DISORDERS

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I. Introduction
- A. Up to 30% of all hospitalized patients have alcohol problems regardless of diagnosis[1]
- B. 37% of US population have tried marijuana, cocaine, or another illicit drug at least once[1]
- C. 7% of US population is alcohol dependent[1]
  1. In elderly, prevalence is 3-15%
  2. One-third of elderly alcoholics began drinking after age 60
- D. Males are twice as likely as females
- E. Cocaine has been used for more than 2000 years
  1. Used in 1860 as an anesthetic
  2. Used in Coca-Cola until 1903
- F. 25% of elderly use psychoactive drugs
  1. CNS depressants are most common
- G. Health Care Professionals
  1. Highest risk category of professions for developing drug dependence
  2. 46% of pharmacists and 62% of pharmacy students have used controlled substances with a prescription
  3. 19% of pharmacists and 41% of pharmacy students are regular users of controlled substances without a prescription[2]
  4. 33% of pharmacy students have at least one family member with drug dependence[2]
  5. 59% of physicians and 77% of medical students have tried a controlled substance for recreational or self-treatment purposes[2]
  6. 10-15% overall prevalence of drug dependence
- H. Drug addiction is a disease!

II. Definitions:

A. Drug Abuse. The term is difficult to define with precision, but generally refers to illegal or, in the case of licit substances, maladaptive or dangerous use of a substance, without implying dependence. It must be recognized that alcohol and drug-related harm is not only the result of dependence. For example, nondependent alcohol abusers may be responsible for nearly half of alcohol-related problems such as drunk driving, alcohol-related violence, or drunkenness on the job.

B. Dependence. In its narrowest sense, dependence means that, with abstinence from a substance, an individual experiences pathologic symptoms and signs. Until recently, it was thought that the most significant indicator of drug addiction was physical dependence, as manifested by *physical withdrawal* symptoms occurring with drug abstinence, such as tremor or elevated blood pressure. Although physical dependence may certainly be a key symptom of addiction to certain drugs (eg, alcohol or opiates), it is neither necessary nor sufficient. Some highly addictive drugs, such as cocaine or amphetamine, do not produce physical dependence or withdrawal. Moreover, many drugs with no abuse potential, such as clonidine and propranolol, may produce physical dependence (eg, severe rebound hypertension or angina with discontinuation). Indeed, because cocaine does not produce physical dependence, it was widely held until the 1980s that cocaine was not addictive--a misconception that contributed to the recent epidemic of cocaine abuse in the United States.

C. Addiction. This is a special case of dependence. The core concept of addiction is *compulsive substance use* and *inability to control intake despite negative consequences.* Obtaining, using, and recovering from the effects of the substance come to dominate the individual's life, despite medical illness, failure in life roles, or interpersonal difficulties. Because the term *addiction* has gained many imprecise and pejorative meanings, the American Psychiatric Association uses the term *drug dependence* instead of addiction in its current *Diagnostic and Statistical Manual* (DSM-IV) . However, this terminology has the unfortunate side effect of confusing the status of patients who are physically dependent on appropriately prescribed

psychotropic or analgesic drugs, but who exhibit no addictive behaviors whatsoever (ie, no behaviors indicating compulsive, out of control use) with individuals who are addicted. The confusion of dependence with addiction may contribute to underprescription of narcotic analgesics by physicians even when indicated for cancer pain, and undertreatment of anxiety disorders with benzodiazepines.

D. Tolerance

E. Withdrawal or Abstinence syndrome

F. Cross-tolerance and Cross-dependence

[1]Dipiro (3rd edition) p.1345
[2]Data obtained from surveys in the mid-1980's

III. Drugs of abuse

A. Alcohol (See APPENDIX A)

1. Self-induced intoxication in our culture is socially acceptable
2. 88% of US population has consumed alcohol
3. 49-59% of adults are monthly users
4. 14% of adults meet criteria for dependence sometime in their lives
5. Medical complications
    a. liver disease, cardiomyopathy, pancreatitis, GI disease, anemia
    b. CNS disturbances, fetal alcohol syndrome
6. Withdrawal
    a. Phase I
        1. Begins within hours and lasts 3-5 days
        2. Autonomic hyperactivity (tachycardia, diaphoresis, labile blood pressure, anxiety, nausea and vomiting)
    b. Phase II
        1. Perceptual disturbances
        2. Auditory or visual hallucinations
    c. Phase III
        1. seizures (clonic-tonic) lasting 30 seconds – 4 minutes
        2. 3% progress to status epilepticus
        3. 10-15% of untreated withdrawals
    d. Phase IV
        1. *delirium tremens*
        2. occurs in < 1% of patients
        3. autonomic hyperactivity, delirium, severe hyperthermia

4. 20% mortality rate (stroke or CV collapse)

B. Benzodiazepine and sedative-hypnotics (See APPENDIX A)

1. Most abuse is from prescriptions
2. 3% of adults have tried a sedative for non-medical use
3. Includes: pentobarbital, amobarbital, meprobamate, methyprylon, ethchlorvynol, chloral hydrate, glutethimide, diazepam, alprazolam, etc.
4. Zolpidem (Ambien®) has been reported to cause tolerance and withdrawal
5. Short-acting, lipophilic drugs are preferred agents of abuse
6. Withdrawal times depend on the half-life of the drug abused
7. Severity of withdrawal depends on amount and time period of abuse
8. Rebound anxiety can occur after discontinuation
9. Severe withdrawal can cause hallucinations and seizures

C. Opiates (See APPENDIX A)

1. Use causes a warm flushing reaction (similar to sexual orgasm)
2. A period of apathetic detachment follows for a few hours
3. 1% of adult population has tried heroin (1/2 million individuals)
4. 6% of adult population has tried an opiate analgesic for non-medical use
5. Hydromorphone (Dilaudid®) has a pharmaceutical profile similar to heroin
6. Opiates are commonly combined with stimulants or sedatives
7. Abusers may start out as pain patients receiving prescriptions
8. New treatment
    1. Levo-alpha-acetylmethadol (LAAM or Orlaam®)
    2. Prodrug related to methadone
    3. Very slowly inactivated and excreted
9. Withdrawal times range from 3 to 14 days, depending on half-life of drug
10. Withdrawal is <u>not</u> fatal unless there is a concurrent medical problem

D. Cocaine (See APPENDIX A)

1. Most behaviorally reinforcing drug of abuse
2. Causes intense drug-seeking behavior
3. 11% of adults have tried cocaine
4. Blocks the reuptake of NE and Dopamine in the CNS
5. Causes euphoria, ↓ fatigue, and ↑ alertness (like amphetamines)

6. Combination with alcohol produces a metabolite (cocaethylene)
    a. Longer-acting, equally potent compound
7. Absorption is rapid through injection or inhalation
8. Metabolism and elimination are rapid (half-life of 1 hour)
9. “Crack” is free-based cocaine that can be smoked
    a. Produces higher plasma concentrations
10. Cocaine can cause bradycardia, tachycardia, and hyperthermia
11. May produce psychosis similar to paranoid schizophrenia
    a. Auditory, visual, and tactile hallucinations
    b. Paranoid thinking
    c. Loose associations
12. Withdrawal is <u>not</u> life threatening

E. Amphetamines and stimulants
1. 6% of adults have tried stimulants at least once
2. Effects similar to cocaine (differences are pharmacokinetic)
    a. Slower onset of effect
    b. Longer duration of action
3. Effect catecholamines (NE and Dopamine)
    a. Block reuptake
    b. Increase release presynaptically
    c. Inhibit monoamine oxidase
4. Methamphetamine has a longer duration of action
5. Includes “designer” drugs
    a. Methylenedioxymethamphetamine (MDMA) or “ecstasy”
    b. Made by amateur organic chemists
    c. Can be dangerous if improperly manufactured
    d. Included by FDA as illegal (Schedule I)
6. Chronic use can cause a catecholamine depletion in the brain $\rightarrow$ depression
7. No detox regimen is recommended for these agents

F. Phencyclidine (PCP) (See APPENDIX A)
1. First used as a veterinary anesthetic
2. Similar to ketamine

3. Effects include CNS stimulation, depression, and hallucinations
4. Blocks 5HT, Dopamine, and NE reuptake
5. Blocks the NMDA subtype of the glutamate receptor
6. Binds to the σ-opiate receptor (psychotomimetic)
7. Low doses – sedation, ataxia, nystagmus, slurred speech, and paresthesias
8. High doses -- ↑ heart rate, ↑ BP, ↑ temp., diaphoresis, and muscle rigidity
9. Effects are highly unpredictable
10. No detox regimen is recommended for this agent

G. Hallucinogens (See APPENDIX A)

1. Includes LSD, psilocybin, dimethyltryptamine (DMT), mescaline, etc.
2. 9% of adults have tried these drugs
3. Used for a psychedelic effect
4. Stimulate presynaptic $5HT_{1A}$ and $5HT_{1B}$ and postsynaptic $5HT_2$ receptors in the brain (may agonize or antagonize serotonin activity)
5. LSD is the most potent and long-acting
6. Cross-tolerance exists among LSD, psilocybin, and mescaline
7. No physical withdrawal syndrome is seen
8. Flashbacks occur in 15% of users
    a. Can occur several years later
    b. May be triggered by other drugs

H. Marijuana (See APPENDIX A)

1. 34% of adults have tried marijuana
2. 12% of children 12-17 years old have tried marijuana
3. Active compound is THC
4. Acute symptoms are similar to alcohol (sedation, disinhibition, etc.)
5. May also cause hallucinations
6. Endocrine effects include amenorrhea and ↓ testosterone production
7. Amotivational syndrome
    a. apathy, dullness, impaired judgment, ↓ goal-directed behavior
    b. ↓ concentration and memory, ↓ personal hygiene,
8. No physical withdrawal syndrome is seen with chronic exposure

I. Inhalants

1. 10% of adults (18-25 years old) and 6% of youth (12-17 years old)
2. Includes gasoline, glue, aerosols, amyl nitrite, nitrous oxide, toluene, etc.
3. Causes CNS depression similar to alcohol
4. May experience headache, nausea, hallucinations, delusions
5. Can cause arrythmias and death
6. Long-term exposure is toxic to all organ systems

J. Tobacco (See APPENDIX A)

1. 71% of adults have tried smoking tobacco
2. 24% of adults smoke regularly
3. Withdrawal occurs within 24 hours and lasts for weeks

K. Caffeine

1. Available in coffee, tea, soft drinks, chocolate, and OTC / Rx analgesics
2. Intoxication can be from 300mg or more
    a. restlessness, anxiety, insomnia, flushed face, diuresis, GI complaints
    b. muscle twitching, palpitations, and motor agitation
3. 25% of adults consume > 500mg a day
4. Physical withdrawal occurs in 24 hours and lasts several days
5. Withdrawal includes headache, anxiety, restlessness

L. Anticholinergic drugs (See APPENDIX A)

1. Includes scopolamine, trihexyphenidyl, benztropine, etc.
2. Induces a toxic psychosis
    a. Euphoria, disorientation, hallucinations, and paranoia
3. Patients may feign EPS to get prescriptions

M. Anabolic steroids

1. Abused for their athletic performance-enhancing properties
2. Derived from testosterone
3. 2-20% of adults have used steroids
4. Long-term consequences on organ systems
    a. Hepatic and endocrine dysfunction

b. In women – infertility, gynecomastia, and masculinization
c. In men – acne, oily skin, hypogonadism, rage
d. Also, irritability, aggression, psychosis, mania, psychological dependence

IV. Pathophysiology of tolerance, dependence, and withdrawal
A. Multifactorial reasons for drug dependence
1. Susceptible host (?Genetic predisposition)
2. Favorable environmental conditions
3. Drug-oriented society
4. Advertising legal drugs
5. Social acceptance / peer pressure
B. Phases
1. Euphoriant / pleasurable effects reinforce drug-seeking behavior
2. Tolerance develops
a. Pleasurable effects decrease
b. Higher doses are needed
3. Avoidance of abstinence syndromes (withdrawal)
C. Mechanisms of physical dependence
1. Homeostasis of body systems are changed
2. Tolerance is a compensatory mechanism
3. Withdrawals is a result of a compensatory dominated change
D. Withdrawal
1. Symptoms seen are usually the opposite of the abused drug
2. May last several months or longer (ie. opiates)
a. “conditioned abstinence syndrome”
b. Craving for drug is associated with environmental influences
1. smells, tastes, people, places, etc.
E. Tolerance – 2 types
1. Metabolic (pharmacokinetic tolerance)
a. Metabolism increases to compensate for drug concentrations
b. Alcohol and barbiturates
2. Pharmacodynamic (cellular or functional tolerance)
a. Adaptive changes at the site of action of the drugs
b. Changes in receptor binding sensitivity
c. Alcohol and opiates

V. Treatment of intoxication (see Dipiro (3rd edition) Table 65.8, p1357).

DRUG CLASS	PHARMACOLOGIC THERAPY	NON-PHARMACOLOGIC THERAPY
Benzodiazepines	Flumazenil 0.1-0.2mg/min IV up to 1mg*	Support vital functions
Alcohol, barbiturates, and sedative-hypnotics	None	Support vital functions
Opiates	Naloxone 0.4-2.0mg IV q3min*	Support vital functions
Cocaine and CNS stimulants	Lorazepam 2-4mg IM q30min to 6h prn agitation + Haloperidol 2-5mg q30min to 6h prn psychotic behavior	Monitor cardiac function
Hallucinogens, marijuana, and inhalants	Lorazepam and/or haloperidol as above	Reassurance; "talk-down therapy"
Phencyclidine (PCP)	Lorazepam and/or haloperidol as above	Minimize sensory input

*Give only enough to bring patient out of danger, not into withdrawal

VI. Treatment of withdrawal

A. Alcohol

1. Give Vitamin B1 (thiamine) to prevent Wernicke's encephalopathy
    a. 100mg IM, then 100mg po QD
2. Give multivitamin supplement and Folic Acid 1mg po QD
3. Magnesium sulfate 1gm IM QD for 1-3 days can be given also
4. Detox is done with a benzodiazepine to prevent seizures and DT's
    a. Chlordiazepoxide or diazepam are preferred (long-acting)
    b. Oxazepam or lorazepam can be used in sever liver impairment
    c. Taper drug over 5-7 days
    d. Treat w/d symptoms with a prn benzodiazepine (ie. IM lorazepam)
    e. Do not treat seizures with an anticonvulsant – use a benzo or similar
5. Withdrawal schedule depends on several factors
    a. Amount of alcohol consumed
    b. Length of alcohol abuse (years)
    c. Previous detox complications

B. Benzodiazepines

1. Detox is similar to alcohol detox (use long-acting benzodiazepines)
2. Withdrawal may not manifest for several days, so a longer detox may be needed

C. Barbiturates and sedative-hypnotics

1. Tolerance testing is advised
2. Pentobarbital tolerance test
    a. Give pentobarbital 200mg po q2-3 hours until intoxication is observed
    b. Detox at cumulative dosage achieved
    c. Taper daily dose by 100mg q 2-3 days

D. Opiates
1. Withdrawal is not life-threatening unless a concurrent life-threatening medical condition exists
2. Methadone taper by 5-10mg/d
3. Clonidine attenuates the noradrenergic hyperactivity of withdrawal
    a. Start at 6μg/kg/d divided TID
    b. Max dose of 17μg/kg/d divided
    c. Maintain dose for 7 days, then taper over next 3 days
    d. Time can be shortened as tolerated
    e. Watch for orthostatic hypotension
    f. Hold dose if Systolic BP (lying down) is < 90mmHg
    g. Catapres TTS Patch has also been used
4. Combination therapy has also been used
    a. Clonidine + Naltrexone (caution: may withdraw immediately!)
    b. Buprenorphine + Naltrexone

E. Cocaine and Stimulants
1. Primarily supportive therapy
2. Bromocriptine (Parlodel®)
    a. Dopamine agonist at high doses
    b. Start at 2.5mg BID-TID and increase as tolerated
    c. Decreases cravings also
    d. Generally for short-term use only

F. Nicotine (cigarettes, tobacco products)
1. Nicotine replacement and taper
    a. Nicotine (Nicorette®) Gum
    b. Nicotine patches
    c. Now OTC products are available
2. Bupropion (Zyban®, Wellbutrin®) tablets – by Rx only
    a. May increase dopamine in certain areas of the brain responsible for

nicotine craving

b. See Antidepressants for detailed information on medication

c. May only work in 50-60% of patients in conjunction with nicotine replacement products and a smoking cessation program

d. Begin bupropion 2 weeks before stopping smoking

3. Clonidine has also been used

a. Studies are not conclusive as to efficacy

b. Not a primary therapy

VII. Treatment of Substance Dependence

A. Continued treatment is primarily behavioral

B. Drug therapy

1. Alcohol dependence

a. Disulfiram (Antabuse®)

1. Irreversibly inhibits aldehyde dehydrogenase

2. Two week duration of action

3. Increases acetaldehyde when alcohol is ingested

a. Reaction can cause flushing, n/v, headache, palpitations, sweating, fever, hypotension, respiratory depression, arrhythmias, MI, CV collapse, and death

b. Caution with any alcohol (cough syrups, mouthwashes)

4. Dose at 250mg to 500mg QD

5. Common side effects include rash, headache, lethargy, metallic taste, and impotence

b. Naltrexone (Revia®)

1. May block opiate receptors that are stimulated by endogenous opiates released while drinking alcohol

2. May decrease amount of alcohol consumed

3. Not a very effective treatment

4. Dose at 50mg QD with food

5. Most common side effect is GI upset

2. Opiate dependence
    a. Naltrexone therapy
        1. Blocks effects of any ingested exogenous opiates
        2. Can be dosed 50mg QD or 350mg a week in 3 divided doses
        3. Efficacy depends on patient compliance with medication
3. Cocaine dependence
    a. Tricyclic antidepressants
        1. Desipramine is the most studied
        2. May block cocaine-induced euphoria (?)
    b. Dopaminergic agents
        1. Bromocriptine, Amantadine
        2. Bupropion (?) – not well studied

C. Treatment of coexisting psychiatric disorders
1. Up to 50% of addicts have another psychiatric disorder
2. It is unknown which came first, addiction or mental illness
3. Ideally, patient should be drug-free for 2 weeks before treating psychiatrically
    a. Need a clear presentation of symptoms
    b. May not be able to wait to treat a patient with severe mental problems

APPENDIX A
INTOXICATION / DETOXIFICATION INFORMATION

MINOR ALCOHOL WITHDRAWAL
Anorexia
Diaphoresis
Diarrhea
Elevated blood pressure
Generalized weakness
Insomnia
Nausea and vomiting
Perception disorder
-nightmares, illusions, hallucinations
Seizures
Tachycardia
Tremors

MAJOR ALCOHOL WITHDRAWAL (DTs)
Extreme restlessness
Fever
Gross tremors
Increased psychomotor activity
Profound disorientation
Profuse diaphoresis
Tachycardia
Vivid hallucinations

LIBRIUM AND ALCOHOL INTOXICATION

Ataxia	Impaired attention	
Confusion	Loquacity	
Diminished reflexes	Mood changes	**Mild intoxication can cause disinhibition
Euphoria or irritability	Nystagmus	
Flushed face	Somnolence	
Hypotension Coma	Slurred speech	

OPIATE INTOXICATION
Apathy
Attention impairment
Dysphoria
Euphoria
Miois
Motor retardation
Sedation
Slurred speech

OPIATE WITHDRAWAL
Diaphoresis
Diarrhea
Fever
Insomnia
Lacrimation
Muscle aching
Mydriasis
Piloerection
Rhinorrhea
Yawning

COCAINE INTOXICATION
Elation / Euphoria
Elevated or lowered blood pressure
Grandiosity
Hypervigilance
Loquacity
Motor agitation
Mydriasis
Nausea and Vomiting
Sweating or chills
Tachycardia

COCAINE WITHDRAWAL
Depression
Fatigue
Increased appetite
Nightmares
Sleep disturbance

APPENDIX A (continued)

HALLUCINOGEN INTOXICATION

PSYCHOLOGICAL	PHYSICAL
Perceptual intensification	Mydriasis
Depersonalization	Tachycardia
Derealization	Diaphoresis
Illusions	Palpitations
Hallucinations	Blurred vision
Synesthesias	Tremor
	Incoordination
	Dizziness
	Weakness
	Drowsiness
	Paresthesias

MARIJUANA INTOXICATION

Apathy	Hallucinations
Conjunctival congestion	Increased appetite
Dry mouth	Sensory Intensification
Euphoria	Tachycardia

NICOTINE WITHDRAWAL

Anxiety	Irritability
Difficulty concentrating	Restlessness
Headache	Sleep disturbances
Increased appetite	

ANTICHOLINERGIC INTOXICATION

Ataxia	Mydriasis
Constipation	Tachycardia
Dry mouth	Warm dry skin

URINE DETECTION OF DRUGS

AGENT	TIME DETECTABLE IN URINE
Alcohol	12 to 24 hours
Amobarbital	2 to 4 days
Amphetamine	2 to 4 days
Butalbital	2 to 4 days
Cocaine (benzoylecgonine)	12 to 72 hours
Codeine	2 to 4 days
Chlordiazepoxide	30 days
Diazepam	30 days
Dilaudid(R)	2 to 4 days
Ethanol	12 to 24 hours
Heroin (morphine)	2 to 4 days
Hydromorphone	2 to 4 days
Librium(R)	30 days
Marijuana (Cannabinoids)	
-Occasional use	2 to 7 days
-Regular use	30 days
Methamphetamine	2 to 4 days
Methaqualone	2 to 4 days
Morphine	2 to 4 days
Pentobarbital	2 to 4 days
Phencyclidine (PCP)	
-Occasional use	2 to 7 days
-Regular use	30 days
Phenobarbital	30 days
Quaalude(R)	2 to 4 days
Secobarbital	2 to 4 days
Valium(R)	30 days

The periods of detection for the various abused drugs listed above should be taken as estimates since the actual figures will vary due to metabolism, user, laboratory, and excretion.

NON-ADDICTIVE TREATMENTS OF PAIN

NON-MEDICATION:

- Hot or Cold Packs
- Stretching / Limited motion exercises
- Deep Breathing
- Bio-feedback
- Relaxation Tapes
- TENS unit (electrical stimulation)

MEDICATION:

- NSAIDs (Non-Steroidal Anti-Inflammatory Drugs):
  - Motrin®, Advil®, Aleve®, Toradol®, Daypro®, Clinoril®, Vioxx, Celebrex, Mobic, many more
- Steroids (anti-inflammatory):
  - Prednisone, Methylprednisone, many more
- Muscle Relaxants (non-addictive):
  - Skelaxin®, Robaxin®, others
- Antidepressants – for neuropathic (nerve) pain:
  - Tricyclic Antidepressants (TCAs) – Elavil®, Tofranil®, others
  - Effexor®, Serzone®
- Anticonvulsants - for neuropathic (nerve) pain:
  - Depakote®, Depakene®, Tegretol®, Neurontin®, others
- Antihistamines:
  - Atarax®, Vistaril®, Benadryl®, others
- Patches and Creams:

  Catapres TTS® Patch, BenGay®, Aspercreme®, Flexall 454®, Arthriticare®, Therapatch®, Ela-max®, Lidoderm®

NON-ADDICTIVE TREATMENTS OF INSOMNIA

NON-MEDICATION:

- Warm Milk and Toast with Jelly
- Juice or Graham Crackers
  - Think low-protein, high carbohydrate!
- Hot Bath or Shower
- Reading a Book or Magazine
- Relaxation Techniques & Tapes
- Deep Breathing Exercises
- Expressing Yourself to Peers and Staff
  - Maybe by talking it out, you'll be able to fall asleep

MEDICATION:

- Desyrel®, Tricyclic Antidepressants, Remeron®, Serzone®, Ambien® (5 to 10mg), Benadryl® and other antihistamines

MEDICATIONS & DRUGS THAT CAN CAUSE INSOMNIA

- Amphetamines, steroids, Wellbutrin®, cocaine, Selective Serotonin Reuptake Inhibitors / SSRIs (Prozac®, Paxil®, Zoloft®, Celexa®, Luvox®)
- Avoid caffeine, soda, and other stimulating substances late in the day.

Þ REMEMBER:

- ✓ Mid-afternoon exercise aids sleep.
- ✓ Alcohol and tobacco upset sleep.
- ✓ Naps often make it difficult to sleep at night.

OPIOID COMPARISON CHART (EQUIANALGESIC DOSING)

DRUG	★	PEAK (hours)	EQUIVALENT DOSE SC / IV	EQUIVALENT DOSE PO	HALF-LIFE	DURATION OF ACTION	COMMENTS
AGONIST							
Codeine	N	1 PO / 0.25-0.5 IM	120-130	200	2-3	2-6	Portion is demethylated to morphine / May be combined with non-opioid
Fentanyl (Duragesic®, Sublimaze®)	S	0.5 IM	0.1-0.2	-	1-2	1-6 SL / patch 72	Chest wall rigidity
Hydromorphone (Dilaudid®)	SS	1.5-2 PO / 0.5-1 IM	1.5-2	6-7.5	2-4	2-5	No active metabolite / Can be given rectally
Levorphanol (Levo-Dromoran®)	SS	1.5-2 PO / 0.5-1 IM	2-3	4	12-16	4-8	
Meperidine (Demerol®)	S	1-2 PO / 0.5-1 IM	75-100	300	2-5	2-4	Nor-meperidine toxicity limits utility
Methadone (Dolophine®)	S	1.5-2 PO / 0.5-1 IM	7.5-10	15-20	15-25	3-8	Accumulation = longer t½
Morphine	N	1.5-2 PO / 0.5-1 IM	10	30-40	2-3.5	3-7 / CR 8-12	Histamine release
Oxycodone (Percocet®, Percodan®, Oxycontin®, others)	SS	0.5-1 PO	-	15-30	2-3	2-6	May be combined with non-opioid
Oxymorphone (Numorphan®)	SS	1.5-2 PO / 0.5-1 IM	1-1.5	10	2-3	3-6	Can be given rectally
Propoxyphene (Darvon® / Darvocet®)	S	2-3 PO	-	180-240	6-12	2-6	Nor-propoxyphene toxicity may cause seizures – has long t½ of 30-36h
Heroin (diacetylmorphine)	SS		5	60	2-4	2-4	
MIXED AGONIST-ANTAGONIST	-- All are agonists at κ and σ receptors and antagonist at μ receptors						
Pentazocine (Talwin®)	S	1.5-2 PO / 0.5-1 IM	60	180	2-3	3-4	All can precipitate withdrawal in patients addicted to opioid agonists
Nalbuphine (Nubain®)	SS	0.5-1 IM	10-20	50-60	5	3-6	
Butorphanol (Stadol®)	S	0.5-1 IM	2	-	2.5-3.5	3-4	
PARTIAL AGONIST							
Buprenorphine (Buprenex®, Subutex®)	SS	2-3 SL 0.5-1 IM	0.3-0.6	0.4-0.8 SL	2-3	6-9	Can precipitate withdrawal in patients addicted to opioid agonists

★ ® **N=natural / S=synthetic / SS=semi-synthetic**

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