Several metabolic and cardiovascular effects may be exacerbated by second generation antipsychotics. This issue of CLIPs briefly summarizes an article that examines second-generation antipsychotics (SGAs) and their potential to cause or worsen cardiovascular disease secondary to weight gain, hyperglycemia, hyperlipidemia, and other cardiovascular effects. If you need further information, please contact the Samford University Drug Information Service at (205) 726-2659.


Weight Gain
- Obesity incidence is 40%-60% in medicated individuals with schizophrenia, which is double the percentage of the general population.
- Weight gain associated with SGAs has been linked to the following mechanisms: 5-HT2c antagonism leading to increased appetite, sedation and decreased activity through histamine (H1) antagonism and medication-induced hyperprolactinemia.
- The following table displays drug-induced weight gain ranges with various SGAs in clinical trials of 12 weeks duration.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Associated Weight Gain</th>
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<tbody>
<tr>
<td>clozapine and olanzapine</td>
<td>4.1 to 9.2 kg</td>
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<tr>
<td>quetiapine, risperidone, and paliperidone</td>
<td>1.8 to 4.6 kg</td>
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<tr>
<td>ziprasidone and aripiprazole</td>
<td>Little to no weight gain</td>
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</tbody>
</table>

- Weight gain is greatest within the first three months of SGA therapy.
- Recommend monitoring weight at baseline at initiation of SGA, every 4 weeks for 3 months of therapy, then every 4-6 months if weight is stable.
- Regularly measure waist circumference for central obesity as it is associated with an increased risk for several cardiovascular disease (CVD) symptoms including hypertension, metabolic syndrome, coronary heart disease, stroke, diabetes, and sleep apnea.

Hyperglycemia
- Second-generation agents have been associated with glucose abnormalities leading to development of type 2 diabetes mellitus and rare reports of diabetic ketoacidosis (DKA) have been documented.
- Second-generation antipsychotic-related glucose abnormalities include insulin resistance secondary to weight gain. Redistribution of adipose tissue, central obesity and increased insulin resistance secondary to leptin interference on the hypothalamus, direct pancreatic effects leading to decreased beta-cell function, and elevated ghrelin levels leading to inhibition of insulin secretion and increased hepatic gluconeogenesis may occur.
- Clozapine and olanzapine are associated with the most severe development of hyperglycemia. Quetiapine and risperidone are associated with moderate hyperglycemia, while aripiprazole and ziprasidone are at the lowest risk for development of changes in glucose regulation.
- Abnormalities in glucose regulation most commonly occur within the first three months of therapy with approximately 4.7% to 6.9% of patients developing new onset type 2 diabetes upon initiating or switching between SGAs.
- Recommend monitoring fasting plasma glucose at baseline, at 12 weeks, and annually thereafter if glucose is within normal limits. Guidelines recommend hemoglobin A1C measurements if fasting glucose values are unavailable.
**Hyperlipidemia**
- Second-generation antipsychotic effects on lipids are less well studied. Possible mechanisms include associated weight gain and insulin resistance.
- Triglyceride, total cholesterol, and low-density lipoprotein (LDL) levels have been reported to increase with SGA use. High-density lipoproteins (HDLs) have been shown to decrease levels with SGAs.
- **Second-generation therapy appear to have the most pronounced effect on elevating triglyceride concentrations.**
- Clozapine and olanzapine have been shown to elevate triglycerides, total cholesterol and LDL levels more than other SGAs. Risperidone and quetiapine have reported moderate effects on lipid levels.
- Aripiprazole and ziprasidone have shown to have the least effect on worsening the lipid profile with some data supporting a potential for improvement of lipid concentrations with these agents.
- Recommendations for monitoring include a fasting lipid panel at baseline, and 12 weeks of therapy, and every 2-5 years thereafter if lipid values are within normal limits.

**Hyperprolactinemia**
- Females, children, and adolescents have been shown to be at a higher risk for developing antipsychotic-induced hyperprolactinemia.
- Elevated plasma prolactin concentrations are due to the blockade of dopamine receptors by SGAs, which is the predominant inhibiting factor of prolactin release.
- Dual inhibition of dopamine and 5-HT2 by SGAs may provide more selectivity for the mesolimbic pathway when compared to first-generation antipsychotics (FGAs), leading to decreased prolactin elevation.
- Risperidone and paliperidone have been associated with the most pronounced increases of prolactin concentrations while olanzapine-induced hyperprolactinemia is sparingly reported.
- After discontinuation of SGAs, elevated prolactin levels self-resolve within 48 to 96 hours. Depending on the half-life of the medication, it may take up to 3 weeks for prolactin levels to return to baseline.

**Cardiac Adverse Effects**
- QT changes, widened QRS complexes, orthostatic hypotension, and syncope are the major cardiovascular concerns associated with SGAs.
- Ziprasidone, risperidone, olanzapine, and quetiapine have all been reported to produce QT prolongation with the possibility of developing torsades de pointes.
- Aripiprazole has not demonstrated QT prolongation effects, and may possibly shorten the interval.
- Individuals more likely to develop QT prolongation include the aged, females, and persons with cardiac history or electrolyte disturbances (hypokalemia and hypomagnesemia).
- Clozapine-induced myocarditis is a rare, but serious cardiac side effect that is associated with a rapid progression and a mortality rate as high as 50%. The vast majority of myocarditis cases are seen within the first 6 weeks of clozapine treatment.
- Orthostatic hypotension has been associated with a high incidence of occurrence with clozapine, quetiapine, and risperidone. Clozapine has a black box warning regarding risk for orthostasis and syncope. Orthostasis with clozapine is usually self-limiting.
- Electrolyte and ECG monitoring should occur after dose escalations and at 6-month intervals.

**Conclusions**
- Olanzapine and clozapine have been associated with the most evidence involving the risk of weight gain and the development or worsening of diabetes and lipid profile.
- Aside from the ability of ziprasidone to lengthen the QT interval, both aripiprazole and ziprasidone have been associated with the least number of CVD effects. Both medications have even shown potential to possibly improve weight management and lipid profile.
- Monitoring for SGA-associated effects should include weight gain, waist circumference, blood pressure, fasting blood glucose or hemoglobin A1C, and lipid profile. If risk factors are present for QT prolongation, then patient should have ECGs checked regularly.

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