Pharmacology/Therapeutics II Block I lectures

2011-2012

58. Antipsychotics – Schilling
59. Pharmacology of Antidepressant Drugs – Battaglia (to be posted later)
60. Drugs Used to Treat Anxiety & Bipolar Affective Disorders – Battaglia (to be posted later)
61. Anti-Parasitic Agents – Johnson
62. Palliation of Constipation & Nausea/Vomiting – Kristopaitis

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 different mechanisms of action for antipsychotic medications. This includes:
      - Mechanism of action of "typical" antipsychotics (dopamine D2 receptor blockade)
      - Mechanism of action of atypical antipsychotics (dopamine D2 and serotonin 5-HT2 receptor antagonists)
      - Mechanism of action of Aripirprazole (Abilify), (Partial agonism)

   b) Recall the common side effects and recall the rare, but dangerous side effects for:
      - First generation "typical" anti-psychotics: High potency antipsychotic vs a low potency antipsychotic
        - haldol (haloperidol) vs. thorazine (chlorpromazine)
      - Second generation anti-psychotics
      - Clozapine (clozaril)

   c) Predict the clinical outcome based on an action on a particular area of the dopamine system

   d) Predict what area in the dopamine system the site of action is based on the clinical outcome

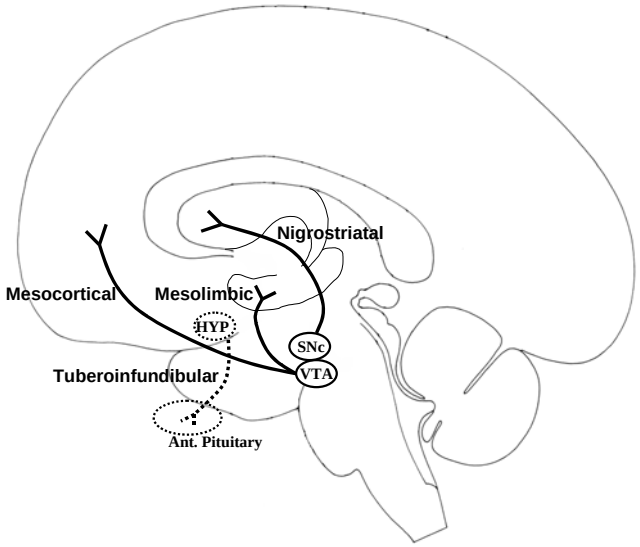
3) Explain the "Metabolic Syndrome" problem

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 DA_2 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 DA_2 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 DA_2 receptors in basal ganglia lead to Extrapyramidal Side Effects (EPS)
D. Tuberoinfundibular system = DA neurons projecting from the hypothalamus to the anterior pituitary;
   Blockade of DA_2 receptors in anterior pituitary lead to Hyperprolactinemia and associated adverse effects.

II. Pathophysiology/Disease state

Dopamine Hypothesis

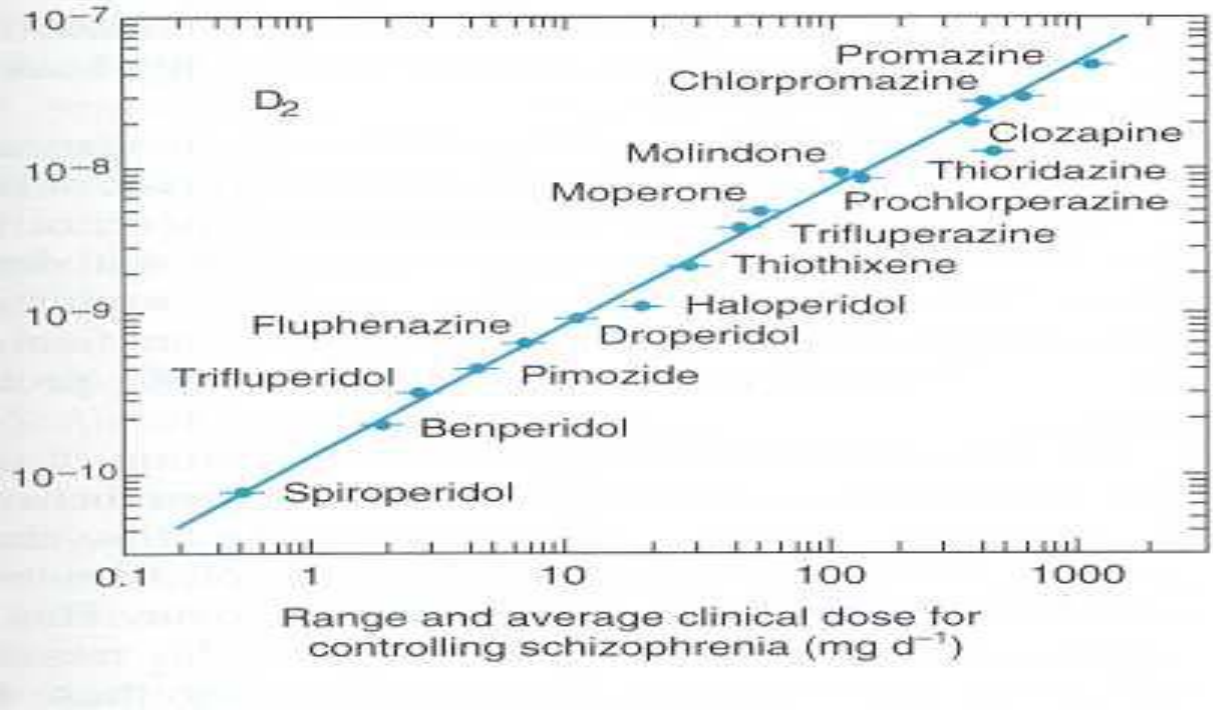
Hyperactivity of Dopamine (DA) neurotransmitter pathways → Schizophrenia

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

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 that 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-HT2A blockade enhances DA release in basal ganglia (from nigrostriatal DA system); This DA competes with the antipsychotic for DA_2 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-HT2A blockade may normalize cortical function (possibly by enhancing DA release and acetylcholine release in frontal cortex), thereby reducing negative symptoms/cognitive deficits

2. Hit & run concept
   Lower potency DA_2 blockade of atypical antipsychotics has also led to "hit and run" concept; i.e. atypical drug-induced blockade of DA_2 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 DA_2 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 DA_2 occupancy levels below those achieved by typical antipsychotics
Aripirprazole 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, Dibetes Mellitus, Dyslipidemia

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

Clozapine > Olanzapine >>> Quetiapine > Risperadone/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.

#61 - 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:

Protozoa	**Helminths**
• 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** vs. **Intermediate Host** vs. **Incidental Host**
(Harbors sexual parasitic stage) (Harbors larval or asexual parasitic stage) (Not necessary for parasitic survival)

• **Gametogony** vs. **Schizogony**
(Sexual development) (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-14α 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**
   a. Used for prophylaxis and treatment
   b. Initial half-life: 3-5 d; Terminal half-life: 1-2 mo
   c. Schizonticidal to all plasmodial species; not active against exoerythrocytic (liver phase) parasites
   d. MOA: Prevents polymerization of heme to hemozoin leading to a build up of free heme which is toxic to parasite
   e. Resistance in *P falciparum* is wide-spread
   f. ADRs: pruritis; Uncommon - nausea, vomiting abdominal pain, HA, anorexia, malaise, blurred vision

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

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

7. **Alternatives to Mefloquine Prophylaxis**
   a. Atovaquone and proguanil *(Malarone)*
   b. Proguanil with chloroquine
   c. Pyrimethamine and sulfadoxine *(Fansidar)*
   d. 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 choloroquine
   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 (Quinghausu)**
   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)**

	Start	Stop
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/kd/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)

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

2. Neurocysticercosis (CNS Manifestations)

a. Vesicular cysticerci: Cystic lesions, viable parasites, immune tolerance
b. Colloidal cysticerci: Enhancing lesions, implies degenerating parasite
c. 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, tichuriasis, 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, chlonorchiasis, 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 *P. vivax & ovale)*	Treatment of *P. falciparum*	Cinchonism* Hypoglycemia Blackwater fever	OK	Quinine - **OK, if needed** Quinidine - OK, but contractions in 3rd trimester	Only iv quinidine available in US; DOC for severe malaria; cardiac 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 *P. vivax & ovale*	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 atovoquone)	
Atovaquone	Inhibit parasite mitochondial 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 treament of *P. falciparum* 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, dizzines, flushing and visual disturbances

Antihelmintic 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

#62 - **Pharmacologic Palliation of Constipation & Nausea/Vomiting**

Date: Ja**n**uary 26, 2012– 10:30 AM

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

LEARNING OBJECTIVES

1. 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)
        - Polyethyelene glycol
    - Stimulant laxatives (Senna; Bisacodyl)
    - Detergent laxatives (Docusate)
    - Lubricants (Glycerin suppository, mineral oil enema)
    - Enemas (Warm water; Soap suds; sodium phosphate)

2. 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)

#62 – **Pharmacologic Palliation of Constipation & Nausea/Vomiting**

I. A goal of palliative 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 by patients with serious and advanced diseases 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 colits 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

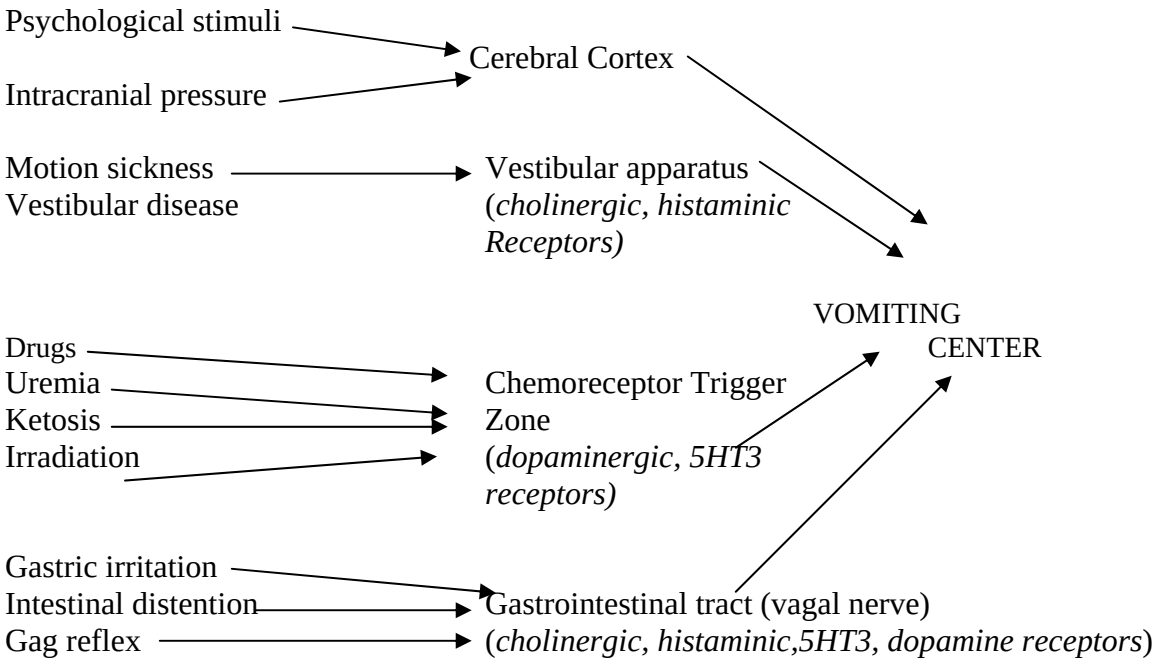
Warms water enema
Soapsuds enema
Sodium phosphate enema (Fleet's enema)

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-HT 3) receptors. 5-HT 3 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-HT 3 receptors causes transmission of sensory signals to the vomiting center via vagal afferent fibers to induce vomiting. By binding to 5-HT 3 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 antiemetogenics

- **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 an no longer swallow their own secretions, it is used to decrease production of saliva