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

THE EMERGING SPECIALTY OF METABOLIC PSYCHIATRY

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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 ***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

Risk Factor	Defining Level
Abdominal Obesity Men Woman	Waist Circumference >102 cm (>40 “) >88 cm (>35”)
TG	> or =1.7 mmol/L *
HDL-C Men Women	 <1.03 mmol/L* <1.3 mmol/L*
Fasting Plasma Glucose	> or =**5.6 mmol/L***
BP	> Or = 130/85 mmHg*

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

Males			Females		
CATIE N=509	**NHANES N=509**	**P value**	**CATIE**	**NHANES**	**P value**
36%	19.7%	0.0001	51.6%	25.1%	0.0001

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:

Routinely obtain BP	17%
Routinely monitor changes in weight	31%
Routinely monitor waist circumference	2%
Routinely monitor changes in lipids	11%

Metabolic Disturbance Risk

Medication	Weight Gain	Diabetes Risk	Lipid Risk
Aripiprazole: Part 1 coverage	Low	No Effect	No Effect
Clozapine	High	Increased Effect	Increased Effect
Olanzapine	High	Increased Effect	Increased Effect
Quetiapine	Intermediate	Intermediate	Probably Increased
Risperidone/Paliperidone	Intermediate	Intermediate	Intermediate
Ziprasidone: Part 1 coverage	Low	Low	Low

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 to increased risk of rhabdomyolysis; not the case any longer (note: best to avoid gemfibfozil 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!!