Pharmacology/Therapeutics II Block II Lectures

2012-13

59. Drugs of Abuse, tolerance & Dependence – Dr. Bakowska
60. Pharmacology of Sedative Hypnotic Drugs – Dr. Battaglia
61. Sedative Hypnotic Drugs in Treating Anxiety & Sleep Disorders – Dr. Battaglia
62. Drugs to Treat Rheumatoid Arthritis & Gout – Dr. Clipstone
63. Treatment of Parkinsonism & Dementia – Dr. Lee (To be posted Later)
64. HIV – Dr. Cuevas
65. Anti-Viral Drugs – Dr. Gallagher
66. Pediatric PsychoPharm-Treatment of ADHD – Dr. Gutierrez

Drugs of Abuse

Date: Feb 6, 2013

Instructor: Joanna C. Bakowska, Ph.D., Assistant Professor, Department of Pharmacology

Reading Assignment: Basic & Clinical Pharmacology, B.G. Katzung, 9th Ed. Chapter 32

KEY CONCEPTS AND LEARNING OBJECTIVES

1. To understand the basis underlying the conceptualization of addiction as a disease.

3. To understand the differential diagnostic criteria for drug abuse vs dependence

5. To know the mechanism of action within the central nervous system of major drugs of abuse

6. To know the signs and symptoms of overdosage caused by the major drugs of abuse and appropriate therapeutic interventions

7. To know the signs and symptoms of opioid withdrawal

8. To know the options for pharmacotherapy of opioid abuse/dependence and alcohol dependence

Drugs of Abuse

1. Introduction

1.1 Why medical students need to learn to **recognize a substance abuse problem** regardless of your specialty

1. You will be encountering individuals with drug problems in your practice
   a. 15.6% of adults (29 million) used illegal drugs in 2007
   b. Two-thirds of those who abuse or are dependent visit a primary care physician or emergency department every 6 months
2. Failure to consider substance use as a contributor to the clinical picture will compromise treatment

1.2 Drugs of Abuse

A. Psychomotor stimulants – cocaine, amphetamines
B. Opiates and Opioids – heroin, morphine, codeine, oxycodone, hydromorphine
C. Cannabinoids – marijuana
D. Alcohol
E. Anti-depressants – barbiturates, benzodiazepines
F. Nicotine
G. Hallucinogens – LSD, mescaline "club drugs", MDMA

1.3 DSM-IV-TR Criteria for **Abuse**

(Prevalence 1.4% in recent national sample)
A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following occurring at any time in the same 12-month period (but symptoms can never meet criteria for dependence, thus dependence and abuse are mutually exclusive)

1. Recurrent use resulting in failure to fulfill major role obligations at work, school or home (missing work, missing school, neglect of children)
2. Recurrent use in situations in which it is physically hazardous (driving, operating a machine)
3. Recurrent substance-related legal problems (DUI)
4. Continued use despite persistent or recurrent social or interpersonal problems caused or exacerbated by effects of the drug (fights with spouse)

1.5 Diagnostic and Statistical Manual (DSM)-IV-TR Criteria for **Dependence**

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following occurring at any time in the same 12-month period

1. **Tolerance**
2. **Withdrawal** (marker of **physiological [physical] dependence**)
3. Use of larger amounts of substance than intended

4. Persistent desire or unsuccessful efforts to cut down or control use
5. Great deal of time spent in obtaining drug, use, or recovery
6. Recreational activities given up or reduced
7. The substance use is continued despite knowledge of physical and psychological problems caused by drugs

1.6 Withdrawal (marker of physiological dependence)

1) Signs and symptoms emerge when use of the drug is stopped
2) Signs and symptoms are reversed when drug is administered again

Tolerance

a) decreased effect with repeated use of the drug
b) a need to use more drug to have the same effect

1.7 Tolerance due to decreased effect with repeated use of the drug (constant amount of the drug)

1.8 Tolerance – increased dose of the drug needed to have the same effect (shift to right in dose-effect curve).

1.9 Drug abuse and drug dependence

- Drug abuse is using a drug excessively, or for purposes for which it was not medically intended.
- Drug dependence (addiction) is compulsively using a substance, despite its negative and sometimes dangerous effects
- Drug dependence results in:
  a) stereotyped withdrawal syndrome due to discontinuation of a drug
  b) tolerance

1.10 Important distinctions between abuse and dependence

- Abuse and dependence in DSM-IV are mutually exclusive
- Abuse does not necessarily lead to dependence and this trajectory varies across drugs

1.11. Mesolimbic dopamine system- a major target of addictive drugs

1. General neurobiological theory of reinforcement (most clearly established for stimulants)
   a. Ability of a drug to control behavior (be abused) is related to the release of dopamine in the **mesolimbic dopaminergic pathway** (VTA⇒nucleus accumbens⇒prefrontal cortex), termed the “pleasure center” or “reward center”
   b. Inhibitory inputs onto dopamine neurons come from GABA-ergic neurons present within the VTA or as a feedback loop from the nucleus accumbens

2. Given evidence of these brain changes, addiction/dependence has come to be considered a **disease**

a. Disease rooted in neuropathology produced by the repeated administration of the drug (pharmacological insult)
b. Pathological changes in brain function are in circuits that regulate how a person interprets and behaviorally respond to motivationally relevant stimuli

A.1 Psychostimulants: Cocaine and Amphetamines

Cocaine

1. Derived from *Erythoxylon coca*, which is a cultivated plant from South America
2. Isolated in 1855 by Niemann in Germany
3. First human experiments conducted by Freud on himself were published in 1884
4. Regulated by Pure Food and Drug Act of 1906 and Harrison Narcotic Act of 1914

Amphetamines

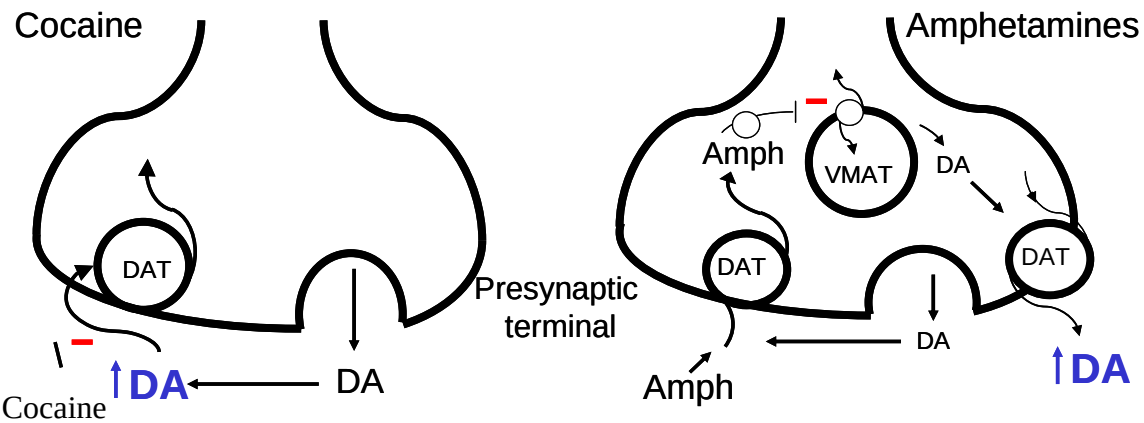
1. Synthetic phenylethylamine synthesized in 1800s
2. Marked to treat asthma and narcolepsy and later for obesity
3. Used extensively by military during WWI and left over supplies led to epidemic use in several countries.

A2. Cocaine

1) used for medical purposes
   - powerful stimulant of central nervous system (used by Freud to treat depression)
   - an appetite suppressant (used for obesity)
   - topical anesthetic (historically used for eye and nasal surgery, currently used for nasal and lacrimal duct surgery)
2) Used for popularization before; 1906 when the Pure Food and Drug Act was passed

   - coca leaves were included in several wines and ciragettes
   - Coca leaves were included in original 1886 recipe for Coca-Cola for nearly 20 years

A3 and A4. Site of action of Cocaine and Amphetamines in Presynaptic Neurons



Cocaine

Cocaine –inhibits the action of dopamine transporters
Amphetamine – inhibits the function of VMAT and impedes the filling of synaptic vesicles, cytoplasmic DA increases – leads to reversal of DAT direction and increase of extracellular DA concentration

A5. Acute Effects of Psychostimulants

Behavioral and physiological effects (**sympathomimetic**-mimicking the effects of the sympathetic nervous system)

1. Euphoria, **arousal**, well-being, increased energy and activity, decreased appetite, self-confidence, reduces feelings of fatigue and boredom, "rush" often described as orgasmic
2. Increases in **heart rate and blood pressure**, bronchodilation, pupillary dilation

A6. Pharmacokinetics of Cocaine

1. Rapidly absorbed into the brain and **short-acting**.
2. Onset, magnitude of effect (differences in potency), and duration depend upon route of administration (smoked reaches peak in 2 min, injected 1-3 min, "snorting" – 10 min; oral – 30 min)
3. Half-life varies from 40-80 min, requiring repeated administration to maintain blood levels
4. Rapidly metabolized by cholinesterases into **benzoylecgnonine** (inactive compound) monitored in biological fluids (salive, blood, urine, milk), measured in urine test where; it remains detectable for up to 8 days.
5. **Cocaethylene** is formed in the body when cocaine is ingested with alcohol; it is pharmacologically active and enhances the effects of cocaine. Cocaethylane has a longer duration action than cocaine itself and is more cardiotoxic than cocaine.
6. Cocaine also blocks voltage-gated membrane sodium ion channels; this action accounts for local anesthetic effect and may contribute to cardiac arrhythmias.

A7. Consequences of Long term use of psychostimulants
Results either in

1) Sensitization – increased drug response (low-doses and intermittent exposure)
2) Tolerance – decreased drug response

Impairment of neurocognitive functions
- visuomotor performance, attention

Increased risk of infections to viral hepatitis and HIV
Physical dependence is controversial
Increased risk of developing autoimmune or connective tissue diseases such as lupus, Goodpature's syndrome, Stevens-Johnson syndrome

A8. Overdose signs and symptoms
1. Hyperactivity, agitation, diaphoresis, dilated pupils, tremor, tachycardia, hypertension, hyperpyrexia, stereotypical behavior, chills, nausea/vomiting, weight loss, muscle weakness, tactile hallucination, chest pain, cardiac dysrhythmias, confusion, dyskinesia, seizures, paranoia, coma
2. These can be exacerbated with co-administration of alcohol (formation of cocaethylene)
3. Death can occur secondary to myocardial infarction, cerebrovascular accident, cardiac arrhythmias, seizures or respiratory depression

A9. Withdrawal (peaks at 2-4 days) Signs
1. Anxiety, agitation, fatigue, depression, nightmares, headache, sweating, muscle cramps, hunger, craving

A10. Detection of Use
1. Look for symptoms noted above
2. Urine tests (2 to 4 days)
3. Other clues: AIDS, hepatitis, track marks, abscesses, bacterial endocarditis, chronic respiratory symptoms

A11. Treatment of Cocaine Withdrawal

A. Acute withdrawal-symptomatic treatment
- Bromocriptine (dopamine agonist) – ameliorates dopamine deficiency state of cocaine withdrawal
- Benzodiazepines (lorazepam) - in patients with severe agitation and sleep disturbance

B. Treatment of Long-term addiction
- No FDA-approved pharmacological therapies
- in 2011, the researchers invented vaccine against cocaine by combining a cocaine-like molecule with a part of virus (tests in mice)

- Cognitive-Behavioral Therapies – two components
1) Functional analysis – to identify the patient's thoughts, feelings, and circumstances before and after the cocaine use to understand reason for using cocaine
3) Skills Training to help cocaine users to cope with intrapersonal and interpersonal problems

B. Opioids (opium, morphine, codeine, heroin, oxycodone)

B1. History
1. Opium is derived from extracts of the juice of the opium poppy, *Papaver somniferum*, and has been used since 3400 BC to relieve suffering, largely pain and asthma
2. Morphine and codeine are derived from opium.
3. Heroin is semi-synthetic opioid synthesized from morphine

B2. Mechanisms of action

1. Opioids exert their pharmacodynamic effects through three principal opioid receptors- **mu**, **delta** and **kappa**
2. Opioids cuase disinhibition of mesolimbic dopaminergic system
3. The dependence producing properties of opioids are mediated through the mu receptors

B3. Patterns of Abuse

1. Oral, intravenous, subcutaneous (skin popping), smoking, snorting (becoming more prevalent because of fear of AIDS) and intravenous

B4. Patterns of Use

1. Heroin's effects last about 3-5 hrs.
2. Average addict uses 2-4 times/day
2. **Tolerance** develops which results in a gradually increasing frequency/quantity of use. **Physical dependence** also develops

B5. Sings of Opioid Overdoes

1. Unconsciousness
2. Miosis
3. Hypotension
4. Bradycardia
5. Respiratory depression
6. Pulmonary edema

B6. Pharmacokinetics

1. Tolerance to one opioid is usually associated with tolerance to other opioids (cross-tolerance)

1. Heroin is a pro-drug that is rapidly converted into 6-monoacetylmorphine by esterases present in the blood, brain and very tissue
2. 6-monoacetylmorphine is further metabolized to morphine which contributes to the duration of effect of heroin
3. Withdrawal begins 12 hours after last dose, peaks at 1½ - 3 days, and is mostly over by 5-7 days
4. Lingering symptoms can persist for months ("Protracted Abstinence Syndrome") and are associated with relapse.
5. Withdrawal is profoundly painful and unpleasant though not life-threatening

B7. **Withdrawal** Symptoms

1. Anxiety and dysphoria
2. Craving and drug-seeking
3. Sleep disturbances
4. Nausea, **vomiting** and **diarrhea**
5. Lacrimation

6. Rhinorrhea
7. Yawning
8. **Sweating**, chills, gooseflesh ("cold turkey")
9. **Mydriasis (**excessive dilation of the pupil)
10. Cramps
11. Hyperpyrexia
12. Involuntary movements ("kicking the habit")

B8. Treatment of Opioid Addiction

- Pharmacotherapy
- Many individuals are not treated with medications (drug free)
  - Self-help groups such as Narcotics Anonymous
  - Inpatient detoxification facilities/residential
  - Individual therapy rare largely due to sociodemographic characteristics of users
  - Dependence on prescription opioids presents a new challenge for treatment

B9. Goals of Pharmacotherapy

- "Cure" of withdrawal or overdose
- To improve the holding power of outpatient treatment
- To reduce drug craving
- To create a "window of opportunity" during which patients can receive psycho-social intervention to decrease the risk of relapse
- To serve as short or long-term maintenance agents for patients who can't function without them, but can lead productive lives with them

B10. Treatment approaches of opioid overdose and withdrawal syndrome

- Treatment of opioid overdose (bradykardia, respiratory depression, pulmonary edema)
  - Naloxone (m-opioid receptor antagonist)
- Treatment of withdrawal syndrome and maintenance
  - Methadone - m-opioid receptor agonist
  - Buprenorphine partial - m-opioid receptor agonist

B11. Treatment of Opioid Overdose

- **Naloxone [Narcan, Nalone]**
  m-opioid antagonists with very high affinity –
  Fast acting (2 min) but the duration of action (about 45 min) is much shorter than heroin
- Therefore, individuals treated for overdose with these antagonists must be kept under observation for the duration of the opioid drug's effects to determine if additional antagonist treatment is needed

B12. Treatment with Methadone

- Methadone – agonist to m-opioid receptor with long half-life (15-60h)

  - Oral administration
  - Lasts at least 24 hrs
- Methadone: Prevents withdrawal symptoms and cravings, has a cross-tolerance with other opioids
- Can only be dispensed in federally licensed clinics
  - Requires almost daily clinic visits even for individuals with long term success

B14. Treatment with Buprenorphine

- Buprenorphine is a partial m-opioid receptor agonist
  - has less potential for respiratory depression (hard to overdose)
- It has both high affinity for receptors (competes easily) and dissociates slowly (long acting so withdrawal is minimized)
- Marketed in a formulation with naloxone (Suboxone) taken sublingually. When misused iv will result in withdrawal symptoms due to the presence of Naloxon (m-opioid receptor antagonist). .
- If buprenorphine is initiated prior to the onset of acute withdrawal signs, it may lead to abrupt withdrawal syndrome resulting from displacement of full agonists (e.g. heroin) for the mu-opiod receptor by a buprenorphine

C. Cannabinoids: Marijuana

C1. History

1. Like other drugs of abuse derived from natural plant products, marijuana has been used for 1000s of years
2. **Delta-9-tetrahydrocannabinol** (THC) is active constituent
3. There are 400 additional constituents that are found in Cannabis

C2. Mechanism of action

1. THC activates a **cannabinoid receptor in the VTA** to initiate its action, a relatively new scientific finding
2. THD inhibits GABA-ergic interneurons
3. Cannobinoids cause disinhibition of mesolimbic DA system.

C3. Acute Effects of Marijuana

- Sedation, relaxation
- Mood alteration, sense of well-being
- Altered perception and time estimation
- Impaired judgment, memory, and concentration
- Increased heart rate, dry mouth
- Increased appetite (“munchies”) – due to drop of sugar levels and also stimulation of cannabinoid receptors in the hypothalamus.
- Injection of the conjunctiva (“red eyes”) – due to decreased pressure in the eyes and increased blood pressure

C4. Overdose effects of Marijuana Use

1. Panic, delirium, psychosis (often paranoid)
2. Long-term use: Amotivational syndrome, inattention, poor judgment, distractability, impaired social relationships but results from field and laboratory studies are often inconsistent
3. **Tolerance** occurs but whether or not physical dependence develops in humans remains an open question (but has been demonstrated in mice)
4. Personality changes and cognitive deficits (loss of short-term memory)
5. Many believe it is a "gateway" drug, i.e., its use leads to initiation of use of other drugs of abuse

C5. Withdrawal Symptoms

- is not life threatening
- begin on 1 or 2 day of abstinence, peak day 2-6, resolve within 7-14 days
- fatigue (31%)
- hypersomia (26%)
- psychomotor retardation (25%)
- anxiety (19%)
- depression (16%)
- anorexia
- irritability
-

C6. Differential Diagnosis of Cannabis Intoxication

- Intoxication from other addictive substances
- Panic disorder
- Major depressive disorders
- Bipolar I or II disorder
- Schizophrenia

C7.. Treatment of Marijuana Abuse is Symptomatic

- Anxiolytics (benzodiazepines) for anxiety and panic
- Antipsychotics for delirium and paranoia
- Cognitive behavioral therapy for dependence
- No pharmacotherapies but discovery of CB1 receptor and development of an antagonist is promising

D. Alcohol

- Health care cost of alcohol problems - $186 Billion
- Alcohol dependence is a complex disorder in which many factors act together to produce the illness
- Approximately 50% of the risk is attributed to genetics
- May arise in individuals without family history of alcohol dependence as a result of environmental factors

D1. Subtypes of Alcohol Dependence

Type A Alcohol Dependence

- Late onset (>25 years old)
- Few familial alcohol-dependency
- Slower disease progression
- Milder form of alcohol dependence
- Important environmental influence
- Minimal criminality

Type B Alcohol Dependence

- Early onset (≤25 years old)
- Paternal type B alcohol dependence
- More severe form of alcohol dependence
- Little environmental influence
- Frequent criminality
- Frequent presence of personality disorder

D2. Disease Associated with Chronic Alcohol Use

Primary Diseases

- Alcohol poisoning
- Alcoholic heart disease (cardiomyopathy)
- Alcoholic gastritis
- Alcoholic liver cirrhosis
- Alcoholic nerve disease (polyneuropathy)
- Alcoholic psychoses

Secondary Diseases

- Cancer (lip, mouth, pharynx, esophagus, larynx, liver, stomach)
- Diabetes
- Gastrointestinal disease
- Heart disease (hypertension, stroke)
- Liver disease
- Pancreatitis (acute, chronic)

D3. Effects of Acute Alcohol on Neural Circuits I

Dopamine and Opioid Systems

- Indirectly increases dopamine levels in the mesocorticolimbic system
  - Associated with positively reinforcing effects of alcohol
- Indirect interaction with opioid receptors results in activation of opioid system
  - Associated with reinforcing effects via μ-receptors

D4. Effects of Acute Alcohol on Neural Circuits I

GABA and Glutamine Systems

- Increases the effects of GABA, the major inhibitory neurotransmitter in the brain

- Inhibits the effects of glutamate, the major excitatory neurotransmitter in the brain

Chronic exposure of alcohol leads to a compensatory
1) Reduction in the levels of GABA-gic receptors
2) Up-regulation of NMDA receptor

Sudden reduction in chronic alcohol intake results in overactivation of NMDA system

D5. Treatment Stages of Alcohol Dependence

Stage 1: Identification

- obtain history of current and past alcohol use and family history of alcohol problem
  - use standardized screening tests (e.g., 4-question CAGE)
  - evaluate patients in terms of the *DSM-IV* criteria for alcohol abuse and dependence and determine whether patient wants to abstain

Stage 2: Detoxification/Withdrawal

- Mild or severe withdrawal symptoms
  mild withdrawal symptoms - agitation, anxiety, insomnia, nausea
  severe withdrawal symptoms – autonomic hyperactivity, seizures, delirium tremens
- relieve immediate symptoms of withdrawal – **benzodiazepines** – indirect agonist for GABA receptors (reverses effect of alcohol)
- Benzodiazepines with long half-life have less chance of recurrent withdrawal.
  Diazepam has a long half-life
  Lorazepam has as shorter half-life but is not metabolized by liver – good for patients with cirrhosis

Stage 3: Rehabilitation

- restructure life without alcohol

- relapse prevention – psychotherapy, pharmacotherapy

Stage 4: Aftercare

- AA meetings, family support

D6. Symptoms of Alcohol Withdrawal

1) minor withdrawal (6-36 hrs)
   - due to CNS hyperactivity – Hyperarousal
   - mild anxiety, headache, sweating, GI upset, insomnia, nausea
2) Seizures – 6-48 hrs after the last drink
   3% of chronic alcoholics can develop tonic-clonic seizures, some develop status epilepticus (seizures without regaining consciousness for 30 min)
   Can be life threatening
3) alcoholic hallucinations (12-48 hrs after the last drink)
   visual, auditory, tactile – can last for months
4) delirum tremens (48-96 hrs after the last drink, can last 1-5 days)

D7. Delirium Tremens (DT)

- Caused by withdrawal from long-term alcohol consumption
- 5% of alcohol withdrawal leads to DT (mortality can be up to 35% when untreated)
- Caused by withdrawal from benzodiazepines

Symptoms
- Confusion, disorientation, paranoia, hallucinations – mostly visual and tactile
- Uncontrollable tremors of the extremities
- Severe autonomic instability (fever, tachycardia, hypertension)
- Some patients experience seizures

Treatment
- Pharmacotherapy is symptomatic and supportive
- Benzodiazepines, such as diazepam (Valium), lorazepam (Ativan)
- In extreme cases stronger benzodiazepines like temazepam (Restoril) might be used

D8. FDA-Approved Pharmacotherapies for Alcohol Dependence

Disulfiram – Alcohol Aversion Therapy
Naltrexone – Opioid antagonist
Acamprosate – restores balance between neuronal excitation and inhibition

D9. Disulfiram (Antabuse) – alcohol aversion therapy
- Inhibits aldehyde dehydrogenase
- When taken with alcohol, increased levels of [acetaldehyde] that leads to nausea, dizziness, headache, hypotension, vomiting
- Decreases desire to drink alcohol but does not increase abstinence
- Increased risk of hepatotoxicity

NOTE: Asian descents who have an ALDH2*2 genetic variant of the ALDH enzyme that metabolizes acetaldehyde slowly – protects against alcohol dependence

D 10. Naltrexone (ReVia)
- Opioid antagonist
- Blocks release of dopmine from the Nucleus Accumbens
- Reduces alcohol cravings
- Avoid Naltrexone with Disulfiram – both are potential hepatotoxins
- Avoid Naltrexone in patients dependent on opioids- it will precipitate acute withdrawal syndrome

D. 11 Acamprosate – (Campral)
- Decreases excitatory glutamate neurotransmission and increases GABA-ergic activity
- Minor side effects: diarrhea, allergic reactions, irregular heartbeats
- Dose adjustment in patients with moderate renal disease (ceratinine clearance 30-50 mL/min)
- Contradicted in severe renal disease (ceratinine clearance < 30 mL/min

E. Anti-depressants: Benzodiazepines

Therapeutic Uses of Benzodiazepines
- Benzodiazepines are the most commonly prescribed sedative drugs
- Severe anxiety, panic attacks and phobias (because of their anxiolytic properties)

- Insomnia
- In muscular disorders - effective muscle relaxants
- Alcohol withdrawal
- Epilepsy – anticonvulsant

Benzodiazepines are; indirect agonists of the GABA receptor

E1. Benzodiazepine Withdrawal Syndrome

- Anxiety, agitation
- Increased sensitivity to light and sound
- Muscle cramps
- Sleep disturbance
- Dizziness
- Mycolonic jerks

Withdrawal Management

Treatment with diazepam (Valium)

- benzodiazepine with a long-half life
- gradually tapering off the drug over a period of months

F. Nicotine

- Is among the most addictive drugs, accounts for 440,000 deaths yearly
- Selective agonist of the nicotinic acetylcholine receptor (nAChR) that is normally activated by acetylcholine
- Nicotine acts on nAChR receptors, stimulate dopaminergic neurons in the VTA and increases the release of dopamine in the nucleus accumbens

Treatment

- Nicotine patches, nasal spray, nicotine lozenge
- Varenicline [Chantrix]

– non-nicotine medication – partial agonist that binds subunits of nicotine acetylcholine receptors. Because it stimulates the receptors, it relives cravings and withdrawal symptoms during abstinence from smoking

- binds to the nAChR receptors with greater affinity than nicotine – thus reduces the pharmacologic reward from cigarette smoking

G. Hallucinogens (LSD, mescaline)

- Cause change of sensation, illusions, called – mind-bening drugs
- The drugs do not induce dependence or addition
- Serotonin receptors 5-HT2A in cortex are molecular targets
- Treatment: for nonpychotic agitation – anti-anxiety drugs (Diazepam)
  for severe agitation – use antipsychotic drugs

LIST OF DRUGS DISCUSSED IN THIS LECTURE. For more detail see on-line reference www.rxlist.com

Generic Name	Trade Name	Half-life	Mechanism of Action	Rx
Bromocriptine	Cycloset	12-14 hrs	Dopamine agonist	Symptomatic treatment in cocaine withdrawal
Lorazepam (is not metabolized by liver)	Ativan	10-20 hrs	Indirect Agonist of GABA receptor	In severe agitation and sleep disturbance during cocaine, alcohol and benzodiazepines withdrawal
Diazepam	Valium	20–100 hrs (36-200 hrs for main active metabolite desmethyldiazepam)	Indirect Agonist of GABA receptor	In severe agitation and sleep disturbance during cocaine, alcohol and benzodiazepines withdrawal
Naloxone	Narcan, Nalone	45 min – 1 hr	μ-opioid antagonist	Opioid Overdose
Methadone	Symoron	15-60 hrs	μ-opioid agonist	Opioid withdrawal syndrome
Bupernorphine	Subutex	20-60 hrs	Partial μ-opioid receptor agonist, has very high affinity	Opioid withdrawal syndrome
Buprenorphine: Naloxone (4:1)	Suboxone	Bupernorphine – 20-60 hrs Naloxone – 1 hr	Partial μ-opioid receptor agonist in a formulation with Naloxone (m-opioid antagonist)	Opioid withdrawal syndrome
Disulfiram	Antabuse	60-120 hrs	Inhibits Aldehyde Dehydrogenase	Therapy for Alcohol Dependence
Naltrexone	ReVia	Naltrexone – 4 hrs, is metabolized to 6-beta-naltrexol –13 hrs	Opioid Receptor Antagonist	Therapy for Alcohol Dependence
Acamprosate	Campral	20-30 hrs	Mechanism unknown	Therapy for Alcohol Dependence (renal elimination)
Varenicline	Chantrix	24 hrs	Partial agonist of nicotine acetylcholine receptors	Nicotine addiction

PHARMACOLOGY OF SEDATIVE –HYPNOTIC DRUGS & DRUGS

Date: February 13, 2013 – 9:30 am
Reading Assignment: **Katzung, Basic & Clinical Pharmacology**; 12th Edition, Chapter 22, pp. 373-385.

KEY CONCEPTS AND LEARNING OBJECTIVES

1. You should understand the structural aspects of the $GABA_A$ receptor and the receptor components (i.e. binding sites) mediating the effects of various drugs that can modulate $GABA_A$ receptor activity.

2. You should understand the difference between $GABA_A$ receptors that contain a BZ1 versus a BZ2 binding sites and the know the effects various sedative–hypnotics will have on these different isoforms of $GABA_A$ receptors.

3. You should understand the differences in the pharmacokinetics of the benzodiazepines with respect to the type of metabolism they undergo, the production of active metabolites and the relative overall half-lives (i.e. short, intermediate or long) of the different drugs.

4. You should know the similarities and differences among the benzodiazepines with respect to their relative: (1) time of onset, (2) potency, (3) metabolism and (4) elimination half-lives.

5. You should know the general pharmacodynamic and pharmacokinetc characteristics of the barbiturates and the pharmacological characteristics of this class of drugs that contributed to their limited clinical use relative to the benzodiazepines or other sedative-hypnotics.

6. You should know the similarities, differences and distinguishing characteristics between the different classes of sedative-hypnotics and among the drugs within a given class.

PHARMACOLOGY OF SEDATIVE–HYPNOTIC DRUGS

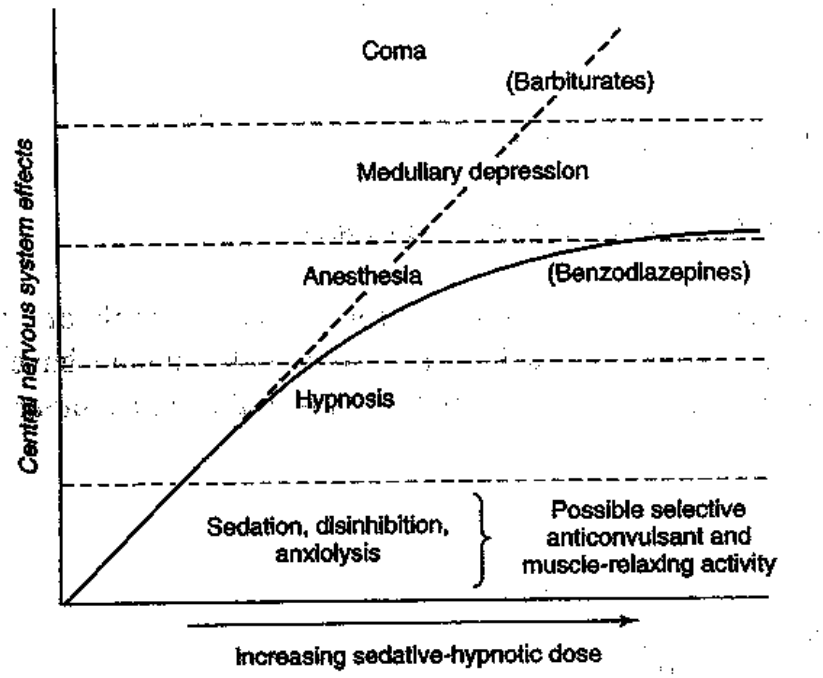
What do we mean by the term Sedative-Hypnotic?

Sedative (Anxiolytic) – reduces anxiety and exerts a calming effect.

Hypnotic – produces drowsiness and facilitate the onset and maintenance of sleep (involves a greater depression of CNS than sedation).

1. All sedative-hypnotics produce *graded* *dose-dependent depression of CNS function.*

2. The magnitude of the depression of CNS function with increasing dose is not the same for all classes of sedative-hypnotic drugs. This is shown below.



From: Trevor and Katzung's Pharmacology, Examination and Board review, 6th ed.page 206

3. All sedative-hypnotic drugs produce their effects by interacting with $GABA_A$ receptors and potentiating GABAergic activity at all levels of the neuraxis, from spinal cord to cerebral cortex.

Gamma-Amino Butyric Acid (GABA) is a major inhibitory neurotransmitter in the CNS
(approximately 30% of synapses in mammalian cerebral cortex are GABAergic)

. – Two (2) major classes of GABA receptors have been identified based on function.

1. **$GABA_A$ Receptors** – **an ionotropic receptor** whose activation increases the opening of chloride channels leading to an inhibitory post-synaptic potential (hyperpolarization). ***$GABA_A$ receptor activation can be modulated by benzodiazepines and other sedative-hypnotic drugs***.

Musimol is a prototypic agonist and bicuculline the antagonist, can bind to the same site (i.e. the same pharmacophore) that GABA binds to on the receptor to pharmacologically mimic or antagonize, respectively, the effects of GABA.

2. **$GABA_B$ Receptors** - **a metabotropic G-protein linked receptor** located on:

(1) presynaptic terminals controlling the release of GABA ("homoreceptors") or other neurotransmitters ("heteroreceptors") via decreases in Ca^{++} conductance, and
(2) postynaptic membranes producing hyperpolarization of the membrane via increases in K^+ conductance.

(-)-baclofen (Lioresal®) is a selective $GABA_B$ agonist that is used clinically as an anti-spastic drug. ***$GABA_B$ receptors are not modulated by benzodiazepines or other sedative-hypnotic drugs***.

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The COMPLEXITY OF THE $GABA_A$ RECEPTOR COMPLEX

$GABA_A$ receptors are hetero**pentameric** glycoprotein receptors that are formed from the co-assembly of **five(5) subunits** (420- 450 amino acids) from various polypeptide classes designated as: **α, β, γ,** and $\delta, \varepsilon, \pi,$ & ρ.

Each subunit has: a) 4 transmembrane domains with both the amino and carboxy terminus in the extracellular side and **b)** 2 intracellular loops that provide sites for phosphorylation.

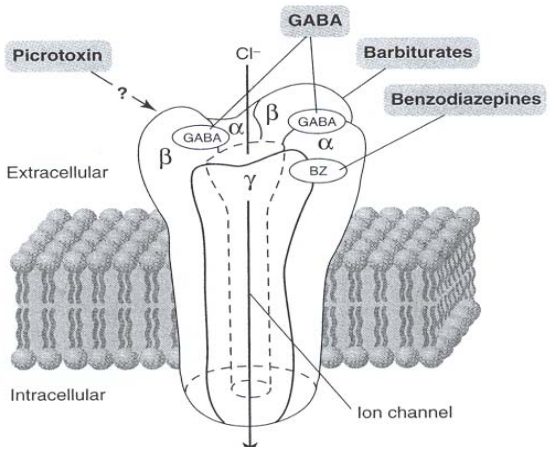
Isoforms of these subunits have been identified. There are **6 isoforms of the α subunit** (i.e. α1-6)**, 3 isoforms of β** (i.e. β1-3), **3 isoforms of γ** (i.e γ1-3) as well as 3 isoforms of ρ.

The most abundant $GABA_A$ receptor subtype consists of a generic composition of:
Two(2) α subunits, **two(2) β** subunits, and **one(1) γ** subunit.

Given the number of identified subunits/isoforms, thousands of pentameric subunit combinations are theoretically possible. Yet, the majority of $GABA_A$ receptors identified are heteropentamer combinations derived from a relatively few number of different subunit isoforms.

The majority of $GABA_A$ receptors (≈60%) consist of: **α1β2γ2** while 15-20% consist of **α2β3γ2** with the remaining receptors being represented by various combinations of the isoform subtypes.

The figure below illustrates **the organization of the subunits that form the $GABA_A$ receptor** and the different regions of the receptor that different drugs can target (i.e. bind to and alter function)



From: Trevor and Katzung's Pharmacology, Examination and Board review, 6th ed.,page 205

The **binding of GABA** (or GABA agonists & antagonists) is to a region located at the **α and β interface, providing two sites that can bind GABA.**

The **binding of benzodiazepine (and imidazopyridines)** occurs at a ***"binding site"*** that resides at the **α/γ interface**, providing one binding site for BZ1 or BZ2 drugs. Although this ***"binding sitet"*** is called a ***"benzodiazepine receptor", it*** is actually an **allosteric modulatory site,** since binding to these sites can not alter $GABA_A$ receptor function in the absence of GABA.

The benzodiazepine and imidazopyridine) binding pocket ("receptor") is largely determined by the type of **α subunit** that is co-assembled with the **γ2 subunit** (the most abundant of the gamma subunits in the brain).

$GABA_A$ receptors with either α1,2,3 & 5 exhibit sensitivity to diazepam while **those with α4 & α6** are diazepam-insensitive**.**

The imidazopyridine class (e.g. zolpidem) exhibit a greater degree of selectivity for $GABA_A$ receptors that have the **α1 isoforms** with the following degree of selectivity for zolpidem ($\alpha1 > \alpha2 = \alpha3 >> \alpha5$).

Based on **α isoforms and drug selectivity**, 2 types of ***"benzodiazepine"*** binding sites have been identified that can modulate $GABA_A$ receptor function:
BZ_1 (omega$_1$) - contains the α1 isoform (**Imidazopyridines** bind selectively to the BZ1 receptor)
BZ_2 (omega$_2$) – contains α2,3 or 5 isoforms receptor subtypes

Benzodiazepines can bind appreciably to both BZ1 and BZ2 sites (**receptors with α1,2,3 or 5**).

The type of alpha subunit may also contribute to the qualitative effects produced by these drugs. Preclinical studies of point mutations (histadine → arginine) in the N-terminal domain of various isoforms of the α subunit suggest that:

1. **α1 subunits** may mediate the sedative, amnesia and ataxic effects of the benzodiazepines and non-benzodiazepine (BZ1 selective) drugs but not the anxiolytic or muscle relaxing effects.

2. **α2 (and possibly α3)** subunits may contribute to the anxiolytic and muscle relaxant effects of BZs.

3. **α5** may be important in memory impairment and the development of tolerance to the sedative effects of the benzodiazepines.

PHARMACODYNAMICS of Drugs that Modulate $GABA_A$ Receptor Function

1. **Non-Selective "Agonists" –** Benzodiazepines that bind to both BZ1 and BZ2 sites and are positive allosteric modulators of $GABA_A$ receptors. They DO NOT compete directly with GABA for its binding site (at the **α/β interface**) on the $GABA_A$ receptor and are ineffective in the absence of GABA (or GABA agonists).

2. **Non-Benzodiazepine "Agonists"** - The FDA approved imidazopyridines (*Zolpidem* & *Zaleplon*) and pyrrolopyrazine drug eszopiclone (Lunestra®) that bind to BZ1 sites act as positive allosteric moduators of $GABA_A$ receptor function , as they also require GABA to produce their therapeutic effects.

3. **Antagonists (flumazenil;** Romazicon®) - a competitive antagonist that has a high affinity for the benzodiazepine (BZ1 and BZ2) receptor and blocks the actions of benzodiazepines and imidazopyradine (e.g. zolpidem) & pyrrolopyrazine drugs (e.g.Eszopiclone) but does not anatgonize the actions of other sedative-hyponotics such as the barbiturates, meprobamate or ethanol. When given i.v., flumazenil acts rapidly but has a short t1/2 (0.7-1.3h) due to hepatic clearance. It may precipitate a severe abstinence syndrome in patients physiologically dependent on BDZs.

4. **Inverse Agonists**- act as **negative allosteric modulators** of $GABA_A$ receptor function (decrease $GABA_A$ binding). Inverse agonists (e.g. Beta Carbolines) **bind to BZ1 and BZ2 type modulatory sites** and can produce anxiety and seizures (via reducing GABA receptor function) as well as block the effects of drugs that bind to BZ1 and BZ2 binding sites.

5. **Barbiturates –** bind to sites on the $GABA_A$ receptor that are distinct from the benzodiazepine binding site and are likely on the β subunits of the receptor. In the presence of GABA, barbiturate binding **increases the duration** of opening of the chloride channel. ***At very high doses, barbiturates can directly produce channel opening.***

6. **Neuroactive steroids** - bind to the $GABA_A$ receptor at other sites distinct from the BZ binding site to increase the effects of GABA. Some neurosteroids (e.g. alphaxalone) may directly open chloride channels at high concentrations.

7. **Ethanol** - thought to alter $GABA_A$ neurotransmission, since it produces many of the same effects as the BDZs (e.g., anxiolysis) and stimulates Cl^- uptake into isolated brain vesicles.

THE BENZODIAZEPINES

- since being introduced in the 1960s, the BZs remain among the most widely prescribed drugs in the world. This is primarily due to the fact that these drugs have less capacity to produce extreme and potentially fatal CNS depression in comparison with the barbiturates and older sedative-hypnotics. ***In healthy patients, hypnotic doses of benzodiazepines produce no significant effects on respiration and cardiovascular function*.**

(**REMEMBER**: "I **AM PAM**, a **LAM**, a benzodiazepine")

PHARMACODYNAMICS

- Benzodiazepines act as non-selective positive allosteric modulators ("agonists") of GABA receptor function. ***Benzodiazepines can bind to BZ1 or BZ2 sites on the $GABA_A$ receptor and their effects at BZ1 or BZ2 sites can be antagonized by the BZ antagonist, flumazenil*** .

Mechanism of Action: - the therapeutic efficacy of the benzodiazepines is due to their ability to potentiate $GABA_A$ receptor-mediated inhibition. Benzodiazepine binding to BZ1 or BZ2 sites on the $GABA_A$ receptor increases the affinity of GABA for its binding site on the receptor and increases the frequency of opening of chloride channels. This results in hyperpolarization and a greater degree of inhibition of neuronal firing. Thus, because they require GABA to affect receptor function, they act as ***positive allosteric modulators*** of GABA receptor function, rather than true receptor agonists (e.g. musimol) that can mimic the effects of GABA.

In addition to their use as sedative hypnotics, some benzodiazepines have ***anticonvulsant effects*** (diazepam, clonazepam & nitrazepam), produce ***relaxation of skeletal muscles*** (diazepam) and can be given IV as ***adjuncts for anesthesia*** (midazolam & diazepam).

PHARMACOKINETICS

Absorption & Distribution: Although all benzodiazepines are lipid soluble, the lipophilicity, which can vary over 50–fold, contributes to differences in their rates of absorbtion, onset of action & redistribution. ***Pregnancy*:** All sedative-hypnotics cross the placental barrier during pregnancy, and appear in breast milk. Thus, they can reduce neonatal vital functions and may be teratogenic if continued throughout pregnancy

Bioavailability - is very good; 60-100% depending on the individual drug.

Protein binding – moderate, 70% (alprazolam) to high, 99% (diazepam); thus drug interactions with other highly protein bound agents are likely (e.g., between phenytoin and diazepam).

Metabolism: Most benzodiazepines undergo metabolism via **both** microsomal oxidation (**Phase I**), by the P450 family CYP**3A4** and CYP**2C19**, and conjugation (**Phase II**) to form glucuronides that are excreted in the urine. **Three** benzodiazepines are only conjugated and excreted **(i.e. undergo only Phase II metabolism)**.

**Pharmacokinetic differences largely determine the clinical applications of the Benzodiazepines.*

Important factors for consideration include: elimination half-life of parent drug and any bioactive intermediates, rapidity of onset of effects and drug potency.

Drugs Whose Metabolism includes both Phase I (oxidation) and Phase II (conjugation)

**The overall elimination half-life of these drugs is often longer than the half life of the parent compound due to formation of one or more bioactive metabolites (Phase I) each of which may be active for an extensive period of time before they are conjugated and excreted (Phase II).

Diazepam; Flurazepam **(2-Keto derivatives) and** ***Clordiazepoxide:***
Although chlordiazepoxide is not a 2-keto-benzodiazepine it is converted to desmethyldiazepam.

Parent compounds vary in their elimination half-lives ($t_{½}$ = 0.1-35 h), but their active metabolites (N-desmethyldiazepam and N-desalkylflurazepam) have half-lives between 50-100 hr.

Clonazepam, flunitrazepam **(7-Nitro derivatives)**
7-nitro substitution appears to enhance anticonvulsant activity.

Clonazepam (t ½ = 22-33 h) is reduced to a 7-amino derivative that is inactive centrally but is extensively metabolized (via acetylation, hydroxylation and conjugation) then eliminated.

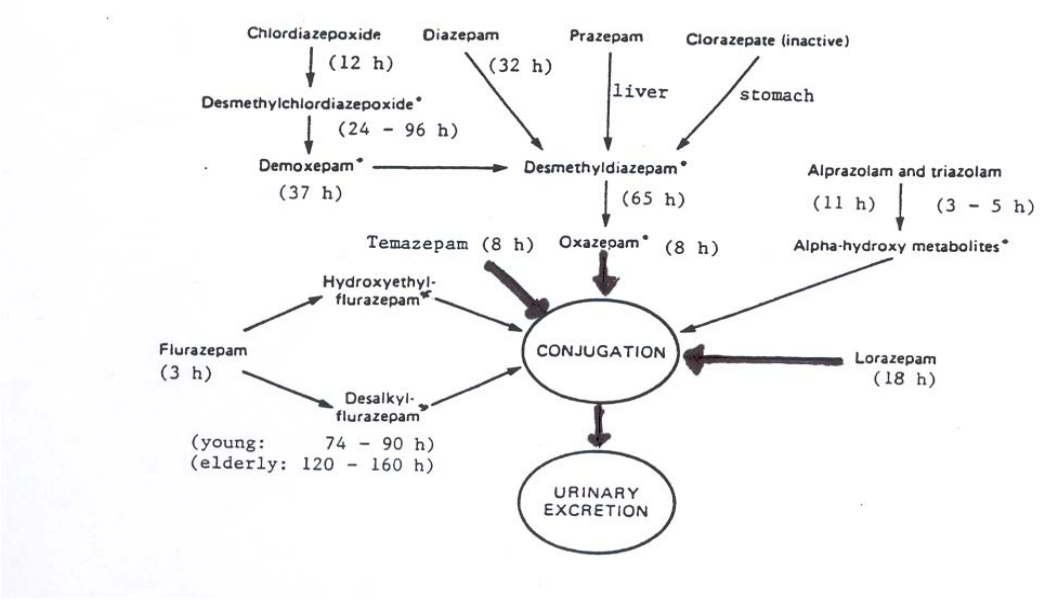
Flunitrazepam (Rohypnol®) is not approved in the U.S.; it is highly abused and is the"date rape" drug.

Midazolam , alprazolam and triazolam **(Triazolo derivatives):**
Mean elimination half-lives of these drugs vary (2.5h for midazolam and 11.0 h for alprazolam). They are oxidized to form compounds that are rapidly eliminated.

Drugs Whose Metabolism is Exclusively Phase II Conjugation (L O T)

Lorazepam, Oxazepam and Temazepam **(3-hydroxy derivative):** These agents are conjugated (Phase II biotransformation only) and thus are **not metabolized to bioactive intermediates**. Elimination half-lives range between 5-25 h. ***These are preferred for aged patients and those with impaired hepatic function.***

Comparative Pharmacokinetics of Various Benzodiazepines



Adapted from: B.G. Katzung, Basic and Clinical Pharmacology 9th ed.,page 354

"Side" & Adverse Effects:

Frequent: Drowsiness, ataxia, amnesia (don't remember events during the drugs duration).

Occasional: Confusion*, paradoxical excitement* (in children and the elderly), dizziness.

Rare: Paradoxical rage reaction*; extrapyramidal symptoms with chlordiazepoxide, allergic reaction, etc.

* Middle age and elderly patients (50+ years) are especially susceptible to these reactions when given daily high doses of potent benzodiazepines such as triazolam.

Tolerance and Dependence:

Pharmacodynamic tolerance seen with chronic use – there is a decrease in the drugs effects requiring higher doses to achieve effects comparable to that before drug exposure (may be due to ↓ in BZ bindig sites. Cross-tolerance can develop to ethanol and other sedative-hypnotics that affect $GABA_A$ receptor function.

Psychological dependence highly possible; BZ are often abused in conjunction with alcohol.

Withdrawal symptoms (anxiety, insomnia) appear upon discontinuation after frequent use.

BZ1- Selective Non-Benzodiazepines (Primarily Used to Treat Sleep Disorders)

The non-benzodiazepine imidazopyridine drugs ***zolpidem (Ambien®)*** and ***zaleplon (Sonata®)*** and the newer pyrrolopyrazine drug, ***eszopiclone (Lunestra®)*** bind selectively to the BZ1 binding site on the $GABA_A$ receptor and act as positive allosteric modulators of GABA receptor function in a fashion similar to the benzodiazepines (that bind to BZ1 & BZ2 sites). In addition, these drugs:

- do not produce a dangerous degree of CNS depression (even in overdose) unless taken in combination with other CNS depressants, a combination that can be lethal.
- produce effects that can be antagonized by the BZ1 & BZ2 antagonist, flumazenil
- may be habit forming with long-term use
- lack anxiolytic, anticonvulsant and muscle relaxant efficacy of some of the benzodiazepines
- have side effects similar to the benzodiazepines which include: headache and dizziness and somnolence; nausea, vomiting, diarrhea, anterograde amnesia and rebound insomnia (especially at high doses)
- can cause ***"sleep-driving"*** or ***"sleep-eating"*** without any memory of the event
- have recently (1/10/13) received an FDA recommendation to lower the dose in females since the data indicate a slower metabolism than in males.

1. Zolpidem *(Ambien®)* – the first FDA-approved BZ1 selective drug

- also available in an extended release form (Intermezzo®)
- rapidly and completely absorbed from the GI tract, reaching peak plasma levels in 1-2 hours.

- hepatic metabolism via Phase I and Phase II biotransformation; $\mathbf{t_{1/2}}$ of 1.5-3.0 hours.

- Half life is prolonged in the elderly and in patients with liver disease.

- lacks significant muscle relaxant, anxiolytic and anticonvulsant properties.

2. <u>Zaleplon</u> ***(Sonata®)****:* resembles zolpidem in its effects. Also rapidly absorbed (peak concentration reached in 1.0 h) from the GI tract, and has a very short t1/2 (1.0 h.) with no active metabolites.

Biotransformed hepatically (Type I), thus dosage should be reduced in the elderly and patients with liver disease. Note that the metabolism of zaleplon is <u>inhibited</u> by the OTC H-2 histamine receptor blocker, cimetidine (generic; Tagamet®).

Next day effects are less common than after zolpidem or other sedative-hypnotics due to the very short half-life.

3. <u>Eszopiclone</u> ***(Lunestra®)*** – the S(+) isomer of zopiclone (a pyrrolopyrazine drug already approved for use in Canada) with no structural similarity to zolpidem, zaleplon or the benzodiazepines.

- FDA approved (12/04) for treatment of sleep disorders. It does not significantly alter the stages of sleep.

- unlike zolpidem and zaleplon, eszopliclone is <u>not</u> restricted in its labeling to short-term use.

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Pharmacokinetics:

rapid absorbtion from the GI tract; peak plasma concentrations at 1-2 hrs
$t_{1/2} \cong 6$ hrs (slightly longer than the other BZ1 selective drugs).

Typical dose is 2-3 mg. The elimination is slower in the elderly and doses should be started at 1 mg.

<u>Drug Interactions</u>:
Various CYP3A4 inhibitors such as itraconazole (Sporanox®) clarithyromycin (Biaxin®) and ritonovir (Norvir®) can increase serum concentrations and prolong the duration of action.

Conversely, Rifampin, a CYP3A4 inducer can decrease serum concentrations and the effectiveness of a given dose of eszopiclone.

The BARBITURATES: (One of "Mothers Little Helpers" referred to in the 60's Rolling Stones song).

Derivatives of barbituric acid that once enjoyed great popularity to induce and maintain sedation and sleep. However, with the exception of phenobarbital, methohexital and thiopental, their clinical use as sedative-hypnotic agents has waned significantly since the introduction of the benzodiazepines and other drugs. (Remember: "**AL**"the barbiturate)

Mechanisms of Action

- Bind to sites on the ionotropic $GABA_A$ receptors at sites distinct from the site that binds benzodiazepines and are likely on the β subunits.

- They do not exhibit $GABA_A$ receptor subtype specificity

- At low doses, the binding facilitates the actions of GABA by **increasing the duration** of opening of the chloride channels.

- At high doses, barbituarates can be "GABA-mimetic" and directly activate the opening of the chloride channels in the absence of GABA (i.e no ceiling effect on CNS depression).

- Barbiturates also depress the actions of excitatory neurotransmitters and exert non-synaptic membrane effects.

Pharmacokinetics

The barbiturates are classified primarily based their duration of action, as observed for the benzodiazepines.

Short Acting: (hours) - Thiopental, Mexihexital; rapid onset – used for induction of anesthesia,

Intermediate Acting (18-48hrs): - Amobarbital (Amytal), secobarbital (Seconal) and pentobarbital (Nembutal)

Long acting (4-5 days): - Phenobarbital (Luminol Sodium)

Limited Clinical Uses:

Treatment of Epilepsy - Phenobarbital

Induction of Anesthesia - Thiopental and methohexital .

Adverse Effects of the Barbiturates

1. *They have a **low therapeutic index**, related to their potency to depress respiration (especially in combination with alcohol). A lethal dose can be < 10x the hypnotic dose.

2. They **produce physical dependence**; discontinuation of barbiturates after repeated use leads to a withdrawal syndrome which can be life threatening and difficult to treat.

3. **Stimulate cytochrome P450 activity and induce hepatic microsomal oxidases**.

    a. Pharmacokinetic tolerance – higher doses of barbiturates may be required over time due to the increase in their own metabolism.

    b. Cross tolerance - to benzodiazepines or other sedative hypnotics

    c. Drug interactions – due to increased metabolism of other drugs metabolized by microsomal oxidases.

4. In contrast to the benzodiazepines, the **barbiturates can induce anaesthesia.**

The Older Sedative–Hypnotics

1. Carbamates (Meprobamate) – introduced in 1955 as an antianxiety drug, and remains its only approved use in U.S, although clinical proof for its efficacy as an anxiolytic is lacking.Properties resembling the benzodiazepines.

2. Alcohols – (chloral hydrate) - transformed to trichloroethanol is the pharmacologically active metabolite; 6-10 hour half-life.

A Novel Sedative-Hypnotic

Ramelteon (Rozerem®) – a melotonin receptor agonist that received FDA approval in July 2005 for the treatment of insomnia characterized by difficulty in falling asleep.

- no evidence of physical dependence or abuse potential

- appears to be well tolerated when administered for long treatment courses

Mechanism of Action: binds selectively to MT1 and MT1 melatonin receptors to mimic and enhance the actions of the endogenous melatonin that has been associated with the maintenance of circadian sleep rhythms. No measurable affinity for BZ receptors or other sites.

Pharmacokinetics

- rapid absorbtion – high fat meals delays T_{max} and increases AUC (≈ 30%)
- extensive first pass metabolism
- short half-life of 1-3 hrs
- moderate protein binding (82%)
- large Vd (≈ 74 L)
- metabolism via CYP 1A2, 2C9, 3A4
- metabolism may be ***decreased by***: Fluvoxamine (Luvox), a broad inhibitor of CYP isozymes, the strong 3A4 inhibitor Ketoconazole (Nizoral) & the strong 2C9 inhibitor Fuconazole (Difulcan)
- metabolism may be ***increased by*** the strong CYP inducer, Rifampin

Side Effects – occurred at rates generally comparable to placebo and included headache, somnolence, fatigue, dizziness, nausea, exacerbated insomnia

Caution is advised in using Rameteon in patients with:

- liver disease
- sleep apnea
- depression or suicidal thoughts
- individuals over 65; may need to adjust dose

RELATIVE LONGEVITY OF ACTION BASED ON THE OVERALL HALF-LIVES OF DRUGS DICUSSED IN THE LECTURES ON SEDATIVE/HYPNOTICS

SHORT-ACTING
Diphendydramine (Benadryl®)
Eszopiclone (Lunestra®)
Zolpidem (Ambien®)
Zaleplon (Sonata®)
Flumazenil (generic, Romazicon®)
Midazolam (Versed®)
Triazolam (Halcion®)
Ramelteon (Rozerem®)
Thiopental Sodium (Pentathal®)

INTERMEDIATE-ACTING
Alprazolam (Xanax®)
Estazolam (ProSom®)
Lorazepam (generic; Ativan®)
Oxazepam (Serax®)
Temazepam (Restoril®)
Hydroxyzine(Atarax®)
Meprobamate (Equinil®,Miltown®)
Trazadone(Deseryl)
Nefazodone (Serzone®)

LONG-ACTING
Amitriptyline (generic; Elavil®)
Clonazepam (generic, Klonopin®)
Chlordiazepoxide (generic, Librium®)
Chlorazepate (generic, Tranxene®)
Cyclobenzaprine (Flexeril®)
Diazepam (Valium®)
Flunitrazepam (Rohypnol®)
Flurazepam (Dalmane®)
Imipramine (Trofanil®)
Doxepin (Sinequan®)
Phenobarbital (generic, Luminol Sodium®)
Pentobarbital (generic, Nembutol Sodium®)
Mirtazapine (Remeron®)

DRUGS TO TREAT SLEEP DISORDERS

Date: February 13, 2013 – 10:30 am.

Reading Assignment: Katzung, Basic & Clinical Pharmacology; 12th Edition, Chapter 22, pp. 373-385.

KEY CONCEPTS AND LEARNING OBJECTIVES

1. You should know the target sites of action of the benzodiazepines and other drugs that can be used to treat sleep disorders

2. You should understand the distinguishing differences in the pharmacokinetics and metabolism of the benzodiazepines and the clinical implications of these respective drug differences.

3. You should understand how the different classes of sedative–hypnotics are used clinically, know the factors to consider in choosing the most appropriate drug for specific clinical situations and/or individuals and understand the potential adverse effects that can be produced by drugs from the respective classes.

4. You should understand the characteristics of benzodiazepines and other sedative-hypnotics that contribute to their different degrees of abuse liability and withdrawal symptoms.

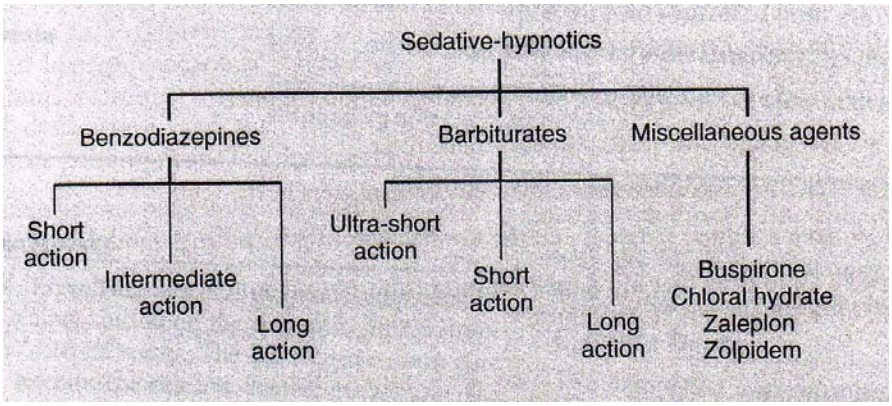
5. You should understand the concepts of psychological and physiological dependence and tolerance and the pharmacokinetic & pharmacodynamic factors that contribute to the expression of these phenomena.

6. .

DRUGS TO TREAT SLEEP DISORDERS

In prescribing drugs for "insomnia", **it is essential to first establish the** etiology of the disorder (drug dependence, sleep apnea, restless leg syndrome, psychological). If a rational basis for hypnotics can be established, then various factors can be considered in choosing an appropriate hypnotic drug.

Overview of Sedative Hypnotics



Sleep Disorders are most often treated with **(a)** benzodiazepines (that bind to both BZ1 and BZ2 sites on the $GABA_A$ receptor), **(b)** drugs that bind selectively to the BZ1 receptors, & **(c)** drugs that bind to Melotonin receptors. However, other classes of sedating drugs (discussed later and included in Talbe on page 10) can also used to induce sleep.

Although a number of different benzodiazepines may be used to treat sleep disorders, the **benzodiazepines specifically approved** for the treatment of insomnia include:

Estazolam (Prosom®),
Temazepam (Restoril®),
Quazepam (Doral®),
Flurazepam (Dalmane®)
Triazelam (Halcion®)

[*Triazolam (Halcion®)*** should be avoided, if possible, due to its high abuse potential].

Lorazepam **(Ativan®)** is also commonly prescribed, but not specifically FDA-approved for treatment of insomnia.

The non-benzodiazepine **BZ1-selective** sedative hypnotics approved for sleep disorders:

Zolpidem (Ambien®),

Zaleplon (Sonata®)

Eszopiclone (Lunestra®)

And now for something completely different (w/respect to site of action)……

Ramelteon (Rozarem®), an **MT1 & MT2 melatonin receptor agonist** that has been FDA approved to treat sleep disorders.

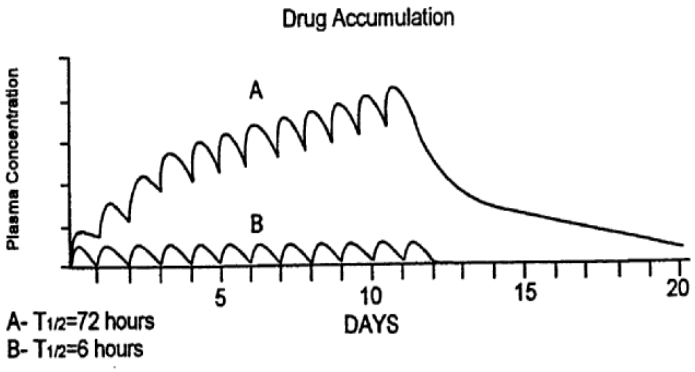
Important Considerations in Choosing a Benzodiazepine to Treat Sleep Disordrs

1. Rapidity of onset of action
2. Duration of action
3. The half-life of the drug and its route of metabolism
4. the patients age, medical condition and prior drug history

It is advised that benzodiazepines be used only for a short-term (1 -3 months)

General Pharmacokinetic Considerations in Choosing a Benzodiazepine for Sleep Disorders

The half-life of Elimination - drugs with long half-lives (either the parent compound or the active metabolite) will accumulate with prolonged use (as shown in the figure below).



Drug accumulation as a function of t1/2 (6 h vs 72 h). Each drug administered once per day.

Figure from Dr. Lorens 2002 Therapeutics lecture notes which was graciously provided by Dr. David Greenblatt

Pharmacokinetic Considerations in Choosing a Benzodiazepine in the Elderly

Benzodiazepine half-lives are longer in older people because they metabolize the drugs more slowly. Thus, drug concentrations will be ***greater*** in the elderly upon daily dosing.

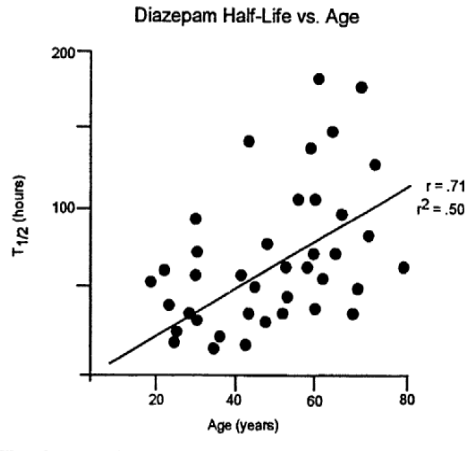
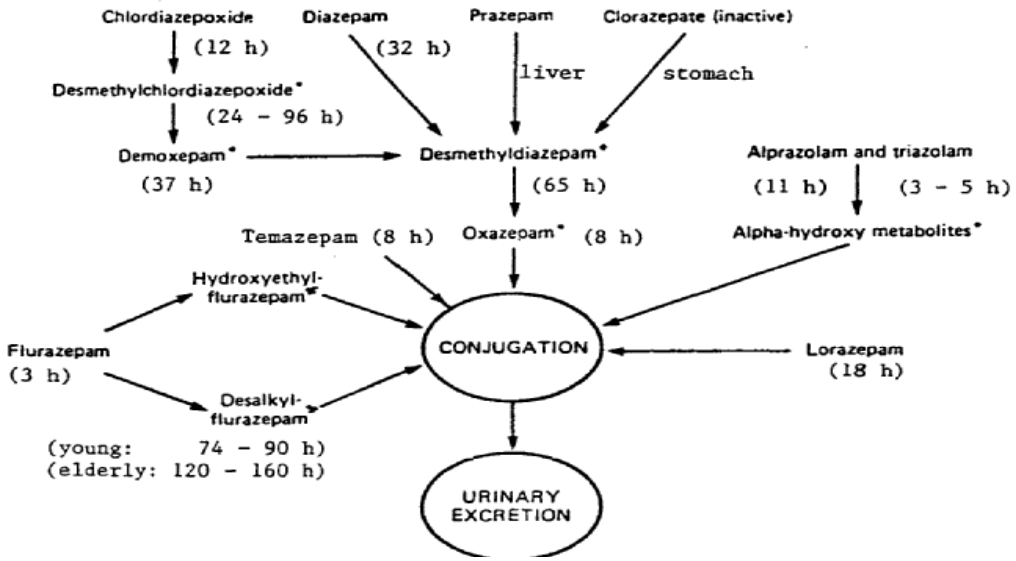


Figure from Dr. Lorens 2002 Therapeutics lecture notes which was graciously provided by Dr. David Greenblatt

Age-related effects on drug half-lives:

- Most likely for drugs that are converted into active metabolites by the liver, drugs such as chlordiazepoxide, diazepam, chlorazepate, quazepam, flurazepam.

- Least likely for benzodiazepines that are only conjugated by the liver and have no active metabolites such as: ***Lorazepam, Oxazepam & Temazepam***.



Metabolism of the Benzodiazepines (Figure a*dapted from B.G. Katzung, Basic and Clinical Pharmacology, 9th ed. 2004, page 354)*

Benzodiazepine issues in treating insomnia

1. Rebound insomnia upon stopping medication. This could involve:

(a) the reoccurrence of the original symptoms, or
(b) symptoms that are the same as original - but greater in intensity.

2. **Risk of Abuse, Dependence and Withdrawal** – not as great a risk for the BZs as for the barbiturates.

The Development of Tolerance and Dependence

1. **Psychological Dependence** – similar to the behavioral pattern observed with heavy coffee drinkers or cigarette smokers. If more compelling, it can lead to physiologic dependence and tolerance.

2. **Tolerance** – this is a reduction in the effect of the drug over time that requires higher doses to achieve the original effect. This is analogous to the phenomena of desensitization and is due in part to decreases in the number of benzodiazepine receptors. Tolerance has been observed to the sedating effects of benzodiazepines but not to their anxiolytic or muscle relaxant effects.

3. **Physiologic Dependence** – a state of response to a drug in which the removal of the drug ("withdrawal") produces unpleasant symptoms that differ from the original symptoms. The symptoms are usually opposite (compensatory) to the drug's effects. Common withdrawal symptoms include: sweating, irritability, tachycardia, and abdominal discomfort.

Benzodiazepines and other sedative-hypnotics (e.g. barbiturates, alcohol) all can produce:

(1) Dependence (2) Tolerance (3) Addiction (4) Withdrawal symptoms

The propensity to develop addiction, tolerance and dependence, and more severe withdrawal depend on a number of factors:

1) The rapidity of the time of onset of a drug's affect.

2) The drug's potency (can usually be assessed from the clinically prescribed dose).

3) The dose of drug taken.

4) The half-life of the drug.

5) The length of time that the drug has been taken.

<u>In general;</u> a the severity of withdrawal from sedative-hypnotic drugs will be greater given the factors listed below – (not listed in any order of priority)

1) higher doses
2) longer duration of use
3) higher potency
4) shorter half-life
5) shorter time of onset to produce their effects

***As the withdrawal from some sedative hypnotic drugs may be fatal, they should never be abruptly discontinued**

<u>Strategy for Discontinuation</u>:

1. Taper down dose and/or

2. Switch to a longer half-life drug, and preferably one of lower potency and less rapid onset of effect (decreases the reinforcement properties of the drug).

***Some Drugs that do not produce the characteristics described above*:**

<u>Non-Benzodiazepines Used to Treat Sleep Disorders</u>

Immidazopyridines and Pyrrolopyrazines

- these drugs do not produce a dangerous degree of CNS depression (even in overdose) unless taken in combination with other CNS depressants, a combination that can be lethal.

- may be habit forming with long-term use

- do not exhibit significant muscle relaxant, anxiolytic or anticonvulsant effects

- may produce anterograde amnesia and rebound insomnia, especially at high doses

<u>Zolpidem</u> (Ambien®) – first BZ1-selective drug to receive FDA approval to treat sleep disporders. Approved only for short –term use.

<u>Zaleplon</u> (Sonata®): resembles zolpidem in its effects with a slightly shorter half-life (1 hr). Recommendation that dosage be reduced in the elderly and patients with liver disease. The metabolism of zaleplon is <u>inhibited</u> by the OTC H-2 histamine receptor blocker, cimetidine (generic; Tagamet®).

- next day effects are less common than after zolpidem due to very short half- life.

- similar to zolpidem, its approved only for short-term use.

Eszopiclone (Lunestra®) – the S(+) isomer of zopiclone (a pyrrolopyrazine drug already approved for use in Canada) with no structural similarity to zolpidem, zaleplon or the benzodiazepines. FDA approved (12/04) for treatment of sleep disorders. It does not significantly alter the stages of sleep.

- unlike zolpidem & zaleplon, ***eszopliclone is not restricted in its labeling to short-term use***.

- its elimination is slower in the elderly and doses should be started at 1 mg instead of the typical dose of 2-3 mg.

Drug Interactions: Various CYP3A4 inhibitors (e.g. clarithyromycin -Biaxin®) or inducers (e.g. Rifampin) can increase and decrease, respectively, serum concentrations and alter the duration of action of a given dose of eszopiclone.

Drugs Used to Treat Sleep Disorders that Target Sites other than The $GABA_A$ Receptor

1. A Melatonin Receptor Agonist

Ramelteon **(Rozerem®)** – the M1 & M2 melotonin receptor agonist does not appear to have high abuse potential.

However, **caution should be used in patients with**:

- liver disease
- sleep apnea
- depression or suicidal thoughts
- individuals over 65; may still use but dose may need to be adjusted

2. The Tricyclic Antidepressants (TCAs)

Amitriptyline **(Elavil®) -**a tricyclic antidepressant (TCA) that is particularly effective in treating sleep disorders associated with or contributing to chronic pain syndromes such as fibromyalgia

Doxepin (Sinequan®) & Imipramine (Trofanil®)

The TCAs are relatively high affinity antagonists at H-1 histamine receptors, and lower affinity (but comparable) blockade of muscarinic cholinergic and $alpha_1$-adrenergic receptors.

Consequently, the TCAs produce several aversive side effects such as: 1) postural (orthostatic) hypotension, 2) cardiotoxicity, and 3) confusion with memory dysfunction, particularly in the elderly.

Tricyclic antidepressants **SHOULD NOT** be prescribed for elderly patients (65+ years) because of their liability for inducing a toxic and confused state.

3. The Atypical Antidepressants

Mirtazapine (Remeron®) is an **alpha$_2$-adrenergic receptor antagonist**. It blocks presynaptic alpha$_2$ receptors on both noradrenergic and serotonergic nerve terminals leading to an increase in the release of NE and 5-HT.

Mirtazapine also blocks H1-histamine, 5-HT$_{2A}$, 5-HT$_{2C,}$ 5-HT$_3$ serotonin receptors & increases 5-HT at 5-HT$_{1A}$ receptors, inducing anxiolytic & antidepressant effects at longer treatment times

At low doses, mirtazapine is **highly sedating.** Increasing the dose produces less sedation and greater excitation. Mirtazapine does not produce sexual dysfunction, nausea or GI problems.

Trazadone **(Deseryl®)** – originally approved as an antidepressant, it is highly sedating and currently is marketed primarily as a hypnotic drug

Nefazodone (**Serzone®)** is a **5-HT$_{2A}$ receptor antagonist and 5-HT reuptake inhibitor**. It is **mildly sedating and does not interfere with sexual function**. Nefazodone is chemically related to the antidepressant drug, trazodone (Desyrel®).

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4. The Antihistamines

Cyclobenzaprine **(Flexeril®)** - an H-1 histamine receptor antagonist.

Hydroxyzine (**Atarax®)** – another H-1 histamine receptor antagonist (antihistamine).

Diphenhydramine **(over the counter Benadryl®)** – an H-1 histamine receptor antagonist.

5. Nonprescription "sleeping pills":

Many "sleeping pills", previously available as OTC sleep agents contained the antihistamines pyrilamine or methapyriline, and possibly an analgesic or anticholinergic drug. These were found to produce tolerance and rebound insomnia and **to not be** more effective than placebo and subsequently removed from the market. Unisom is the only FDA approved OTC sleep aid that is available at this time.

Compoz - methapyrilene and pyrilamine
Nytol - methapyrilene and salicylamide (salicyate)
Sleep-Eze - methapyrilene and scopolamine
Sominex - methapyrilene, scopolamine and salicylamide (salicyate)

****Unisom** - contains the antihistamine, doxylamine.

5. **Herbal Preparations**:

These may be worth trying since there is some evidence that they contain constituents that may be biologically active.

Consideration should be given to any prescribed medications, or other OTC medications that may interact with these herbal preparations.

Valeriana officinalis (**Valerian)** - as a standardized 70% ethanol extract (600 mg HS) is a safe hypnotic. Sesquiterpenes are the active compounds that mediate GABA release and the inhibition of GABA breakdown. Its usefulness to treat insomnia for up to 4 weeks has been documented. Valerian does not produce a "next day" hangover or other aversive effects and does not induce any serious drug interactions.

Chamomile (*Matricaria recutita*) - Apigenin is the active indgredient; benzodiazepine agonist Chamomile tea is relaxing when ingested HS.

Kava - Kava lactones are the active components that facilitate the binding of GABA; reported to have calming effects.

"**Passion flower"** - Chrysin is the active compound that is a benzodiazepine partial agonist; has been reported to be an effective and safe hypnotic but this view has not been substantiated.

Generic Name	Trade Name	Half-life	Mech. of Action	Characteristics &/or Use
BENZODIAZEPINES (Actions at BZ1 and BZ2 receptors)				
Alprazolam	Xanax	Intermediate	BZ1 & BZ2 agonist, ↑ freq. of Cl^- channel opening	Panic Disorders, cocaine withdrawal
Clonazepam	Klonopin	Intermediate	Same as above	Anxiety & sleep disorders, fibromyalgia
Clorazepate	Tranxene	Very long	Same as above	Inactive parent compound, multiple active metabolites
Chlordiazepoxide	Librium	Very long	Same as above	Multiple active metabolites
Diazepam	Valium	Very long due to active metabolites	Same as above	Rapid onset, long half life, high abuse liability
Estazolam	ProSom	Long	Same as above	
Flunitrazepam	Rohypnol	Short	Same as above	Not approved in U.S., date rape drug, high abuse liability
Flurazepam	Dalmane	Very Long	Same as above	Short acting parent drug but 2 long half life active metabolites that are longer in the elderly
Flumazanil	Romazicon	Short	**BZ1 &BZ2 ANTAGONIST**	Can trigger BZ withdrawal, useful in BZ overdose
Lorazepam	Ativan	Intermediate	BZ1 & BZ2 agonist, ↑ freq. of Cl^- channel opening	No bioactive metabolites **Phase II only**
Oxazepam	Serax	Intermediate	Same as above	No bioactive metabolites **Phase II only**
Temazepam	Restoril	Intermediate	Same as above	No bioactive metabolites **Phase II only**
Midazolam	Versed	Very Short (2.5hrs)	Same as above	Strong antereograde amnesia used in operative procedures
Triazolam	Halcion	Very Short (2-3 hrs)	Same as above	Very rapid onset, high potency, high abuse liability
Non-Benzodiazepine Drugs (BZ1 Selective)				
Zaleplon	Ambien	Very Short (1 hr)	BZ1 selective agonist	Sleep aid, rapid absorbtion, no anxiolytic, anticonvulsant & muscle relaxation
Zolpidem	Sonata	Very Short (1.5–3 hrs)	BZ1 selective agonist	Sleep aid, rapid absorbtion, no anxiolytic, anticonvulsant and muscle relaxant efficacy
Eszopiclone	Lunestra	Short (6 hrs)	BZ1 selective agonist	Sleep aid, rapid absorbtion, no anxiolytic, anticonvulsant or muscle relaxant efficacy
Melatonin Receptor Agonist				
Ramelteon	Rozarem	Very Short	M1 & M2 melatonin receptor agonist	Rapid absorbtion, large Vd, No abuse potential, No BZ receptor binding, metabolism decreased by Fluvoxamine, Ketoconazole & Fluconazole (via CYP inhibition)

Generic Name	Trade Name	Half-life	Mech. of Sedation	Other Characteristics
Barbiturates				
Pentobarbital	Nembutol	Intermediate to Long	Bind to $GABA_A$ & ↑ the duration of Cl^- channel opening	High abuse liability, low therapeutic index, induces microsomal oxidases, may be GABA-mimetic at high conc.
Phenobarbital	Luminol	Very long	Same as above	Same as above
Thiopental Sodium	Pentathal	Short	Same as above	Same as above
TCAs Used to Treat Sleep Disorders				
Amitriptyline	Elavil	Intermediate	Antihistaminergic & anticholinergic	TCA, anticholinergic, antiadrenergic effects
Doxepin	Sinequin	Short to Interrnediate	Same as Above	TCA, anticholinergic, antiadrenergic effects
Imipramine	Trofanil	Interrmediate to long	Same as Above	TCA, anticholinergic, antiadrenergic effects
Other Sedating Drugs Used for Sleep Disorders				
Cyclobenzaprine	Flexeril	Intermediate	Antihistaminergic	
Diphendydramine	Benadryl	Short to intermediate	Same as above	OTC meds for sleep and allergies
Hydroxyzine	Atarax	Intermediate to long	Same as above	
Mirtazapine	Remeron	Long (20-40 hrs)	Antihistaminergic, $\alpha 2$ alpha rec. antagonist	Antiadrenergic & stimulatory at higher doses
Nefazodone	Serzone	Intermediate	5-HT_{2A} antagonist & 5HT uptake inhibitor	Liver toxicity, only generic,
Trazadone	Deseryl	Intermediate	Same as above	Highly sedating
Meprobamate	Equinil, Miltown	Intermediate	Likely similar to BZs	Anti anxiety (only approved use) & sedative effects
Herbs and OTC Meds				
Camomile			Apigenin is a GABA rec. agonist	Relaxing effects at bedtime
Kava			lactones facilitate GABA binding	Reported calming effects
Valerian			Releases GABA & inhibits its breakdown	No next day hangover
methapyrilene and pyrilamine	Compoz		Antihistaminergic	No longer approved by FDA
methapyrilene and salicylamide	Nytol		Antihistaminergic	No longer approved by FDA
methapyrilene and scopolamine	Sleep-Eze, Sominex		Antihistaminergic & anticholinergic	No longer approved by FDA
Doxylamine	Unisom		Antihistaminergic	Regained FDA approval (2004) for use as OTC sleep aid

Drugs Used in the treatment of Rheumatoid Arthritis and Gout

Date: Friday February 15th, 2012 – 9:30-10:30am
Reading Assignment: **Pharmacology: Board Review**- Trevor, Katzung and Masters, Chapter 36

KEY CONCEPTS AND LEARNING OBJECTIVES

1. Understand the rationale behind the use of Analgesics, NSAIDs and glucocorticoids in the treatment of Osteoarthritis.

2. Understand the relative therapeutic benefit of NSAIDs, Analgesics, Glucocorticoids, DMARDs and Biological Response Modifiers/Biologics in the treatment of Rheumatoid Arthritis.

3. For the frequently used DMARDs class of drugs used in the treatment of RA (methotrexate, hydrochloroquine, sulfasalazine and leflunomide)

Know a) Their major indications
b) Their mechanism of action
c) Their approximate time to effect
d) Their major adverse effects
e) Their contraindications especially during pregancy

4. Recognize the less frequently used DMARDs such as Azathioprine, D-penicillamine, Gold Salts, Cyclosporin and Cyclophosphamide in the treatment of Rheumatoid Arthritis. No need to learn specifics of these drugs as they are **rarely used** now in treatment of RA due to their toxicity.

5. Understand the roles of the distinct classes of Biological Response Modifiers/Biologics in the treatment of Rheumatoid Arthritis.

6. For each of the Biological Response Modifiers/Biologics i.e. TNF-α blockers: Etanercept, Infliximab and Adalimumab; Abatacept; Rituximab; Anakinra; Tocilizumab and Tofacitinib

Know: a) Their major indications
b) Their mechanism of action
c) Their major adverse effects
d) Their major contraindications

7. Understand the pathophysiology of Gout; the role of uric acid in the etiology of the disease; and the typical disease course including hyperuricemia, acute gouty attack, intercritical phase and chronic gout.

8. Understand the rationale for the use of Colchicine and NSAIDs in the treatment of an acute gouty attack

9. Understand the rationale behind the use of drugs used to treat Chronic Gout (e.g. the Uricosuric probenecid; the Xanthine Oxidase inhibitors: Allopurinol and Febuxostat; and the Uric acid degrading enzyme Pegloticase).

For each drug Know: a) Their specific indications
b) Their mechanism of action
c) Their major adverse effects
d) Their major contraindications

Drugs to be covered in this lecture:

Particular emphasis should be placed on the drugs that are highlighted in BOLD TEXT.

1. NSAIDs

2. Acetaminophen (Tylenol®/Paracetemol®)

3. Topical Analgesics e.g. Capsaicin

4. Glucocorticoids (Injectable/Oral)

5. Disease-Modifying anti-Rheumatic Drugs (DMARDs)

Commonly used DMARDs:	**Methotrexate (Rheumatrex®)**
	Hydroxychloroquine (Plaquenil®)
	Sulfasalazine (Azulifidine®)
	Leflunomide (Arava®)
Less frequently used DMARDs:	*Azathioprine (Imuran®)*
	D-penicillamine (Depen®)
	Gold salts
	Cyclosporin A (Sandimmune® & Neural®)
	Cyclophosphamide (Cytoxan®)

6. Biological-response Modifiers

Etanercept (Enbrel®) - TNFa inhibitor
Infliximab (Remicade®) - TNFa inhibitor
Adalimumab (Humira®) - TNFa inhibitor

Anakinira (Kineret®) - IL-1R antagonist
Abatacept (Orenica®) –inhibitor of T cell co-stimulation
Rituximab (Rituxan®) – anti-B cell agent
Tocilizumab (Actemra®) – anti-IL-6R agent
Tofacitinib (Xeljanz®) –small molecule inhibitor of immune cytokine receptor signaling

7. Colchicine

8. Uricosuric agents

Probenecid

9. Uric Acid Synthesis Inhibitor

Allopurinol (Zyloprim®)
Febuxostat (Uloric®)

10. Pegloticase

- PEG-coupled PORCINE URICASE- degrades Uric acid to soluble byproduct

A. Osteoarthritis

Overview

- Most common joint disease affecting 21 million in the US
- Characterized by loss of articular cartilage, bone remodeling and bone hypertrophy
- Most commonly affects the weight bearing joints of the hips knees and lower back
- Exact cause unknown, but may result from either excessive load on the joints or the presence of abnormal cartilage or bone
- Risk factors include age > 50yrs, joint injury, obesity, high bone density, long-term immobilization of the joint, mechanical stress to the joints (e.g. occupational/sports), and genetics

Symptoms

- Joint soreness after periods of overuse or inactivity
- Stiffness after periods of rest that disappear when activity is resumed
- Redness, tenderness and swelling of the affected joints
- Pain when moving the knee, Pain and swelling of the finger joints
- Stiffness and pain in the neck, shoulders, arms or lower back

Pathophysiology

- Cartilage loses its elasticity and is more easily damaged
- Mechanical wear and tear of the cartilage promotes the proliferation of chondrocytes.
- Chondrocytes release proteases and pro-inflammatory mediators
- Proteases degrade the matrix and result in the formation of abnormal cartilage
- Breakdown of the cartilage can cause bones to rub together causing pain
- Inflammation of the cartilage (mild c.f. with RA) causes new bone spurs to form, which causes pain and decreases the mobility of the joint

Treatment

Treatment goals

a) Control pain and other symptoms with medication
b) Improve functionality and quality of life- weight loss, exercise and physical therapy

Medications

1. Analgesics:

- For mild to moderate pain- **Acetaminophen** is the drug of choice for pain relief with minimal side effects (see below).

2. Topical Analgesics:

- A topical analgesic such as Capsaicin (derived from hot peppers) can be used together with oral acetaminophen for pain relief.
- Capsaicin works by depleting Substance P, which is present in painful joints and is involved in the transmission of pain to the CNS

3. NSAIDs: e.g. Aspirin, Ibuprofen and Naproxen

- For patients with moderate to severe pain and signs of inflammation.
- However use of NSAIDs may be limited by their side effects.
-

4. Injectable glucocorticoids

- Glucocorticoids can be injected directly into the joint for fast targeted pain relief as an alternative to patients with mild to moderate pain that do not respond to acetaminophen or NSAID treatment.
- ~80% of patients exhibit a therapeutic response
- Injections not given more frequently than once every three months

B. Rheumatoid Arthritis.

Overview

- Chronic inflammatory disease of the joints
- Affects 1.5% of Americans, 9 million physician visits and >250,000 hospitalizations/year
- Systemic autoimmune disease of unknown etiology
- Characterized by inflammation and pain in the joints with progressive joint destruction
- Additional extra-articular involvement of the skin, cardiovascular system, lungs and muscle
- Causes significant disability, deformity and can even precipitate premature death
- **Although the exact cause is unknown, disease progression clearly involves the immune system with evidence of both T cell and B cell immune response to self-antigen**

Pathophysiology

- Chronic lymphocytic inflammatory infiltration develops in the synovium (joint lining)
- Swelling of the synovium causes pain, warmth, stiffness and redness of the joint
- Rapid proliferation of synovial fibroblasts and infiltrating leukocytes causes the snovium to thicken and invade the local cartilage and bone
- Macrophages and lymphocytes secrete proteolytic enzymes (e.g. collagenase) and inflammatory mediators **(e.g. TNF-α, IL-6, IL-1 and prostaglandins)** causing further inflammation, the activation of bone-resorbing osteoclasts and ultimately the destruction of bone and cartilage.

B1 Treatment of Rheumatoid Arthritis

B1.1 Treatment goals

a) Decrease pain
b) Prevent or control joint damage
c) Prevent loss of function and preserve quality of life

B1.2 Medications used to treat Rheumatoid Arthritis: An overview

B1..2A Drugs to treat Acute Joint Pain-Symptomatic Relief Only

1. NSAIDs (e.g. Aspirin, Ibuprofen, Naproxen and Celecoxib)

- Drugs of choice for the reduction of inflammation and pain
- Patients usually started on an NSAID immediately after diagnosis
- **For symptomatic relief only!** - NSAIDs **do not** affect disease course
- Choice of NSAID determined by efficacy and side effects
- If a particular NSAID is ineffective after a 2 week trial an alternative NSAID is warranted

2. Analgesics (e.g. Acetaminophen, Capsaicin or an Opioid analgesic)

- For symptomatic pain relief
- Can be combined with a NSAID for improved pain relief and anti-inflammatory effect
- A topical analgesic such as Capsaicin (derived from hot peppers) can be used together with oral acetaminophen for pain relief. Capsaicin works by depleting Substance P, which is present in painful joints and is involved in the transmission of pain to the CNS

3. Glucocorticoids

a) Glucocorticoids exhibit both anti-inflammatory and immunoregulatory activity
b) Can be administered orally, intravenously, or by direct injection into the joint
c) Useful early in disease while waiting for slow acting DMARDs to work

Shown to: Decrease joint tenderness
Decrease joint pain
Increase grip strength

d) Short term/low dose glucocorticoids are seldom associated with serious side effects

e) The use of chronic glucocorticoid therapy is controversial- there is some evidence for the inhibition of disease progression, although their use is associated with increased side effects

Adverse Effects: Weight gain
Hypertension
Osteoporosis
Hyperglycemia
Increased risk of infection

f) Withdrawal from long-term glucocorticoid use is difficult, as this can result in increased disease severity due to suppression of the Hypothalamus-Pituitary-Adrenal axis

B1.2B Drugs that can acto to prevent or control joint damage

4. Disease modifying anti-Rheumatic Drugs (DMARDS) (e.g. methotrexate) **(SEE BELOW)**
- To slow joint damage and modify the course of the disease

5. Biological Response Modifiers (BRM)/Biologics (e.g. TNF inhibitors etc) **(SEE BELOW)**
- Specific recombinant protein drugs that inhibit the immune responses that contribute towards joint inflammation.
- Shown to slow joint damage and modify the course of the disease

B2 Disease-Modifying anti-Rheumatic Drugs (DMARDs)

Overview

a) Unlike NSAIDs and corticosteroids, DMARDs can potentially **reduce/prevent** joint damage
b) DMARDs work to inhibit the overactive immune system that is present in Rheumatoid Arthrisis
c) DMARDs should be considered in Rheumatoid Arthritis where the use of NSAIDs/steroids has not prevented ongoing joint pain or other clinical symptoms
d) Use of DMARDs should not be delayed beyond 3 months in these patients
e) DMARDs are **slow acting** anti-rheumatic drugs that can take several weeks to many months to show efficacy and are typically taken for long periods (i.e. months to years)

B2.1. Frequently used DMARDs

1. Hydroxychloroquine (e.g. Plaquenil®)

a) An anti-malarial drug that is moderately effective for mild rheumatoid arthritis
b) Effectiveness only becomes apparent after 3-6 months
c) Often combined with other DMARDs e.g. sulfasalazine and methotrexate
d) Considered **safe** for use during **pregnancy**

Mechanism of action*:* Unclear- thought to inhibit immune responses in a variety of ways
- inhibition of TLR signaling in dendritic cells and B cells
- inhibition of antigen presentation to CD4+ T cells

Adverse Effects
- Nausea, epigastric pain, rash and diarrhea
- **Rare (1/40,000) retinal toxicity has been reported in elderly patients that can result in irreversible visual loss**

2. Sulfasalazine (Azulifidine®)

a) Decreases signs and symptoms of disease and slows radiographic evidence of joint destruction (effective in up to 50% of patients).
b) more toxic than hydroxychloroquine/somewhat less effective than methotrexate
c) Sulfasalazine is a combination of 5-aminosalicylic acid covalently linked to sulfapyridine that is cleaved by colonic bacteria to its active components- it is thought that sulfapyridine is responsible for the therapeutic effect
d) Effect can be seen in 1-3 months

e) Does not appear to be a teratogen- therefore unlike methotrexate it is **safe during pregnancy**
f) Often combined with other DMARDs e.g. hydroxychloroquine
g) Generally well tolerated

Mechanism of action: Unclear, but thought to interfere with T and B cell immune responses, potentially by inhibiting the activity of the NF-kB transcription factor

Adverse Effects: Nausea, headache, anorexia and rash are common (~30% of patients)
Rare – Agranulocytosis with Fever/Rash within 2 weeks of treatment
- fully reversible following drug discontinuation

3. Methotrexate (Rheumatrex®)*******

a) **Drug of choice** for treatment of Rheumatoid Arthritis- especially for patients with active disease
b) Oral methotrexate in low doses (15-27.5 mg/week) decreases the appearance of new bone erosions and improves the longterm clinical outcome – up to 70% of patients experience some response to the drug
c) N.B. the levels of methotrexate used in RA are ~100-1000x lower than used in cancer treatment
d) Effects are apparent after 4-6 weeks
e) Well tolerated >50% of patients continue taking the drug for >3 yrs

Mechanism of action*:* Unclear, but appears to be independent of its anti-proliferative activity. Thought to be due to an indirect effect on the increased production of adenosine, which is known to exhibit immunosuppressive properties

Adverse Effects

- Generally well tolerated (>50% of patients continue taking the drug for > 3 yrs)
- MTX is 80-90% renally excreted- side effects more common in patients with renal impairment

  Common side effects:
  - Dose-dependent hepatotoxicity
  - Not recommended for those with pre-existing liver disease or consuming alcohol

  Rarer Side effects:
  - bone marrow suppression
  - Acute pneumonitis occurs in 1-2% of patients
  - Increased risk of lymphoma

- **Contraindicated during pregnancy (MTX is actually used as an abortifacient)**

4. Leflunomide (Arava®)

a) As effective as either slufasalazine or methotrexate in decreasing symptoms of disease
b) Alternative to those unable to take MTX or for those non-responsive to MTX
c) low cost alternative to expensive TNF inhibitors or for those with a preference for oral vs IV medication
d) Responses evident in 1-2 months

Mechanism of action: Oral pyrimidine synthesis inhibitor that inhibits dihydrotoroate dehydrogenase and therefore blocks the de novo synthesis of uridine, which leads to cell growth arrest in the G1 phase of the cell cycle. Inhibits both T cell proliferation and the production of autoantibodies by B cells

Adverse Effects

- Diarrhea occurs frequently (~10-15% of patients)
- Alopecia, weight gain, rash, increased blood pressure and an increase in liver enzymes can

occur
- Severe hepatotoxicity (including several fatalities) have been reported in patients taking both Leflunomide and Methotrexate
- Contraindicated during pregnancy
- Should not be taken concomitantly with rifampin (anti-tuberculosis medication), as it is known to elevate serum leflunomide levels leading to increased risk of toxicity

B2.2. Less frequently used DMARDs

1. Azathioprine

a) Orally active purine analog that is cytotoxic to inflammatory cells
b) Used for patients with refractory Rheumatoid Arthritis and those with systemic involvement, such as rheumatoid vasculitis
c) Treatment for 3-6 months is required to be effective
d) Drug is not always well tolerated

Adverse effects
- Nausea, vomiting, abdominal pains, hepatitis, reversible bone marrow suppression and increased risk of lymphoma

2. Gold salts

a) Gold compounds (oral/injected intramuscularly) have been used to treat arthritis since the 1960's
b) Can induce a complete remission
c) Sometimes used in patients who cannot tolerate methotrexate
d) Gold particles are taken up by macrophages and impair their function
e) Response requires 3-6 months

Adverse effects
- stomatitis, dermatitis, proteinuria, thrombocytopenia, leukopenia and bone marrow suppression (**RARELY USED NOW DUE TO TOXIC SIDE EFFECTS**)

3. Cyclosporin (e.g. Sandimmune®, Neural®)

a) Approved for use in Rheumatoid arthritis and retards appearance of bony erosions
b) Acts by inhibiting T lymphocyte activation pathways leading to cytokine production
c) Maybe useful in patents with refractory arthritis
d) However, associated with significant nephrotoxicity, neurotoxicity, hepatotoxicity and increased hypertension
e) Toxicity and costs associated with drug level monitoring limit use

4. Cyclophosphamide (Cytoxan®)

a) Major metabolite is phosphoramide mustard, which promotes DNA crosslinks and thereby inhibits DNA replication
b) Acts to inhibit T and B cell function by 30-40%
c) Is useful in the treatment of severe rheumatoid vasculitis
d) Long term use is associated with leukopenia, increased risk of infection, cardiotoxicity, alopecia and an increase risk of malignancy, especially bladder cancer.

5. D-penicillamine (Depen®)

a) Can be effective in patients with refractory Rheumatoid Arthritis
b) However, **more toxic** than either methotrexate or sulfasalazine- **RARELY USED NOW**

Because of the increased toxicities of these drugs they are now typically only utilized in RA with severe life-threatening extra-articular symptoms such as systemic vasculitis, or in very severe RA that is refractory to other medications.

B3 Biological Response Modifier/Biologic Drugs

Overview

Biological response modifiers are recombinant protein drugs that are specifically designed to inhibit either cytokines (e.g. TNF-α and IL-1) or cell types (e.g. T cells/B cells) involved in the regulation of the *in vivo* immune response.

a) Drugs that specifically inhibit the action of TNF-α:
   (i) Etanercept (Enbrel®)
   (ii) Infliximab (Remicade®)
   (iii) Adalimumab (Humira®)

b) Drugs that interfere with the actions of IL-1
   - Anakinra (Kineret®) is an IL-1 blocker

c) Drugs that inhibit T lymphocyte activation/co-stimulation:
   - Abatacept (Orenica®)

d) Drugs that deplete B lymphocytes:
   - Rituximab (Rituxan®)

e) Drugs that block the actions of IL-6
   - Tocilizumab (Actemra®)

f) Drugs that inhibit immune cytokine receptor signaling
   - Tofacitinib (Xeljanz®))

B3.1The critical role played by TNF-α in the pathogenesis of Rheumatoid arthritis: An overview

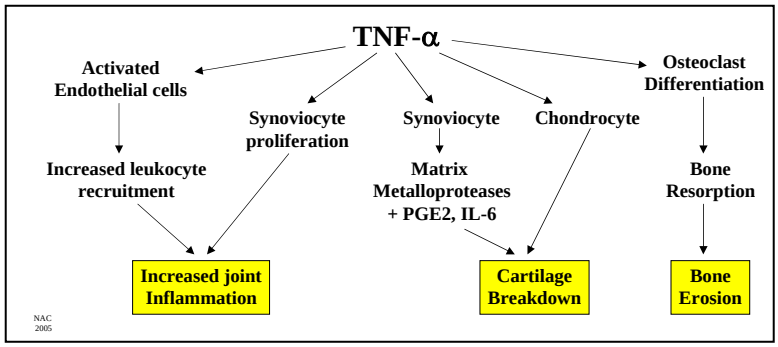
a) TNF-α is a pivotal cytokine in the regulation of the immune response

b) It is synthesized by macrophages, mast cells and activated CD4+ Th1 cells

c) It activates macrophages increasing their phagocytic activity and the production of cytotoxic molecules

d) It activates the endothelium and promotes the recruitment of leukocytes to site of inflammation

e) It promotes the differentiation of bone-resorbing osteoclasts



f) It induces the proliferation of synoviocytes and their production of proteases & inflammatory molecules

g) It exhibits pyrogenic activity causing fever and acts systemically to cause pain

B3.2. Anti-TNF-α drugs

a) Etanercept (Enbrel®)

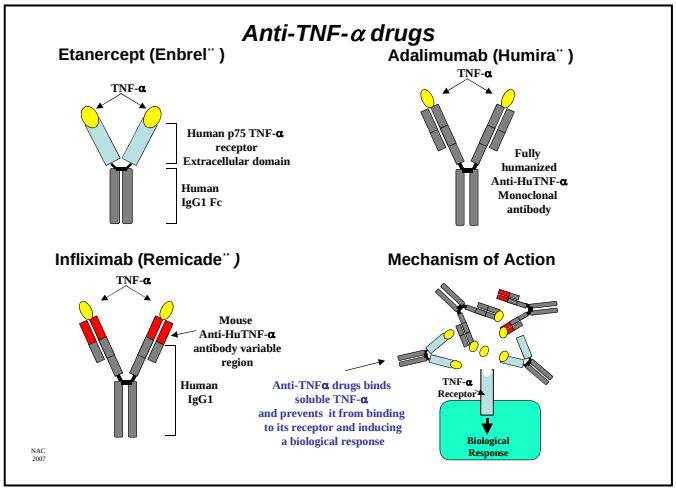
Recombinant protein consisting of two soluble p75 TNF-α receptor moieties linked to the Fc portion of a human IgG1 antibody molecule

b) Infliximab (Remicade®)

Chimeric human/mouse anti-TNF-α monoclonal antibody

c) Adalimumab (Humira®)

Recombinant fully human monoclonal antibody



Anti-TNF-α drugs: Mechanism of Action.

All three anti-TNFα drugs work by binding to soluble TNF-α and prevent it from interacting with its cognate receptor expressed on the surface of specific cell types.

Anti-TNF-α drugs: Clinical Use

a) Anti-TNFα drugs are given either subcutaneously or intravenously and are typically administered weekly/bi-weekly

b) Typical time to effect is 1- 4 weeks

c) Clinically shown to: (i) reduce joint pain and swelling
(ii) decrease the formation of new bone erosions
(iii) slow progression of structural joint damage

d) ~ 30-60% of patients will exhibit a 20-50% improvement in their symptoms

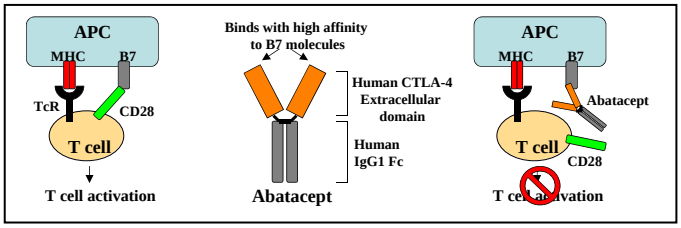
e) Are used as both monotherapy and in combination with methotrexate. When combined with low dose methotrexate the addition of anti-TNFα drugs have been shown to significantly prevent disease progression versus the use of methotrexate alone

Anti-TNF-α drugs: Common Adverse effects.

a) Injection site reactions, injection site pain, headache and rash are common, but usually do not require discontinuation of treatment
b) Increased risk of opportunistic infections
c) Can result in the reactivation of latent tuberculosis and Hepatitis B virus
d) Should not be given to patients with either acute or chronic infections
e) Treatment should be discontinued if a serious infection or sepsis develop
f) May rarely be associated with the exacerbation of pre-existing congestive heart failure and the development of demyelinating diseases such as multiple sclerosis, and the appearance of malignancies, especially lymphoma
g) Should not be given to patients with a recent history of malignancy

B3.3 Abatacept (Orenica®)

a) Is a recombinant protein fusion between the T cell surface molecule CTLA-4 and human IgG1 (CTLA4-Ig)



b) It inhibits T cell activation by binding to the CD80/CD86 (B7) family of co-stimulatory ligands expressed on antigen presenting cells, thereby blocking the delivery of co-stimulation signals to the T cell via the CD28 molecule, which is essential for efficient T cell activation

c) Slows damage to bone and cartilage and relieves both the symptoms and signs of arthritis

d) Effective in patients non-responsive to anti-TNF-α drugs

Adverse effects

- Increased risk of serious infections- screen for latent TB and HBV
- Not to be given to patients with either acute or chronic infections
- Should **not** be given in combination with a TNF-α blocker as this increases infections

B3.4 Rituximab (Rituxan®)

a) Rituximab is a chimeric humanized antibody that binds to the CD20 molecule expressed on B lymphocytes

b) I.V. infusion of Rituximab depletes B cells from the blood.

- since B cells are implicated in disease etiology through antigen presentation and formation of autoantibodies their depletion can slow disease progress

c) Clinically shown to decrease signs and symptoms of disease and reduce radiographic evidence of disease progression.

d) Effects not seen for 3 months, although effects may last 6 months - 2 yrs following a single infusion.

e) Effective in patients not responsive to TNF-α inhibitors

Adverse Effects

- Increased infections
- Reactivation of latent viruses e.g. CMV, HSV and Hepatitis B&C
- Progressive multifocal leukoencephalopathy (PML-RARE)
  - fatal demyleinating disease associated with reactivation of the JC virus

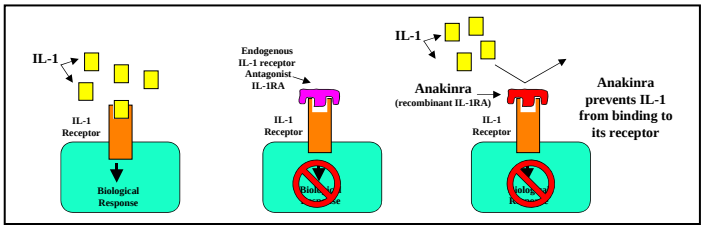
B3.5 Anakinra (Kineret®)

a) Genetically engineered recombinant version of an endogenous IL-1 receptor antagonist (IL-1RA)

b) Competitively inhibits the pro-inflammatory effects of endogenous IL-1

c) A subcutaneous dose of 150 mg/day gives a modest reduction in pain and swelling, but a significant reduction in new bone erosions (due to the effects of IL-1 on synoviocyte-mediated cartilage degradation).

d) Also given in combination with methotrexate



Adverse effects

- Local injection site reactions are frequent (~40%) and can lead to discontinuation of the drug
- Only a small increase in infections
- Should not be given to patients with either acute or chronic infections
- Complications (neutropenia and severe bacterial infections) occur more frequently when given together with an anti-TNF-α drug

B3.6 Tocilizumab (Actemra®)

a) Chimeric humanized antibody directed against the IL-6 receptor

b) Acts as an antagonist of the IL-6 receptor

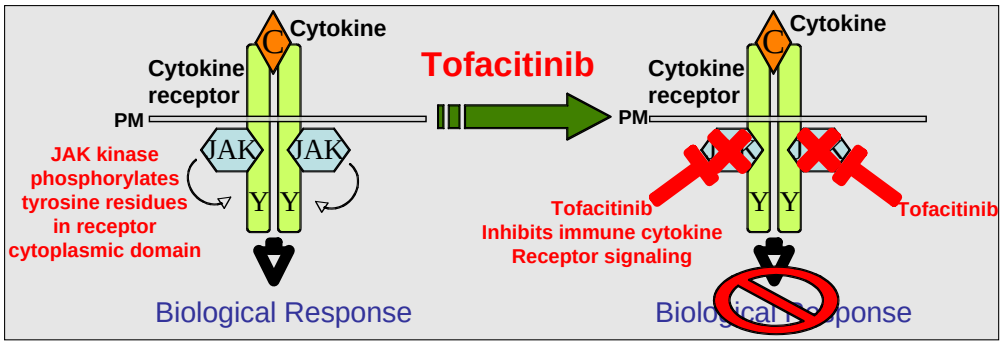
c) Used in patients non-responsive to TNF inhibitors

Adverse Effects

- Increased risk of BM suppression (Lymphocytopenia, neutropenia, anemia)
- Increased risk of serious infections (including TB and HBV)
- Hepatotoxicity (routine liver monitoring)
- Increased levels of cholesterol
- Increased risk of malignancy (especially in setting of immunosuppression)

B3.7 Tofacitinib (Xeljanz®)

a) New class of anti-rheumatic drug
b) Small molecule inhibitor that inhibits JAK tyrosine kinases involved in immune cell cytokine signaling



Adverse Effects

- Lymphocytopenia, neutropenia and anemia
- Increased risk of serious infections including TB
- Lipid abnormalities (increased cholesterol)
- Increased liver enzymes

B4 Treatment strategy in Rheumatoid Arthritis

a) Initial symptomatic treatment for relief of pain and joint inflammation
- NSAIDs (e.g. Naproxen, Indomethacin)
- Glucocorticoids (e.g. Prednisone)

b) DMARDs therapy should be initiated within 3 months of diagnosis
- Hydroxychloroquine + Sulfasalazine is used for mild disease
- Methotrexate is the drug of choice for active and/or moderate-severe disease

c) NSAID are used in the early stages of DMARD therapy to reduce pain while waiting for the clinical effect of DMARDs to "kick-in"

d) If Methotrexate is ineffective- other DMARDs (e.g. Leflunomide) and/or Biological Response Modifiers either alone or in combination should be tried.

e) Clinical trials have shown that combination therapy with multiple agents is likely to be more effective than monotherapy.
e.g. Methotrexate + Hydroxychloroquine and Sulfasalazine
Methotrexate + either Etancerpet, Infliximab or Adalimumab

C. Gout

Overview

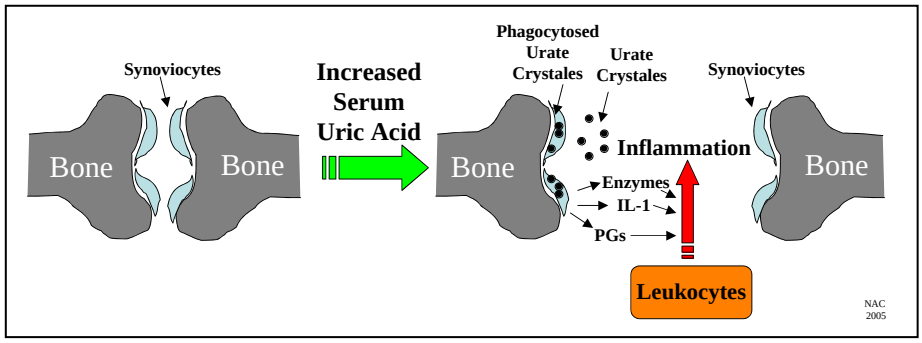
a) Gout is an extremely painful form of arthritis.
b) It is associated with **HYPERURICEMIA**: **high** serum levels of **uric acid** (>7 mg/dL)
- uric acid is a poorly soluble end product of purine metabolism
- however not all individuals with hyperuricemia will develop gout

c) Hyperuricemia can result from either **over production** of uric acid (10% of patients), or from **decreased excretion** of uric acid by the kidney (~90% of all patients).

d) It affects primarily men in their 30's and 40's (frequency 1 in 100) and is associated with obesity,

hypertension, hyperlipidemia, type 2 diabetes, a diet rich in purines and the excessive consumption of alcohol. - Historically referred to as the “Disease of Kings”

Gout: Pathophysiology
a) Urate crystals are deposited in the joints
b) Synoviocytes phagocytose urate crystals
c) Synoviocytes secrete inflammatory mediators- prostaglandins, IL-1 and lysosmal enzymes
d) Inflammatory leukocytes are recruited into the joint
e) Recruited macrophages phagocytose urate crystals and release additional inflammatory mediators that promote further recruitment of inflammatory cells
f) Inflammation causes pain, heat and swelling and damage to the joint



C1. Gout Disease Course

1. Initial stage: Asymptomatic hyperuricemia

-only a small percentage of patients with hyperuricemia will go onto develop gout

2. Acute Gouty Attack

- rapid onset of an **intense** period of painful swelling in a single joint, most often in the feet (esp. big toe; first metatarsophalangeal joint).
- the symptoms of the attack typically resolve within 3-10 days.

3. Intercritical Phase

- hyperuricemia without acute symptoms
- 10% of patients may never experience another attack

4. Chronic Gout

- recurrent attacks of increasing frequency and severity involving additional joints
- chronic high levels of urate crystals lead to the formation of **TOPHI** - a deposition of urate crystals around the synovial joint that can induce an inflammatory response resulting in the **destruction of cartilage and the synovial lining**

C2. Pharmacological strategies for the treatment of gout

C2.1. Drugs that relieve the symptoms of the acute gouty attack

(A) Colchicine

- traditional treatment,
- plant alkaloid that prevents tubulin polymerization into microtubules
- blocks leukocyte migration and phagocytosis
- anti-inflammatory, but **no** analgesic properties
- effective typically only when given during the first 24-48 hrs of the attack
- limited by side effects (especially at high doses)- ~80% of patients develop diarrhea/vomiting within 24hrs
- overdose can be life threatening due to bone marrow suppression
- because of toxicity now generally relegated to a second line agent

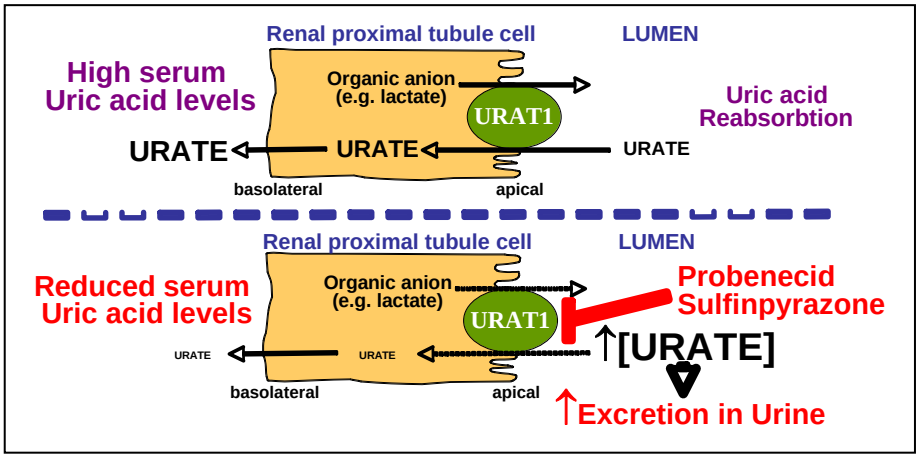
(B) NSAIDs

- commonly used as a replacement for Colchicine
- **all** NSAIDs **except** Aspirin and Salicylates have been used successfully in the treatment of gout
- effective at reducing pain and disability due to attack
- COX-2 inhibitors should be used when other NSAIDs are contraindicated because of history of GI bleeds or use of blood thinners

C2.2. Drugs that lower plasma uric acid levels by promoting uric acid excretion – URICOSURIC AGENTS

Probenecid

a) Probenecid are both weak organic acids that inhibit anion transporters in the **proximal tubules** of the kidney and **decrease net reabsorption of uric acid**- thereby promoting uric acid excretion



b) Indicated in patients that under excrete uric acid

c) Should not be given until 2-3 weeks **after** the initial attack as drugs can actually **initiate** and/or **prolong** the symptoms of an acute gouty attack (due to disruption of urate homeostasis)- usually prophylactic NSAID treatment is given at same time to reduce risk of inducing an attack

d) Should not be given to patients that **naturally produce** high levels of **uric acid** due to increased risk of **kidney stones**

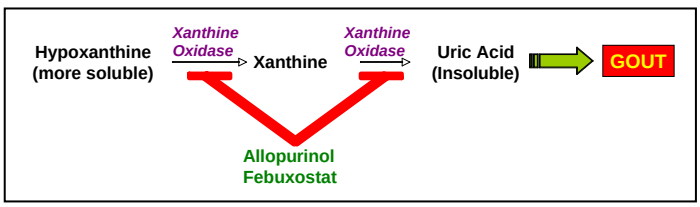
e) To reduce risk of kidney stones urine volume should be maintained at a high level and the urine pH should be kept > pH 6.

Contraindicated: Patients with kidney stones and/or renal insufficiency

C2.3. Drugs that lower plasma uric acid levels by decreasing uric acid synthesis

Allopurinol (Zyloprim®) and Febuxostat (Uloric®)

a) Used in the treatment of chronic gout to block production of Uric Acid
b) structural analogue of **hypoxanthine** that inhibits **Xanthine Oxidase**, an enzyme that catalyses the finall two steps in purine degradation



c) particularly useful in patients with:
- a high level of endogenous uric acid synthesis,
- Recurrent Kidney stones
- Renal Impairment
- Grossly elevated Uric Acid Levels ie. The presence of **TOPHI**

d) Should **not** be given during an **acute gouty attack** as this can actually worsen symptoms
An NSAID is usually prophylatically co-administered at the onset of Allpurinol therapy to reduce the chances of precipitating an acute attack of gout

Adverse Effects:
a) Can induce an acute gouty attack if NSAID prophylaxis not provided
b) Rash, leukopenia, thromobocytopenia & fever can occur in 3-5% of patients
c) Allopurinol hypersensitivity syndrome (<0.1% of patients) **[NOT FEBUXOSTAT]**
- a rare, but potentially **life threatening reaction** (25% mortality rate)
- most likely to occur in patients with renal insufficiency + diuretic dosage reduction required in presence of renal impairement
- symptoms include: Erythematous rash, fever, hepatitis esinophilia and acute renal failure

Drug Interactions: 6-mercaptopurine and azathioprine
- purine synthesis inhibitors used in immunosuppression and treatment of leukemia
- metabolized by xanthine oxidase to inactive metabolites
- toxicity is increased in the presence of allopurinol

C3. Management of Chronic Gout

a) Hyperuricemia by itself does not indicate that treatment is necessary

b) Treatment is indicated for:
- Patients with multiple gouty attacks
- Those that are more susceptible to future attacks e.g. Renal insufficiency
- Patients with very high levels of uric acid (>12 mg/dL)

Treatment Goal: To reduce serum uric acid levels to <6mg/dL

c) Which drug to use is dependent upon whether the patient is either an over producer or an under secretor of uric acid.
24 hr urinary uric acid excretion < 700 mg/dL - Undersecretion - Probenecid
24 hr urinary uric acid excretion >700 mg/dL - Overproduction - Allopurinol

d) Allopurinol is specifically indicated for:
- Patients with a uric acid kidney stone
- Patients with renal insufficiency- as uricosuric agents are not effective
- Patients with TOPHI

e) Effective therapy will require lifelong treatment

C4. Treatment of drug-resistant chronic gout

a) New drug Pegloticase (PEG-coupled Porcine Uricase) is an enzyme that degrades insoluble uric acid to more soluble byproduct. Note: Humans lack the Uricase enzyme

b) Reserved for patients that have advanced, actively symptomatic gout that is uncontrolled with other uric acid lowering drugs
Especially
- presence of frequent flares
- Presence of tophi
- Contraindication to other gout drugs

Traditional DMARDs

	Indications	MOA	Adverse Effects	Misc.
Hydroxychloroquine Anti-malarial drug	Mild RA	Inhibits: a) TLR signaling b) Antigen presentation	Rare Occular toxicity	Safe in pregnancy Often combined with Sulfasalazine
Sulfasalazine Pro Drug:Sulfayradine/ 5-aminosalicylic acid -metabolized to active component by colonic bacteria	Mild RA	Sulfapyridine - active component MOA unknown Inhibits T & B cells probably via NF-kB	Hepatotoxicity Agranuocytosis (Rare)	Safe in pregnancy Often combined with HCQ
Methotrexate	**Drug of Choice** moderate/severe RA	MOA in RA different from use in cancer - Increases Adenosine leading to Immunosuppression	Hepatotoxicity (common) Pulmonary toxicity BM suppression Risk of lymphoma	Contraindicated in Pregnancy and Liver disease Not recommended In Renal impairment (80-90 % renal CL)
Leflunomide	Alternative to MTX Moderate/severe RA	Inhibitor of dihydroorotate dehydrogenase (Uridine synthesis) -(G1 cell cycle arrest) -- inhibits T and B cell Immune responses	Hepatotoxicity (esp with MTX) Hypertension (esp NSAIDs) Diarrhea, nausea (~15%)	Contraindicated in Pregnancy and Liver disease

Biologics/Biological Response Modifiers

	Indications	MOA	Adverse Effects	Misc.
TNFα inhibitors Etanercept Adlimumab Infliximab	Active RA (monotherapy or combine with MTX)	Binds to TNFα and prevents its interaction with its receptor	↑Risk of infection Reactivation latent TB/HBV Exacerbates CHF ↑Risk Demyelinating disease ↑Risk of malignancy	Screen for latent TB and HBV Contraind acute/ chronic infections
Abatacept	Active RA Alt. to TNF inhibs DO NOT COMBINE with other Biologics	CTLA4-IgG fusion protein Binds CD80/CD86 Blocks T cell co-stimulation via CD28	↑Risk of infection	Screen for latent TB and HBV Contraind acute/ chronic infections
Rituximab	Active RA Alt. to TNF inhibs DO NOT COMBINE with other Biologics	Binds to CD20 on B cells IV infusion depletes B cells	↑Risk of infection PML: Progressive Multifocal Leukoencepalopathy - reactivation JC virus	Screen for latent TB and HBV Contraind acute/ chronic infections
Anakinra	Active RA Alt. to TNF inhibs DO NOT COMBINE with other Biologics	rIL-1RA IL-1R antagonist Blocks IL-1 signaling	↑Risk of infection (inc TB) BM suppression ↑Risk of malignancy	
Tocilizumab	Active RA Alt. to TNF inhibs DO NOT COMBINE with other Biologics	Humanized anti-IL6R mAb Binds IL6R Blocks IL-6 signaling	↑Risk of infection (inc TB) Hepatotoxicity Hypercholesterolemia BM suppression ↑Risk of malignancy (esp Immuno)	Screen for latent TB and HBV Contraind acute/ chronic infections Monitor for Demyelinõdisease
Tofacitinib	Active RA Alt. to TNF inhibs DO NOT COMBINE with other Biologics	Small molecule inhib Inhibits JAK kinases Blocks Immune Cytokine signaling	↑Risk of infection (inc TB) Hepatotoxicity Hypercholestrolemia BM suppression ↑Risk of malignancy (esp Immuno)	Screen for latent TB and HBV Contraind acute/ chronic infections

Drugs to Treat Gout

	Indications	MOA	Adverse Effects	Misc.
NSAIDs	Acute Gouty attack Prophylaxis for other gout medications	Inhibits COX-2 Anti-inflammatory and Analgesic	GI Toxicity Renal Etc etc	
Colchicine	Acute Gouty Attack Prophylaxis for other gout medications	Inhibits tubulin Polymerization Blocks leukocyte migration/phagocytosis	Narrow therapeutic window Nausea, Diarrhea Vomiting (~80%)	Anti-inflammatory No analgesic effects Should be given within 24-48 hrs of attack
Uricosurics Probenecid	Chronic Gout Due to decreased Uric acid excretion	Inhibits Renal anion transporter Promotes uric acid excretion	Can cause Kidney stones In high producers of URIC ACID	Contraindicated: Kidney Stones Renal insufficiency Uric acid overproduction
Xanthine Oxidase Inhibitors Allopurinol Feboxostat	Chronic Gout Due to Uric Acid Overproduction	Inhibits Xanthine Oxidase Decreases URIC ACID production	Rash Leukopenia Thrombocytopenia ↑Liver enzymes	Allopurinol Hypersensitivity Syndrome (25% mortality) **(Allopurinol only)** Esp. High dose/Renal Failure Dosage reduction required In renal insufficiency Increased toxicity with Azathioprine
Pegloticase	Drug resistant gout	Enzymatic degradation of Insoluble URIC ACID	↑Risk of CV events	Generation of Anti-drug Abs limits treatment

TREATMENT OF PARKINSONISM AND DEMENTIA

Date: Tues February 19, 2012 – 8:30AM

Reading Assignment: **Basic & Clinical Pharmacology, 12th ed.,** - B.G. Katzung, Chapter 28 and Chapter 60 pgs 1053-56.

KEY CONCEPTS AND LEARNING OBJECTIVES (Treatment of Parkinson's Disease)

(Section orignially prepared by Dr. B. Wolozin and edited and updated by Dr. J. Lee)

1. Know the presentation of Parkinson's disease
    a. Know other movement disorder diseases
2. Know the function of the 4 dopaminergic systems in the brain:
    a. Be able to identify pathways in figure 1.
3. Know the functional circuitry of the nigrostriatal system.
    a. The direct and indirect pathway
    b. Know which neurons have Dopaminergic (D1, D2) and Muscarinic (M) receptors
    c. Know which neurons have which neurotransmitters in the striatum: Acetylcholine, GABA, Glutamate, Enkephalin, Substance P
4. Know the classes of pharmacotherapy for PD and the timeline for their use
5. Know individual drugs used for treating PD:
    a. Precursor and peripheral degradation inhibitors (Sinemet®)
        i. Mechanism
        ii. Clinical use
        iii. Side effects (i.e. dystonia, behavioral and fluctuations)
    b. Dopaminer Receptor Agonists: Bromocriptine (Parlodel®), Ropinirole (Requip®) and Pramipexole (Mirapex®)
        i. Mechanism, Clinical Use (Example: For rx of On-Off syndrome)
        ii. Pharmacokinetics: Bromocriptine
        iii. Side effects: Ropinerole vs. Bromocriptine vs Pramipexole

    c. DA releaser (Amantatine): Mechanism of action
    d. Degradation inhibitors (MAO-B and COMT): Mechanisms and clinical uses
    e. Anticholinergics (Benztropine)
        i. Mechanism
        ii. Side effects

6. Know nature/mechanism of alternative treatments for PD (deep brain stimulation etc) as well as those in development.

Generic Name	Trade Name	Half Life	Mechanism of Action	Elimination	Benefit
Levodopa	Dopar	1-3 hrs	Dopamine Precursor	Decarbox.	Replenishes DA
Carbidopa	Lodosyn		Inhibits DOPA Decarbox.		Inhibits DA degradation
Levo./Carbi.	Sinemet	1-3 hrs	Combination	Decarbox.	Increases DA in brain
Bromocriptine	Parlodel	3 hrs	D1/D2 receptor agonist	Phase I/II	Alternative to Sinemet
Pramipexole	Mirapex	8 hrs	D3 receptor agonist	Unchanged-Urine	Reduces On/Off
Ropinirole	Requip	6 hrs	D2 receptor agonist	CYP450-1A2	Reduces On/Off
Selegiline	Eldepryl	1-3 hrs	MAO-B inhibitor		Early/Late treatment
Talcapone	Tasmar	2-3 hrs	COMT inhibitor	Glucuronidation	Prolongs L-DOPA
Amantadine	Symmetrel	2-4 hrs	DA releaser	Unchanged-Urine	Early treatment
Entacapone	Comatan		COMT inhibitor		Reduces off time
Rasagiline	Azilect		MAO-B inhibit		Reduces off time

KEY CONCEPTS & LEARNING OBJECTIVES (Treatment of Dementia)

1. Know what are the laboratory and clinical tests for ruling out reversible forms of dementia in the elderly.

2. Know the basic drug treatments for the reversible forms of dementia?

3. Know the current symptomatic and theoretical preventive drug therapies for Alzheimer's disease.

4. Know what are the theoretical drug therapies for Huntington's disease and ALS.

5. Know what are the preventive and symptomatic drug treatments for cerebrovascular disease.

DRUG LIST

Generic Name	Trade Name	Half-life	Mechanism of Action	Elimination	Benefit	Side Effects
tacrine	Cognex®	> 300 h.	Acetylcholinesterase Inhibitor	CYP450- IA2 Glucuronidation	Increase AcH	Liver tox.
donepezil	Aricept®	70 h.	Acetylcholinesterase Inhibitor	CYP450- 2D6, 3A4 Glucuronidation	Increase AcH	Diarrhea GI
rivastigmine	Exelon®	1.5 h.	Acetylcholinesterase Inhibitor	Rapid cholinesterase mediated	Increase AcH	Nausea Vomiting GI

cevimeline (AF102B)	Evoxac®	5 h.	Muscarinic Agonist	CYP450- 2D6, 3A3144	Off label use for AD	
fluoxetine	Prozac®	1-3 days	Serotonin reuptake blocker	CYP 450 - 2D6	Depression +/- memory	GI insomnia
indomethacin	Indocin®	5 h.	Prostaglandin synthesis	Primarily renal excretion, unchanged	anti-inflammatory	GI Ulcers
ibuprofen	Motrin®	2 h.	Related to PGE inhibition	Primarily renal excretion, unchanged	anti-inflammatory	GI Ulcers
celocoxib	Celebrex®	11 h.	Cyclooxygenase 2 Inhibitor	CYP 450- 2C9	anti-inflammatory	GI Ulcers, less than NSAIDs
vitamin E Tetrabenzine	Unique E®	very long	Co - factor	very slow, days to weeks Fat soluble	anti-oxidant For abnormal movements in Huntingtons	Hyper-vitaminosis Less side effects than Reserpine

Generic Name	Trade Name	Half-life	Mechanism of Action	Elimination	Benefit	Side Effects
haloperidol	Haldol®	3 weeks	D2 receptor blockage	NA	Decrease agitation	Tardive dyskinesia
creatine (OTC)	Cardiotropin ®	NA	precursor mitochondrial substrates	NA	ATP	none
riluzole	Rilutek®	12 h.	glutamate release Na channels	CYP450 - 1A2	neuronal toxicity	liver tox
Clofibrate	Atromid®	22 h.	liver release LDL's	renal	CV disease	nausea
captopril	Capoten®	2 h.	ACE I inhibitor	renal	HTN	allergic rxn
warfarin	Coumadin®	2 - 5 days	mult. clotting factors	CYP450 multiple isoforms	strokes	bleeding
heparin		10 - 20 min.	Anti-coagulant	liver metabolism	strokes	blood thinner
atorvastatin	Lipitor®	14 h.	HMG - CoA reductase inhibitor	CYP450 - 3A4	CHL AD	liver tox muscle weakness
Thiamine (OTC)		short water soluble	co-enzyme pyruvate metabol.	renal	protects cells from oxidative damage	?
vitamin B_{12}	Mega B®	short water soluble	enzyme co-factor for folate system	renal	blocks demyelination in spinal cord	
levothyroxine	Synthroid®	6 - 7 days	substitutes for endogenous T_4	glucuronidation into bile	treat hypo thyroidism	Hyper -thyroidism
memantine	Ebixa ® Axura®		NMDA antagonist			

THERAPEUTICS OF HIV INFECTION

Date: Monday, February 19, 2013: 10:00AM-12:00PM
Reading assignment:

Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents. Department of Health and Human Services. Updated as a Living Document on March 27, 2012. Available from the AIDSinfo website. Extensive information concerning treatment options with numerous summary tables.

http://aidsinfo.nih.gov/guidelines/

KEY CONCEPTS AND LEARNING OBJECTIVES

1. Understand how distinct antiretroviral agent classes target different phases of the HIV replication cycle.

2. Be able to recognize the diagnostic criteria and therapeutic goals for the treatment of HIV infection.

3. For each of the major classes of antiretroviral medications used in the treatment of HIV infection, you should be able to describe:

a) Mechanism of action
b) Indications and clinical use
c) Onset and duration of action
d) Major adverse effects
e) Contraindications
f) Significant drug interactions (if any)

4. To understand the utility of combination therapy in the treatment of HIV infection, and that co-morbid conditions may require a modified regimen.

5. Be able to recommend an appropriate antiretroviral regimen for a newly diagnosed patient.

Drugs to be covered in this lecture:

1. NUCLEOSIDE/NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS

Abacavir
Didanosine
Emtracitabine
Lamivudine
Stavudine
Tenofovir
Zidovudine

2. NON-NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS

Delavirdine
Efavirenz
Etravirine
Nevirapine
Rilpivirine

3. PROTEASE INHIBITORS

Fosamprenavir
Atazanavir
Darunavir
Indinavir
Lopinavir
Nelfinavir
Ritonavir
Saquinavir
Tipranavir

4. VIRAL INTEGRASE INHIBITORS

Raltegravir
Elvitegravir (new drug)

5. FUSION INHIBITORS

Enfuvirtide

6. CCR5 ANTAGONISTS

Mariviroc

Therapeutics of HIV infection

I. HIV introduction

A. HIV is a retrovirus that infects and kills a subset of immune cells leading to reduced immune function
    1. HIV is managed as a chronic disease with antiretrovirals and therapy of opportunistic infections.
    2. **ARV** (**A**nti**R**etro**v**iral therapy) doesn't cure or eliminate HIV infection.
    3. HIV targets CD4+ or T-helper lymphocytes, destroying the cells.
    4. CD4+ depletion leads to severe immuno-deficiency.
    5. CD4+ counts below 500 cells/mm^3 associated with opportunistic infections.
    6. periodic CD4 counts of infected patients are performed to assess:
        i. immunologic status
        ii. risk of opportunistic infections
        iii. need for ARV
        iv. response to ARV

B. Goal of anti-retroviral therapy-reduce viral load and maintain immune function
    1. maximal and durable suppression of viral load to reduce the risk of disease progression
    2. restoration and/or preservation of immunologic function
    3. improvement in quality of life
    4. reduction in HIV-related morbidity and mortality
    5. prevent vertical transmission of HIV

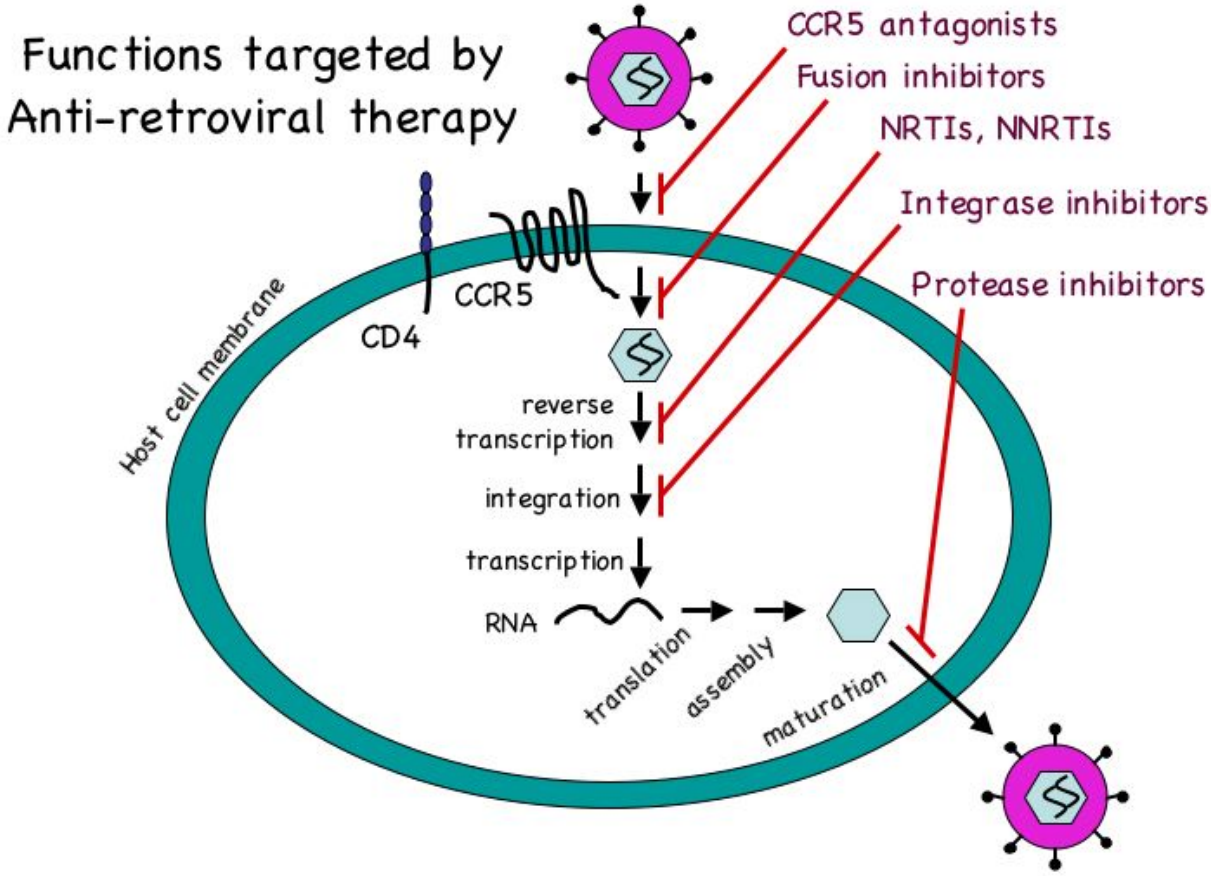
C. laboratory parameters for HIV
    1. virologic suppression can be defined as a sustained reductiojn in HIV RNA level below the assay limit of detection (<50 copies/ml)
    2. viral load assessment predicts:
        i. course of disease
        ii. need for ARV
        iii. which ARV to utlize
        iv. clinical response to ARV
    3. genotypic resistance testing to determine the resistance mechanism, perform before initiating ARV and after regimen failure

D. When to begin ARV
    1. The decision to begin ARV is based on an assessment of disease progression risk.
    2. Indicators for initiation of ARV include:
        i. a history of AIDS-defining illness
        ii. CD4 count <500 cells/mm^3
        iii. Pregnancy
        iv. HIV-associated neuropathy
        v. HBV co-infection when HBV treatment is indicated
    3. Check for latest ARV guideline updates on **AIDSinfo.nih.gov.**

E**.** HIV-2 infection

1. Endemic to west Africa, should be considered in that population or if patient has contact with that population
2. Generally shows longer asymptomatic stage, lower viral loads and mortality
3. Multispot HIV-1/HIV-2 Rapid test is approved for differentiating HIV-1 from HIV-2, but most serology and viral load tests are unreliable for HIV-2
4. HIV-2 should be considered in patients when serology and/or viral load are negative but CD4 and clinical conditions suggest HIV infection
5. NNRTI **not** effective against HIV-2. Use clinical improvement and CD4 count improvement to assess response to treatment.

II. FDA approved drugs available for treatment of HIV infection- 6 major drug classes



A. Nucleoside/nucleotide reverse transcriptase inhibitors (NRTI)

1. **General mechanism of action**-nucleoside or nucleotide analogs that lack 3' hydroxyl group enter the cells, are phosphorylated and form sythetic substrates for viral RT. NRTI compete with native nucleotides, and terminate proviral DNA when incorporated
2. **Onset and duration**- NRTIs generally eliminated from plasma by renal excretion with half-lifes of 1-10 hours, intracellular reservoirs more persistent. One or two doses daily except zalcitabine (every 8h). Only didanosine has food restrictions.

3. **Relative effectiveness at reducing viral load-** Modestly effective as monotherapy (not recommended), valuable when used in combination therapy. Resistance develops slowly compared to NNRTIs or PIs.
4. **Major adverse effects-** Some in this class capable of inhibiting mitochondrial DNA polymerase, toxicities include anemia, myopathy, and pancreatitis and are associated with serious **lactic acidosis-hepatic steatosis syndrome.** (**didanosine > stavudine > zidovudine**)

5. **Class members currently in use:**
   a. **Abacavir**
      i. **Indication**: activity against HIV-1
      ii. **Adverse effect**: associated with serious hypersensitivity reaction in patients with HLA-B 5701 genotype
      iii. **Contraindicated**: in patients with HLA-B 5701 genotype***
   b. **Zidovudine (AZT)**
      i. **Indications:** activity against HIV-1 and HIV-2, used as exposure prophylaxis, OK for children or adults and in pregnancy
      ii. **Major adverse effects:** anemia and neutropenia
      iii. **Contraindications:** do not co-administer with stavudine (antagonist)
      iv. **Significant drug interactions:** cotrimoxazole or ganciclovir (bone marrow toxicity), ribavirin (antagonist)

B. *Nonnucleotide reverse transcriptase inhibitors (NNRTI)*

1. **General mechanism of action-** noncompetitive inhibitors that bind to reverse transcriptase and induce a corformational change that greatly reduces enzyme activity
2. **Onset and duration-** rapidly absorbed and metabolized by hepatic CYPs, half-lives range from delavirdine (2-11h) to efavirenz (40-50h)
3. **relative effectiveness at reducing viral load-** Activity against HIV-1 but not HIV-2. Resistance can develop rapidly, never use a monotherapy. One **advantage** of NNRTI-based regimen is that PIs can be reserved for later and thus avoid PI adverse effects. The **disadvantages** are the prevalence of resistant virus, low genetic barrier to resistance.
4. **Major adverse effects/drug interactions:** all influence CYP activity, so drug interactions common.

Cytochrome P450 system and HIV drug metabolism

- the P450 cytochromes influence drug metabolism by oxidizing or reducing substrate drugs
- P450 substrate drug metabolism is dependent on one or more P450 enzymes (e.g. CYP3A4)
- a P450 inhibitor is a drug that inhibits the metabolism of a P450 substrate
- a P450 inducer, stimulates increased expression of P450 enzymes

5. **FDA-approved class members currently in use:**
   a. **Efavirenz**
      i. **Indications:** preferred as part of initial antiretroviral therapy, the only once daily dose NNRTI
      ii. **Major adverse effects:** birth defects, transient CNS effects
      iii. **Contraindications:** 1st trimester pregnancy or women planning to conceive***
      iv. **Significant drug interactions:** CYP3A4 inducer, so reduces concentration of PIs, methadone
   b. **Nevirapine**
      i. **Indications:** recommended as an alternative to Efavirenz in treatment naïve women with pretreatment CD4<250 cells/mm and men with CD4<400 cells/mm
      ii. **Major adverse effects:** severe hepatotoxicity
      iii. **Contraindications:** women with pretreatment CD4 >250 cells/mm^3 and men with pretreatment CD4 >400 cells/mm^3 ***
      iv. **Significant drug interactions:** CYP inducer, reduces concentration of methadone, PIs

C. Protease inhibitors (PI)

1. **General mechanism of action-** specifically and reversibly inhibit the HIV aspartyl protease and thereby block post-translational processing of viral proteins required to produce a mature viral particle
2. **Onset and duration-** Most PIs have poor bioavailability, absorption of some enhanced by high fat meals, all metabolized by hepatic CYP system
3. **Relative effectiveness at reducing viral load:** highly effective as part of combination therapy
4. **Major adverse effects:** associated with metabolic syndrome, lipodystrophy, lipoatrophy of face and limbs, lipemia, nausea, vomiting, diarrhea and paresthesias. All are substrates and inhibitors of CYPs.
5. **Ritonavir (RTV) "boosting" of PIs*****
   a. ritonavir is a PI that is a potent CYP3A4 inhibitor
   b. co-administration of low dose ritonavir enhances or "boosts" exposure of other PIs

c. RTV boosting allows for reduced dose and dosing frequency
d. low dose RTV improves tolerance and is effective at CYP3A4 inhibition

6. Class members currently in use:

a. Ritonavir

i. **Indications:** active against HIV-1 and 2, **potent CYP3A4 inhibitor** that is used to boost availability of drugs that are CYP3A4 substrates and to reduce dose and dosing frequency

ii. **Major adverse effects:** not well tolerated at doses required for antiviral activity, but low doses used for boosting are well tolerated, paresthesias

iii. Contraindications/significant drug interactions: similar to other PIs

PI-induced metabolic syndrome

Definition: a cluster of metabolic risk factors that tend to occur together that increases chances of developing heart disease, stroke, and/or diabetes and are associated with PI therapy

-hyperlipidemia, hypertriglyceridemia, decreased HDL and increased LDL

-insulin resistance, hyperinsulinemia

-lipodystrophy, central obesity, facial and limb lipoatrophy

-increased macrophage CD36 leading to increased cholesterol uptake, atherosclerosis

ARV and management of dyslipidemia/statin usage

- prior to treating cholesterolemia in HIV-infected patients undergoing ARV, consider statin metabolism
- should avoid combining CYP3A4 substrate statins with boosted PIs
- switching from PIs to NRTIs may alleviate lipodystrophy, hyperlipidemia

Statins as CYP3A4 substrates

Yes	No
simvastatin	pravastatin
atorvastatin	fluvastatin
lovastatin	

D. ***Viral integrase inhibitors***- **Raltegravir**

1. **Mechanism of action:** blocks insertion of reverse-transcribed viral DNA into the host DNA
2. **Indications:** in combination therapy for experienced patients with suppression failure or excess toxicity
3. **Onset and duration:** twice daily dose following high fat meal
4. **Relative effectiveness at reducing viral load:** effective when combined with PI and NRTI
5. **Major adverse effects:** diarrhea, headache, and nausea
6. **Contraindications:** not for use as monotherapy
7. **NEW DRUG: Elvitegravir** introduced this year, but only as a pre-packaged combo drug including Tenofovir, Emtricitabine, and Cobicistat (CYP3A4 inhibitor).

E. ***Fusion inhibitors***- **Enfuvirtide**

1. **General mechanism of action:** peptide inhibitor that binds HIV surface glycoprotein gp41 to block conformation required for membrane fusion with host cell
2. **Indications:** combination therapy component in experienced patients with viral suppression failure. **Injected** twice daily
3. **Relative effectiveness at reducing viral load:** not active against HIV-2, mutation of the HR1 region of gp41 associated with resistance
4. **Major adverse effects:** Injection site reaction/inflammation is very common, hypersensitivity
5. **Contraindications:** do not use in patients with known hypersensitivity

F. ***CCR5 antagonists***- **Maraviroc**

1. **General mechanism of action:** small molecule slowly-reversible antagonist of the CCR5 interaction with gp120, blocks CCR5-tropic HIV-1 entry

2. **Indications:** combination therapy component for experienced patients with viral suppression failure, should perform **tropism test** first
3. **Resistance mechanisms:** mutation of the CCR5-binding amino acid sequence in HIV gp120, or emergence of CXCR4-tropic virus
4. **Major adverse effects:** hepatotoxicity and possible hypersensitivity
5. **Contraindications:** liver dysfunction
6. **Significant drug interactions:** CYP substrate, concentration altered by CYP inducers and inhibitors

III. Combination therapy for HIV infection

A. Complicating conditions and considerations:

1. comorbid conditions such as cardiovascular disease, chemical dependency, **tuburculosis**, renal, liver, or psychiatric disease
2. potential adverse drug effects
3. potential drug interactions with other medications
4. pregnancy
5. results of drug resistance testing
6. HLA-B5701 testing if considering Abacavir
7. gender and pretreatment CD4 count if considering Nevirapine
8. likelihood of patient adherence with the regimen

B. Combination ARV options for treatment-naïve patients-recommended starting regimen consists of either **1 NNRTI + 2 NRTI**, or **1 PI (preferably boosted with ritonovir) + 2 NRTI.*****

NNRTI options:

Recommended	Efavirenz	**Do not use** in 1st trimester of pregnancy or patients with high pregnancy potential
Alternate	Nevirapine	**Do not use** in patients with moderate to severe hepatic impairment, or in women with pre-ART CD4>250 mm^3 or men with pre-ART CD4>400 mm^3

PI options:

preferred	Atazanavir + ritonavir	Do not use in patients who require high dose proton pump inhibitors
preferred	Darunavir + ritonavir	
preferred	Fosamprenavir + Ritonavir (twice daily)	
preferred	Lopinavir + ritonavir	Do not use in pregnant women
alternative	Unboosted atazanavir	Do not use in combination with tenofovir or didanosine/lamivudine
alternative	Fosamprenavir + RTV (once daily) or unboosted	
alternative	Saquinavir + ritonavir	

Dual-NRTI options

preferred	Tenofovir + emtricitabine	Do not use with unboosted atazanavir. Use with caution with nevirapine or in patients with underlying renal insufficiency
alternative	Abacavir + lamivudine	Do not use when positive for HLA-B 5701. Caution: HIV RNA>100,000 copies/ml or in high risk of cardiovascular disease.
	Didanosine + lamivudine (or emtricitabine)	Do not use with unboosted atazanavir or in patients with history of pancreatitis or peripheral neuropathy.
	Zidovudine + lamivudine	Use with caution in presence of pretreatment anemia and/or neutropenia

C. Changing drug regimen due to treatment failure (virologic or immune)
    1. **Definition of virologic suppression failure:** the inability to achieve or maintain suppression of viral replication to levels below the limit of detection (<50 copies/mL) and may manifest as:
        a. incomplete virologic response to therapy, or
        b. virologic rebound (after virologic suppression, repeated detection of HIV RNA above the assay limit of detection)
    2. **Definition of immune failure:** the inability to achieve and maintain adequate CD4 T-cell response despite virologic suppression

D. Tuberculosis treatment for HIV-infected patients
    1. Rifampin-based antimycobacterials are highly effective in treating MTB infection. Rifamycin is a potent inducer of CYP activity, and markedly effects exposure to multiple ARV drugs.
    2. Rifampin dramatically reduces exposure to all PIs and multiple NNRTIs and should not be coadministered (except efavirenz).***
    3. Rifabutin is preferred drug for HIV patients with active MTB, but still interacts with PIs and requires caution.
    4. Bottom line is that coadministration of rifabutin and ARV will require monitoring and dose adjustment.

F. What **NOT** to use

Regimens	**rationale**	**exception**
Monotherapy with NRTI	1. Rapid resistance development. 2. Inferior antiretroviral activity	none
Dual NRTI regimens	1. Rapid resistance development. 2. Inferior antiretroviral activity	none
Triple NRTI regimens	High rate ofnonresponse in treatment-naïve patients	Abacavir/zidovudine/ Lamivudine or tenofovir/ Zidovudine/lamivudine in patients for whom other options are worse.

What **NOT** to use (continued)

Components	rationale	exception
Atazanavir + indinavir	Potential hyperbilirubinemia	none
Didanosine + stavudine	High incidence of toxicity, potential serious lactic acidosis	When other options not available
Double NNRTI combo.	EFV + NVP has more adverse effects than separate, both reduce ETV	none
EFV in 1st trimester	teratogenic	When other options not available
Emtricitabine + lamivudine	Similar resistance profile	none
Etravirine + unboosted PI	Induced PI metabolism	none
Etravirine + boosted ATV, FPV, or TPV	Induced PI metabolism	none
Nevirapine in naïve women with CD4>250, men CD4>400	High incidence hepatotoxicity	When other options not available
Stavudine and zidovudine	antagonistic	none
Unboosted darunavir, saquinavir, or tipranavir	Inadequate bioavailability	none

Example of a test question:

A 29 year-old male was previously diagnosed with M. tuberculosis infection and rifampin treatment was initiated. In a follow up exam, lab results reveal the patient to be infected with HIV, and lab results are as follows: CD4+ count = 460 cells/mm^3
viral load = 41,000 copies/ml
resistance testing = HIV1
Which of the following treatment regimens would be a recommended option, if any?

A. efavirenz, tenofovir, and emtricitabine
B. Nevirapine, tenofovir, and emtricitabine
C. Atazanavir, abacavir, and lamivudine
D. Didanosine, abacavir, and lamivudine
E. None of the above

Summary tables:

NRTI summary table

Agent	Preferred for naïve patients	Adverse effects	Contra-indications	Drug interactions
Abacavir		hypersensitivity	HLA-B 5701+	
Didanosine		peripheral neuropathy	Stavudine, zalcitabine	tenofovir
Emtracitabine	yes	HBV flare	lamivudine resistance	
Lamivudine		HBV flare	emtracitabine resistance	zalcitabine
Stavudine		lactic acidosis, lipid metabolism	Zidovudine res., ddI co-admin.	zidovudine
Tenofovir	yes	HBV flare, renal toxicity	ddI/EFV Co-admin.	↑didanosine, ↓atazanavir
Zidovudine		anemia and neutorpenia	coadministering stavudine	Cotrimoxazole or ganciclovir, ribavirin

Examples of drugs that should NOT be coadministered PIs due to CYP-dependent metabolism

Drug	CYP3A4 role	Class
Quinidine	substrate	antiarrhythmic
Ergotamine	substrate	Ergot derivative
Rifampin	strong inducer	antimycobacterial
Midazolam	substrate	benzodiazepine
Phenobarbitol	strong inducer	barbiturate
Warfarin	substrate	anticoagulant
St. John's Wart	strong inducer	herbal

NNRTI summary table

Agent	Preferred for naïve patients	Adverse effects	Contra-indications	Drug interactions
Delavirdine		Rash	Naïve patients	PIs, phenytoin, phenobarbitol, carbamazepine
Efavirenz	Yes	Birth defects, transient CNS	1st trimester pregnancy	PIs, methadone
Etravirine		Rash	coadministering with other NNRTIs or some PIs	PIs, other CYP substrates
Nevirapine		Severe hepatotoxicty	female CD4>250 male CD4>400	Methadone, some PIs
Rilpivirine		?	?	PIs

PI summary table

Agent	Preferred for naïve patients	Adverse effects	Contra-indications	Drug interactions
atazanavir	yes	bilirubinemia	Hepatic insuff.	See list
fosamprenavir	yes	rash	Sulfa allergy	" (and glucuronidation inh)
indinavir		Kidney stones, bilurubinemia, IR	Rifampin co-administration	"
lopinavir	yes	Lipemia, GI, lipodystrophy	Rifampin co-administration	"
nelfinavir		diarrhea	"	"
ritonavir		paresthesias	"	"
saquinavir		lipodystrophy rash, anemia	Co-administration with rifampins, efavirenz, nevirapine	"
darunavir	yes	rash	Sulfa allergy	"
tipranavir		Hepatitis, ↑lipids,glucose	Sulfa allergy	"

OVERVIEW OF PEDIATRIC PSYCHOPHARMACOLOGY

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- Clinical practice of pediatric psychopharmacology is challenging
  - Over the past 10 years, significant increase in the use of psychotropic medications in the pediatric population.
  - The largest increase was the use of
    - atypical antipsychotics (138.4%)
    - atypical antidepressants (42.8%)
- Treatment with psychotropic drugs managed
  - a large proportion of children receive these medications from primary care doctors and pediatric specialists

OBJECTIVES

- To be cognizant of the general pharmacological properties of psychotropic medication for the pediatric population
- To know the clinical indications/usage of psychotropic medications for childhood presentations of psychiatric disorders as recommended by the FDA
- To know the major warnings and precautions associated with psychotropic medications
- To appreciate the evidence based medicine treatment of pediatric psychiatric disorders

- For more detailed and up-to-date information on FDA regulations http://www.fda.gov/medwatch/index.html

MEDICATIONS FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

- **Stimulants**
- **Methylphenidate**
  - Ritalin, Ritalin LA/SA, Metadate CD/ER
  - Concerta
  - Daytrana
- **Dexmethylphenidate**
  - Focalin
- **Amphetamine Sulfate**
  - Dextroamphetamine (Dexedrine)
  - Mixed Amphetamine Salts (Adderall)
  - Vyanse
- **Selective Norepinephrine Reuptake Inhibitor**
  - Atomoxetine (Strattera)

NEUROBIOLOGY OF ADHD

Conceptualization of etiology

- **Underactivity** of the catecholamergic system mediated by **dysregulation** of the dopaminergic(DA) and noradrenergic(NE) CNS systems

NEUROBIOLOGY OF ADHD

- Dopamine neurotransmission
  - Pathways
    - Tuberoinfundibular
    - Nigrostriatal
    - Mesolimbic
    - **Mesocortical (executive functioning)**
  - Functions
    - Neurophysiologically dopamine **enhances** the signal for attention skills

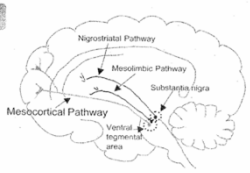
- Stimulants **block** (inhibition of the neurotransmitter reuptake pump)
  - 1-reuptake of norepinephrine (NE) and of
  - 2-dopamine (DA) in the presynaptic neurons which
  - 3-increase their concentrations (DA) in the intrasynaptic space.

- Atomoxetine (non-stimulant) increases norepinephrine in the synaptic cleft by inhibiting its presynaptic transporter(5).
  - Children who are CYP2D6 "slow metabolizers"
    - may experience atomoxetine's serum peak concentrations 5-fold greater than fast metabolizers (6).

Dopamine Neurotransmission Relative to ADHD

Dopamine

- Enhances signal
- Improves attention
  - Focus
  - On-task behavior
  - On-task cognition



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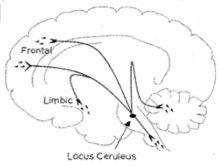
Solanto. *Stimulant Drugs and ADHD*. Oxford; 2001.

Norepinephrine Neurotransmission Relative to ADHD

Norepinephrine

- Dampens noise
- Executive operations
- Increases inhibition



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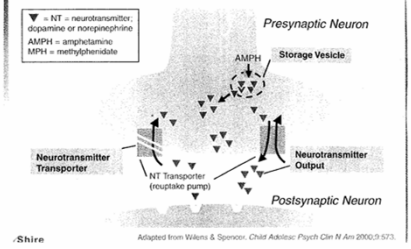
Solanto. *Stimulant Drugs and ADHD*. Oxford; 2001.

Stimulants' Proposed Mechanism of Action



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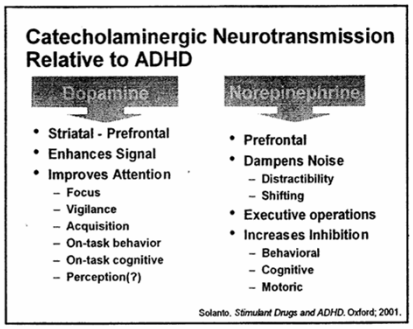
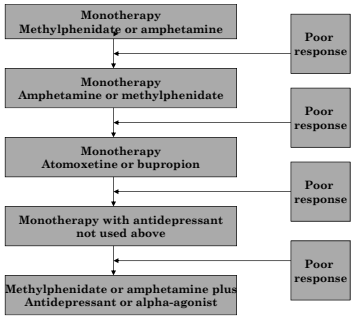
Adapted from Wilens & Spencer. *Child Adolesc Psych Clin N Am* 2000;9:573.



INDICATIONS AND USAGE

- Stimulants have FDA indications for the treatment of ADHD and narcolepsy (2).
- MPH and d-MPH are approved for use in patients at least 6 years old
- Amphetamines in children > 3 years old.
- Atomoxetine has FDA indication for the treatment of ADHD in individuals at least 6 years old (2).

ALGORITHM FOR THE MEDICATION TREATMENT OF ADHD ADAPTED FROM J AM ACAD CHILD ADOLESC PSYCHIATRY 41: 26S-49S, 2002



STIMULUS PRACTICAL CONSIDERATIONS

- Start with MPH or AMPH
- If one stimulant not effective, try the other one
- Short-acting easier to titrate, then may wish to switch to long acting
- Start with long acting if school dose a problem
- Titrate to optimum response
- Example starting dose
  - Methylphenidate 5mg ½ tab BID-TID

- Atomoxetine, a suggested second line treatment option for ADHD [4].
- Optimal effective dose of atomoxetine
  - 1.2-1.3 mg/kg/day, administered once daily.

MAJOR WARNINGS AND PRECAUTIONS

- The FDA issued a Black Box Warning reporting sudden death in children prescribed stimulants [2],
  - therefore stimulants should not be used in patients
    - with known structural cardiac abnormalities, cardiomyopathy, and serious heart rhythm abnormalities.
- Precaution:
  - Temporary slowing in growth has also been found in children medicated with stimulants [8].

EVIDENCE BASED (appreciate)

- MPH has strong evidence supporting its use as the first line treatment for ADHD.
- Multimodal Treatment Study of Children with Attention-Deficit/Hyperactivity Disorder (MTA)
  - 14-month multisite trial
  - of 4 different treatment strategies for 579 children, aged 7 to 9.9 years (9)
- MTA compared the following treatments:
  - (a) the fixed-dose of MPH titrated to the child's "best dose",
  - (b) intensive behavioral treatment,
  - (c) combined MPH and intensive behavioral treatment, and
  - (d) standard community care.
- **All four groups improved,**
- But children in the MPH and combination groups improved significantly more

EVIDENCE BASED (appreciate)

Only a few studies have examined the long-term safety of stimulant use in pediatric populations(12).

- **Several studies comparing the safety and efficacy of MPH and Adderall (15, 16, 17).**
  - **Adderall was reported to exhibit longer lasting therapeutic effects than MPH (15, 16), but more stomachaches and sad mood.**
  - **Swanson et al. (1998) (18) reported that MPH had a faster onset of clinical effect than Adderall (1.8 hours and 3 hours respectively).**
- **Stimulants are available in short (4 hours), intermediate (6-8 hours), and long-acting sustained-release (10-12 hours) formulations (3).**
  - **A short-acting medication may be added to a sustained-release medication in the late afternoon to maintain ADHD symptom control in the evening.**
  - **It is recommended that stimulants be given seven days per week (20), but patients with decreased appetite, irritability, or sleep problems may discontinue stimulants on weekends and holidays (21).**
- **Weight-based dosing guidelines are available, but effective maintenance dose of stimulants is guided by the clinical response and the side effects.**

Red Light, Green Light

- Red Light, Green Light
  - (Complex Rules)
- Simon Says
  - (Mental Flexibility and Self-Control)
- Row, Row, Row Your Boat
  - (Focus, Memory, Flexibility and Self-Control)

"Executive Function"

- Interactive games require high levels of executive function, test a child's ability to pay attention, remember rules and exhibit self-control — qualities that predict academic success.

- Rule of thumb with Pediatric Pharmacology
  - Go low (dosing), Go slow (titration/taper)

REFERENCES ARE LISTED IN BOOK CHAPTER

- Overview of Pediatric Psychopharmacology. Sigita Plioplys, M.D., Jennifer Kurth, D.O. and Mary Lou Gutierrez, M.D. Anna Ivanenko, M.D., Ph.D., editor: Sleep and Psychiatric Disorders in Children and Adolescents, Informa Healthcare; 1 edition, May 19, 2008.

- Slides contributed with direct consent from Shire, U.S.