

Pharmacology/Therapeutics Semester IV – Block One Lectures
2010-2011

61. Pharmacology of Antidepressant Drugs – Battaglia
62. Drugs Used to Treat Anxiety and Bipolar Affective Disorders – Battaglia
63. Antipsychotics – Schilling
64. Anti-Parasitic Agents – Johnson
65. Palliation of Constipation & Nausea/Vomiting - Kristopaitis

#61 - PHARMACOLOGY OF ANTIDEPRESSANT DRUGS

Date: January 13, 2011 – 10:30 a.m.

Reading Assignment: Katzung, Basic & Clinical Pharmacology; 11th Edition, Chapter 30, pp. 509 - 530

LEARNING OBJECTIVES

1. To understand the primary sites of action of different classes of antidepressant drugs.
2. To understand the adverse/side effects of the different classes of antidepressant drugs and considerations for their use in certain populations (e.g. in the elderly, in pregnancy, etc).
3. To understand why antidepressant drugs produce some of their effects in the short-term but require at least 2-3 weeks of administration before the onset of therapeutic improvement.
4. To understand some of the proposed mechanisms underlying the delayed therapeutic effects of antidepressant drugs.
5. To understand the considerations in using irreversible versus reversible MAOIs, the potential adverse effects of MAOIs, and the important considerations in switching between SSRIs and MAOIs.

#61 - PHARMACOLOGY OF ANTIDEPRESSANT DRUGS

INTRODUCTION

What is depression?

Depression is not a disease per se, but a clinical disorder that is manifested by a variety of symptoms that likely represent several neurochemical/neuropathological disorders in the brain.

Biological/chemical Diagnostic tests

There are no reliable biological/biochemical diagnostic tests to determine the cause of depression. A substantial number of depressed patients (up to about 40%) show elevated activity of the hypothalamic-pituitary-adrenal axis (elevated plasma cortisol, lack of feedback inhibition by dexamethasone).

Various theories, factors and changes associated with depression include:

- a) Genetic factors –interactions with environment
- b) Pharmacogenetics - different P450 metabolizers, variants of the 5-HT_{2A} receptor or 5HT transporters may affect response to antidepressant medications
- c) Neuroanatomical –neuroimaging and post mortem studies indicate regional changes
- d) Neuroendocrine – increased activity in HPA axis associated with depression and antidepressants normalize HPA function.
- e) Neurotrophic factors such as BDNF (brain derived neurotrophic factor)
- f) Neurotransmitter and signal transduction (receptors and 2nd messenger systems for monoamines)
- g) Other systems implicated: dopamine, acetylcholine, opiates, GABA and CRF.

Simple Take Home Message on Depression & Antidepressant Medications

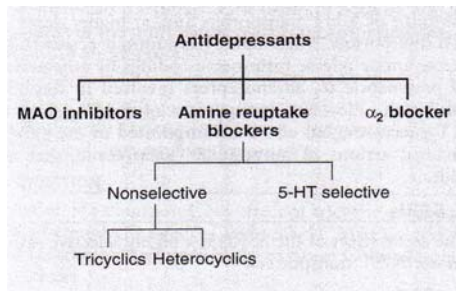
1. Currently, depression is conceived of as a disorder involving deficiency in serotonin and/or norepinephrine neurotransmission – supported by the “monoamine hypothesis of depression” proposed in the 1950’s (reserpine depletion of monoamines or tryptophan deficient diets invoke or precipitate depression, while drugs that increase serotonin or other monoamines alleviate depression).
2. Currently - All clinically effective antidepressant medications act on **serotonin (5-HT) and/or norepinephrine (NE)** systems. Dopamine also may contribute to the effects of some antidepressants.

Important Caveat in Theory & Treatment:

- *The therapeutic efficacy of all Antidepressants is not immediate, but requires repetitive administration over a prolonged period of time (at least 2-3 weeks before improvement starts)*

3. Antidepressant side effects can occur upon drug administration or shortly thereafter and be dependent on the specific pharmacological profile of the drug (i.e. the propensity of the drug to interact with any number of target receptors at clinical concentrations of drug).

Overview of Classes of Antidepressant Drugs

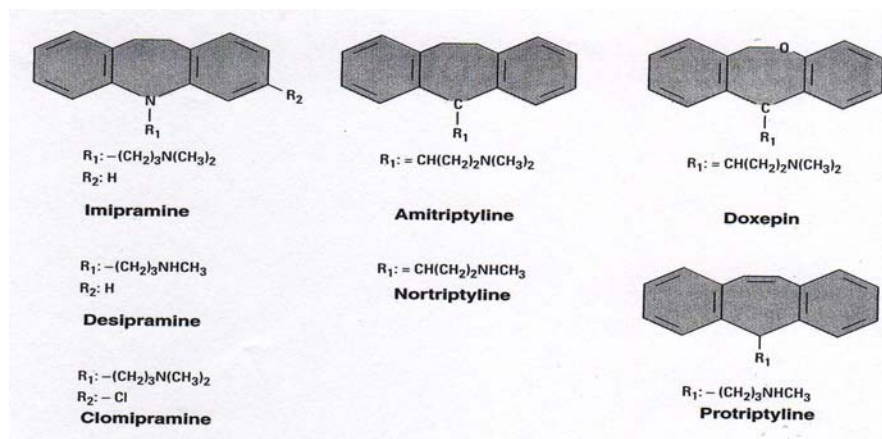


(from Katzung & Trevor's Pharmacology Examination and Board Rev. 7th ed. pp255)

A. TRICYCLIC Antidepressants (TCAs)

These are the “older antidepressants”,

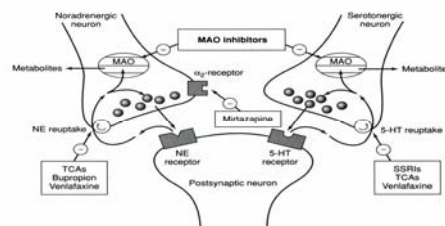
- also referred to as the 1st generation antidepressants
- structurally related to the phenothiazine antipsychotics
- tricyclic antidepressants can be either tertiary or secondary amines (see figure below)



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

Therapeutic Sites of Action

TCAs produce mixed blockade of both 5-HT and NE transporters (blocks reuptake of respective amines)



(source for same fig indicated on pg 6)

Representative TCAs

Imipramine (Trofanil®) - the prototype TCA that blocks reuptake of both 5-HT and NE, tricyclic antidepressants such as imipramine are demethylated to secondary amines (e.g. desipramine).

Desipramine (Norpramine®) – a secondary amine, and active metabolite of imipramine, that preferentially blocks the reuptake of NE

Amitriptyline (Elavil®) - 5-HT and NE reuptake inhibitor that is demethylated to **nortriptyline**,

Nortriptyline (Pamelor®) - an active preferential NE vs 5-HT uptake inhibitor.

Others TCAs that you should recognize:

- **Clomipramine (Anafranil®)** – preferential NE vs 5-HT uptake blockade
- **Doxepin (Sinequin®)** – preferential NE vs 5-HT uptake blockade, very sedating

Pharmacokinetics

- high lipid solubility
- large volume of distribution (Vd)
- rapid absorption
- serum concentrations peak within a few hours
- significant first pass metabolism
- half-life of 8-36 hours (active metabolites of imipramine and amitriptyline)
- high protein binding
- substrates of CYP2D6 (which exhibits genetic polymorphisms)

Prominent Side Effects of TCAs

In addition to blocking monoamine transporters, the tricyclic antidepressants produce prominent antagonist effects at:

alpha-1 adrenergic, muscarinic M1 and H-1 histamine receptors.

These non-selective effects of the TCAs produce several aversive side effects such as:

- 1) postural (orthostatic) hypotension,
- 2) cardiotoxicity,
- 3) confusion with memory dysfunction
- 4) excessive sedation and fatigue
- 5) weight gain.

Tricyclic antidepressants are not recommended for elderly patients (65+ years) because of their liability for inducing a toxic and confused state.

TCA's can produce additive CNS depression with other CNS depressants such as: alcohol, barbiturates, opiates and benzodiazepines.

TCA Overdose - extremely hazardous (ingestion of only a 2 wk supply may be lethal)

Manifestations include:

- agitation & delirium
- respiratory depression and circulatory collapse
- hyperpyrexia
- cardiac conduction defects and severe arrhythmias

B. Tetracyclic, Unicyclic and SNRI Drugs, – these will be discussed later but include drugs such as:

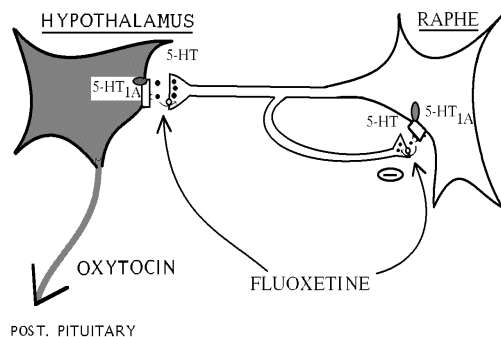
- **amoxepine, mirtazapine, maprotiline & bupropion (unicyclic)**
- **trazadone, nefazadone,**
- **venlafaxine, desvenlafaxine, duloxetine & the SSRIs (3rd generation and beyond)**

C. Selective Serotonin Reuptake Inhibitors (SSRIs)

- fewer adverse effects than the tricyclic antidepressants (TCAs)

Therapeutic Sites of Action

- selective blockade of the reuptake of 5-HT (SERT) in forebrain projection areas (e.g. hypothalamus, cortex, etc) as well as in midbrain regions containing 5-HT cell bodies (e.g. raphe nuclei).



The SSRIs are structurally distinct from the tricyclics and are not chemically related or chemical "look-alikes" to each other. Thus, if a patient does not respond to one SSRI, they may respond to a different SSRI.

However, despite having a better side effect profile than the tricyclics, *there are no substantial*

overall differences in antidepressant efficacy among the SSRIs, or between SSRIs and tricyclics.

SSRIs share the property of being “**selective**” (not exclusive) blockers of 5-HT transporters and primarily differ in:

- **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).

SSRIs also are used to treat a variety of other disorders including

- anxiety disorders,
- eating disorders,
- pre-menstrual dysphoric disorder (PMDD, PMS)
- obsessive compulsive disorder (OCD).

FDA Approved SSRIs

- **Fluoxetine (Prozac®)** – the first FDA approved and prototype SSRI (1987), the least 5-HT selective, long half life (1-4 days) and longer acting (7-15 days) demethylated active metabolite, **norfluoxetine** resulting in considerable drug accumulation. However, this pharmacokinetic reality is not accompanied by any deleterious effect. Major consideration in switching to MAOIs.

Other SSRIs

- paroxetine (Paxil®) - the highest affinity for the 5-HT transporter, no active metabolites
- sertraline (Zoloft®) - has desmethyl active metabolite
- citalopram (Celexa®) – the most selective for the 5-HT transporter, active desmethyl metabolite
- escitalopram (Lexapro®), - the S(+) isomer of (±) citalopram, that retains the highest 5-HT selectivity
- fluvoxamine (Luvox®) - no active metabolites, shorter half live (4-10hrs) than other SSRIs
-

Pharmacokinetics

Bioavailability - ranges from 50% (paroxetine) to > 90% (fluvoxamine)

Protein Binding - ranges from 50%(escitalopram) to 95 % (sertraline)

Plasma half-lives - all SSRIs range from 15-50 hrs, except for fluoxetine (1-4days) and its active metabolite (7-15 days)

Side Effects of SSRIs

- ***often occur prior to the onset of antidepressant efficacy and will depend on;***
 - a) the pharmacological profile of the specific drug (its propensity to interact with sites other than 5-HT uptake sites) and***
 - b) dose of drug***

SSRIs can be stimulatory and anxiogenic (paroxetine in particular) during the first week of use. (These compounds thus should be taken in the morning as opposed to before going to sleep, and in low doses which can be increased gradually).

- often induce sexual dysfunction (loss of libido, impotence, anorgasmia).
- may inhibit certain hepatic cytochrome P450 (CYP) enzymes that could lead to an elevation in plasma levels (thus toxicity) of other drugs that are catabolized by these liver enzymes.

SSRI Discontinuation Syndrome

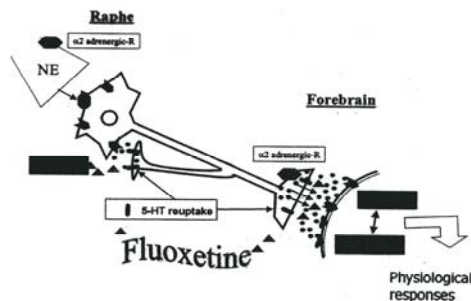
- *SSRIs should NOT be stopped Abruptly** - the dose should be tapered down over time
Abrupt discontinuation of the SSRIs may result in a cluster of symptoms that could include the following:
- dizziness, nausea, fatigue, headache, insomnia, restlessness, unstable gait and shock like sensations (rare).

More apparent with short acting SSRIs (paroxetine > fluvoxamine > sertraline > citalopram >> fluoxetine).

Noradrenergic-Serotonergic Interactions Relevant to Antidepressant Drug Action

In 5-HT Cell Body Regions(Raphe Nuclei): Release of norepinephrine activates α_1 -adrenergic receptors on 5-HT perikarya and enhances the firing rate of 5-HT neurons, resulting in **increased** release of 5-HT from nerve terminals. This is illustrated below:

(figure from GB)



Therefore, drugs that increase synaptic NE would increase 5-HT release from terminals;
This could be accomplished by:

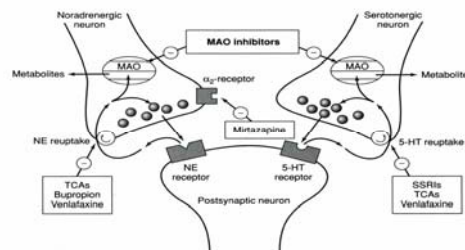
- blockade of NE transporters (NET) and/or
- antagonists at inhibitory alpha2 adrenergic autoreceptors on noradrenergic terminals.

In limbic and cortical regions (i.e. forebrain regions)

Alpha2-adrenergic receptors function as *inhibitory autoreceptors* on both noradrenergic & serotonergic nerve terminals.

Activation of these **alpha2 adrenergic autoreceptors** results in **decreased** release of norepinephrine from noradrenergic terminals and a **decreased** release of 5-HT from serotonergic terminals.

Therefore, antidepressant drugs that antagonize alpha2 adrenergic adrenergic receptors would result in an **increase** the release of norepinephrine and 5-HT from their respective nerve terminals.



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

D. The Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)

- these drugs exhibit the combined blockade of 5-HT/NE as exhibited by the TCAs but in the absence of many of the adverse effects of the latter.
- minimal effects on the major CYP isoenzymes in contrast to SSRIs (e.g. fluoxetine)

Venlafaxine (Effexor®)

- a 5-HT and NE reuptake inhibitor. It is approved by the FDA for the treatment of both generalized anxiety disorder (GAD) and unipolar depression.

Side Effects

- sexual dysfunction
- hypertension

Desvenlafaxine (Pristig®) – the desmethyl metabolite of venlafaxine, received FDA approval in 2008

Duloxetine (Cymbalta®) – a more balanced blocker of 5-HT and NE reuptake. Received FDA approval in 2004 for treatment of major depressive disorder (MDD) and treatment of peripheral neuropathic pain associated with diabetic neuropathy.

(Milnacipran - not approved in the U.S. market but is an equipotent NE & 5-HT uptake blocker)

Side Effects

- may elevate liver enzymes
- may worsen narrow angle glaucoma
- may cause sexual side effects of urinary hesitancy
- may produce drug interactions via effects on CYP2D6
- may produce discontinuation syndrome

E. Mixed Action or “Atypical” Antidepressants (not for the treatment of atypical depression)

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 also available in a sustained release form and as the generic compound.

Mechanism of Action – recent preclinical studies indicate that its antidepressant mechanism of action may involve desensitization of both 5-HT_{1A} serotonin receptors and α ₂ adrenergic receptors, although a primary mechanism of action remains to be determined.

FYI – Remember: FDA approval only requires demonstration that a drug is safe and efficacious, its mechanism of efficacy does not need to be determined for approval.

Side Effects - profile of side effects that differ from the other antidepressants, devoid of:
anticholinergic, antihistaminergic and orthostatic hypotensive effects

Similar to some of the selective serotonin reuptake inhibitors (SSRIs), bupropion has an "energizing" or stimulating effect and should be taken in the A.M.

May decrease the seizure threshold in susceptible individuals and is contraindicated in individual with a prior history of eating disorders.

Bupropion has a relatively favorable side effect profile:

- weight loss rather than weight gain,
- does not interfere with sexual function.

Mirtazapine (*Remeron*[®]) is an α ₂-adrenergic receptor antagonist.

Mechanism of Action

- blockade of presynaptic α ₂ receptors on both noradrenergic and serotonergic nerve terminals that leads to an increase in NE and 5-HT neurotransmission.
- also blocks postsynaptic 5-HT_{2A}, 5-HT_{2C}, 5-HT₃ and H₁ histamine receptors that likely contributes more to the “side effects” than therapeutic effects of the drug.

Side Effect Profile

- highly sedating at low doses, should be administered before sleep
- can induce weight gain
- does not produce sexual dysfunction,
- does not produce nausea or GI problems,

Nefazodone (Serzone®) - a 5-HT_{2A} serotonin receptor antagonist and 5-HT reuptake inhibitor.

Side Effect Profile - mildly sedating but does not interfere with sexual function, other effects include nausea, dry mouth and increased appetite.

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.

E. The Monoamine Oxidase Inhibitors (MAOIs)

Monoamine oxidase (MAO) is the principal enzyme responsible for the metabolism of 5-HT, NE tyramine and dopamine. There are two types of MAO, MAO-A and MAO-B which differ in their substrate specificity and regional distribution in brain and periphery.

The MAOIs are effective antidepressants, particularly in the treatment of atypical depression (hypersomnolence and hyperphagia with depressed mood).

These drugs **bind** to the mitochondrial enzyme, MAO, either **reversibly** (no chemical bond) or **irreversibly** (forming a covalent bond with the enzyme)

Inhibition of MAO (by either type of interaction) results in an increased amount of NE and 5-HT available for release when the neuron depolarizes ("fires").

Irreversible MAOIs

- phenelzine (Nardil®) - inhibits both MAO-A and MAO-B
- tranylcypromine (Parnate®) - inhibits both MAO-A and MAO-B.
- selegiline (l-deprenyl;Eldepryl®),– preferential MAO-B inhibitor ; a transdermal patch of selegiline, (Emsam®), was approved by the FDA in February 2006 for the treatment of major depression

Once an irreversible inhibitor binds to MAO, the cell must replace the inactivated enzyme. This synthetic process requires 10-14 days.

Reversible MAOIs

In contrast, a reversible inhibitor or monoamine oxidase (a “**RIMA**”), such as moclobemide, is uncoupled from the enzyme. Once a RIMA is discontinued, MAO activity recovers completely in

Reversible inhibition of MAO (**RIMA**) does not result in aversive dietary interactions if the RIMA is taken an hour before or two hours after eating foods with a high tyramine content.

Adverse Effects:

The major problem with MAOIs is that they can lead to potentially lethal **1) dietary and 2) drug interactions**. These scenarios include; *Hypertensive Crisis & The Serotonin Syndrome*

The Emsam patch, at the lowest dose (6 mg/24 hr), does not require a modified diet as for the other irreversible MAOIs

Hypertensive Crisis

- characterized by a major elevation in BP because of the increased catecholaminergic activity that results.
- may result in a ruptured aneurysm and stroke

Hypertensive crisis may be brought on by:

- ingestion of foods containing high concentrations of **tyramine** (e.g., aged cheeses, liqueurs, cured meats)
- use of certain drugs [e.g., cocaine, “ecstasy” (MDMA), certain opioids (such as fentanyl or meperidine),
- over the counter “cold medications” containing sympathomimetics (e.g. pseudoephedrine).

The Serotonin Syndrome

a syndrome characterized by the following:

- myoclonus, autonomic dysfunction, hyperactive reflexes, disorientation, unstable BP

Should avoid drugs (e.g., the SSRIs) that lead to a major increase in 5-HT activity because a **serotonin syndrome** can result.

Although by using RIMAs one can avoid aversive dietary interactions, the patient is still vulnerable to negative drug interactions.

Summary of Antidepressant Drugs and Drug Classes

Tricyclic antidepressants (TCAs)	Selective Serotonin reuptake inhibitors (SSRIs)	5-HT/NE reuptake inhibitor (SNRI)	Atypical (Mixed Action) Antidepressants	Monoamine oxidase inhibitors (MAO-I)
Imipramine	Fluoxetine	Duloxetine	Bupropion	Tranlycypromine
Amitriptyline	Paroxetine	Venlafaxine	Mirtazapine	Phenelzine
Doxepin	Sertraline	Desvenlafaxine	Nefazodone	Moclobemide (reversible MAO-I)
Desipramine	Fluvoxamine		Trazodone	Selegiline

Nortryptaline	Citalopram			
Clomipramine	Escitalopram			

Why do ALL antidepressants (Tricyclics, SSRIs or Mixed Action) have a delayed onset of action (i.e. delayed efficacy) ?

While the antidepressants may block reuptake of neurotransmitters or inhibit their metabolism (via MAOIs) within minutes of clearing the GI system, their therapeutic effects are not apparent for at least 2-3 weeks. This suggests that antidepressant efficacy requires induction of one or more time-dependent compensatory changes to occur. These can include:

1. The need to overcome auto-inhibitory receptor effects (see fig below).
2. Neuroadaptive changes in post-synaptic receptor signaling that occur subsequent to increased levels of 5-HT (or NE) in the synaptic cleft (e.g. desensitization of β -adrenergic receptors & 5-HT_{1A} serotonin receptors).
3. Potential compensatory changes in gene transcription (e.g. BDNF, trkB, CREB), structural changes in various brain regions and neurogenesis.

Desensitization of the 5-HT_{1A} inhibitory Autoreceptor on serotonergic perikarya
(both figures from GB)

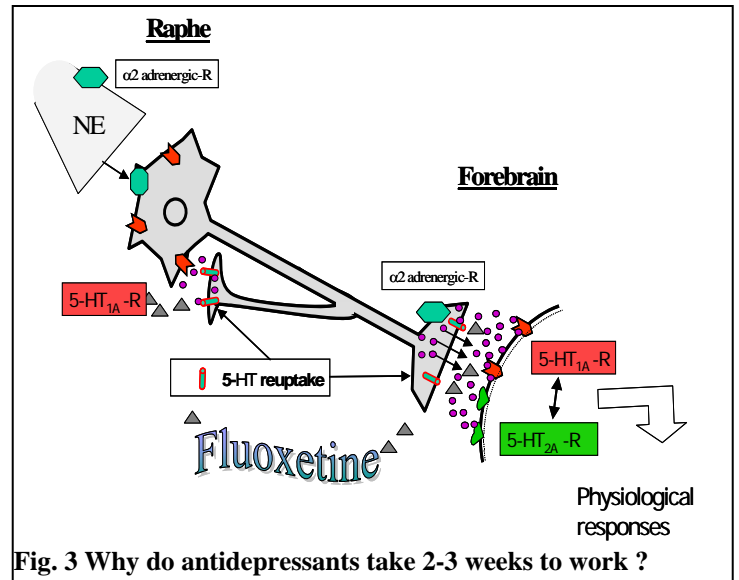
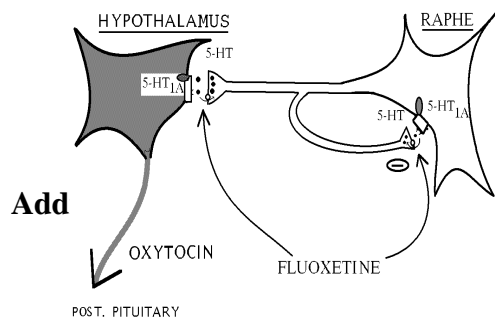


Fig. 3 Why do antidepressants take 2-3 weeks to work ?

Other Considerations with Antidepressant Medications

1. Switching between SSRIs (or Tricyclics) and MAOIs

From SSRI to MAOI

- Consideration of the half-life of the parent compound and any bioactive metabolite. Should wait a minimum of 5 half lives before starting the MAOI.

From MAOIs (irreversible) to SSRI

- Inhibition of MAO may persist long after these drugs are detectable in plasma (i.e. pharmacokinetic parameters are not very useful). Effects may persist from 7 days (tranylcypromine) to 2-3 weeks (phenylzine) after discontinuation.

2. Use of Antidepressants During Pregnancy

- Recent studies indicate that paroxetine may cause cardiovascular defects in babies' hearts. Paxil® taken during the first trimester increases (1.5-2 x) the chances of a heart defect (holes in the walls of the chambers of the heart) in offspring.
- Some studies indicate SSRI withdrawal symptoms in newborns

3. Use of Antidepressants in Children and Adolescents

- FDA black box warning of increased potential for suicidal thoughts in young patients taking SSRIs
- preclinical studies indicating long-term behavioral consequences of SSRI administration prior to maturation

4. Pharmacokinetic Considerations:

Interaction of SSRIs with various drugs such as TCAs, benzodiazepines and antipsychotics are metabolized by cytochrome P450 isozymes – SSRIs can inhibit enzyme activity.

IMPORTANT DRUGS MENTIONED IN THIS ECTURE

Tricyclic antidepressants (TCAs)

Imipramine (generic; Tofranil®)
Amitriptyline (generic; Elavil®)
Clomipramine (Anafranil®)
Desipramine (Nopramin®)
Doxepin (Sinequan®)

SSRIs

Citalopram (Celexa®) and
S-Citalopram (Lexapro®)
Fluoxetine (generic; Prozac®)
Fluvoxamine (Luvox®)
Paroxetine (Paxil®)
Sertraline (Zoloft®)

Atypical antidepressants

Bupropion (Wellbutrin®, Zyban®)
Mirtazapine (Remeron®)
Nefazodone (Serzone®)

Norepinephrine/serotonin reuptake inhibitors (SNRIs)

Venlafaxine (Effexor®)
Desvenlafaxine (Pristig®)
Duloxetine (Cymbalta®)

MAOIs (monoamine oxidase inhibitors)

Irreversible: Phenelzine (generic; Nardil®)
 Tranlycypromine (generic; Parnate®)
 Selegiline (l-deprenyl); Eldepryl®, Emsam®

Reversible (RIMA): Moclobemide (Manerix®, in Canada)

#62 - DRUGS TO TREAT ANXIETY AND BIPOLAR AFFECTIVE DISORDER

Date: January 14, 2011 – 8:30 a.m.

Reading Assignment: Katzung, Basic & Clinical Pharmacology; 11th Edition,
Chapters 29, pp 487-507 and 24, pp. 405-415

KEY CONCEPTS AND LEARNING OBJECTIVES

1. To understand the target sites of action of the benzodiazepines and SSRIs and the strategy for using benzodiazepines in combination with SSRIs in the treatment of anxiety disorders.
2. To understand lithium's target sites of action, its pharmacokinetics, adverse effects and considerations in the use of lithium to treat bipolar disorder.
3. To understand the pharmacokinetics, adverse effects and considerations in using the anticonvulsants to treat bipolar affective disorder.
4. To understand the sites of action, adverse effects and considerations in using the atypical antipsychotics to treat bipolar affective disorder.

#62 - DRUGS TO TREAT ANXIETY & BIPOLAR AFFECTIVE DISORDER

I. Treatment of Anxiety Disorders

The long-term pharmacotherapy of primary anxiety disorders utilizes many of the SSRI/SNRI drugs used for depression as well as sedative-hypnotics in the interim. Initially, the anxiety symptoms need to be controlled by benzodiazepines until the antidepressants or buspirone can exert their delayed effects.

Anxiety disorders treated with Antidepressants & Benzodiazepines:

Alprazolam (Xanax®), clonazepam (Klonopin®) and lorazepam (Ativan®) are the most commonly used benzodiazepines in conjunction with SSRIs, SNRIs or buspirone for treatment of anxiety disorders such as:

Generalized anxiety disorder (GAD): venlafaxine, duloxetine, paroxetine and escitalopram have been FDA approved for GAD, although other SSRI and TCAs may be effective; buspirone (a 5-HT_{1A} receptor agonist), benzodiazepines such as lorazepam or clonazepam

Panic disorder: SSRIs considered 1st line (fluoxetine, sertraline, paroxetine and venlafaxine), Benzodiazepines: alprazolam (widely used but may cause rebound anxiety), clonazepam (longer acting)

Social anxiety disorder (SAD): best treated with SSRIs or MAOIs, FDA has approved sertraline, paroxetine and venlafaxine (SNRI) for this disorder. Duloxetine also may be effective.

Post-traumatic stress disorder (PTSD): generally treated with SSRIs (paroxetine and sertraline have FDA approval for PTSD); adding an antipsychotic to the SSRIs may prove beneficial in some patients while MAOIs or TCAs make sometimes work for PTSD.

Obsessive-compulsive disorder (OCD): SSRIs (fluvoxamine, fluoxetine, sertraline and paroxetine), the SNRI venlafaxine and the TCA, clomipramine, are drugs of choice for OCD.

Some Adverse Effects:

Benzodiazepines; sedation, mental confusion, ataxia, anterograde amnesia, physical dependence and tolerance with chronic use, rebound anxiety and withdrawal symptoms upon abrupt discontinuation (these may include insomnia, irritability, nausea, twitching, tinnitus, paresthesias and delirium).

Buspirone: headache, dizziness and nausea

Fluvoxamine, same side effects as other SSRIs but its additional inhibition of CYP1A2, 2C19 and 3A4 provides for a greater extent interactions with other drugs using these metabolic pathways.

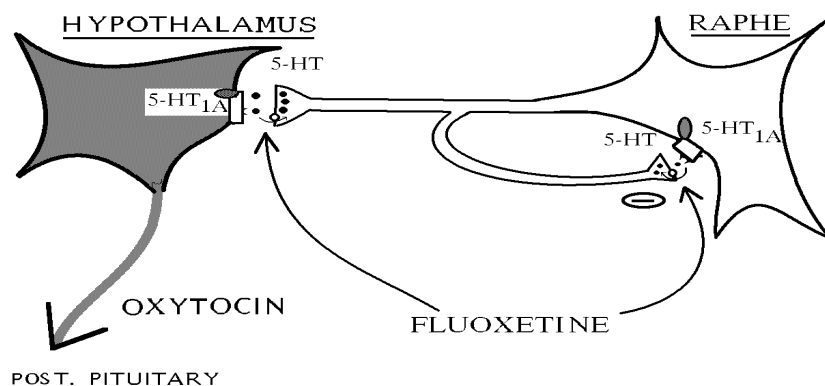
A 5-HT_{1A} Receptor Agonist

Buspirone (Buspar®) is a (partial) 5-HT_{1A} receptor agonist that is approved for the treatment of generalized anxiety disorder (GAD). Buspirone has low bioavailability, is slower acting than the benzodiazepines, less effective than the SSRIs for GAD and of questionable therapeutic efficacy. As with antidepressants used to treat anxiety disorders, the therapeutic response to buspirone is not immediate, but requires a period of time (at least 2 weeks). This is likely due to time-dependent desensitization of 5-HT_{1A} receptors that needs to occur to achieve its anxiolytic efficacy. Buspirone also is a dopamine D₂ receptor antagonist.

Drug Combination Strategy

SSRIs used to treat anxiety disorders have the same problem of delayed therapeutic effects as seen with the treatment of depression. Therefore, it might make sense to start with a benzodiazepine (e.g. alprazolam, lorazepam or clonazepam) combined with an SSRI (or buspirone). This could also reduce the initial pro-anxiety effects of some SSRIs and help patients to continue to take an SSRI until the therapeutic effects become clear. Subsequently, the use of benzodiazepines in these patients should be tapered down to avoid withdrawal problems.

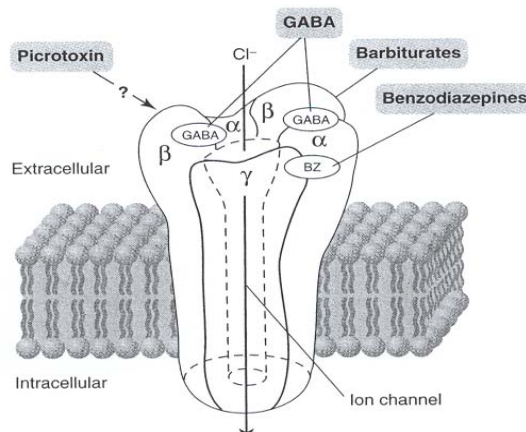
Time dependent adaptations (e.g. desensitization of 5-HT_{1A} inhibitory autoreceptors on 5-HT neurons) are required to achieve anxiolytic effects of the SSRIs.



Schematic of 5-HT neuronal projection and representative postsynaptic cell (a hypothalamic cell in this example) (figure from GB)

Mechanism of Action of Benzodiazepines: The therapeutic efficacy of the benzodiazepines as anxiolytics and sedatives is due to their potent effects on GABA_A receptor-mediated inhibition. They bind to sites on GABA_A receptors that modulate the activity of GABA receptor binding. Benzodiazepine binding increases the affinity of GABA_A for its binding site on the receptor and increases the frequency of opening of chloride channels.

As shown below, the receptors for benzodiazepine are located on GABA_A receptor subunits.



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

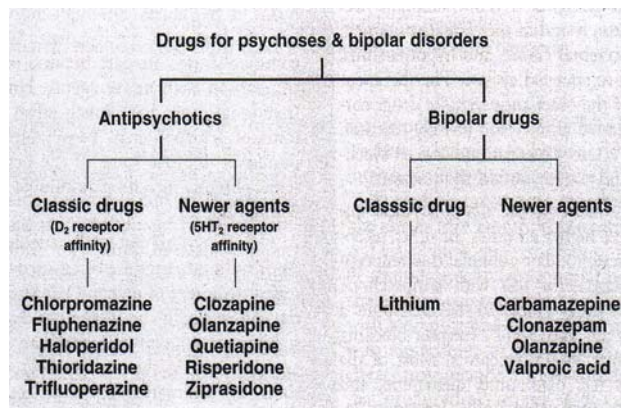
II. DRUGS TO TREAT BIPOLAR DISORDER

Bipolar Disorder is a primary affective disorder (aka manic-depressive illness) that causes dramatic mood swings.

- nearly 5.7 million adults have bipolar disorder
- a long-term disorder that usually develops in adolescence or early adulthood
- needs careful management throughout ones lifetime

The “high” episodes can include either elevated (euphoric), expansive (unceasing or indiscriminate enthusiasm) or irritable moods (labile moods altering between euphoria and dysphoria) that change to moods that are sad or hopeless (the depressive episode).

The pharmacotherapy of bipolar affective disorders is quite different from that for unipolar affective disorders. The use of an SSRI alone is contraindicated, as it may trigger a manic reaction in bipolar patients (this occurs in bipolar patients misdiagnosed as having unipolar depression).



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

The drugs of choice are: (A) **lithium** and (B) the **anticonvulsant drugs**, sodium valproate and carbamazepine. Another anticonvulsant, **lamotrigine** has more recently received FDA approval for maintenance treatment of bipolar disorder.

In addition, the Atypical Antipsychotics (C) have also been FDA approved for use in treatment of acute mania or mixed episodes. **Olanzapine** and **aripiprazole** are two atypical antipsychotics that have received FDA approval for maintenance treatment of bipolar disorder.

Risperidone and quetiapine (other atypical antipsychotics) have been shown to be useful to control manic episodes.

Gabapentin and topiramate have also been used, but have no proven efficacy and do not have FDA approval for treating mania

Mood stabilizers may be continued for an extensive period of time (years)

A. LITHIUM in the Treatment of Bipolar Disorder

- continues to be the first-line treatment for bipolar disorder
- proven effective in all phases of the illness, devoid of autonomic blocking effects and of activating or sedating effects
- only drug proven to reduce suicide in bipolar patients

**Lithium may take days to weeks to produce a full therapeutic effect*

Mechanism of Action:

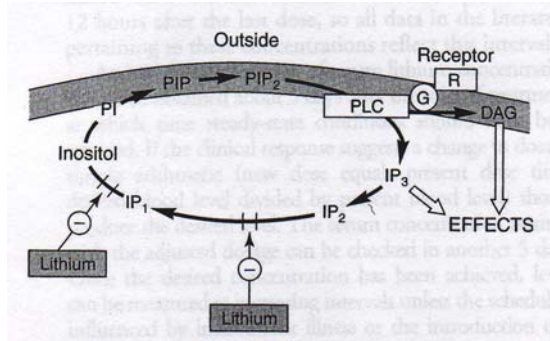
The exact mode of action of lithium in Bipolar Disorder is unclear. However, lithium produces a number of pharmacological effects:

- ***can effect electrolytes and ion transport***
Li⁺ acts like Na⁺. Li⁺ can substitute for Na⁺ in generating action potentials. Influx during depolarization is extremely rapid; efflux is 10-25 times slower than Na⁺.
- ***can effect neurotransmitters and their release***
 - seems to enhance the effects of serotonin
 - may decrease norepinephrine and dopamine turnover (may be relevant to antimanic effects)
 - may augment synthesis of acetylcholine

The most accepted mechanism of action for the therapeutic effects of lithium involves effects mediated on second messenger enzymes affecting neurotransmitter action

- lithium **inhibits** a number of enzymes involved in inositol recycling (inositol monophosphatase & inositol polyphosphate 1-phosphatase) resulting in depletion of substrate for IP3 production. (shown in the next figure).
- lithium also may (a) affect specific isozymes of protein kinase C (activated by DAG), (b) alter G protein function via shifts in phosphorylation and (c) uncouple receptors from their G proteins

Reductions in intracellular levels of inositol also have been postulated to underlie the mechanism of anti-bipolar effects of carbamazepine and sodium valproate.



(fig from Katzung, Basic and Clinical Pharmacology, 10ed., chapt 29, pp470)

Increasing recent evidence suggests a role for GSK-3 (**glycogen synthase kinase-3**) in mediating the therapeutic effects of lithium.

- GSK-3 regulates over 40 proteins that include structural, metabolic and signaling proteins as well as transcription factors.
- Lithium inhibits GSK-3 at concentrations within the effective range for the drug and has been shown to antagonize dopamine signaling via its Akt/GSK-3 pathway.
- Most drugs used for the treatment of bipolar disorder regulate GSK-3

Pharmacokinetics of Lithium

- readily and appreciably absorbed from the GI tract (peak levels in 0.5-2 hrs)
- no appreciable protein binding
- no metabolism, excretion is entirely in urine
- half-life of ≈ 20 hrs
- Li^+ has a narrow therapeutic window; 450 mg t.i.d. (1350 mg/day) produces a plasma concentration between 0.6 - 1.4 meq/L.
- changes in body water can alter plasma levels of the drug
- toxic effects are seen with plasma levels > 1.4 meq/L.

Some adverse side effects and complications of lithium:

- Slurred speech, fine tremor
- Nausea and fatigue in the initial weeks of treatment despite normal serum concentrations
- Excessive thirst and urination (nephrogenic diabetes insipidus); renal toxicity.
- Lithium inhibits thyroid hormone secretion (hypothyroidism)
- Edema and weight gain
- Confusion and ataxia associated with Li^+ toxicity
- Can induce/exacerbate psoriasis or cause acne

Other Considerations:

Use of lithium requires monitoring to maintain appropriate serum concentrations (0.6-1.2 meq/L for acute treatment and 0.6-0.7 mEq/L for maintenance) and avoid toxicity (>1.4 mEq/)

As Li^+ is excreted unchanged by the kidneys, patients with renal impairment and the elderly require dosage adjustment. Renal function and thyroid function should be monitored in patients taking lithium.

Common drug interactions;

- Thiazides, NSAIDs, ACE inhibitors and furosemide can increase serum lithium
 - Theophylline and caffeine can lower lithium levels (via increase in clearance)
- Lithium has been shown to have protective effects against suicide and self-harm in treating depression in patients with bipolar disorder.
 - Lithium also can be used to enhance the efficacy of antidepressant agents for the treatment of **unipolar** depression

Pregnancy

- lithium levels may be altered during pregnancy and after delivery
- Lithium use during pregnancy has been associated with congenital cardiac abnormalities
- Lithium toxicity in newborns (lethargy, cyanosis, poor suck and Moro reflexes, cardiac abnormalities)

B. ANTICONVULSANT Drugs That are Used to Treat Bipolar Affective Disorder

- these anticonvulsant drugs work as mood stabilizers in bipolar disorder
- ** recent FDA black box warning on all anticonvulsants for a potential increased risk of suicide*

1. Valproic Acid; Sodium Valproate (generic, Depakene® and Depakote®)

- the active form of the drug is thought to be the valproate ion, as sodium valproate it is fully ionized at body pH

Pharmacological Effects:

- GABA reuptake inhibitor that may increase GABA content in synapse or mimic its effects at postsynaptic receptors.
- influences 2nd messenger enzymes such as GSK-3
- blocks sustained high frequency neuronal firing rates (antiepileptogenic effect).

Pharmacokinetics

- highly protein bound (90%); displaces protein bound phenytoin resulting in an increase in phenytoin free fraction and potential toxicity.
- inhibits metabolism of the anticonvulsants phenytoin, phenobarbital and carbamazepine (toxic levels of these agents thus can be reached).

Adverse Effects and Toxicity of Valproate

- nausea, vomiting, diarrhea (can avoid by giving valproic acid with food or as enteric coated Depakote®)
- abdominal pain and heartburn
- may produce a fine tremor, weight gain, increased appetite and hair loss
- hepatotoxicity that may be severe (especially for those under 2 yr); pancreatitis
- teratogenic (neural tube defect, cardiovascular, urogenital, craniofacial and skeletal malformations and decreased IQ in offspring)
- some reports of blood dyscrasias (e.g. agranulocytosis)

2. Carbamazepine (generic, Tegretol®)

- a tricyclic compound that may be used alone or in combination with lithium in refractory patients

Pharmacological Effects:

- 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

- medium protein binding (70-80%)
- strong inducer of various CYP450 enzymes that are likely to increase the metabolism of other drugs

Side/Toxic Effects

- GI reactions (gastric distress, diarrhea, etc)
- dermatological reactions (rashes)
- ataxia and other neurological reactions
- Rare, but serious & sometimes fatal blood dyscrasias (bone marrow suppression)
- Increased risk of suicidality
- Increased risk of neural tube defect (Spina Bifida; about 0.9%) if used during pregnancy
- *Overdose of the drug presents a major medical emergency and should be managed like overdoses of tricyclic antidepressants.

FDA ALERT (12/12/07) – dangerous and even fatal skin reactions (Stevens Johnson syndrome & toxic epidermal necrolysis) can be caused by carbamazepine therapy; significantly more common in patients with a particular human leukocyte antigen (HLA) allele HLA-B*1502 occurring almost exclusively in individuals of Asian ancestry.

3. Lamotrigine (Lamictal ®) - an anticonvulsant that was approved in 2003 for the long-term maintenance treatment of bipolar disorder and may be helpful in depression. No generic lamotrigine in the USA. Dose of lamotrigine is most often between 100 and 200 mg/day (up to 600 mg/day).

- chemically unrelated to any other anticonvulsant or mood regulating medication.
- it seems to be effective in about two-thirds of people with bipolar mood disorders that have not responded to lithium or other mood-stabilizers
- has had been successful in controlling rapid cycling and mixed bipolar states in people who have not received adequate relief from lithium, carbamazepine and/or valproate.

Pharmacological Effects:

- has significantly more antidepressant potency than either carbamazepine or valproate
- may inhibit release of glutamate (excitatory a.a.) and inhibit voltage sensitive Na⁺ channels with the stabilization of neuronal membranes that mediate presynaptic transmitter release of excitatory amino acids.

Side Effects - relatively benign side-effect profile that include:

- dizziness & headache
- double vision & blurred vision
- unsteadiness
- sleepiness
- rash
- vomiting

Other Adverse Effects/Interactions:

- birth defects (increased risk of cleft lip or palate during 1st trimester)
- alcohol may increase the severity of the side-effects of lamotrigine
- oral contraceptives can lower the plasma level of lamotrigine by as much as 50%
- carbamazepine-induced enzymes (i.e. CYP3A4) can facilitate the metabolism of lamotrigine.
- valproate has the ability to double plasma levels of lamotrigine
- also can cause Stevens-Johnson syndrome (1 in 1000 patients)

C. ATYPICAL ANTIPSYCHOTICS Used to Treat Bipolar Disorder

1. **Risperidone (Risperidal®)** - an atypical antipsychotic approved in 2003 by the FDA for the treatment of the mixed and manic states associated with bipolar disorder.

Mechanism of Action

- antagonist at D2 dopamine and 5-HT₂ serotonin receptors as well as 5-HT₇ receptors

Side Effects:

Common: drowsiness & fatigue, increased appetite, anxiety, heartburn, akathisia, insomnia, low blood pressure, muscle stiffness & pain, minimal to marked weight gain.

2. **Ziprasadone (Geodon®)** – an atypical antipsychotic used in the treatment of bipolar disorder

Side Effects: tired or sleepy, upset stomach, constipation or diarrhea, feeling dizzy, rash, restlessness, tremor or shuffling

Drug Interactions:

- carbamazepine (Tegretol) can reduce the effectiveness of Geodon.

- no reported interaction problems between Ziprasadone and Lithium or oral contraceptives.

3. **Olanzapine (Zyprexa®)** – an atypical antipsychotic that is FDA approved for the treatment of Bipolar Disorder

Drug Interactions

- Carbamazepine may increase the metabolism of olanzapine thus making it less effective.

- Common side effects are: sleepiness, dizziness and dry mouth

4. **Quetiapine (Seroquel®)** - an atypical antipsychotic that received an initial indication in 2004 to treat the manic phase of bipolar disorder either alone or as an adjunct to lithium or divalproex; in 2006 received FDA approval to treat Bipolar Disorder.

Seroquel XR approved on November 16, 2007 for use in acute and maintenance treatment of schizophrenia.

Target Sites of Action

Antagonist actions at: D₁ & D₂ dopamine receptors, alpha₁-adrenoreceptors, 5-HT_{1A} & 5-HT₂ serotonin receptors and H₁-histamine receptors (thought to mediate its sedative properties).

Pharmacokinetics

- low bioavailability
- short-half life (6 hrs)

Side Effects

Common: dry mouth, sedation (most common), sleepiness and constipation

Less common: abnormal liver tests, dizziness, upset stomach, risk of development of tardive dyskinesia with prolonged use

Rare – serious and life-threatening development of the neuroleptic malignant syndrome (NMS)

Neuroleptic Malignant Syndrome:

- Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia).

5. Aripipazole (Abilify®) – approved in 2002 for mixed and manic episodes in bipolar patients; more recently approved as “add on” option (to antidepressants) in unipolar depression

- mechanism of action different from other atypical antipsychotics (e.g. olanzapine, quetiapine, ziprasidone)
- is a partial agonist at D2 dopamine receptors and 5-HT_{1A} serotonin receptors and retains its 5-HT₂ antagonist properties
- has moderate affinity for histamine and alpha adrenergic receptors, but no appreciable anticholinergic effects.

Pharmacokinetics

- good bioavailability (90%)
- metabolized primarily by CYP 3A4 and 2D6 , thus plasma concentrations of aripipazole may be increased by fluoxetine or paroxetine and decreased by carbamazepine

Side Effects

Common: akathisia, headache, unusual tiredness or weakness, nausea, constipation, trouble sleeping, restlessness and blurred vision,

Rare: neuroleptic malignant syndrome

D. Combination Medications & Others

Symbyax® – a combination medication of olanzapine & fluoxetine approved for the treatment of bipolar disorder

Side Effects: Dizziness, drowsiness, diarrhea, dry mouth, constipation, increased appetite, weight gain or trouble sleeping

- may also cause significant weight gain and a rise in your blood cholesterol (or triglyceride) levels

Drug Interactions

- serious (possibly fatal) interactions may occur with pimozide, sibutramine, thioridazine and if used concurrently or < 5 weeks after Symbyax is discontinued.

-MAO inhibitors should be stopped at least 2 weeks prior to Symbyax or not started until 5 weeks after Symbyax

(**Note:** On March 1, 2004, the US Food and Drug Administration "asked all manufacturers of atypical antipsychotic medications to add a Warning statement describing the increased risk of hyperglycemia and diabetes in patients taking these medications.)

The Benzodiazepines

– may also be used instead of, or in addition to, antipsychotics to treat the acute manic phase in bipolar disorder.

Diazepam (Valium®) Lorazepam (Ativan®) & Clonazepam (Klonopin®)

- diazepam has more rapid onset and longer long half-life
- lorazepam does not undergo Phase I metabolism

Non-Pharmacologic Therapeutic Approaches:

Bipolar Disorders -Electro-convulsive shock therapy (ECT). Also requires repeated application (approx 6 over 2 weeks) before improvement is observed. Can be very effective for severe manic or depressive episodes.

Anxiety Disorders - Behavioral modification, Biofeedback

IMPORTANT DRUGS MENTIONED IN THIS LECTURE

SSRI/SNRIs for anxiety disorders (see list of SSRIs in class notes for 1/13/11)

Benzodiazepines

Alprazolam (Xanax®)
Clonazepam (generic, Klonopin®)
Diazepam (generic, Valium®)
Lorazepam (generic; Ativan®)

5-HT_{1A} receptor agonist

Bupirone (Buspar®)

Drugs to Treat Bipolar Disorder

Lithium (generic; Eskalith®)

Anticonvulsants

Carbamazepine (generic, Tegretol®)
Lamotrigine (no generic, Lamacital ®)
Valproic acid (generic; Depakene®, Depakote®)

Atypical Antipsychotics

Aripipazole (Abilify®)
Olanzapine (Zyprexa®)
Quetiapine (Seroquel ®)
Risperidone (Risperidal®)
Ziprasidone (Geodon®)

Combination Drugs

Symbyax® (the atypical olanzapine and the SSRI fluoxetine)

ANTIPSYCHOTIC DRUGS

KEY CONCEPTS AND LEARNING OBJECTIVES:

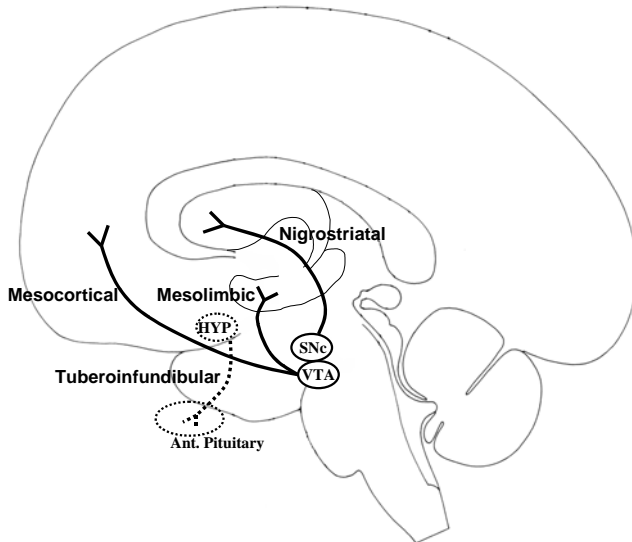
- 1) Recall the 4 well-defined dopamine systems in the brain as they relate to antipsychotic drug action and side effects.
- 2) Explain the distinction between “typical” and “atypical” antipsychotics
 - a) Recall the difference in mechanism(s) of action
 - “typical” antipsychotics mechanism (dopamine D2 receptor blockade)
 - atypical antipsychotics mechanism (dopamine D2 and serotonin 5-HT2 receptor antagonists)
 - Partial agonism mechanism of Aripiprazole (Abilify)
 - b) Recall the common side effects and the rare, but dangerous side effects
 - First generation anti-psychotics: High potency “typical” antipsychotic (haloperidol) versus a low potency “typical” antipsychotic (chlorpromazine).
 - Second generation anti-psychotics and clozaril
 - c) Predict the clinical outcome based on an action on a particular dopamine system
 - d) Predict the site of action in the dopamine system took place based on the clinical outcome
- 3) Explain the “Metabolic Syndrome” problem

IMPORTANT DRUGS

1.	Chlorpromazine	(Thorazine)**	Prototype
2.	Haloperidol	(Haldol)**	Prototype
3.	Clozapine	(Clozaril)**	Prototype
4.	Risperidone	(Risperidal)**	Prototype
5.	Olanzapine	(Zyprexa)	
6.	Quetiapine	(Seroquel)	
7.	Ziprasidone	(Geodon)	
8.	Aripiprazole	(Abilify)**	Prototype
9.	Paliperidone	(Invenga)	
10.	Asenapine	(Saphris)	
11.	Lurasidone	(Latuda)	

ANTIPSYCHOTIC DRUGS

I. Normal Physiology



Location of Dopamine system desired effect from anti-psychotic medications

- A. Mesolimbic system = Dopamine (DA) neurons projecting from ventral tegmental area to subcortical structures of the brain (e.g. nucleus accumbens); Positive (psychotic) symptoms involve “mesolimbic dopamine hyperactivity.”

Blockade of DA₂ receptors in mesolimbic system reduces psychotic symptoms.

Locations of Dopamine system side effects from anti-psychotic medications

- B. Mesocortical system = DA neurons projecting from ventral tegmental area to frontal cortex; Negative symptoms (and possibly positive symptoms to a small extent) related to mesocortical DA dysfunction.

Blockade of DA₂ receptors in mesocortical system may exacerbate negative symptoms.

- C. Nigrostriatal system = DA neurons projecting from substantia nigra pars compacta to striatum (comprises part of basal ganglia motor circuit);

Blockade of DA₂ 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 DA₂ receptors in anterior pituitary lead to Hyperprolactinemia and associated adverse effects.

II. Pathophysiology/Disease state

Dopamine Hypothesis

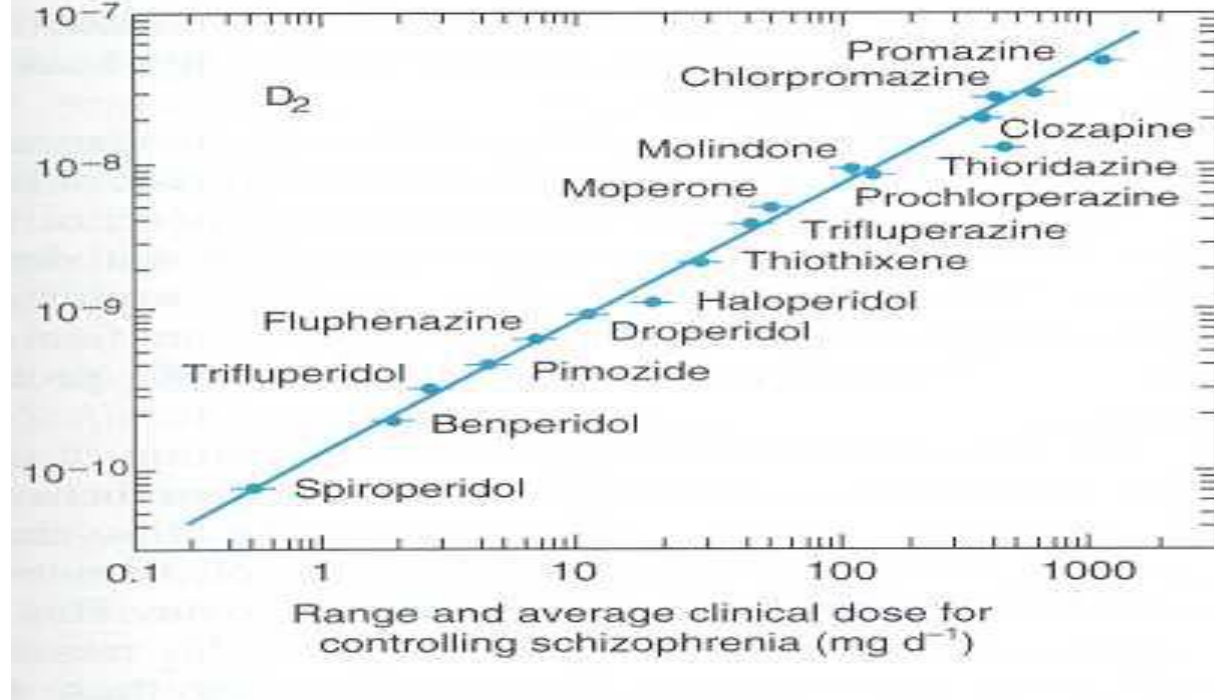
Hyperactivity of Dopamine (DA) neurotransmitter pathways → Schizophrenia

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.

III. Description of Drugs used to treat Disease

First Generation Antipsychotics (FGA's)

Also called: Conventional antipsychotics, Typical Antipsychotics, Neuroleptics, Major Tranquilizers

Phenothiazines

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

Thioxanthines

- Thiothixene (Navane)

Butyrophenones

- Haloperidol (Haldol) high potency***

Second Generation Antipsychotics (SGA's)
Also called: Atypical antipsychotics

Risperidone (Risperdal)	Paliperidone (Invega)	Ziprasidone (Geodon)
Olanzapine (Zyprexa)	Quetiapine (Seroquel)	Asenapine (Saphris)
Lurasidone (Latuda)		
Aripiprazole (Abilify)		
Clozapine (Clozaril)		

IV. 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: Psychosis treatment

Schizophrenia
Mood disorders-Bipolar disorder, Major Depression
Medical Illness-Dementia, delirium, Substance abuse

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

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, in patients

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

	Risperidone	Ziprasidone	Quetiapine	Olanzapine	Clozapine
Alpha1	8.5	8.5	8	7.5	8.2
M1	--	--	6	7.5	8
H1	7.3	8.5	7.7	10	8.5
5-HT2A	10	10	7.5	9	8.7
D2	8.5	8.5	6.1	7.7	6.7
5-HT2A:D2 affinity ratio	32	32	25	20	100

Atypical Antipsychotic Drug Affinities at Various Neurotransmitter Receptors
(Value expressed as pKi = -logKi; higher number means higher affinity)

5-HT2A:D2 affinity ratio >20:1 for atypical antipsychotics (100:1 for clozapine)

Therapeutic Window for Treatment

Treatment of psychosis—block >60-65% of dopamine D2 receptors in the Mesolimbic tract

A substantial EPS risk—block >80% of the dopamine D2 receptors in the Nigrostriatal tract

Risk of ↑Prolactin—block >80% of the D2 receptors in Tuberoinfundibular tract

What mechanism of action allows for greater than 65% dopamine receptor blockage in the mesolimbic system but less than 80% dopamine receptor blockage in the nigrostriatal system? How do the drugs work to hit this therapeutic window?

1. Serotonin-Dopamine Antagonism hypothesis

- Nigrostriatal tract & Mesolimbic tract
5-HT_{2A} blockade enhances DA release in basal ganglia (from nigrostriatal DA system); This DA competes with the antipsychotic for DA₂ receptors;
Result is blockage of > 65% receptors but < 80% of receptors (therapeutic window).
Consequence is antipsychotic efficacy (mesolimbic tract) & reduced EPS (nigrostriatal tract).
- Mesocortical
5-HT_{2A} 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 DA₂ blockade of atypical antipsychotics has also led to “hit and run” concept; i.e. atypical drug-induced blockade of DA₂ receptors is not as long-lasting as with typical drugs.

Partial Agonism & Aripiprazole (Abilify)

Partial agonist

- rheostat analogy; the receptor (light) is neither completely on nor 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 transmitter environments

Little agonist activity (the cell is not completely off)

In low dopaminergic environment, aripiprazole binds to the DA₂ receptor with high affinity (potent) & has a partial agonist effect

In high transmitter environments

Exerts antagonist action (the cell is not completely on)

In high dopaminergic environment aripiprazole has the effect of an antagonist

Leads to important concept of “dopamine system stabilization” (i.e. not too much, not too little); supported by observation that clinical efficacy of atypical antipsychotics may be seen at DA₂ occupancy levels below those achieved by typical antipsychotics
Aripiprazole is the first Dopamine-Serotonin System Stabilizer

VI. 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

Half-life about 20 hours, steady state 4-7 days

VII. Important side effects: Common & Rare

	Chlorpromazine (Low potency)	Haloperidol (High potency)
Dopamine-D2-related Extrapyramidal (EPS/TD); Increased prolactin	++	+++
Muscarinic-M1-Anticholinergic Blurred vision, dry mouth, urinary retention etc.	+++	0
Adrenergic-Alpha1-related Orthostasis	+++	0
Histamine-H1-related Sedation, weight gain	+++	0

	Risperidone (Risperdal)	Ziprasidone (Geodon)	Quetiapine (Seroquel)	Olanzapine (Zyprexa)	Clozapine (Clozaril)
Dopamine-D2-related Extrapyramidal (EPS/TD) Increased prolactin	+ / ++	+	0 / +	+	0
Muscarinic-M1-Anticholinergic Blurred vision, dry mouth, urinary retention etc.	0	0	0 / +	++	+++
Adrenergic-Alpha1-related Orthostasis	+ / ++	0 / +	++	0 / +	+++
Histamine-H1-related Sedation	0 / +	0 / +	+ / +++	+ / +++	+++
Weight gain	++	0 / +	++	+++	+++
Glucose intolerance	+	0	+	++	+++
Lipids	+	0	+	++	++

Prominent atypical drug-related effects-

- Risperidone-EPS side effects at higher doses (>6 mg/day)
- Clozapine (clozaril) - agranulocytosis in 1-2% of patients. Requires weekly blood monitoring
- Clozapine (clozaril) and Olanzapine (zyprexa) - weight gain, glucose intolerance, hyperlipidemia, sedation
- Quetiapine (seroquel) – weight gain, sedation, orthostasis
- Ziprasidone Geodon) - QTc elongation, may contribute to cardiac arrhythmias (also seen with the typical drug, thioridazine); other atypical drugs suspect for QTc elongation but insufficient data to attribute great significance

- **Metabolic Syndrome**

Weight gain, Hyperglycemia, Diabetes Mellitus, Dyslipidemia

All SGA antipsychotics can result in significant weight gain, but there are differences among the medications.

Clozapine > Olanzapine >>> Quetiapine > Risperidone/Paliperidone >> Asenapine(?) > Ziprazodone/Aripiprazole

Among patients with Schizophrenia, there are metabolic risk factors for cardiovascular disease that are far higher than the general population. Evidence suggests that SGA antipsychotics are associated with metabolic disturbances that can further increase this risk.

Rare Side Effects

All antipsychotics: Neuroleptic Malignant Syndrome

Clozapine: Agranulocytosis

FGA's & SGA's: ↑ Mortality in elderly pts with Dementia; death from stroke and related disorders is greater than placebo.

VIII. Important drug-drug interactions

- May increase (↑) levels of various antipsychotics:
ciprofloxacin (Cipro®), erythromycin, ritonavir (Norvir®),
fluoxetine (Prozac®), fluvoxamine (Luvox®),
- May decrease (↓) levels of various antipsychotics:
carbamazepine (Tegretol®), phenobarbital, phenytoin (Dilantin®), rifampin (Rifadin®)
- Combining clozapine with carbamazepine (Tegretol®) may increase the risk of agranulocytosis.

IX. Contraindications

No absolute contraindications.

#64 - ANTI-PARASITIC AGENTS

I. INTRODUCTION

A. General Comments:

- a. Drugs intermittently difficult to obtain
- b. Available drugs lack FDA approval
- c. Lagging new drug development
- d. Many agents have limited efficacy or serious toxicity

B. Distinction between protozoal & helminthic Infections:

<u>Protozoa</u>	<u>Helminths</u>
• Complete replication within definitive host	Life-cycle involves more than definitive host
• Clinical illness results from single exposure	Repeated exposures necessary for disease
• Treatment goal: Eradication	Treatment goal: Eradication or reduction of worm burden

C. Definitions:

- | | | | | |
|--|-----|---|-----|--|
| • Definitive Host
(Harbors sexual parasitic stage) | vs. | • Intermediate Host
(Harbors larval or asexual parasitic stage) | vs. | • Incidental Host
(Not necessary for parasitic survival) |
| • Gametogony
(Sexual development) | vs. | • Schizogony
(Asexual development) | | |

II. GENERAL APPROACH TO ANTIPARASITIC CHEMOTHERAPY

A. Targets of Chemotherapy: *Comparison of biochemical and physiologic processes between humans and parasites reveals differences in biochemical processes that provide selective inhibition in parasites. Three major types of potential targets of parasites include:*

1. Unique enzymes found only in the parasite (e.g., pyruvate:ferridoxin oxireductase in *Giardia*)
2. Enzymes found in both host and parasite, but indispensable only for the parasite (e.g., lanosterol C-14 α demethylase in *Leishmania*)
3. Common biochemical functions found in both host and parasite, but with different properties (e.g., dihydrofolate reductase-thymidylate synthetase bifunctional enzyme in *Plasmodium* and *Toxoplasma*)

III. THERAPY OF PROTOZOAN PARASITES

A. MALARIA

1. **Four species of plasmodia cause human malaria**
 - P. falciparum*
 - i. responsible for nearly all serious complications and deaths
 - ii. drug resistance is an important therapeutic problem
 - P. vivax*
 - P. malariae*
 - P. ovale*

2. **Plasmodium life cycle**
 - a. Anopheline mosquito inoculates plasmodium sporozoite to initiate human infection
 - b. **Exoerythrocytic stage:** tissue schizonts mature in liver to merozoites and are released into the circulation to invade erythrocytes
 1. *P. falciparum* and *P. malariae* have only 1 cycle of liver cell invasion and multiplication. Liver infection ceases spontaneously in 4 weeks. Therefore treatment that eliminates erythrocytic parasites will cure the infection
 2. *P. vivax* and *P. ovale* have a dormant liver stage (the hypnozoite) and eradication of both the liver and erythrocyte stages is required to cure the infection. No one agent can eliminate both hepatic and erythrocytic stages
 - c. **Erythrocytic stage:** intraerythrocytic merozoites develop into trophozoites then to schizonts and rupture RBC releasing multiple merozoites that invade other RBCs
 - d. Repeated cycles of infection can lead to the infection of many erythrocytes and serious diseases
 - e. Sexual stage (gametocytes) also develop in RBCs and are taken up into mosquitoes where they develop into infective sporozoites to continue cycle in next host

3. **General Principles of Malaria Treatment**
 - a. Because of increasing drug resistance, it is important to emphasize prevention (repellants, insecticides, nets)
 - b. Specific treatment will depend on geographical area visited, patient's age, pregnancy, etc.
 - b. The CDC website is a good source to check on current resistance patterns and experience with new drugs:
www.cdc.gov/malaria/clinicians.htm

3. **Major Antimalarial Drugs**

Chloroquine	Quinine and Quinidine	Amodiaquone
Mefloquine	Primaquine	Pyrimethamine
Proguanil	Atovaquone	Halofantrine
Artemisinin and its derivatives (<not available in US, but highly active)		
Antibiotics (tetracycline, doxycycline, azithromycin, clindamycin)		

4. **Chloroquine**

- Used for prophylaxis and treatment
- Initial half-life: 3-5 d; Terminal half-life: 1-2 mo
- Schizonticidal to all plasmodial species; not active against exoerythrocytic (liver phase) parasites
- MOA: Prevents polymerization of heme to hemozoin leading to a build up of free heme which is toxic to parasite
- Resistance in *P. falciparum* is wide-spread
- ADRs: pruritis; Uncommon - nausea, vomiting abdominal pain, HA, anorexia, malaise, blurred vision

5. **Chloroquine & antimalarial Drug Resistance**

- Chloroquine resistance in *P. falciparum* is wide-spread
- Chloroquine-susceptible *P. falciparum*: Central America, Caribbean, Middle East (although pockets of resistance noted)
- P. falciparum* resistance to quinine in SE Asia
- Resistance rare with other species (recent exception is Chloroquine resistance in *P. vivax* from Papua New Guinea & Indonesia)

6. **Mefloquine**

- Used for prophylaxis and treatment all forms malaria
- Schizonticidal; MOA: similar to chloroquine
- DOC for prophylaxis in areas of chloroquine resistant *falciparum* (see resistance in Thailand border areas)
- Adverse: nausea, vomiting, sleep & behavioral problems; Neuropsychiatric toxicities (seizures, psychosis) risk is similar to other antimalarials; Rare - cardiac arrhythmias
- Contraindications: seizures, psych d/o, arrhythmia
- Drug interactions: quinine, quinidine, halofantrine

7. **Alternatives to Mefloquine Prophylaxis**

- Atovaquone and proguanil (*Malarone*)
- Proguanil with chloroquine
- Pyrimethamine and sulfadoxine (*Fansidar*)
- Doxycycline (DOC: Prophylaxis against mefloquine-resistant *P. falciparum*)

8. **Quinine and Quinidine**
 - a. DOC for treatment of severe disease with chloroquine-resistant *P. falciparum* malaria
 - b. Quinine only oral in USA, Quinidine IV in USA (cardiac monitoring recommended with IV Rx)
 - c. Used with a second agent (e.g., doxycycline) to shorten duration and limit toxicity
 - d. ADRs: GI, Cinchonism (headache, nausea, visual disturbances, dizziness, tinnitus)
 - e. Quinine can be used, if needed, in pregnancy

9. **Primaquine**
 - a. Used to treat exoerythrocytic forms of vivax and ovale malaria;
 - b. DOC for RADICAL CURE after chloroquine
 - c. Used in terminal prophylaxis, but rarely required
 - d. MOA: Probably similar to chloroquine
 - e. ADRs: Infrequent - nausea, abdominal pain, cramps; Rare - hematologic, arrhythmias
 - f. Contraindications: granulocytopenia
 - g. Relative Contraindication: G6PD deficiency → hemolysis; Testing recommended prior to Rx

10. **Artemisinin (Qinghaosu)**
 - a. Used in China >2000 years; no resistance yet!
 - b. Several derivatives, e.g., Artemether
 - c. Rapidly acting schizonticide
 - d. Second agent used to prevent recrudescence (ACT: artemisinin combination therapies)
 - e. MOA: production of toxic free radicals in parasite food vacuole

11. **Malaria Prevention**
 - a. Chloroquine (only in areas without resistant *P. falciparum*)
 - b. Mefloquine
 - c. Atovaquone and proguanil (Malarone)
 - d. Doxycycline (DOC in areas with multi-drug resistance)
 - e. Chloroquine and proguanil (not available in the US)
 - f. Primaquine (terminal prophylaxis for *P. vivax* & *P. ovale*)

12. **Malaria Prevention (Recommended schedule in relation to travel)**

	<u>Start</u>	<u>Stop</u>
a. Chloroquine	1-2 wks prior	4 wks after
b. Mefloquine	1-2 wks prior	4 wks after
c. Malarone	1-2 days prior	7 days after
d. Doxycycline	1-2 days prior	4 wks after

13. **Malaria Treatment**

- a. Chloroquine-sensitive *P. falciparum* infections- Chloroquine
- b. *P. vivax* and *P. ovale* infections- Chloroquine
- c. Chloroquine-resistant *P. falciparum* infections, Uncomplicated
 - Atovaquone plus proguanil (Malarone)
 - Quinine 3-7 days* plus doxycycline, tetracycline, or clindamycin, (*7 days for non-immune travelers & cases from SEA)
 - Artemether plus lumefantrine (Coartem)
 - Mefloquine
- d. Chloroquine-resistant *P. falciparum* infections, Complicated
 - Quinidine (iv) plus doxycycline, tetracycline, or clindamycin
 - Artesunate (iv) followed by atovaquone/proguanil, doxycycline, or mefloquine

B. AMEBIASIS

1. **Antiamebic Drugs**

a. **Tissue Amebicides**

- Metronidazole
- Emetine
- Chloroquine

b. **Luminal Amebicides**

- Diloxanide furoate (*not avail in US*)
- Iodoquinol
- Paromomycin

2. **Metronidazole**

- a. DOC extraluminal (tissue) amebiasis
 - Also treats giardia, trichomonas (and anaerobic bacteria)
 - Used for tissue stages of amebiasis (dysentery, ameboma, liver abscess)
- b. MOA: ferredoxin-linked processes reduce nitro group to product lethal against anaerobic organisms
- c. ADRs: nausea, vomiting, metallic taste, disulfuram-like
- d. Drug interactions: anticoagulants, alcohol, anticonvulsants

3. **Iodoquinol**

- a. Used for luminal amebic infections, other intestinal protozoa
- b. MOA: unknown
- c. ADRs: Neurotoxicity and nausea and vomiting reported but rare at recommended doses

4. Treatment of Specific Forms of Amebiasis

- a. **Asymptomatic intestinal infections** (carriers)
 - generally not treated in endemic areas
 - in nonendemic areas luminal agents used
 - iodoquinol (650mg TID x 21d), paromomycin (10mg/kg TID x 7d), diloxanide furoate (500mg TID x 10 days)
 - single course effective in >90%
- e. **Amebic colitis**
 - Metronidazole (750mg TID x 10d) plus a luminal agent
- f. **Liver abscess**
 - DOC is metronidazole* (750 mg TID x 10d) plus a luminal agent (96% effective) * *Less than 10 d is probably effective, large abscesses need drainage in addition to treatment with metronidazole*
 - Chloroquine reserved for failures
- g. **Ameboma and other Extraintestinal infections**
 - Metronidazole (750mg TID x 10d) plus a luminal agent

C. AFRICAN TRYPANOSOMIASIS

1. **Pentamidine** (intravenous administration)
 - Alternative to or combination with suramin for early lymphoid stage but not CNS disease (2-4mg/kg/d or QOD x 10-15 doses).
 - Also used as an alternative to sodium stibogluconate for visceral leishmaniasis (2-4 mg/kg/d or QOD x 15 doses IV)
 - Many toxicities; rapid infusion see hypotension, tachycardia, dizziness, dyspnea; with IM, pain at injection site and sterile abscesses may develop; pancreatic toxicity first hypoglycemia then IDDM; Nephrotoxic
2. **Suramin** (intravenous administration)
 - First line therapy for hemolymphatic disease; does not cross BBB, therefore not effective for CNS disease; prophylaxis against trypanosomiasis
 - 200mg test dose followed by 1g on days 1,3,7,14,21 or 1g weekly x 5 doses
 - Combined with pentamidine to improve efficacy
 - Toxicities: (common) immediate-fatigue, nausea, vomiting and rarely seizures, shock and death; late-fever, rash, HA, paresthesias, neuropathies, renal tox (proteinuria), chronic diarrhea, hemolytic anemia, agranulocytosis
3. **Melarsoprol** (intravenous administration)
 - First line therapy for advanced CNS disease
 - IV in propylene glycol 3.6mg/kg/d x 3-4d repeated weekly PRN

- Extremely toxic: *immediate*-fever, vomiting, abdominal pain, arthralgias;
late- reactive encephalopathy (w/in 1 week in 1-10%) w/cerebral edema, seizures, coma and death (due to disruption of trypanosomes); renal, cardiac, and hypersensitivity reactions

4. **Eflornithine**

- Second therapy for advanced CNS disease; less toxic; equal efficacy against *T brucei gambiense* but limited against *T brucei rhodesiense*
- IV /IM 100mg/kg q 6 h x 14 d followed by PO 3-4 weeks
- Toxicities: diarrhea, vomiting, anemia, TCP, leukopenia and seizures

D. AMERICAN TRYPANOSOMIASIS (Chagas Disease)

1. **Nifurtimox** (oral administration)

- Decreases severity and eliminated detectable parasites but ineffective at eradication of infection; not active against chronic disease
- Efficacy variable with resistance in some areas S. America
- Toxicities (common)- nausea, vomiting, abdominal pain, fever, rash, restlessness, insomnia, neuropathies, and seizures

2. **Benznidazole** (oral administration)

- Efficacy similar to nifurtimox for Chagas' disease
- Toxicities: peripheral neuropathy, rash, GI, and myelosuppression.

E. LEISHMANIASIS

1. **Sodium Stibogluconate**

- Pentavalent antimonial DOC for cutaneous and visceral leishmaniasis
- Efficacy varies with endemic resistance in some areas (alternative therapies include liposomal amphotericin B, miltefosine)
- IV/ IM 20mg/kg/d (x 20 d for cutaneous / x 28 d for visceral)
- Toxicities: (increases with therapy) GI, fever, HA, myalgias, arthralgias, rash; QT prolongation

F. CRYPTOSPORIDIOSIS

1. **General management principles:**

- Lactose-free diet
- Antimotility agents
- Restoration of immune response in HIV infection with HAART (esp.PIs)
- Few active drugs available

2. **Nitazoxanide** (oral administration)

- 500 mg to 1 gm BID
- No better than placebo if CD4 count < 50 (Rossignol et al. Trans R Soc Trop Med 1998;92:663)

3. **Paromomycin** (oral administration)
- 25 – 35 mg/kg/d in 2-4 divided doses
4. **Other potential agents:** Azithromycin, spiramycin, clarithromycin

G. GIARDIASIS

1. **Metronidazole** (oral administration)
-250 mg TID x 5 – 7 d
2. **Nitazoxanide** (oral administration)
- Pediatric indication: 100 mg BID
3. Other agents: quinacrine (no longer available in US), furazolidone, albendazole
4. Pregnancy: paromomycin, metronidazole in 2nd & 3rd trimester

H. TOXOPLASMOSIS

1. **Pyrimethamine**
- Most effective agent, need to add folinic acid
- No role for monotherapy, need to add **sulfadiazine** or **clindamycin**
2. Alternate agents: azithromycin, clarithromycin, atovaquone, dapsone, TMP-SMX
3. Lymphadenopathy in immunocompetent – Self-limiting disease
4. Encephalitis in HIV
- Treat 4-6 weeks after resolution of signs/symptoms (usually > 6 mos)
pyrimethamine 200 mg loading dose, then 50 – 75 mg daily
+ sulfadiazine 1 – 1.5gm QID
or, + clindamycin 600 mg QID
- Life-long maintenance unless CD4 count rises to > 200 for at least 6 mos
Pyrimethamine 25 mg daily + sulfadiazine 500 mg QID

IV. THERAPY OF HELMINTHS

A. GENERAL COMMENTS

- Used to eradicate or reduce the number of parasites in the intestines or tissues
- Diagnosed by finding the parasite, eggs, or larvae in the feces, urine, blood, sputum, or tissues of the host
- Oral drugs should be taken with water or after a meal
- Stools should be re-examined 2 weeks after the end of treatment
- Children's doses based on weight or BSA
- Contraindicated in pregnancy or in those with GI tract ulcers

C. SPECIFIC AGENTS:

Albendazole	Diethylcarbamazine citrate
Ivermectin	Mebendazole
Praziquantel	Pyrantel Pamoate
Emetine Hydrochloride	Bithionol
Metrifonate	Niclosamide (not available in the U.S.)
Oxamniquine	Oxantel Pamoate & Oxantel/Pyrantel Pamoate
Piperazine	Thiabendazole
Suramin	

D. NEUROCYSTICERCOSIS

1. Neurocysticercosis (General Comments)

- Humans become intermediate hosts
- Cysts enlarge slowly with minimal to no symptoms until several years or decades after onset of infection
- Symptoms usually begin as cysts die, lose osmoregulation and swell or leak antigens causing inflammation

2. Neurocysticercosis (CNS Manifestations)

- Vesicular cysticerci:** Cystic lesions, viable parasites, immune tolerance
- Colloidal cysticerci:** Enhancing lesions, implies degenerating parasite
- Involution of the cyst is in three stages**
 - Colloidal; fluid is turbid and scolex degenerates; Capsule is thick with surrounding edema
 - Granular stage; wall thickens and the scolex is mineralized
 - Calcification; final stage

3. Neurocysticercosis (Treatment)

a. Intraparenchymal disease

- Recent Meta-Analysis suggests benefit
(Del Brutto OH, et al. Ann Intern Med 2006;145:43-51)

b. Intraventricular disease

- No controlled trials, but treatment usually involves surgery & corticosteroids
± antihelmintics

c. Active agents: Albendazole* and Praziquantel

*(*No direct comparisons, but likely more efficacious & less interactions with corticosteroids and anticonvulsants)*

E. OTHER ANTI-HELMINTIC AGENTS (Albendazole)

- a. Useful in pinworm, ascariasis, hookworm, trichuriasis, strongyloidiasis, echinococcus, neurocysticercosis
- b. no effect on calcified brain cysts of neurocysticercosis
- c. ADRs:
 - Short term – minimal
 - Longer therapy – elevated aminotransferases, GI effects
 - 2 days after treatment may see inflammation and increased ICP with neurocysticercosis

F. OTHER ANTI-HELMINTIC AGENTS (Praziquantel)

- a. Useful in schistosomiasis, clonorchiasis, paragonimiasis, neurocysticercosis
- b. Decreased bioavailability with corticosteroid therapy
- c. ADRs: (mild) HA, drowsiness, dizziness, abdominal Pain
 - need to swallow whole as drug is emetogenic
- d. Contraindications: ocular cysticercosis (inflammation)
- e. Cautions: pregnancy and lactation

G. OTHER ANTI-HELMINTIC AGENTS (Mebendazole)

- a. Useful for Ascariasis, hookworm, pinworm, Taeniasis, Trichinosis, Strongyloidiasis
- b. ADRs: minimal GI to neutropenia and hepatic with long term therapy; hypersensitivity
- c. Avoid first trimester and children under two
- d. Drug interactions: carbamazepine and dilantin

H. OTHER ANTI-HELMINTIC AGENTS (Pyrantel Pamoate)

- a. Used for pinworm, *Ascaris*, hookworm
 - Not trichuriasis or Strongyloidiasis
- b. Luminal agent
- c. MOA: depolarizing neuromuscular blocking
 - Causes release of ACh and inhibition of cholinesterase > worm paralysis
- d. ADRs: mild/transient
- e. Cautions: Liver disease; kids <2; pregnancy

I. OTHER ANTI-HELMINTIC AGENTS (Ivermectin)

- a. DOC strongyloidiasis and onchocerciasis
 - Alternative for scabies especially in AIDS patients
 - Bancroftian filariasis, cutaneous larva migrans
- b. MOA: paralyzes nematodes and arthropods by intensifying GABA-mediated

- signals
- c. ADRs: (mild) hypersensitivity from worm death
 - *Mazotti* reaction – severe in onchocerciasis
 - d. Cautions: pregnancy, coexisting CNS inflammation

J. OTHER ANTI-HELMINTIC AGENTS (DEC*)

- a. DOC: filariasis, loiasis, tropical eosinophilia
 - Combination with ivermectin for *W bancrofti*
 - Ivermectin preferred in onchocerciasis (if used must combine with suramin)
- b. Mechanism – immobilizes microfilariae, alters surface structure increasing susceptibility to host defenses
- c. ADRs: mild headache, weakness, nausea, sleepiness
 - Hypersensitivity reaction to dying parasite – severe reactions in case of onchocerciasis (damage to retina and optic disc)

* *Diethylcarbamazine citrate*

Antimalarial Drugs Used for Treatment or Prophylaxis

Drug	Method of action	Stage of life cycle inhibited	Use	Unique or major adverse reactions	Use in Children	Use in Pregnancy	Comments
Chloroquine	Inhibit heme polymerase; incr free heme	RBC Schizont	Treatment and chemo-prophylaxis	Pruritis (Africans)	Safe	Safe	Resistance is major limitation
Quinine, Quinidine	Inhibit heme polymerase; incr free heme (toxic)	RBC Schizont (gametocytes of <i>P. vivax & ovale</i>)	Treatment of <i>P. falciparum</i>	Cinchonism* Hypoglycemia Blackwater fever	OK	Quinine - OK, if needed Quinidine - DOC for severe malaria; cardiac OK, but contractions in 3rd trimester	Only iv quinidine available in US; monitoring recommended; used with a 2nd agent
Mefloquine	Inhibit heme polymerase; incr free heme (toxic)	RBC Schizont	Treatment and chemo-prophylaxis	Neuropsychiatric toxicities (less common with prophylaxis)	Safe	OK for prophylaxis (no data for 1st trimester), NO for treatment	DOC for chemoprophylaxis in most regions; Not recommended for treatment of severe malaria
Primaquine	Inhibit heme polymerase; incr free heme (toxic)	Hypnozoite, Gametocyte	Radical cure for <i>P. vivax & ovale</i>	Hemolysis in G6PD-deficiency	OK	UNSAFE	Testing for G6PD-deficiency recommended; Terminal prophylaxis is rarely necessary
Proguanil	Inhibit plasmodial DHFR	RBC Schizont + some hypnozoite activity	With chloroquine or atovaquone for chemo-prophylaxis		OK	(never given alone, see atovaquone)	
Atovaquone	Inhibit parasite mitochondrial electron transport	RBC Schizont	With proguanil (Malarone) for chemo-prophylaxis	GI side affects, contraindicated in severe renal impairment	NO, if < 5kg	NO, unless benefit outweighs risk (Category C)	Give with food or milky drink
Doxycycline	Inhibit protein synthesis in parasite organelles	RBC Schizont	Adjuvant treatment of <i>P. falciparum</i> and chemo-prophylaxis	Photosensitivity, Esophagitis	NO	NO	Used for chemo-prophylaxis in areas with high mefloquine resistance (e.g., areas within Southeast Asia)
Artemisinin	Binds Iron in malaria pigment producing free radicals	RBC Schizont, Gametocyte	Treatment	Potential neurotoxicity (ototoxicity) unresolved	Probably OK, Not approved in US	Probably OK, Not approved in US	Used for treatment (Asia/Africa) in combination with other antimalarial agents

*Cinchonism: tinnitus, headache, nausea, dizziness, flushing and visual disturbances

Anthelmintic drugs used for treatment:

Drug	Disease for which agent is the Drug of Choice	Dose	Special Considerations
Albendazole	Cysticercosis	15 mg/kg/d (Max 800 mg) in 2 divided doses x 21 d	Absorption increased 5-fold with fatty meals, No interaction with corticosteroids
	Hydatid disease	400 mg BID x 3 mos	Check CBC, LFTs Q 2 weeks
Mebendazole	(Pinworm)	100 mg x 1, repeat in 2-4 wks	Absorption increased with fatty meals; chew before swallowing
	(Ascaris, Trichuria, Hookworm)	100 mg BID x 3 d	
Ivermectin	Strongyloidiasis	200 mcg/kg daily x 2	check stool by concentration method x 3 monthly to ensure eradication
	Onchocerciasis	150 mcg/kg x 1, repeat Q 3 mo x 4, then yearly x 10	Mazzotti reaction* occurs due to microfilariae death
Pyrantel pamoate	(Pinworm, Ascaris)	11 mg/kg x 1, repeat 2-4 wks	Treat all family members
Praziquantel	Schistosomiasis**	20 mg/kg Q 4-6 h x 3 doses	Swallow without chewing
	(Cysticercosis)	50 - 60 mg/kg/d in 3 divided doses x 14 d	Bioavailability decreased ~ 50% with phenytoin and corticosteroids
Diethyl carbamazine citrate	Filariasis, Loiasis, Tropical eosinophilia	2 mg/kg TID for 3 weeks, titrate up from Q daily to TID over first 3 d	Reactions to dying microfilariae are common, sometimes serious (BLINDNESS may occur in Onchocerciasis)

*Mazzotti reaction: fever, headache, dizziness, somnolence, weakness, rash, increased pruritis, diarrhea, joint & muscle pains, hypotension, tachycardia,

** Oxamiquine is DOC for S. mansoni

#65 - – Pharmacologic Palliation of Constipation & Nausea/Vomiting

Date: January 27, 2011– 10:30 AM

Reading Assignment: Katzung, Basic and Clinical Pharmacology, 9th Ed., pp. 1044-1047, 1051-1053

LEARNING OBJECTIVES

1. List the most common physical symptoms experienced at the end of life
2. Explain the mechanisms of action, indications, and contraindications of the following classes of drugs used for the relief of constipation and prototype drugs in each class:
 - Bulk laxatives (Psyllium; Bran)
 - Osmotic laxatives
 - Nonabsorbable sugars (Lactulose; Sorbitol)
 - Saline and magnesium laxatives (Magnesium citrate, magnesium hydroxide, sodium phosphate)
 - Polyethylene glycol
 - Stimulant laxatives (Senna; Bisacodyl)
 - Detergent laxatives (Docusate)
 - Lubricants (Glycerin suppository, mineral oil enema)
 - Enemas (Warm water; Soap suds; sodium phosphate)
3. Explain the mechanisms of action, indications, and contraindications of the following antiemetics and know prototype drugs in each class:
 - Dopamine receptor antagonists
 - Benzamides (Metoclopramide)
 - Phenothiazines (Prochlorperazine)
 - Butyrophenones (Haloperidol)
 - Prokinetic agents (Metoclopramide)
 - Antihistamines (Promethazine, Diphenhydramine)
 - Serotonin antagonists (Odansetron; Granisetron)
 - Anticholinergics (Scopolamine)
 - Benzodiazepenes (Lorazepam)
 - Corticosteroids (Dexamethasone)

#65 – Pharmacologic Palliation of Constipation & Nausea/Vomiting

- I. A goal of palliative care and end of life care is to relieve the suffering of patients. Control of pain and other physical symptoms, as well as psychological, social and spiritual problems is paramount.
- II The most common symptoms experienced at the end of life include
- A. Asthenia
 - B. Anorexia
 - C. Pain
 - D. Nausea
 - E. Constipation
 - F. Sedation/Confusion
 - G. Dyspnea

III. Pharmacologic Palliation of Constipation

A. BULKING AGENTS

Agents

- Dietary fiber (bran)
- Psyllium (Metamucil)

Mechanisms of Action

- Bulk-forming laxatives cause retention of fluid and an increase in fecal mass, resulting in stimulation of peristalsis.
- They usually have an effect within 12 to 24 hours and reach a maximum after several days

Side Effects

Flatulence

Contraindications

In debilitated patients who cannot drink adequate fluid (1.5 – 2 liters/day) could result in fecal impaction, intestinal obstruction

B. OSMOTIC LAXATIVES

These are soluble but nonabsorbable compounds that result in increased stool liquidity due to an obligate increase in fecal fluid.

● Nonabsorbable sugars

Agents

- Lactulose
- Sorbitol

Mechanism of Action

Lactulose is a synthetic disaccharide. Bacteria in the colon degrade lactulose into lactic acid, acetic acid and formic acid resulting in an increase in osmotic pressure and acidification of intestinal contents which in turn, softens the stool by promoting stool water content

Side Effects

- Bloating, cramps, flatulence
- Very sweet – may be difficult for patients to tolerate
- Can worsen dehydration by drawing body water into the bowel lumen

○ **Saline and magnesium salt laxatives**

Agents

- Magnesium citrate
- Magnesium hydroxide (Milk of Magnesia)
- Sodium Phosphate (Fleets Phospho-Soda)

Mechanism of Action

- Saline laxatives have an osmotic effect causing increased intraluminal volume that acts as a stimulus for intestinal motility.
- Laxatives that contain magnesium have been shown to release cholecystokinin that causes intraluminal accumulation of fluid and electrolytes and promotes small bowel and possibly even colonic transit.
- Rapid movement of water into distal small bowel and colon leads to high volume of liquid stool.
- High doses produce bowel evacuation in 1-3 hours.

Side Effects/Contraindications

- Contraindicated in any form of bowel obstruction
- Can produce dehydration without adequate fluid replacement
- Because the ions can be partially absorbed, laxatives containing magnesium and phosphorous are contraindicated in patients with impaired renal function
- Avoid sodium phosphate-containing formulations in patients with congestive heart failure, liver failure – severe electrolyte abnormalities can occur.
- Rare reports of ischemic colitis with magnesium citrate and sodium phosphate thought secondary to a rapid fluid shift from the intravascular compartment to the gut lumen resulting in transient colonic hypoperfusion and ischemia

Clinical Indications

- Magnesium citrate and sodium phosphate indicated for bowel cleansing in preparing patients for surgery or the colon for x-ray or endoscopy
- Magnesium hydroxide is indicated for relief of constipation

● **Polyethylene Glycol**

Trade names

Constipation - Miralax, GlycoLax

Bowel Cleanser - Colyte, Golytely

Mechanism of Action:

- Polyethylene glycol is an osmotic agent that causes retention of water in the stool resulting in a softer stool and more frequent bowel movements.
- It appears to have no effect on active absorption or secretion of glucose or electrolytes
- No significant intravascular fluid or electrolyte shifts occur

Side Effects

Minimal

Clinical Indications

- Large volume (ie 4 liters) ingested rapidly causes rapid evacuation for bowel cleansing before endoscopy
- Smaller daily doses can be used for constipation.

C. STIMULANT LAXATIVES

Agents:

- Senna
- Bisacodyl (Dulcolax)

Mechanism of Action:

- Bisacodyl is a contact laxative that acts on the large intestine to produce strong but brief peristaltic movements. This agent stimulates sensory nerve endings to produce parasympathetic reflexes that results in peristalsis of the colon. Local axon reflexes and segmental reflexes are stimulated, which produces widespread peristalsis of the colon.
- Senna undergoes conversion to active metabolites in the colon that stimulate the myenteric plexus and induce net fluid secretion.
- Response in 6-12 up to 24 hours.

Side Effects

- Electrolyte abnormalities depending on volume of stool
- Melanosis coli – brown pigmentation of the colon

Clinical Indication

Relief of constipation

D. DETERGENT LAXATIVES

Agent

Docusate (Colace)

Mechanism of Action

- Docusate is an anionic surfactant that is believed to stimulate intestinal secretion and increase the penetration of fluid into the stool by emulsifying feces, water, and fat
- Soft feces = easier passage
- Minimal effect on peristalsis
- Initial response in 1-3 days

Clinical Indications

Docusate is used to soften or prevent the formation of hard stools.

E. LUBRICANTS

Agents

- Glycerin suppository/enema
- Mineral oil enema

Mechanism of Action

- Due to its osmotic effect, glycerin softens, lubricates, and facilitates the elimination of inspissated feces. By serving as a bowel irritant it may also stimulate rectal contractions.
- Mineral oil helps soften (by coating fecal material with mineral oil) and lubricate hard stools, easing their passage without irritating the mucosa.
- Lubricants may stimulate a response within 30 minutes.

Side effects/contraindications

Mineral oil should **never be administered orally**, particularly to debilitated patients - inhalation/aspiration of the oil can lead to lipoid pneumonitis.

Clinical Indications

Usually reserved for treatment of fecal impaction

F. LARGE VOLUME ENEMAS

Agents

Warms water enema
Soapsuds enema
Sodium phosphate enema (Fleet's enema)

Mechanism of Action

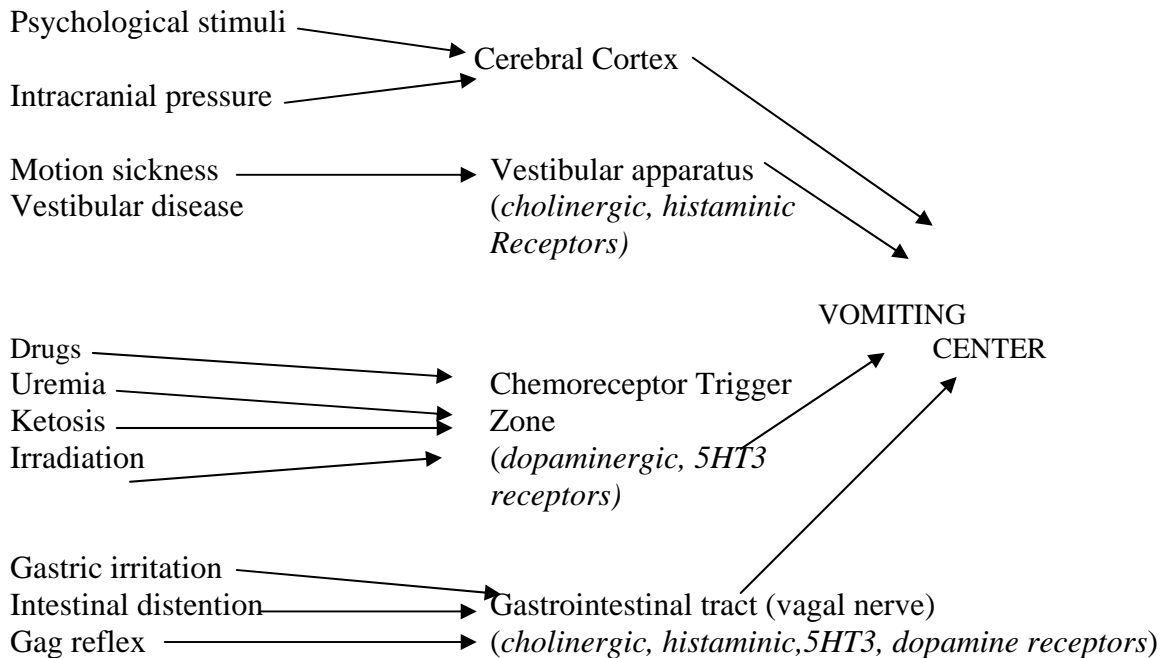
Soften stool by increasing water content
Distend distal colon inducing peristalsis

Clinical Indications

Usually reserved for treatment of fecal impaction

IV. Pharmacologic Palliation of Nausea and Vomiting

A. Pathophysiology of nausea and vomiting



Chemoreceptor trigger zone is located in the area postrema outside the blood brain barrier
Vomiting Center is located in the lateral reticular formation of the medulla and coordinates the motor mechanisms of vomiting

B. Antiemetic Drugs

Dopamine receptor antagonists

Phenothiazines - **Prochlorperazine (Compazine)**

Butyrophenones - Haloperidol (Haldol)

Benzamides – Metoclopramide (Reglan)

Serotonin (5HT₃) antagonists

Ondansetron (Zofran)

Granisetron (Kytril)

Antihistamines

Promethazine (Phergan)

Diphenhydramine

Anticholinergics

Scopolamine

Corticosteroids

Dexamethasone

Benzodiazepenes

Lorazepam

Alprazolam

C. Select Antiemetics

● **Agent - Metoclopramide (Reglan)**

Mechanism of Action

- Antiemetic properties are due to central and peripheral dopamine receptor inhibition
- Metoclopramide promotes motility in the upper gastrointestinal tract by sensitizing tissues to the action of acetylcholine, which is independent from intact vagal innervation and does not stimulate biliary, gastric, or pancreatic secretions.

It hastens gastric emptying and intestinal transit by increasing tone and amplitude of gastric contractions, relaxing the pyloric sphincter and duodenal bulb, and enhancing peristalsis of the duodenum and jejunum.

Adverse Effects

- Extrapyramidal effects, such as dystonia, akathisia, parkinsonism, may develop due to central dopamine receptor blockade.
- Acute dystonic reactions, such as trismus, torticollis, facial spasms, can be treated with an anticholinergic agent (benztropine or diphenhydramine).
- Cautious use in patients with Parkinson's Disease

Clinical Indications

- Vomiting due to dysmotility of the upper GI tract - gastric stasis and diabetic gastroparesis
- Chemotherapy induced nausea and vomiting

● **Agent - Prochlorperazine (Compazine)**

Mechanisms of Action

- Prochlorperazine acts centrally by inhibiting the dopamine receptors in the medullary chemoreceptor trigger zone
- It peripherally blocks the vagus nerve in the gastrointestinal tract

Adverse Effects

Extrapyramidal effects, dystonic reactions

Clinical Indications

- Opioid related nausea and vomiting
- Moderately effective for nausea caused by various GI disorders (ie gastroenteritis)

● **Agent - Promethazine (Phenergan)**

Mechanism of Action

Antiemetic effects come from its H(1) receptor blocking properties.

Adverse Effects

Sedation

Clinical Indications

Promethazine is effective in the active and prophylactic treatment of motion sickness

● **Agent - Ondansetron (Zofran)**

Mechanism of Action

- Ondansetron is a competitive, highly selective antagonist of 5-hydroxytryptamine (serotonin) subtype 3 (5-HT₃) receptors. 5-HT₃ receptors are present peripherally on vagal nerve terminals and centrally in the area postrema of the brain. It is not certain whether ondansetron's action is mediated peripherally, centrally, or both. Cytotoxic drugs and radiation appear to damage gastrointestinal mucosa, causing the release of serotonin from the enterochromaffin cells of the gastrointestinal tract. Stimulation of 5-HT₃ receptors causes transmission of sensory signals to the vomiting center via vagal afferent fibers to induce vomiting. By binding to 5-HT₃ receptors, ondansetron blocks vomiting mediated by serotonin release.

Side Effects

Most common side effect is headache

Small but statistically significant prolongation of the QT interval.

Clinical Indications

- Chemotherapy induced nausea and vomiting and its prophylaxis
- Radiation induced nausea and vomiting and its prophylaxis
- Most expensive of the antiemetics

● **Agent Scopolamine**

Mechanism of Action

Pure anticholinergic agent

Adverse Effects

- *Dry mouth (xerostomia)
- Acute narrow angle glaucoma (contraindicated in patients with known glaucoma)
- Urinary retention
- Confusion

Clinical Indications

- Treatment of motion sickness
- *In patients who are hours to days from death and who can no longer swallow their own secretions, it is used to decrease production of saliva

#61 - PHARMACOLOGY OF ANTIDEPRESSANT DRUGS

Date: January 13, 2011 – 10:30 a.m.

Reading Assignment: Katzung, Basic & Clinical Pharmacology; 11th Edition, Chapter 30, pp. 509 - 530

LEARNING OBJECTIVES

1. To understand the primary sites of action of different classes of antidepressant drugs.
2. To understand the adverse/side effects of the different classes of antidepressant drugs and considerations for their use in certain populations (e.g. in the elderly, in pregnancy, etc).
3. To understand why antidepressant drugs produce some of their effects in the short-term but require at least 2-3 weeks of administration before the onset of therapeutic improvement.
4. To understand some of the proposed mechanisms underlying the delayed therapeutic effects of antidepressant drugs.
5. To understand the considerations in using irreversible versus reversible MAOIs, the potential adverse effects of MAOIs, and the important considerations in switching between SSRIs and MAOIs.

#61 - PHARMACOLOGY OF ANTIDEPRESSANT DRUGS

INTRODUCTION

What is depression?

Depression is not a disease per se, but a clinical disorder that is manifested by a variety of symptoms that likely represent several neurochemical/neuropathological disorders in the brain.

Biological/chemical Diagnostic tests

There are no reliable biological/biochemical diagnostic tests to determine the cause of depression. A substantial number of depressed patients (up to about 40%) show elevated activity of the hypothalamic-pituitary-adrenal axis (elevated plasma cortisol, lack of feedback inhibition by dexamethasone).

Various theories, factors and changes associated with depression include:

- a) Genetic factors –interactions with environment
- b) Pharmacogenetics - different P450 metabolizers, variants of the 5-HT_{2A} receptor or 5HT transporters may affect response to antidepressant medications
- c) Neuroanatomical –neuroimaging and post mortem studies indicate regional changes
- d) Neuroendocrine – increased activity in HPA axis associated with depression and antidepressants normalize HPA function.
- e) Neurotrophic factors such as BDNF (brain derived neurotrophic factor)
- f) Neurotransmitter and signal transduction (receptors and 2nd messenger systems for monoamines)
- g) Other systems implicated: dopamine, acetylcholine, opiates, GABA and CRF.

Simple Take Home Message on Depression & Antidepressant Medications

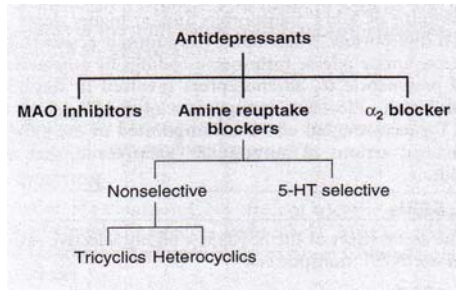
1. Currently, depression is conceived of as a disorder involving deficiency in serotonin and/or norepinephrine neurotransmission – supported by the “monoamine hypothesis of depression” proposed in the 1950’s (reserpine depletion of monoamines or tryptophan deficient diets invoke or precipitate depression, while drugs that increase serotonin or other monoamines alleviate depression).
2. Currently - All clinically effective antidepressant medications act on **serotonin (5-HT) and/or norepinephrine (NE)** systems. Dopamine also may contribute to the effects of some antidepressants.

Important Caveat in Theory & Treatment:

- *The therapeutic efficacy of all Antidepressants is not immediate, but requires repetitive administration over a prolonged period of time (at least 2-3 weeks before improvement starts)*

3. Antidepressant side effects can occur upon drug administration or shortly thereafter and be dependent on the specific pharmacological profile of the drug (i.e. the propensity of the drug to interact with any number of target receptors at clinical concentrations of drug).

Overview of Classes of Antidepressant Drugs

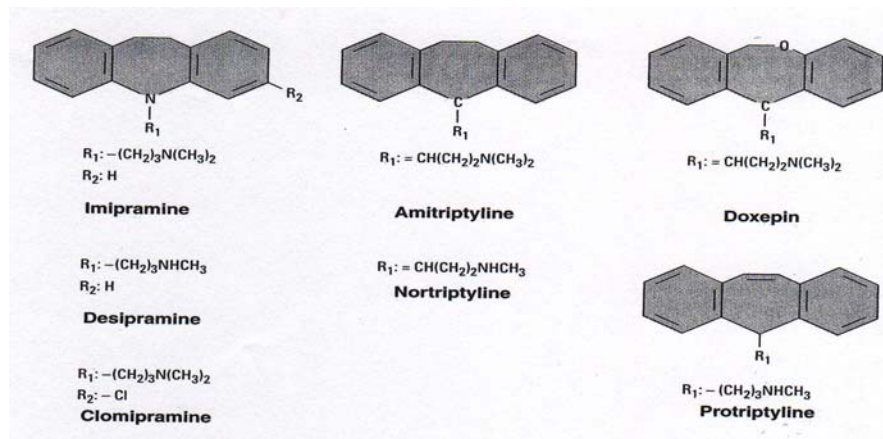


(from Katzung & Trevor's Pharmacology Examination and Board Rev. 7th ed. pp255)

A. TRICYCLIC Antidepressants (TCAs)

These are the “older antidepressants”,

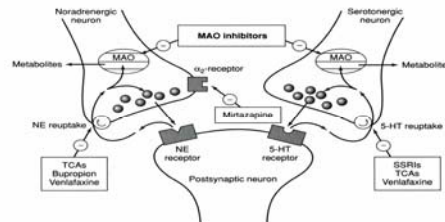
- also referred to as the 1st generation antidepressants
- structurally related to the phenothiazine antipsychotics
- tricyclic antidepressants can be either tertiary or secondary amines (see figure below)



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

Therapeutic Sites of Action

TCAs produce mixed blockade of both 5-HT and NE transporters (blocks reuptake of respective amines)



(source for same fig indicated on pg 6)

Representative TCAs

Imipramine (Trofanil®) - the prototype TCA that blocks reuptake of both 5-HT and NE, tricyclic antidepressants such as imipramine are demethylated to secondary amines (e.g. desipramine).

Desipramine (Norpramine®) – a secondary amine, and active metabolite of imipramine, that preferentially blocks the reuptake of NE

Amitriptyline (Elavil®) - 5-HT and NE reuptake inhibitor that is demethylated to **nortriptyline**,

Nortriptyline (Pamelor®) - an active preferential NE vs 5-HT uptake inhibitor.

Others TCAs that you should recognize:

- **Clomipramine (Anafranil®)** – preferential NE vs 5-HT uptake blockade
- **Doxepin (Sinequin®)** – preferential NE vs 5-HT uptake blockade, very sedating

Pharmacokinetics

- high lipid solubility
- large volume of distribution (Vd)
- rapid absorption
- serum concentrations peak within a few hours
- significant first pass metabolism
- half-life of 8-36 hours (active metabolites of imipramine and amitriptyline)
- high protein binding
- substrates of CYP2D6 (which exhibits genetic polymorphisms)

Prominent Side Effects of TCAs

In addition to blocking monoamine transporters, the tricyclic antidepressants produce prominent antagonist effects at:

alpha-1 adrenergic, muscarinic M1 and H-1 histamine receptors.

These non-selective effects of the TCAs produce several aversive side effects such as:

- 1) postural (orthostatic) hypotension,
- 2) cardiotoxicity,
- 3) confusion with memory dysfunction
- 4) excessive sedation and fatigue
- 5) weight gain.

Tricyclic antidepressants are not recommended for elderly patients (65+ years) because of their liability for inducing a toxic and confused state.

TCA's can produce additive CNS depression with other CNS depressants such as: alcohol, barbiturates, opiates and benzodiazepines.

TCA Overdose - extremely hazardous (ingestion of only a 2 wk supply may be lethal)

Manifestations include:

- agitation & delirium
- respiratory depression and circulatory collapse
- hyperpyrexia
- cardiac conduction defects and severe arrhythmias

B. Tetracyclic, Unicyclic and SNRI Drugs, – these will be discussed later but include drugs such as:

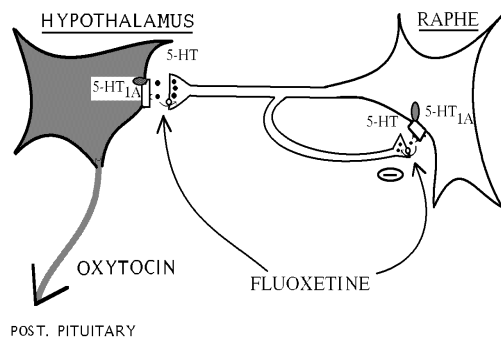
- **amoxepine, mirtazapine, maprotiline & bupropion (unicyclic)**
- **trazadone, nefazadone,**
- **venlafaxine, desvenlafaxine, duloxetine & the SSRIs (3rd generation and beyond)**

C. Selective Serotonin Reuptake Inhibitors (SSRIs)

- fewer adverse effects than the tricyclic antidepressants (TCAs)

Therapeutic Sites of Action

- selective blockade of the reuptake of 5-HT (SERT) in forebrain projection areas (e.g. hypothalamus, cortex, etc) as well as in midbrain regions containing 5-HT cell bodies (e.g. raphe nuclei).



The SSRIs are structurally distinct from the tricyclics and are not chemically related or chemical "look-alikes" to each other. Thus, if a patient does not respond to one SSRI, they may respond to a different SSRI.

However, despite having a better side effect profile than the tricyclics, *there are no substantial*

overall differences in antidepressant efficacy among the SSRIs, or between SSRIs and tricyclics.

SSRIs share the property of being “**selective**” (not exclusive) blockers of 5-HT transporters and primarily differ in:

- **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).

SSRIs also are used to treat a variety of other disorders including

- anxiety disorders,
- eating disorders,
- pre-menstrual dysphoric disorder (PMDD, PMS)
- obsessive compulsive disorder (OCD).

FDA Approved SSRIs

- **Fluoxetine (Prozac®)** – the first FDA approved and prototype SSRI (1987), the least 5-HT selective, long half life (1-4 days) and longer acting (7-15 days) demethylated active metabolite, **norfluoxetine** resulting in considerable drug accumulation. However, this pharmacokinetic reality is not accompanied by any deleterious effect. Major consideration in switching to MAOIs.

Other SSRIs

- paroxetine (Paxil®) - the highest affinity for the 5-HT transporter, no active metabolites
- sertraline (Zoloft®) - has desmethyl active metabolite
- citalopram (Celexa®) – the most selective for the 5-HT transporter, active desmethyl metabolite
- escitalopram (Lexapro®), - the S(+) isomer of (±) citalopram, that retains the highest 5-HT selectivity
- fluvoxamine (Luvox®) - no active metabolites, shorter half live (4-10hrs) than other SSRIs
-

Pharmacokinetics

Bioavailability - ranges from 50% (paroxetine) to > 90% (fluvoxamine)

Protein Binding - ranges from 50%(escitalopram) to 95 % (sertraline)

Plasma half-lives - all SSRIs range from 15-50 hrs, except for fluoxetine (1-4days) and its active metabolite (7-15 days)

Side Effects of SSRIs

- ***often occur prior to the onset of antidepressant efficacy and will depend on;***
 - a) the pharmacological profile of the specific drug (its propensity to interact with sites other than 5-HT uptake sites) and***
 - b) dose of drug***

SSRIs can be stimulatory and anxiogenic (paroxetine in particular) during the first week of use. (These compounds thus should be taken in the morning as opposed to before going to sleep, and in low doses which can be increased gradually).

- often induce sexual dysfunction (loss of libido, impotence, anorgasmia).
- may inhibit certain hepatic cytochrome P450 (CYP) enzymes that could lead to an elevation in plasma levels (thus toxicity) of other drugs that are catabolized by these liver enzymes.

SSRI Discontinuation Syndrome

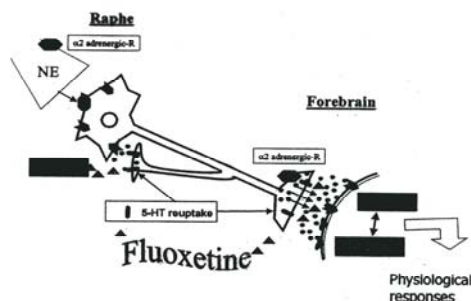
- *SSRIs should NOT be stopped Abruptly** - the dose should be tapered down over time
Abrupt discontinuation of the SSRIs may result in a cluster of symptoms that could include the following:
- dizziness, nausea, fatigue, headache, insomnia, restlessness, unstable gait and shock like sensations (rare).

More apparent with short acting SSRIs (paroxetine > fluvoxamine > sertraline > citalopram >> fluoxetine).

Noradrenergic-Serotonergic Interactions Relevant to Antidepressant Drug Action

In 5-HT Cell Body Regions(Raphe Nuclei): Release of norepinephrine activates α_1 -adrenergic receptors on 5-HT perikarya and enhances the firing rate of 5-HT neurons, resulting in **increased** release of 5-HT from nerve terminals. This is illustrated below:

(figure from GB)



Therefore, drugs that increase synaptic NE would increase 5-HT release from terminals;
This could be accomplished by:

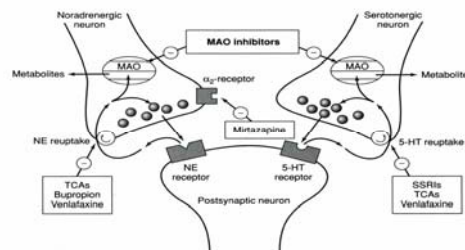
- blockade of NE transporters (NET) and/or
- antagonists at inhibitory α_2 adrenergic autoreceptors on noradrenergic terminals.

In limbic and cortical regions (i.e. forebrain regions)

α_2 -adrenergic receptors function as *inhibitory autoreceptors* on both noradrenergic & serotonergic nerve terminals.

Activation of these **α_2 adrenergic autoreceptors** results in decreased release of norepinephrine from noradrenergic terminals and a decreased release of 5-HT from serotonergic terminals.

Therefore, antidepressant drugs that antagonize α_2 adrenergic receptors would result in an increase the release of norepinephrine and 5-HT from their respective nerve terminals.



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

D. The Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)

- these drugs exhibit the combined blockade of 5-HT/NE as exhibited by the TCAs but in the absence of many of the adverse effects of the latter.
- minimal effects on the major CYP isoenzymes in contrast to SSRIs (e.g. fluoxetine)

Venlafaxine (Effexor®)

- a 5-HT and NE reuptake inhibitor. It is approved by the FDA for the treatment of both generalized anxiety disorder (GAD) and unipolar depression.

Side Effects

- sexual dysfunction
- hypertension

Desvenlafaxine (Pristig®) – the desmethyl metabolite of venlafaxine, received FDA approval in 2008

Duloxetine (Cymbalta®) – a more balanced blocker of 5-HT and NE reuptake. Received FDA approval in 2004 for treatment of major depressive disorder (MDD) and treatment of peripheral neuropathic pain associated with diabetic neuropathy.

(Milnacipran - not approved in the U.S. market but is an equipotent NE & 5-HT uptake blocker)

Side Effects

- may elevate liver enzymes
- may worsen narrow angle glaucoma
- may cause sexual side effects of urinary hesitancy
- may produce drug interactions via effects on CYP2D6
- may produce discontinuation syndrome

E. Mixed Action or “Atypical” Antidepressants (not for the treatment of atypical depression)

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 also available in a sustained release form and as the generic compound.

Mechanism of Action – recent preclinical studies indicate that its antidepressant mechanism of action may involve desensitization of both 5-HT_{1A} serotonin receptors and α ₂ adrenergic receptors, although a primary mechanism of action remains to be determined.

FYI – Remember: FDA approval only requires demonstration that a drug is safe and efficacious, its mechanism of efficacy does not need to be determined for approval.

Side Effects - profile of side effects that differ from the other antidepressants, devoid of:
anticholinergic, antihistaminergic and orthostatic hypotensive effects

Similar to some of the selective serotonin reuptake inhibitors (SSRIs), bupropion has an "energizing" or stimulating effect and should be taken in the A.M.

May decrease the seizure threshold in susceptible individuals and is contraindicated in individual with a prior history of eating disorders.

Bupropion has a relatively favorable side effect profile:

- weight loss rather than weight gain,
- does not interfere with sexual function.

Mirtazapine (*Remeron*[®]) is an α ₂-adrenergic receptor antagonist.

Mechanism of Action

- blockade of presynaptic α ₂ receptors on both noradrenergic and serotonergic nerve terminals that leads to an increase in NE and 5-HT neurotransmission.
- also blocks postsynaptic 5-HT_{2A}, 5-HT_{2C}, 5-HT₃ and H₁ histamine receptors that likely contributes more to the “side effects” than therapeutic effects of the drug.

Side Effect Profile

- highly sedating at low doses, should be administered before sleep
- can induce weight gain
- does not produce sexual dysfunction,
- does not produce nausea or GI problems,

Nefazodone (Serzone®) - a 5-HT_{2A} serotonin receptor antagonist and 5-HT reuptake inhibitor.

Side Effect Profile - mildly sedating but does not interfere with sexual function, other effects include nausea, dry mouth and increased appetite.

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.

E. The Monoamine Oxidase Inhibitors (MAOIs)

Monoamine oxidase (MAO) is the principal enzyme responsible for the metabolism of 5-HT, NE, tyramine and dopamine. There are two types of MAO, MAO-A and MAO-B which differ in their substrate specificity and regional distribution in brain and periphery.

The MAOIs are effective antidepressants, particularly in the treatment of atypical depression (hypersomnolence and hyperphagia with depressed mood).

These drugs **bind** to the mitochondrial enzyme, MAO, either **reversibly** (no chemical bond) or **irreversibly** (forming a covalent bond with the enzyme)

Inhibition of MAO (by either type of interaction) results in an increased amount of NE and 5-HT available for release when the neuron depolarizes ("fires").

Irreversible MAOIs

- phenelzine (Nardil®) - inhibits both MAO-A and MAO-B
- tranylcypromine (Parnate®) - inhibits both MAO-A and MAO-B.
- selegiline (l-deprenyl; Eldepryl®), - preferential MAO-B inhibitor ; a transdermal patch of selegiline, (Emsam®), was approved by the FDA in February 2006 for the treatment of major depression

Once an irreversible inhibitor binds to MAO, the cell must replace the inactivated enzyme. This synthetic process requires 10-14 days.

Reversible MAOIs

In contrast, a reversible inhibitor of monoamine oxidase (a "**RIMA**"), such as moclobemide, is uncoupled from the enzyme. Once a RIMA is discontinued, MAO activity recovers completely in

Reversible inhibition of MAO (**RIMA**) does not result in aversive dietary interactions if the RIMA is taken an hour before or two hours after eating foods with a high tyramine content.

Adverse Effects:

The major problem with MAOIs is that they can lead to potentially lethal **1) dietary and 2) drug interactions**. These scenarios include; *Hypertensive Crisis & The Serotonin Syndrome*

The Emsam patch, at the lowest dose (6 mg/24 hr), does not require a modified diet as for the other irreversible MAOIs

Hypertensive Crisis

- characterized by a major elevation in BP because of the increased catecholaminergic activity that results.
- may result in a ruptured aneurysm and stroke

Hypertensive crisis may be brought on by:

- ingestion of foods containing high concentrations of **tyramine** (e.g., aged cheeses, liqueurs, cured meats)
- use of certain drugs [e.g., cocaine, “ecstasy” (MDMA), certain opioids (such as fentanyl or meperidine),
- over the counter “cold medications” containing sympathomimetics (e.g. pseudoephedrine).

The Serotonin Syndrome

a syndrome characterized by the following:

- myoclonus, autonomic dysfunction, hyperactive reflexes, disorientation, unstable BP

Should avoid drugs (e.g., the SSRIs) that lead to a major increase in 5-HT activity because a **serotonin syndrome** can result.

Although by using RIMAs one can avoid aversive dietary interactions, the patient is still vulnerable to negative drug interactions.

Summary of Antidepressant Drugs and Drug Classes

Tricyclic antidepressants (TCAs)	Selective Serotonin reuptake inhibitors (SSRIs)	5-HT/NE reuptake inhibitor (SNRI)	Atypical (Mixed Action) Antidepressants	Monoamine oxidase inhibitors (MAO-I)
Imipramine	Fluoxetine	Duloxetine	Bupropion	Tranlycypromine
Amitriptyline	Paroxetine	Venlafaxine	Mirtazapine	Phenelzine
Doxepin	Sertraline	Desvenlafaxine	Nefazodone	Moclobemide (reversible MAO-I)
Desipramine	Fluvoxamine		Trazodone	Selegiline

Nortryptaline	Citalopram			
Clomipramine	Escitalopram			

Why do ALL antidepressants (Tricyclics, SSRIs or Mixed Action) have a delayed onset of action (i.e. delayed efficacy) ?

While the antidepressants may block reuptake of neurotransmitters or inhibit their metabolism (via MAOIs) within minutes of clearing the GI system, their therapeutic effects are not apparent for at least 2-3 weeks. This suggests that antidepressant efficacy requires induction of one or more time-dependent compensatory changes to occur. These can include:

1. The need to overcome auto-inhibitory receptor effects (see fig below).
2. Neuroadaptive changes in post-synaptic receptor signaling that occur subsequent to increased levels of 5-HT (or NE) in the synaptic cleft (e.g. desensitization of β -adrenergic receptors & 5-HT_{1A} serotonin receptors).
3. Potential compensatory changes in gene transcription (e.g. BDNF, trkB, CREB), structural changes in various brain regions and neurogenesis.

Desensitization of the 5-HT_{1A} inhibitory Autoreceptor on serotonergic perikarya
(both figures from GB)

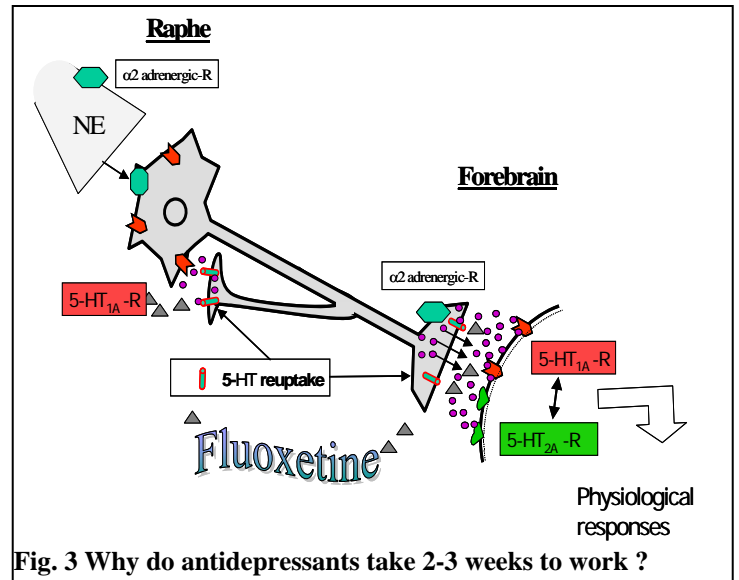
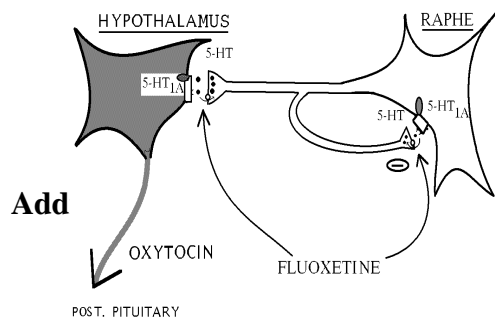


Fig. 3 Why do antidepressants take 2-3 weeks to work ?

Other Considerations with Antidepressant Medications

1. Switching between SSRIs (or Tricyclics) and MAOIs

From SSRI to MAOI

- Consideration of the half-life of the parent compound and any bioactive metabolite. Should wait a minimum of 5 half lives before starting the MAOI.

From MAOIs (irreversible) to SSRI

- Inhibition of MAO may persist long after these drugs are detectable in plasma (i.e. pharmacokinetic parameters are not very useful). Effects may persist from 7 days (tranylcypromine) to 2-3 weeks (phenylzine) after discontinuation.

2. Use of Antidepressants During Pregnancy

- Recent studies indicate that paroxetine may cause cardiovascular defects in babies' hearts. Paxil® taken during the first trimester increases (1.5-2 x) the chances of a heart defect (holes in the walls of the chambers of the heart) in offspring.
- Some studies indicate SSRI withdrawal symptoms in newborns

3. Use of Antidepressants in Children and Adolescents

- FDA black box warning of increased potential for suicidal thoughts in young patients taking SSRIs
- preclinical studies indicating long-term behavioral consequences of SSRI administration prior to maturation

4. Pharmacokinetic Considerations:

Interaction of SSRIs with various drugs such as TCAs, benzodiazepines and antipsychotics are metabolized by cytochrome P450 isozymes – SSRIs can inhibit enzyme activity.

IMPORTANT DRUGS MENTIONED IN THIS ECTURE

Tricyclic antidepressants (TCAs)

Imipramine (generic; Tofranil®)
Amitriptyline (generic; Elavil®)
Clomipramine (Anafranil®)
Desipramine (Nopramin®)
Doxepin (Sinequan®)

SSRIs

Citalopram (Celexa®) and
S-Citalopram (Lexapro®)
Fluoxetine (generic; Prozac®)
Fluvoxamine (Luvox®)
Paroxetine (Paxil®)
Sertraline (Zoloft®)

Atypical antidepressants

Bupropion (Wellbutrin®, Zyban®)
Mirtazapine (Remeron®)
Nefazodone (Serzone®)

Norepinephrine/serotonin reuptake inhibitors (SNRIs)

Venlafaxine (Effexor®)
Desvenlafaxine (Pristig®)
Duloxetine (Cymbalta®)

MAOIs (monoamine oxidase inhibitors)

Irreversible: Phenelzine (generic; Nardil®)
 Tranylcypromine (generic; Parnate®)
 Selegiline (l-deprenyl); Eldepryl®, Emsam®

Reversible (RIMA): Moclobemide (Manerix®, in Canada)

#62 - DRUGS TO TREAT ANXIETY AND BIPOLAR AFFECTIVE DISORDER

Date: January 14, 2011 – 8:30 a.m.

Reading Assignment: Katzung, Basic & Clinical Pharmacology; 11th Edition, Chapters 29, pp 487-507 and 24, pp. 405-415

KEY CONCEPTS AND LEARNING OBJECTIVES

1. To understand the target sites of action of the benzodiazepines and SSRIs and the strategy for using benzodiazepines in combination with SSRIs in the treatment of anxiety disorders.
2. To understand lithium's target sites of action, its pharmacokinetics, adverse effects and considerations in the use of lithium to treat bipolar disorder.
3. To understand the pharmacokinetics, adverse effects and considerations in using the anticonvulsants to treat bipolar affective disorder.
4. To understand the sites of action, adverse effects and considerations in using the atypical antipsychotics to treat bipolar affective disorder.

#62 - DRUGS TO TREAT ANXIETY & BIPOLAR AFFECTIVE DISORDER

I. Treatment of Anxiety Disorders

The long-term pharmacotherapy of primary anxiety disorders utilizes many of the SSRI/SNRI drugs used for depression as well as sedative-hypnotics in the interim. Initially, the anxiety symptoms need to be controlled by benzodiazepines until the antidepressants or buspirone can exert their delayed effects.

Anxiety disorders treated with Antidepressants & Benzodiazepines:

Alprazolam (Xanax®), clonazepam (Klonopin®) and lorazepam (Ativan®) are the most commonly used benzodiazepines in conjunction with SSRIs, SNRIs or buspirone for treatment of anxiety disorders such as:

Generalized anxiety disorder (GAD): venlafaxine, duloxetine, paroxetine and escitalopram have been FDA approved for GAD, although other SSRI and TCAs may be effective; buspirone (a 5-HT_{1A} receptor agonist), benzodiazepines such as lorazepam or clonazepam

Panic disorder: SSRIs considered 1st line (fluoxetine, sertraline, paroxetine and venlafaxine), Benzodiazepines: alprazolam (widely used but may cause rebound anxiety), clonazepam (longer acting)

Social anxiety disorder (SAD): best treated with SSRIs or MAOIs, FDA has approved sertraline, paroxetine and venlafaxine (SNRI) for this disorder. Duloxetine also may be effective.

Post-traumatic stress disorder (PTSD): generally treated with SSRIs (paroxetine and sertraline have FDA approval for PTSD); adding an antipsychotic to the SSRIs may prove beneficial in some patients while MAOIs or TCAs make sometimes work for PTSD.

Obsessive-compulsive disorder (OCD): SSRIs (fluvoxamine, fluoxetine, sertraline and paroxetine), the SNRI venlafaxine and the TCA, clomipramine, are drugs of choice for OCD.

Some Adverse Effects:

Benzodiazepines; sedation, mental confusion, ataxia, anterograde amnesia, physical dependence and tolerance with chronic use, rebound anxiety and withdrawal symptoms upon abrupt discontinuation (these may include insomnia, irritability, nausea, twitching, tinnitus, paresthesias and delirium).

Buspirone: headache, dizziness and nausea

Fluvoxamine, same side effects as other SSRIs but its additional inhibition of CYP1A2, 2C19 and 3A4 provides for a greater extent interactions with other drugs using these metabolic pathways.

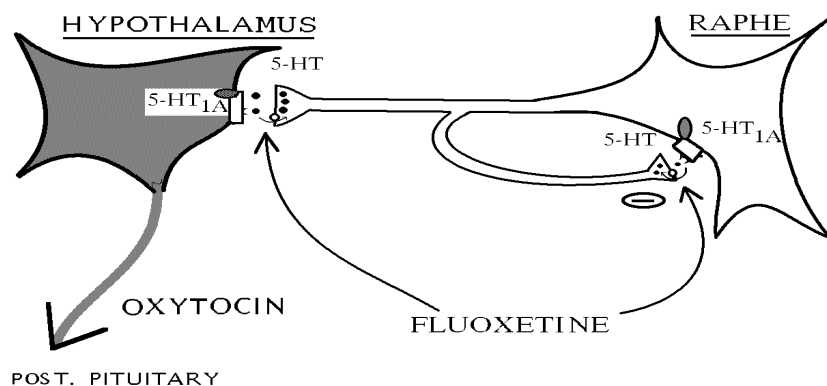
A 5-HT_{1A} Receptor Agonist

Buspirone (Buspar®) is a (partial) 5-HT_{1A} receptor agonist that is approved for the treatment of generalized anxiety disorder (GAD). Buspirone has low bioavailability, is slower acting than the benzodiazepines, less effective than the SSRIs for GAD and of questionable therapeutic efficacy. As with antidepressants used to treat anxiety disorders, the therapeutic response to buspirone is not immediate, but requires a period of time (at least 2 weeks). This is likely due to time-dependent desensitization of 5-HT_{1A} receptors that needs to occur to achieve its anxiolytic efficacy. Buspirone also is a dopamine D₂ receptor antagonist.

Drug Combination Strategy

SSRIs used to treat anxiety disorders have the same problem of delayed therapeutic effects as seen with the treatment of depression. Therefore, it might make sense to start with a benzodiazepine (e.g. alprazolam, lorazepam or clonazepam) combined with an SSRI (or buspirone). This could also reduce the initial pro-anxiety effects of some SSRIs and help patients to continue to take an SSRI until the therapeutic effects become clear. Subsequently, the use of benzodiazepines in these patients should be tapered down to avoid withdrawal problems.

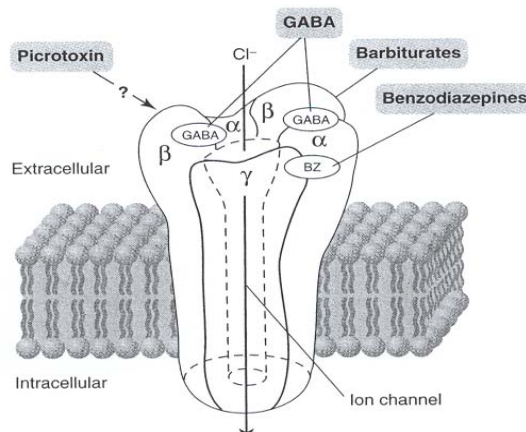
Time dependent adaptations (e.g. desensitization of 5-HT_{1A} inhibitory autoreceptors on 5-HT neurons) are required to achieve anxiolytic effects of the SSRIs.



Schematic of 5-HT neuronal projection and representative postsynaptic cell (a hypothalamic cell in this example) (figure from GB)

Mechanism of Action of Benzodiazepines: The therapeutic efficacy of the benzodiazepines as anxiolytics and sedatives is due to their potent effects on GABA_A receptor-mediated inhibition. They bind to sites on GABA_A receptors that modulate the activity of GABA receptor binding. Benzodiazepine binding increases the affinity of GABA_A for its binding site on the receptor and increases the frequency of opening of chloride channels.

As shown below, the receptors for benzodiazepine are located on GABA_A receptor subunits.



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

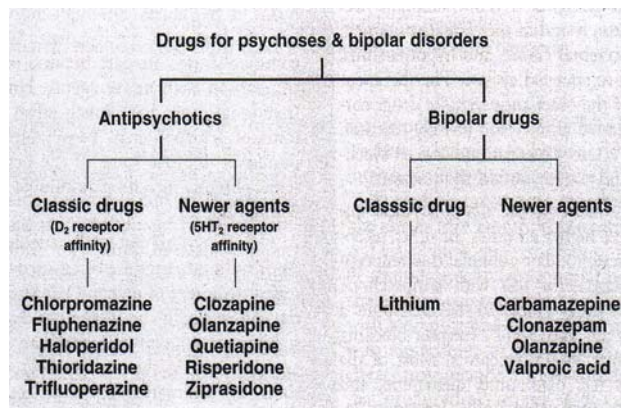
II. DRUGS TO TREAT BIPOLAR DISORDER

Bipolar Disorder is a primary affective disorder (aka manic-depressive illness) that causes dramatic mood swings.

- nearly 5.7 million adults have bipolar disorder
- a long-term disorder that usually develops in adolescence or early adulthood
- needs careful management throughout ones lifetime

The “high” episodes can include either elevated (euphoric), expansive (unceasing or indiscriminate enthusiasm) or irritable moods (labile moods altering between euphoria and dysphoria) that change to moods that are sad or hopeless (the depressive episode).

The pharmacotherapy of bipolar affective disorders is quite different from that for unipolar affective disorders. The use of an SSRI alone is contraindicated, as it may trigger a manic reaction in bipolar patients (this occurs in bipolar patients misdiagnosed as having unipolar depression).



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

The drugs of choice are: (A) **lithium** and (B) the **anticonvulsant drugs**, sodium valproate and carbamazepine. Another anticonvulsant, **lamotrigine** has more recently received FDA approval for maintenance treatment of bipolar disorder.

In addition, the Atypical Antipsychotics (C) have also been FDA approved for use in treatment of acute mania or mixed episodes. **Olanzapine** and **aripiprazole** are two atypical antipsychotics that have received FDA approval for maintenance treatment of bipolar disorder.

Risperidone and quetiapine (other atypical antipsychotics) have been shown to be useful to control manic episodes.

Gabapentin and topiramate have also been used, but have no proven efficacy and do not have FDA approval for treating mania

Mood stabilizers may be continued for an extensive period of time (years)

A. LITHIUM in the Treatment of Bipolar Disorder

- continues to be the first-line treatment for bipolar disorder
- proven effective in all phases of the illness, devoid of autonomic blocking effects and of activating or sedating effects
- only drug proven to reduce suicide in bipolar patients

**Lithium may take days to weeks to produce a full therapeutic effect*

Mechanism of Action:

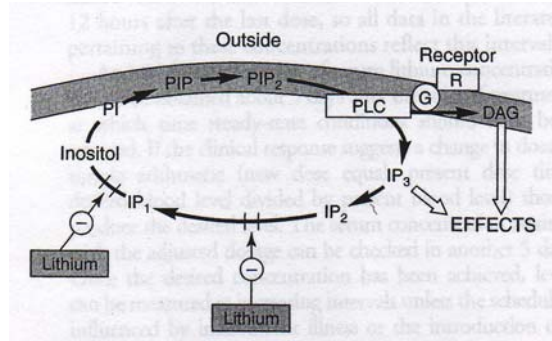
The exact mode of action of lithium in Bipolar Disorder is unclear. However, lithium produces a number of pharmacological effects:

- ***can effect electrolytes and ion transport***
Li⁺ acts like Na⁺. Li⁺ can substitute for Na⁺ in generating action potentials. Influx during depolarization is extremely rapid; efflux is 10-25 times slower than Na⁺.
- ***can effect neurotransmitters and their release***
 - seems to enhance the effects of serotonin
 - may decrease norepinephrine and dopamine turnover (may be relevant to antimanic effects)
 - may augment synthesis of acetylcholine

The most accepted mechanism of action for the therapeutic effects of lithium involves effects mediated on second messenger enzymes affecting neurotransmitter action

- lithium **inhibits** a number of enzymes involved in inositol recycling (inositol monophosphatase & inositol polyphosphate 1-phosphatase) resulting in depletion of substrate for IP3 production. (shown in the next figure).
- lithium also may (a) affect specific isozymes of protein kinase C (activated by DAG), (b) alter G protein function via shifts in phosphorylation and (c) uncouple receptors from their G proteins

Reductions in intracellular levels of inositol also have been postulated to underlie the mechanism of anti-bipolar effects of carbamazepine and sodium valproate.



(fig from Katzung, Basic and Clinical Pharmacology, 10ed., chapt 29, pp470)

Increasing recent evidence suggests a role for GSK-3 (**glycogen synthase kinase-3**) in mediating the therapeutic effects of lithium.

- GSK-3 regulates over 40 proteins that include structural, metabolic and signaling proteins as well as transcription factors.
- Lithium inhibits GSK-3 at concentrations within the effective range for the drug and has been shown to antagonize dopamine signaling via its Akt/GSK-3 pathway.
- Most drugs used for the treatment of bipolar disorder regulate GSK-3

Pharmacokinetics of Lithium

- readily and appreciably absorbed from the GI tract (peak levels in 0.5-2 hrs)
- no appreciable protein binding
- no metabolism, excretion is entirely in urine
- half-life of ≈ 20 hrs
- Li^+ has a narrow therapeutic window; 450 mg t.i.d. (1350 mg/day) produces a plasma concentration between 0.6 - 1.4 meq/L.
- changes in body water can alter plasma levels of the drug
- toxic effects are seen with plasma levels > 1.4 meq/L.

Some adverse side effects and complications of lithium:

- Slurred speech, fine tremor
- Nausea and fatigue in the initial weeks of treatment despite normal serum concentrations
- Excessive thirst and urination (nephrogenic diabetes insipidus); renal toxicity.
- Lithium inhibits thyroid hormone secretion (hypothyroidism)
- Edema and weight gain
- Confusion and ataxia associated with Li^+ toxicity
- Can induce /exacerbate psoriasis or cause acne

Other Considerations:

Use of lithium requires monitoring to maintain appropriate serum concentrations (0.6-1.2 meq/L for acute treatment and 0.6-0.7 mEq/L for maintenance) and avoid toxicity (>1.4 mEq/)

As Li^+ is excreted unchanged by the kidneys, patients with renal impairment and the elderly require dosage adjustment. Renal function and thyroid function should be monitored in patients taking lithium.

Common drug interactions;

- Thiazides, NSAIDs, ACE inhibitors and furosemide can increase serum lithium
 - Theophylline and caffeine can lower lithium levels (via increase in clearance)
- Lithium has been shown to have protective effects against suicide and self-harm in treating depression in patients with bipolar disorder.
 - Lithium also can be used to enhance the efficacy of antidepressant agents for the treatment of **unipolar** depression

Pregnancy

- lithium levels may be altered during pregnancy and after delivery
- Lithium use during pregnancy has been associated with congenital cardiac abnormalities
- Lithium toxicity in newborns (lethargy, cyanosis, poor suck and Moro reflexes, cardiac abnormalities)

B. ANTICONVULSANT Drugs That are Used to Treat Bipolar Affective Disorder

- these anticonvulsant drugs work as mood stabilizers in bipolar disorder
- ** recent FDA black box warning on all anticonvulsants for a potential increased risk of suicide*

1. Valproic Acid; Sodium Valproate (generic, Depakene® and Depakote®)

- the active form of the drug is thought to be the valproate ion, as sodium valproate it is fully ionized at body pH

Pharmacological Effects:

- GABA reuptake inhibitor that may increase GABA content in synapse or mimic its effects at postsynaptic receptors.
- influences 2nd messenger enzymes such as GSK-3
- blocks sustained high frequency neuronal firing rates (antiepileptogenic effect).

Pharmacokinetics

- highly protein bound (90%); displaces protein bound phenytoin resulting in an increase in phenytoin free fraction and potential toxicity.
- inhibits metabolism of the anticonvulsants phenytoin, phenobarbital and carbamazepine (toxic levels of these agents thus can be reached).

Adverse Effects and Toxicity of Valproate

- nausea, vomiting, diarrhea (can avoid by giving valproic acid with food or as enteric coated Depakote®)
- abdominal pain and heartburn
- may produce a fine tremor, weight gain, increased appetite and hair loss
- hepatotoxicity that may be severe (especially for those under 2 yr); pancreatitis
- teratogenic (neural tube defect, cardiovascular, urogenital, craniofacial and skeletal malformations and decreased IQ in offspring)
- some reports of blood dyscrasias (e.g. agranulocytosis)

2. Carbamazepine (generic, Tegretol®)

- a tricyclic compound that may be used alone or in combination with lithium in refractory patients

Pharmacological Effects:

- 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

- medium protein binding (70-80%)
- strong inducer of various CYP450 enzymes that are likely to increase the metabolism of other drugs

Side/Toxic Effects

- GI reactions (gastric distress, diarrhea, etc)
- dermatological reactions (rashes)
- ataxia and other neurological reactions
- Rare, but serious & sometimes fatal blood dyscrasias (bone marrow suppression)
- Increased risk of suicidality
- Increased risk of neural tube defect (Spina Bifida; about 0.9%) if used during pregnancy
- *Overdose of the drug presents a major medical emergency and should be managed like overdoses of tricyclic antidepressants.

FDA ALERT (12/12/07) – dangerous and even fatal skin reactions (Stevens Johnson syndrome & toxic epidermal necrolysis) can be caused by carbamazepine therapy; significantly more common in patients with a particular human leukocyte antigen (HLA) allele HLA-B*1502 occurring almost exclusively in individuals of Asian ancestry.

3. Lamotrigine (Lamictal ®) - an anticonvulsant that was approved in 2003 for the long-term maintenance treatment of bipolar disorder and may be helpful in depression. No generic lamotrigine in the USA. Dose of lamotrigine is most often between 100 and 200 mg/day (up to 600 mg/day).

- chemically unrelated to any other anticonvulsant or mood regulating medication.
- it seems to be effective in about two-thirds of people with bipolar mood disorders that have not responded to lithium or other mood-stabilizers
- has had been successful in controlling rapid cycling and mixed bipolar states in people who have not received adequate relief from lithium, carbamazepine and/or valproate.

Pharmacological Effects:

- has significantly more antidepressant potency than either carbamazepine or valproate
- may inhibit release of glutamate (excitatory a.a.) and inhibit voltage sensitive Na⁺ channels with the stabilization of neuronal membranes that mediate presynaptic transmitter release of excitatory amino acids.

Side Effects - relatively benign side-effect profile that include:

- dizziness & headache
- double vision & blurred vision
- unsteadiness
- sleepiness
- rash
- vomiting

Other Adverse Effects/Interactions:

- birth defects (increased risk of cleft lip or palate during 1st trimester)
- alcohol may increase the severity of the side-effects of lamotrigine
- oral contraceptives can lower the plasma level of lamotrigine by as much as 50%
- carbamazepine-induced enzymes (i.e. CYP3A4) can facilitate the metabolism of lamotrigine.
- valproate has the ability to double plasma levels of lamotrigine
- also can cause Stevens-Johnson syndrome (1 in 1000 patients)

C. ATYPICAL ANTIPSYCHOTICS Used to Treat Bipolar Disorder

1. **Risperidone (Risperidal®)** - an atypical antipsychotic approved in 2003 by the FDA for the treatment of the mixed and manic states associated with bipolar disorder.

Mechanism of Action

- antagonist at D2 dopamine and 5-HT₂ serotonin receptors as well as 5-HT₇ receptors

Side Effects:

Common: drowsiness & fatigue, increased appetite, anxiety, heartburn, akathisia, insomnia, low blood pressure, muscle stiffness & pain, minimal to marked weight gain.

2. **Ziprasadone (Geodon®)** – an atypical antipsychotic used in the treatment of bipolar disorder

Side Effects: tired or sleepy, upset stomach, constipation or diarrhea, feeling dizzy, rash, restlessness, tremor or shuffling

Drug Interactions:

- carbamazepine (Tegretol) can reduce the effectiveness of Geodon.

- no reported interaction problems between Ziprasadone and Lithium or oral contraceptives.

3. **Olanzapine (Zyprexa®)** – an atypical antipsychotic that is FDA approved for the treatment of Bipolar Disorder

Drug Interactions

- Carbamazepine may increase the metabolism of olanzapine thus making it less effective.

- Common side effects are: sleepiness, dizziness and dry mouth

4. **Quetiapine (Seroquel®)** - an atypical antipsychotic that received an initial indication in 2004 to treat the manic phase of bipolar disorder either alone or as an adjunct to lithium or divalproex; in 2006 received FDA approval to treat Bipolar Disorder.

Seroquel XR approved on November 16, 2007 for use in acute and maintenance treatment of schizophrenia.

Target Sites of Action

Antagonist actions at: D₁ & D₂ dopamine receptors, alpha₁-adrenoreceptors, 5-HT_{1A} & 5-HT₂ serotonin receptors and H₁-histamine receptors (thought to mediate its sedative properties).

Pharmacokinetics

- low bioavailability
- short-half life (6 hrs)

Side Effects

Common: dry mouth, sedation (most common), sleepiness and constipation

Less common: abnormal liver tests, dizziness, upset stomach, risk of development of tardive dyskinesia with prolonged use

Rare – serious and life-threatening development of the neuroleptic malignant syndrome (NMS)

Neuroleptic Malignant Syndrome:

- Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia).

5. Aripipazole (Abilify®) – approved in 2002 for mixed and manic episodes in bipolar patients; more recently approved as “add on” option (to antidepressants) in unipolar depression

- mechanism of action different from other atypical antipsychotics (e.g. olanzapine, quetiapine, ziprasidone)
- is a partial agonist at D2 dopamine receptors and 5-HT_{1A} serotonin receptors and retains its 5-HT₂ antagonist properties
- has moderate affinity for histamine and alpha adrenergic receptors, but no appreciable anticholinergic effects.

Pharmacokinetics

- good bioavailability (90%)
- metabolized primarily by CYP 3A4 and 2D6 , thus plasma concentrations of aripipazole may be increased by fluoxetine or paroxetine and decreased by carbamazepine

Side Effects

Common: akathisia, headache, unusual tiredness or weakness, nausea, constipation, trouble sleeping, restlessness and blurred vision,

Rare: neuroleptic malignant syndrome

D. Combination Medications & Others

Symbyax® – a combination medication of olanzapine & fluoxetine approved for the treatment of bipolar disorder

Side Effects: Dizziness, drowsiness, diarrhea, dry mouth, constipation, increased appetite, weight gain or trouble sleeping

- may also cause significant weight gain and a rise in your blood cholesterol (or triglyceride) levels

Drug Interactions

- serious (possibly fatal) interactions may occur with pimozide, sibutramine, thioridazine and if used concurrently or < 5 weeks after Symbyax is discontinued.

-MAO inhibitors should be stopped at least 2 weeks prior to Symbyax or not started until 5 weeks after Symbyax

(**Note:** On March 1, 2004, the US Food and Drug Administration "asked all manufacturers of atypical antipsychotic medications to add a Warning statement describing the increased risk of hyperglycemia and diabetes in patients taking these medications.)

The Benzodiazepines

– may also be used instead of, or in addition to, antipsychotics to treat the acute manic phase in bipolar disorder.

Diazepam (Valium®) Lorazepam (Ativan®) & Clonazepam (Klonopin®)

- diazepam has more rapid onset and longer long half-life
- lorazepam does not undergo Phase I metabolism

Non-Pharmacologic Therapeutic Approaches:

Bipolar Disorders -Electro-convulsive shock therapy (ECT). Also requires repeated application (approx 6 over 2 weeks) before improvement is observed. Can be very effective for severe manic or depressive episodes.

Anxiety Disorders - Behavioral modification, Biofeedback

IMPORTANT DRUGS MENTIONED IN THIS LECTURE

SSRI/SNRIs for anxiety disorders (see list of SSRIs in class notes for 1/13/11)

Benzodiazepines

Alprazolam (Xanax®)
Clonazepam (generic, Klonopin®)
Diazepam (generic, Valium®)
Lorazepam (generic; Ativan®)

5-HT_{1A} receptor agonist

Bupirone (Buspar®)

Drugs to Treat Bipolar Disorder

Lithium (generic; Eskalith®)

Anticonvulsants

Carbamazepine (generic, Tegretol®)
Lamotrigine (no generic, Lamacital ®)
Valproic acid (generic; Depakene®, Depakote®)

Atypical Antipsychotics

Aripipazole (Abilify®)
Olanzapine (Zyprexa®)
Quetiapine (Seroquel ®)
Risperidone (Risperidal®)
Ziprasidone (Geodon®)

Combination Drugs

Symbyax® (the atypical olanzapine and the SSRI fluoxetine)

ANTIPSYCHOTIC DRUGS

KEY CONCEPTS AND LEARNING OBJECTIVES:

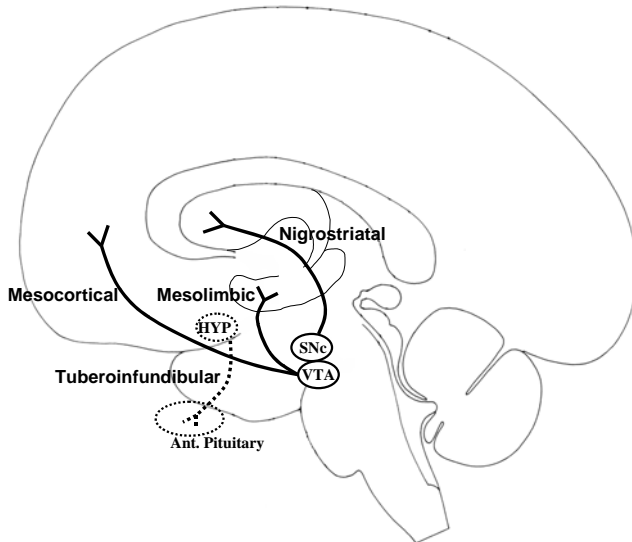
- 1) Recall the 4 well-defined dopamine systems in the brain as they relate to antipsychotic drug action and side effects.
- 2) Explain the distinction between “typical” and “atypical” antipsychotics
 - a) Recall the difference in mechanism(s) of action
 - “typical” antipsychotics mechanism (dopamine D2 receptor blockade)
 - atypical antipsychotics mechanism (dopamine D2 and serotonin 5-HT2 receptor antagonists)
 - Partial agonism mechanism of Aripiprazole (Abilify)
 - b) Recall the common side effects and the rare, but dangerous side effects
 - First generation anti-psychotics: High potency “typical” antipsychotic (haloperidol) versus a low potency “typical” antipsychotic (chlorpromazine).
 - Second generation anti-psychotics and clozaril
 - c) Predict the clinical outcome based on an action on a particular dopamine system
 - d) Predict the site of action in the dopamine system took place based on the clinical outcome
- 3) Explain the “Metabolic Syndrome” problem

IMPORTANT DRUGS

1.	Chlorpromazine	(Thorazine)**	Prototype
2.	Haloperidol	(Haldol)**	Prototype
3.	Clozapine	(Clozaril)**	Prototype
4.	Risperidone	(Risperidal)**	Prototype
5.	Olanzapine	(Zyprexa)	
6.	Quetiapine	(Seroquel)	
7.	Ziprasidone	(Geodon)	
8.	Aripiprazole	(Abilify)**	Prototype
9.	Paliperidone	(Invenga)	
10.	Asenapine	(Saphris)	
11.	Lurasidone	(Latuda)	

ANTIPSYCHOTIC DRUGS

I. Normal Physiology



Location of Dopamine system desired effect from anti-psychotic medications

- A. Mesolimbic system = Dopamine (DA) neurons projecting from ventral tegmental area to subcortical structures of the brain (e.g. nucleus accumbens); Positive (psychotic) symptoms involve “mesolimbic dopamine hyperactivity.”

Blockade of DA₂ receptors in mesolimbic system reduces psychotic symptoms.

Locations of Dopamine system side effects from anti-psychotic medications

- B. Mesocortical system = DA neurons projecting from ventral tegmental area to frontal cortex; Negative symptoms (and possibly positive symptoms to a small extent) related to mesocortical DA dysfunction.

Blockade of DA₂ receptors in mesocortical system may exacerbate negative symptoms.

- C. Nigrostriatal system = DA neurons projecting from substantia nigra pars compacta to striatum (comprises part of basal ganglia motor circuit);

Blockade of DA₂ 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 DA₂ receptors in anterior pituitary lead to Hyperprolactinemia and associated adverse effects.

II. Pathophysiology/Disease state

Dopamine Hypothesis

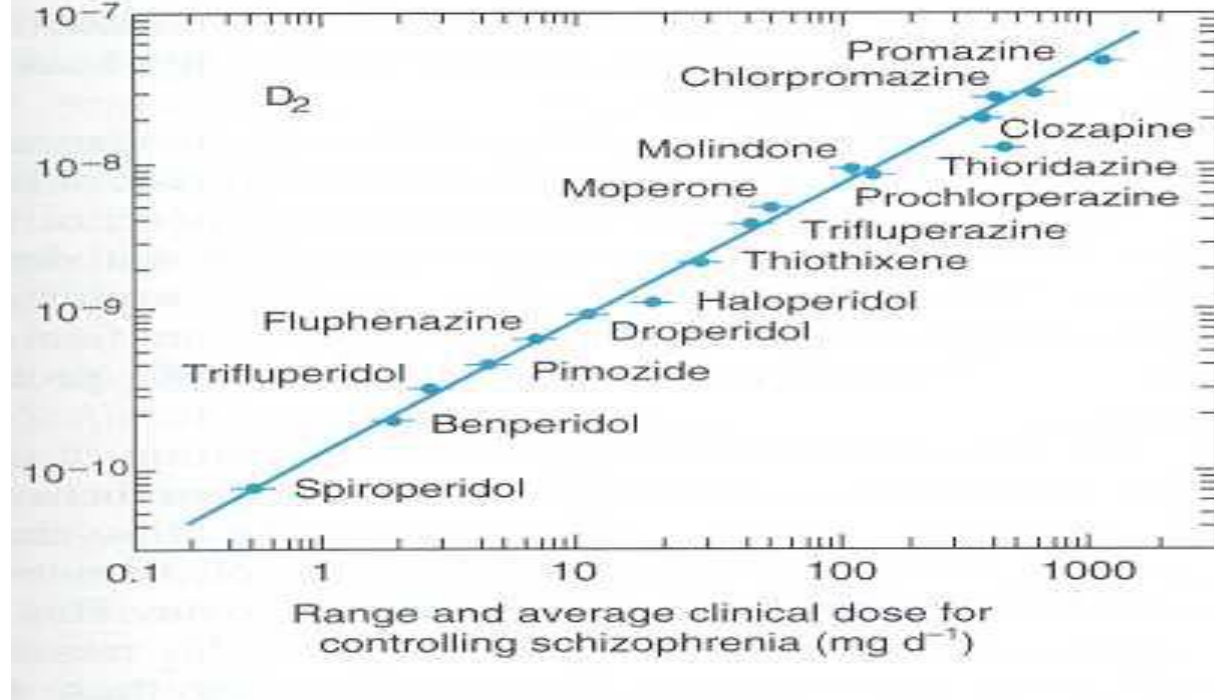
Hyperactivity of Dopamine (DA) neurotransmitter pathways → Schizophrenia

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.

III. Description of Drugs used to treat Disease

First Generation Antipsychotics (FGA's)

Also called: Conventional antipsychotics, Typical Antipsychotics, Neuroleptics, Major Tranquilizers

Phenothiazines

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

Thioxanthines

- Thiothixene (Navane)

Butyrophenones

- Haloperidol (Haldol) high potency***

Second Generation Antipsychotics (SGA's)
Also called: Atypical antipsychotics

Risperidone (Risperdal)	Paliperidone (Invega)	Ziprasidone (Geodon)
Olanzapine (Zyprexa)	Quetiapine (Seroquel)	Asenapine (Saphris)
Lurasidone (Latuda)		
Aripiprazole (Abilify)		
Clozapine (Clozaril)		

IV. 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: Psychosis treatment

Schizophrenia
Mood disorders-Bipolar disorder, Major Depression
Medical Illness-Dementia, delirium, Substance abuse

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

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, in patients

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

	Risperidone	Ziprasidone	Quetiapine	Olanzapine	Clozapine
Alpha1	8.5	8.5	8	7.5	8.2
M1	--	--	6	7.5	8
H1	7.3	8.5	7.7	10	8.5
5-HT2A	10	10	7.5	9	8.7
D2	8.5	8.5	6.1	7.7	6.7
5-HT2A:D2 affinity ratio	32	32	25	20	100

Atypical Antipsychotic Drug Affinities at Various Neurotransmitter Receptors
(Value expressed as pKi = -logKi; higher number means higher affinity)

5-HT2A:D2 affinity ratio >20:1 for atypical antipsychotics (100:1 for clozapine)

Therapeutic Window for Treatment

Treatment of psychosis—block >60-65% of dopamine D2 receptors in the Mesolimbic tract

A substantial EPS risk—block >80% of the dopamine D2 receptors in the Nigrostriatal tract

Risk of ↑Prolactin—block >80% of the D2 receptors in Tuberoinfundibular tract

What mechanism of action allows for greater than 65% dopamine receptor blockage in the mesolimbic system but less than 80% dopamine receptor blockage in the nigrostriatal system? How do the drugs work to hit this therapeutic window?

1. Serotonin-Dopamine Antagonism hypothesis

- Nigrostriatal tract & Mesolimbic tract
5-HT_{2A} blockade enhances DA release in basal ganglia (from nigrostriatal DA system); This DA competes with the antipsychotic for DA₂ receptors;
Result is blockage of > 65% receptors but < 80% of receptors (therapeutic window).
Consequence is antipsychotic efficacy (mesolimbic tract) & reduced EPS (nigrostriatal tract).
- Mesocortical
5-HT_{2A} 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 DA₂ blockade of atypical antipsychotics has also led to “hit and run” concept; i.e. atypical drug-induced blockade of DA₂ receptors is not as long-lasting as with typical drugs.

Partial Agonism & Aripiprazole (Abilify)

Partial agonist

- rheostat analogy; the receptor (light) is neither completely on nor 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 transmitter environments

Little agonist activity (the cell is not completely off)

In low dopaminergic environment, aripiprazole binds to the DA₂ receptor with high affinity (potent) & has a partial agonist effect

In high transmitter environments

Exerts antagonist action (the cell is not completely on)

In high dopaminergic environment aripiprazole has the effect of an antagonist

Leads to important concept of “dopamine system stabilization” (i.e. not too much, not too little); supported by observation that clinical efficacy of atypical antipsychotics may be seen at DA₂ occupancy levels below those achieved by typical antipsychotics
Aripiprazole is the first Dopamine-Serotonin System Stabilizer

VI. 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

Half-life about 20 hours, steady state 4-7 days

VII. Important side effects: Common & Rare

	Chlorpromazine (Low potency)	Haloperidol (High potency)
Dopamine-D2-related Extrapyramidal (EPS/TD); Increased prolactin	++	+++
Muscarinic-M1-Anticholinergic Blurred vision, dry mouth, urinary retention etc.	+++	0
Adrenergic-Alpha1-related Orthostasis	+++	0
Histamine-H1-related Sedation, weight gain	+++	0

	Risperidone (Risperdal)	Ziprasidone (Geodon)	Quetiapine (Seroquel)	Olanzapine (Zyprexa)	Clozapine (Clozaril)
Dopamine-D2-related Extrapyramidal (EPS/TD) Increased prolactin	+ / ++	+	0 / +	+	0
Muscarinic-M1-Anticholinergic Blurred vision, dry mouth, urinary retention etc.	0	0	0 / +	++	+++
Adrenergic-Alpha1-related Orthostasis	+ / ++	0 / +	++	0 / +	+++
Histamine-H1-related Sedation	0 / +	0 / +	+ / +++	+ / +++	+++
Weight gain	++	0 / +	++	+++	+++
Glucose intolerance	+	0	+	++	+++
Lipids	+	0	+	++	++

Prominent atypical drug-related effects-

- Risperidone-EPS side effects at higher doses (>6 mg/day)
- Clozapine (clozaril) - agranulocytosis in 1-2% of patients. Requires weekly blood monitoring
- Clozapine (clozaril) and Olanzapine (zyprexa) - weight gain, glucose intolerance, hyperlipidemia, sedation
- Quetiapine (seroquel) – weight gain, sedation, orthostasis
- Ziprasidone Geodon) - QTc elongation, may contribute to cardiac arrhythmias (also seen with the typical drug, thioridazine); other atypical drugs suspect for QTc elongation but insufficient data to attribute great significance

- **Metabolic Syndrome**

Weight gain, Hyperglycemia, Diabetes Mellitus, Dyslipidemia

All SGA antipsychotics can result in significant weight gain, but there are differences among the medications.

Clozapine > Olanzapine >>> Quetiapine > Risperidone/Paliperidone >> Asenapine(?) > Ziprazodone/Aripiprazole

Among patients with Schizophrenia, there are metabolic risk factors for cardiovascular disease that are far higher than the general population. Evidence suggests that SGA antipsychotics are associated with metabolic disturbances that can further increase this risk.

Rare Side Effects

All antipsychotics: Neuroleptic Malignant Syndrome

Clozapine: Agranulocytosis

FGA's & SGA's: ↑ Mortality in elderly pts with Dementia; death from stroke and related disorders is greater than placebo.

VIII. Important drug-drug interactions

- May increase (↑) levels of various antipsychotics:
ciprofloxacin (Cipro®), erythromycin, ritonavir (Norvir®),
fluoxetine (Prozac®), fluvoxamine (Luvox®),
- May decrease (↓) levels of various antipsychotics:
carbamazepine (Tegretol®), phenobarbital, phenytoin (Dilantin®), rifampin (Rifadin®)
- Combining clozapine with carbamazepine (Tegretol®) may increase the risk of agranulocytosis.

IX. Contraindications

No absolute contraindications.

#64 - ANTI-PARASITIC AGENTS

I. INTRODUCTION

A. General Comments:

- a. Drugs intermittently difficult to obtain
- b. Available drugs lack FDA approval
- c. Lagging new drug development
- d. Many agents have limited efficacy or serious toxicity

B. Distinction between protozoal & helminthic Infections:

<u>Protozoa</u>	<u>Helminths</u>
• Complete replication within definitive host	Life-cycle involves more than definitive host
• Clinical illness results from single exposure	Repeated exposures necessary for disease
• Treatment goal: Eradication	Treatment goal: Eradication or reduction of worm burden

C. Definitions:

- | | | | | |
|--|-----|---|-----|--|
| • Definitive Host
(Harbors sexual parasitic stage) | vs. | • Intermediate Host
(Harbors larval or asexual parasitic stage) | vs. | • Incidental Host
(Not necessary for parasitic survival) |
| • Gametogony
(Sexual development) | vs. | • Schizogony
(Asexual development) | | |

II. GENERAL APPROACH TO ANTIPARASITIC CHEMOTHERAPY

A. Targets of Chemotherapy: *Comparison of biochemical and physiologic processes between humans and parasites reveals differences in biochemical processes that provide selective inhibition in parasites. Three major types of potential targets of parasites include:*

1. Unique enzymes found only in the parasite (e.g., pyruvate:ferridoxin oxireductase in *Giardia*)
2. Enzymes found in both host and parasite, but indispensable only for the parasite (e.g., lanosterol C-14 α demethylase in *Leishmania*)
3. Common biochemical functions found in both host and parasite, but with different properties (e.g., dihydrofolate reductase-thymidylate synthetase bifunctional enzyme in *Plasmodium* and *Toxoplasma*)

III. THERAPY OF PROTOZOAN PARASITES

A. MALARIA

1. **Four species of plasmodia cause human malaria**
 - P. falciparum*
 - i. responsible for nearly all serious complications and deaths
 - ii. drug resistance is an important therapeutic problem
 - P. vivax*
 - P. malariae*
 - P. ovale*

2. **Plasmodium life cycle**
 - a. Anopheline mosquito inoculates plasmodium sporozoite to initiate human infection
 - b. **Exoerythrocytic stage:** tissue schizonts mature in liver to merozoites and are released into the circulation to invade erythrocytes
 1. *P. falciparum* and *P. malariae* have only 1 cycle of liver cell invasion and multiplication. Liver infection ceases spontaneously in 4 weeks. Therefore treatment that eliminates erythrocytic parasites will cure the infection
 2. *P. vivax* and *P. ovale* have a dormant liver stage (the hypnozoite) and eradication of both the liver and erythrocyte stages is required to cure the infection. No one agent can eliminate both hepatic and erythrocytic stages
 - c. **Erythrocytic stage:** intraerythrocytic merozoites develop into trophozoites then to schizonts and rupture RBC releasing multiple merozoites that invade other RBCs
 - d. Repeated cycles of infection can lead to the infection of many erythrocytes and serious diseases
 - e. Sexual stage (gametocytes) also develop in RBCs and are taken up into mosquitoes where they develop into infective sporozoites to continue cycle in next host

3. **General Principles of Malaria Treatment**
 - a. Because of increasing drug resistance, it is important to emphasize prevention (repellants, insecticides, nets)

 - b. Specific treatment will depend on geographical area visited, patient's age, pregnancy, etc.

 - b. The CDC website is a good source to check on current resistance patterns and experience with new drugs:
www.cdc.gov/malaria/clinicians.htm

3. **Major Antimalarial Drugs**

Chloroquine	Quinine and Quinidine	Amodiaquone
Mefloquine	Primaquine	Pyrimethamine
Proguanil	Atovaquone	Halofantrine
Artemisinin and its derivatives (<not available in US, but highly active)		
Antibiotics (tetracycline, doxycycline, azithromycin, clindamycin)		

4. **Chloroquine**

- Used for prophylaxis and treatment
- Initial half-life: 3-5 d; Terminal half-life: 1-2 mo
- Schizonticidal to all plasmodial species; not active against exoerythrocytic (liver phase) parasites
- MOA: Prevents polymerization of heme to hemozoin leading to a build up of free heme which is toxic to parasite
- Resistance in *P. falciparum* is wide-spread
- ADRs: pruritis; Uncommon - nausea, vomiting abdominal pain, HA, anorexia, malaise, blurred vision

5. **Chloroquine & antimalarial Drug Resistance**

- Chloroquine resistance in *P. falciparum* is wide-spread
- Chloroquine-susceptible *P. falciparum*: Central America, Caribbean, Middle East (although pockets of resistance noted)
- P. falciparum* resistance to quinine in SE Asia
- Resistance rare with other species (recent exception is Chloroquine resistance in *P. vivax* from Papua New Guinea & Indonesia)

6. **Mefloquine**

- Used for prophylaxis and treatment all forms malaria
- Schizonticidal; MOA: similar to chloroquine
- DOC for prophylaxis in areas of chloroquine resistant *falciparum* (see resistance in Thailand border areas)
- Adverse: nausea, vomiting, sleep & behavioral problems; Neuropsychiatric toxicities (seizures, psychosis) risk is similar to other antimalarials; Rare - cardiac arrhythmias
- Contraindications: seizures, psych d/o, arrhythmia
- Drug interactions: quinine, quinidine, halofantrine

7. **Alternatives to Mefloquine Prophylaxis**

- Atovaquone and proguanil (*Malarone*)
- Proguanil with chloroquine
- Pyrimethamine and sulfadoxine (*Fansidar*)
- Doxycycline (DOC: Prophylaxis against mefloquine-resistant *P. falciparum*)

8. **Quinine and Quinidine**
 - a. DOC for treatment of severe disease with chloroquine-resistant *P. falciparum* malaria
 - b. Quinine only oral in USA, Quinidine IV in USA (cardiac monitoring recommended with IV Rx)
 - c. Used with a second agent (e.g., doxycycline) to shorten duration and limit toxicity
 - d. ADRs: GI, Cinchonism (headache, nausea, visual disturbances, dizziness, tinnitus)
 - e. Quinine can be used, if needed, in pregnancy

9. **Primaquine**
 - a. Used to treat exoerythrocytic forms of vivax and ovale malaria;
 - b. DOC for RADICAL CURE after chloroquine
 - c. Used in terminal prophylaxis, but rarely required
 - d. MOA: Probably similar to chloroquine
 - e. ADRs: Infrequent - nausea, abdominal pain, cramps; Rare - hematologic, arrhythmias
 - f. Contraindications: granulocytopenia
 - g. Relative Contraindication: G6PD deficiency → hemolysis; Testing recommended prior to Rx

10. **Artemisinin (Qinghaosu)**
 - a. Used in China >2000 years; no resistance yet!
 - b. Several derivatives, e.g., Artemether
 - c. Rapidly acting schizonticide
 - d. Second agent used to prevent recrudescence (ACT: artemisinin combination therapies)
 - e. MOA: production of toxic free radicals in parasite food vacuole

11. **Malaria Prevention**
 - a. Chloroquine (only in areas without resistant *P. falciparum*)
 - b. Mefloquine
 - c. Atovaquone and proguanil (Malarone)
 - d. Doxycycline (DOC in areas with multi-drug resistance)
 - e. Chloroquine and proguanil (not available in the US)
 - f. Primaquine (terminal prophylaxis for *P. vivax* & *P. ovale*)

12. **Malaria Prevention (Recommended schedule in relation to travel)**

	<u>Start</u>	<u>Stop</u>
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13. **Malaria Treatment**

- a. Chloroquine-sensitive *P. falciparum* infections- Chloroquine
- b. *P. vivax* and *P. ovale* infections- Chloroquine
- c. Chloroquine-resistant *P. falciparum* infections, Uncomplicated
 - Atovaquone plus proguanil (Malarone)
 - Quinine 3-7 days* plus doxycycline, tetracycline, or clindamycin, (*7 days for non-immune travelers & cases from SEA)
 - Artemether plus lumefantrine (Coartem)
 - Mefloquine
- d. Chloroquine-resistant *P. falciparum* infections, Complicated
 - Quinidine (iv) plus doxycycline, tetracycline, or clindamycin
 - Artesunate (iv) followed by atovaquone/proguanil, doxycycline, or mefloquine

B. AMEBIASIS

1. **Antiamebic Drugs**

a. **Tissue Amebicides**

- Metronidazole
- Emetine
- Chloroquine

b. **Luminal Amebicides**

- Diloxanide furoate (*not avail in US*)
- Iodoquinol
- Paromomycin

2. **Metronidazole**

- a. DOC extraluminal (tissue) amebiasis
 - Also treats giardia, trichomonas (and anaerobic bacteria)
 - Used for tissue stages of amebiasis (dysentery, ameboma, liver abscess)
- b. MOA: ferredoxin-linked processes reduce nitro group to product lethal against anaerobic organisms
- c. ADRs: nausea, vomiting, metallic taste, disulfuram-like
- d. Drug interactions: anticoagulants, alcohol, anticonvulsants

3. **Iodoquinol**

- a. Used for luminal amebic infections, other intestinal protozoa
- b. MOA: unknown
- c. ADRs: Neurotoxicity and nausea and vomiting reported but rare at recommended doses

4. Treatment of Specific Forms of Amebiasis

- a. **Asymptomatic intestinal infections** (carriers)
 - generally not treated in endemic areas
 - in nonendemic areas luminal agents used
 - iodoquinol (650mg TID x 21d), paromomycin (10mg/kg TID x 7d), diloxanide furoate (500mg TID x 10 days)
 - single course effective in >90%
- e. **Amebic colitis**
 - Metronidazole (750mg TID x 10d) plus a luminal agent
- f. **Liver abscess**
 - DOC is metronidazole* (750 mg TID x 10d) plus a luminal agent (96% effective) * *Less than 10 d is probably effective, large abscesses need drainage in addition to treatment with metronidazole*
 - Chloroquine reserved for failures
- g. **Ameboma and other Extraintestinal infections**
 - Metronidazole (750mg TID x 10d) plus a luminal agent

C. AFRICAN TRYPANOSOMIASIS

1. **Pentamidine** (intravenous administration)
 - Alternative to or combination with suramin for early lymphoid stage but not CNS disease (2-4mg/kg/d or QOD x 10-15 doses).
 - Also used as an alternative to sodium stibogluconate for visceral leishmaniasis (2-4 mg/kg/d or QOD x 15 doses IV)
 - Many toxicities; rapid infusion see hypotension, tachycardia, dizziness, dyspnea; with IM, pain at injection site and sterile abscesses may develop; pancreatic toxicity first hypoglycemia then IDDM; Nephrotoxic
2. **Suramin** (intravenous administration)
 - First line therapy for hemolymphatic disease; does not cross BBB, therefore not effective for CNS disease; prophylaxis against trypanosomiasis
 - 200mg test dose followed by 1g on days 1,3,7,14,21 or 1g weekly x 5 doses
 - Combined with pentamidine to improve efficacy
 - Toxicities: (common) immediate-fatigue, nausea, vomiting and rarely seizures, shock and death; late-fever, rash, HA, paresthesias, neuropathies, renal tox (proteinuria), chronic diarrhea, hemolytic anemia, agranulocytosis
3. **Melarsoprol** (intravenous administration)
 - First line therapy for advanced CNS disease
 - IV in propylene glycol 3.6mg/kg/d x 3-4d repeated weekly PRN

- Extremely toxic: *immediate*-fever, vomiting, abdominal pain, arthralgias;
late- reactive encephalopathy (w/in 1 week in 1-10%) w/cerebral edema, seizures, coma and death (due to disruption of trypanosomes); renal, cardiac, and hypersensitivity reactions

4. **Eflornithine**

- Second therapy for advanced CNS disease; less toxic; equal efficacy against *T brucei gambiense* but limited against *T brucei rhodesiense*
- IV /IM 100mg/kg q 6 h x 14 d followed by PO 3-4 weeks
- Toxicities: diarrhea, vomiting, anemia, TCP, leukopenia and seizures

D. AMERICAN TRYPANOSOMIASIS (Chagas Disease)

1. **Nifurtimox** (oral administration)

- Decreases severity and eliminated detectable parasites but ineffective at eradication of infection; not active against chronic disease
- Efficacy variable with resistance in some areas S. America
- Toxicities (common)- nausea, vomiting, abdominal pain, fever, rash, restlessness, insomnia, neuropathies, and seizures

2. **Benznidazole** (oral administration)

- Efficacy similar to nifurtimox for Chagas' disease
- Toxicities: peripheral neuropathy, rash, GI, and myelosuppression.

E. LEISHMANIASIS

1. **Sodium Stibogluconate**

- Pentavalent antimonial DOC for cutaneous and visceral leishmaniasis
- Efficacy varies with endemic resistance in some areas (alternative therapies include liposomal amphotericin B, miltefosine)
- IV/ IM 20mg/kg/d (x 20 d for cutaneous / x 28 d for visceral)
- Toxicities: (increases with therapy) GI, fever, HA, myalgias, arthralgias, rash; QT prolongation

F. CRYPTOSPORIDIOSIS

1. **General management principles:**

- Lactose-free diet
- Antimotility agents
- Restoration of immune response in HIV infection with HAART (esp.PIs)
- Few active drugs available

2. **Nitazoxanide** (oral administration)

- 500 mg to 1 gm BID
- No better than placebo if CD4 count < 50 (Rossignol et al. Trans R Soc Trop Med 1998;92:663)

3. **Paromomycin** (oral administration)
- 25 – 35 mg/kg/d in 2-4 divided doses
4. **Other potential agents:** Azithromycin, spiramycin, clarithromycin

G. GIARDIASIS

1. **Metronidazole** (oral administration)
-250 mg TID x 5 – 7 d
2. **Nitazoxanide** (oral administration)
- Pediatric indication: 100 mg BID
3. Other agents: quinacrine (no longer available in US), furazolidone, albendazole
4. Pregnancy: paromomycin, metronidazole in 2nd & 3rd trimester

H. TOXOPLASMOSIS

1. **Pyrimethamine**
- Most effective agent, need to add folinic acid
- No role for monotherapy, need to add **sulfadiazine** or **clindamycin**
2. Alternate agents: azithromycin, clarithromycin, atovaquone, dapsone, TMP-SMX
3. Lymphadenopathy in immunocompetent – Self-limiting disease
4. Encephalitis in HIV
- Treat 4-6 weeks after resolution of signs/symptoms (usually > 6 mos)
pyrimethamine 200 mg loading dose, then 50 – 75 mg daily
+ sulfadiazine 1 – 1.5gm QID
or, + clindamycin 600 mg QID
- Life-long maintenance unless CD4 count rises to > 200 for at least 6 mos
Pyrimethamine 25 mg daily + sulfadiazine 500 mg QID

IV. THERAPY OF HELMINTHS

A. GENERAL COMMENTS

- Used to eradicate or reduce the number of parasites in the intestines or tissues
- Diagnosed by finding the parasite, eggs, or larvae in the feces, urine, blood, sputum, or tissues of the host
- Oral drugs should be taken with water or after a meal
- Stools should be re-examined 2 weeks after the end of treatment
- Children's doses based on weight or BSA
- Contraindicated in pregnancy or in those with GI tract ulcers

C. SPECIFIC AGENTS:

Albendazole	Diethylcarbamazine citrate
Ivermectin	Mebendazole
Praziquantel	Pyrantel Pamoate
Emetine Hydrochloride	Bithionol
Metrifonate	Niclosamide (not available in the U.S.)
Oxamniquine	Oxantel Pamoate & Oxantel/Pyrantel Pamoate
Piperazine	Thiabendazole
Suramin	

D. NEUROCYSTICERCOSIS

1. Neurocysticercosis (General Comments)

- Humans become intermediate hosts
- Cysts enlarge slowly with minimal to no symptoms until several years or decades after onset of infection
- Symptoms usually begin as cysts die, lose osmoregulation and swell or leak antigens causing inflammation

2. Neurocysticercosis (CNS Manifestations)

- Vesicular cysticerci:** Cystic lesions, viable parasites, immune tolerance
- Colloidal cysticerci:** Enhancing lesions, implies degenerating parasite
- Involution of the cyst is in three stages**
 - Colloidal; fluid is turbid and scolex degenerates; Capsule is thick with surrounding edema
 - Granular stage; wall thickens and the scolex is mineralized
 - Calcification; final stage

3. Neurocysticercosis (Treatment)

a. Intraparenchymal disease

- Recent Meta-Analysis suggests benefit
(Del Brutto OH, et al. Ann Intern Med 2006;145:43-51)

b. Intraventricular disease

- No controlled trials, but treatment usually involves surgery & corticosteroids
± antihelmintics

c. Active agents: Albendazole* and Praziquantel

*(*No direct comparisons, but likely more efficacious & less interactions with corticosteroids and anticonvulsants)*

E. OTHER ANTI-HELMINTIC AGENTS (Albendazole)

- a. Useful in pinworm, ascariasis, hookworm, trichuriasis, strongyloidiasis, echinococcus, neurocysticercosis
- b. no effect on calcified brain cysts of neurocysticercosis
- c. ADRs:
 - Short term – minimal
 - Longer therapy – elevated aminotransferases, GI effects
 - 2 days after treatment may see inflammation and increased ICP with neurocysticercosis

F. OTHER ANTI-HELMINTIC AGENTS (Praziquantel)

- a. Useful in schistosomiasis, clonorchiasis, paragonimiasis, neurocysticercosis
- b. Decreased bioavailability with corticosteroid therapy
- c. ADRs: (mild) HA, drowsiness, dizziness, abdominal Pain
 - need to swallow whole as drug is emetogenic
- d. Contraindications: ocular cysticercosis (inflammation)
- e. Cautions: pregnancy and lactation

G. OTHER ANTI-HELMINTIC AGENTS (Mebendazole)

- a. Useful for Ascariasis, hookworm, pinworm, Taeniasis, Trichinosis, Strongyloidiasis
- b. ADRs: minimal GI to neutropenia and hepatic with long term therapy; hypersensitivity
- c. Avoid first trimester and children under two
- d. Drug interactions: carbamazepine and dilantin

H. OTHER ANTI-HELMINTIC AGENTS (Pyrantel Pamoate)

- a. Used for pinworm, *Ascaris*, hookworm
 - Not trichuriasis or Strongyloidiasis
- b. Luminal agent
- c. MOA: depolarizing neuromuscular blocking
 - Causes release of ACh and inhibition of cholinesterase > worm paralysis
- d. ADRs: mild/transient
- e. Cautions: Liver disease; kids <2; pregnancy

I. OTHER ANTI-HELMINTIC AGENTS (Ivermectin)

- a. DOC strongyloidiasis and onchocerciasis
 - Alternative for scabies especially in AIDS patients
 - Bancroftian filariasis, cutaneous larva migrans
- b. MOA: paralyzes nematodes and arthropods by intensifying GABA-mediated

- signals
- c. ADRs: (mild) hypersensitivity from worm death
 - *Mazotti* reaction – severe in onchocerciasis
 - d. Cautions: pregnancy, coexisting CNS inflammation

J. OTHER ANTI-HELMINTIC AGENTS (DEC*)

- a. DOC: filariasis, loiasis, tropical eosinophilia
 - Combination with ivermectin for *W bancrofti*
 - Ivermectin preferred in onchocerciasis (if used must combine with suramin)
- b. Mechanism – immobilizes microfilariae, alters surface structure increasing susceptibility to host defenses
- c. ADRs: mild headache, weakness, nausea, sleepiness
 - Hypersensitivity reaction to dying parasite – severe reactions in case of onchocerciasis (damage to retina and optic disc)

* *Diethylcarbamazine citrate*

Antimalarial Drugs Used for Treatment or Prophylaxis

Drug	Method of action	Stage of life cycle inhibited	Use	Unique or major adverse reactions	Use in Children	Use in Pregnancy	Comments
Chloroquine	Inhibit heme polymerase; incr free heme	RBC Schizont	Treatment and chemo-prophylaxis	Pruritis (Africans)	Safe	Safe	Resistance is major limitation
Quinine, Quinidine	Inhibit heme polymerase; incr free heme (toxic)	RBC Schizont (gametocytes of <i>P. vivax & ovale</i>)	Treatment of <i>P. falciparum</i>	Cinchonism* Hypoglycemia Blackwater fever	OK	Quinine - OK, if needed Quinidine - DOC for severe malaria; cardiac OK, but contractions in 3rd trimester	Only iv quinidine available in US; monitoring recommended; used with a 2nd agent
Mefloquine	Inhibit heme polymerase; incr free heme (toxic)	RBC Schizont	Treatment and chemo-prophylaxis	Neuropsychiatric toxicities (less common with prophylaxis)	Safe	OK for prophylaxis (no data for 1st trimester), NO for treatment	DOC for chemoprophylaxis in most regions; Not recommended for treatment of severe malaria
Primaquine	Inhibit heme polymerase; incr free heme (toxic)	Hypnozoite, Gametocyte	Radical cure for <i>P. vivax & ovale</i>	Hemolysis in G6PD-deficiency	OK	UNSAFE	Testing for G6PD-deficiency recommended; Terminal prophylaxis is rarely necessary
Proguanil	Inhibit plasmodial DHFR	RBC Schizont + some hypnozoite activity	With chloroquine or atovaquone for chemo-prophylaxis		OK	(never given alone, see atovaquone)	
Atovaquone	Inhibit parasite mitochondrial electron transport	RBC Schizont	With proguanil (Malarone) for chemo-prophylaxis	GI side affects, contraindicated in severe renal impairment	NO, if < 5kg	NO, unless benefit outweighs risk (Category C)	Give with food or milky drink
Doxycycline	Inhibit protein synthesis in parasite organelles	RBC Schizont	Adjuvant treatment of <i>P. falciparum</i> and chemo-prophylaxis	Photosensitivity, Esophagitis	NO	NO	Used for chemo-prophylaxis in areas with high mefloquine resistance (e.g., areas within Southeast Asia)
Artemisinin	Binds Iron in malaria pigment producing free radicals	RBC Schizont, Gametocyte	Treatment	Potential neurotoxicity (ototoxicity) unresolved	Probably OK, Not approved in US	Probably OK, Not approved in US	Used for treatment (Asia/Africa) in combination with other antimalarial agents

*Cinchonism: tinnitus, headache, nausea, dizziness, flushing and visual disturbances

Anthelmintic drugs used for treatment:

Drug	Disease for which agent is the Drug of Choice	Dose	Special Considerations
Albendazole	Cysticercosis	15 mg/kg/d (Max 800 mg) in 2 divided doses x 21 d	Absorption increased 5-fold with fatty meals, No interaction with corticosteroids
	Hydatid disease	400 mg BID x 3 mos	Check CBC, LFTs Q 2 weeks
Mebendazole	(Pinworm)	100 mg x 1, repeat in 2-4 wks	Absorption increased with fatty meals; chew before swallowing
	(Ascaris, Trichuria, Hookworm)	100 mg BID x 3 d	
Ivermectin	Strongyloidiasis	200 mcg/kg daily x 2	check stool by concentration method x 3 monthly to ensure eradication
	Onchocerciasis	150 mcg/kg x 1, repeat Q 3 mo x 4, then yearly x 10	Mazzotti reaction* occurs due to microfilariae death
Pyrantel pamoate	(Pinworm, Ascaris)	11 mg/kg x 1, repeat 2-4 wks	Treat all family members
Praziquantel	Schistosomiasis**	20 mg/kg Q 4-6 h x 3 doses	Swallow without chewing
	(Cysticercosis)	50 - 60 mg/kg/d in 3 divided doses x 14 d	Bioavailability decreased ~ 50% with phenytoin and corticosteroids
Diethyl carbamazine citrate	Filariasis, Loiasis, Tropical eosinophilia	2 mg/kg TID for 3 weeks, titrate up from Q daily to TID over first 3 d	Reactions to dying microfilariae are common, sometimes serious (BLINDNESS may occur in Onchocerciasis)

*Mazzotti reaction: fever, headache, dizziness, somnolence, weakness, rash, increased pruritis, diarrhea, joint & muscle pains, hypotension, tachycardia,

** Oxamiquine is DOC for S. mansoni

#65 - – Pharmacologic Palliation of Constipation & Nausea/Vomiting

Date: January 27, 2011– 10:30 AM

Reading Assignment: Katzung, Basic and Clinical Pharmacology, 9th Ed., pp. 1044-1047, 1051-1053

LEARNING OBJECTIVES

1. List the most common physical symptoms experienced at the end of life
2. Explain the mechanisms of action, indications, and contraindications of the following classes of drugs used for the relief of constipation and prototype drugs in each class:
 - Bulk laxatives (Psyllium; Bran)
 - Osmotic laxatives
 - Nonabsorbable sugars (Lactulose; Sorbitol)
 - Saline and magnesium laxatives (Magnesium citrate, magnesium hydroxide, sodium phosphate)
 - Polyethylene glycol
 - Stimulant laxatives (Senna; Bisacodyl)
 - Detergent laxatives (Docusate)
 - Lubricants (Glycerin suppository, mineral oil enema)
 - Enemas (Warm water; Soap suds; sodium phosphate)
3. Explain the mechanisms of action, indications, and contraindications of the following antiemetics and know prototype drugs in each class:
 - Dopamine receptor antagonists
 - Benzamides (Metoclopramide)
 - Phenothiazines (Prochlorperazine)
 - Butyrophenones (Haloperidol)
 - Prokinetic agents (Metoclopramide)
 - Antihistamines (Promethazine, Diphenhydramine)
 - Serotonin antagonists (Odansetron; Granisetron)
 - Anticholinergics (Scopolamine)
 - Benzodiazepenes (Lorazepam)
 - Corticosteroids (Dexamethasone)

#65 – Pharmacologic Palliation of Constipation & Nausea/Vomiting

- I. A goal of palliative care and end of life care is to relieve the suffering of patients. Control of pain and other physical symptoms, as well as psychological, social and spiritual problems is paramount.
- II The most common symptoms experienced at the end of life include
- A. Asthenia
 - B. Anorexia
 - C. Pain
 - D. Nausea
 - E. Constipation
 - F. Sedation/Confusion
 - G. Dyspnea

III. Pharmacologic Palliation of Constipation

A. BULKING AGENTS

Agents

- Dietary fiber (bran)
- Psyllium (Metamucil)

Mechanisms of Action

- Bulk-forming laxatives cause retention of fluid and an increase in fecal mass, resulting in stimulation of peristalsis.
- They usually have an effect within 12 to 24 hours and reach a maximum after several days

Side Effects

Flatulence

Contraindications

In debilitated patients who cannot drink adequate fluid (1.5 – 2 liters/day) could result in fecal impaction, intestinal obstruction

B. OSMOTIC LAXATIVES

These are soluble but nonabsorbable compounds that result in increased stool liquidity due to an obligate increase in fecal fluid.

● Nonabsorbable sugars

Agents

- Lactulose
- Sorbitol

Mechanism of Action

Lactulose is a synthetic disaccharide. Bacteria in the colon degrade lactulose into lactic acid, acetic acid and formic acid resulting in an increase in osmotic pressure and acidification of intestinal contents which in turn, softens the stool by promoting stool water content

Side Effects

- Bloating, cramps, flatulence
- Very sweet – may be difficult for patients to tolerate
- Can worsen dehydration by drawing body water into the bowel lumen

○ **Saline and magnesium salt laxatives**

Agents

- Magnesium citrate
- Magnesium hydroxide (Milk of Magnesia)
- Sodium Phosphate (Fleets Phospho-Soda)

Mechanism of Action

- Saline laxatives have an osmotic effect causing increased intraluminal volume that acts as a stimulus for intestinal motility.
- Laxatives that contain magnesium have been shown to release cholecystokinin that causes intraluminal accumulation of fluid and electrolytes and promotes small bowel and possibly even colonic transit.
- Rapid movement of water into distal small bowel and colon leads to high volume of liquid stool.
- High doses produce bowel evacuation in 1-3 hours.

Side Effects/Contraindications

- Contraindicated in any form of bowel obstruction
- Can produce dehydration without adequate fluid replacement
- Because the ions can be partially absorbed, laxatives containing magnesium and phosphorous are contraindicated in patients with impaired renal function
- Avoid sodium phosphate-containing formulations in patients with congestive heart failure, liver failure – severe electrolyte abnormalities can occur.
- Rare reports of ischemic colitis with magnesium citrate and sodium phosphate thought secondary to a rapid fluid shift from the intravascular compartment to the gut lumen resulting in transient colonic hypoperfusion and ischemia

Clinical Indications

- Magnesium citrate and sodium phosphate indicated for bowel cleansing in preparing patients for surgery or the colon for x-ray or endoscopy
- Magnesium hydroxide is indicated for relief of constipation

● **Polyethylene Glycol**

Trade names

Constipation - Miralax, GlycoLax

Bowel Cleanser - Colyte, Golytely

Mechanism of Action:

- Polyethylene glycol is an osmotic agent that causes retention of water in the stool resulting in a softer stool and more frequent bowel movements.
- It appears to have no effect on active absorption or secretion of glucose or electrolytes
- No significant intravascular fluid or electrolyte shifts occur

Side Effects

Minimal

Clinical Indications

- Large volume (ie 4 liters) ingested rapidly causes rapid evacuation for bowel cleansing before endoscopy
- Smaller daily doses can be used for constipation.

C. STIMULANT LAXATIVES

Agents:

- Senna
- Bisacodyl (Dulcolax)

Mechanism of Action:

- Bisacodyl is a contact laxative that acts on the large intestine to produce strong but brief peristaltic movements. This agent stimulates sensory nerve endings to produce parasympathetic reflexes that results in peristalsis of the colon. Local axon reflexes and segmental reflexes are stimulated, which produces widespread peristalsis of the colon.
- Senna undergoes conversion to active metabolites in the colon that stimulate the myenteric plexus and induce net fluid secretion.
- Response in 6-12 up to 24 hours.

Side Effects

- Electrolyte abnormalities depending on volume of stool
- Melanosis coli – brown pigmentation of the colon

Clinical Indication

Relief of constipation

D. DETERGENT LAXATIVES

Agent

Docusate (Colace)

Mechanism of Action

- Docusate is an anionic surfactant that is believed to stimulate intestinal secretion and increase the penetration of fluid into the stool by emulsifying feces, water, and fat
- Soft feces = easier passage
- Minimal effect on peristalsis
- Initial response in 1-3 days

Clinical Indications

Docusate is used to soften or prevent the formation of hard stools.

E. LUBRICANTS

Agents

- Glycerin suppository/enema
- Mineral oil enema

Mechanism of Action

- Due to its osmotic effect, glycerin softens, lubricates, and facilitates the elimination of inspissated feces. By serving as a bowel irritant it may also stimulate rectal contractions.
- Mineral oil helps soften (by coating fecal material with mineral oil) and lubricate hard stools, easing their passage without irritating the mucosa.
- Lubricants may stimulate a response within 30 minutes.

Side effects/contraindications

Mineral oil should **never be administered orally**, particularly to debilitated patients - inhalation/aspiration of the oil can lead to lipoid pneumonitis.

Clinical Indications

Usually reserved for treatment of fecal impaction

F. LARGE VOLUME ENEMAS

Agents

Warms water enema
Soapsuds enema
Sodium phosphate enema (Fleet's enema)

Mechanism of Action

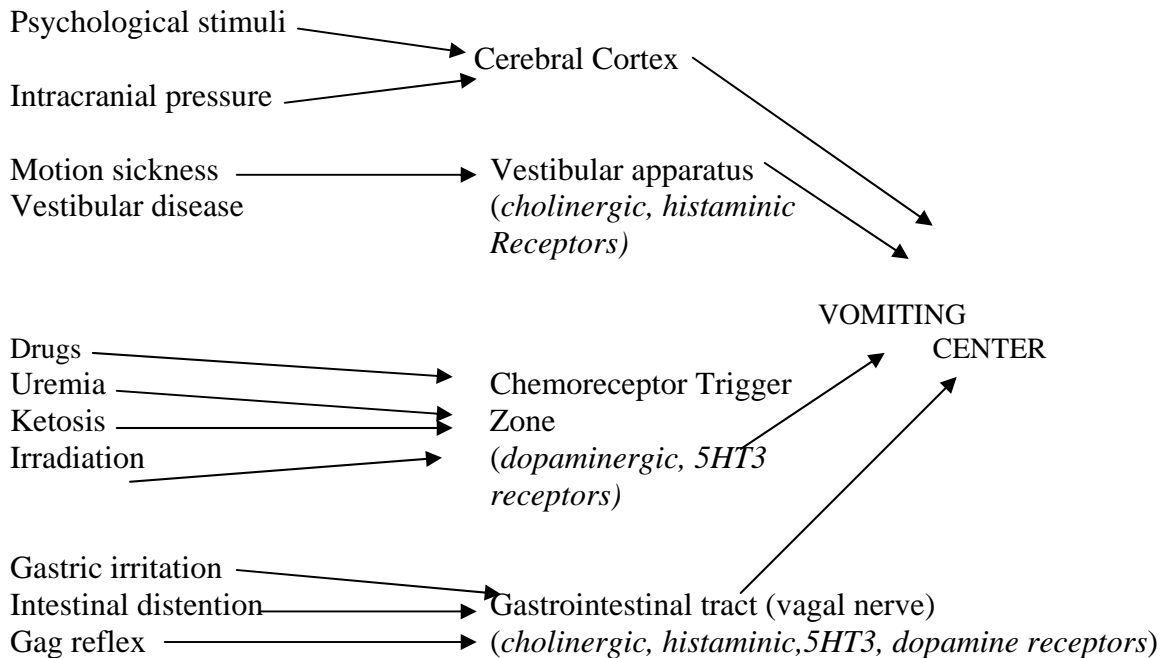
Soften stool by increasing water content
Distend distal colon inducing peristalsis

Clinical Indications

Usually reserved for treatment of fecal impaction

IV. Pharmacologic Palliation of Nausea and Vomiting

A. Pathophysiology of nausea and vomiting



Chemoreceptor trigger zone is located in the area postrema outside the blood brain barrier
Vomiting Center is located in the lateral reticular formation of the medulla and coordinates the motor mechanisms of vomiting

B. Antiemetic Drugs

Dopamine receptor antagonists

Phenothiazines - **Prochlorperazine (Compazine)**

Butyrophenones - Haloperidol (Haldol)

Benzamides – Metoclopramide (Reglan)

Serotonin (5HT₃) antagonists

Ondansetron (Zofran)

Granisetron (Kytril)

Antihistamines

Promethazine (Phergan)

Diphenhydramine

Anticholinergics

Scopolamine

Corticosteroids

Dexamethasone

Benzodiazepenes

Lorazepam

Alprazolam

C. Select Antiemetics

● **Agent - Metoclopramide (Reglan)**

Mechanism of Action

- Antiemetic properties are due to central and peripheral dopamine receptor inhibition
- Metoclopramide promotes motility in the upper gastrointestinal tract by sensitizing tissues to the action of acetylcholine, which is independent from intact vagal innervation and does not stimulate biliary, gastric, or pancreatic secretions.

It hastens gastric emptying and intestinal transit by increasing tone and amplitude of gastric contractions, relaxing the pyloric sphincter and duodenal bulb, and enhancing peristalsis of the duodenum and jejunum.

Adverse Effects

- Extrapyramidal effects, such as dystonia, akathisia, parkinsonism, may develop due to central dopamine receptor blockade.
- Acute dystonic reactions, such as trismus, torticollis, facial spasms, can be treated with an anticholinergic agent (benztropine or diphenhydramine).
- Cautious use in patients with Parkinson's Disease

Clinical Indications

- Vomiting due to dysmotility of the upper GI tract - gastric stasis and diabetic gastroparesis
- Chemotherapy induced nausea and vomiting

● **Agent - Prochlorperazine (Compazine)**

Mechanisms of Action

- Prochlorperazine acts centrally by inhibiting the dopamine receptors in the medullary chemoreceptor trigger zone
- It peripherally blocks the vagus nerve in the gastrointestinal tract

Adverse Effects

Extrapyramidal effects, dystonic reactions

Clinical Indications

- Opioid related nausea and vomiting
- Moderately effective for nausea caused by various GI disorders (ie gastroenteritis)

● **Agent - Promethazine (Phenergan)**

Mechanism of Action

Antiemetic effects come from its H(1) receptor blocking properties.

Adverse Effects

Sedation

Clinical Indications

Promethazine is effective in the active and prophylactic treatment of motion sickness

● **Agent - Ondansetron (Zofran)**

Mechanism of Action

- Ondansetron is a competitive, highly selective antagonist of 5-hydroxytryptamine (serotonin) subtype 3 (5-HT₃) receptors. 5-HT₃ receptors are present peripherally on vagal nerve terminals and centrally in the area postrema of the brain. It is not certain whether ondansetron's action is mediated peripherally, centrally, or both. Cytotoxic drugs and radiation appear to damage gastrointestinal mucosa, causing the release of serotonin from the enterochromaffin cells of the gastrointestinal tract. Stimulation of 5-HT₃ receptors causes transmission of sensory signals to the vomiting center via vagal afferent fibers to induce vomiting. By binding to 5-HT₃ receptors, ondansetron blocks vomiting mediated by serotonin release.

Side Effects

Most common side effect is headache

Small but statistically significant prolongation of the QT interval.

Clinical Indications

- Chemotherapy induced nausea and vomiting and its prophylaxis
- Radiation induced nausea and vomiting and its prophylaxis
- Most expensive of the antiemetics

● **Agent Scopolamine**

Mechanism of Action

Pure anticholinergic agent

Adverse Effects

- *Dry mouth (xerostomia)
- Acute narrow angle glaucoma (contraindicated in patients with known glaucoma)
- Urinary retention
- Confusion

Clinical Indications

- Treatment of motion sickness
- *In patients who are hours to days from death and who can no longer swallow their own secretions, it is used to decrease production of saliva