Madness and Confusion of Mind: Schizophrenia Pharmacotherapy
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CPPI Annual Meeting 2014

Learning Objectives
1. Apply the current evidence on the efficacy of pharmacologic and nonpharmacologic treatment options in the management of schizophrenia
2. Design a monitoring plan for efficacy and toxicity of antipsychotics used for the management of schizophrenia
3. Identify information for patient education, including supportive strategies and available community resources

Disclosure
- I have no commercial or financial relationships to disclose relating to the content of this presentation.

Overview
- Diagnosis and proposed pathophysiology of schizophrenia
- Rating scales used in schizophrenia
- Non-pharmacologic and pharmacological treatment options
  - Indications, adverse events and warnings
  - Place of therapy
  - Comparative efficacy and toxicity
- Support for the patients and the families

Review of Schizophrenia

Diagnosis (DSM 5)
- Two or more of the following for a significant amount of time during 1-month period
  - Delusions
  - Hallucinations
  - Disorganized speech
  - Grossly disorganized or catatonic behavior
  - Negative symptoms
- Social/occupational dysfunction
- Duration: at least 6 months
- Ruled out: schizoaffective disorder, substance-induced, medical condition, pervasive developmental disorder

Target Symptoms

- Positive
  - Hallucination
  - Delusion
  - Disorganized speech
  - Psychomotor agitation
  - Bizarre behavior

- Negative
  - Anhedonia
  - Flat affect
  - Alogia
  - Amotivation
  - Disorganization

- Cognitive
  - Inattention
  - Memory impairment
  - Poor executive functioning
  - Poor skill acquisition

Common Misunderstanding of Pathology of Schizophrenia

- Secondary to bad parenting
- Secondary to emotional weakness
- Secondary to sin
- Secondary to willful invitation

Schizophrenia and Demon Possession

- Demon-possession in the Gospels
  - Mute (Matt 12:22)
  - Blind (Matt 12:22, Matt 9:32)
  - Violent (Mark 5:4, Matt 8:28)
  - Strength beyond ordinary (Mark 5:4)
  - Convulsion (Luke 9:39, Mark 4:26)
  - Seizure (Luke 9:39)
  - Self-harm (Luke 9:39, Mark 5:5)
  - Being led by the spirit (Mark 5:3)
  - Oppressed by the spirit ((Matt 15:22)
  - Spirits knew who Christ was (Mark 1:24, Mark 1:34, Mark 5:7)
  - Spirits spoke clearly to Christ (Mark 1:24, Mark 1:34, Mark 5:7)

Confusion and Madness of Mind as Chastisement

- Result of disobedience to the voice of the Lord God (Deuteronomy 28)
  - Wasting disease
  - Fever
  - Inflammation
  - Fiery heat, drought, blight, mildew
  - Boils
  - Tumors and scabs and itch
  - Madness
  - Blindness
  - Confusion of mind

Insanity In the Bible

- Assumed
  - Paul in trial (Acts 26:24-25)
  - David before Achish (1 Sam 21:12-15)

- Verified
  - Insanity as punishment: Nebuchadnezzar (Dan 4:28-34)
  - Insanity as chastisement (Deut 28:28)

Epidemiology

- Lifetime prevalence 0.3% - 0.7%
- First symptoms seen between the late teens and the mid-30’s
- Remains largely a chronic disease, though full recovery has been reported in a small number of individuals
Typical Course

- Prodromal phase
- Onset
- Chronic illness
- Remission and exacerbation

Etiology

- Genetic
  - Ten-fold increased risk for someone whose first-degree relative has diagnosis of schizophrenia
  - Twin studies

- Neuroanatomy
  - Larger ventricles
  - Smaller brain size

- Neurochemistry
  - Excessive dopaminergic activity in mesolimbic area
  - Diminished dopaminergic activity in mesocortical area
  - Serotonergic activity in mesocortical area
  - Glutamate deficiency
  - Diminished GABAergic (inhibitory) activity

Pathophysiology

- Excessive dopamine activity in mesolimbic area
- Diminished dopamine activity in mesocortical area

<table>
<thead>
<tr>
<th>Dopamine Tract</th>
<th>Function</th>
<th>DA Antagonist Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nigrostrial</td>
<td>Extrapyramidal system, movement</td>
<td>Movement disorders</td>
</tr>
<tr>
<td>Mesolimbic</td>
<td>Emotional functioning, motivational behavior</td>
<td>Relief of psychosis</td>
</tr>
<tr>
<td>Mesocortical</td>
<td>Cognition, executive function</td>
<td>Relief of psychosis?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Akathisia?</td>
</tr>
<tr>
<td>Tubero-hypophyseal</td>
<td>Regulates prolactin release</td>
<td>Increased prolactin concentration</td>
</tr>
</tbody>
</table>

Audience Response Question I

- True or False: Schizophrenia is a chronic disorder.
  - True
  - False

Patient Assessment

Rating Scales in Schizophrenia

- Brief Psychiatric Rating Scale (BPRS)
  - Widely used
  - Both for clinical treatment and research purposes
  - Symptom assessment by clinician (trained)
  - 18 symptom items are assessed from 0 (not present) to 7 (extremely severe)
    - E.g. Suspiciousness
    - E.g. Blunted affect
Rating Scales in Schizophrenia (cont)

- Positive And Negative Symptom Scale (PANSS)
  - Widely used in research setting
  - Done by trained personnel
  - 30-40 minutes to complete
  - E.g. Write the appropriate number in the box adjacent to each symptom
    - PI. Delusion
    - P2. Conceptual disorganization
    - P3. Hallucinatory behavior
    - N1. Blunted affect
    - N2. Emotional withdrawal
    - N3. Poor rapport
    - 1. Absent
    - 2. Minimal
    - 3. Mild
    - 4. Moderate
    - 5. Moderately severe
    - 6. Severe
    - 7. Extreme

Non-Pharmacologic Interventions (cont)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Description</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assertive Community Treatment</td>
<td>Multidisciplinary team</td>
<td>Reduces hospitalization and homelessness</td>
</tr>
<tr>
<td>Sponsored Employment</td>
<td>Individually tailored job development, job search, ongoing job support</td>
<td>More working hours, greater wages</td>
</tr>
<tr>
<td>Skills Training</td>
<td>Skills needed for community functioning</td>
<td>Provided as one component of integrated intervention</td>
</tr>
</tbody>
</table>

Audience Response Question II

- A 29-year old male presents to psychiatric ER with first onset of psychosis. Which of the following tools may be useful for patient assessment?
  1. Hamilton Depression Rating Scale (HAM-D)
  2. Brief Psychiatric Rating Scale (BPRS)
  3. Abnormal Involuntary Movement Scale (AIMS)
  4. Serum electrolytes

Pharmacologic Interventions

- First line of therapy: antipsychotics
  - Mechanism of action
    - First-generation antipsychotics: D2 receptor antagonists
    - Second-generation antipsychotics: D2 and 5-HT2A receptors antagonists
    - Third-generation antipsychotic (controversial): D2 receptor partial agonists
Indications

<table>
<thead>
<tr>
<th>Indication</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>First-generation, second-generation</td>
</tr>
<tr>
<td>Treatment-resistant schizophrenia</td>
<td>Clozapine</td>
</tr>
<tr>
<td>Acute mania</td>
<td>Risperidone, olanzapine, quetiapine, ziprasidone, quetiapine, asenapine</td>
</tr>
<tr>
<td>Depressive episodes</td>
<td>Lurasidone</td>
</tr>
<tr>
<td>Maintenance treatment of mania</td>
<td>Olanzapine, aripiprazole, ziprasidone (adjunct)</td>
</tr>
<tr>
<td>Agitation associated with mania</td>
<td>Olanzapine, loxapine</td>
</tr>
<tr>
<td>Agitation associated with schizophrenia</td>
<td>Ziprasidone</td>
</tr>
</tbody>
</table>

First Generation Antipsychotics (FGA)

- Prototypical: Chlorpromazine (1950s)
- Chlorpromazine-equivalent dose (CPZ 100 mg)
  - D₂ receptor binding affinity
- Observation
  - High incidence of extrapyramidal symptoms (EPS)
  - Little improvement in negative and cognitive symptoms

FGA Equivalent Dosing

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose Equivalence</th>
<th>Starting Daily Dose</th>
<th>Acute Phase (per day)</th>
<th>Maintenance Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>100</td>
<td>50-200</td>
<td>300-1,500</td>
<td>150-800</td>
</tr>
<tr>
<td>Thoridazine</td>
<td>100</td>
<td>50-200</td>
<td>300-800</td>
<td>150-600</td>
</tr>
<tr>
<td>Loxapine</td>
<td>10</td>
<td>10-20</td>
<td>50-350</td>
<td>25-100</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>10</td>
<td>4-16</td>
<td>32-64</td>
<td>8-48</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>2</td>
<td>2-10</td>
<td>5-100</td>
<td>2-20</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>2</td>
<td>2-10</td>
<td>5-80</td>
<td>2-20</td>
</tr>
</tbody>
</table>

Potency of FGA

- Low Potency
  - Chlorpromazine
  - Thoridazine
- Mid Potency
  - Loxapine
  - Perphenazine
- High Potency
  - Haloperidol
  - Fluphenazine
  - Thiothixene

FGA on CYP450 Interaction

- Most FGA metabolized via CYP1A2, 2D6, 3A4
- Inhibitors of CYP450
  - Chlorpromazine (2D6)
  - Haloperidol (3A4)
  - Pimozide (2D6)
  - Thoridazine (2D6)

Second Generation Antipsychotics (SGA)

- Currently 10 agents on the US market
- Pharmacology
  - Rapid dissociation at D₂
  - Strong affinity for blocking 5HT₂A
  - Additional receptor binding affinity (D₅, D₆, SHT₆, SHT₁C, SHT₈, SHT₉, SHT₁₀, H₁, M₁, SHT reuptake, NE reuptake)
  - Sustained antipsychotic property with little or no EPS risk
SGA on CYP450 Interaction

- Most SGAs metabolized via CYP1A2, 2D6, 3A4
- Clozapine and olanzapine susceptible to 1A2 induction by cigarette smoking
- Non-CYP450 route (ziprasidone, asenapine)

Adverse Events of Antipsychotic Drugs (cont)

- Neuroleptic Malignant Syndrome
  - Usually within 10 days of initiation or dose change
- ECG changes
  - QT prolongation
- Mild elevation in liver enzymes
- Weight gain
  - Complex receptor activity (D2, SHT2C, H1, M3)
  - Decreased activity, increased appetite
  - Lack of long-term follow up

SGA Dosing

<table>
<thead>
<tr>
<th>SGA</th>
<th>Usual Dose Range</th>
<th>Daily Maximum Dose</th>
<th>Dosage Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>15-30 mg daily</td>
<td>30</td>
<td>Tab, ODT, liquid</td>
</tr>
<tr>
<td></td>
<td>400 mg q month</td>
<td>N/A</td>
<td>Long acting IM</td>
</tr>
<tr>
<td>Asenapine</td>
<td>10-20 mg daily</td>
<td>20</td>
<td>Sublingual tab</td>
</tr>
<tr>
<td>Clozapine</td>
<td>50-500 mg daily</td>
<td>900</td>
<td>Tab, liquid</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>2-24 mg daily</td>
<td>24</td>
<td>Tab</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>40-160 mg daily</td>
<td>160</td>
<td>Tab</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>15-20 mg daily</td>
<td>20</td>
<td>Tab, ODT, injectable</td>
</tr>
<tr>
<td></td>
<td>150-300 mg q 2 wk</td>
<td>N/A</td>
<td>Long acting IM</td>
</tr>
<tr>
<td></td>
<td>405 mg q 4 wk</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Paliperidone</td>
<td>3-9 mg daily</td>
<td>12</td>
<td>ER tab</td>
</tr>
<tr>
<td></td>
<td>117 mg q 4 wk</td>
<td>N/A</td>
<td>Long acting IM</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>250-800 mg daily</td>
<td>800</td>
<td>Tab</td>
</tr>
<tr>
<td>Risperidone</td>
<td>2-8 mg daily</td>
<td>16</td>
<td>Tab, ODT, liquid</td>
</tr>
<tr>
<td></td>
<td>25-50 mg q 2wk</td>
<td>N/A</td>
<td>Long acting IM</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>40-160 mg daily</td>
<td>200</td>
<td>Tab, inj</td>
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</table>

Reports of Weight Gain Over Various Follow-up Periods

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Olanzapine</th>
<th>Risperidone</th>
<th>Haloperidol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term (10-12 weeks)</td>
<td>7.1 to 9.2 kg</td>
<td>4.0 to 5.6 kg</td>
<td>2.6 to 3.8 kg</td>
</tr>
<tr>
<td>Long-term (1-2 years)</td>
<td>10.2 to 15.4 kg</td>
<td>6.6 to 8.9 kg</td>
<td>4.0 to 9.7 kg</td>
</tr>
</tbody>
</table>

Adverse Events of Antipsychotic Drugs (cont)

- Sedation
  - First-generation, low potency
- Reduced initiative or interest
- “Secondary” negative symptom
- Extrapyramidal side effects (EPS)
  - Tardive dyskinesia after a long-term use
- Orthostatic hypotension
  - Tolerance usually develops
- Anticholinergic
  - Peripheral and central

Hyperprolactinemia
- Amenorrhea, osteoporosis, sexual dysfunction
- Lowering seizure threshold
- After rapid dose increase
- Lipid abnormalities
- Glucose intolerance
- Agranulocytosis
- Clozapine (1% in trials)
- Case reports with other SGAs
- Myocarditis
- Clozapine (<1%)

Adverse Events of Antipsychotic Drugs (cont)
Monitoring Protocol for Patients on Antipsychotics (Obesity and Diabetes)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4 wks</th>
<th>8 wks</th>
<th>12 wks</th>
<th>Quarterly</th>
<th>Annually</th>
<th>Q 5 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal/family hx</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (BMI)</td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist circumference</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting BG</td>
<td></td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting lipid</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>


Warnings
- All SGAs and FGAs
- BBW: increased risk of death in elderly patients with dementia-related psychosis
- SGAs indicated in Major Depressive Disorder or Depressive episodes (aripiprazole, lurasidone, quetiapine)
- BBW: increased risk of suicidal thinking and behaviors in patients of 18-24 years with MDD and other psychiatric disorders

Audience Response Question III
- Which of the following is an appropriate monitoring parameter for a patient who has been on olanzapine 10 mg once daily by mouth for the past 5 months?
  1. Neuroleptic malignant syndrome
  2. Orthostatic hypotension
  3. Weight gain
  4. Agranulocytosis

Treatment Guidelines
- Texas Medication Algorithm Project (TMAP) – 2006
  - First episode: SGA (exc Clozapine)
  - Second episode: SGA (exc Clozapine), FGA
  - Clozapine after 2 antipsychotic trials
- Schizophrenia Patient Outcomes Research Team (PORT) – 2009
  - Treatment response: any antipsychotic other than Clozapine
  - Treatment-resistant schizophrenia, treatment-residual symptoms, suicidality: Clozapine

Treatment Algorithm

Combination of Antipsychotics
- Limited, if any, proven efficacy
- Often done in clinical setting for difficult-to-treat schizophrenia
- After failing clozapine (treatment-refractory)
- Unwilling to try clozapine therapy
- Cross-titration of antipsychotics: clinician stops following up inadvertently
- Broaden receptor binding activity
Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)

- Funded by National Institute of Mental Health
- Measured the duration patients stayed on medication \((n=1,460)\)
- Compared older (since 1950s) vs newer (1990s) antipsychotics
  - Perphenazine
  - Olanzapine
  - Quetiapine
  - Risperidone
  - Ziprasidone
- Long term study (18 months)

Results: Clozapine and Other Atypicals

- Time to discontinuation (all causes)
  - Clozapine: 10.5 months (7.3-16.1)
  - Olanzapine: 2.7 months (1.9-11.9)
  - Quetiapine: 3.3 months (1.0-4.9)

Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE): Result

- Seventy-four percent of patients dropped out before 18 months
- Duration completed by 18%-36% patients across the groups
- Olanzapine slightly better than others; significance disappeared when adjusted for variables
- Olanzapine associated with greatest increase in weight and indices of glucose and lipid metabolism
- EPS rate similar among perphenazine and second-generation antipsychotics

CATIE Phase 2: Implications

- Effectiveness of clozapine in patients with unsatisfactory response to another antipsychotic
- Clozapine treatment rendering more frequent patient contact \(\Rightarrow\) Greater efficacy
- Clozapine under-utilization
  - "Clozapine clinic"

CATIE Phase 2: Clozapine vs Other Atypicals

- Patients \((n=99)\) who discontinued treatment with prior atypical antipsychotic randomized to clozapine or another atypicals
  - Clozapine
  - Olanzapine
  - Quetiapine
  - Risperidone

Clozapine

- Remains the only antipsychotic known to be efficacious in people who fail on other antipsychotics (treatment-resistant)
- Reserved for patients who fail two adequate trials of antipsychotics (FGA or SGA)
  - Adequate dose: therapeutic/daily maximum dose
  - Adequate duration: 6 weeks per each period
- Superior efficacy in decreasing suicidal behavior
- History of violence or comorbid substance abuse
Clozapine: Lab Monitoring

- Agranulocytosis seen in 1% in clinical trials, <1% in post-marketing studies
- Risk of agranulocytosis (WBC<3500/mm³ or Absolute Neutrophil Count <2000/mm³)
- Lab follow-up required
  - CBC weekly x 6 months
  - Then bi-weekly x 6 months
  - Then monthly thereafter
- Strictly regulated and monitored (patients, prescriber, pharmacy and pharmacists must be registered)

State of Antipsychotic Drugs

- Reduction in psychotic symptoms (positive symptoms) by FGAs and SGAs
- FGAs may improve positive and negative symptoms equally
- SGAs may improve negative symptoms more than FGAs
- Limitations on assessment of negative symptoms
  - Definition
  - Distinction between primary vs secondary symptoms

State of Antipsychotic Drugs (cont)

- SGAs no more effective than FGAs in terms of efficacy and dropout rate
- When a comparator FGA dose (e.g. haloperidol) exceeded 12 mg/day, greater efficacy and tolerability seen with SGAs
- FGAs and SGAs improve cognitive symptoms alike

Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis

- Multiple-treatments meta-analysis of 212 trials
- Acute treatment of schizophrenia (n=43,049)
- @ Munich, Germany
- Excluded:
  - Predominant negative symptoms
  - Concomitant medical illness
  - Treatment resistance
  - Relapse prevention

Comparative Efficacy

Comparative Risk of Weight Gain
Comparative Risk of EPS

C. Somnolence side effects of SGAs

- Clozapine: 10 (0.52 to 19.05)
- Sertindole: 0.5 (0.14 to 2.14)
- Olanzapine: 0.21 (0.17 to 0.70)
- Quetiapine: 0.08 (0.04 to 0.14)
- Aripiprazole: 0.21 (0.17 to 0.70)
- Risperidone: 0.01 (0.00 to 0.07)
- Ziprasidone: 0.01 (0.00 to 0.07)
- Aripiprazole: 0.01 (0.00 to 0.07)
- Paliperidone: 0.01 (0.00 to 0.07)
- Lamotrigine: 0.01 (0.00 to 0.07)
- Ziprasidone: 0.01 (0.00 to 0.07)
- Chlorpromazine: 0.01 (0.00 to 0.07)
- Haloperidol: 0.01 (0.00 to 0.07)

More somnolence side effects with placebo

Comparative Risk of Sedation

F. Selection of Antipsychotic Drug

- All antipsychotics superior to placebo
- Clozapine may not be more effective than any other SGA in non-treatment refractory schizophrenia
- Most SGAs going off patent; price no longer the major determinant
- Individual antipsychotic's property should guide the selection process

Selection of Antipsychotic Drug

- All antipsychotics superior to placebo
- Clozapine may not be more effective than any other SGA in non-treatment refractory schizophrenia
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Audience Response Question IV

- How would you select an initial antipsychotic regimen for schizophrenia?
  1. Always newest SGAs over FGAs for better efficacy
  2. Clozapine
  3. Based on antipsychotic's ADR profile and patient's risk for toxicity
  4. FGAs over SGAs for better cost
Support for the Patients and Families

Church As Support
- Patients and families usually look for help in church
- Little help from clergy (Waterhouse, 2002, pg 9)
- Scriptures addresses the emotional turmoil experienced in mental illnesses

Christ’s Commands to the Believers
- Ask the Lord to send out laborers into harvest (Matt 9:37)
- Heal the sick, cast out demons (Matt 10:8)
- Be wise as serpents and innocent as doves (Matt 10:16)

Community Support
- National Alliance on Mental Illness (www.nami.org)
- National Suicide Prevention Lifeline (http://www.suicidepreventionlifeline.org)
- National Mental Health Consumer’s Self-Help Clearinghouse (http://mhselfhelp.squarespace.com)

Administering to the Families of Patients with Schizophrenia
- Tremendous guilt
- Anger
- Loneliness
- Stress (e.g. marital)
- Fear
- Denial
- Confusion

SUMMARY
1. Schizophrenia is a chronic, debilitating disease that affects individual patients, families, church and community
2. Both pharmacological and non-pharmacological treatment modalities have shown to help reduce symptoms of schizophrenia and build disease-coping skills
3. A number of antipsychotics of comparable efficacy are available to manage schizophrenia
4. Despite its superior efficacy, clozapine continues to be under-utilized
5. Pharmacists can help prevent, monitor and manage the acute and long-term side effects of antipsychotics