Weight Gain and Metabolic Abnormalities in Patients with Schizophrenia

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What is Metabolic Syndrome (MetS)?

- A public health concept
- MetS (also referred to as “Syndrome X” or “Insulin Resistance Syndrome”) describes a cluster of CVD risk factors and metabolic alterations associated with excess fat weight
- Has been compared to cigarette smoking as an equal risk partner to premature CHD
- A starting point for clinical interventions known to reduce risk for obesity-related type 2 diabetes, CVD, and perhaps even cancer

There are several competing definitions for MetS; these include:
- World Health Organization (WHO)

How is This All Related?

Insulin Resistance

- Complex Dyslipidemia
  - TG, LDL, HDL
- Disordered Fibrinolysis
- Hypertension
  - DM2/GT/FPG

Endothelial Dysfunction

Systemic Inflammation

Atherosclerosis

Visceral Obesity

TG = triglyceride, HDL = high-density lipoprotein, LDL = low-density lipoprotein, DM2 = type 2 diabetes mellitus, GT = impaired glucose tolerance, FPG = impaired fasting glucose

### My Favorite MetS Definition

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity</td>
<td>Waist circumference: men &gt; 102 cm (&gt; 40 in); women &gt; 88 cm (35 in)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥ 150 mg/dL (1.695 mmol/L)</td>
</tr>
<tr>
<td>HDL-Cholesterol</td>
<td>Men: &lt; 40 mg/dL (1.036 mmol/L), women: &lt; 50 mg/dL (1.295 mmol/L)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥ 130/85 mm Hg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥ 100 mg/dL (5.5 mmol/L)</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>Not included in this list, but found in other definitions</td>
</tr>
</tbody>
</table>

This requires a tape measure; we usually measure body weight as a proxy, but keep in mind that muscle weighs more than fat. BMI > 30 kg/m² defines obesity.

### Cultural/Ethnic Issues

- BMI and waist circumference for Asians is generally lower
- Need a lower cutoff, eg, 90 cm in men (instead of 102 cm) or 80 cm in women (instead of 88 cm)
- In Japan, definition of obesity is BMI > 25 kg/m² (instead of 30 kg/m²)
Overlap of Obesity, DM2, and MetS

Prevalence of Obesity, DM2, and MetS among Persons with Schizophrenia (CATIE Study, USA)

MetS and Outpatients with Schizophrenia (United States)

MetS in Schizophrenia (Meta-Analytic Rates)

You Can Be “Metabolically Obese”

Consequences of MetS

Overall prevalence (SE) of the metabolic syndrome within each ethnicity, sex, and BMI category

MetS is associated with a 4× relative risk of developing diabetes (in the general population)

MetS is associated with a 2-fold risk of CHD, stroke, and premature mortality (in the general population)

MetS is significantly associated with cognitive impairment in schizophrenia and can potentially contribute to functional decline observed in some patients with schizophrenia throughout the course of illness

BMI is an independent predictor of psychiatric rehospitalization
How the Disease State of Schizophrenia Contributes to the Risk of Developing DM2

Why is the prevalence of diabetes 2- to 3-fold higher than in the general population?

Epidemiology
- High prevalence of undiagnosed diabetes, estimated to be up to 70% of all cases
- Prevalence of diabetes in SMI is 2- to 3-fold higher than in the general population
- Incidence of diabetes is higher and the onset of diabetes appears to be 10 to 20 years earlier than in the general population
  - In a study of NY State hospitals, prevalence increased from 0.9% to 1.8% in 4 years
- As diabetes is uncommon in young healthy adults, the increased relative risk of diabetes is greatest in adolescents and young adults with SMI

Mechanisms

Genetics?
- Both schizophrenia and DM2 are highly heritable disorders
- Recent studies have identified at least 37 common genes that increase the risk of both diabetes and schizophrenia
- Approximately 11% and 14% of these risk genes for diabetes and schizophrenia, respectively, may account for the risk of the other disease
- In addition to affecting an individual’s risk of diabetes directly, genetic polymorphisms in various genes, may also affect the risk of weight gain
Genetics?

Genes that have been Linked to both Diabetes and Schizophrenia

<table>
<thead>
<tr>
<th>Gene</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycogen synthase kinase 3</td>
<td>Regulates birth glucose metabolism and cognitive function</td>
</tr>
<tr>
<td>Serotonin-threonine</td>
<td>Reduced expression in lymphocytes and the frontal cortex in schizophrenia. Mediates insulin signaling and glucose metabolism; reduced action leads to diminished phosphorylation of its substrates, including GSK3</td>
</tr>
<tr>
<td>Dopamine D2 receptor</td>
<td>Implicated in obesity and DM2. Increased attention of insulin sensitivity and secretion. Affects risk of schizophrenia</td>
</tr>
<tr>
<td>Tyrosine hydroxylase gene</td>
<td>Associated with insulin resistance and schizophrenia</td>
</tr>
<tr>
<td>TCF7L2 gene</td>
<td>Encodes for a transcription factor involved in Wnt/beta-catenin signaling, that has a role in pancreatic beta-cell function and is a susceptibility gene for DM2. Wnt signaling pathway plays a role in CNS development and is associated with schizophrenia</td>
</tr>
</tbody>
</table>

Environment and Biological Effects of the Illness?

- Intra-uterine environmental factors: J-shaped relationship between birth weight and plasma glucose, insulin concentrations, and diabetes
- Childhood obesity
- Adult environment: diet and lifestyle, neighborhood environment, and poverty
- Inflammatory and neuroendocrine changes, including hypothalamic-pituitary-adrenal (HPA) dysfunction (also observed in depression)

Antipsychotic Medication?

Pharmacoepidemiologic database studies report that antipsychotics are associated with more diabetes than no treatment and treatment with an SGA is associated with a small 32% (15%–51%) increase in diabetes risk compared with FGAs

Caveat: SGAs

- Although the risk of diabetes for the newer SGAs is widely believed to be lower, this has not always been apparent in pharmaco-epidemiology studies
- For example, aripiprazole and ziprasidone were not associated with lower rates of diabetes than olanzapine, quetiapine, and risperidone in a pharmaceutical claims database

Antipsychotic Medication

Contribution of Weight Gain?

- Weight gain increases insulin resistance; this will eventually blossom into diabetes in vulnerable people with low pancreatic reserve
  - Weight gain is likely the most common reason for developing DM2, especially for those with increased genetic risk and unhealthy lifestyle
- However, weight gain does not explain all the excess diabetes risk as some individuals develop diabetes without being overweight or gaining weight
- Furthermore, weight gain does not explain why some people develop diabetic ketoacidosis which occurs as a result of markedly impaired insulin secretion

Antipsychotic Medication

Glucose Homeostasis

- Through their interaction with multiple receptors, antipsychotics may affect insulin secretion by the beta cells of the pancreas
- Central control of glucose homeostasis may also be affected by antipsychotics
- In addition to these pancreatic effects, in vitro work suggests that antipsychotics may directly impair insulin action by inhibiting insulin-mediated glucose uptake and glycogen synthesis
Antipsychotic Medication
Pharmacologic Effects on β Cell Function?

Antipsychotics may decrease pancreatic β cell responsiveness to blood glucose by blocking SSTR5 and SSTR3 receptors.

Antipsychotics may increase insulin secretion by blocking SSTR5, receptor.

Antipsychotics may blunt glucose-stimulated insulin release by blocking the dopamine D2 receptor.


Summary: Schizophrenia and Diabetes

- **Multiple mechanisms** are involved in the association between SMI and diabetes
- Likely that the contributions of these risk factors operate differently between individuals
- Overall, it appears that an excess of traditional diabetes risk factors, such as obesity, poor diet, physical inactivity, and family history, convey a higher risk than treatment, but this does not discount the possibility that antipsychotics are the major contributor to the development of diabetes in certain individuals, particularly where the onset of diabetes is rapid after treatment initiation and other risk factors are absent

Antipsychotics and Weight Gain

Are There Differences? Can We Measure Them?

Antipsychotic-Related Weight Gain

The heterogeneity of weight gain results from poorly understood drug-gene-environment interactions. **Moderators** include patient demographics, treatment setting, illness characteristics, past and baseline antipsychotic and comedication treatments, and baseline diet, activity and body composition. **Mediators** include antipsychotic dose, comedications, medication side effects, and changes in diet and activity.

Almost all antipsychotics are associated with weight gain
- More pronounced in antipsychotic naïve patients
- Can occur over time
- Not clearly dose-dependent
- Antipsychotic-related weight gain is polygenic and associated with specific genetic variants, especially in genes coding for antipsychotic pharmacodynamic targets
- Nonetheless, there are differences that can be quantified when comparing groups of patients in clinical trials
- "Your individual mileage may vary"

NNH vs Placebo

- How many patients would you need to treat with a medication instead of placebo before you would encounter one additional adverse outcome?
- The smaller the NNH, it takes fewer patients to treat with a medication vs placebo before encountering an additional adverse outcome.
- Thus, the higher the NNH, the less likely one would encounter that outcome.
- NNH is a measure of clinical significance.
- NNH does not measure statistical significance; it is not the same as a P-value.
- NNH is an absolute effect size measure.
- NNH is not a relative effect size measure such as the relative risk or odds ratio that are sometimes used to describe adverse outcomes.

NNH vs Placebo
Easy to Calculate

- What is the NNH for an outcome for Drug A vs placebo?
  - \( f_A \) = frequency of outcome for Drug A
  - \( f_B \) = frequency of outcome for placebo
  - \( \text{ARI} = f_A - f_B \)
  - \( \text{NNT} = 1/\text{ARI} \)
  - By convention, when not presenting fractions, we round up the NNT to the next higher whole number in order to avoid exaggerating a difference (lower NNH values = larger effect)

For example, Drug A results in a headache 50% of the time, but placebo results in a headache 20% of the time:

\[
\text{NNH} = \frac{1}{0.50-0.20} = 1/0.30 = 3.33 \rightarrow \text{Round up to 4}
\]

“For every 4 persons randomized to Drug A instead of placebo, you would encounter 1 additional person with a headache.”

What is an Acceptable NNH for Drug vs Placebo?

<table>
<thead>
<tr>
<th>NNH</th>
<th>Acceptable NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10</td>
<td>Adverse events that are mild or moderate, usually do not lead to discontinuation, and are usually temporary or cause no distress and do not pose a serious health risk eg, Mild nausea, or sedation during mania.</td>
</tr>
<tr>
<td>10–100</td>
<td>Adverse events that may lead to discontinuation but not associated with serious immediate health risks; alternatives do not have a better profile eg, Moderate weight gain.</td>
</tr>
<tr>
<td>&gt; 100</td>
<td>Adverse events that pose a significant health risk; for very severe adverse outcomes NNH values greater than 1000 may be more acceptable eg, Acute hemorrhage, serious rash.</td>
</tr>
</tbody>
</table>

Weight Gain ≥ 7% of Baseline*

<table>
<thead>
<tr>
<th>Medication</th>
<th>Schizophrenia</th>
<th>Bipolar Mania</th>
<th>Major Depressive Disorder</th>
<th>Bipolar Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lurasidone</td>
<td>10</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Asenapine</td>
<td>35</td>
<td>19</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>0.048</td>
<td>0.033</td>
<td>0.048-0.033 = 0.015</td>
<td>1/0.015 = 66.6</td>
</tr>
</tbody>
</table>

*Among Adults on SGAs from Short-Term RCTs.
Olanzapine Pattern of Weight Gain

- Patients with higher baseline BMI (> 27.6) gained significantly less weight during treatment with olanzapine than their lighter counterparts.
- The effect of olanzapine dose on weight was not significant.

In long-term (≥ 48 weeks) studies, the proportions of patients who gained at least 7%, 15%, or 25% of their baseline weight were 64%, 32%, and 12%, respectively.

Olanzapine Early Weight Gainers

- 15% showed rapid increases in weight (RWG group).
- In the RWG group patients gained an average of 4% of their body weight (4–7 lb) within the first 2 weeks of treatment with olanzapine.
- Patients in the RWG group were younger and had a lower baseline BMI.
- Over the course of 52 weeks, patients in the RWG group gained significantly more weight and reached a higher plateau for mean weight increase at 38 weeks.

Similarly, in patients with bipolar mania or mixed mania, a substantial amount of weight gain after 30 weeks was predicted by weight increases of 2 to 3 kg within the first 3 weeks of treatment. However, patients with less pronounced early weight gain might still be at risk if they have close to normal BMI at treatment initiation.

MetS Provides a Framework

- Eliminate or reduce **modifiable** risks
  - Overweight or obese: diet/nutrition counseling
  - Physically inactive: exercise 150 minutes/week minimum
- If pre-diabetic, begin measures to slow and/or prevent progression to diabetes
  - Lifestyle and dietary modifications
  - Regular screening
- Evaluate, monitor, and manage hypertension, atherogenic dyslipidemia, and other risk factors
- Refer to a primary care provider and/or specialist when necessary.

Interventions

- **Weight loss**
  - 10 lb loss leads to a 30% decrease in risk for DM, a decrease in BP, and improvement in lipids
- **Exercise**
  - Leads to decrease in weight, BP, and mortality
- **Control of HbA1c**
  - Leads to a decrease in DM complication rate
- **Control of BP**
  - Leads to a decrease in DM complication rate
MetS: Incremental Improvements


- **BP** by 6 mm Hg (>140/90)
- **Chol.** by 10% (TC: 180–200)
- **LDL-C** by 30 mg/dl (any LDL-C)

Healthy Weight (BMI 18.5–25)
Active Lifestyle (>20 min Walk)
Smoking Cessation

Prevention is Best: Especially ↑Weight
Young Adults CARDIA Study


- Men and women aged 18–30 years (n = 4192) were followed for 15 years
- Risk for MetS increased 23% (20%–27%) per 4.5 kg (10 lb) of weight gained, whereas regular physical activity over time vs low activity was protective (RR 0.49 [0.34–0.70])
- Bottom line: BMI and weight gain are important risk factors for MetS; regular physical activity may counter this risk

Prevention is Best: Especially ↑Weight
Insulin Resistance Atherosclerosis Study (IRAS)


- 714 white, black, and Hispanic participants free of MetS at baseline
- 139 of these developed MetS in the subsequent 5 years
- Predictors of incident MetS were waist circumference (OR 1.7 [1.3–2.0] per 11 cm), HDL cholesterol (0.6 [0.4–0.7] per 15 mg/dL), and proinsulin (1.7 [1.4–2.0] per 3.3 pmol/L)
- Signal detection analysis identified waist circumference (>89 cm in women, >102 cm in men) as the optimal predictor
- Bottom line: obesity may precede the development of other MetS components; interventions that address obesity and reduce waist circumference may reduce the incidence of MetS in nondiabetic adults

Prevention is Best: Especially ↑Weight
How Often Should We Check?
Consensus Statement on Antipsychotic Drugs, Obesity, and Diabetes: Monitoring Protocol for Patients on SGAs


- More frequent assessments may be warranted based on clinical status; consider also HbA1C.
- Monthly vs quarterly vs annually vs annually

Barriers to Addressing CVD Risk in Patients with SMI

Call to Action: We Can Do Better
CATIE: Rates of Pharmacologic Interventions for Abnormal Blood Pressure, Lipids, and Glucose

Prevalence / Lack of Intervention (%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>n = 481</th>
<th>n = 300</th>
<th>n = 75</th>
<th>n = 421</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>33.2</td>
<td>62.4</td>
<td>45.3</td>
<td>68.3</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>10.9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Call to Action: We Can Do Better
Self-Reported Lack of Medical Treatment in SMI Patients with Directly Assessed MetS and Self-Reported Hypertension, Hypercholesterolemia, and Diabetes

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<th>n = 300</th>
<th>n = 75</th>
<th>n = 421</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>60</td>
<td>46</td>
<td>59</td>
<td>40</td>
</tr>
<tr>
<td>Metabolic Syndrome</td>
<td>819/1359</td>
<td>1646/3608</td>
<td>2225/3732</td>
<td>699/1794</td>
</tr>
<tr>
<td>Elevated Cholesterol</td>
<td>919/1359</td>
<td>1646/3608</td>
<td>2225/3732</td>
<td>699/1794</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0</td>
<td>10</td>
<td>20</td>
<td>30</td>
</tr>
</tbody>
</table>


Medical Risk Management Strategies

Primary Risk Management

- Treatment Initiation
  - Healthy lifestyle counseling
  - Start with lower-risk antipsychotic

Secondary Risk Management

- If Adverse Effect is Present
  - Healthy lifestyle counseling/intervention
  - Consider changing to lower-risk antipsychotic
  - Consider weight loss intervention

Tertiary Risk Management

- If Adverse Effect Progresses/Serious
  - Healthy lifestyle counseling/intervention
  - Considering changing to lower-risk antipsychotic
  - Add targeted treatment for pathological values
  - Consider referral to specialist


Non-Pharmacologic Interventions for Antipsychotic-Associated Weight Gain
Meta-analysis

- 17 studies (n = 810, mean age: 38.8 years, 52.7% male, 40.8% white, 85.6% with schizophrenia spectrum disorders)
- Significant reduction in weight (~3.12 kg) and BMI (~0.94 kg/m²) compared with control groups
- Benefits extended to all secondary outcomes, except for HDL-C and systolic BP
- Subgroup analyses showed effects only in outpatient trials; effective treatments ranged from nutritional interventions to cognitive-behavioral therapy


Pharmacologic Interventions for Antipsychotic-Associated Weight Gain
Meta-analysis

- 21 RCTs (n = 1547) that tested metformin and placebo in patients taking antipsychotics
- Metformin was significantly superior to placebo in the primary outcome measures (body weight, BMI, fasting glucose, fasting insulin, triglycerides, and total cholesterol)
- Significantly higher frequencies of nausea/vomiting and diarrhea were found in the metformin group, but no differences were found in other adverse effects
- Adjunctive metformin is an effective, safe, and reasonable choice for antipsychotic-induced weight gain and metabolic abnormalities


More about Metformin
Meta-analysis

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- Adjunctive metformin is an effective, safe, and reasonable choice for antipsychotic-induced weight gain and metabolic abnormalities

Using Metformin Early

- The best weight outcomes are from preventing initial weight gain rather than attempting weight loss later in treatment
- Initiate metformin concomitantly with or soon after the initiation of antipsychotic medication use; particularly important for young, healthy patients who receive olanzapine or clozapine
- When combined with diet and lifestyle changes, metformin's effects appear more pronounced
- Start with 500 mg, twice a day, or 850 mg, once a day, with meals; dosage should be increased in increments of 500 mg/weekly or 850 mg, every 2 weeks, up to 2000 mg/day, given in divided doses

Using Metformin Safely

- GI adverse effects are common with metformin: nausea, vomiting, abdominal discomfort, flatulence, and diarrhea
  - Minimize by using gradual dose up-titration, administration of the drug with meals, and use of a time-release formulation
  - Lactic acidosis is very rare with metformin
  - Reduce risk by avoidance in patients with significantly impaired renal, liver, or cardiac functioning; check creatinine levels annually
  - Metformin can impair vitamin B12 absorption: assess serum B12 levels annually

Using Metformin Safely

- GI = gastrointestinal.

Other Rx for Weight Loss

- Medications approved for weight loss have generally not been assessed in RCTs in persons with schizophrenia
  - An exception is liraglutide (a GLP-1 receptor agonist) in patients with schizophrenia in stable treatment with clozapine or olanzapine, and who were overweight or obese, and had prediabetes; trial demonstrated efficacy
  - Orlistat (a GI lipase inhibitor) added to clozapine or olanzapine did not show efficacy
  - Topiramate (may also be helpful in decreasing symptoms of schizophrenia); watch for cognitive effects
  - Adding aripiprazole to clozapine (or olanzapine) may be another option

Conclusions

- People with schizophrenia/SMI are at increased risk for MetS and related cardiovascular morbidity
- The risk for physical disorders in patients with SMI is conferred by mental illness, unhealthy lifestyle, and psychiatric treatments
- Medication-induced weight gain has predictable adverse cardiometabolic effects, and some antipsychotics alter glucose and lipid metabolism independent of changes in adiposity
- Educate and counsel about nutrition and exercise
- Regularly monitor weight, blood pressure, fasting glucose, or HbA1C and lipids
- Proactively manage physical illness in the SMI