Schizophrenia and Weight Gain – Strategies to Improve Medication Adherence

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Learning Objectives

- At the conclusion of this knowledge-based activity, the participant will be able to:
  1. Identify the main causes of medication non-compliance in schizophrenia patients to include the results of recent studies involving antipsychotics, weight gain, and metabolic abnormalities.
  2. Compare and contrast the pharmacological approaches to the management of schizophrenia to include efficacy, dosing, safety, and tolerability profiles.
  3. Describe the active role that pharmacists can play in collaboration with patients and physicians when weight gain and/or metabolic abnormalities cause medication adherence problems.

Target Audience:

Pharmacists, Technicians & Nurses

Contact Hours: 1.0 contact hour

Accreditation:

Pharmacists: 0798
Pharmacy Technicians: 0798
Nurses: N-693

Program Overview:

Schizophrenia is a chronic, relapsing, and devastating illness that involves antipsychotics, weight gain, and metabolic abnormalities. Antipsychotics are the fundamental therapy for schizophrenia. Antipsychotics are typically started at low doses in order to minimize side effects and facilitate adherence. However, many patients are not able to tolerate the initial doses and require a dose increase to achieve therapeutic levels. This webinar will review the pharmacological approaches to the management of schizophrenia to include efficacy, dosing, safety, and tolerability profiles. The webinar will also review the main causes of medication non-compliance in schizophrenia patients to include the results of recent studies involving antipsychotics, weight gain, and metabolic abnormalities. The webinar will compare and contrast the pharmacological approaches to the management of schizophrenia to include efficacy, dosing, safety, and tolerability profiles. The webinar will also review the main causes of medication non-compliance in schizophrenia patients to include the results of recent studies involving antipsychotics, weight gain, and metabolic abnormalities.

Speaker Disclosure:

Dr. Noel has no actual or potential conflicts of interest in relation to this program.

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Disclosures
- Dr. Noel reports no financial interest with any organization that represents products or services discussed in this activity.

Severe Mental Illness (SMI)
- Generally refers to chronic psychiatric disorders capable of causing persistent functional impairment
  - Schizophrenia
  - Bipolar Disorder
  - Major Depression
  - Obsessive-Compulsive Disorder
- Account for 4 of the top 10 leading causes of disability worldwide
- Estimated 90% of persons who commit suicide have a psychiatric disorder at time of death


Epidemiology
- Lifetime prevalence of 0.5 – 1%
- No gender or racial differences
- Onset in late teens to mid 30s
  - Women have later onset then men (median age late 20s vs. early to mid 20s)
- Older individuals usually present with delusions and hallucinations and less disorganization and negative symptom features
- More frequent in lower socioeconomic class (probably social drift phenomenon)

Societal Burden of Schizophrenia
  - Direct – $22.7 billion
  - Indirect – $32.4 billion
- Family costs
  - Time needed to care for patients
  - Psychological impacts
- Criminal Justice System
  - Patients with SMI have slightly higher rates of criminal activity
  - Disproportionately involved as victims of crime and in incarceration

Schizophrenia and Weight Gain – Strategies to Improve Adherence

Schizophrenia Symptom Clusters
- Positive
  - Delusions
  - Hallucinations
  - Disorganized speech
  - Psychomotor agitation
- Negative
  - Affective flattening
  - Alogia
  - Avolition
  - Poverty of speech
  - Anhedonia
- Cognitive
  - Attention
  - Memory
  - Executive function

Diagnosis
- Characteristic Symptoms
  - Delusions
  - Hallucinations
  - Disorganized speech
  - Grossly disorganized/catatonic behavior
  - Negative symptoms
- Social and Occupational Dysfunction
  - Work
  - Interpersonal relations
  - Self care
- Duration of at least 6 months


Schizophrenia Subtypes
- Paranoid
  - Prominent delusions or hallucinations
- Disorganized
  - Disorganized speech, behavior, and/or inappropriate affect
- Catatonic
  - Motoric changes (immobility, excess, or peculiarities); extreme negativism; and or echolalia/echopraxia
- Undifferentiated
  - Criteria not met for subtypes above
- Residual
  - Prominent positive symptoms absent, continuing negative symptoms

Assessment of Schizophrenia
- Severity
  - Disruptive or dangerous behaviors
  - Behaviors influenced by delusions or hallucinations
  - Severe social or occupational dysfunction
  - Suicidality
- Why now?
  - Episodic nature of illness
  - Psychosocial stressor(s)
  - Drugs – cocaine/stimulants, levodopa, corticosteroids
  - Medication adherence
### First-Generation Antipsychotics (FGAs)

- Introduced in 1950’s (chlorpromazine)
- MOA – Antagonism of dopamine-D2 receptors
- Primarily effective for positive symptoms
- Notable for association with motor symptoms and secondary negative symptoms

#### Relative Potency of FGAs

“ALL FGAs are equally efficacious when given in equipotent doses”

<table>
<thead>
<tr>
<th>Drug</th>
<th>Relative potency</th>
<th>Dose range mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>chlorpromazine</td>
<td>100</td>
<td>50-2000</td>
</tr>
<tr>
<td>thioridazine</td>
<td>100</td>
<td>50-800</td>
</tr>
<tr>
<td>loxapine</td>
<td>10</td>
<td>20-250</td>
</tr>
<tr>
<td>molindone</td>
<td>10</td>
<td>15-225</td>
</tr>
<tr>
<td>perphenazine</td>
<td>8-10</td>
<td>8-64</td>
</tr>
<tr>
<td>trifluoperazine</td>
<td>5</td>
<td>2-80</td>
</tr>
<tr>
<td>thiothixene</td>
<td>4</td>
<td>5-60</td>
</tr>
<tr>
<td>fluphenazine</td>
<td>2</td>
<td>1-50</td>
</tr>
<tr>
<td>haloperidol</td>
<td>2</td>
<td>1-100</td>
</tr>
</tbody>
</table>


### Motor Adverse Effects

- **Acute Dystonia**
  - Onset: 24-96 hours
  - Description: Involuntary tonic contractions of skeletal muscles
  - High risk group: Young males
  - Treatment: Anticholinergic (PO or IM)

- **Pseudoparkinsonism**
  - Onset: 1-3 months
  - Description: Rigidity, tremor, bradykinesia
  - High risk group: Older patients
  - Treatment: Anticholinergic

- **Akathisia**
  - Onset: 3 months
  - Description: Subjective inner restlessness; fidgeting, pacing
  - High risk group: All patients
  - Treatment: Beta-blockers, benzodiazepines

- **Tardive dyskinesia**
  - Onset: Months-years
  - Description: Stereotyped involuntary movements (e.g. sucking and lip smacking)
  - High risk group: Older; female; h/o mood disorder
  - Treatment: Focus on prevention; may consider clozapine

### Neuroleptic Malignant Syndrome (NMS)

- Muscular rigidity, hyperthermia, change in mental status, autonomic dysfunction
- Incidence - approx. 1%
- Mortality rate - 10% (50% in patients with myoglobinemia and renal failure)
- Treat with hydration and cooling blankets
- Bromocriptine and/or dantrolene may also be useful
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### FGA’s – Systemic Adverse Events

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sedative effects</th>
<th>ACH effects</th>
<th>EPS</th>
<th>Hypotensive effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>chlorpromazine</td>
<td>high</td>
<td>high</td>
<td>low</td>
<td>IM-high</td>
</tr>
<tr>
<td>thiothixene</td>
<td>high</td>
<td>high</td>
<td>low</td>
<td>PO-low</td>
</tr>
<tr>
<td>loxapine</td>
<td>mod</td>
<td>low</td>
<td>mod</td>
<td>mod</td>
</tr>
<tr>
<td>molindone</td>
<td>very low</td>
<td>low</td>
<td>mod</td>
<td>low</td>
</tr>
<tr>
<td>perphenazine</td>
<td>low</td>
<td>low</td>
<td>high</td>
<td>low</td>
</tr>
<tr>
<td>trifluoperazine</td>
<td>low</td>
<td>low</td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td>thiothixene</td>
<td>low</td>
<td>low</td>
<td>high</td>
<td>low</td>
</tr>
<tr>
<td>haloperidol</td>
<td>very low</td>
<td>very low</td>
<td>very high</td>
<td>low</td>
</tr>
</tbody>
</table>

### Second Generation Antipsychotics (SGAs)

- Clozapine first introduced in 1970s; first line SGAs in 1990s-2000s
- MOA – Antagonism of D₂ and 5-HT₂ receptors
- Profile
  - Effective for positive symptoms
  - Modest beneficial effects on negative symptoms
  - Low EPS/prolactin elevation risks at therapeutic doses
  - Antimanic in monotherapy and with mood stabilizer
  - Bipolar depression (quetiapine and olanzapine-fluoxetine) and adjunct for major depression (aripiprazole and quetiapine)
- Many agents strongly associated with adverse metabolic effects

### Second-Generation Antipsychotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name</th>
<th>Introduced</th>
<th>Dosage Forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>Clozaril</td>
<td>1990</td>
<td>PO, ODT</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Risperdal</td>
<td>1994</td>
<td>PO, ODT, Liq, LAI</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Zyprexa</td>
<td>1996</td>
<td>PO, ODT, LAI, SAI</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Seroquel</td>
<td>1997</td>
<td>PO, XR</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Geodon</td>
<td>2001</td>
<td>PO, SAI</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Abilify</td>
<td>2002</td>
<td>PO, ODT, Liq, SAI</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>Invega</td>
<td>2006</td>
<td>XR, LAI</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>Fanapt</td>
<td>2009</td>
<td>PO</td>
</tr>
<tr>
<td>Asenapine</td>
<td>Saphris</td>
<td>2009</td>
<td>SL</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>Latuda</td>
<td>2010</td>
<td>PO</td>
</tr>
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</table>

### SGA Receptor Binding Affinities

<table>
<thead>
<tr>
<th>Drug</th>
<th>D₁</th>
<th>D₂</th>
<th>5HT₂</th>
<th>α₁</th>
<th>H₁</th>
<th>M₁</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>85</td>
<td>128</td>
<td>16</td>
<td>7</td>
<td>6</td>
<td>1.9</td>
</tr>
<tr>
<td>Risperidone</td>
<td>430</td>
<td>4</td>
<td>0.5</td>
<td>2</td>
<td>20</td>
<td>&gt;10,000</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>31</td>
<td>11</td>
<td>4</td>
<td>19</td>
<td>7</td>
<td>1.9</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>455</td>
<td>160</td>
<td>295</td>
<td>7</td>
<td>11</td>
<td>120</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>525</td>
<td>5</td>
<td>0.4</td>
<td>11</td>
<td>50</td>
<td>&gt;1000</td>
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<tr>
<td>Aripiprazole</td>
<td>265</td>
<td>0.34</td>
<td>3.4</td>
<td>57</td>
<td>61</td>
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<tr>
<td>Paliperidone</td>
<td>-</td>
<td>2.8</td>
<td>1.2</td>
<td>10</td>
<td>3.4</td>
<td>8800</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>216</td>
<td>6.3</td>
<td>5.6</td>
<td>36</td>
<td>473</td>
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<tr>
<td>Asenapine</td>
<td>1.4</td>
<td>1.3</td>
<td>0.06</td>
<td>1.2</td>
<td>6.2</td>
<td>8128</td>
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<tr>
<td>Lurasidone</td>
<td>262</td>
<td>0.994</td>
<td>0.47</td>
<td>47.9</td>
<td>-</td>
<td>-</td>
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</table>
SGA Adverse Effect Profiles

<table>
<thead>
<tr>
<th>SGA</th>
<th>EPS/Prolactin</th>
<th>Anticholinergic</th>
<th>Hypotension</th>
<th>Sedation</th>
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<tbody>
<tr>
<td>Clozapine</td>
<td>Low</td>
<td>Highest</td>
<td>Highest</td>
<td>Highest</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Highest</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Low, Minimal</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>Highest</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Asenapine</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

SGA Adverse Effects

- **QTc Prolongation**
  - Seen frequently with certain FGAs (thioridazine, mesoridazine)
  - Modest effects observed with ziprasidone
  - Recent case reports with high-dose quetiapine

- **Increased mortality in dementia**
  - Class warning

- **Clozapine effects**
  - Agranulocytosis
  - Myocarditis
  - Seizure

Metabolic Effects of Antipsychotics

- **Weight gain**
  - Increased bodyweight gain as central adiposity (i.e. increased weight circumference) occurring gradually over weeks to months of therapy
  - Changes in food cravings and decreases in basal metabolic rate

- **Diabetes Risk**
  - Elevations in fasting blood sugar and impairments in glucose tolerance
  - Exacerbations in Type 1 and Type 2 DM as well as new-onset Type 2 DM
  - Pathophysiology is separate from weight gain
  - Hyperosmolar nonketotic state may be initial presentation

- **Hyperlipidemia**
  - Increases in triglycerides, LDL, and total cholesterol have been observed
  - May lead to an increased risk of coronary heart disease
  - Obesity, poor diet, and lack of exercise are implicated as causes
Weight Gain in Acute Antipsychotic Treatment

SGA's: Clinically Significant (≥7%) Weight Gain

* Fried study safety analysis, data on file, Janssen
† Int J Neuropsychopharmacol. 2002; 5(suppl 1): S185
¤ Pooled studies safety analysis; data on file, Janssen
¶ Data from US product labels.

Changes in Fasting Lipids with SGAs

SGAs: Metabolic Effects

- Weight gain
  - Olan = Cloz > Quet > Risp = Pali > Ilop > Asen > Zip = Ari
- Lipid abnormalities
  - Cloz = Olan > Quet > Ilop > Asen > Risp = Pali > Zip = Ari
- Glucose Intolerance
  - Cloz = Olan > Quet > Risp = Pali > Zip = Ari > Ilop > Asen

Diabetes Care 2004; 27: 596-601; Data on File Janssen
Treatment Adherence in Schizophrenia

- Rates
  - ~ 50% of pts with schizophrenia will be non-adherent to medications by 1 yr after discharge
  - ~ 75% will be non-adherent to medications by 2 yrs after discharge
- Partial or complete non-adherence is associated with suboptimal treatment outcomes
- The more relapses = the more difficult to get patient into remission each time

Frequent Causes of Nonadherence in Schizophrenia

- Poor insight into illness
- Slow onset of symptom relief
- Symptomatic improvement
  - Sense of feeling better
  - Reluctance to give up pleasant symptoms
- Poor cognition
- Costs
- Feelings of hopelessness/worthlessness
- Medication adverse effects

Management of Adverse Effects

- Motor symptoms
  - Periodic assessments using standardized rating scales (e.g. AIMS) and subjective reporting
  - Use of medications for EPS as appropriate
  - Dose reduction
  - Use of medication with lower EPS liability
- Sedation and hypotension
  - Dose reduction
  - Bedtime dosing

Management of Adverse Effects

- Anticholinergic
  - Milder cases – Hard candy for dry mouth, bowel regimen for constipation
  - Moderate-severe cases – dose reduction of antipsychotic or EPS treatment
- Prolactin elevation/Sexual dysfunction
  - Assess subjective complaints of sexual dysfunction, gynecomastia
  - May confirm by obtaining serum prolactin level
  - Dose reduction or change of drug if clinically significant
Management of Metabolic Effects
- Identify patients at high risk for adverse metabolic effects prior to selecting drug
  - Baseline monitoring
  - History of metabolic syndrome
- Education on dietary and exercise approaches
  - Nutritional counseling
  - Caloric expenditure
  - Portion control
  - Regular weigh-ins

Metabolic Effects – Pharmacologic Approaches
- Switching to a lower-liability agent
  - Strategies
    - Cross-taper
    - Start new at therapeutic dose and taper off old
    - Stop old drug abruptly and gradually increase new
    - Start new at therapeutic dose and stop old abruptly
  - Generally produces favorable results for weight gain and metabolic effects
  - Significant risk of worsening psychosis

Management of Metabolic Effects
- Identify patients at high risk for adverse metabolic effects prior to selecting drug
  - Baseline monitoring
  - History of metabolic syndrome
- Education on dietary and exercise approaches
  - Nutritional counseling
  - Caloric expenditure
  - Portion control
  - Regular weigh-ins

Metabolic Effects – Pharmacologic Approaches
- Use of medications for prophylaxis or treatment-emergent metabolic effects (off-label usage)
  - Metformin
  - Topiramate
  - Orlistat
  - H2-antagonists
  - Amantadine
  - Sibutramine
  - Modafinil

ADA Monitoring Protocol for Patients on SGAs*

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1 week</th>
<th>6 weeks</th>
<th>12 weeks</th>
<th>Quarterly</th>
<th>Annually</th>
<th>Every 5 years</th>
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<tbody>
<tr>
<td>Personal/family history</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Weight (BMI)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Waist circumference</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>Blood pressure</td>
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<td>Fasting plasma glucose</td>
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<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

*More frequent assessments may be warranted based on clinical status


Mukundan A et al. Cochrane Database 2010;12.

### Antipsychotic Oral Dosing Intervals

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Interval</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most FGAs</td>
<td>Daily – BID</td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>BID</td>
<td>Hypotension and sedation at peak levels</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Daily-BID</td>
<td>EPS and hypotension at peak levels</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Daily</td>
<td>Usually at bedtime due to sedation</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>IR: BID-TID, XR: Daily</td>
<td>Hypotension and sedation at peak levels</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>BID</td>
<td>Bioavailability increased with food</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Daily</td>
<td>Bioavailability increased with food</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>Daily</td>
<td>Bioavailability increased with food</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>BID</td>
<td>Potent hypotensive effects</td>
</tr>
<tr>
<td>Asenapine</td>
<td>BID</td>
<td>Separate from food/drink</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>Daily</td>
<td>Take with at least 350 cal</td>
</tr>
</tbody>
</table>

### Adherence and Formulation Issues

- **Long-acting (depot) formulations**
  - Useful for patients who tolerate medication well, but do not remember to take daily oral doses
  - Every 2 weeks – fluphenazine, risperidone
  - Up to every 4 weeks – haloperidol, paliperidone, olanzapine
- **Orally disintegrating tablets and liquids**
  - For swallowing difficulty and “cheekers”
- **Sublingual asenapine**
  - Bioavailability optimized if food/drink is avoided within 10 minutes after dosing

### Treatment Duration

- **Start drug as soon as clinically feasible, especially for distressing symptoms**
  - **Week 1**: Resolution of agitation and hostility
  - **2-4 Weeks**: Decreased hallucinations, paranoia; more organized behavior and thinking
  - **6-12 Weeks**: Continued reduction in delusions; effects on negative symptoms
- **Indefinite treatment duration indicated for history of multiple prior acute episodes or two episodes in five years (American Psychiatric Assn.)**
### Role of the Pharmacist
- Work with prescriber to optimize drug and formulation selection
- Develop a therapeutic relationship with the patient
  - Identify goals and aspirations and relate them to treatment outcomes
  - Patient participation
- Focus on patients attitude and behaviors with respect to medications
  - Risk versus benefit of medication
  - Possibilities of adverse events
- Identify barriers that may lead to nonadherence
- Maintain availability should the patient have any questions or concerns regarding medications

### Minimizing Metabolic Effects
- Identifying high risk patients and high risk drugs
- Stressing diet and exercise approaches
- Ongoing monitoring
  - Weight and waist circumference
  - Blood glucose
  - Lipid panel
- Judicious use of pharmacologic treatments for targeted metabolic effects
- Careful switching to lower-risk antipsychotic if indicated