The Pharmacological Basis of Schizophrenia Treatment and Tolerability

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April 21, 2007

Learning Objectives

- Briefly describe schizophrenia, its manifestations, clinical course, and prognosis
- Review the diagnosis of schizophrenia, distinguishing between positive, negative and cognitive symptoms
- Discuss the different treatment options for schizophrenia, listing the atypical antipsychotics currently available on the market
- Understand the characteristics of antipsychotic medications and their different receptor effects
- Describe the tolerability of antipsychotics focusing on extrapyramidal symptoms and the metabolic syndrome

Definition of Schizophrenia

- A syndrome of disorganized and bizarre thoughts, delusions, hallucinations, inappropriate affect, impaired social functioning and cognitive deficits
- A complex disorder with many possible etiologies: biological, psychosocial, and environmental

Clinical Symptoms

Positive Symptoms
- Delusions
- Hallucinations
- Disorganized speech
- Catatonia

Negative Symptoms
- Affective flattening
- Alogia
- Avolition
- Anhedonia
- Social withdrawal

Cognitive Deficits
- Attention
- Memory
- Executive functions (e.g., abstraction)
- Mood
- Substance use disorder
- Anxiety
- Aggression

Social/Occupational Dysfunction
- Work
- Interpersonal relationships
- Self-care

Comorbid Conditions
- Mood
- Depression
- Anxiety
- Aggression
- Hostility
- Hopelessness
- Suicidality

Features of Schizophrenia

Diagnosis Multiaxial Assessment System

- Axis I Clinical Disorders
- Axis II Personality Disorders, Mental Retardation
- Axis III General Medical Conditions
- Axis IV Psychosocial and Environmental Problems
- Axis V Global Assessment of Functioning

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Diagnosis of Schizophrenia

- DSM-IV-TR Diagnostic Criteria for Schizophrenia
  - Characteristic symptoms; two or more of the following
    - Delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, negative symptoms
    - Social/occupational dysfunction
  - Duration of at least 6 months
  - Schizoaffective or mood disorder has been excluded
  - Disorder is not due to a medical disorder or substance abuse
  - History of pervasive developmental disorder

Epidemiology

- Lifetime prevalence ranges from 0.6%-1.9%
- Worldwide prevalence is similar among all cultures
- Onset is most common in late adolescence and early adulthood
- Male: Female is 1:1
- Men may develop earlier than women

Clinical Course/Prognosis

- Usually poor long-term outcome prognosis
- First episode patient may have a relapse rate of 60% in the first two years following the initial episode
- Remission is sustained in only a small group of patients

Epidemiology

- Lifetime prevalence ranges from 0.6%-1.9%
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Long-term Outcomes

- Lifetime risk of suicide is approximately 10%
- Approximately 50% of people discharged on conventional antipsychotics will be rehospitalized within 1 year
- About two-thirds of first-episode patients continue to have positive symptoms after 1 year
- About 2/3 of people on conventional antipsychotics have persistent parkinsonism
- Subjective and objective measures of quality of life are poor, even when compared with other chronically ill patients.
- Less than 20% of patients with schizophrenia are employed in competitive work at any time

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Goals for Improving Long-term Outcomes

- Foundation for stability and reducing relapse
- Improving positive, negative and cognitive symptoms
- Reducing side effect burden
- Maintain adherence

Etiology

- Various abnormalities in brain structure and function
- Genetic susceptibility
- Early developmental insults
- Environmental

Pathophysiology—Neuroanatomical

- Enlarged lateral and third ventricles
  - Imply changes in the limbic-striatal area
- Decreased size of frontal and temporal lobes

Pathophysiology—Neurochemical

- Enzymes
- Neurotransmitters
- Reuptake transporter
- Neurotransmitter receptor

Treatment

- Goals:
  - Induce remission
  - Prevent recurrence
  - Restore baseline level of functioning
- There is no cure at this time
- Decrease target symptoms
- Non-drug therapy is important—helps with social difficulties

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

- Rapid Onset of Action
- Once Daily Dosing
- Activity in a Range of Disorders
- Cost Effective
- Minimal Side Effects
- Safety in Overdose
- No Drug Interactions

Antipsychotic Drugs: Development Timeline

- **“Typical Antipsychotics”**
  - 1960
  - 1975
  - 1985
  - 1990
  - 2000

- **“Atypical Antipsychotics”**
  - 1960
  - 1975
  - 1985
  - 1990
  - 2000

- Minimal efficacy with regard to positive symptoms in 20-30% of patients
- More effective than typical agents with regard to negative symptoms
- Much lower incidence of parkinsonian symptoms and anticholinergic effects than typical agents
- TD does occur but at much lower incidence
- Elevated risk of metabolic side effects

Typical Antipsychotics - the older agents

Examples
- Chlorpromazine (Thorazine®)
- Thoridazine (Mellaril®)
- Mesoridazine (Serentil®)
- Haloperidol (Haldol®)
- Fluphenazine (Prolixin®)
- Thiothixene (Navane®)
- Molindone (Moban®)

Typical Antipsychotics - the older agents

Mechanism of action:
- Most of these agents work specifically by blocking post-synaptic dopamine receptors in the brain
- Most of these agents have more selectivity for dopamine-2 receptors
- Increased dopamine receptor blockade can lead to extrapyrimidal side effects, tardive dyskinesia, and increased prolactin release

Haloperidol and D₂ Occupancy

11C-Raclopride PET Scan (Before Treatment)
11C-Raclopride PET Scan
Haloperidol 2 mg/day (74% occ.)

Pathophysiology

- Medial forebrain bundle
- Striatum
- Frontal cortex
- Nigrostriatal
- Limbic system
- Hypothalamus
- Pituitary
- Substantia nigra (A9)
- Zona compacta
- Ventral tegmentum (A10)
- Mesocortical
- Mesolimbic
- Tuberoinfundibular

From Kapur, 1999 (presentation)

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Dopaminergic Tracts

<table>
<thead>
<tr>
<th>Dopaminergic Tract</th>
<th>Origin</th>
<th>Innervation</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesolimbic</td>
<td>Substantia nigra (A9 area)</td>
<td>Medial ventral tegmentum (A10 area)</td>
<td>Limbic areas (e.g., amygdala, olfactory tubercle, septal nuclei, olfactory system)</td>
</tr>
<tr>
<td>Mesocortical</td>
<td>Substantia nigra (A9 area)</td>
<td>Frontal and prefrontal lobe cortex</td>
<td>Cognition, communication, social function, response to stress</td>
</tr>
<tr>
<td>Tuberoinfundibular</td>
<td>Hypothalamus</td>
<td>Pituitary gland</td>
<td>Regulates prolactin release</td>
</tr>
</tbody>
</table>

Movement Disorders

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Features</th>
<th>Minimum Risk</th>
<th>Proposed Mechanism</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute dystonia</td>
<td>Spasm of muscles of tongue, face, neck, back</td>
<td>1-5 days</td>
<td>Unknown</td>
<td>Antiparkinson agents</td>
</tr>
<tr>
<td>Akathisia</td>
<td>Motor restlessness</td>
<td>5-60 days</td>
<td>Unknown</td>
<td>Reduce dose; Change drug; Propranolol, BZDs</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>Bradykinesia, rigidity, tremor, mask facies, shuffling gait</td>
<td>5-30 days</td>
<td>Dopamine antagonism</td>
<td>Antiparkinson agents</td>
</tr>
<tr>
<td>Tardive Dyskinesia</td>
<td>Oral-facial dyskinesias; widespread choreoathetosis or dystonia</td>
<td>Months or years of treatment; worse upon withdrawal</td>
<td>Excess dopaminergic functioning</td>
<td>Treatment is unsatisfactory; PREVENTION is key</td>
</tr>
</tbody>
</table>

Atypical Antipsychotics

- Mechanism of action:
  - Like the typical antipsychotics, atypical medications also block post-synaptic dopamine receptors in the brain
  - Unlike most of the typical agents, atypicals also have antagonistic effects at serotonin receptors, specifically 5HT2a receptors
  - These agents also work at many other receptors

Atypical Antipsychotics

- Clozapine (Clozaril®)
- Olanzapine (Zyprexa®)
- Risperidone (Risperdal®)
- Quetiapine (Seroquel®)
- Aripiprazole (Abilify®)
- Ziprasidone (Geodon®)
- Paliperidone (Invega®)

Comparative Receptor Binding Profiles

<table>
<thead>
<tr>
<th>Receptor Blockade</th>
<th>Associated Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopaminergic (D2)</td>
<td>EPS, prolactin elevation</td>
</tr>
<tr>
<td>Histaminergic (H1)</td>
<td>Sedation, weight gain</td>
</tr>
<tr>
<td>Muscarinic (M1)</td>
<td>Dry mouth, urinary retention, blurred vision, constipation, sinus tachycardia, cognition and memory problems</td>
</tr>
<tr>
<td>α1-adrenergic</td>
<td>Orthostatic hypotension, reflex tachycardia, sexual dysfunction</td>
</tr>
</tbody>
</table>
Aripiprazole and Bifreprunox

- Partial agonist at D2 receptors
  - Functional antagonist under conditions of dopamine hyperactivity (i.e. possible control of positive symptoms)
  - Functional agonist in conditions of dopamine hypoactivity (i.e. possible improvement in negative symptoms, cognitive improvement, minimal EPS)
- Antagonist at 5-HT2a receptors
- Partial agonist at 5-HT2a receptors

Transient D2 Receptor Occupancy with Quetiapine

<table>
<thead>
<tr>
<th>57% D2 occupancy</th>
<th>20% D2 occupancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRL 19 ng/mL, ELEVATED</td>
<td>PRL 2 ng/mL, BELOW NORMAL</td>
</tr>
<tr>
<td>8 hours</td>
<td>24 hours</td>
</tr>
</tbody>
</table>

Relative Dissociation of Antipsychotics From the D2 Receptor

Quetiapine/clozapine
Olanzapine
Ziprasidone
Risperidone
Typical antipsychotics

D2 affinity

more

less

EPS

The Old Concerns and the New Ones in Schizophrenia Management

<table>
<thead>
<tr>
<th>Issue</th>
<th>Old Era</th>
<th>New Era</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPS</td>
<td>Major patient tolerability issues, effects on medication compliance</td>
<td>Infrequent</td>
</tr>
<tr>
<td>Tardive dyskinesia</td>
<td>Major long-term risk</td>
<td>Seems rare</td>
</tr>
<tr>
<td>Social, cognitive, and vocational efficacy</td>
<td>Disappointment, Accepted</td>
<td>New hope and expectations</td>
</tr>
<tr>
<td>Poor patient adherence</td>
<td>Common</td>
<td>Expected improvement</td>
</tr>
</tbody>
</table>

Baseline Risk of Medical Illness Is High in Schizophrenia

- Patients with schizophrenia have about a twofold increased risk of death from medical causes\(^1,2\)
- Cardiovascular death is a major contributor to increased mortality in schizophrenia\(^1,3\)

Metabolic Syndrome

- Central obesity as measured by waist circumference:
  Men — Greater than 40 inches
  Women — Greater than 35 inches
- Fasting blood triglycerides greater than or equal to 150 mg/dL
- Blood HDL cholesterol:
  Men — Less than 40 mg/dL
  Women — Less than 50 mg/dL
- Blood pressure greater than or equal to 130/85 mmHg
- Fasting glucose greater than or equal to 100 mg/dL (ADA guidelines)

Body Mass Index

- Body Mass Index (BMI)
  - Is a measure of body fat based on height and weight that applies to both adult men and women
  - To calculate: Weight in Kilograms / Height in Meters²
  - Underweight = <18.5
  - Normal weight = 18.5-24.9
  - Overweight = 25-29.9
  - Obesity = BMI of 30 or greater

Risk Factors for Heart Disease in the General Population

Obesity and Mortality Risk in the General Population

BMI = body mass index (kg/m²); TC = total cholesterol (mg/dL); DM = diabetes mellitus; HTN = hypertension.


Based on data from: Low and Garfinkel. J Chronic Dis. 1979;32:563; American Cancer Society study of 750,000 men and women.

BMI Distributions in General Pop. and in Patients With Schizophrenia

Atypical Antipsychotics: Clinically Significant (≥7%) Weight Gain

Data for aripiprazole, ziprasidone, risperidone, quetiapine, and olanzapine are from US product labels.
Atypical Antipsychotics: Clinically Significant Weight Gain

Body Mass Index and Diabetes Risk

Schizophrenia and Diabetes

Atypical Antipsychotics and Diabetes

Changes in Fasting Lipids Levels Associated with Atypical Antipsychotics

- Prevalence of adult-onset diabetes in schizophrenia populations is about 13%.
  - Adjusted odds ratio ~2
  - Increased risk for diabetes predates arrival of antipsychotics.

• New data suggest 2 separate issues
  - Diabetic ketoacidosis
    • May occur early in treatment
    • May not be associated with weight gain
  - New/ongoing diabetes cases
    • Impaired glucose tolerance/new cases of diabetes occur over extended time frame
    • Often, but not always, associated with weight gain

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Identification of Metabolic Syndrome

<table>
<thead>
<tr>
<th>≥ 3 Risk Factors Required for Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Factor</td>
</tr>
<tr>
<td>Abdominal Obesity</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>Triglycerides</td>
</tr>
<tr>
<td>HDL cholesterol</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>BP</td>
</tr>
<tr>
<td>Fasting blood glucose</td>
</tr>
</tbody>
</table>

HDL = high density lipoprotein; BP = Blood pressure
NCEP III. Circulation 2002;106:3143-3421

Modifiable Risk Factors

- Overweight/Obesity
- Insulin Resistance
- Diabetes/hyperglycemia
- Dyslipidemia


Hyperglycemia/Diabetes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight Gain</th>
<th>Risk for Diabetes</th>
<th>Worsening Lipid Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>+++</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+++</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Risperidone</td>
<td>++</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>++</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>Aripiprazole*</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ziprasidone*</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

- +/- increase effect - no effect
- Diiscomparant results
- Newer drugs with limited long-term data

Monitoring and Treatment

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4 weeks</th>
<th>8 weeks</th>
<th>12 weeks</th>
<th>Quarterly</th>
<th>Annually</th>
<th>Every 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal Family History</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (BMI)</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Fasting Plasma Glucose</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Fasting Lipid Profile</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Prevalence of Metabolic Syndrome

CATIE Study - Individuals with schizophrenia (Schizophrenia Research 2005; 80: 19-32)
- 1,458 subjects enrolled in the CATIE Study
- Baseline Characteristics
  - Mean Age = 40.4 yrs, BMI = 29.7, Male (74%)
  - White (60%), Black (35.2%), Hispanic (11.6%)
- Prevalence of metabolic syndrome
  - NCEP Criteria - 42% (only 14% had no risk factors)
  - Men = 39% and women = 52%*
  - White = 44.2%, Black = 29.6%, and Hispanic = 39.5%

*Note: Women were significantly older than men in this trial

Prevalence of Metabolic Syndrome

CATIE Study - Prevalence of Risk Factors (Schizophrenia Research 2005; 80: 19-32)
- HDL cholesterol ≤ 40 or 50 mg/dL = 52.7%
- Triglycerides ≥ 150 mg/dL = 48.5%
- Blood Pressure ≥ 130/85 mmHg = 47.2%
- Waist Circumference ≥ 40 or 35 inches = 46.1%
- Glucose ≥ 110 mg/dL = 16.1%
- Glucose ≥ 100 mg/dL = 25.7%
Prevalence of Metabolic Syndrome

CATIE Study – Cardiovascular Risk
(Shizophrenia Research 2005; 80: 45-53)
Baseline CV risks in subjects enrolled in CATIE trial vs. NHAINES III (matched controls)
Smokers 68% vs. 35% (p<0.0001)
Diabetes 13% vs. 3% (p<0.0001)
Hypertension 27% vs. 17% (p<0.0001)
HDL Cholesterol 43.7 vs. 49.3 mg/dL (p<0.0001)

Antipsychotic Drugs - Metabolic Risk

Do antipsychotic medications increase the risk of developing the metabolic syndrome?
(CATIE trial. NEJM 2005; 353: 1209-23)
- Subjects: Previously treated schizophrenia but not treatment resistant (n=1432)
- Randomized to olanzapine, perphenazine, quetiapine, risperidone, or ziprasidone.
- Outcome - treatment discontinuation was high (74%)
- From a metabolic standpoint, olanzapine-treated subjects had significantly poorer outcomes
  - More likely to discontinue tx due to weight gain or metabolic effect

Current Challenges in Treatment of Schizophrenia

- Cure remain elusive
- More medication choices than ever before
- Uncertainty about
  - Finding the right treatment objectives
  - Balancing competing goals
  - What is amenable to psychopharmacology Vs other interventions?
  - When is the right time to increase the dose or decrease the dose?
  - When is the right time to switch to another antipsychotic