Second Generation Antipsychotics: Weighing in on Metabolic Issues and Sobering Statistics
Outline

- Rationale for metabolic monitoring
- Overview of metabolic syndrome
- Why we should be concerned
- Individual components of the metabolic syndrome & medication info
- Conclusion
Rationale:

- Serious mental illness associated with significant physical morbidity and mortality in comparison to the general population.

- Life span estimated to be 25-30 years shorter vs. general population; primarily due to metabolic sequelae—especially CVD.

- Type 2 diabetes three times more common in those with schizophrenia.

- Schizophrenia is recognized by the Canadian Diabetes Association as an \textit{independent risk factor} for diabetes.

- Mental illness significant risk factor for development of metabolic syndrome and a number of chronic diseases.
Rationale:

- A diagnosis of schizophrenia imparts significantly greater odds of having metabolic syndrome for almost every age group; especially females.
- Psychotropic medications associated with metabolic sequelae
- Accrued experience demonstrates concern primarily with the atypical antipsychotics.
- Other factors contribute to poor health status of mental health patients as well: lifestyle, systemic, and patient/illness.
The Metabolic Syndrome

- Describes a group of cardiometabolic risk factors/conditions that place individuals at increased risk of heart disease, stroke and diabetes.

- Conditions include:
  - Abdominal obesity
  - Atherogenic dyslipidemia
  - Hypertension
  - Insulin resistance or glucose intolerance
  - Proinflammatory state
  - Prothrombotic state
National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III Criteria For Metabolic Syndrome

3 or > criteria (risk factors) required for diagnosis; *= or on treatment

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
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</thead>
<tbody>
<tr>
<td>Abdominal Obesity</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>Waist Circumference &gt;102 cm (&gt;40 “) &gt;88 cm (&gt;35”)</td>
</tr>
<tr>
<td>Woman</td>
<td></td>
</tr>
<tr>
<td>TG</td>
<td>&gt; or =1.7 mmol/L *</td>
</tr>
<tr>
<td>HDL-C</td>
<td>&lt;1.03 mmol/L *</td>
</tr>
<tr>
<td>Men</td>
<td>&lt;1.3 mmol/L *</td>
</tr>
<tr>
<td>Women</td>
<td></td>
</tr>
<tr>
<td>Fasting Plasma Glucose</td>
<td>&gt; or =5.6 mmol/L *</td>
</tr>
<tr>
<td>BP</td>
<td>&gt; Or = 130/85 mmHg *</td>
</tr>
</tbody>
</table>
Why the Concern?
Prevalence of Metabolic Syndrome in Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE)

Prevalence of Metabolic Syndrome in CATIE vs NHANES III*

*comparison by gender between fasting subjects from CATIE and matched NHANES III controls

<table>
<thead>
<tr>
<th></th>
<th>CATIE N=509</th>
<th>NHANES N=509</th>
<th>P value</th>
<th>CATIE</th>
<th>NHANES</th>
<th>P value</th>
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<tbody>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>36%</td>
<td>19.7%</td>
<td>0.0001</td>
<td>51.6%</td>
<td>25.1%</td>
<td>0.0001</td>
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<tr>
<td><strong>Females</strong></td>
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</table>
Why The Concern?

• A large percentage of these patients were not receiving treatment for hypertension (62%), dyslipidemia (89%), or diabetes (45%); medical care often deemphasized.

• Atypical antipsychotics are being prescribed with increasing frequency:

  A study in MB found that the number of prescriptions for atypical antipsychotics increased from 9694 in 1996 to 259,376 in 2006.

• Atypicals increasingly prescribed for off-label use; some studies suggesting this accounts for up to 50% of prescriptions.
Why The Concern?

- Increased frequency of prescribing by general practitioners; unaware of appropriate practice guidelines and psychiatric diagnosis.

- The Harvard Medical Practice Study reported that diagnostic errors resulted in more adverse events than medication errors (14% vs 9%) and more often resulted in serious disability (47% vs 14%).

- Metabolic effects being found in children and adolescents; studies suggesting this population may be at higher risk than adults for developing atypical induced metabolic sequelae; less likely to receive metabolic screening and monitoring.
Lack of Medical Management in Psychiatric Care

- National Ambulatory Medical Care Survey (1992-1999) found that in 3,198 office visits, psychiatrists provided preventative medical care (asked about smoking, checked BP) in only 11% of office visits.

- The Atypical Antipsychotic Therapy and Metabolic Issues (AATMI) National Survey (2004) reported the % of psychiatrists who routinely do the following all the time:

<table>
<thead>
<tr>
<th>Routine Activity</th>
<th>%</th>
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<tbody>
<tr>
<td>Routinely obtain BP</td>
<td>17%</td>
</tr>
<tr>
<td>Routinely monitor changes in weight</td>
<td>31%</td>
</tr>
<tr>
<td>Routinely monitor waist circumference</td>
<td>2%</td>
</tr>
<tr>
<td>Routinely monitor changes in lipids</td>
<td>11%</td>
</tr>
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</table>
# Metabolic Disturbance Risk

<table>
<thead>
<tr>
<th>Medication</th>
<th>Weight Gain</th>
<th>Diabetes Risk</th>
<th>Lipid Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole: Part 1 coverage</td>
<td>Low</td>
<td>No Effect</td>
<td>No Effect</td>
</tr>
<tr>
<td>Clozapine</td>
<td>High</td>
<td>Increased Effect</td>
<td>Increased Effect</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>High</td>
<td>Increased Effect</td>
<td>Increased Effect</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Probably Increased</td>
</tr>
<tr>
<td>Risperidone/Paliperidone</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Ziprasidone: Part 1 coverage</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>
Management: Metabolic Issues Must be Identified and Addressed From the Beginning of Treatment

- Identification of high-risk patients
- Evaluate both physical and psychological dynamics prior to antipsychotic selection.
- Early detection critical!!
- Implement aggressive pharmacological strategies to treat diabetes, dyslipidemia and hypertension.
Individual Components of Metabolic Syndrome
1. Abdominal Obesity

- Modest wt loss of 5-10% of initial body wt can substantially improve insulin sensitivity, lipid, BP, and glycemic control.

- May prove *problematic/unrealistic* in psychiatric populations.

- Dietician consult in hospital may be an option
2. Triglycerides/HDL

- **Atherogenic** dyslipidemia primarily seen in metabolic syndrome: low HDL, **elevated TG’s** (LDL often normal).

- Initiation of therapy often occurs *simultaneously* with lifestyle modification for those with metabolic syndrome.

- Ensure *adequate fasting* (10-12 h) prior to blood draw

- 3 main classes of medications used:
  - statins (HMG-CoA reductase inhibitors)
  - niacin (nicotinic acid)
  - fibrates
Statins

- Robust evidence in both primary and secondary prevention trials for significant reductions in major coronary events.

- LDL 20-65%, TG 7-30%, HDL 5-15%

- Dose-dependent log linear LDL reduction; each doubling of dose reduces LDL ~6% (note: at higher doses, only modest effects on TG and HDL).

- TG response to statins highly variable: TG levels of 3.5 mmol/L or less show inconsistent response, while levels of 5 mmol/L and above show TG levels fall in direct proportion to LDL.
Statins

- Best taken PM or HS due to cholesterol synthesis; high first pass metabolism and short half-life of statins (exception: atorvastatin).

- Varied metabolic clearance; pravastatin NOT metabolized by p-450

- Dose dependent increase in LFT’s; CI in active liver ds and ++ ETOH

- Myopathy/rhabdomyolysis most likely in those with complex medical issues; monitor CK (>3-5x ULN=concern).

- ALL statins covered under part 1

- Assess efficacy 6 weeks post start; require dose titration
When Best to Use a Statin?

- Consider for any patient with diabetes at high risk for a vascular event and all with established CV disease.

- Elevated LDL

- Further lowering of LDL beneficial; every 1 mmol/L reduction in LDL offers a 20% reduction in CV events regardless of baseline level.

- If TG levels are between 4.5-10 mmol/L use either a statin or fibrate first line.
Fibrates

- Evidence for primary and secondary CHD prevention outcomes; not as robust as for statins.

- Primarily target atherogenic dyslipidemia: TG’s 20-50%, HDL 10-35%

- Modest effect on LDL: LDL 5-20%

- Dose titration NOT required; initial dose is max dose

- GI complaints, myopathy, increase risk of gallstones as fibrates increase lithogenicity of bile.
Fibrates

- CI in severe hepatic or renal insufficiency, gallbladder disease
- All fibrates covered under part 1
- No seemingly serious long term side effects
- Assess in 6-8 weeks time
When Best to Use a Fibrate?

- Option when LDL at goal
- Isolated TG elevation
- Atherogenic picture: high TG, low HDL
What About Combining a Statin with a Fibrate?
Combination Statin/Fibrate

- Proven highly effective for improvement of lipoprotein profile in combined hyperlipidemia.

- May have role in atherogenic hyperlipidemia; *in many instances*, the TG goal will require addition of a TG lowering medication.

- Previously believed to be contraindicated to increased risk of rhabdomyolysis; not the case any longer (note: best to avoid gemfibrozil with a statin).

- Still important to be cautionary in approach; drug interactions with other medications key.
Nicotinic Acid

- Favorably affects all lipids and lipoproteins when given in pharmacological doses (generally 2-3 grams/day).

- Most often used in combination with other medications, as intolerable to most at high doses.

- LDL 5-25%, TG 20-50%, HDL 15-35%

- Available in crystalline form (IR), SR/inositol hexanicotinate (no flush), and ER (Niaspan; requires Rx).

- Flushing, hyperglycemia, hyperuricemia, GI, hepatotoxicity
Nicotinic Acid

- CI: chronic liver disease, severe gout and *overt* diabetes, severe peptic ulcer disease.

- *Best to avoid inositol/SR formulations as greater risk for severe hepatotoxicity and decreased efficacy.*

- Long term use limited due to side effect profile

- Generally reserved for those at higher short term risk
N-3 (Omega) Fatty Acids

- At higher doses (3-5 g/day) DHA and EPA proposed to lower serum TG (25-30 %) via reduction in hepatic secretion of TG-rich lipoprotein.

- Recent evidence to suggest no reduction in rate of coronary events in those with established CV disease at high risk for events (NEJM: July 2012). *Significant reduction in TG was found.*

- Common side effects include nausea and poor aftertaste

- Not covered; price varies
3. Fasting Plasma Glucose

- In general, one can achieve an A1C reduction of ~0.5-1.5% with monotherapy; target A1C attained within 6-12 months.

- As A1C approaches normal levels, post prandial glucose control assumes more importance for further A1C reductions.

- Combinations of sub-maximal doses of antihyperglycemic agents produces more rapid and greater glycemic control vs. max dose monotherapy (fewer side effects also).
3. Fasting Plasma Glucose

- Metformin first line; however, if *CrCl is 30 mmol/L or less*, **CONTRAINDICATED**.

- Metformin also contraindicated if hepatic failure present.

- Second line: many options

- Gliclazide MR: once daily dosing; covered under part 1, **LOWEST** incidence of hypoglycemia and less weight gain vs glyburide!!

- TZD’s offer longer duration of glycemic control vs. metformin or glyburide; 6-12 weeks for full effect; CI as monotherapy and in combination with insulin; heart failure.
Vascular/BP

- Those with DM develop CAD 10-12 years earlier; suffer worse short and long term outcomes following acute coronary events.

- BP should be aggressively treated to <130/85 mm Hg to reduce micro and macrovascular complications.

- Vascular protection paramount: 1st line Tx with ace-inhibitor or ARB; add on DHP CCB or diuretic following.

- Antiplatelet therapy controversial
Thank-You!!