More Than Just Weight Gain? An Examination of Antipsychotic Induced Insulin Resistance

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Objectives:
1) Describe glucose regulation and the mechanisms of insulin resistance
2) Apply appropriate consideration and monitoring to the use of atypical antipsychotics
3) Evaluate the risks of atypical antipsychotic use in relation to insulin resistance based on available evidence
BACKGROUND

1) Second Generation Antipsychotic Agents (SGAs)\textsuperscript{1-5}

a) Place in therapy
   i) Indicated for the treatment of schizophrenia, bipolar disorder, agitation/aggression associated with schizophrenia, bipolar disorder, and autism, and as an adjunct for treatment resistant depression
   ii) Off-label uses include Obsessive-Compulsive disorder, Post traumatic stress disorder, personality disorders, pervasive development disorder, and Tourette's syndrome
   iii) In 2003, 3.2 million patients were prescribed antipsychotics, 2.3 million of which were taking SGAs, with an estimated annual cost of $2.63 billion for the ambulatory population\textsuperscript{6}
   iv) By 2007 the overall number of people prescribed antipsychotics rose to approximately 3.9 million and the estimated annual cost rose to $7.4 billion\textsuperscript{7}

b) Concerns and considerations
   i) There are multiple case reports of nonketotic hyperosmolar syndrome as well as diabetic ketoacidosis\textsuperscript{8-12}
   ii) All antipsychotics carry a black box warning regarding use for dementia related psychosis due to increased mortality associated with use in this population
   iii) SGAs are also associated with significant metabolic adverse effects (Table 1) and require regular monitoring for the metabolic syndrome (Table 2)\textsuperscript{13-21}

Table 1: Metabolic Abnormalities Associated with Atypical Antipsychotics\textsuperscript{19}

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight Gain</th>
<th>Risk for Diabetes</th>
<th>Worsening of Lipid Profile</th>
</tr>
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<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>Quetiapine</td>
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<td>+/-</td>
<td>+++</td>
</tr>
<tr>
<td>Risperidone</td>
<td>+++</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>+++</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>++</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Asenapine</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
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<td>Ziprasidone</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>+/-</td>
<td>-</td>
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</table>
Table 2: Metabolic Monitoring for Atypical Antipsychotics

<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>
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<tbody>
<tr>
<td>Personal/family history</td>
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<td></td>
<td></td>
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<tr>
<td>Weight (BMI)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Waist circumference</td>
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<td></td>
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<td>X</td>
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<tr>
<td>Blood pressure</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Fasting lipid profile</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
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</table>

2) Normal insulin action\(^{22,23}\)
   a) Stimulates glucose uptake and storage by peripheral tissues
   b) Suppresses gluconeogenesis in the liver and kidney
   c) Suppresses lipolysis in adipose tissue
   d) Decreases free fatty acid (FFA) concentration

Figure 1: Mechanism of glucose homeostasis.
3) Hyperglycemia\textsuperscript{22-28}
   a) Results from the breakdown of a complex system involving the pancreatic β-cells, muscles, adipose tissue, and the liver
   b) β-cells\textsuperscript{23}
      i) Significant hyperglycemia only develops when insulin secretion can no longer compensate for insulin resistance in peripheral tissues
         (1) In type 1 diabetes this is caused by β-cell destruction
         (2) In type 2 diabetes this is caused by β-cells burning out
      ii) C peptide is cleaved from proinsulin during insulin production
         (1) Equimolar amounts of C-peptide and insulin are released by β-cells
         (2) C peptide can be measured to monitor insulin production by the pancreas
   c) Muscles\textsuperscript{27}
      i) Responsible for approximately 80% of total body glucose uptake\textsuperscript{23}
      ii) Decreased uptake of glucose by skeletal muscles is seen in insulin resistance
   d) Adipose Tissue\textsuperscript{26,28}
      i) Free fatty acids (FFAs) are stored as triglycerides in adipose tissue
      ii) Small changes in insulin levels can have profound effects on plasma FFA concentrations
      iii) Increasing FFA concentrations will inhibit glucose uptake by the muscle and increase glucose production by the liver
   e) Liver\textsuperscript{28}
      i) Glycogen stores are the major source of glucose during periods of fasting
      ii) Insulin resistance or lack of insulin leads to
         (1) Decreased uptake and storage of glucose from the blood stream
         (2) Increased release of glucose due to gluconeogenesis even after a glucose load
Figure 2: Mechanism of normal glucose uptake by peripheral tissues.\textsuperscript{24} (1) Insulin binds to its receptor, (2) which in turn starts protein activation cascades including, (3) translocation of Glut-4 transporter to the plasma membrane and influx of glucose, (4) glycogen synthesis, (5) glycolysis, and (6) fatty acid synthesis.

4) Pathophysiology of Insulin Resistance\textsuperscript{22-29}
   a) Over exposure of tissues to insulin causes decreased insulin receptor sensitivity
   b) Weight gain
      i) Levels of visceral adipose tissue (VAT) have been shown to correlate with insulin resistance
      ii) VAT has a higher rate of lipolysis and FFA production compared to subcutaneous fat
      (1) FFAs release into the portal circulation and drain into the liver
      (2) Stimulates production of very low density lipoproteins
      iii) Adipose cells produce adiponectin and inflammatory cytokines TNF-\(\alpha\) and IL-6
         (1) Adiponectin is a hormone which improves insulin sensitivity
            (a) Produced in decreasing amounts as obesity increases
            (b) Counterbalances TNF-\(\alpha\)
      iv) Obese nondiabetic patients have been shown to have the same levels of insulin resistance as do lean type 2 diabetic patients
   c) Inflammation\textsuperscript{29}
      i) Insulin resistance has been associated with chronic low grade inflammation and expression of several different cytokines
      ii) TNF-\(\alpha\), IL-1, IL-18, and IL-6 are cytokines produced in adipocytes
         (1) Levels increase with increasing obesity
         (2) These cytokines activate intracellular pathways to inhibit insulin receptors thus leading to increased insulin resistance (Figure 3)
Figure 3: Intracellular regulation of insulin resistance.\textsuperscript{29}

5) Possible Mechanisms of SGA Induced Insulin Resistance
   a) SGA induced weight gain associated with H\textsubscript{1} histamine, M\textsubscript{3} muscarinic, and 5HT\textsubscript{2C} serotonin receptor antagonism\textsuperscript{1,2}
   b) Direct effects of SGAs on insulin resistance may be mediated by several actions\textsuperscript{30}
      i) The role of 5HT\textsubscript{2A} receptors has not been clearly defined
         (1) Antagonism at 5HT\textsubscript{2A} receptors may decrease the number of glucose
             transporters found in the cell membrane of peripheral tissue cells
         (2) Antagonism at 5HT\textsubscript{2A} receptors has also been found to improve insulin induced
             capillary recruitment in skeletal muscle which improves glucose uptake
      ii) Some SGAs may also directly inhibit the insulin receptors in peripheral tissues
          leading to decreased effects of insulin on these tissues\textsuperscript{31-35}
      iii) Antagonism of M\textsubscript{3} muscarinic may also play a more direct role in insulin resistance
           beyond weight gain\textsuperscript{31-35}
          (1) Antagonism of M\textsubscript{3} receptors on β-cells may suppress insulin production
          (2) Inhibition of sympathetic and parasympathetic cholinergic pathways in the liver
               may disrupt glucose regulation there
Table 3: Antipsychotic Receptor Binding Affinity (Ki)\textsuperscript{36}

<table>
<thead>
<tr>
<th></th>
<th>Dopamine $D_2$</th>
<th>Serotonin 5-HT\textsubscript{2A}</th>
<th>Dopamine $D_1$</th>
<th>Alpha 1</th>
<th>Alpha 2</th>
<th>Histamine $H_1$</th>
<th>Muscarinic $M_1$</th>
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<tr>
<td>Aripiprazole</td>
<td>0.34</td>
<td>3.4</td>
<td>265</td>
<td>57</td>
<td>-</td>
<td>61</td>
<td>&gt;10,000</td>
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<tr>
<td>Asenapine</td>
<td>1.3</td>
<td>0.06</td>
<td>1.4</td>
<td>1.2</td>
<td>1.2</td>
<td>6.2</td>
<td>8128</td>
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<tr>
<td>Paliperidone</td>
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<td>1.2</td>
<td>-</td>
<td>10</td>
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<td>3.4</td>
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<td>Risperidone</td>
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<td>0.5</td>
<td>430</td>
<td>2</td>
<td>56</td>
<td>20</td>
<td>&gt;10,000</td>
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<tr>
<td>Haloperidol</td>
<td>4</td>
<td>36</td>
<td>45</td>
<td>6.2</td>
<td>3800</td>
<td>1890</td>
<td>&gt;20,000</td>
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<tr>
<td>Ziprasidone</td>
<td>5</td>
<td>0.4</td>
<td>525</td>
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<td>154</td>
<td>50</td>
<td>&gt;1,000</td>
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<td>Iloperidone</td>
<td>6.3</td>
<td>5.6</td>
<td>216</td>
<td>-</td>
<td>-</td>
<td>473</td>
<td>&gt;1,000</td>
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<tr>
<td>Olanzapine</td>
<td>11</td>
<td>4</td>
<td>31</td>
<td>19</td>
<td>230</td>
<td>7</td>
<td>1.9</td>
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<tr>
<td>Clozapine</td>
<td>126</td>
<td>16</td>
<td>85</td>
<td>7</td>
<td>160</td>
<td>6</td>
<td>1.9</td>
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<tr>
<td>Quetiapine</td>
<td>160</td>
<td>295</td>
<td>455</td>
<td>7</td>
<td>2500</td>
<td>11</td>
<td>120</td>
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METHODS FOR ASSESSING INSULIN RESISTANCE

1) Glucose Clamp Techniques\textsuperscript{37}
   a) Used to measure glucose metabolism or insulin sensitivity
   b) Hyperglycemic clamp is a way to quantify beta-cell response to glucose\textsuperscript{37}
      i) Raise glucose concentration to 125 mg/dL above optimal glucose level by giving an infusion of glucose
      ii) Give continuous infusion of glucose to keep blood glucose at a constant level
      iii) Measure GIR to determine how fast the body is metabolizing glucose
      iv) Advantage over the OGTT is that the time course for the amount of glucose metabolized can be quantified
   c) Hyperinsulinemic euglycemic clamp is a way to quantify insulin sensitivity\textsuperscript{37}
      i) Plasma insulin concentration is raised to approximately 100 muU/ml by infusing insulin through a peripheral vein
      ii) Variable rates of continuous infusion of a 20% glucose solution are used to keep plasma glucose concentration constant at a normal level
      iii) Glucose infusion rate (GIR) equal to the amount of glucose taken up by body tissues
         (1) Measures insulin sensitivity by measuring the amount of glucose needed to compensate for increased insulin levels
         (2) GIR during the last 30 minutes of the test usually determines insulin sensitivity
            (a) High GIR (7.5 mg/min or higher) indicates insulin sensitivity
            (b) Low GIR (4.0 mg/min or lower) indicates insulin resistance
            (c) Intermediate GIR (4.0 and 7.5 mg/min) is nonspecific, but may indicate glucose intolerance
      iv) Advantage over the insulin tolerance test (ITT) is that the danger of hypoglycemia as well as the neuroendocrine response to it is avoided giving a more reliable estimate of tissue insulin sensitivity

2) Glucose Tolerance Tests\textsuperscript{37}
   a) Oral glucose tolerance test
      i) Commonly used to test for diabetes or insulin resistance
      ii) Patient in a fasting state is given a 75 g oral glucose load and has their blood glucose checked two hours after the glucose load
   b) Mixed meal tolerance test
      i) Uses a milkshake-like drink which contains fats and protein in addition to the glucose load provided
      ii) May hold a lower risk of reactive hypoglycemia than the OGTT
GLUCOSE CLAMP TRIALS USING SHORT DURATION TREATMENT

1) Effect of Olanzapine on Insulin Resistance in Sprague-Dawley Rats


<table>
<thead>
<tr>
<th>Purpose</th>
<th>To assess the acute effects of olanzapine on specific measures of insulin sensitivity and secretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Non-blinded, placebo controlled, animal trial</td>
</tr>
<tr>
<td>Enrollment</td>
<td>Male, Sprague-Dawley rats weighing between 300 to 325 g</td>
</tr>
</tbody>
</table>
| Methods | • Both groups:  
  - Either hyperglycemic clamp or hyperinsulinemic-euglycemic clamp was done 3 days after catheter placement surgery  
  - Rats were fasted overnight prior to the clamp procedure  
    - Given 3 mg/kg of olanzapine subcutaneously or vehicle (1% acetic acid)  
  - Hyperinsulinemic-euglycemic clamp  
    - Continuous infusion of insulin at 10 μL/min  
    - Glucose levels measured every 5 minutes throughout the 220 minute clamp period and GIR adjusted to maintain euglycemia  
    - Exogenous glucose was radiolabeled in order to be able to tell it apart from endogenous glucose  
    - Drug or vehicle were given 90 minutes after the clamp began  
    - Plasma samples were taken every 10 minutes for 30 minute prior to the clamp period, 30 minutes prior to injection, and from 100-130 minutes after injection  
  - Hyperglycemic clamp  
    - Drug or vehicle were given 90 minutes before the clamp began  
    - Then a glucose bolus was given to elevate plasma levels to >300 mg/dL and a continuous infusion of glucose was given to maintain plasma glucose at approximately 300 mg/dL for an additional 90 minutes after injection  
    - Plasma samples were taken every 10 minutes after injection  
  - Second hyperglycemic clamp  
    - A second, smaller clamp was done because olanzapine elevated plasma glucose prior to the original clamp and may have confounded effects on insulin secretion  
    - Plasma glucose was sampled every 10 minutes after olanzapine injection until 2 consecutive readings were observed to be 10 to 20 mg/dL above the basal plasma glucose level  
    - Hyperglycemic clamp was then initiated as above |
| Outcomes | • Hyperinsulinemic-euglycemic clamp  
  - FFA levels  
  - Calculated GIR, rate of appearance of glucose (R_A), and rate of glucose disappearance (R_D)  
  • Hyperglycemic clamp  
    - GIR, insulin, and C peptide levels |
| Statistics | • Used t tests or ANOVA for repeated measurements, as appropriate  
  • Significance was accepted at P ≤ 0.05 |
| Results | • There were 8 rats per treatment and control group  
  - There were only 6 rats in the second hyperglycemic clamp |
• Hyperinsulinemic-euglycemic clamp
  o There were no differences between groups during the basal/pre-injection period
  o Olanzapine caused a marked decrease in GIR (olanzapine, 91 ± 7 μL/kg per minute; vehicle, 199 ± 5 μL/kg per minute; P < 0.001)
  o Olanzapine increased Rb (6 ± 0.5 vs. 3 ± 0.5 mg/kg per minute for olanzapine and vehicle groups, respectively; P = 0.04)
  o Olanzapine caused a decrease in Ro (olanzapine, 22 ± 0.9 mg/kg per minute; vehicle, 35 ± 0.6 mg/kg per minute; P < 0.001)
  o No difference in FFA levels was seen between the groups

• Hyperglycemic clamp
  o Basal insulin and C peptide levels were similar between the two groups
  o Ninety minutes after injection, rats treated with olanzapine exhibited marked hyperglycemia (olanzapine, 209 ± 11 mg/dL; vehicle, 136 ± 4 mg/dL; P < 0.001)
    ▪ The second hyperglycemic clamp did not find a difference in basal hyperglycemia
  o Glucose infusion rate was decreased in the olanzapine treatment group (P < 0.001)
  o Mean plasma insulin levels of the olanzapine group were 230 ± 16 pM, significantly lower than that of the vehicle group (465 ± 28 pM; P = 0.002)
  o C-peptide assay showed a similar decrease for rats treated with olanzapine (2.2 ± 0.2 nM vs. vehicle, 4.0 ± 0.2 nM; P = 0.04)
  o The supplementary olanzapine group (i.e., without hyperglycemia before the clamp) also displayed decreased plasma insulin and C-peptide (insulin, 264 ± 17 pM, P = 0.02; C-peptide, 2.7 ± 0.1 nM, P = 0.03)

Conclusions
• Olanzapine has a direct and rapid impact not only on insulin sensitivity but also on insulin secretion
  o A single injection decreased whole-body insulin sensitivity, inducing hepatic and peripheral insulin resistance as well as stimulated direct hyperglycemia and impaired pancreatic β-cell function
• This study provides compelling evidence that at least part of SGA-associated metabolic side effects relate to direct, acute effects as opposed to increased weight gain over the course of treatment

Strengths
• Well designed study utilizing radiolabeled tracer analysis
• Placebo controlled
• Looked at both effects on insulin resistance and pancreatic β-cell function

Limitations
• Study done in rats
• Small sample size
• Only tested olanzapine
Figure 4: Effect of a single subcutaneous dose of olanzapine on (A) GIR, (B) RA, (C) RD, and (D) insulin levels during a hyperinsulinemic-euglycemic clamp.

Figure 5: Effect of a single subcutaneous dose of olanzapine on (A) plasma glucose levels, (B) GIR, (C) plasma insulin, and (D) C-peptide levels during a 90-minute basal period followed by a hyperglycemic clamp.
2) Clozapine vs. Olanzapine vs. Risperidone vs. Ziprasidone in Wistare-Han Rats


| Purpose | To investigate whether antipsychotics can acutely cause metabolic effects before any change in body composition |
| Design | Non-blinded, placebo controlled, parallel group, animal trial |
| Enrollment | Male, Wistar-Han rats weighing between 280 to 350 g |
| Methods | • Hyperinsulinemic-euglycemic clamp was done 5-7 days after catheter placement surgery  
  o Rats were fasted overnight prior to the clamp procedure  
  • First hyperinsulinemic-euglycemic clamp  
  o Continuous infusion of insulin at 3 mU/kg min  
  o Continuous infusion of somatostatin at 3 μg/kg min to inhibit endogenous insulin secretion  
  o Glucose levels measured every 5-10 minutes throughout the clamp period and GIR adjusted to maintain euglycemia (~120 mg/dL)  
  o Drug or vehicle were given once steady state glucose concentrations were achieved  
  ▪ Three consecutive glucose concentrations between 110-130 mg/dL without change in GIR  
  ▪ Clozapine doses of 1, 3.2, or 10 mg/kg were used  
  ▪ Olanzapine doses of 1, 3.2, or 10 mg/kg were used  
  ▪ Ziprasidone doses of 3.2, 10, or 32 mg/kg were used  
  ▪ Risperidone dose of 2 mg/kg was used  
  o Plasma samples were taken every 10 minutes prior to injection and for 120 minutes after injection  
  • Second hyperinsulinemic-euglycemic clamp  
  o All steps were the same as in the first clamp except  
  ▪ Risperidone was not used due to lack of effect on GIR in the first clamp  
  ▪ Doses of 10 mg/kg were used for all other treatments  
  ▪ Exogenous glucose was radiolabeled in order to monitor tissue uptake in all groups |
| Outcomes | • Both hyperinsulinemic-euglycemic clamps  
  o Calculated GIR, rate of appearance of glucose (R\text{A}), and rate of glucose disappearance (R\text{D}) |
| Statistics | • Used Fischer’s exact test or ANOVA for repeated measurements, as appropriate  
  • Significance was accepted at P ≤ 0.05 |
| Results | • There were 2-8 rats per treatment and control group  
  • First hyperinsulinemic-euglycemic clamp  
  o Clozapine and olanzapine (3.2 and 10 mg/kg doses) caused a large, dose-dependent reduction in GIR following a single dose  
  o No significant differences in GIR were seen with either risperidone or ziprasidone (even with ziprasidone doses up to 32 mg/kg)  
  • Second hyperinsulinemic-euglycemic clamp  
  o Clozapine and olanzapine, but not ziprasidone caused significant insulin resistance as indicated by a large fall in GIR following a single 10 mg/kg dose |
Significant reduction in R\textsubscript{d} was seen with olanzapine, (17.0 ± 5.1% reduction; P < 0.03) and with clozapine, (34.5 ± 4.4% reduction; P < 0.001) when compared to vehicle or ziprasidone treatment

- HGP was significantly increased by a single dose of olanzapine and clozapine (18.5- and 22.7-fold increase, respectively; P < 0.001)

**Conclusions**
- Showed acute negative effects of olanzapine and clozapine, but not ziprasidone or risperidone, on whole-body insulin sensitivity that are independent of drug-induced changes in body composition
- Provided convincing evidence that the primary target tissue for the drug-induced insulin resistance is the liver, as demonstrated by a large increase in HGP following single doses of olanzapine or clozapine

**Strengths**
- Well designed study utilizing radiolabeled tracer analysis
- Placebo controlled
- Tested several different atypical antipsychotics
- Tested several different doses of antipsychotics

**Limitations**
- Study done in rats
- Small sample size
- Only used one dose of risperidone in the initial hyperinsulinemic-euglycemic clamp

**Figure 6:** Dose-dependent reduction in GIR with clozapine and olanzapine but not ziprasidone or risperidone treatment in normal rats. *P < 0.01; ≠P < 0.0001 vs. vehicle.\textsuperscript{31}

### Purpose
To evaluate the effect of olanzapine or risperidone treatment on β-cell function in healthy volunteers

### Design
Randomized, single-blind, placebo controlled, parallel group, hyperglycemic clamp trial

### Enrollment
- **Inclusion**
  - Healthy men and women between the ages of 18 and 65 years, without preexisting conditions that could significantly alter glycemic status
  - History of normal glucose metabolism, a normal physical examination, a fasting glucose below 6.1 mmol/L, and a body mass index (BMI) of 30 kg/m² or less
- **Exclusion**
  - Significant comorbid illness, recent hospitalization, a first degree family history of type 1 or type 2 diabetes mellitus, previous exposure to antipsychotic medication, or current use of recreational drugs
  - Pregnant or lactating women and sexually active women of childbearing age not actively practicing birth control

### Methods
- Hyperglycemic clamp was done at baseline and after 15-17 days of treatment
- Subjects admitted 48 hours prior to clamp procedure for diet/exercise stabilization
- Randomized to one of three treatments
  - Olanzapine 10 mg/day
  - Risperidone 4 mg/day
  - Placebo
- Glucose levels measured every 5 minutes throughout the 240 minute clamp period and GIR adjusted to maintain hyperglycemia at 11.1 mmol/L
  - Insulin and C peptide levels were taken throughout the clamp period

### Outcomes
- **Primary endpoint**
  - Pancreatic β-cell function as measured by change in glucose, insulin, and C peptide
- **Secondary endpoint**
  - Weight gain from baseline
- **Other analyses**
  - Ratio of mean GIR (M) to average insulin level (I)

### Statistics
- ANOVA model was used to examine the baseline to end point changes in fasting measures (glucose, insulin, and C peptide)
- T test and linear regression were used for comparison of treatment group outcomes to placebo group outcomes
- Used a two-sided α with 5% level of significance

### Results
- Screened 73 subjects and 48 were included
  - Olanzapine = 17, risperidone = 13, Placebo = 18
- No significant differences between groups at baseline, except there were no females and fewer subjects in the risperidone group
- Weight, fasting glucose, fasting insulin, and fasting C peptide increased significantly in both treatment groups from baseline (Table 1)
- There were no significant differences in GIR or insulin levels between the groups despite an increase in insulin levels with active treatment (Table 2)
  - There were no significant differences between active treatment and placebo with regard to insulin sensitivity index
Table 1: Changes in weight and fasting measures of glucose, insulin, and C peptide

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Weight (kg)</th>
<th>Glucose (mmol/L)</th>
<th>Insulin (pmol/L)</th>
<th>C peptide (nmol/L)</th>
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<tr>
<td>Olanzapine</td>
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<td>0.02</td>
<td>19.8†,‡</td>
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<td>Risperidone</td>
<td>3.1†,‡</td>
<td>0.14</td>
<td>15.0†</td>
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<td>Placebo</td>
<td>0.5</td>
<td>-0.08</td>
<td>-13.8</td>
<td>-0.15‡</td>
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† = P<0.05 within group, ‡ = P<0.05 vs. placebo

Table 2: Baseline to endpoint changes in GIR, insulin levels, and insulin sensitivity index

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Change in M [mmol/min x kg (x10^{-3})]</th>
<th>Change in I (pmol/L)</th>
<th>Change in M/I (x10^{-5})</th>
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<td>81.6</td>
<td>-3.7</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.3</td>
<td>-112.6</td>
<td>0.92</td>
</tr>
</tbody>
</table>

† = P<0.05 within group

Conclusions
- Found no evidence that patients treated with SGAs olanzapine and risperidone, experienced a direct impairment of insulin secretion
  - The absence of a decrease in insulin or C peptide levels during the hyperglycemic clamps strongly argues against a direct negative effect of these antipsychotic drugs on pancreatic β-cell function
- Healthy volunteers treated with olanzapine or risperidone for 15–17 days exhibited very similar changes in insulin levels (fasting and clamp) that appear to be largely related to weight gain
- These data do not support a direct effect of olanzapine or risperidone to decrease insulin secretion or insulin sensitivity

Strengths
- Randomized
- Placebo controlled
- Took weight changes into consideration with statistics

Limitations
- Small sample size
- Healthy non-psychiatric subjects were studied
  - The prevalence of diabetes in schizophrenics appears to exceed that in the general population
- Subjects treated for 15-17 days
  - Unknown when last dose of antipsychotic was taken
- Subjects were asked, but not assessed, for diet/exercise control in between clamp procedures
4) Olanzapine Vs. Risperidone in Humans, Part 2

|---|---|---|

**Purpose**
- To evaluate insulin sensitivity in healthy subjects treated with olanzapine or risperidone

**Design**
- Randomized, single-blind, placebo controlled, parallel group, hyperglycemic clamp trial

**Enrollment**
- **Inclusion**
  - Healthy men and women between the ages of 18 and 65 years, without preexisting conditions that could significantly alter glycemic status
  - History of normal glucose metabolism, a normal physical examination, BMI between 20–27 kg/m², fasting glucose of 100 mg/dL (5.6 mmol/liter) or less, and no personal or family history of diabetes
- **Exclusion**
  - Significant comorbid illness, recent hospitalization, previous exposure to antipsychotic medication, or current use of recreational drugs
  - Pregnant or lactating women and sexually active women of childbearing age not actively practicing birth control

**Methods**
- Hyperinsulinemic euglycemic clamp was done at baseline and after 21 days of treatment
  - Subjects admitted 72 hours prior to clamp procedure for diet/exercise stabilization
  - Clamped blood glucose at 90 mg/dL using continuous infusion of insulin and glucose
- Randomized to one of three treatments
  - Olanzapine 10 mg/day
  - Risperidone 4 mg/day
  - Placebo
- Subjects were also given 2 MMTTs 4 hours apart after 21 days of treatment
  - Blood glucose and insulin levels were measured hourly beginning 1 hour before the first meal and continuing for 3 hours after the second meal

**Outcomes**
- **Primary endpoint**
  - Calculated GIR, rate of appearance of glucose (Rₐ), and rate of glucose disappearance (R₀)
- **Secondary endpoint**
  - Blood glucose and insulin levels

**Statistics**
- ANOVA model was used to examine the change from baseline to endpoint in insulin sensitivity index
- T test and linear regression were used for comparison of treatment group outcomes to placebo group outcomes
- Used a two-sided α with 5% level of significance

**Results**
- 64 subjects were included
- Olanzapine = 22, risperidone = 14, Placebo = 19 completed the trial
- No significant differences between groups at baseline
- Weight increased significantly in both treatment groups from baseline to the end of the study period
- There were no significant differences between active treatment and placebo with regard to insulin sensitivity index
There were no significant differences in peak glucose or insulin levels after MMTT between the groups

**Conclusions**
- Found no evidence that patients treated with the atypical antipsychotic drugs, olanzapine and risperidone, experienced a decrease in whole body insulin sensitivity or maximal tissue responsiveness to insulin.
- Results of the MMTT also suggest that treatment with these medications was not associated with clinically significant changes in overall integrated glucose metabolism after the ingestion of a mixed composition meal.
- Overall, results of this study do not support the hypothesis that olanzapine or risperidone has an acute, direct effect to decrease insulin sensitivity.

**Strengths**
- Randomized
- Placebo controlled
- Used an MMTT in addition to the clamp to check for insulin resistance

**Limitations**
- Small sample size
- Healthy non-psychiatric subjects were studied
  - The prevalence of diabetes in schizophrenics appears to exceed that in the general population
- Subjects treated for 21 days
  - Unknown when last dose of antipsychotic was taken
- Subjects were asked, but not assessed, for diet/exercise control in between clamp procedures
CONCLUSIONS

1) Conclusions
   a) The mechanisms leading to insulin resistance are multifaceted and involve the breakdown of a complex system which includes the pancreatic β-cells, skeletal muscle, adipose tissue, the liver, and inflammatory processes.
   b) Insulin resistance and hyperglycemia has been seen shortly after initiating SGA therapy
      i) There are multiple case reports of nonketotic hyperosmolar syndrome as well as diabetic ketoacidosis
      ii) At least one death has been attributed to suspected SGA induced DKA
   c) There is conflicting data on what role SGAs may play in causing clinically significant non-weight medicated insulin resistance
      i) No clear mechanism of SGA induced insulin resistance has been elucidated at present
      ii) Glucose clamp data in rats gives an indication that clozapine and olanzapine may have rapid and direct effects on insulin sensitivity, glucose production via the liver, and insulin production via pancreatic β-cells
      iii) Clamp data in humans did not find any direct, non-weight medicated impact of SGAs on either insulin resistance or β-cell insulin production
   d) Trials utilizing other glucose tolerance techniques in non-obese schizophrenic patients treated with antipsychotics for several months or more, have found significant weight-independent impacts of SGAs on glucose homeostasis
   e) Further studies should be conducted in larger, mentally ill patient populations, utilizing glucose clamp techniques, to determine if a clinically significant impact does indeed exist
References:


Appendix A

Abbreviations:
Ari: Aripiprazole
Asen: Asenapine
BMI: Body Mass Index
Cloz: Clozapine
FFA: Free Fatty Acid
GIR: Glucose Infusion Rate
HGP: Hepatic Glucose Production
IL-6: Interleukin-6
Ilop: Iloperidone
ITT: Insulin Tolerance Test
MMTT: Mixed Meal Tolerance Test
OGTT: Oral Glucose Tolerance Test
Olan: Olanzapine
Pali: Paliperidone
Quet: Quetiapine
RA: Rate of appearance of glucose
RD: Rate of disappearance of glucose
Ris: Risperidone
SGA: Second Generation Antipsychotic
TNF-α: Tumor Necrosis Factor-α
VAT: Visceral Adipose Tissue
VLDL: Very Low Density Lipoprotein
Zip: Ziprasidone
<table>
<thead>
<tr>
<th>Author</th>
<th>Type of Trial</th>
<th>Population</th>
<th>Intervention</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chintoh AF, et al. 2008</td>
<td>Non-blinded, placebo controlled, animal trial</td>
<td>Male, Sprague-Dawley rats weighing between 300 to 325 g</td>
<td>Either hyperglycemic clamp or hyperinsulinemic-euglycemic clamp in rats treated with 3 mg/kg of olanzapine or vehicle subcutaneously Exogenous glucose was radiolabeled in order to monitor tissue uptake in all groups</td>
<td>Olanzapine caused a marked decrease in GIR (91 ± 7 μL/kg per minute vs. 199 ± 5 μL/kg per minute; P &lt; 0.001) Olanzapine increased R_{A} (6 ± 0.5 vs. 3 ± 0.5 mg/kg per minute; P = 0.04) Olanzapine caused a decrease in R_{D} (22 ± 0.9 mg/kg per minute vs. 35 ± 0.6 mg/kg per minute; P &lt; 0.001)</td>
<td>Olanzapine has a direct and rapid impact not only on insulin sensitivity but also on insulin secretion</td>
</tr>
<tr>
<td>Houseknecht KL, et al. 2007</td>
<td>Non-blinded, placebo controlled, parallel group, animal trial</td>
<td>Male, Wistare-Han rats weighing between 280 to 350 g</td>
<td>First hyperinsulinemic-euglycemic clamp  ▪ Clozapine doses of 1, 3.2, or 10 mg/kg were used ▪ Olanzapine doses of 1, 3.2, or 10 mg/kg were used ▪ Ziprasidone doses of 3.2, 10, or 32 mg/kg were used ▪ Risperidone dose of 2 mg/kg was used Second hyperinsulinemic-euglycemic clamp ▪ Risperidone was not used due to lack of effect on GIR in the first clamp ▪ Doses of 10 mg/kg were used for all other treatments ▪ Exogenous glucose was radiolabeled in order to monitor tissue uptake in all groups</td>
<td>First hyperinsulinemic-euglycemic clamp  ▪ Clozapine and olanzapine (3.2 and 10 mg/kg doses) caused a large, dose-dependent reduction in GIR following a single dose Second hyperinsulinemic-euglycemic clamp ▪ Clozapine and olanzapine, but not ziprasidone caused significant insulin resistance as indicated by a large fall in GIR</td>
<td>Showed acute negative effects of olanzapine and clozapine, but not ziprasidone or risperidone, on whole-body insulin sensitivity that are independent of drug-induced changes in body composition</td>
</tr>
<tr>
<td>Sowell MO, et al. 2002</td>
<td>Randomized, single-blind, placebo controlled, parallel group, hyperglycemic clamp trial</td>
<td>Healthy men and women between the ages of 18 and 65 years, without preexisting conditions that could significantly alter glycemic status ▪ Olanzapine = 17 ▪ Risperidone = 13 ▪ Placebo = 18</td>
<td>Hyperglycemic clamp was done at baseline and after 15-17 days of treatment  ▪ Olanzapine 10 mg/day ▪ Risperidone 4 mg/day ▪ Placebo</td>
<td>▪ Weight, fasting glucose, fasting insulin, and fasting C peptide increased significantly in both treatment groups from baseline. ▪ There were no significant differences in GIR or insulin levels between the groups despite an increase in insulin levels with active treatment</td>
<td>Found no evidence that patients treated with the atypical antipsychotic drugs, olanzapine and risperidone, experienced a direct impairment of insulin secretion</td>
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</table>

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<table>
<thead>
<tr>
<th>Study Authors and Year</th>
<th>Study Design</th>
<th>Population</th>
<th>Treatment Details</th>
<th>Findings</th>
</tr>
</thead>
</table>
| Sowell MO, et al. 2003 | Randomized, single-blind, placebo controlled, parallel group, hyperinsulinemic euglycemic clamp trial | Healthy men and women between the ages of 18 and 65 years, without preexisting conditions that could significantly alter glycemic status | - Olanzapine = 22
- Risperidone = 14
- Placebo = 19 | - Weight increased significantly in both treatment groups from baseline to the end of the study period
- There were no significant differences between active treatment and placebo with regard to insulin sensitivity index
- Found no evidence that patients treated with the atypical antipsychotic drugs, olanzapine and risperidone, experienced a decrease in whole body insulin sensitivity or maximal tissue responsiveness to insulin |
| Ader M, et al 2005 | Randomized, non-blinded, placebo controlled, animal trial | Male, mongrel dogs weighing an average of 28 kg | - Olanzapine = 10
- Risperidone = 10
- Placebo = 6 | - No significant changes in weight gain
- Significant shift in fat distribution with olanzapine (P = 0.009)
- Significant decrease in hepatic insulin sensitivity with olanzapine (P = 0.009) | Found that treatment with olanzapine, but not risperidone, caused marked hepatic insulin resistance and abolished the compensatory β-cell response to obesity-induced insulin resistance |
| Newcomer JW, et al 2002 | Cross sectional, controlled trial | Forty eight schizophrenic patients, age and BMI matched, with thirty one untreated healthy control subjects | - Olanzapine = 12
- Risperidone = 10
- Clozapine = 9
- Typical = 17
- Control = 31 | - Baseline fasting insulin was significantly higher in the olanzapine and clozapine groups (P < 0.005) | Indicates that newer antipsychotic treatments such as clozapine and olanzapine, in comparison with typical agents, are associated with adverse effects on plasma glucose regulation, which can vary in severity independent of adiposity and age |
| Henderson DC, et al 2005 | Cross sectional trial | Thirty six schizophrenic patients, BMI matched | - Olanzapine = 12
- Clozapine = 12
- Risperidone = 12 | - Baseline fasting insulin was significantly higher in the olanzapine and clozapine groups (P = 0.03)
- Insulin resistance was significantly higher in the olanzapine and clozapine groups (P = 0.001) | Found that non-obese clozapine and olanzapine treated groups displayed significant insulin resistance compared with risperidone treated subjects |
| Henderson DC, et al 2006 | Cross sectional, controlled trial | Fifteen schizophrenic patients, BMI matched, to nine untreated healthy control subjects | A intravenous glucose tolerance test was given to subjects after a 12 hour fast  
• Avg. Olanzapine 18 mg/day  
• Avg. Quetiapine 607 mg/day  
Glucose and insulin were measured from 10 minutes prior to 180 minutes after glucose load | • Baseline fasting glucose was significantly higher in the olanzapine group ($P = 0.01$)  
• Insulin resistance was significantly higher in the olanzapine group ($P = 0.01$)  
Found that non-obese olanzapine treated subjects exhibited significantly more insulin resistance compared to quetiapine and control subjects |
|------------------------|---------------------------------|----------------------------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|