Lipid profile screening in second-generation antipsychotic users: the gap between policy and practice.

Despite advancements in treatment options and preventive strategies, cardiovascular disease (CVD) remains the leading cause of death in the United States (US).\(^1\) The burden of CVD is even higher among individuals with chronic mental illness.\(^2\) When compared to standard US population statistics, persons with serious mental illness have been shown to be more than three times more likely to die of CVD.\(^3\) Many reasons for this increased risk have been described. Individuals with mental illness are more likely to smoke, have a more sedentary lifestyle, have substance abuse problems, and be overweight or obese relative to a non-mentally ill population.\(^4\) Additionally, those with psychiatric disorders face significant institutional barriers for receiving high quality care for co-morbid medical conditions.\(^5\) Research suggests that individuals with chronic mental illness are significantly less likely to receive lifesaving interventions following acute myocardial infarction such as aspirin, beta-blockers, and angiotension-converting enzyme inhibitors.\(^6\) Finally, individuals with chronic mental illness have higher rates of diabetes, hypertension, hypercholesteremia, and obesity, all of which are independent risk factors for CVD.\(^7\)

While obesity, hypertension, dyslipidemia, and glucose intolerance are well known risk factors for CVD, their co-occurrence is becoming more prevalent. The clustering of these risk factors is termed metabolic syndrome and increases the risk for all cause mortality (relative risk (RR) = 1.27), CVD (RR = 1.65), and diabetes (RR=2.99).\(^7\) The prevalence of metabolic syndrome is higher in individuals with serious mental illness relative to the general population. While the overall population prevalence of metabolic syndrome in the US is estimated to be 24%, recent data suggest 43% of individuals with schizophrenia have metabolic syndrome.\(^8\) Many psychotropic medications used to treat serious mental illness cause weight gain, and likely also contribute to the risk of metabolic syndrome in this population. Additionally, studies suggest that mental illness may be independently associated with the development of CVD risk factors such as type 2 diabetes mellitus (T2DM), lipid abnormalities, weight gain, and obesity.\(^9,10\)

Second generation antipsychotics (SGA) have become first line agents for the treatment of schizophrenia, largely supplanting older first generation agents because of their perceived advantage for improving the negative symptoms of psychosis (e.g. apathy, anhedonia, flat affect) as well as having fewer acute extrapyramidal side effects (e.g. akathisia, parkinsonism, dystonic reactions) and late onset tardive dyskinesia. Recently, indications for their use have expanded rapidly to include the treatment of bipolar disorder, refractory major depression, irritability associated with autistic disorder, and late onset tardive dyskinesia. While the overall population prevalence of metabolic syndrome in the US is estimated to be 24%, recent data suggest 43% of individuals with schizophrenia have metabolic syndrome.\(^8\)

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Second generation antipsychotics have also been associated with hyperlipidemia, which primarily manifests through elevated triglycerides.\(^18\) Unfavorable effects of SGA on LDL and HDL cholesterol have also been documented.\(^18\) Similar to diabetes risk, evidence suggests that lipid abnormalities caused by SGAs are partly mediated through long term weight changes, although the exact process is not clearly understood and independent effects may exist that occur early in treatment and are not related to weight changes.\(^19\) Those SGAs known to produce the most dramatic increases in weight (clozapine, olanzapine), are also associated with the most pronounced effects on lipid profiles.\(^17\) Data from CATIE demonstrate that olanzapine is associated with the greatest weight gain (mean 9.4 lb), total cholesterol (9.7 mg/dL), and triglyceride (42.9 mg/dL) increase. Case reports and clinical trials support the assertion that quetiapine may be associated with increases in triglycerides and total cholesterol, however, the magnitude of these elevations is of questionable clinical relevance.\(^17\) Quetiapine treated patients in CATIE had increases of 5 and 19 mg/dL for total cholesterol and triglycerides respectively. While risperidone has been reported to be associated with modest weight gain, its impact on the lipid profile is unclear. Case reports have suggested that risperidone may be associated with small increases triglycerides and fasting cholesterol. Epidemiologic evidence and data from the CATIE trial suggest that risperidone is not associated with significant adverse lipid effects.\(^16,20\) Treatment with ziprasidone or aripiprazole have not been associated with significant weight gain or changes in lipid levels.\(^16,17,21\)

### Table 1 - Summarized metabolic effects of SGAs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight Gain</th>
<th>Risk for T2DM</th>
<th>Lipid effects</th>
</tr>
</thead>
<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>Risperidone</td>
<td>+</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Paliperidone (based on risperidone)(^+)</td>
<td>++</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>Iloperidone(^+)</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Asenapine(^+)</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**+increased risk**

**-no effect**

**D discrepant results**

\(^+\) based on limited data
Three new SGAs have been approved recently and long term metabolic safety data remain limited. Paliperidone (Invega®), the active metabolite of risperidone, is believed to have a similar adverse effect profile. Iloperidone (Fanapt®) is associated with modest weight gain (2kg in 4-6 week trials) and clinically insignificant changes in lipid profile and glucose chemistry. Prescribing information for asenapine (Saphris®) suggest it is associated weight increases (average of approximately 1-2 kg over 3 to 52 weeks). Serum lipid and glucose fluctuations were negligible. Table 1 was adapted from Newcomer and summarizes metabolic effects of SGAs.

In light of the metabolic risk signals, the U.S. Food and Drug Administration (FDA) issued class wide warnings in December of 2003 relating to the hyperglycemic effects of SGAs. The label changes recommended that patients with, or at risk for, diabetes be monitored closely following initiation with a SGA. In early 2004, a joint consensus statement issued by the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity was published reaffirming the risk articulated by FDA, summarized the other associated metabolic adverse effects associated with SGA use, and provided clear guidance about monitoring parameters for patients treated with SGAs. Their recommendations clearly state that all patients receiving SGAs, regardless of diagnosis, “should receive appropriate baseline [metabolic] screening and ongoing monitoring.” The Consensus Statement specifically recommended that fasting lipids be assessed at baseline and monitored regularly. Numerous studies, from before and after the Consensus Statement and involving a variety of commercially insured, Medicare and Veteran Affairs populations from the United States, have consistently shown that on average less than one-fifth of patients taking second-generation antipsychotics receive baseline lipid testing and less than one half receive on-going lipid monitoring.

The use of SGAs in children has been a growing concern because their expanded use in this population segment and the unique vulnerability of children to metabolic related adverse effects. A recent prospective observational cohort sought to clarify metabolic safety among children ages 4-19 who were new users of SGAs compared with children who refused treatment. After a median follow-up of 10 weeks, significant weight gain was observed with all studied SGA including olanzapine (8.5 kg), quetiapine (6.1 kg), risperidone (5.3 kg), and aripiprazole (4.4 kg), compared to 0.19 kg for non-treated subjects. Olanzapine was associated with significant increases in fasting glucose, insulin, total and LDL cholesterol, and triglycerides. Children receiving risperidone and quetiapine had significant increases in triglycerides. Qualitatively, all SGA, except aripiprazole, were shown to increase fasting glucose levels. In light of these data, the decision to use these agents in children and adolescents should be balanced against the limited evidence of efficacy in this population. Additionally, clinicians should exercise vigilant cardiometabolic monitoring especially in this vulnerable population.

Evaluting and managing modifiable CVD risk factors is of vital importance given the burden of CVD in patients with serious mental illness. Given the significant cardiometabolic risks associated with the use of SGAs, it is particularly troubling that rates of dyslipidemia and monitoring are so low. The scope and importance of metabolic surveillance to clinicians will only grow as the use of SGAs expand to treat other conditions (e.g. treatment resistant depression). All patients receiving SGAs should receive metabolic screening and weight change assessments, regardless of diagnosis or age, at baseline, 12 weeks, and annually thereafter.

References:

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23. Scott LJ. Iloperidone in schizophrenia. CNS Drugs 2009;23:867-80.

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