More than We Bargained For: Metabolic Side Effects of Antipsychotic Medications

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University of Michigan
Disclosure

In the past 12 months I have received the following:

<table>
<thead>
<tr>
<th>Company</th>
<th>Activity</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up-to-Date</td>
<td>Authorship</td>
<td>$3,254</td>
</tr>
</tbody>
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Learning Objectives

Participants will:

• Recognize the specific metabolic risks of antipsychotic medications

• Classify first and second generation antipsychotics according to degree of risk for metabolic side effects

• List potential interventions to reduce metabolic side effects
Use of all antipsychotics is associated with metabolic dysregulation

- Weight gain
- Hyperglycemia
- Elevated LDL cholesterol
- Elevated triglycerides
- Decreased HDL cholesterol
Glucose Dysregulation

Glucose dysregulation associated with antipsychotic medications is not true type 2 diabetes

- Moderately dependent on weight gain
- Not exclusively driven by insulin resistance
- Higher rate of metabolic complications
  - Ketoacidosis
  - Hyperosmotic coma
Weight Gain

Weight gain appears to be driven by multiple factors

- Increased appetite
- Dysregulation of glucose metabolism
- Baseline elevated risk
Baseline Risk

• Prevalence of obesity and diabetes in patients with schizophrenia is 1.5-2.0 times higher than the general population

• No studies on obesity and diabetes in adult drug-naïve schizophrenia patients are available

• Life expectancy with schizophrenia is 20 years less than the general population
Relative Risk

- Increased risk of weight gain and metabolic complications with antipsychotics are not dependent on diagnosis
- Comparable degrees of weight gain are seen in nonschizophrenic patients
- Schizophrenia patients experience combined risk of the diagnosis and the medication
Child/Adolescent Risk

- Risks of weight gain and other metabolic complications are at least as great in children and adolescents as in adults
- Stimulants given for ADHD do not reverse the weight gain
Medication Classes

Risk is not unique to newer medications

- Conventional, low potency antipsychotics (e.g., chlorpromazine) carry moderate-high risk
- Conventional, high potency antipsychotics (e.g., haloperidol) carry low-intermediate risk
Meta-analysis of Antipsychotic-related Weight Gain
Estimate at 10 Weeks

95% Confidence Interval for Weight Change

Weight (kg) vs. Weight (lb)

Placebo, Molindone, Ziprasidone, Fluphenazine, Haloperidol, Risperidone, Quetiapine*, Chlorpromazine, Thioridazine, Mezoridazine, Olanzapine, Clozapine

*Quetiapine weight gain estimated at 6 weeks

### Metabolic Effect Size (48 wks)

<table>
<thead>
<tr>
<th></th>
<th>High Risk</th>
<th>Low Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average weight gain (lbs)</td>
<td>12.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Pts gaining &gt;7% of baseline weight</td>
<td>64%</td>
<td>10%</td>
</tr>
<tr>
<td>Average increase in fasting glucose</td>
<td>4.2</td>
<td>0</td>
</tr>
<tr>
<td>(mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients developing high fasting</td>
<td>16.3%</td>
<td>0</td>
</tr>
<tr>
<td>glucose (&gt;126 mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average change in total cholesterol</td>
<td>+5.6</td>
<td>-5.0</td>
</tr>
<tr>
<td>(mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pts gaining &gt;40mg/dl total cholesterol</td>
<td>32.9%</td>
<td>0</td>
</tr>
</tbody>
</table>
Risk of Metabolic Complications

Relative risk of medications

- Clozapine/Olanzapine
- Low potency first generation antipsychotics
- Quetiapine/Risperidone/Paloperidone/Iloperidone/Asenapine
- High potency first generation antipsychotics
- Aripiprazole/Lurasidone/Ziprasidone
## Patient Monitoring

### Recommended monitoring for patients on atypical antipsychotics

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4 wks</th>
<th>8 wks</th>
<th>12 wks</th>
<th>Quarterly</th>
<th>Annual</th>
<th>5 yrs</th>
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</thead>
<tbody>
<tr>
<td>Personal/family history</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Weight (BMI)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</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>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting lipid profile</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

ADA et al., Diabetes Care 2004; 27:596
Patient Monitoring

Metabolic monitoring

• 46% of adults at high risk for metabolic side effects received a moderate-high risk drug

• Only 45% of adults on moderate-high risk drugs get monitoring

• Only 31% of children on moderate-high risk drugs get monitoring

Metabolic Syndrome

At least 3 of the following:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist Circumference</td>
<td>&gt;40 in</td>
<td>&gt;35 in</td>
</tr>
<tr>
<td>Fasting Glucose</td>
<td>≥126</td>
<td>≥126</td>
</tr>
<tr>
<td>Elevated Triglycerides</td>
<td>&gt;150 mg/dl</td>
<td>&gt;150 mg/dl</td>
</tr>
<tr>
<td>Decreased HDL Cholesterol</td>
<td>&lt;40 mg/dl</td>
<td>&lt;50 mg/dl</td>
</tr>
<tr>
<td>Hypertension</td>
<td>&gt;130/85</td>
<td>&gt;130/85</td>
</tr>
</tbody>
</table>

Adopted from L. John Schloss, MD, with permission
Treatment Options

Diet and Exercise

- Avoid changes in medication and dose
- Work as effectively as in the general population

*but*…

- Work no more effectively than in the general population
Change Medication

- Wide range of risk among medications
- Benefits have been shown in controlled studies
  
  *but*...
  
- Patients respond differentially to the medications
- Switches carry elevated risk of relapse
- Other side effects may be more important
Treatment Options

Combine Medications

- Combinations of high- and low-risk antipsychotics show moderate risk reduction
- Consider combinations if patient preferentially responds to high-risk medication
Treatment Options

Reduce Dose

• Moderate evidence of effectiveness
• Avoids medication switch
  
  but…

• Metabolic effects are not entirely dose dependent (eg, olanzapine)
• Relapse is associated with dose reduction
Treatment Options

Metformin*

• Several small studies show moderate benefit
• Allows continuation of current antipsychotic and dose
• but…
• Larger, population-based studies are lacking
• Effect size is moderate

*Metformin is not FDA approved for weight loss

- 128 first-episode schizophrenia patients
- Clozapine, olanzapine, risperidone, or sulpiride continued throughout study
- Patients had gained 10% of body weight in 1st year of treatment
- Compared metformin 750 mg/day, lifestyle change, and placebo
Metformin Treatment

Wu et. JAMA 2008; 299:185
Treatment Recommendations

1. Monitor metabolic parameters
2. Encourage diet and exercise
3. Consider alternative antipsychotic, alone or in combination
4. Consider dose reduction
5. Consider metformin