PHARMACOLOGY/THERAPEUTICS II BLOCK II HANDOUTS – 2016-17

59. ON-LINE LEARNING: Anti-Depressants – Schilling

60. ON-LINE LEARNING: Bipolar Medications – Schilling

61. & 62 ON-LINE LEARNING: Sedative-Hypnotics – Part I & II – Battaglia

63. Drugs of Abuse, tolerance and dependence - Bakowska

64. ON-LINE LEARNING: AntiPsychotics – Schilling

65. ACTIVE LEARNING SESSION: Psycho-Pharm – Schilling (Lumen Only)

66. Drugs to Treat Rheumatoid Arthritis & Gout - Clipstone

ANTIDEPRESSANTS

1. Know, for the following classes of Antidepressant medications:
   - Monoamine Oxidase Inhibitors (MAO-I's)
   - Tricyclic Antidepressants (TCA's)
   - Selective Serotonin Reuptake Inhibitors (SSRI's)
   - Serotonin-Noradrenergic Reuptake Inhibitor (SNRI's)
   - Atypical Antidepressants
     - Noradrenergic and Serotonergic alpha2 Adrenergic Receptor Blocker
     - Norepinephrine Dopamine Reuptake Inhibitor (NDRI's)
     - Serotonin/Norepinephrine Reuptake Inhibitor & Serotonin 2S receptor antagonist
     - Serotonin re-uptake blockade & serotonin 1A receptor partial agonist

   A. The prototype medication(s) for each class;
   B. The mechanism of action (often the class name);
   C. Relevant pharmacodynamics (such as the common and serious adverse effects)
      Common adverse effects:
      ↑ 5HT activity → GI, CNS, Sexual dysfunction, risk of discontinuation syndrome
      ↑ NE activity → ↑ blood pressure, sweating
      ↑ histamine blocking → weight gain, sedation
      ↑ acetylcholine blocking → blurred vision, urinary hesitancy, dry mouth, constipation, risk of confusion
      Serious adverse effects:
      serotonin syndrome, mania, hyponatremia, activation of suicidal ideation; seizures; cardiac arrhythmia; hypertensive crisis
   D. Relevant pharmacokinetics
      Half- life of fluoxetine vs. other antidepressants, MAO-I's;
   E. Important potential drug-drug interactions,
      MAO-I's & sympathomimetic drugs; MAO-I's & other antidepressants, Fluoxetine and/or Paroxetine & TCA's
   F. Considerations for special patient populations (elderly, pregnant patients)
      Elderly & TCA's,

2. Explain the importance of reversible versus irreversible MAOI's in terms of potential serious side effects and dangerous drug-drug interactions
3. Explain the difference between tertiary and secondary TCA's regarding their blockade of serotonin and norepinephrine reuptake.
4. Explain what effects, side effects, therapeutic effects, and toxic effects take place as the concentration of plasma TCA increases.
5. Trace the development of antidepressants from MAOI's and TCA's to SSRI's, SNRI's and atypical antidepressants in terms of the changes in the drug's mechanism of action and the receptor blocking profiles.
6. Compare and contrast the side effects of SSRI's and SNRI's and explain the reason for the overlap and differences of side effects.

PHARMACOLOGY OF ANTIDEPRESSANTS

What are antidepressants used to treat?

Depression diagnosis treated with antidepressants

- Major depression or Persistent depressive disorder (Dysthymia)
  With: mixed features, melancholic features, catatonia, psychotic features, atypical features, peripartum onset, seasonal pattern
- Pre-Menstrual Dysphoric Disorder (PMDD)
- Substance Induced/Medication Induced Depressive Disorder
- Other specified Depressive disorders
- Unspecified Depressive disorders
- Schizoaffective disorder-depressive type
- Bipolar depression (incomplete agreement)

Meds not likely to be very helpful; Focus on treating underlying medical/substance issue

Some drug classes work better than others for the different disorders

Anxiety disorders: Panic disorder, Generalized Anxiety Disorder, Social Phobia
Trauma & Stressor Related disorders: Acute Stress Disorder, Post Traumatic Stress Disorder
Obsessive Compulsive Disorder
Eating disorders: Bulimia, Binge Eating Disorder

Diagnosis is made clinically

- No reliable biological/biochemical diagnostic tests for depression
- 40% show ↑ activity of the hypothalamic-pituitary-adrenal axis (↑ plasma cortisol)

A. Cause? Multiple Theories

Original Theory: Monoamine Hypothesis of Depression

Depression involves a **deficiency** in serotonin and/or norepinephrine neurotransmission.
The evidence in support of this hypothesis:

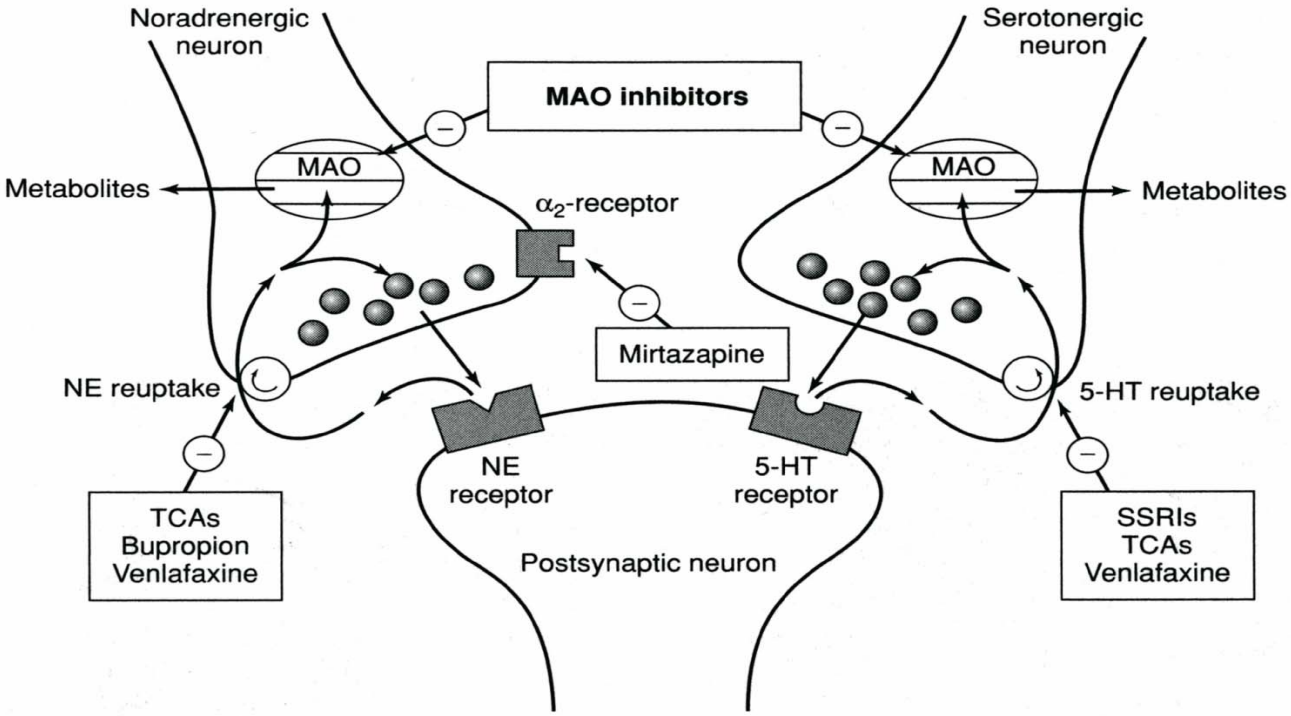
- reserpine depletion of monoamines or tryptophan deficient diets can invoke or precipitate depression
- drugs that increase serotonin or other monoamines alleviate depression
- all clinically effective antidepressant medications target and/or produce functional changes on **serotonin (5-HT) and/or norepinephrine (NE)**. Dopamine (DA) also may contribute to the effects of some antidepressants.

B. Antidepressant Treatment

- achieve plasma antidepressant drug concentrations that occupies respective therapeutic targets (e.g. monoamine transporters) to attain therapeutic efficacy
- requires repetitive drug administration over a prolonged period of time
- There is **no appreciable difference in efficacy** either between the different antidepressant classes, or among the various antidepressants within any class

C. Antidepressant Side Effects

May occur once medication treatment is started, but before the onset of antidepressant efficacy. The type of "side effects" will depend on the medication's specific pharmacological profile (what target receptors the medication interacts with at the dose (concentration) used in treatment)



(from B.G. Katzung and A.J. Trevor, Examination and Board Review Pharmacology, 7th ed. page 270)

ANTIDEPRESSANT DRUG CLASSES

MAOI's: **M**ono**a**mine **O**xidase **I**nhibitors
TCAs: **T**ri**c**yclic **A**ntidepressants
SSRI's: **S**elective **S**erotonin **R**euptake **I**nhibitors
SNRI's: **S**erotonin & **N**orepinephrine **R**euptake **i**nhibitors
Mixed Action Antidepressants
Noradrenergic & Serotonergic alpha2 adrenergic antagonist
Serotonin re-uptake blockade & serotonin 1A partial agonist
NDRI: **N**orepinephrine & **D**opamine **R**euptake **I**nhibitor
Serotonin/norepinephrine reuptake inhibitor & serotonin 2A antagonist

A. Monoamine Oxidase Inhibitors (MAO-Is)

Monoamine oxidase (MAO) is the principal metabolic enzyme of the catecholamines (dopamine, norepinephrine, epinephrine) serotonin (5-HT), and tyramine.
There are two types of monoamine oxidase: MAO-A & MAO-B
MAO-A: metabolizes serotonin (5-HT), norepinephrine (NE)
MAO-B: metabolizes trace amines (phenethylamine),
metabolizes serotonin (5-HT) only when 5HT is at high concentrations
Both MAO-A & MAO-B: metabolize dopamine (DA), & tyramine

Distribution MAO-A : MAO-B
Brain: 25% A : 75% B NE & DA neurons 50% A : 50% B 5HT neurons 0% A : 100% B
Liver: 50% A : 50% B
Intestine: 80% A : 20% B Peripheral adrenergic neurons: 90% A : 10% B

MAO-A must be inhibited for the antidepressant effect
The MAOI drugs **bind reversibly** (no chemical bond) **or irreversibly** (forms covalent bond) to the mitochondrial enzyme, MAO. Once an irreversible MAOI binds to MAO, the inactivated enzyme must be replaced by the cell. This synthesis takes the cell 10-14 days.

Inhibition of MAO (irreversibly or reversibly) ➔
↑NE & 5-HT that is available to be released when the neuron depolarizes ("fires")

Irreversible MAOIs

Phenelzine (Nardil®) - inhibits both MAO-A & MAO-B
Tranylcypromine (Parnate®) - inhibits both MAO-A & MAO-B
Isocarboxazid (Marplan®) - inhibits both MAO-A & MAO-B
Selegiline (l-deprenyl; Eldepryl®) – at low doses preferentially inhibits MAO-B; at high doses selegiline loses its selectivity and also inhibits MAO-A
Selegiline (Emsam®) transdermal patch, at the lowest dose (6 mg/24 hrs), does <u>not</u> require a modified diet like the other irreversible MAOIs do

Pharmacokinetics

- There is not a lot of information available on MAO-I pharmacokinetics
- Half-life is brief, 2-4 hours
- Details about metabolism not fully determined

Q: Why is there so little scientific info available on MAOI pharmacokinetics?

Side Effects of MAOI's

- GI-nausea, constipation
- Orthostasis/dizziness
- Sexual dysfunction
- Sleep disturbance-insomnia & day/night shifting-sleeping during the day, awake at night
- Sedation (from day/night shifting?)
- Weight gain

Prominent Adverse Effects: Hypertensive Crisis & Serotonin Syndrome
Drug-drug interactions (DDI) between MAO-I & dietary tyramine or between MAO-I & other drugs may result in Hypertensive crisis or Serotonin syndrome and are potentially lethal

- **Hypertensive Crisis**
  May be brought on by:
  - ingestion of foods containing high concentrations of **tyramine** (e.g., aged cheeses, liqueurs, cured meats)
    - Normally MAO A in the intestinal wall & liver metabolize tyramine
    - With MAO-I, unmetabolized tyramine enters bloodstream ➔ NE sympathetic neurons ➔ Displaces NE from synaptic vesicles ➔↑cytosolic NE (NE not metabolized by the MAO A in the neuron) ➔reversal of NE reuptake transporter ➔ ↑NE post synaptic receptor stimulation ➔↑BP ➔ possible hemorrhagic stroke

Normal person can digest 200-800 mg tyramine before any ↑in blood pressure
On MAOI, 6-10 mg tyramine ➔ mild reaction
10-25 mg tyramine ➔severe reaction

Q: How can the MAO-I Emsam® produce an anti-depressant effect but not require a modified diet?

- Treatment with the Emsam transdermal patch decreases this risk: At doses high enough to block MAO-A, transdermal Emsam hits the brain without a 1st pass through the liver. When it recirculates to the intestines then it is also doing a "1st pass" through the liver resulting in ↓drug levels and mostly only the intestine's MAO-B is inhibited

o DDI with drugs that boost adrenergic stimulation by a mechanism other than MAO inhibition
  - α_1-agonists: many decongestants/OTC "cold medications"
  - NE reuptake blockers: stimulants (amphetamines), cocaine, antidepressants-SNRI's, TCA's ; appetite suppressants-sibutramine (meridia); tramadol (ultram),

- **Serotonin Syndrome** mild severe*

Characterized by :
- o Neuromuscular hyperactivity – myoclonus, hyperactive reflexes, seizures*
- o Autonomic hyperactivity - unstable BP, fever, cardiovascular collapse*, permanent hyperthermic brain damage*
- o Altered Mental Status – disorientation, psychosis, coma*

May be brought on by:
- o DDI with medications that ↑serotonin by blocking the 5HT reuptake pump. When MAO-I inhibit MAO-A & MAO-B, there is a build-up in the amount of intracellular and extracellular 5HT, NE, & DA. This triple monoaminergic boost is believed to provide the robust antidepressant effect. Since the NE and 5HT reuptake pumps are working, NE & 5HT is still being reabsorbed into the 5HT or NE neurons. The amount of extracellular synaptic 5HT & NE which interacts with the post synaptic receptors is increased but not to dangerous levels.

  With an MAO-I blocking the monoamine oxidases, if a 2nd medication then blocks the 5HT reuptake pump, the amount of extracellular 5HT greatly increases. This much larger concentration of extracellular synaptic 5HT interacts with post-synaptic receptors and can result in serotonin syndrome.
- o Many antidepressants: SSRI's, SNRI's, TCA's
- o Opioids with 5HT reuptake inhibitory properties: meperidine (Demerol), tramadol (ultram), propoxyphene (Darvon), methadone
- o "ecstasy" (MDMA)-indirect 5HT agonist
- o Dextromethorphan-weak 5HT reuptake inhibitor

- o Treatment: stopping the medications; supportive care

Reversible MAOIs

Moclobemide-not available in the United States

- **R**eversible **i**nhibitor of **m**ono**a**mine oxidase (a "**RIMA")** is uncoupled from the enzyme. When discontinued, MAO activity completely recovers within 24-48 hours.

- If the RIMA is taken an hour before or two hours after eating foods with a high tyramine content there are no problematic interactions
- Although by using RIMAs one can avoid aversive dietary interactions, the patient is still vulnerable to negative drug-drug interactions.

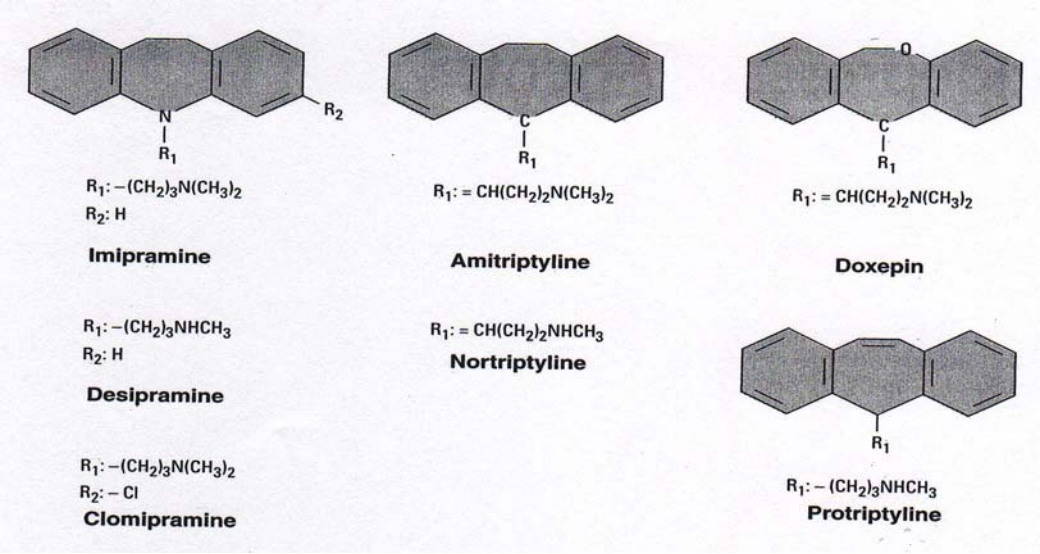
The **MAOIs** are at least as effective at treating depression as any other antidepressants.
Clinical situations MAOI's used:

- treatment resistant depression: ≥ 3 antidepressant trial failures
  - studies in 1960's resulted in MAOI's being 2nd line treatment to TCA's
  - After SSRI's and other antidepressants came out, MAOI's →3rd line
- treatment of depression with atypical or melancholic features
- treatment of dysthymia (persistent depressive disorder)

B. TRICYCLIC Antidepressants (TCAs)

The 1st generation antidepressants, are also referred as the "older antidepressants",
-structurally related to the phenothiazine antipsychotics
- tricyclic antidepressants can be either ***tertiary*** or ***secondary*** amines (see figure below)

(from Katzung 's Basic & Clinical Pharmacology . 10th ed. pp476)



Therapeutic Sites of Action

All TCAs block the re-uptake pumps of both 5-HT and NE thus preventing their re-uptake. However, different TCAs differ in the magnitude of the re-uptake blockade of these amines.

Tertiary TCAs (i.e. TCAs having 2 methyl groups on N)

Imipramine (Tofranil®) & Amitriptyline (Elavil®) - produces a comparable blockade of both 5-HT and NE reuptake.

Secondary TCAs (i.e. TCA having 1 methyl group on N)

Desipramine (Norpramin®) & Nortriptyline (Pamelor®) - preferentially blocks the reuptake of NE vs 5-HT

Others TCAs: as the secondary TCA's do, they preferentially block reuptake of NE vs 5-HT

- **Clomipramine (Anafranil®) & Doxepin (Sinequan®)**

Pharmacokinetics

- high lipid solubility
- high protein binding
- large volume of distribution (Vd)

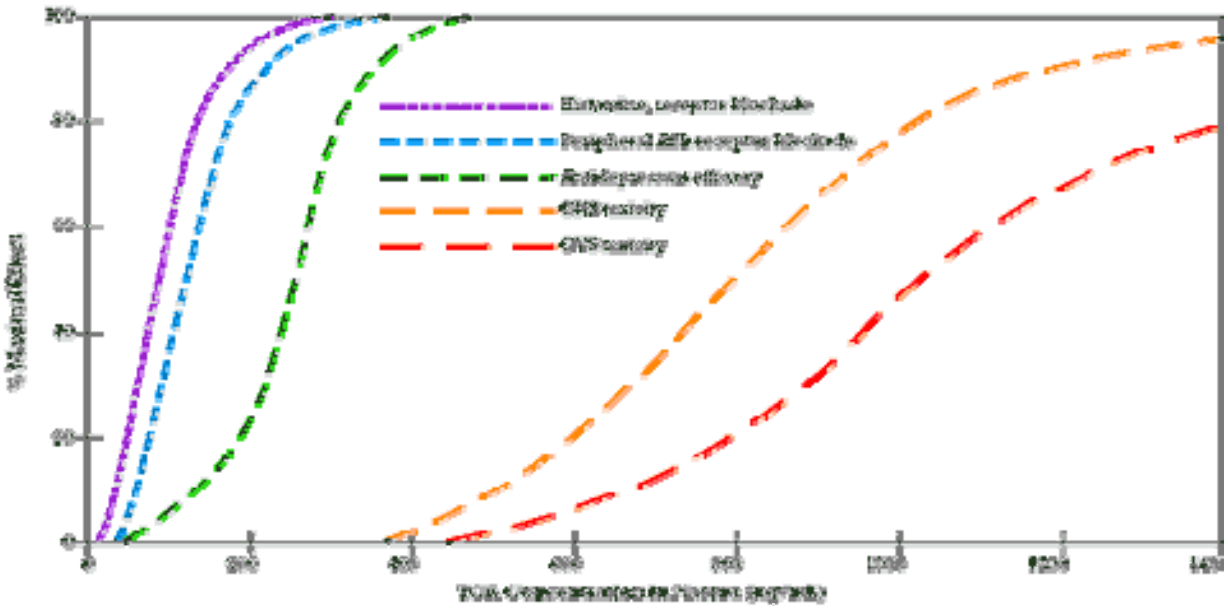
All psychotropic drugs are very lipophilic which allows them to pass across the blood brain barrier & reach site of action in the brain; the lipophilicity and (often) high protein binding result in a large Vd

- rapid absorption
- significant first pass metabolism
- serum concentrations peak within a few hours
- substrates of CYP2D6 (which exhibits genetic polymorphisms)
- half-life of 8-36 hours (active metabolites)
- Tertiary TCA's are metabolized (demethylated) into a Secondary TCA's
  - Imipramine is metabolized into Desipramine
  - Amitriptyline is metabolized into Nortriptyline
- Lab values

	Therapeutic range	Toxic
amitriptyline & nortriptyline	80-200 ng/mL	≥ 300 ng/mL
nortriptyline	70-170 ng/mL	≥ 300 ng/mL
imipramine & desipramine	175-300 ng/mL	≥ 300 ng/mL
desipramine	100-300 ng/mL	≥ 300 ng/mL

Prominent Side Effects of TCAs

Clinically effective doses of TCAs also may produce a variety of *"side effects"* via actions at one or more targets other than the monoamine transporters.



(Preskorn, J Clin Psychiatry. 1991;52(suppl 6):23-33)

Medications & their mechanism of actions that, together, have same effect as Amitriptyline (Elavil)

Drug sharing mechanism of action with Amitriptyline	Action	Consequences of the Action
Chlorpheniramine (Chlor-Trimeton)	Histamine-1 receptor blocker	Sedation, anti-pruritic effect
Cimetidine (Tagamet)	Histamine-2 receptor blocker	↓ production of gastric acid
Benztropine (Cogentin)	Acetylcholine (M-1 muscarinic) receptor blocker	Dry mouth, constipation, ↑ heart rate, memory impairment
Desipramine (Norpramin)	Norepinephrine uptake inhibition	Antidepressant effect, ↑ blood pressure, tremors, diaphoresis
Sertraline (Zoloft)	Serotonin reuptake inhibition	Antidepressant effect, nausea, loose stools, insomnia, sexual side effects
Nefazodone (Serzone)	5-HT2 receptor blocker	Antidepressant effect, ↑ REM sleep, anti-anxiety effect
Prazosin (Minipress)	NE-alpha-1 receptor blocker	Orthostatic hypotension, sedation
Yohimbine (Yocon)	NE-alpha-2 receptor blocker	Antidepressant effect, arousal, ↑ libido
Quinidine (Quinidine sulfate)	Direct membrane stabilizer	Na+ fast channels inhibition → Delayed repolarization → arrhythmias, seizures, delirium

The most prominent side effects of tricyclic antidepressants are produced by antagonist actions at three targets:

1) H-1 histamine receptors: excessive sedation, fatigue, weight gain
2) M-1 muscarinic receptors: confusion & memory dysfunction, excessive sedation, fatigue
3) NE alpha-1 receptors: postural (orthostatic) hypotension, excessive sedation

Clinical Considerations

- TCA's are not recommended for elderly patients (65+ years) because of their liability for inducing a toxic and confused state
- TCAs can produce additive CNS depression with other CNS depressants such as: alcohol, barbiturates, opiates and benzodiazepines.
- **TCA Overdose**-ingestion of as little as a 10-14 day prescription may be lethal
  TCA's inhibit Na+ fast channels at concentrations that are only 5 times higher than what is needed for the antidepressant effect. This Na+ fast channel inhibition is responsible for cardiotoxicity, cardiac conduction defects and severe arrhythmias. TCA overdose also leads to agitation, delirium, hyperpyrexia, respiratory depression, and circulatory collapse
  High lethality when taken in an overdose.

Antidepressant rational drug development

TCA's & MAOI's prominent side effects and safety issues led to the development of new antidepressants. The tertiary TCA's were used as blueprint for what antidepressants should do and should not do. This led to the development of:

(a) SSRIs: selective serotonin reuptake inhibitors
(b) SNRIs: selective serotonin and norepinephrine reuptake inhibitors
(c) mixed action drugs: targeting sites other than, or in addition to, the monoamine transporters

C. Selective Serotonin Reuptake Inhibitors (SSRIs)

- are structurally distinct from the TCAs and are not chemical "look-alikes" to each other
- fewer adverse effects than the tricyclic antidepressants (TCAs)
- produce preferential (selective) blockade of 5-HT uptake sites vs other transporters;

Are **"selective"** (but not exclusive) blockers of 5-HT transporters

SSRIs differ from each other in their:

- ***affinity*** to block 5-HT transporters
- ***selectivity*** for 5-HT transport blockade versus other transporters or receptors
- ***pharmacokinetics*** (the half-lives of the parent compound and active metabolites)

FDA Approved SSRIs

	Protein binding	$t_{1/2}$	Metabolite	Metabolite $t_{1/2}$	CYP450 inhibitor		Notes
					2D6	3A4	
Fluoxetine (Prozac®)	95%	1-4d	Norfluoxetine	7-15 days	++	+	SSRI prototype 1987 FDA approved least 5-HT selective
Paroxetine (Paxil®)	95%	21 hrs	Inactive	n/a	++		SSRI with highest affinity for 5-HT transporter Is a CYP2D6 substrate; slows own metabolism
Sertraline (Zoloft®)	98%	26 hrs	Desmethyl sertraline	3 days	+/-	+/-	better absorbed with food
Citalopram (Celexa®)	80%	35 hrs	Desmethyl citalopram	2 days	+/-		
Escitalopram (Lexapro®)	56%	27 hrs	Desmethyl citalopram	2 days	+/-		citalopram's S(+) isomer
Fluvoxamine (Luvox®)	80%	16 hrs	Inactive	n/a	+/-	+	SSRI most likely to have drug-drug interactions inhibits more CYP enzymes (1A2, 2C19, 2D6 & 3A4)

Q: Which SSRI's is most likely and which is least likely to cause a discontinuation syndrome (withdrawal) if abruptly stopped?

Side Effects of SSRIs: <u>often occur prior to the onset of antidepressant efficacy</u>

When looking at data on side effects, please consider that

a) a specific side effect may be dose dependent

b) the data will not indicate if side effect happened once, intermittently, or was persistent

c) how severe the side effect was

d) the drug's propensity to interact with sites other than the target site

In the case of SSRI's, virtually all of the adverse effects of one SSRI are also seen with the other SSRI's. These side effects are consistent with too much serotonin agonist effects due to the SSRI induced blockade of the serotonin reuptake pump. They include:

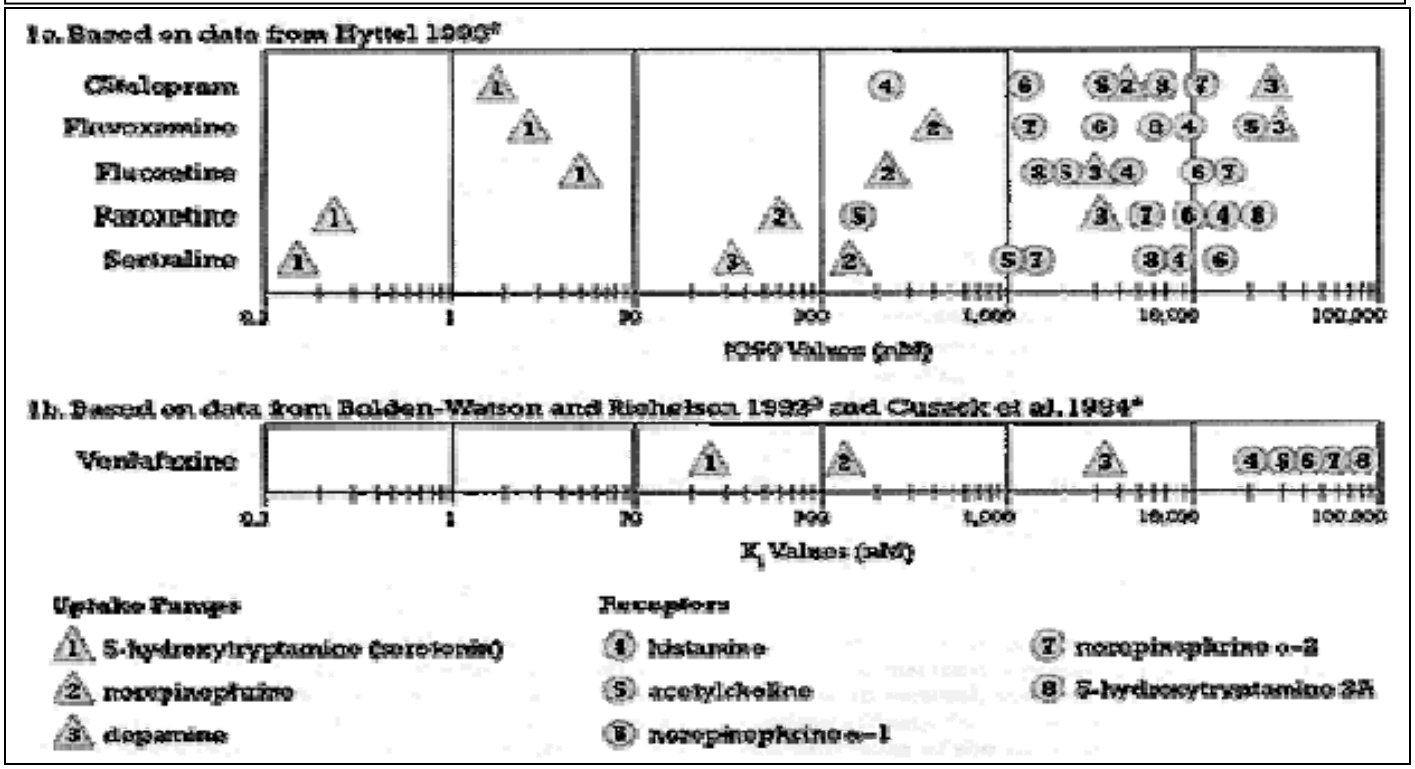
a) GI-↓ appetite, nausea, diarrhea, constipation, dry mouth
b) Anxiety during 1st week of use; (paroxetine in particular)
c) CNS-insomnia, sedation, headache, dizziness
d) Sexual dysfunction-loss of libido, impotence, anorgasmia
e) **SSRI Discontinuation Syndrome**

Not dangerous; if SSRI's stopped abruptly instead of tapered over time may cause dizziness, nausea, fatigue, headache, insomnia, restlessness, unstable gait and shock like sensations-brain zaps (uncommon).

More likely with short acting SSRIs

paroxetine > (effexor/pristiq) >> fluvoxamine > sertraline > citalopram >>> fluoxetine

Q: What is the likelihood a specific SSRI will interact with sites other than the 5-HT uptake sites?



(from Preskorn, J of Practical Psychiatry & Behavioral Health, May 2000, p 154)

For each drug, there is at least one order of magnitude separation between the binding affinities for the serotonin reuptake pump and the drug's affinity for its next most potent site of action.

D. The Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)

- vs. TCS's: Fewer side effects while like TCA's the SNRI's block both 5-HT/NE
- vs. SSRI's: Minimal CYP 450 effects

	Protein binding	$t_{1/2}$	Metabolite	Metabolite $t_{1/2}$	Notes
Venlafaxine (Effexor®)	27%	5 hrs	Desvenlafaxine	11 hrs	CYP2D6 substrate
Desvenlafaxine (Pristiq®)	30%	11 hrs	Inactive	n/a	is venlafaxine's metabolite so metabolism by Phase II only
Duloxetine (Cymbalta®)	90%	12 hrs	Inactive	n/a	CYP2D6 substrate

Duloxetine (Cymbalta®)

- more balanced blocker of 5-HT and NE reuptake than the other two
- also used to treat peripheral neuropathic pain associated with diabetic neuropathy

Side Effects of SNRI's

a) See SSRI side effects
b) Dose dependent increase in blood pressure
c) Diaphoresis
d) Discontinuation syndrome (especially venlafaxine & desmethylvenlafaxine)

E. Atypical Antidepressants

a) Noradrenergic & Serotonergic alpha2 adrenergic receptor blocker
b) Norepinephrine & Dopamine reuptake inhibition
c) Serotonin/norepinephrine reuptake inhibitor & serotonin2A receptor antagonist
d) Serotonin re- uptake blockade & serotonin1A receptors partial agonist

a) Noradrenergic & Serotonergic alpha2 adrenergic receptor blockers

Alpha2-adrenergic receptors

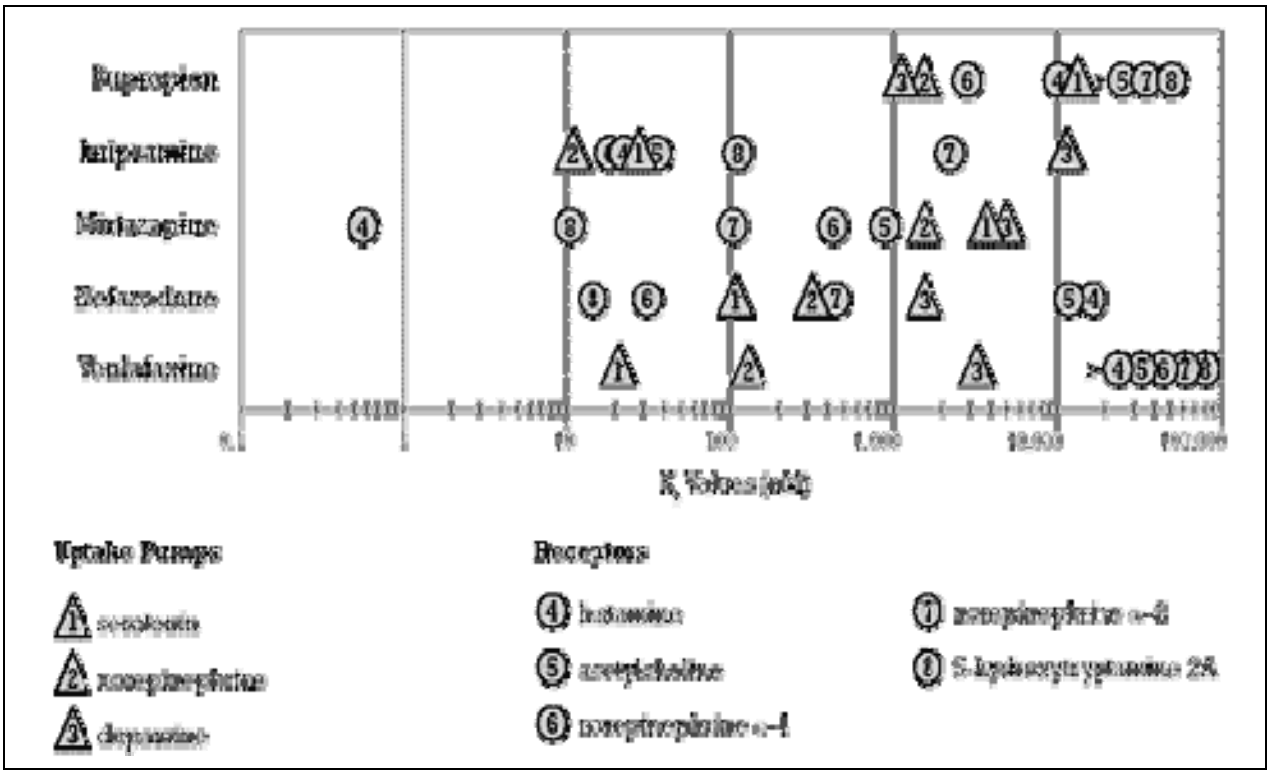
- are <u>inhibitory</u> autoreceptors on noradrenergic & serotonergic nerve terminals
  alpha2 adrenergic autoreceptors activation →
  ↓ release of norepinephrine from noradrenergic terminals and
  ↓ release of 5-HT from serotonergic terminals.

So, **alpha2-adrenergic receptor antagonist** drugs decrease the inhibitory effects and lead to ↑ release of norepinephrine & 5-HT from their respective nerve terminals.

Mirtazapine (Remeron®) is an **alpha2-adrenergic receptor antagonist**

Mechanism of Action

- blockade of both noradrenergic and serotonergic nerve terminal's presynaptic alpha2 receptors → ↑ NE and ↑ 5-HT neurotransmission.



(from Preskorn, Journal of Psychiatric Practice, July 2000, p 218)

Side Effect Profile

- also blocks postsynaptic 5-HT_{2A}, 5-HT_{2C}, 5-HT_3 & H1 histamine receptors which contributes to which side effects the drug does and does not have from the increased serotonin system activity
  - 5-HT_{1A} agonist-antidepressant & anti-anxiety effect
  - 5-HT_{2A} antagonism-sleep restoration, no sexual dysfunction (agonist activity at 5-HT_{2A} causes sexual dysfunction)
  - 5-HT_{2C} antagonism- weight gain
  - 5-HT_3 antagonism-GI side effects (agonist activity at 5-HT_3 causes GI side effects)

- While highly sedating at low doses and can help with insomnia, at higher doses is less sedating and may even be stimulating
- Can induce weight gain
- No sexual dysfunction or GI problems (nausea, vomiting, diarrhea)

Q: Why the decrease in the level of sedation with increased dose?

b) Norepinephrine & Dopamine reuptake inhibition

Bupropion (Wellbutrin®; Zyban®)

Bupropion is marketed under two trade names:

Wellbutrin® (as an antidepressant) &

Zyban® (reduces craving for nicotine- probably by acting as a noncompetitive antagonist of nicotinic acetylcholine receptors). It is available in a sustained release form and as well as the generic compound.

Mechanism of Action – dual inhibition of norepinephrine and dopamine reuptake mechanism of action is devoid of any clinically significant serotonergic effects.

Side Effects-in general has a relatively favorable side effect profile

- no serotonergic activity, so side effects differ from the other antidepressants also no anticholinergic or antihistaminergic effects
- will not cause weight gain (may cause minor weight loss!), will not cause sexual side effects, sedation or orthostatic hypotension
- can cause dry mouth, nausea, insomnia
- increased seizure risk: spontaneous seizure rate in general population is 0.1%
  At low/moderate doses of immediate release bupropion-seizure incidents is 0.4%
  At high doses, seizure incidents is 4%
- contraindicated in patients with eating disorders due to risk of appetite suppression and increased risk of seizures

c) Serotonin/norepinephrine reuptake inhibitor & serotonin2A receptor antagonist

Nefazodone (Serzone®)

Mechanism of Action - 5-HT_{2A} serotonin receptor antagonist & 5-HT reuptake inhibitor

Side Effect Profile

- other effects include nausea, dry mouth and increased appetite.
- **does not interfere with sexual function**,
- mildly sedating
  Nefazodone is chemically related to the antidepressant drug, trazodone (Desyrel®), which is highly sedating and currently is marketed primarily as a hypnotic drug.

***Serzone has been removed from the market due to potential liver toxicity, although the generic (nefazodone) is still available.

d) Serotonin re- uptake blockade & serotonin1A receptors partial agonist

Vilazodone (Viibryd®) -FDA approved for treating depression in January 2011

Mechanism of Action

- blockade of ***5-HT uptake*** & ***partial agonist at 5-HT_{1A}*** receptors
  (2 actions promoting 5-HT1A receptor desensitization)

Side Effect Profile

- GI-Diarrhea, Nausea, Vomiting
- Insomnia
- Does not produce weight gain
- Does not produce sexual dysfunction

Vortioxetine (Brintellix®) - FDA approved for treating depression in January 2013

Mechanism of Action- similar to Vilazodone with respect to:

- blockade of 5-HT uptake
  has 50 & 500-fold lower affinities at NE and DA uptake sites, respectively.
  - full agonist at 5-HT_{1A} receptors & 2-fold lower affinity partial agonist at 5-HT1B
  - relatively high affinity antagonist at 5-HT3 and 5-HT7 receptors (target of atypical antipsychotic drugs)

Side Effects

- GI: nausea > diarrhea/constipation/vomiting
- some sexual dysfunction at higher doses; no significant weight gain

Special Clinical Considerations with Antidepressant Medications

1. **Switching to/from other antidepressants and MAOIs**

From MAOIs (irreversible) to other antidepressant

- Inhibition of MAO may persist long after these drugs are discontinued. It takes at least 10-14 days for the cells to regenerate MAO enzymes.

From other antidepressant to MAOI

- Consider the half-life of the parent compound and any bioactive metabolite. Wait a minimum of 5 half-lives before starting the MAOI.

2. **Use of Antidepressants During Pregnancy**

http://womensmentalhealth.org/specialty-clinics/psychiatric-disorders-during-pregnancy/

3. **Pharmacokinetic Considerations:**

Various antidepressants, mainly SSRI's have drug-drug interaction via their inhibition of p450 enzymes. Fluoxetine (Prozac) and Fluvoxamine (Luvox) are most likely to have drug-drug interactions

Summary of Antidepressant Drugs and Drug Classes

Tricyclic antidepressants (TCAs)	**Selective Serotonin reuptake inhibitors (SSRIs)**	**5-HT/NE reuptake inhibitor (SNRI)**	**Atypical Antidepressants**	**Monoamine oxidase inhibitors (MAO-I)**
Imipramine	Fluoxetine	Duloxetine	Bupropion	Tranylcypromine
Amitriptyline	Paroxetine	Venlafaxine	Mirtazapine	Phenelzine
Desipramine	Sertraline	Desvenlafaxine	Nefazodone	Moclobemide (reversible MAO-I)
Nortriptyline	Fluvoxamine		Trazodone	Selegiline
Clomipramine	Citalopram		Vilazodone	
Doxepin	Escitalopram		Vortioxetine	

Bipolar Disorder Medications

Goals & Objectives:

Describe the pharmacologic profiles of major drugs/drug classes used in the treatment of bipolar disorder. These drugs include: Lithium, Divalproex (Depakote), Carbamazepine (Tegretol), Lamotrigine (Lamictal)

1. List the major drugs/drug classes used in the treatment of bipolar disorder

2. Describe the mechanism of action of each of the major drugs/drug classes used in the treatment of bipolar disorder

3. Describe the principle pharmacokinetic properties of the major drugs used to treat bipolar disorder. This includes: half-life & time to steady state, trough levels, metabolic auto-induction, P450 system induction, therapeutic index

4. Describe the pharmacodynamics (common adverse effects) of the major drugs used to treat bipolar disorder.

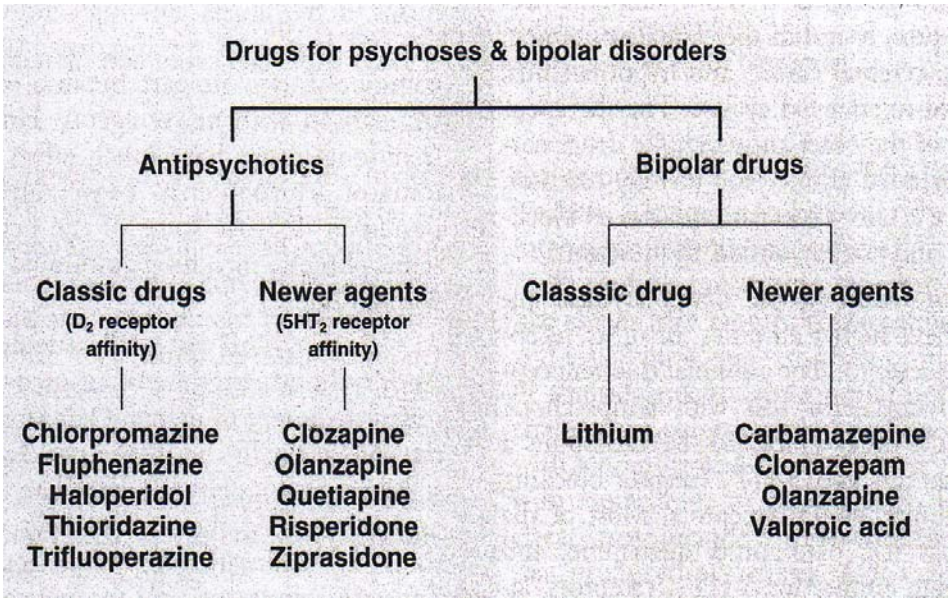
5. Describe the pharmacodynamics (serious adverse effects) of the major drugs used to treat bipolar disorder. This includes: lithium toxicity, agranulocytosis, aplastic anemia, hepatic failure, exfoliative dermatitis, pancreatitis, Steven's Johnson syndrome

6. Identify the laboratory tests that may be used to monitor for common and serious major adverse effects of the major drugs used to treat bipolar disorder.

7. Discuss potential drug-drug interactions that may occur with the use of drugs for treating bipolar disorder. This includes: drugs interactions that increase or decrease lithium levels; interaction of depakote & lamictal; interaction of depakote-tegretol

8. Describe the potential teratogenic adverse effects of drugs used in the treatment of bipolar disorder if administered to a woman who is pregnant

II. PHARMACOLOGY OF BIPOLAR DISORDER MEDICATIONS



(fig from Katzung & Trevor's Pharmacology, Examination & Board Rev. 7th ed., pp247)

Bipolar Disorder can be treated with:
(A) Lithium (Li^+)
(B) Anticonvulsant drugs:
Valproic Acid (VPA) (Depakene®); Sodium Valproate (Depakote)
Carbamazepine (Tegretol) and Lamotrigine (Lamictal)
(C) Atypical antipsychotics

A. LITHIUM (Li^+)

- first-line treatment for bipolar disorder
- effective in all illness phases: acute mania, depression, maintenance treatment
- only drug proven to reduce suicide in bipolar patients
- can enhance antidepressant effectiveness in the treatment of major depression
- may take days to weeks to produce a full therapeutic effect

Mechanism of Action:

- Li^+ therapeutic action in treatment of bipolar disorder is unclear
- Most accepted mechanism of action involves second messenger enzymes that affect neurotransmitter action
    - Inositol recycling: Li^+ **inhibits** a number of enzymes involved in inositol recycling
    - Protein kinase C: Li^+ may affect specific isozymes of protein kinase C
    - Glycogen synthase kinase-3 (GSK-3): Li^+ inhibits GSK-3
- can effect neurotransmitters and their release
    - may enhance the effects of serotonin
    - may ↓ NE & DA turnover (may be relevant to antimanic effects)
    - may augment synthesis of acetylcholine

Pharmacokinetics

- 100% absorbed from the GI tract (peak levels in 0.5-2 hrs)
- Blood level monitoring
  - half-life ≈ 20 hrs; draw 5-7 days after starting med or med dose change
  - requires trough blood level, draw ~12 hours after last dose of medication
  - narrow therapeutic window
    - acute mania treatment (0.6-1.2 mEq/L)
    - Bipolar maintenance treatment (0.6-0.7 mEq/L)
    - Lithium toxicity (>1.5 mEq/L)
- 0% protein binding; No metabolites
- Lithium removal is almost entirely by the kidney;

  Glomerulus: Li^+ freely filtered

  Proximal renal tubule: Li^+ mostly reabsorbed in parallel with Na^+;

  Collecting duct: Li^+ reabsorbed by principal cells epithelial Na^+ channel

  - Drug-drug interactions with Li^+ involve the kidney:

    Diuretics
    - Urinary alkalization (Acetazolamide, dichlorphenamide, methazolamide)
      - Inhibition of proximal tubule reabsorption of HCO_3^-

        → Na^+ (Li^+) accompanying HCO_3^- (instead of being reabsorbed)

        →↑ HCO_3^- at distal convoluted tubule & some Na^+ (Li^+) Reabsorption, but is a net loss of Na^+ (Li^+)

        →↓ (Li^+) level
    - Osmotic diuretics (Mannitol, Urea):
      - ↑tubular fluid osmolality

        →impaired reabsorption of fluid

        →↑ excretion of H_2O (some Na^+ (Li^+) accompanies)

        →↓ (Li^+) level
    - Loop diuretics:
      - Inhibits co-transport system of thick ascending loop of Henle

        → ↓Medulla hypertonicity

        → inability to concentrate urine

        → Na^+ loss (Li^+ loss?-- exception to the rule)

        Minor variable effects on Li^+ level-different sources say ↑ Li^+, ↓ Li^+, or no change
    - Thiazide diuretics:
      - Inhibits NaCl reabsorption in distal convoluted tubule

        → diuresis → Na^+ (Li^+) loss initially

        <u>But</u>, compensatory proximal tubular reabsorption of Na^+ (Li^+)

        → ↑ Li^+ level

- K+ sparing diuretics (Spironolactone):
  - Antagonize aldosterone receptors in the cortical collecting tubule
    - → ↓ Na^+ (Li^+) reabsorption in late distal convoluted tubule
    - →↑ Li^+ levels (compensatory proximal tubular reabsorption?)
- K+ sparing diuretics (Amiloride):
  - Lithium's action after being absorbed by the collecting tubule's principal cells is believed to be part of the cause of Li^+ induced Nephrogenic Diabetes Insipidus (NDI)
  - Amiloride blocks Na^+ (Li^+) reabsorption at the collecting tubule and may successfully treat Li^+ induced NDI

ACE Inhibitors & Angiotensin II receptor antagonists

- Inhibits Angiotensin II production
  - →↓ aldosterone
    (aldosterone normally ↑ Na^+ resorption at the collecting tubule)
    →↓ Na^+ resorption: Na^+ loss (Li^+ loss)
    →↑ Li^+ levels (compensatory proximal tubular reabsorption?)

Drug-Drug Interactions & Lithium		
↑ clearance / ↓Li level	**No change in Li level**	**↓ clearance / ↑Li level**
	Amiloride (Midamor)?	
Acetazolamide (Diamox)		NSAIDs
Mannitol (Osmitrol)	Furosemide (Lasix)	COX-2 Inhibitors
Aminophylline	Acetaminophen (Tylenol)	ACE inhibitors (Lisinopril)
Theophylline	Aspirin	Angiotensin II (Losartan)
Caffeine	Sulindac	Thiazides
		K+ sparing diuretics (Spironolactone)
Pregnancy		Dehydration
		Na+ depletion
		Renal Impairment
		Advance age

Lithium's Side effects common rare*

- Derm: acne, psoriasis, rashes, alopecia
- Endocrine: ↓ thyroid, ↑ parathyroid*
- GI: Nausea, diarrhea
- Heme: ↑ WBC's
- Neuro: fine tremor, ↓ conc, sedation (sedation may ↓ over time)
- Other: Edema & weight gain

Thyroid

- ↓ thyroid function (hypothyroidism)
  - Weight gain, mental slowness, fatigue, depressed mood, constipation, cold intolerance
  - Symptoms overlap with depression and other lithium side effects (↑ weight)
- Common; seen in 10%, up to 50% of patients; ♀ 5x's > ♂

Weight gain risk

- Initial weight gain: lithium acting like sodium → thirst and some water accumulation
- Long term weight gain: slowly over time; may also be due to ↓ thyroid function, may be from ↑ eating secondary to depression
- ♀ > ♂

More serious potential complications

- Renal issues:
  - Nephrogenic diabetes insipidus (NDI)
    Commonly effects kidney ability to concentrate urine (polyuria) which leads to ↑ fluid intake (polydipsia); this is drug induced NDI
    - Not a short term risk; risk for patients on lithium long term (10+ years)
    - A common risk; different studies indicate from 10% up to 60% patients on long term lithium may develop NDI
    - Episode(s) of lithium toxicity increase risk
    - Amiloride may treat NDI (see diuretic section)
  - Mild renal insufficiency
    Glomerular & interstitial changes seen from chronic (years) lithium treatment. Slow ↓ in function—is suggested that 20% of patient's glomerular filtration rate slowly decreases; progression to end stage renal disease due to Li^+ (rare)
  - Patients with renal impairment require more cautious (lower) dosing of Li^+

- Cardiac-rare
  arrhythmia, severe sinus node dysfunction (bradycardia*,sick sinus syndrome*)

- **Li^+ toxicity:**

Li^+ toxicity	**Mild**	**Moderate**	**Severe**
Li^+ level	1.5 to 2.0 mEq/L	2.0 to 2.5 mEq/L	>2.5 mEq/L
GI symptoms	Nausea, Vomiting, Diarrhea		
State of Consciousness	Lethargy drowsiness	Confusion	Grossly Impaired Consciousness Coma
Neurologic	Muscle weakness Coarse hand tremor	Myoclonic twitches Dysarthria Nystagmus Ataxia	↑DTRs Seizures
Cardiac		ECG changes	Syncope

Lab tests with Li^+ Treatment

- Lithium level
- Renal function & thyroid function should be routinely monitored 1-2x's/yr
- ECG if >50 y/o
- Pregnancy test

B. ANTICONVULSANTS (sometimes referred to as mood stabilizers)

1. Valproic Acid (VPA) (Depakene®); Sodium Valproate (Depakote®)

- First line treatment of bipolar mania; bipolar maintenance treatment

Mechanism of Action: not completely clear

- GABA reuptake inhibitor; may ↑ GABA in synapse or mimic its affects at postsynaptic receptors.
- influences 2nd messenger enzymes such as GSK-3
- blocks sustained high frequency neuronal firing rates (anti-epileptogenic effect).

Pharmacokinetics

- 100% absorbed
- Half-life 12 hours
- Therapeutic range: 50 – 125 ug/mL (monitor blood levels)
  Bipolar disorder manic episode: response↑ as the VPA level ↑
- Drug-drug interactions with VPA involve blood protein displacement or an effect on the other drug's hepatic metabolism
  - Highly protein bound (90%)
    unbound fraction crosses blood brain barrier and exerts pharmacologic activity
    - VPA may be displaced from protein by other drugs
      Aspirin & caffeine displace VPA from serum proteins
      → ↑ free fraction & ↑ risk toxicity
    - VPA also displaces other drug-bound proteins;
      Carbamazepine, phenytoin, diazepam
      Phenytoin displaced → ↑ phenytoin free fraction & possible toxicity
  - inhibits metabolism of other anticonvulsants: phenytoin, phenobarbital & carbamazepine (may result in toxic levels of these agents)
  - VPA interaction with lamotrigine:
    Inhibits phase II glucuronidation pathway that inactivates & eliminates lamotrigine (CYP450 system NOT involved)
    → ↑ lamotrigine levels (2-3x's) → ↑ risk lamotrigine side effects

VPA Side Effects common rare*

- Derm: alopecia*
- GI: Nausea (avoid by giving with food or use enteric coated Depakote®)
  vomiting, diarrhea, mild ↑ LFT's; pancreatitis*
- Heme: ↓ platelets*
- Neuro: ataxia, headache, dizziness, tremor, sedation
- Other: ↑ ammonia level, weight gain, polycystic ovarian syndrome (PCOS)
  ↑ suicide risk*

VPA toxicity

Typically from med OD: CNS depression, ↓BP, metabolic acidosis, abnormal electrolytes

Toxicity can happen from therapeutic use:

Mild↑LFT's-very common, almost 50% pts; reversible with med discontinuation

Hepatotoxicity-greatest risk: children <2 y/o who are also treated with other drugs

Hyperammonemia

may be dose related; LFT's may be normal

if ammonia level high, VPA is discontinued;

if severe (hyperammonemic encephalopathy) treat with L-carnitine

2. Carbamazepine (Tegretol ®)

- Used to be 2nd line treatment; now 3rd line behind SGA for treatment of bipolar mania; bipolar maintenance treatment

Mechanism of Action: not completely clear

- reduces Na^+ influx and depresses synaptic transmission;
- reduces release of norepinephrine and excitatory amino acids such as glutamate
- adenosine receptor agonist (caffeine is an adenosine receptor antagonist)

Pharmacokinetics

- erratic absorption
- medium protein binding (70-80%)
- is structurally similar to TCA's (a tricyclic compound)
- Therapeutic range: 4 – 12 ug/mL (monitor blood levels)

  Therapeutic range established for treating seizures; therapeutic range for treating a manic episode not established, though clinically the range for treating seizure disorders is what is used
- CYP450 effects
  - strong inducer of various CYP450 enzymes (1A2, 2C8, 2C9, 2D6, 3A4) that ↑ metabolism of many drugs (oral contraceptives, warfarin, theophylline, doxycycline, haloperidol, TCA's, valproic acid-most anticonvulsants, benzodiazepines)
  - carbamazepine levels can ↑ by CYP 450 3A4 inhibitors (fluoxetine, cimetidine, erythromycin, isoniazid)
  - carbamazepine auto-induces its own metabolism

    pre-auto induction half-life = 24 hours

    post-auto-induction half-life = 8 hours
  - carbamazepine levels can be ↓ by P450 3A4 inductors (phenobarbital, phenytoin, primidone)

- hepatic metabolism →10,11-epoxide: can cause neurologic side effects

Side/Toxic Effects common rare*

- Derm: rash (Stevens Johnson Syndrome)*
  SJS is more common in patients of Asian ancestry who have human leukocyte antigen (HLA) allele HLA-B*1502
- GI: Nausea, vomiting, mild ↑ LFT's, hepatotoxic*
- Heme: ↓ WBC's, aplastic anemia**, agranulocytosis** 1/100,000 (0.001%)**
- Neuro: ataxia, diplopia, dizziness, tremor, sedation
- Other: ↓ Na, weight gain; ↑ suicide risk*

3. Lamotrigine (Lamictal ®)

- **NOT** useful in treating acute manic episode
- approved for bipolar long-term maintenance treatment
- approved for bipolar depression

Mechanism of Action: not completely clear

- inhibits release of glutamate (excitatory amino acid)
- inhibits voltage sensitive Na+ channels resulting in stabilization of neuronal membranes that mediate presynaptic transmitter release of excitatory amino acids

Pharmacokinetics

- low protein binding (55%)
- metabolized primarily by glucuronidation
  - valproate can double lamotrigine's plasma levels
- oral contraceptives can ↓ lamotrigine's plasma level by 50%
  carbamazepine-induced enzymes (i.e. CYP3A4) can ↑ metabolism of lamotrigine & ↓ lamotrigine's plasma level
- can induce own metabolism

Side Effects: common rare*

alcohol may ↑ the side effects severity

- Derm: rash (benign or Stevens Johnson Syndrome*)
  Benign: ~10%, SJS: 0.02-0.1%
- GI: Nausea, vomiting
- Neuro: ataxia, headache, dizziness, double vision, blurred vision, fatigue
- Other-insomnia, blood dyscrasias* (agranulocytosis, aplastic anemia)

C. ATYPICAL ANTIPSYCHOTICS

Pretty much all second generation antipsychotics have uses in the treatment of one or more phases of bipolar disorder.

See antipsychotic lecture for details on the medications pharmacology

	Acute Mania	Maintenance	Bipolar Depression
Lithium	**Yes**	**Yes**	**Yes**
Valproic Acid (VPA) (Depakene®);	**Yes**	**Yes**	**No**
Carbamazepine (Tegretol ®)	**Yes**	**Yes**	**No**
Lamotrigine (Lamacital ®)	**No**	**Yes**	**Yes**

Mood stabilizers are FDA approved (as above) and are the most frequently used in the treatment of the different phases of bipolar disorder. Carbamazepine (Tegretol ®) is now used more like a second or third line option. Others are used as first line options

Haloperidol (Haldol) & other high potency FGS's	**Yes**		
Chlorpromazine (Thorazine)	**Yes**		

First Generation Antipsychotics are FDA approved for the treatment of acute mania. Approval was made in 1970s' when Lithium was only other option. Now FGA's are used more like a third line option and are usually prescribed in combination with a mood stabilizer.

Risperidone (Risperdal)	**Yes**	**Yes**	
Paliperidone (Invega)			
Geodone (Ziprasidone)	**Yes**		**No**
Iloperidone (Fanapt)			
Lurasidone (Latuda)			**Yes**
Clozapine (Clozaril)			
Olanzapine (Zyprexa)	**Yes**	**Yes**	
Olanzapine + Fluoxetine (Symbyax)			**Yes**
Quetiapine (Seroquel)	**Yes**	**Yes**	**Yes**
Asenapine (Saphris)	**Yes**		
Aripiprazole (Abilify)	**Yes**	**Yes**	**No**

Many Second Generation Antipsychotics have been approved for the treatment of the different phases of bipolar disorder. Likely more FDA approvals are to come. Because so many have received approval, many SGA's that have not been approved are presently used off label—particularly for acute mania or maintenance treatment. Off label uses are typically 2nd or 3rd line uses.

SGA's in combination with a mood stabilizer are commonly used for treating severe acute mania (mania with psychosis and/or suicidal/homicidal/dangerous behavior). These patients generally also require in-patient hospitalization.

Pregnancy & Bipolar Medications

Background

- Baseline incidents of major fetal malformation in general population is 2-5%
- For pregnant women with bipolar disorder, their risk of a manic episode is increased during the pregnancy and in the post-partum period

Valproic Acid (VPA) (Depakene®); Sodium Valproate (Depakote®)

- Greatest potential for serious birth defects of all meds used for psychiatric disorders; neural tube defect 1-2% (10-20x's gen population rate)

Carbamazepine (Tegretol)

- ↑risk of neural tube defect (Spina Bifida; about 0.9%) if used during pregnancy

Lithium

- Li^+ levels may ↓ during pregnancy (↑ GFR as pregnancy progresses) and are ↑ after delivery (↓GFR late 3rd trimester)
- Li^+ use during pregnancy has historically resulted in concerns about congenital cardiac defects (Ebstein's anomaly) associated with 1st trimester exposure. Recent data suggest the risk is less than previously thought and is between 1 in 2,000 (0.05%) and 1 in 1,000 (0.1%); General pop risk is 1 in 20,000 (0.005%)
- Lithium toxicity in newborns (lethargy, cyanosis, poor suck and Moro reflexes, cardiac arrhythmias, muscle flaccidity)

Lamotrigine (Lamictal)

- 3 different registries report 1.9-3.2% incidence of major malformation; this is similar to estimates from general population cohorts
- Some studies suggest ↑risk of cleft lip or palate

Antipsychotics

- FGA or SGA prenatal exposure does not appear to increase the risk of major physical malformations beyond the baseline incidence seen in the general population

PHARMACOLOGY OF SEDATIVE–HYPNOTICS & OTHER DRUGS TO TREAT SLEEP DISORDERS

Learning Objectives:

1. GABA receptor
   - Compare and contrast $GABA_A$ and $GABA_B$ receptors' general structure & process of activation
   - Describe the $GABA_A$ receptor structure in terms of:
     - the overall subunit assembly
     - the 7 polypeptide subunits
     - the subunit isoforms-especially the α subunit isoforms
     - the significant of $GABA_A$ receptor subtype $\alpha 1 \beta 2 \gamma$
   - Explain the significance of the α - β subunit interface and the α - γ subunit interface
   - Explain the significance of $GABA_A$ receptors with different α isoforms in the receptor structure and how this effects the pharmacodynamics of which drugs bind, how well a drug binds, and the clinical outcome from different isoform-drug binding situations.
   - Explain what an allosteric modulatory site is and how this applies to the process of $GABA_A$ receptor activation

2. Benzodiazepines
   - Compare and contrast the pharmacodynamics of non-selective $GABA_A$ receptor agonists (benzodiazepines) with the non-benzodiazepine $GABA_A$ receptor agonists (Imidazopyridines & Pyrrolopyrzines)
   - For commonly used benzodiazepines (1), compare and contrast the pharmacokinetics (2), side effects, and risk of tolerance or dependence (3)
     (1) Commonly used benzodiazepines:
       - alprazolam, clonazepam, chlordiazepoxide, diazepam, lorazepam

     (2) Pharmacokinetics:
       - Half-lives:
         - which benzodiazepines go thru Phase I & II metabolism & have bioactive intermediates
         - which benzodiazepines go thru Phase II metabolism only (LOT)
         - how drug accumulation happens & which type of benzodiazepines are at risk for this
         - the clinical significance of drug accumulation & which patient population is most vulnerable
       - Rapidity of onset of effects
       - Drug potency

     (3) Tolerance & Dependence:
       - Factors that increase this clinical risk
       - Treatment options to lower the risk or prevent this
       - Clinical treatment options

3. Non-benzodiazepines sedative hypnotics
   - Compare and contrast the mechanism of action, pharmacokinetics, risk of tolerance & dependence, and clinical uses for medication classes used to treat insomnia:
     - Benzodiazepines, Imidazopyridines, Pyrrolopyrzines, Barbiturates, & Melatonin receptor agonist

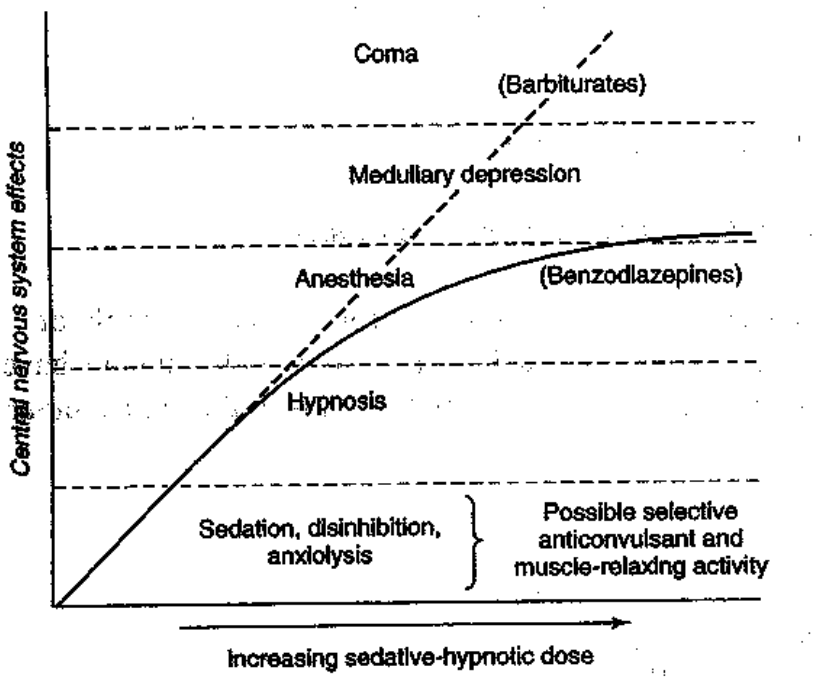
4. Buspirone
   - Compare and contrast buspirone with the benzodiazepines and SSRI's in terms of mechanism of action, risk of dependence/withdrawal, and clinical uses for the medications in the treatment of anxiety and mood disorders

PHARMACOLOGY OF SEDATIVE–HYPNOTICS & OTHER DRUGS USED TO TREAT SLEEPING DISORDERS

What do we mean by the term Sedative-Hypnotic?

- **Sedative (Anxiolytic) –** reduces anxiety and exerts a calming effect.
- **Hypnotic –** produces drowsiness and facilitates the onset and maintenance of sleep (more CNS depression than sedation).

1. All sedative-hypnotics produce ***graded*** dose-dependent depression of CNS function.
2. All sedative-hypnotic drugs produce their effects by interacting with $GABA_A$ receptors and potentiating GABAergic activity from spinal cord to cerebral cortex.
3. The magnitude of the depression of CNS function with ↑ 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

Gamma-Amino Butyric Acid (GABA)

- Synthesized in the nucleus accumbens
- Is the major inhibitory neurotransmitter in the CNS: ~30% of synapses the cerebral cortex are GABAergic
- Two major classes of GABA receptors have been identified based on function:
    1. $GABA_A$
    2. $GABA_B$

1. $GABA_A$ Receptors-an ionotropic receptor

- activation → ↑ opening of Cl channels → inhibitory post-synaptic potential (hyperpolarization-↓neuron firing)
- Both the prototypic agonist (musimol) & prototypic antagonist (bicuculline) bind to the same site (i.e. the same pharmacophore) on the receptor that GABA binds to. Musimol mimics & bicuculline antagonizes GABA's effects.
- Sedatives lead to ↑ efficacy of GABA signaling; GABA is the major inhibitory neurotransmitter in the CNS

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

- presynaptic terminals:
  via ↓ in Ca^{++} conductance →
  control release of GABA ("homoreceptors") or other neurotransmitters ("heteroreceptors")
- postsynaptic membranes:
  producing hyperpolarization of the membrane via ↑ in K^+ conductance

  Ex. baclofen (Lioresal®) is a selective $GABA_B$ agonist used clinically as an anti-spastic drug

$GABA_A$ receptor's activation is modulated by benzodiazepines & other sedative-hypnotics
$GABA_B$ receptors are **not** modulated by either benzodiazepines nor other sedative-hypnotics

The Complex $GABA_A$ Receptor Complex

$GABA_A$ receptors:

- hetero**pentameric** glycoprotein receptors
  - formed from the co-assembly of **five polypeptide subunits**
    - each subunit is a polypeptide (420-450 amino acids) from various polypeptide classes (**α, β, γ,** and ***δ, ε, π, & ρ***)
    - each subunit has:
      a) 4 transmembrane domains with both the amino and carboxy terminus in the extracellular side
      b) 2 intracellular loops provide sites for phosphorylation
    - Subunit Isoforms for **α, β, γ, & *ρ*** have been identified

6 isoforms of α subunit (α1-6)	α1 α2 α3 α4 α5 α6
3 isoforms of β subunit (β1-3)	β1 β2 β3
3 isoforms of γ subunit (γ1-3)	γ1 γ2 γ3
3 isoforms of ρ subunit (ρ1-3)	ρ1 ρ2 ρ3

While theoretically thousands of pentameric subunit combinations are possible from the number of identified subunits/isoforms, the majority are heteropentamer combinations made from a relatively few different subunit isoforms.

The most abundant $GABA_A$ receptor subtype is a generic composition of:

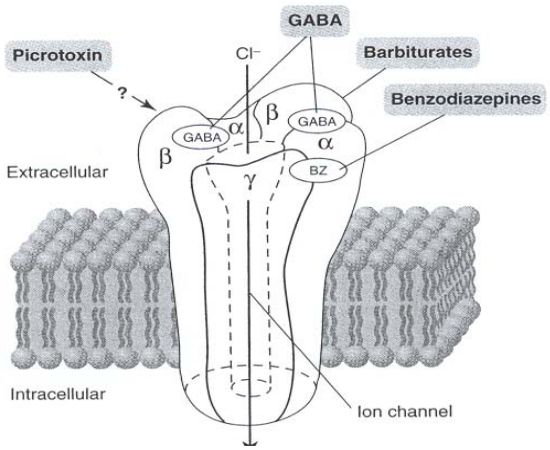
Two(2) α subunits, **two(2)** β subunits, & **one(1)** γ subunit (**γ2 subunit** is most common)

α1β2γ2 ≈60%

α2β3γ2 15-20%

various isoform subtype combinations 15-20%

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 region located at the **α - β interface** provides 2 sites (pharmacophores) for both GABA agonists & antagonists to bind to the receptor

The region located at the **α - γ interface** provides a modulatory "binding pocket" and has been referred to as the benzodiazepine (BZ) receptor. It has also been referred to as the ω receptor. Although the binding pocket may be called a BZ/ω "receptor", it is actually an allosteric modulatory site. For any drug that binds to this "receptor" to alter the function of the $GABA_A$ receptor, GABA must also be present.

The BZ/ω receptor is a binding site for benzodiazepines and, depending on which **α isoform is present,** some non-benzodiazepines.

BZ_1 /$ω_1$ contains the **α1** isoform, is the most common, and bind three drug classes:

1. benzodiazepines
2. imidazopyridines: zolpidem (ambien®), zaleplon (sonata®)
3. pyrrolopyrazine: eszopiclone (lunestra®)

BZ_2/$ω_2$ contains the **α2**, **α3**, or **α5** subunit and can bind one drug class:

1. benzodiazepines

The **α isoform** determines the binding abilities (affinities) of specific drugs for the BZ binding site

GABA$_A$ receptors with **α1,2,3** & **5:** sensitive to diazepam
GABA$_A$ receptors with **α4** & **α6** are diazepam-insensitive
GABA$_A$ receptors have different selectivity (α1 > α2 = α3 >> α5) to the Imidazopyridine class drug zolpidem

Benzodiazepines

- bind to both BZ$_1$ /ω$_1$ and BZ$_2$/ω$_2$ sites (receptors with **α1,or α2,3 or 5**)
- α isoform may contribute to the drug's qualitative effects
  1. BZ$_1$ /ω$_1$ with **α1 subunits** mediate sedative, amnesia and ataxic effects but not anxiolytic or muscle relaxing effects.
  2. BZ$_2$/ω$_2$ with **α2 (and possibly α3)** subunits mediate the anxiolytic and muscle relaxant effects of benzodiazepines
  3. BZ$_2$/ω$_2$ with **α5** may mediate memory impairment and tolerance development to benzodiazepines' sedative effects

GABA$_A$ Receptor Drugs Pharmacodynamics

1. **Non-Selective "Agonists" –** Benzodiazepines
   - bind to both BZ$_1$ /ω$_1$ and BZ$_2$/ω$_2$ sites
   - are positive allosteric modulators of GABA$_A$ receptors and are ineffective unless GABA (or GABA agonists) are present
   - DO NOT compete directly with GABA binding to its pharmacophore at the **α/β interface** on the GABA$_A$ receptor
   - when bound to its binding site→
     ↑ GABA's affinity for its GABA$_A$ receptor binding site→
     ↑ frequency of opening chloride channels →
     inhibitory post-synaptic potential (hyperpolarization-↓neuron firing)

2. **Non-Benzodiazepine "Agonists" -** Imidazopyridines & Pyrrolopyrazine
   - bind selectively to BZ$_1$ /ω$_1$ sites
   - act as positive allosteric modulators of GABA$_A$ receptor function
   - are ineffective unless GABA (or GABA agonists) are present

3. **Antagonists** (flumazenil**;** Romazicon®)
   - competitive antagonist with high affinity for the BZ$_1$ /ω$_1$ and BZ$_2$/ω$_2$ receptor
   - blocks the actions of benzodiazepines, imidazopyradine & pyrrolopyrazine drugs
   - <u>does not</u> anatgonize the actions of other sedative-hypnotics (barbiturates, meprobamate or ethanol)
   - Given i.v., it acts rapidly and has a short $t_{1/2}$ (0.7-1.3h)
   - May precipitate withdrawal in patients physiologically dependent on benzodiazepines

4. **Inverse Agonists-** (Beta Carbolines)
    - act as negative allosteric modulators of $GABA_A$ receptor function (↓ affinity for binding GABA)
    - bind to BZ_1 /ω_1 & BZ_2/ω_2 modulatory sites
    - produce anxiety and seizures (via reducing GABA receptor function) as well as block the effects of drugs that bind to BZ_1 /ω_1 & BZ_2/ω_2 sites.

5. **Barbiturates**
    - Bind to $GABA_A$ receptor at separate sites from the BZ_1 & BZ_2 benzodiazepine binding sites
    - binding ↑ **duration** of the chloride channel opening in presence of GABA
    - At very high concentrations, can directly produce chloride channel opening.

6. **Neuroactive steroids**
    - Separate $GABA_A$ receptor binding sites from the benzodiazepines
    - Can potentiate or attenuate $GABA_A$ function depending on steroid structure
    - At high concentrations, some (e.g. alphaxalone) may directly open chloride channels.

7. **Ethanol**
    - produces many effects of the benzodiazepines (e.g., anxiolysis, sedation)
    - stimulates Cl^- uptake into isolated brain vesicles
    - thought to alter $GABA_A$ neurotransmission

Benzodiazepines

- Introduced in the 1960s, remain among the most widely prescribed drugs in the world
- Clinical uses:
  Common: Anxiety, Insomnia, Anesthesia, Alcohol Withdrawal, Seizures
  Less common: Night terrors, sleepwalking
- Safer than barbiturates and older sedative-hypnotics less likely to result in fatal CNS depression.
- In healthy patients, hypnotic doses of benzodiazepines produce no significant effects on respiration and cardiovascular function

(**REMEMBER**: "If its **AM, PAM**, or **LAM**, it's likely a benzodiazepine")

Midazo**lam** (Versed®)	Triazo**lam** (Halcion®)	Alprazo**lam** (Xanax®)
Estazo**lam** (ProSom®)	Loraze**pam** (Ativan®)	Oxaze**pam** (Serax®)
Temaze**pam** (Restoril®)	Chlorazepate (Tranxene®)	Chlordiazepoxide (Librium®)
Clonaze**pam** (Klonopin®)	Diaze**pam** (Valium®)	

Pharmacodynamics & Mechanism of Action:
(See above-$GABA_A$ RECEPTOR DRUGS PHARMACODYNAMICS)

Pharmacokinetics

Absorption & Distribution:

- all are lipid soluble, but lipophilicity, can vary over 50–fold &contributes to differences in rates of absorption, onset of action, & redistribution

Bioavailability - very good; ranges from 60-100%

Protein binding

- moderate (70%-alprazolam) to high, (99%-diazepam);
- drug interactions with other highly protein bound agents are likely

Metabolism:

- Most metabolized via:
  Phase I:microsomal oxidation by the P450 family CYP**3A4** and CYP**2C19**
  Phase II: conjugation to form glucuronides that are excreted in the urine
- Three benzodiazepines only go through Phase II
  - (**L O T**) **L**orazepam, **O**xazepam, & **T**emazepam

Pregnancy:

- All sedative-hypnotics cross the placental barrier and appear in breast milk
- Teratogenic?
  - initial reports suggested an ↑risk of cleft lip and palate,
  - more recent reports show no association between benzodiazepines exposure and risk for cleft lip or palate

Pharmacokinetic differences largely determine benzodiazepines clinical applications
Important factors for consideration include:

A. Duration of action: Half-life of parent drug & any bioactive intermediates
B. Rapidity of onset of effects
C. Drug potency
D. Patients age, medical condition, and prior drug history

A. Duration of action: Half-life of parent drug & any bioactive intermediates

Phase I & Phase II metabolism
Elimination half-life of **bioactive intermediates** is often longer than that of the parent compound due to (Phase I) formation of ≥ 1 bioactive metabolite(s) which may be active until conjugated and excreted (Phase II).
Long $t_{1/2}$:

- Parent compounds half-lives ($t_{½}$ = 0.1 - 35 hr)
- Bioactive metabolite's half-lives between 50-100 hr.

Chlordiazepoxide → → → N-desmethyldiazepam
2-keto derivative: **Diazepam** → N-desmethyldiazepam
2-keto derivative: **Flurazepam** → N-desalkylflurazepam
7-Nitro derivative: **Flunitrazepam** (Rohypnol®) the "date rape" drug; not

approved in U.S.

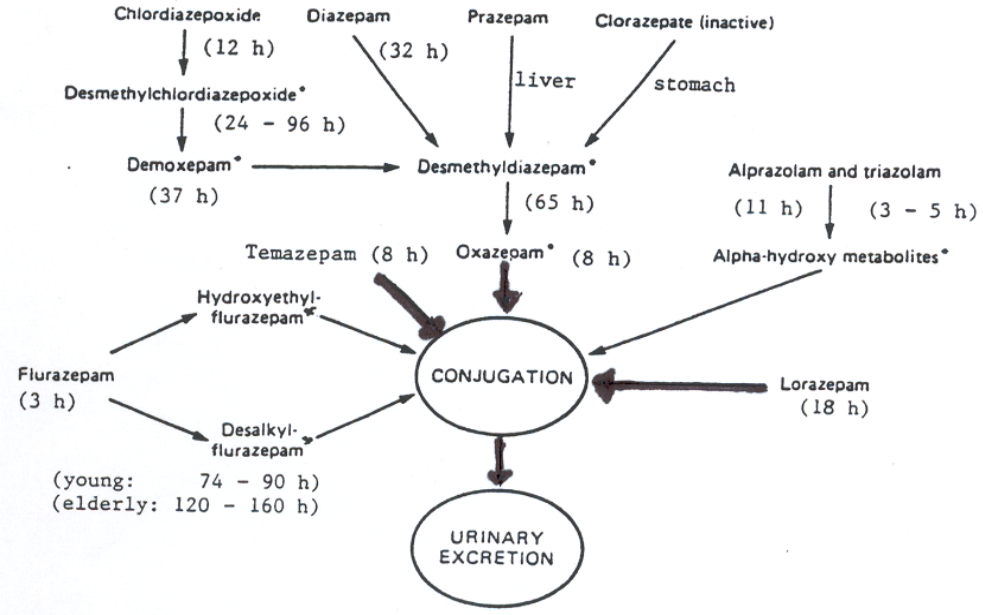
7-Nitro derivative: **Clonazepam** (t ½ = 22-33 hr)

Short(er) $t_{1/2}$:

Triazolo derivative: **Midazolam** (t ½ = 2.5 hr)
Triazolo derivative: **Alprazolam** (t ½ = 11 hr)
Triazolo derivative: **Triazolam** (t ½ = 1.5-5.5 hr)

Phase II metabolism only

- not metabolized to bioactive intermediates
- preferred for geriatric patients and patients with impaired hepatic function
- t ½ half-lives 5 -25 hr
- **3-hydroxy derivative:** (**L O T**) **L**orazepam, **O**xazepam, & **T**emazepam

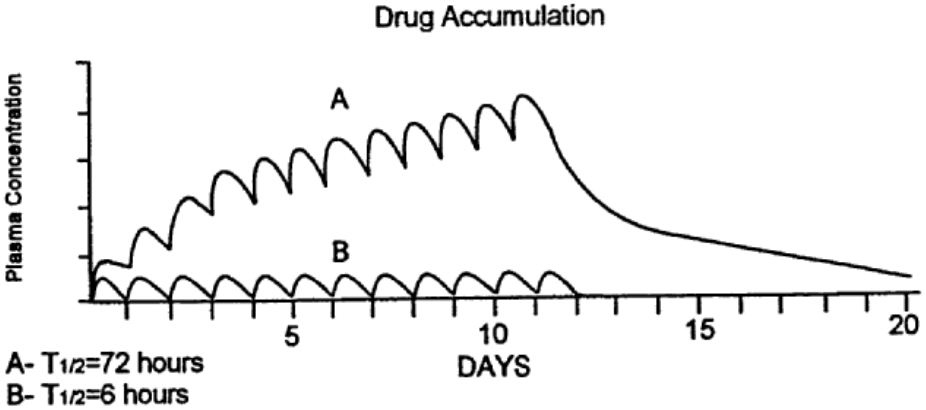


Adapted from: B.G. Katzung, Basic and Clinical Pharmacology 9th ed.,page 354

The half-life (of Elimination)

Drugs with long half-lives (either the parent compound or active metabolite) will accumulate with prolonged use (as shown in the figure).

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



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

B. Rapidity of onset of effects

Rapid-within 15 minutes:

- midazolam (IV most rapid); diazepam, flurazepam, lorazepam (SL, IV)

Initermediate-15-30 minutes

- alprazolam, clonazepam, lorazepam (PO), chlordiazepoxide

Slow-30-60 minutes

- oxazepam, temazepam

C. Drug potency (equivalent dosages)

clonazepam	0.25 mg	diazepam	5 mg	chlordiazepoxide	25 mg
triazolam	0.25 mg	temazepam	10 mg		
alprazolam	0.5 mg	clorazepate	10 mg		
estazolam	1 mg	flurazepam	15 mg		
lorazepam	1 mg	oxazepam	15 mg		

D. Patients age, medical condition, and prior drug history

Benzodiazepine half-lives are longer in older people

- Elderly metabolize the drugs more slowly. Daily dosed drugs will accumulate more in elderly than in a younger patient.
- Least likely for benzodiazepines go through Phase II conjugation only. No active metabolites: (**L O T**) **L**orazepam, **O**xazepam, & **T**emazepam
- Most likely for drugs with bioactive metabolites:

  Chlordiazepoxide → → → N-desmethyldiazepam

  Diazepam → N-desmethyldiazepam

  Flurazepam → N-desalkylflurazepam

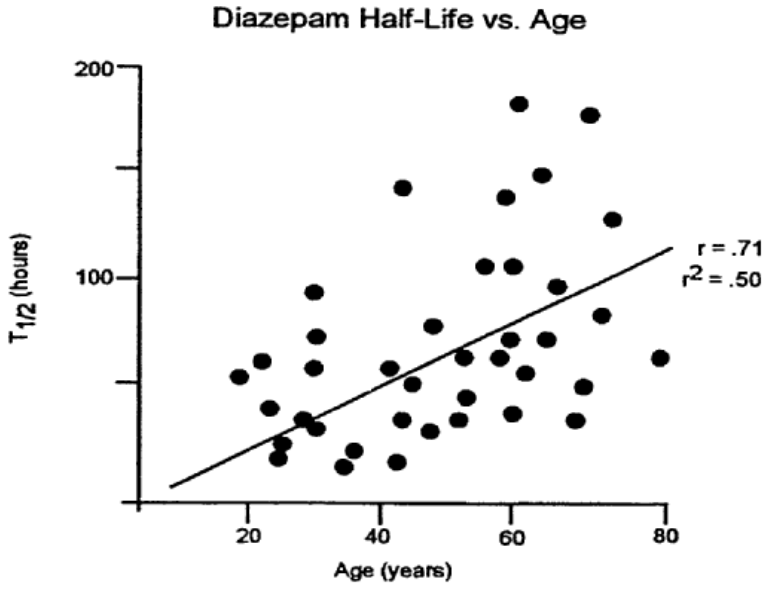


Figure from Dr. Lorens 2002 Therapeutics lecture notes; graciously provided by Dr. David Greenblatt

Side Effects:

Frequent: Sedation & Drowsiness-most common
ataxia, dizziness, cognitive impairment, amnesia (for events during the drug's effect).

Occasional: Confusion

Rare: Paradoxical aggression

Tolerance and Dependence:

Psychological Dependence on Benzodiazepines

- Similar to the behavioral pattern observed with heavy coffee drinkers or cigarette smokers. May contribute to physiologic dependence and tolerance.

Tolerance

- With chronic use there is a ↓ in the drug's effects so need ↑ doses to achieve original effects. May be analogous to the desensitization phenomena and is due to ↓ in BZ binding sites.
- Tolerance to the sedating effects of benzodiazepines has been observed but <u>not</u> to their anxiolytic or muscle relaxant effects.
- Additionally, cross tolerance can develop to ethanol and other sedative-hypnotics that affect $GABA_A$ receptor function.

Physiologic Dependence

- removal of the drug ("**withdrawal**") produces unpleasant symptoms that are usually opposite (compensatory) to the drug's effects.
  Common withdrawal symptoms include: anxiety, insomnia, loss of appetite, headache, muscle aches/twitches, nausea, tremor, sweating, and irritability

The propensity to develop a substance use disorder, tolerance & dependence, and more severe withdrawal depends on:

1) Drug's duration/half-life. ↓ half-life, ↑ risk
2) Amount of time to onset of drug's affect. ↓ time, ↑ risk
3) Drug's potency. ↑ potency, ↑ risk
4) Dose of drug taken. ↑ Dose, ↑risk
5) Time length drug has been taken. ↑ time length, ↑ risk

Highly lipophilic benzos which cross the blood brain barrier (diazepam) and agents with a short half-life and high potency (alprazolam, lorazepam) are the most reinforcing benzos and thus the ones most likely to be associated with abuse

Benzos are rarely the preferred or sole drug of abuse. Estimated 80% of benzo abuse is part of polydrug abuse, most commonly with opioids

*Severe withdrawal from benzodiazepines and some other sedative hypnotic drugs may

be fatal. Should never be discontinued abruptly

Discontinuation Strategy

General advise is benzodiazepine treatment be short-term and limited 1 -3 months

1. Taper down dose and/or
2. Switch to a longer half-life drug, (preferably one of lower potency and less rapid onset of effect; so as to decrease the reinforcement properties of the drug).

BZ_1 /ω_1 - Selective Non-Benzodiazepines

- Imidazopyridine drugs: 1) **zolpidem (Ambien®)** & 2) **zaleplon (Sonata®)**
  Pyrrolopyrazine drug: 3) **eszopiclone (Lunesta®)**
- bind selectively to BZ_1 /ω_1 sites
- act as positive allosteric modulators of $GABA_A$ receptor function
- are ineffective unless GABA (or GABA agonists) are present

These drugs:

- Primarily used to treat sleep disorders, but lack the anxiolytic, anticonvulsant and muscle relaxant efficacy of benzodiazepines
- May be habit forming with long-term use-↓ risk than barbiturates or benzodiazepines
- Even in overdose do not produce a dangerous degree of CNS depression;
  However, can be lethal if taken in combination with other CNS depressants
  Effects can be antagonized by the BZ1 & BZ2 antagonist, flumazenil
- Side effects:
  - similar to the benzodiazepines
  - headache, dizziness, 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

1) Zolpidem (Ambien®) – extended release form **(Intermezzo®)**

- the first FDA-approved BZ1 selective drug
- rapidly & completely absorbed from GI tract, reaches peak plasma levels in 1-2 hours.
- metabolized via Phase I and Phase II metabolism;
- $t_{1/2}$ of 1.5-3.0 hours.
  - prolonged in elderly and patients with liver disease, so ↓ dose

2) <u>Zaleplon</u> (Sonata®) - resembles zolpidem in its effects.

- rapidly absorbed from the GI tract, reaches peak concentration in 1.0 hour
- metabolized via Phase I and Phase II metabolism--no active metabolites
  - metabolism inhibited by histamine-2 receptor blocker, cimetidine (Tagamet®)
- very short $t_{1/2}$ of 1.0 hr.
  - prolonged in elderly and patients with liver disease, so ↓ dose
  - morning after sedation less common than zolpidem or other sedative-hypnotics

3) Eszopiclone (Lunesta®)

- the S(+) isomer of zopiclone (a pyrrolopyrazine drug approved for use in Canada)
- no structural similarity to zolpidem, zaleplon or the benzodiazepines
- is <u>not</u> restricted to short-term use
- rapid absorption from the GI tract; reaches peak concentrations in 1-2 hrs
- $t_{1/2} \cong$ 6 hrs: prolonged in the elderly so ↓ dose

<u>Drug Interactions</u>:

- CYP3A4 inhibitors ↑ serum concentrations and prolong the duration of action
  - itraconazole (Sporanox®) clarithyromycin (Biaxin®) and ritonovir (Norvir®)
- CYP3A4 inducer can ↓ serum concentrations and eszopiclone's effectiveness
  - Rifampin

Barbiturates:

- once popular treatment for sedation and sleep
- Except for phenobarbit**<u>al</u>**, methohexit**<u>al</u>** and thiopent**<u>al</u>** (Remember: "**AL**"the barbiturate), clinical use as sedative-hypnotic agents greatly ↓ since benzodiazepines became available

Mechanisms of Action

- Bind to sites on the ionotropic $GABA_A$ receptors at regions (likely on β subunits) different than where benzodiazepines bind (α - γ interface)
- Do not exhibit specificity to a $GABA_A$ receptor isoform subtype, will affect more subtypes
- Binding **↑ duration** of the chloride channel opening in presence of GABA
- At very high concentrations, can directly produce chloride channel opening. (GABA not needed)
- Depress actions of excitatory neurotransmitters & exert non-synaptic membrane effects.

Pharmacokinetics-Like benzodiazepines, are classified primarily based their duration of action

- **Short Acting**: (hours) - Thiopental, Mexihexital; rapid onset – both used for anesthesia induction
- **Intermediate Acting (18-48hrs):** - amobarbital (Amytal), secobarbital (Seconal) and pentobarbital (Nembutal)
- **Long acting (4-5 days**): - Phenobarbital (Luminol Sodium)-used in epilepsy treatment

Adverse Effects of the Barbiturates

1. Low therapeutic index-due to potency to depress respiration (especially in combination with alcohol). A lethal dose can be < 10x the prescribed hypnotic dose.
2. ↑Risk of Abuse, Physical Dependence and Withdrawal vs. benzodiazepines discontinuation after repeated use may lead to life threatening withdrawal syndrome that is difficult to treat.
3. Stimulate cytochrome P450 activity & induces hepatic microsomal oxidases.
   a. Pharmacokinetic tolerance – over time, ↑ barbiturate doses may be required due to the ↑ in their own metabolism.
   b. Cross tolerance - to benzodiazepines and other sedative hypnotics

c. Drug interactions – from ↑metabolism of other drugs also metabolized by microsomal oxidases

A Novel Sedative-Hypnotic

Ramelteon (Rozerem®)

- a melatonin receptor agonist used in the treatment of initial insomnia
- no evidence of physical dependence or abuse potential
- appears to be well tolerated if administered for long treatment courses

Mechanism of Action:

- selectively binds to M1 and M2 melatonin receptors
- mimics & enhances the actions of melatonin which has been associated with the maintenance of circadian sleep rhythms.
- No measurable affinity for BZ_1 /ω_1 or BZ_2/ω receptors or other sites.

Pharmacokinetics

- rapid absorption – high fat meals delays T_{max} and increases AUC (≈ 30%)
- moderate protein binding (82%), large Vd (≈ 74 L)
- extensive first pass metabolism, metabolism via CYP 1A2, 2C9, 3A4
- short half-life of 1-3 hrs

Side Effects

- occurs at rates comparable to placebo and included headache, somnolence, fatigue, dizziness, nausea, exacerbated insomnia

II. THE PHARMACOLOGICAL TREATMENT OF 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.

Sleep Disorders are most often treated with:

a. benzodiazepines (that bind to both BZ_1 /ω_1 and BZ_2/ω_2 sites on the $GABA_A$ receptor)
b. drugs that bind selectively to the BZ_1 /ω_1 receptors
c. drugs that bind to Melatonin receptors
d. other classes of sedating drugs with anti-histaminergic actions
e. herbal preparations with compounds that may affect GABA neurotransmission.

Barbiturates are generally not prescribed to treat sleep disorders given their low therapeutic index, greater abuse liability and other adverse consequences.

a) 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®)
Triazolam (Halcion®): high abuse potential, avoid if possible
Lorazepam (Ativan®): commonly prescribed, not FDA-approved for insomnia

- Pharmacokinetic differences are important considerations in choosing which benzodiazepine to treat a sleep disorder. (See Benzodiazepine Pharmacokinetic section—pg 6-8)
- It is advised that benzodiazepines be used short-term (1 -3 months)
- Benzodiazepine treatment for the elderly:
  The elderly metabolize drugs more slowly so the benzodiazepine half-lives will be longer in this population. Because drugs with longer half-lives accumulate with prolonged use, if dosed daily, the benzodiazepine concentrations will be significantly greater than intended. (See drug accumulation figure on pg 7)
  - Most likely for drugs with bioactive metabolites such as:
    chlordiazepoxide, diazepam, flurazepam, chlorazepate
  - Least likely for drugs that only go thru Phase II metabolism and have no active metabolites such as:
    (**L O T**) **L**orazepam, **O**xazepam, & **T**emazepam

Benzodiazepine issues in treating insomnia

1. Rebound insomnia: upon stopping medication original symptoms may recur or recur with greater intensity
2. Psychological Dependence – (See side effects section of Benzodiazepines)
3. Tolerance
4. Physiologic Dependence
5. Risk of Substance Use Disorder

b) The non-benzodiazepine BZ1-selective sedative-hypnotics approved for sleep disorders: **Imidazopyridines** & **Pyrrolopyrazines**
Zolpidem (Ambien®) **Eszopiclone** (Lunesta®)
Zaleplon (Sonata®)

c) Melatonin M1 & M2 receptor agonist
Ramelteon (Rozarem®)

d) Sedating drugs with anti-histaminergic actions

- Tricyclic Antidepressants (TCAs)
  Amitriptyline (Elavil®) -particularly effective in treating sleep disorders due to chronic pain syndromes such as fibromyalgia
  Doxepin (Sinequan®)
  Imipramine (Trofanil®)
- Mixed Action Atypical Antidepressants
  Mirtazapine (Remeron®)
  Trazadone (Deseryl®) – originally approved as an antidepressant, is highly sedating and is currently marketed as a hypnotic drug.
  Nefazodone (Serzone®)
- The Antihistamines- H-1 histamine receptor antagonists
  Cyclobenzaprine (Flexeril®)
  Hydroxyzine (Atarax®, Visteril®)
  Diphenhydramine (over the counter **Benadryl®**)
  Over the counter **ZzzQuil**- diphenhydramine is the active ingredient

e) Herbal Preparations:
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)**
  Sesquiterpenes are the active compounds that mediate GABA release & the inhibition of GABA breakdown.
  Shown to be useful for up to 4 weeks in treating insomnia

Does not produce a "next day" hangover or other aversive effects
Does not induce any serious drug interactions.

- **Chamomile (*Matricaria recutita*)**
  A benzodiazepine agonist, active ingredient is Apigenin
  Chamomile tea is relaxing when ingested at bedtime.
- **Kava**
  Facilitates the binding of GABA, active component is Kava lactones;
  Reported to have calming effects.
- "**Passion flower"**
  is a benzodiazepine partial agonist, Chrysin is the active compound
  Reported to be an effective and safe hypnotic but this has not been substantiated.

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 produced tolerance, rebound insomnia, and were NOT more effective than placebo. They were subsequently removed from the market.

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

OTC sleep aid that is available at this time.
Unisom - contains the antihistamine, doxylamine, as the active ingredient.
ZzzQuil- diphenhydramine

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

SHORT-ACTING

Zolpidem (Ambien®)	Zaleplon (Sonata®)	Eszopiclone (Lunesta®)
Diphendydramine (Benadryl®)		
Ramelteon (Rozerem®)		
Thiopental Sodium (Pentathal®)	Midazolam (Versed®)	Triazolam (Halcion®)
Flumazenil (Romazicon®)		

INTERMEDIATE-ACTING

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

LONG-ACTING

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

Drugs of Abuse

Date: Feb 16, 2017 – 8:30 AM

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

Reading Assignment: Basic & Clinical Pharmacology, B.G. Katzung, 12th 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 use disorder** 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 2015
   b. Two-thirds of those who have substance use disorder visit a primary care physician or emergency department every 6 months
2. Failure to consider substance use disorder in the clinical practice often might compromise treatment

1.2 Drugs of Abuse

A. Psychomotor stimulants – cocaine, amphetamines
B. Opiates and Opioids – heroin, morphine, codeine
C. Cannabinoids – marijuana
D. Alcohol
E. Sedatives – benzodiazepines
F. Nicotine
G. Hallucinogens – LSD, mescaline "club drugs"

1.3 Criteria for Substance Use Disorder by DSM-V

1. **Tolerance**
2. **Withdrawal** (marker of **physiological dependence**)
3. Use of larger amounts than intended
4. Persistent desire, inability to control use
5. Excessive time spent obtaining, using, recovering
6. Normal activities given up or reduced
7. Use despite having knowledge of the problems drugs can cause

Mild 2-3 symptoms
Moderate 4-5 symptoms
Severe 5+ symptoms

1.4 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) need to use more of the drug to have the same effect

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

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

1.7 and 1.8 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

1.9. Slides explaining the molecular underpinning of being High and Withdrawal.

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.

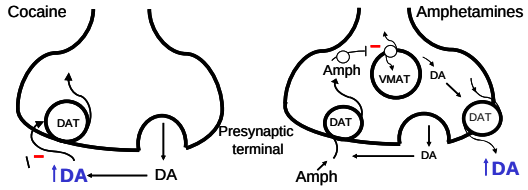
A2. Cocaine

1) Used for medicinal purposes:

- powerful stimulant of the central nervous system (used by Freud to treat depression)
- an appetite suppressant (used for obesity)
- topical anesthetic (used for eye and nasal surgery)

2) Used for popularization before 1906 when the Pure Food and Drug Act was passed
   - Coca leaves were included in several wines and cigarettes
   - Coca leaves were also included in original 1886 recipe for Coca-Cola for nearly 20 years

A2. Site of action of Cocaine and Amphetamines in Presynaptic Neurons



Cocaine

Cocaine –inhibits the action of dopamine transporters. There is an inhibition of dopamine re-uptake that leads to increased levels of dopamine in the synaptic cleft.

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**.**

A3. 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

A4. 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
3. If smoked or taken IV, peak *arterial* blood levels are reached in 15 sec.
4. Acute effects last less than 30 min, resulting in binge use.
5. Half-life varies from 40-80 min, requiring repeated administration to maintain blood levels

6. Rapidly metabolized by cholinesterases into **benzoylecgnonine** and ecgonine methyl ester, the former being what is measured in urine tests and which can remain present for up to 36 hr and perhaps even longer. Cocaine metabolites can also be measured in saliva, hair, and breast milk.
7. **Cocaethylene** is formed in the body when cocaine is ingested with alcohol; it is pharmacologically active and enhances the effects of cocaine

A5. **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

A6. **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 arrhythmia, 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

A7**. Withdrawal Signs (peaks at 2-4 days)**

1. Anxiety, agitation, fatigue, depression, nightmares, headache, sweating, muscle cramps, hunger, craving

A8. **Detection of Use**

1. Observe for symptoms of withdrawal
2. Urine tests (2 to 4 days)
3. Other clues: AIDS, hepatitis, track marks, abscesses, bacterial endocarditis, chronic respiratory symptoms

A9. **Treatment of Cocaine Withdrawal**

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

2. Long-term addiction
   a) No FDA-approved pharmacological therapies
   b) Cognitive-Behavioral Therapies – two components
      - Functional analysis – to identify the patient's thoughts, feelings, and circumstances before and after the cocaine use to understand reason for using cocaine
      - Skills Training to help cocaine users to cope with intrapersonal and interpersonal problems

Development of vaccine against cocaine – successful studies in monkeys

B. Opioids (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, isolated from opium in early 1800s, and codeine is derived from opium. There are semi-synthetic (e.g., heroin, hydromorphone [Dilaudid®]) and synthetic (e.g., fentanyl [Sublimaze®]) drugs with morphine-like effects and together all are called **opioids**, which includes naturally occurring brain neuropeptides (e.g., endorphins)

B2. Mechanisms of action

1. Opioids exert their pharmacodynamic effects through three principal opioid receptors- **mu**, **delta** and **kappa**
2. Opioids cause 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. Signs of Opioid Overdoes

1. Unconsciousness
2. Miosis (pinpoint pupils)
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)
2. Heroin is a pro-drug that is rapidly converted into 6-monoacetylmorphine by esterases present in the blood, brain and every tissue
3. 6-monoacetylmorphine is further metabolized to morphine which contributes to the duration of effect of heroin
4. Withdrawal begins 12 hours after last dose, peaks at 1½ - 3 days, and is mostly over by 5-7 days
5. Lingering symptoms can persist for months ("Protracted Abstinence Syndrome") and are associated with relapse.
6. Withdrawal is profoundly painful and unpleasant, sometimes might be life threatening

B7. Opioid **Withdrawal** (7-10 days, uncomfortable but not medically complicated)

1. Anxiety and dysphoria
2. Craving and drug-seeking
3. Sleep disturbances
4. Nausea, vomiting and diarrhea
5. **Lacrimation**
6. **Rhinorrhea**
7. **Yawning**
8. **Piloerection**, 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 overdose of opioids
  - **Naloxone** (mu-opioid receptor antagonist)

  Treatment of opioid dependence
  - **Naltrexone** [Vivitrol] (mu-opioid receptor antagonist with long half-life)
- Treatment of withdrawal syndrome and maintenance
  - **Methadone** - mu-opioid receptor agonist
  - **Buprenorphine** partial – mu-opioid receptor agonist

B11. Treatment of Opioid Overdose

- **Naloxone [Narcan, Nalone]**
  μ-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 of Opioid Dependence with Naltrexone

Naltrexone [Vivitrol]
μ-opioid agonist with long half-life
FDA approved 1984 – opioid dependence
Orally absorbed, high receptor affinity
Heroin self-administration no longer rewarding
Do not treat patients with Naltrexone who have liver problems

B13. Treatment with Methadone

- Methadone [Symoron] – 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 mu-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) to decrease potential for IV abuse
- 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-opioid receptor by a buprenorphine

B15. Misuse of Suboxone (4:1 Bupernorphine and Naloxone) by IV injections

C. 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

C2. Mechanism of action
1. THC activates a **cannabinoid receptor (CB-1) in the VTA** to initiate its action
2. There are two cannabinoid receptors with CB1, not CB2, most likely mediating the abuse-related effects of THC
3. Cannabinoids 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 appetite ("munchies") – due to the drop of sugar levels and also stimulation of cannabinoid receptors in the hypothalamus.**
- Increase heart rate, dry mouth
- **Injection of the conjunctiva ("red eyes") – due to decreased pressure in the eyes and increased blood pressure**

C4. Adverse Effects of Marijuana Use
1. Panic, delirium, psychosis (often paranoid)
2. Long-term use: Amotivational syndrome, inattention, poor judgment, distractibility, 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. Many believe it is a "gateway" drug, i.e., its use leads to initiation of use of other drugs of abuse
5. Currently 25 states approved marijuana for medicinal purposes (including IL)

and 7 states for recreation.

C5. Treatment of Marijuana Abuse is Symptomatic

- Anxiolytics 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 antecedents
- 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 mechanisms:
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
  Larazepam has as shorter half-life but 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)
   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)
   visual, auditory, tactile – can last for months
4) delirium tremens (48-96 hrs after the last drink, can last 1-5 days)

D7. Delirium Tremens (DT) – 48-96 hrs

- 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, visual hallucinations
- Uncontrollable tremors of the extremities
- Severe autonomic instability (fever, tachycardia, hypertension)

Treatment

- Pharmacotherapy is symptomatic and supportive
- Benzodiazepines, such as diazepam (Valium), lorazepam (Ativan)

D8. FDA-Approved Pharmacotherapies for Alcohol Dependence

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

D9. Disulfiram

- Inhibits aldehyde dehydrogenase
- When taken with alcohol, increased levels of acetaldehyde – metabolite of alcohol
  Leads to nausea, dizziness, headache, hypotension, vomiting
- Decreases desire to drink alcohol but does not increase abstinence
- Increased risk of hepatotoxicity

D 10. Naltrexone [ReVia]

- Opioid antagonist
- Blocks release of dopamine from the Nucleus Accumbens
- Avoid Naltrexone with Disulfiram – both are potential hepatotoxins
- Avoid Naltrexone in patients dependent on opioids- it will precipitate acute withdrawal syndrome

D. 11 Acamprosate

- Restore balance between neuronal excitation and inhibition (mechanism unknown)
- Minor side effects: diarrhea, allergic reactions, irregular heartbeats
- Dose adjustment in patients with moderate renal disease (creatinine clearance 30-50 mL/min)

- Contradicted in severe renal disease (creatinine clearance < 30 mL/min)

E. Anti-depressants: Benzodiazepines

Therapeutic Uses of Benzodiazepines

- Benzodiazepines are the most commonly prescribed sedative-hypnotics
- Severe anxiety, panic attacks and phobias (because of their anxiolytic properties)
- Insomnia
- In muscular disorders - effective muscle relaxants
- Alcohol withdrawal
- Epilepsy – anticonvulsant

E1. Benzodiazepine Withdrawal Syndrome

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

– 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

- Causes change of sensation, illusions, called – mind-bending drugs
- The drugs do not induce dependence or addition
- Serotonin receptors 5-HT2A in cortex are molecular targets
- Treatment: for nonpsychotic agitation – anti-anxiety drugs
  for severe agitation – use antipsychotic drugs

Please see summary slides in PowerPoint presentation

ANTPSYCHOTIC DRUGS
KEY CONCEPTS AND LEARNING OBJECTIVES:

1) Name the 4 well-defined dopamine tracts and recall for which tract dopamine hyperactivity results in psychosis

2) For each of the 4 dopamine systems/tracts, describe what happens when an antipsychotic medication blocks:
   A. less than 60-65% of that tract's dopamine receptors
   B. between 65% and 80% of that tract's dopamine receptors
   C. more than 80% of that tract's dopamine receptors

3) Recall the Dopamine Hypothesis and explain what information supports it and what information does not support it

4) Identify which side effects are caused by antipsychotic medication antagonism of the following:
   A. Dopamine receptors
   B. α-1 adrenergic receptors
   C. muscarinic (cholinergic) receptors
   D. histamine receptors

5) Differentiate the following involuntary movements from each other:
   A. Drug induced Parkinsonism
   B. Dystonia
   C. Akathisia
   D. Tardive Dyskinesia

6) Compare and contrast the following antipsychotic mechanism of action models:
   A. $5HT_2$ D_2 dual antagonism
   B. Hit and run model
   C. Partial agonist model

7) Describe the evolution of antipsychotics from the first antipsychotic medication through the newest one in terms of the mechanism of action and side effects. This description should include the following classes/groups of antipsychotics:
   A. The low potency first generation antipsychotics
   B. The high potency first generation antipsychotics
   C. The second generation antipsychotic clozapine (clozaril)
   D. The second generation antipsychotic "-apine" group including asenapine (saphris)
   E. The second generation antipsychotic "-idone" group including lurasidone (latuda)
   F. The second generation antipsychotic aripiprazole (abilify)

8) Recall the advantages and disadvantages for clozapine (clozaril) such that is it a "high risk/high reward" drug

9) Recall which antipsychotic and non-antipsychotics may cause Neuroleptic Malignant Syndrome (NMS), NMS's clinical presentation, and the recommended treatment.

IMPORTANT DRUGS

Chlorpromazine (Thorazine)**		Risperidone (Risperidal)**
Haloperidol (Haldol)**		Aripiprazole (Abilify)**
		Clozapine (Clozaril)**

Prototype drugs**

Olanzapine (Zyprexa)		Paliperidone (Invega)
Quetiapine (Seroquel)		Ziprasidone (Geodon)
Asenapine (Saphris)		Iloperidone (Fanapt)
		Lurasidone (Latuda)

ANTIPSYCHOTIC DRUGS

I. Drug Indications-FDA approved

Adults

Schizophrenia (acute & maintenance treatment)
Bipolar disorder (acute mania treatment, maintenance treatment, bipolar depression treatment)
Agitation associated with schizophrenia or bipolar disorder

Children & Adolescents

Schizophrenia, Autism

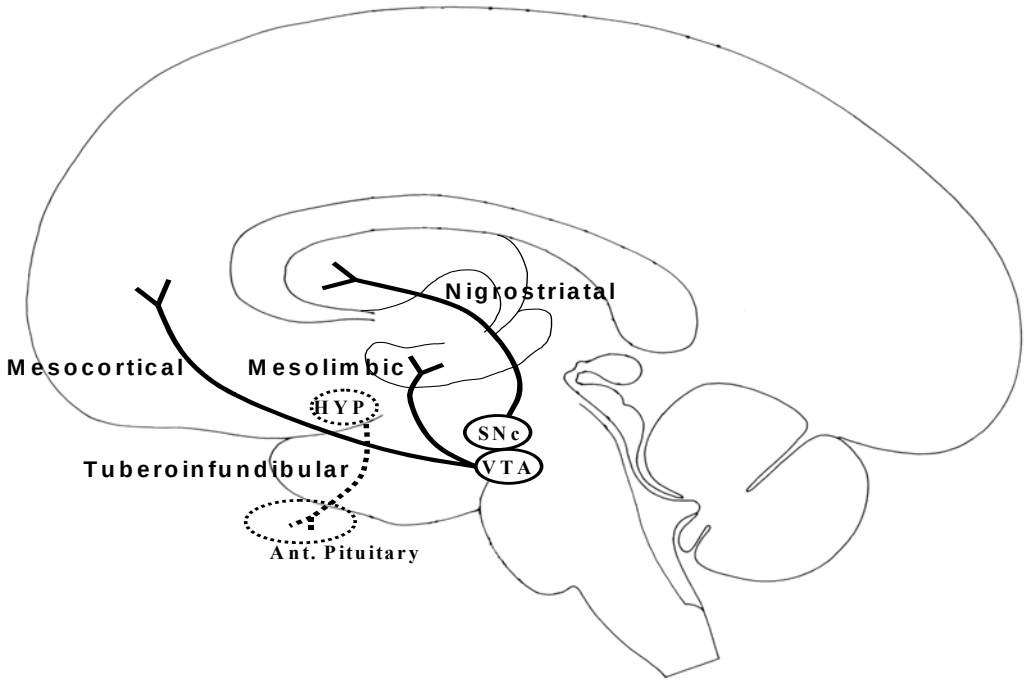
Common use:

Psychotic illnesses:

Schizophrenia, Schizoaffective disorder, Mood disorders with psychotic features
Medical illnesses with psychosis (delirium, dementia); substance induced psychosis

Mood disorders-Bipolar disorder; adjunctive treatment of Major Depression
Agitation
Tourette's; OCD adjunctive treatment, anxiety adjunctive treatment

II. Normal Physiology



A. Mesolimbic system

Dopamine (DA) neurons projecting from ventral tegmental area to subcortical structures of the brain (e.g. nucleus accumbens);
Psychotic symptoms involve "mesolimbic dopamine hyperactivity."
Blockade of DA_2 receptors in mesolimbic system reduces psychotic symptoms.

B. Mesocortical system

DA neurons projecting from ventral tegmental area to frontal cortex;
Schizophrenia negative symptoms (and possibly positive symptoms to a small extent) related to mesocortical DA dysfunction.
Blockade of DA_2 receptors in mesocortical system may worsen negative symptoms.

C. Nigrostriatal system

DA neurons projecting from substantia nigra pars compacta to striatum (comprises part of basal ganglia motor circuit);
Blockade of DA_2 receptors in basal ganglia lead to Extrapyramidal Side Effects (EPS)

D. Tuberoinfundibular system

DA neurons projecting from the hypothalamus to the anterior pituitary;
Blockade of DA_2 receptors in anterior pituitary lead to Hyperprolactinemia and associated adverse effects.

III. Pathophysiology/Disease state

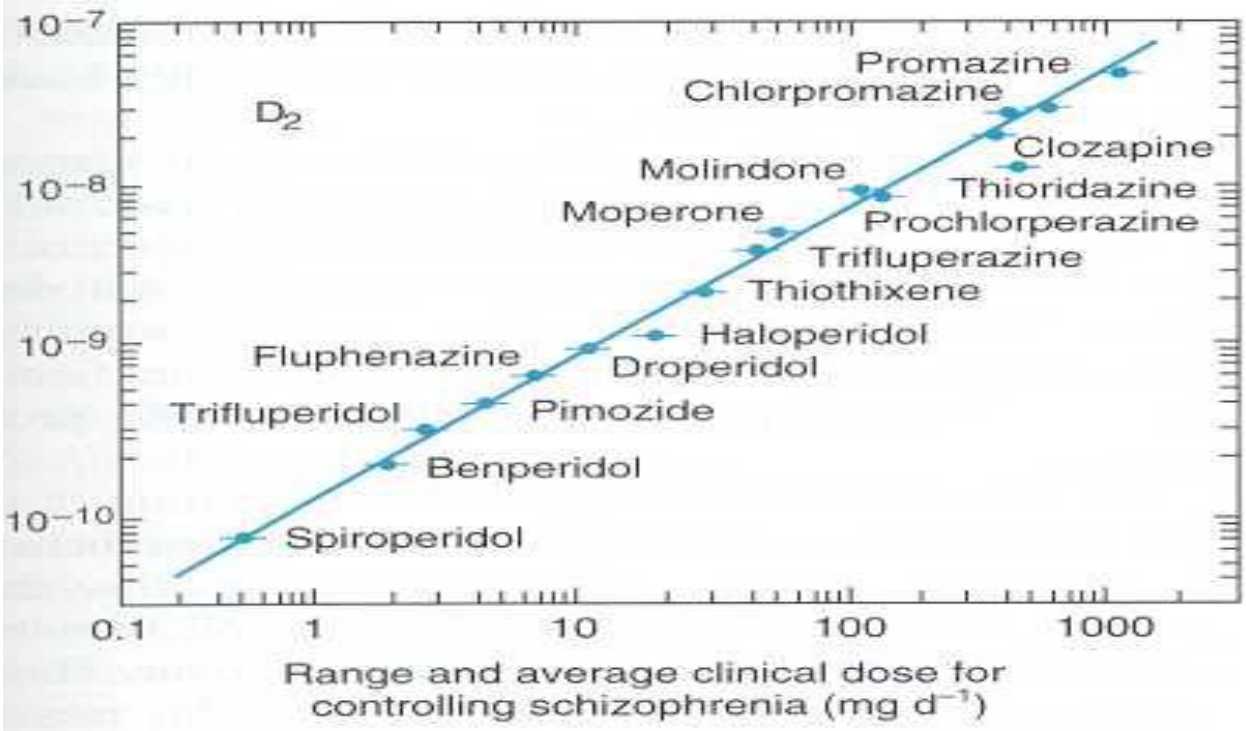
Dopamine Hypothesis

Hyperactivity of Dopamine (DA) neurotransmitter pathways ➔ Schizophrenia

Evidence

1. Typical Anti-psychotics-block DA receptors
2. Drugs, such as cocaine, amphetamines, levodopa, which ↑Dopamine activity ➔ psychosis
3. Increased Dopamine receptors in patients with schizophrenia
4. Treated schizophrenic patients have less Dopamine breakdown products than untreated schizophrenic patients (the dopamine system in treated patients is no longer hyperactive, less dopamine, less dopamine breakdown products)

Binding Affinity & Effectiveness



Dopamine Hypothesis Limitations

- 20 - 40% of schizophrenic pts fail to respond adequately to treatment w/ antipsychotics
- ~30% of pts treated w/ typical antipsychotics relapse each year
- First Generation Antipsychotics (FGA's) are more effective against positive symptoms than negative symptoms.

IV. Anti-psychotic development

Prototypes**

First Generation Antipsychotics (FGA's)

Major Tranquilizers-probably from use in treating agitation and delirium
Neuroleptics-literally, to seize the nerves
Conventional antipsychotics
Typical Antipsychotics

The first antipsychotic, chlorpromazine, was discovered by chance. Improvement attempts inadvertently led to the discovery of the first antidepressant, imipramine. Receptor profiles of the two classes are similar: both are H1 blockers, M1 blockers, & α_1 adrenergic blockers

A. Phenothiazines

Chlorpromazine (Thorazine)**	low potency		
Thioridazine (Mellaril)	low potency	Trifluoperazine (Stelazine)	high potency
Perphenazine (Trilafon)	medium potency	Fluphenazine (Prolixin)	high potency

B. Thioxanthines

Thiothixene (Navane) medium potency

C. Butyrophenones

Haloperidol (Haldol)** high potency

Low Potency vs. High Potency

Low potency FGA's-low D_2 binding affinity; takes a larger dose to have the desired clinical effect
High potency FGA's-high D_2 binding affinity; takes a smaller dose to have the desired clinical effect

Graph on prior page:
Chlorpromazine is a lower potency drug compared to Haloperidol;
Takes more Chlorpromazine to have the same antipsychotic clinical effect as Haloperidol

Second Generation Antipsychotics (SGA's)

Atypical Antipsychotic
Clozapine (Clozaril)**

Clozapine-first "atypical" antipsychotic;
Atypical as it did not cause the involuntary movement side effects (EPS/TD) that are very "typical" for the original antipsychotics

Risperidone (Risperdal)**	Paliperidone (Invega)	Ziprasidone (Geodon)
	Iloperidone (Fanapt)	Lurasidone (Latuda)
Olanzapine (Zyprexa)	Quetiapine (Seroquel)	Asenapine (Saphris)

Aripiprazole (Abilify)**
Brexpiprazole (Rexulti)

Aripiprazole's partial agonist mechanism of action was unique among antipsychotics; Brexpiprazole is now the 2nd and only other antipsychotic with this mechanism of action

V. Pharmacodynamics-mechanism of action; what the drug does to the body

First Generation Antipsychotics (FGA's)

Therapeutic Window for Treatment:

> 65% mesolimbic tract DA_2 receptors blocked ➜ antipsychotic effect
If/when ≥ 80% nigrostriatal tract DA_2 receptors blocked ➜ EPS/TD
If/when ≥ 80% tuberoinfundibular tract DA_2 receptors blocked ➜ hyperprolactinemia

Difficult to hit the 65-80% blocked DA_2 receptors therapeutic window

Each antipsychotic drug has a different level of affinity for the different neurotransmitter receptors; so different medications have different side effects, or different levels of the side effects

Dopamine system: Anti-psychotic, EPS, Tardive dyskinesia, Hyperprolactinemia
Muscarinic system: Anticholinergic-blurred vision, dry mouth, urinary retention, constipation, confusion
α_1 Adrenergic system: Orthostatic hypotension, fall risk
Histamine system: Sedation, weight gain

Side effect profile comparison of FGA's Low potency vs High potency	Chlorpromazine (Low potency)	Haloperidol (High potency)
Dopamine-D2 Extrapyramidal (EPS/TD); Increased prolactin	++	+++
Muscarinic-M1-Anticholinergic Blurred vision, dry mouth, urinary retention etc.	+++	0
α-1 Adrenergic Orthostasis	+++	0
Histamine-H1-related Sedation, weight gain	+++	0

Dopamine System Side Effects

1. **Extra Pyramidal Syndrome (EPS):** 50-90% pts develop EPS

Drug Induced Parkinsonism

- Tremor
  - Resting-tremor improves when holding a posture
  - Essential tremor-present when maintaining/holding a posture; goes away at rest
- Akinesia/Bradykinesia/Hypokinesia
  - General slowness including bradyphrenia (slowed thinking)
  - Loss of automatic movements (blinking) → masked fascies
  - Difficulty initiating movements
- Rigidity: ↑ resistance to passive movement, cogwheel rigidity
- Impaired Posture/balance

Dystonia

- Sustained involuntary muscle contraction or spasm → abnormal posture, twisting
- often made worse or brought out by activity
- young males- ↑ risk for EPS-dystonia; often very early (2 weeks) in treatment-may be thought an "allergic" reaction

Akathisia

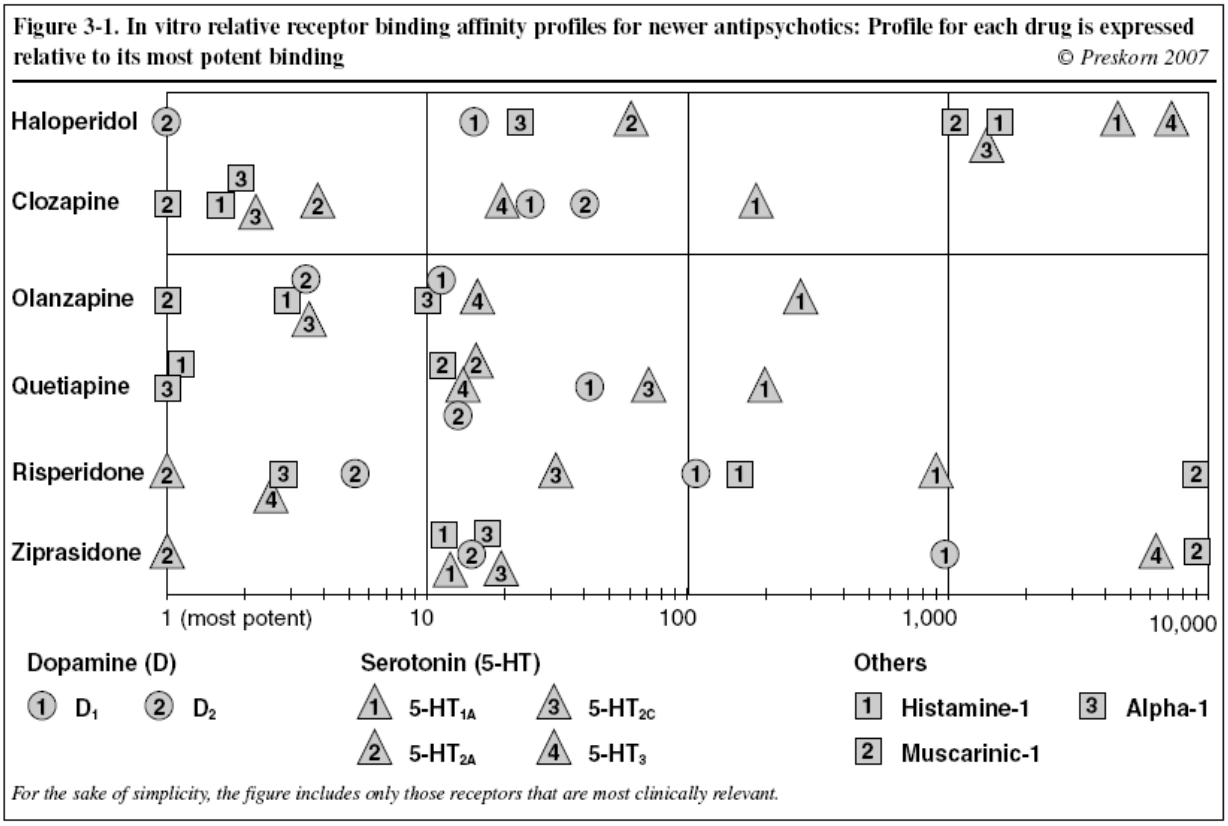
- inner sense of restlessness (often legs) and a need to move that pts find especially distressful; easily mistaken for "agitation"
- women-↑ risk, 2x > men

2. **Tardive Dyskinesia**: 20-50% pts develop TD
   - Abnormal involuntary movement from taking DA blockers medication
     Typically does not remit even after stopping DA blocking drug
   - Classically, especially lower facial movements: Oro-facio-lingual-masticatory movements
     Sometimes resembles chorea, dystonia, myoclonus, tics or tremor

3. **Hyperprolactinemia**:
   - ➔ galactorrhea/lactation & gynecomastia
   - ➔ ↓Gonadotropin releasing hormone (GnRH) ➔ ↓Leutinizing Hormone (LH), &
     ↓ Follicle Stimulating Hormone (FSH)
     ➔ irregular menstruation & fertility issues
   - ➔ osteopenia ➔ ↑ risk of fractures

Second Generation Antipsychotics (SGA's)

Atypical Antipsychotic Drug Affinities at Various Neurotransmitter Receptors



Mechanism of Action

1. **Serotonin-Dopamine Dual Antagonism Hypothesis**
   - Mesolimbic tract, Nigrostriatal tract, &Tuberoinfundibular tract
     5-HT2A blockade enhances DA release in basal ganglia (from nigrostriatal DA system);
     This DA competes with the antipsychotic medication for DA_2 receptors;
     Result: majority (> 65%), but not all (< 80%) of D2 receptors blocked: therapeutic window
     > 65% mesolimbic tract DA_2 receptors blocked ➔ antipsychotic effect
     < 80% nigrostriatal tract DA_2 receptors blocked ➔ reduced/no EPS
     < 80% tuberoinfundibular tract DA_2 receptors blocked ➔ reduced/no hyperprolactinemia

   - Mesocortical
     5-HT2A blockade may normalize cortical function (possibly by enhancing DA release and acetylcholine release in frontal cortex), thereby reducing negative symptoms/cognitive deficits

2. **Hit & run concept**
   - Lower potency DA_2 blockade by atypical antipsychotics has also led to "hit and run" concept; i.e. atypical drug-induced blockade of DA_2 receptors is looser and not as long-lasting as with typical drugs. The blockade is present long enough to have the antipsychotic therapeutic effect but not long enough to cause side effects
     One piece of support for this theory is antipsychotics that bind the weakest to the D2 receptor—clozapine and quetiapine—have the lowest incidence of EPS/TD side effects

Side effect profile comparison of SGA's	Risperidone (Risperdal)	Ziprasidone (Geodon)	Quetiapine (Seroquel)	Olanzapine (Zyprexa)	Clozapine (Clozaril)
Dopamine-D2-related Extrapyramidal (EPS/TD) Increased prolactin	+/++	+	0/+	+	0
α-1 Adrenergic Orthostasis	++	+	++	++	+++
Muscarinic-M1 Anticholinergic Blurred vision, dry mouth, etc.	0	0	+	++	+++
Histamine-H1 Sedation, weight gain	0	+	++	+++	+++
Metabolic Syndrome Wt gain, lipids, glucose intolerance	++	0/+	++	+++	+++

- Metabolic Syndrome: Weight gain, Hyperglycemia, Diabetes Mellitus, Dyslipidemia
  Considered the signature side effect of the SGA's. Metabolic Syndrome worsens a number of cardiac disease risk factors in a patient population that is already at increased risk. The increased rate of cardiovascular disease is the primary reason patients with schizophrenia's life expectancy is about 20 years shorter than the general public.

  All SGA's can result in significant weight gain; are differences among the medications.
  Clozapine > Olanzapine >>Quetiapine >>Risperadone/Paliperidone>>
  Asenapine/Ziprasidone/Aripiprazole/Lurasidone

3. **Partial Agonism**: Aripiprazole (Abilify) & Brexpiprazole (Rexulti)
   - Rheostat analogy; the receptor (light) is partially on (neither completely on nor completely off)
     Partial agonist sits on the receptor like an antagonist & blocks the receptor from other stimulation; Changes the receptor conformation slightly; G protein organization changes slightly & there is a small signal

   In low neuroreceptor stimulation environments
   - Causes a little agonist activity (the cell is not completely off)
     In low dopamine receptor stimulation environment, aripiprazole binds to the DA_2 receptor with high affinity (potent) & has a partial agonist effect

   In high neuroreceptor stimulation environments
   - Exerts antagonist action (the cell is not completely on)
     In high dopaminergic environment aripiprazole has the effect of an antagonist

Dopamine system stabilization idea (i.e. not too much, not too little); supported by observation that clinical efficacy of atypical antipsychotics may be seen at D_2 occupancy levels below those achieved by typical antipsychotics. Aripirprazole is the first Dopamine-Serotonin System Stabilizer

VI. Other Notes

Prominent atypical drug-related effects

- EPS/TD:
  Risperidone (Risperdal)-acts more like a typical antipsychotic at higher doses (>6 mg/day);
  Asenapine (Saphris)-increased risk of EPS
- QTc elongation: Thioridazine (Mellaril) > Ziprasidone (Geodon) > many others with smaller risks
- Sedation: Clozapine > Olanzapine > Quetiapine > Risperidone/Paliperidone

Clozapine (Clozaril): High risk/High reward drug

High Risk

- Common side effects
  - Sedation
  - Anticholinergic
  - Metabolic syndrome, weight gain
- Dangerous side effects
  - **Agranulocytosis 1-2% of pts**
  - Myocarditis
  - Increased risk of seizures

High Reward

- Helps with negative symptoms
- Helps with Tardive dyskinesia
- Helps ↓risk of suicide/violence
- Helps with treatment resistant schizophrenia

Due to agranulocytosis risk, pts on clozapine have their WBC counts checked weekly

Neuroleptic Malignant Syndrome (NMS)

Rare side effect: 0.02-3% estimate
Involving dopamine blockers: any and all antipsychotics, some GI drugs
dopamine system "goes haywire"
Mental status changes (confusion),
Rigidity: ↑ CPK, tremor
Fever: > 40° C common
Dysautonomia: ↑HR, ↑ & ↓ BP, ↑RR/hypoxia
Treatment:
Stop the dopamine blocker
Supportive therapy
No agreement on any medication treatment

Sudden death

↑ Mortality in elderly pts with Dementia; death from stroke and related disorders is greater than placebo. Both FGA and SGA carry similar risk; Risk increases with higher doses.
Possible cause unknown
In general population risk likely to be small and difficult to detect; risk increased with patients who have prior cardiovascular disease

Pharmacokinetics-what the body does to the drug

Bioavailability IM > PO
PO, incomplete GI absorption, 1st pass effect
Peak plasma level
IM: ~ 30 min vs. PO: ~ 1-4 hrs
90% protein bound; unbound passes through blood brain barrier
Very lipid soluble-stored in body fat, slows removal
Half-life about 20 hours, steady state 4-7 days

Drugs Used in the treatment of Rheumatoid Arthritis and Gout

Date: Wednesday, March 1st, 2017 – 8:30-9:30am

KEY CONCEPTS AND LEARNING OBJECTIVES

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

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

3. Describe the major indications, mechanism of action, time to effect, major adverse effects and contraindications of the frequently used DMARDs class of drugs used in the treatment of RA.

4. List the less frequently used DMARDs used in the treatment of Rheumatoid Arthritis.

5. Describe the major indications, mechanism of action, major adverse effects and contraindications of the Biological Response Modifier class of drugs used in the treatment of Rheumatoid Arthritis.

6. Identify the classes of drugs used in the treatment of Rheumatoid arthritis that are safe to use in pregnancy.

7. Apply your knowledge of the pharmacology of the major classes of drugs used to treat rheumatoid arthritis to select the most appropriate medication for a specific patient based upon patient-specific criteria.

8. Describe 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.

9. Discuss the rationale for the use of Colchicine and NSAIDs in the treatment of an acute gouty attack

10. Describe the rationale behind the use of the major drug classes used to treat Chronic Gout

11. Describe the indications, mechanism of action, major adverse effects, contraindications and relevant drug interactions of the major drug classes used in the treatment of chronic gout.

12. Apply your knowledge of the pharmacology of the major classes of drugs used to treat gout to select the most appropriate medication for a specific patient based upon patient-specific criteria.

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 more frequently than once every three months due to risk of adverse effects

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®)

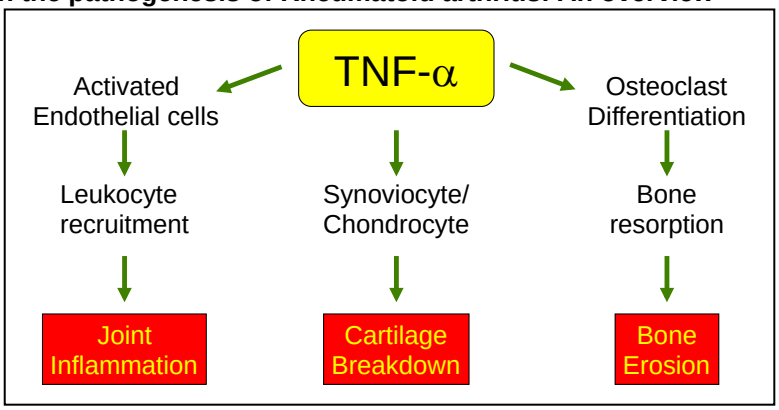
f) Drugs that inhibit immune cytokine receptor signaling
   - Tofacitinib (Xeljanz®))

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®)

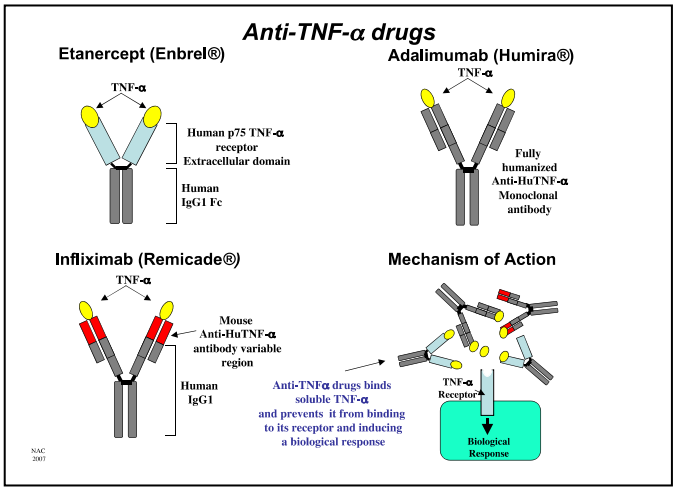
Recombinant protein consisting of two soluble p75 TNF-α receptor moieties linked to the Fc portion of a human IgG1 antibody molecule

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

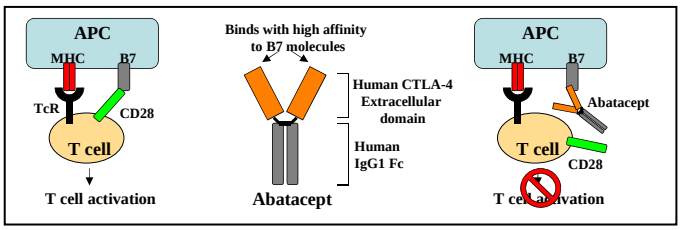
e) Are used as both monotherapy and in combination with methotrexate. When combined with low dose methotrexate the addition of anti-TNFα drugs have been shown to significantly prevent disease progression versus the use of methotrexate alone

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

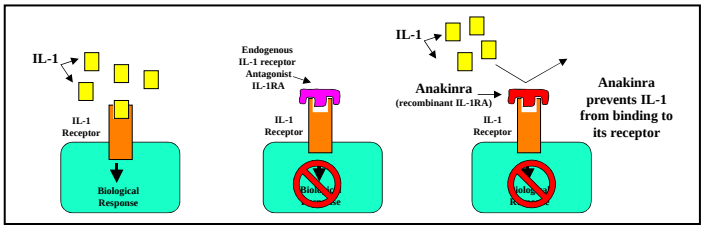
B3.5 Anakinra (Kineret®)

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

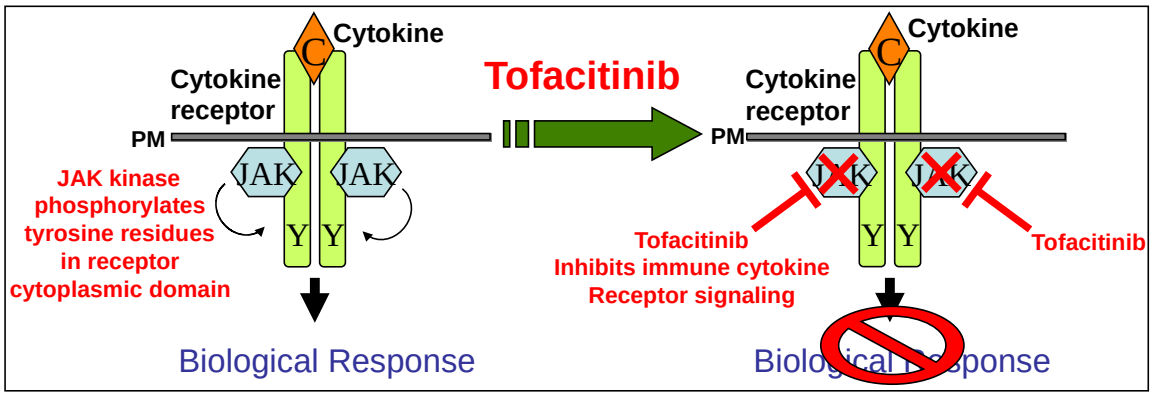
c) Used in patients non-responsive to TNF inhibitors

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

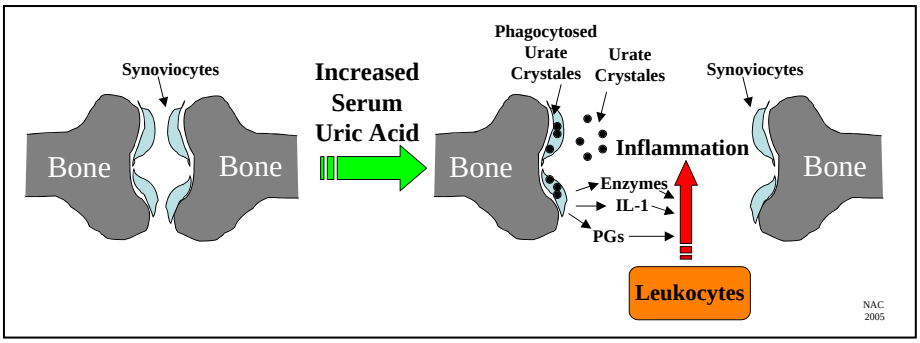
Overview

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

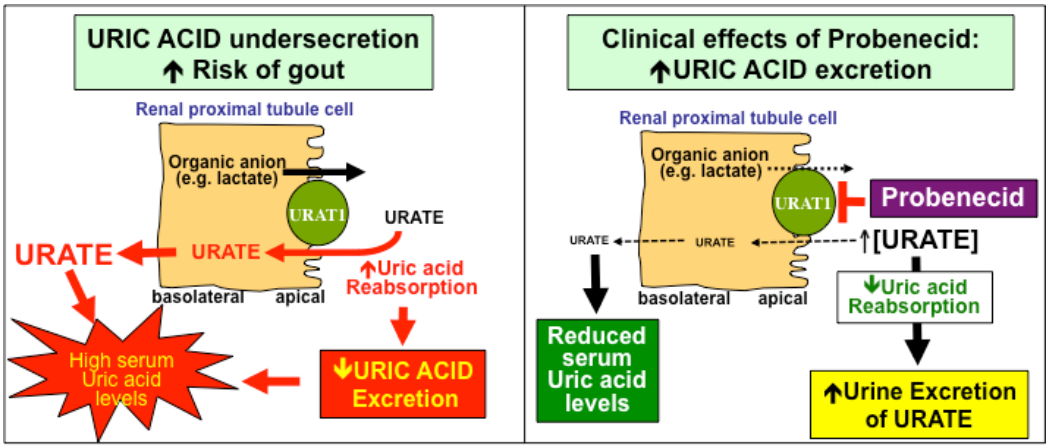
(B) NSAIDs

- 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**

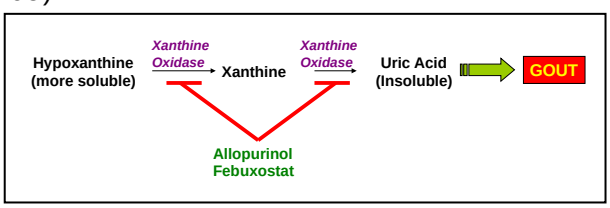
e) To reduce risk of kidney stones urine volume should be maintained at a high level and the urine pH should be kept > pH 6.

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 Ocular 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 Demyelin' disease
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 in: 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) *HLA-B*5801* risk allele Korean Han Chinese, Thai Increased toxicity with Azathioprine
Pegloticase	Drug resistant gout	Enzymatic degradation of Insoluble URIC ACID	Generally well tolerated	Generation of Anti-drug Abs limits treatment