Practice Guidelines
Metabolic Syndrome: Evaluation, Monitoring and Recommended Interventions
2/4/2016
Title
Metabolic Syndrome: Evaluation, Monitoring and Recommended Interventions

Goal/What Do We Want to Achieve Through the Use of this Protocol
The purpose of this document is to provide guidance to Behavioral Health Medical Practitioners (BHMP) within the Cenpatico Integrated Care (Cenpatico) Network. This document describes guidelines for screening, monitoring and managing antipsychotic-induced metabolic abnormalities.

Target Audience
The target audience is medical personnel working within Cenpatico’s outpatient provider network. This includes physicians, nurse practitioners, physican assistants, registered nurses, licensed practical nurses and medical assistants.

Target Population
Members in an open episode of care taking medications with a high risk for metabolic syndrome that have been prescribed by a Cenpatico BHMP.

Background
Metabolic syndrome has been variously defined since 1998. Its prevalence has been noted to be rising worldwide. It is associated with an increased risk for cardiovascular disease and/or type II diabetes mellitus. The two most important risk factors noted for metabolic syndrome are central obesity and insulin resistance. Central obesity is defined as extra weight around the middle and upper parts of the body, i.e., an “apple-shaped” figure. Central or abdominal obesity is highly correlated with insulin resistance and metabolic syndrome. The parameter for central obesity metrics remain population and country specific. The core features of metabolic syndrome are recognized as obesity, atherogenic dyslipidemia, insulin resistance and hypertension.

Various medical and disease-focused organizations have attempted to reconcile the various definitions for metabolic syndrome. In 2009, the International Diabetes Federation (IDF), American Heart Association (AHA) and National Heart, Lung and Blood Institute (NHLBI) agreed to criteria for the clinical diagnosis of metabolic syndrome. ¹ Metabolic syndrome was defined as the presence of three of the following five criteria:

<table>
<thead>
<tr>
<th>Metabolic Syndrome Criteria</th>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated waist circumference</td>
<td>Population specific thresholds</td>
</tr>
<tr>
<td>Elevated triglycerides OR drug treatment for elevated triglycerides</td>
<td>levels greater than 150mg/dL</td>
</tr>
<tr>
<td>Decreased HDL cholesterol levels OR drug treatment for reduced HDL cholesterol</td>
<td>levels less than 40mg/dL in men levels less than 50mg/dL in women</td>
</tr>
<tr>
<td>Elevated blood pressure OR drug treatment for hypertension</td>
<td>Systolic pressures greater than 130mmHg Diastolic pressures greater than 85mmHg</td>
</tr>
<tr>
<td>Elevated fasting glucose levels OR drug treatment for elevated glucose</td>
<td>levels greater than 100mg/dL</td>
</tr>
</tbody>
</table>

It has been recommended that IDF parameters be used for non-Europeans and either the IDF or AHA/NHLBI parameters be used for people of European origin until more data are available.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Threshold for Waist Circumference</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHA/NHLBI</td>
<td>&gt; 102 cm (40.2 inches) for men</td>
</tr>
<tr>
<td></td>
<td>&gt; 88 cm (34.6 inches) for women</td>
</tr>
<tr>
<td>IDF</td>
<td>&gt; 94 cm (37.0 inches) for men</td>
</tr>
<tr>
<td></td>
<td>&gt; 80 cm (31.5 inches) for women</td>
</tr>
</tbody>
</table>

Individuals with schizophrenia and other severe mental illnesses have high rates of metabolic syndrome, and other cardiovascular disease risk factors. Many studies have shown a high rate of early mortality due to cardiovascular disease in people with schizophrenia. These risk factors may be related to:

- Lifestyle choices such as diet, activity level, smoking and substance use;
- genetic predisposition;
- illness-related factors; or
- effects of treatment.²

Persons with serious mental illness are more likely to be overweight, to smoke and to have high rates of diabetes, hypertension, and serum lipid abnormalities. Second generation antipsychotic agents have replaced the older first generation agents as the treatment of choice for some serious mental illnesses and are known to contribute to weight gain, lipid abnormalities and an increased risk for diabetes and/or cardiovascular disease.

Second generation agents (SGA) have variable risk for metabolic disturbance. Weight gain associated with second generation antipsychotic agents occurs in the first four to twelve weeks of use. This weight gain appears to be due to the agents’ relative affinity for the 5-HT₂ receptor. Agents that block this receptor are associated with increased food intake. Clozapine and olanzapine have the greatest affinity for this receptor and this may explain why each has a high
potential for weight gain. Affinity of these antipsychotic drugs for H₁ receptor also correlates with weight gain. H₁ and 5-HT₂ blocking effects may interfere with leptin-mediated appetite suppression.

<table>
<thead>
<tr>
<th>Generic (Trade Name)</th>
<th>Weight Gain</th>
<th>Dyslipidemia</th>
<th>Type II Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine (Zyprexa)</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Clozapine (Clozaril)</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Risperidone (Risperdal)</td>
<td>Moderate</td>
<td>Low to Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Ziprasidone (Geodon)</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Quetiapine (Seroquel)</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Low to Moderate</td>
</tr>
<tr>
<td>Aripiprazole (Abilify)</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Paliperidone (Invega)*</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Asenapine (Saphris)*</td>
<td>Low to Moderate</td>
<td>Low</td>
<td>Unknown</td>
</tr>
<tr>
<td>Iloperidone (Fanapt)*</td>
<td>Low to Moderate</td>
<td>Low</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

*Due to limited trial data for these agents, their profiles are based on their package insert.

**Assessment and Monitoring for Metabolic Syndrome**

In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), one third of the subjects met criteria for Metabolic Syndrome at the start of the study. Eighty eight percent (88%) of the study subjects who had a dyslipidemia were not receiving treatment for it. Sixty two percent (62%) of the study subjects with hypertension were not receiving treatment to lower their blood pressure. Thirty eight percent (38%) of the subjects with diabetes were not in active treatment to control their blood glucose levels. Screening practices by clinicians have been shown to be suboptimal. Despite expert recommendations and FDA warnings, rates of metabolic monitoring have remained low in Medicaid enrollees, and veterans with schizophrenia-related illnesses.

A number of clinical practice guidelines have been developed to assess and monitor for metabolic syndrome in individuals receiving atypical antipsychotic medications. Based on the consensus guidelines, five parameters are measured to evaluate and subsequently monitor for metabolic syndrome:

- weight,
- waist circumference,
- blood pressure
- fasting blood glucose level, and
- fasting blood lipid profile.

As previously noted, abdominal obesity is the most sensitive of the five measures for correctly identifying the presence of the syndrome (92%). Elevated glucose levels were the most specific parameter for identifying the presence of the syndrome. Normal fasting glucose levels correctly excluded 94.2% of those without metabolic syndrome. When both parameters were measured, 100% of persons with metabolic syndrome were correctly identified.
In 2004, the American Diabetes Association (ADA), the American Psychiatric Association (APA) and the American Association of Clinical Endocrinologists developed consensus guidelines for the initial and subsequent monitoring of persons taking atypical antipsychotic agents. The guideline sought to improve the screening of at-risk individuals by encouraging clinicians to make this screening a regular and routine part of the care of at-risk persons. The guidelines are summarized in the table below.

### ADA and APA Consensus Guidelines for Baseline Assessment and Monitoring Frequency of Persons on Atypical Antipsychotic Agents

<table>
<thead>
<tr>
<th>Monitoring</th>
<th>At Baseline</th>
<th>After 4 Weeks</th>
<th>After 6 Weeks</th>
<th>After 8 Weeks</th>
<th>After 12 Weeks</th>
<th>Quarterly Thereafter</th>
<th>Annually thereafter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal Medical History</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Family Medical History</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Weight &amp; 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></td>
<td></td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Fasting Glucose Level</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Fasting Lipid Levels</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Personal and family histories should be reviewed for the presence of obesity, diabetes, dyslipidemia, hypertension, and/or cardiovascular disease. The guidelines note that more frequent assessments may be indicated based on a person’s clinical status.

**Recommended Process for Screening, Monitoring, and Addressing Metabolic Syndrome**:³

- **Baseline and Subsequent Assessment**
  - Screen members according to the ADA/APA protocol outline above.
  - At baseline assessment, in addition to the guideline criteria above, consider ethnicity, dietary habits, physical activity, support systems, tobacco, alcohol and drug abuse.
  - Factor in the effects of other agents e.g., some antidepressants and mood stabilizers also may cause weight gain.
  - Note that glucose and lipid abnormalities may occur without weight gain.
  - Note that second generation antipsychotics have comparable efficacy and differ on their side effect profiles. Consider the following in prescribing an antipsychotic agent:
    - The member’s risk factors and current metabolic state,
    - The metabolic profile of the antipsychotic agent,
    - The member’s response to and tolerance for previous drug trials
    - The member’s preference
    - Avoid concurrent use of drugs associated with weight gain, e.g., certain mood stabilizing, antidepressant and antipsychotic agents.

- **Interventions**
  - Lifestyle modifications are the first-line interventions to reduce cardiovascular risk in persons with metabolic syndrome.² These generally focus on the following three areas:
    - dietary interventions,
- smoking cessation and
- increased physical activity.
- Referral of identified members for the treatment of elevated glucose levels, lipid abnormalities and/or hypertension.
- Educate the member and significant others/caregivers about:

- the member’s illness,
- the importance of consistent use of prescribed medications,
- the expected benefits of treatment,
- the possible side effects of the prescribed medication,
- the symptoms and signs of diabetes, and diabetic ketoacidosis
- concrete interventions to modify identified cardio-metabolic risk factors:
  - safe weight reduction for obese or overweight members,
  - smoking reduction or cessation for tobacco users,
  - safe increases in physical activity levels in sedentary members,
  - increased consumption of a heart-healthy diet:
- Continued monitoring of members on SGA agents to assess for the development of metabolic syndrome according to the ADA/APA guidelines outlined above.
- If metabolic syndrome is identified after the start of a second generation antipsychotic agent:
  - Review the modifiable risk factors with the member and significant others/caregivers.
  - Encourage implementation of the applicable interventions as noted above.
  - Refer the member for further evaluation and treatment of identified laboratory or vital sign abnormalities.
  - Consider and discuss with the member the use of a psychotropic agent with less potential to contribute to a metabolic syndrome.
  - If it is determined continued use of an agent is necessary, the reasons for this decision should be fully documented in the member’s clinical record.

References:
5. Riordan H, Antonini P, Murphy M.: Atypical Antipsychotics and Metabolic Syndrome in
