AN UPDATE ON ANTIPSYCHOTIC DRUGS
TREATING SCHIZOPHRENIA
OUR LEARNING OBJECTIVES:

1) DEFINE SCHIZOPHRENIA AND DESCRIBE SYMPTOMS GENERALLY ASSOCIATED WITH IT

2) DISCUSS THE PHARMACOLOGIC MECHANISMS OF ACTION FOR ANTI-PSYCHOTICS
OUR LEARNING OBJECTIVES

3) COMPARE THE EFFICACY, SAFETY, AND TOLERABILITY PROFILES OF DIFFERENT ATYPICAL ANTI-PSYCHOTICS FOR THE TREATMENT OF SCHIZOPHRENIA

4) DESCRIBE THE ROLE OF THE PHARMACIST IN DEVELOPING STRATEGIES TO SUCCESSFULLY COUNSEL PATIENTS ON THEIR DRUG TREATMENT ADHERENCE PLAN AND MEANS TO ENHANCE COMPLIANCE
THE PSYCHOTIC DISORDERS

HOW DO WE MAKE THE DIAGNOSIS?
PSYCHOSIS

• GROSS IMPAIRMENT IN REALITY TESTING

• CREATION OF A NEW REALITY
SCHIZOPHRENIA AND PSYCHOSIS

PSYCHOTIC DISORDERS
  - SCHIZOPHRENIA
  - SCHIZOAFFECTIVE
  - BRIEF PSYCHOTIC
  - ILLNESS OR SUBSTANCE INDUCED
  - SCHIZOPHRENIFORM
  - DELUSIONAL DISORDER
  - SHARED PSYCHOTIC
  - PSYCHOSIS NOS
SCHIZOPHRENIA

- PARANOID
- CATATONIC
- DISORGANIZED
- UNDIFFERENTIATED
- RESIDUAL
DIAGNOSIS OF SCHIZOPHRENIA

A) CHARACTERISTIC SYMPTOMS
   1. HALLUCINATIONS
   2. DELUSIONS
   3. DISORGANIZED SPEECH
   4. DISORGANIZED BEHAVIOUR
   5. NEGATIVE SYMPTOMS

B) SOCIO/OCCUPATIONAL DYSFUNCTIONING

C) DURATION OF SX FOR 6 MONTHS

D) NO PROMINENT MOOD SX

E) NO SUBSTANCE OR MEDICAL ETIOLOGY

F) SEPARATE FROM A DEVELOPMENTAL DISORDER
SO WHAT DO NEURONS HAVE TO DO WITH ANYTHING?

- There are only about 100,000,000,000,000 of them!

- They are a very “plastic system”: don’t change in numbers, but they modify their strength of existing synapses and form new ones with their neighbors.
Neurotransmitters—Mechanisms of Action

PRESYNAPTIC CELL

Reuptake transporter

SYNAPTIC CLEFT

Neurotransmitter

Autoreceptor

POSTSYNAPTIC CELL

Neurotransmitter receptor

Nemeroff CB. Scientific Amer. 1998;June:43-49.
SYNAPSE

• THAT SPACE BETWEEN NEURONS (THE INTERCELLULAR SPACE)

• CELLS DON’T TOUCH EACH OTHER, BUT CHEMICALS AND DRUGS CROSS THE SPACE TO CAUSE THE COMMUNICATION BETWEEN THE CELLS
PRESYNAPTIC NEURONS

- RELEASES THE NEUROTRANSMITTER
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POSTSYNAPTIC NEURONS

- RECEIVES THE NEUROTRANSMITTER
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LIGANDS

- MOLECULES WHICH BIND TO AND ACTIVATE RECEPTORS (POST-SYNAPTIC CELLS)

- EXAMPLES ARE:
  - NEUROTRANSMITTERS
  - HORMONES
  - DRUGS
MORE ABOUT RECEPTORS

- 2-3,000 PER CELL
- THERE ARE A LARGE # OF RECEPTOR TYPES, e.g.:
  - Opiate
  - Dopamine
  - Serotonin
  - Histamine
  - Benzodiazepine

- They are protein molecules
- They are embedded in the cell wall
- There can be multiple receptor types on A SINGLE CELL: e.g.:
  - Opiate + Dopamine + Histamine
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Phases of schizophrenia and goals of treatment

**ACUTE PHASE**

- ✓ REDUCE ACUTE SYMPTOMS
  - (Psychosis, Hallucinations, Delusions)
- ✓ PREVENT HARM
- ✓ CONTROL DISTURBED BEHAVIOR
- ✓ REDUCE ASSOCIATED SYMPTOMS
  - (Agitation, aggression, negative symptoms, affective symptoms)
Phases of schizophrenia and goals of treatment

**STABILIZATION PHASE**

Minimize the likelihood of relapse; enhance adaptation to community; consolidate remission

**STABLE PHASE**

Maintain or improve level of function and quality of life; prevent relapse; monitor for adverse treatment effects.
Acute Phase Management

*Psychosocial management*

- reduce over-stimulating or stressful events in a structured and predictable environment
- Inform patient on the nature and management of their illness
- Initiate a relationship with family
Acute Phase Management

*Use of Anti-psychotic Medications*

- Indicated for nearly all acute psychotic episodes in schizophrenia
- Assess the ability of patients to participate in decisions about medication
- Administer involuntarily when appropriate
Effectiveness of antipsychotics in schizophrenia

- Well-designed clinical trials invariably demonstrated the superiority of drug to placebo in the treatment of Schizophrenia.

- Early intervention with antipsychotics may reduce long-term morbidity and decrease the number of re-hospitalizations.
CLASSIFICATION OF DRUGS USED IN THE TREATMENT OF SCHIZOPHRENIA AND PSYCHOTIC DISORDERS
PHENOTHIAZINES

CHLORPROMAZINE----------------------------------------THORAZINE
10--25mg 2--4x/day---------------------- MAX of 200-400mg/day

FLUPHENAZINE----------------------------------PROLIXIN
2.5--10mg 2--3x/day------------------- MAX of 40mg/day

*PERPHENAZINE-----------------------------------TRILAFON
4--8mg TID-----------------------------------MAX of 64mg/day

TRIFLUOPERAZINE---------------------------------STELEAZINE**
2-5mg 2—3x/day------------------------ MAX of 100mg/day

*--Used in the CATIE trials
**only available as generic
OTHER PHENOTHIAZINES

PROCHLORPERAZINE--------------------------------------------COMPAZINE
5--10mg 3--4x/day----------------MAX of 50mg/day

THIORIDIZINE--------------------------------------------------------MELLARIL
10--50mg TID-------------------------MAX of 800mg/day

MESORIDIZINE------------------------------------------------------SERENTIL*

*THIS DRUG IS DISCONTINUED IN THE US
<table>
<thead>
<tr>
<th>Other Typical Antipsychotics</th>
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<tr>
<td><strong>Haloperidol</strong> (Haldol)</td>
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<td>0.5--2mg 2--3x/day</td>
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<td><strong>Loxipine</strong> (Loxitane)</td>
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<td>10mg BID</td>
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<td><strong>Molindone</strong> (Moban)</td>
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<td>Max of 225mg/day</td>
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<tr>
<td><strong>Thiothixene</strong> (Navane)</td>
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<td>2mg TID</td>
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<td>Max of 60mg/day</td>
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Acute effects on dopamine systems

• Conventional agents block 65-90% of D$_2$ receptors-- certain atypicals are effective with much lower D$_2$ occupancy
Dopamine blockade and clinical effects of conventional agents

- 65% occupancy associated with efficacy
- 70% occupancy associated with hyperprolactinemia
- 80% occupancy associated with EPS and akathisia
Dopamine Neurons/ Pathways

- **Nigrostriatal** (midbrain to neostriatum), blockade responsible for EPS
- **Mesolimbic** (midbrain to limbic structures) blockade possibly associated with antipsychotic effect?
- **Mesocortical** (midbrain to frontal and temporal cerebral cortex) possibly associated with negative symptoms?
Conventional (Typical) Antipsychotics or “Neuroleptics”

- Dopamine Antagonists
- Blocks Dopamine D$_2$ Receptors
- Over time, results in reduced dopamine transmission
- Reduced dopamine transmission is correlated with antipsychotic effects
- Produce extrapyramidal symptoms (EPS)
- Elevate prolactin levels
- All conventional agents are equally effective but differ in potency and side effects
Acute extrapyramidal symptoms (EPS)

• Akathisia - a subjective feeling of restlessness
• Acute dystonic reactions - abrupt onset muscular spasms affecting the neck, eyes, trunk, extremities
• Parkinsonism - stiffness, tremor, impaired gait
Conventional Neuroleptics: Activity at Other Receptors

- Adrenergic ($\alpha_1$)—hypotension
- Histaminergic ($h_1$)—sedation, weight gain
- Muscarinic ($m_1$)—dry mouth, cognitive & memory, motor activity, sleep

- “Low-potency” agents have relatively higher affinities for these receptors
AND NOW A WORD ABOUT CATIE

WHO IS SHE?
ATYPICAL ANTIPSYCHOTICS

ARIPIPRAZOLE ------------------------------------------- ABILIFY
10--15mg QD----------------------------------------- MAX of 30mg/day

CLOZAPINE ------------------------------------------ CLOZARIL
12.5mg BID----------------------------------------- MAX of 900mg/day

OLANZAPINE ---------------------------------------- ZYPREXA
5—10mg QD----------------------------------------- MAX of 20mg/day
ATYPICAL ANTIPSYCHOTICS

PALIPERIDONE----------------------------------------INVEGA
6mg QAM--------------------------------------------MAX of 12mg/day

RISPERDONE-----------------------------------------RISPERDAL
1—2mg QD or BID-----------------------------------MAX of 8mg/day

QUETIAPINE-----------------------------------------SEROQUEL
25mg BID------------------------------------------MAX of 800mg/day

ZIPRASIDONE----------------------------------------GEODON
20mg BID------------------------------------------MAX of 160mg/day
COMBINATION PRODUCTS

PERPHENAZINE; AMITRIPTYLINE-------------------------TRIAVIL & ETRAFON

OLANZIPIINE; FLUOXETINE-----------------------------------------SYMBYAX

OTHER ANTIPSYCHOTIC AGENTS
(UNDER INVESTIGATION)

ILOPERIDONE------------------------------------------------ZOMARIL

PALIPERIDONE------------------------------------------------SERLECT
Atypical Antipsychotics: Shared Characteristics

1) These drugs combine Dopaminergic D₂ and Serotonergic 5HT₂A activity

2) Have an affinity for dopamine binding high enough to be clinically effective but low enough such that they avoid adverse effects

2) It is presumed that the addition of 5HT₂A activity may:
   - reduce extra-pyramydal symptoms (EPS)
   - improve efficacy for negative symptoms
Additional Receptor Activities of Atypical Antipsychotics

Clozapine also binds to:

- Other dopamine subtypes ($D_1$, $D_3$, $D_4$)
- Alpha adrenergic ($\alpha_1$& $\alpha_2$)
- Histaminergic ($H_1$)
- Muscarinic anticholinergic ($M_1$)
- Other serotonergic subtypes ($5HT_{1A,2C,6,7}$)
- Other atypicals vary in activity at these receptors
Delayed effects (4-6 weeks)

- Conventional agents increase density of post-synaptic $D_2$ receptors (supersensitivity)
- Conventional agents generally produce depolarization blockade in niagrostriatal (EPS) and mesolimbic (anti-psychosis) dopamine neuron tracts
- Atypicals generally produce blockade mostly in mesolimbic dopamine neuron tracts and **NOT** in nigrostriatal tracts
Side effects of newer antipsychotic drugs  
(adapted from Jipson and Tandon)

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Side effects of newer antipsychotic drugs (cont)

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Estimated Weight Gain at 10 Weeks on “Standard” Dose

D. B. Allison et al. American J of Psych 1999
Acute treatment: Considerations in drug selection

- Prior response
- Side effect profile
- Patient preference
- Route of administration
- Cost
Pretreatment Evaluation

- Physical exam w/ neuro
- Basic labs including CBC, LFT’s & FBS
- EKG
- Weight
Antipsychotic dosing strategy

• Start with moderate doses

• Use a fixed dose without prn’s.

• Oral benzodiazepines or intramuscular drugs (eg. Haloperidol, geodon) can be used for agitation.
Acute treatment: Dose selection

- High potency conventional: 5-20 mg of haloperidol or fluphenazine
- Low potency conventional: 300 to 1000 of CPZ
- Risperidone: 4 to 6 mg
- Olanzapine: 10 to 25 mg
- Quetiapine 300 to 750 mg
- Ziprasidone 120-160 mg
- Aripiprazole 10-20 mg
**Time Course of Antipsychotic Response**

- Certain target symptoms may diminish in first few days.
  - Agitation.
  - Psychomotor excitement.

- Improvement in psychotic symptoms typically occurs in the following order.
  - Thought disorder.
  - Hallucinations – decreased intensity, frequency.
  - Delusions – new misinterpretations are first affected.
Evaluate antipsychotic response in 3-5 weeks.

- Partial response continue for 6-12 wks
- No response switch
- Severe side effects switch
Some of the most common factors leading to symptom relapse are:

1) Medication non-compliance
2) Substance Use
3) Stressful Life events
4) Natural course of the illness despite meds
Importance of Side Effects

Decrease compliance
Decrease quality of life
Health issues
What Should We Monitor?

• Physical Exam
  – Check weight - each visit
  – Check blood pressure - each visit

• Lab Tests
  – Hemoglobin A1c - every 3–6 months
  – Fasting blood glucose - every 3 months
  – Triglycerides - every 3 months
  – Cholesterol - every 3 months
Differential diagnosis of depression in schizophrenia

- Depression in psychosis
- Antipsychotic-induced akinesia
- Dysphoria from akathisia
- Demoralization syndrome
- Negative symptoms
Management of depression in schizophrenia

• Assure that depression is not part of a psychotic decompensation
• Rule out EPS, particularly akinesia; change to a different antipsychotic
• Add an antidepressant
Effective Psychosocial Treatments: Schizophrenia

- Supportive, reality-based individual and group therapies
- Family interventions that provide education and support
- Vocational rehabilitation
- Assertive Community Treatment
Drug-psychosocial interactions in schizophrenia

• Psychosocial treatments are more effective when psychotic symptoms are controlled with drugs (May et al, 1968)
• Psychosocial treatments can be toxic when patients are not adequately treated with drugs (Hogarty et al, 1974)
• Psychosocial treatments are more effective when compliance is assured (Hogarty et al, 1979)
Drug-psychosocial interactions in schizophrenia (cont)

- Drugs may be more effective when compliance is enhanced by psychosocial treatment (Marder et al, 1996)
- Drugs and Psychosocial treatments may affect different outcome domains (ie, drugs control symptoms and psychosocial treatments affect social adjustment) (Marder et al, 1996).
Components of PACT

- A multidisciplinary team to organize and deliver comprehensive services to pts in a timely and integrated fashion.
- Team is mobile and provides most services in the community.
- High staff:patient ratio, eg. 1:10 or 1:12
- 24 hrs, 7 days
Components of PACT (cont)

- Social services that are frequently brokered such as housing, benefits, etc are provided by the team.
- Focus on high utilizers of services
Research on the PACT Model

- All studies document a reduction in hospital days.
- Some studies suggest PACT is cost effective.
- PACT improves likelihood of independent living and may reduce symptomatology.
- Effects last as long as PACT management continues.