

Antipsychotic Drugs (Drugs for Schizophrenia and Related Disorders)

Pharmacology 210, 2009

Important note: The corresponding material presented in lecture will cover just the “highlights” of what is in this file. Be sure to study this file in its entirety, and be sure to read the corresponding text chapter(s).

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Background, Signs/Symptoms of Schizophrenia

- **See your text for background and also table summarizing “positive” and “negative” symptoms of schizophrenia, other manifestations or characteristics**

Biochemical Basis of Schizophrenia

- **Seems to involve excessive levels, activity, or effects of dopamine (DA) in certain parts of the brain that control emotion, thought, behavior, because:**
 - **Drugs that block DA receptors or ↓ DA levels at those CNS sites ↓ S/Sx of schizophrenia**
 - **Drugs that stimulate DA receptors or ↑ DA levels in dopaminergic synapses there cause or worsen S/Sx of schizophrenia**

Antipsychotic Drugs

- **Used mainly for schizophrenia, acute or long-term**
- **Are sometimes called “neuroleptic drugs”**
- **Are adjuncts to, not substitutes for, psychotherapy and other treatment modalities**
- **Critical elements of treatment**
 - **Proper diagnosis**
 - **Picking the right drug out of many**
 - **Monitoring therapy**
 - **Proper, effective, support interventions**
 - **Willingness of patient to follow-through on treatment**

Classes of Antipsychotics

- According to potency*
 - Low potency (e.g., chlorpromazine)
 - High potency (e.g., haloperidol)
- According to chemical class
 - Phenothiazines (e.g., chlorpromazine)
 - Butyrophenones (e.g., haloperidol)
 - Others

* Remember: Potency really refers to size of dose, not to efficacy. Although it's not quite proper to refer to antipsychotics as high or low potency, this terminology is fairly common, and you should understand what is meant when you hear these terms. See later slides.

“Low Potency” vs. “High Potency” Antipsychotics

- **Chlorpromazine**, most other phenothiazines, called “**low potency**” antipsychotics
 - Antipsychotics called this have a high incidence of autonomic side effects, relatively low incidence of extrapyramidal side effects (EPS)
- **Haloperidol** is considered “**high potency**”
 - This generally describes antipsychotics that have a low incidence of autonomic side effects, comparatively high risk of EPS

The *Phenothiazines* Prototype: Chlorpromazine (THORAZINE)

- Historically, the major class of antipsychotics
- Side effects/adverse responses numerous and problematic, but these drugs are still used because they are effective and relatively inexpensive
- Considered to be “low potency” antipsychotics

Major Actions of Phenothiazine Antipsychotics

- Block dopamine, ACh (muscarinic), histamine (H1) and alpha-adrenergic receptors in CNS and in periphery
- Antipsychotic effects
 - primarily from central dopamine receptor blockade
 - Initial symptom control may occur after a few days of therapy, but “good” control (normalization of thought processes, mood behavior) may take a month or so of continued tx.
 - These drugs aren't permanent “cures” -- NO antipsychotic is!

Sedation from Antipsychotics

- Depends on which drug is selected, what its dose is
- May/may not be desirable (depends on the Pt's needs)
- ↑ by all/any other drugs with CNS depressant activity

Other Effects of Phenothiazines

- Shared by all drugs in class, but...
- Some of the phenothiazines...
 - have greater ability than others to → certain rather unique effects
 - have special uses in *nonpsychotic* pts. because of these special properties/effects: antihistamine (H-1 blocking) activity; antitussive effects; antiemetic effects
- Examples on next slide

Special Properties/Uses of Some Phenothiazines*

- Promethazine (PHENERGAN)
 - Useful **antihistaminic** (H1 blocking), **antipruritic**, and **antitussive** (cough-suppressant) effects
 - Used for allergy s/sx, esp. when some sedation is desirable
- Prochlorperazine (COMPAZINE)
 - Useful antiemetic effects, e.g., in setting of chemotherapy, surgery, other cases of uncontrollable vomiting

*For the exam you aren't responsible for knowing which phenothiazines exert these "special effects" but you DO need to know that some phenothiazines have these actions, are used clinically for those effects in patients who may have no symptoms of schizophrenia or other mental illness at all. You may want to look back at notes from the antihistamines lecture, where phenothiazines are also mentioned.

SEs, CIs, etc. of Most Antipsychotics

- Incidence, severity, vary from drug to drug, are usually dose-dependent
- Autonomic
 - **Atropine-like** → ___?___
 - **α-adrenergic blockade** → ___?___
- Other
 - Gynecomastia, altered menses, galactorrhea (interferes with hypothalamic-pituitary regulation of prolactin release)
 - ↓ Temperature perception, → ↑ susceptibility to hyperthermia (heat stroke) or hypothermia
 - ↓ **Seizure threshold** → ↑ risk of seizures (especially a problem for, but not limited to, people with epilepsy)
 - Allergic or hypersensitivity rxns (esp. blood, skin; sometimes severe)
 - EKG changes, risk of potentially serious/life-threatening ventricular arrhythmias (some phenothiazines, not all)

Extrapyramidal Side Effects of Phenothiazines

- Affect 15-20% of all patients on long-term tx. with traditional antipsychotics
- Resemble Parkinson's Disease s/sx.
 - bradykinesias – akinesias
 - dyskinesias – akathisia
- Caused by excessive ↓ of DA effects in brain areas (extrapyramidal system) that regulate voluntary/involuntary control of skeletal muscle
- Incidence, severity, vary among the individual drugs
- S/Sx. tend to develop gradually (months, years) with the “low potency” antipsychotics, can occur in days with “high potency” agents.
- **May disappear** w/continued tx., but usually worsen
- May progress to → **tardive dyskinesias** (irreversible)

Early-Developing EPS Side Effects

- Acute dystonias can occur within hours or a few days after starting therapy
 - Severe spasmodic and involuntary movements of skeletal muscles, especially in tongue, neck, back, extremities
 - Oculogyric crisis, opisthotonus (advice: look up these terms)
 - May be medical emergency, is managed with centrally-acting antimuscarinics (e.g. benztropine, diphenhydramine... see Parkinson's disease slides and text chapter)
- Parkinsonism tends to develop within a month or so
 - Skeletal muscle tremor, rigidity, and consequences thereof
 - Managed with centrally-acting antimuscarinic antiparkinson drugs (not with dopaminergic agents)
- Akathisias usually develop by about a month
 - Often intense subjective feelings of jitteriness, restlessness, leading to pacing about, squirming
 - Signs/symptoms can be confused with worsening schizophrenia

Late-Developing Extrapyramidal Side Effects: Tardive Dyskinesias I.

- Affects 15-20% of all patients on long-term tx. with traditional antipsychotics
- Risks: high potency antipsychotics > low potency >>> atypical agents (see clozapine)
- Typically occur after many months, to several years, after start of therapy
- Initial s/sx include *choreoathetoid movements* (mainly tongue and face, eventually progresses to involve extremities, trunk)
- S/sx probably involve central DA receptor supersensitivity: hyperreactivity of DA receptors to DA
- S/sx *irreversible*, so best approach is prevention (e.g., limit antipsychotic tx. duration and dose to minimum that is feasible)

EPS: What to Do When We Start Seeing S/Sx of it?

- ↓ dose of (or stop) current drug (which will likely restore s/sx of schizophrenia), or
- Switch to another antipsychotic with less risk of EPS, or
- “Treat” with antiparkinson drugs, which will...
 - *mask/obscure* mild EPS S/Sx but...
 - *won't* prevent underlying brain biochemical changes that ultimately → development of tardive dyskinesias if use of the offending antipsychotic continues

Other Central Adverse Effects

- Reduction of brain's "seizure threshold" → ↑ risk of seizures, esp. in patients with history of epilepsy
- Neuroleptic malignant syndrome
- Hyperprolactinemia
 - DA receptor blockade prevents normal inhibition of hypothalamic-pituitary prolactin release
 - Main consequences are gynecomastia, galactorrhea, irregular menses
 - Avoid in women with prolactin-dependent breast cancers

What is The "Seizure Threshold?"

- Think of it as the amount of extra or abnormal brain electrical activity needed to "destabilize" normal neurons to start a seizure/convulsion. Exceed that "threshold" and seizures develop.
- Phenothiazines, most other antipsychotics, and several other drugs noted in the CNS section (quite different drug classes) ↓ the threshold (the amount of extra or abnormal electrical activity) necessary to → seizures, making it easier for seizures to develop.
- The seizure risk applies to all patients receiving phenothiazines, but obviously is of more concern for patients who already have a seizure disorder (i.e., epilepsy).

Neuroleptic Malignant Syndrome: A Serious and Rather Common Adverse Response

- Sudden, unpredictable, rapidly worsening onset of...
 - fever
 - muscle tremor → → severe muscle rigidity
 - autonomic hyperactivity
 - catatonia (a detached, trance-like state)
- May occur after 1st few doses, or after months of tx... it's unpredictable
- Overall incidence about 1 in 5 patients, fatal about 5% of the time overall
- Close assessment, early and correct intervention essential to ↓ chance of serious outcomes

Neuroleptic Malignant Syndrome (NMS) Treatment: What to Do.

- Withdraw antipsychotic medications
- ↓ Body temperature promptly with physical means and cautious use of antipyretics (aspirin or acetaminophen)
- Ensure adequate hydration
- Normalize BP and cardiac responses (hypertension, tachycardia often occur) with the proper drugs
- Control anxiety (e.g., IV benzodiazepines)
- Give muscle-relaxants (benzos, dantrolene)
- Give drugs that activate central DA receptors (see parkinson's lecture for more about the drugs that can do this)

Adverse Effects of Most Antipsychotics in the Periphery

- Antimuscarinic side effects may be strong
- Orthostatic hypotension (α -adrenergic blockade)
- Dermatitis, abnormal skin pigmentation, photosensitivity (skin sensitized to UV light \rightarrow \uparrow risk of sunburn)
- Agranulocytosis
- Severe cardiac arrhythmias (with some, not all, phenothiazines)

Nonphenothiazine Antipsychotics

- Major example is haloperidol (HALDOL) – *butyrophenone* class, a “high potency” antipsychotic
- Fast onset (< 30 min with parenteral administration), short acting
- Main drug for acute psychotic S/Sx (given parenterally): it’s what you’re *most likely to give* in the ED or ICU for acute psychosis
- Has some other psychiatric uses besides schizophrenia (e.g., Tourette syndrome)
- Compared w/ chlorpromazine:
 - greater risk and usually faster onset of EPS
 - fewer/milder autonomic SEs
 - also lowers seizure threshold

Atypical Antipsychotics Example: Clozapine (CLOZARIL)

- Antipsychotic actions mainly from CNS blockade of *serotonin* receptors
- Major advantages vs. traditional antipsychotics:
 - Very weak DA receptor blockade \rightarrow *very low incidence of EPS side effects/ drug-induced parkinsonism*
 - Few significant peripheral autonomic side effects
- *Main and most serious adverse response:* $\downarrow\downarrow$ white blood cell (WBC) count, \uparrow risk of serious infection, and potential agranulocytosis (fatal): requires normal WBC counts *before any Rx. can be filled*
- Other side effects:
 - hyperglycemia (\rightarrow prediabetic or true diabetic state, more difficult control of blood glucose in patients already being treated for diabetes)
 - seizures (like all antipsychotics)
 - myocarditis
 - *significant* weight gain (from appetite stimulation)