### Case Presentation 1

- Mr. A, a 61-year-old man with CAD and COPD, was admitted to the ICU for respiratory failure. He was intubated on admission to the hospital; fortunately, his pulmonary function improved, and he was extubated on the third hospital day. Following extubation, he became agitated, and psychiatric consultation was requested. Delirium was diagnosed and IV haloperidol was recommended.

### Case Presentation 1 (Contd.)

- Despite knowing that Mr. A's EKG revealed a normal rate and rhythm, that his QTc was 440 ms, and that the rest of his cardiac intervals were normal, the medical resident was uncomfortable with the recommendation. The resident noted that he had seen “lots of problems” with IV haloperidol and that he would rather not use it to treat Mr. A since he had CAD.
Case Presentation 2

A 46-year-old man was brought to the ER by his wife after she noticed some apparent seizure-like activity lasting one to two minutes, and included tongue biting and urinary incontinence. His PMH included bipolar d/o, DM, HTN and dyslipidemia. His medications included metformin, lantus insulin, simvastatin, lisinopril, paroxetine, lamotrigine and had not changed for many months except for the recent addition of paliperidone four days before his arrival to the ER. EKG revealed A. fib., QTc of 461 ms and no acute ST-T wave changes.

Case Presentation 2 (Contd.)

The pt. had no chest pain, and all other labs and vital signs were normal. He was admitted for evaluation and given IV diltiazem with resultant conversion to NSR, after which his heart rate and QTc interval normalized. He was discharged after one day.

Risk factors for cardiovascular/metabolic disease: Considerations for patients with schizophrenia

- Modifiable risk factors
  - Obesity
  - Dyslipidemia
  - Diabetes
  - Hypertension
  - Smoking

- Non-modifiable risk factors
  - Gender
  - Family history
  - Personal history
  - Age

Cardiovascular health status and mortality rates associated with schizophrenia

- Nearly 60% of the patients are obese.
- Risk of developing diabetes is more than two times higher than the general population.
- 70-80% smoke versus 25% in the general population.
- Approx. two times higher incidence of cardiovascular disease mortality than general population.
- Sedentary lifestyle, poor dietary habits and inadequate access to healthcare worsen the situation.


Herrán A et al. Schizophr Res. 2000;41:373-381.


Risk of cardiovascular and metabolic events in patients with schizophrenia and in the general population

Cardiac complications associated with antipsychotics
- Weight gain
- Adverse lipid profile
- Orthostatic hypotension
- Myocarditis
- Cardiomyopathy
- Torsades de Pointes (TdP)
- V. fib. other than TdP

Consequences of Dyslipidemias
- Elevated cholesterol and LDL increase risk for cardiovascular disease (CVD)
- Increased triglycerides
  - Independent risk factor for CVD
- Lowering lipids by 10% decreases cardiovascular risk by 20%-30%

Consequences of Diabetes
- Increased risk of cardiovascular disease
- Macrovascular complications due to high levels of cholesterol and triglycerides
- Microvascular effects
  - Retinopathies → blindness
  - Nephropathies → kidney failure
  - Peripheral neuropathies → physical pain

Survival of Diabetics Without a History of MI Is Similar to That of Nondiabetics Who Are Post-MI

![Graph showing survival rates for diabetics and nondiabetics post-MI.](image)


Obesity and mortality risk

![Graph showing obesity and mortality risk ratio.](image)

Adapted from Gray 1989

Effects on lipid profile

- Olanzapine, clozapine and quetiapine have been associated with increases in serum triglycerides, modest increases in total cholesterol but limited impact on LDL.
- Minimal effects of aripiprazole and ziprasidone on serum lipids.
- Mechanisms contributing to hyperlipidemia have focused on weight gain, dietary changes and development of insulin resistance.
- Recent switch data also suggest that there may be direct, adipocyte-independent effects of metabolically offending antipsychotic meds on serum lipids.

Diabetes and glucose tolerance

- Mechanisms
- Patients taking olanzapine have a 4-fold greater risk of developing T2DM than do those taking typical antipsychotics. Similar risk with clozapine.
- The incidence of clinically significant weight gain with aripiprazole and ziprasidone is considerably less than that with olanzapine, hence the risk of developing metabolic syndrome with these 2 agents is comparable to placebo.
Mean change in weight gain in patients receiving antipsychotic meds

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight gain</th>
<th>Diabetes Risk</th>
<th>Dyslipidemia</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>D</td>
<td>D</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>+/-</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>+/-</td>
<td>_</td>
<td>_</td>
</tr>
</tbody>
</table>

Metabolic disturbances associated with antipsychotic agents

Tachycardia

- Mostly secondary to anticholinergic effects of antipsychotics.
- Exacerbated by α1-adrenergic receptor antagonism seen commonly among lower potency antipsychotics and clozapine.
- Prolonged tachycardia can increase myocardial oxygen demand and could contribute to cardiac ischemia and subsequently cardiomyopathy.
Orthostatic hypotension

- Most common CV side effect
- Can occur with any antipsychotic
- Mediated by α1-adrenergic antagonism
- Could be of particular concern in the elderly wherein orthostasis could result in neurologic symptoms like lightheadedness in a mild form and presyncope or syncope in the severe form.
- Clozapine has the strongest association, whereas olanzapine and ziprasidone have the lowest incidence.

Myocarditis and Cardiomyopathy

- An uncommon, but potentially fatal effect from clozapine use.
- 15 cases of myocarditis and 8 cases of cardiomyopathy reported between 1993 and 1999 in Australia from approximately 8000 patients starting clozapine during that period.
- All 15 cases of myocarditis occurred within 3 weeks of starting treatment and included 5 patient deaths.

Review of electrocardiogram (ECG) and intervals

- Corrected QT interval (QTc) values adjust QT interval measurements for heart rate.
- A normal QTc interval is defined as <450 ms for women and <430 ms for men.
- The duration of the QT interval varies inversely with heart rate.

Normal QT interval

Guyton and Hall 2000
Moss 1993
**QT prolongation**

- Can predispose patients to syncope, ventricular arrhythmias, and sudden death.
- May increase the risk of torsade de pointes, a potentially fatal ventricular arrhythmia.
- Clinically significant prolonged QTc values are defined as >500 ms.

Welch and Chue 2000; Moss 1986; Glassman and Bigger 2001; Litherland 1997

---

**Effects of Orally-Administered Antipsychotics on the QT Interval**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean Increase in QTc (ms)</th>
<th>% of Subjects With &gt; 60 ms Increase in QTc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thioridazine</td>
<td>35.8</td>
<td>29</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>20.6</td>
<td>21</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>14.5</td>
<td>11</td>
</tr>
<tr>
<td>Risperidone</td>
<td>10.0</td>
<td>4</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>6.4</td>
<td>4</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>4.7</td>
<td>4</td>
</tr>
</tbody>
</table>

Data adapted from the U.S. Food and Drug Administration’s Center for Drug Evaluation and Research, Psychopharmacological Drugs Advisory Committee.  

---

**Potential Consequences of QTc Interval Prolongation**

- Torsade de pointes arrhythmia (syncope)
- Ventricular fibrillation
- Sudden death

Atypicals and the risk of sudden cardiac death

Do atypical antipsychotic meds carry the same or a reduced risk of serious ventricular arrhythmias and sudden cardiac death than typical antipsychotics?

Ray et al conducted a retrospective cohort study of Medicaid enrollees in Tennessee.

Study groups included users of single typical, atypical and matched non users of antipsychotics.

Methods

- Cohort was restricted to persons 30 to 74 years of age.
- Typical antipsychotics analyzed were haloperidol and thioridazine.
- Atypicals included were quetiapine, olanzapine, risperidone and clozapine.

Results

- Current users of typical antipsychotics had an incidence rate ratio of 1.99 compared to non users.
- Atypical antipsychotics had an incidence ratio of 2.26.
- Among users of atypicals, the incidence rate ratios increased from 1.59 for those on low doses to 2.42 for those taking higher doses.
Limitations of this study

- Though several provisions were made to avoid confounding factors, there exists a serious potential for the same.
- This study did not assess the mechanisms by which antipsychotics increased the risk of sudden cardiac death.
- What about ziprasidone??

The CATIE Schizophrenia Study

- The study objective was to examine effects of different antipsychotic treatments on estimates of 10 year CAD risk calculated by the Framingham Heart Study Formula.
- Change in 10 year risk for CHD was compared between treatment groups in 1125 patients followed for 18 months.
- Antipsychotic meds involved were olanzapine, perphenazine, quetiapine, risperidone and ziprasidone.

CATIE Study (Contd.)

- Olanzapine and quetiapine were associated with increased risk; whereas risk decreased in patients treated with perphenazine, risperidone, and ziprasidone.
- Overall differences in CAD risk appeared secondary to lowering of total cholesterol in patients treated with risperidone and ziprasidone, and increase in HDL with perphenazine and ziprasidone.

What Should We Monitor?

- Physical Exam
  - Check weight - each visit
  - Check blood pressure - each visit
- Lab Tests
  - Hemoglobin A1c - every 3–6 months
  - Fasting blood glucose - every 3 months
  - Triglycerides - every 3 months
  - Cholesterol - every 3 months
ADA Screening Guidelines for Patients on Second-Generation Antipsychotics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>4 Weeks</th>
<th>8 Weeks</th>
<th>12 Weeks</th>
<th>Annually</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal family history</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Weight (BMI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight (25.0-29.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese (≥30.0)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>(&lt;40″ in males, &lt;35″ in females)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>IFG (100-125 mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes (≥126 mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting lipid profile</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (&lt;200 mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL (&gt;40)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL (&lt;100)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TG (&lt;150)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Normal values (in parentheses) based on 2007 ADA Guidelines and National Cholesterol Education Program (NCEP) Guidelines.

3. ADA. Diabetes Care. 2007;30(suppl 1):S4-S41.

Clinical insights for optimal cardiac safety with antipsychotics

- Probe for patient and/or family history of dizziness, syncope, palpitations, arrhythmias, or sudden death
- Evaluate overdose risk
- Consider patient’s use of coronary vasospastic substances, such as nicotine or cocaine
- Maintain normal electrolyte levels, especially potassium and magnesium
- Monitor for alcohol use, dehydration, and diuretics which may cause abnormal electrolyte levels
- Monitor for drug interactions with metabolic inhibitors and drugs that prolong the QT interval.

Concerns regarding prolonged QTc

- Prolonged QTc is an unreliable and a crude predictor of TdP.
- There have been rare post-marketing reports of TdP (in the presence of multiple confounding factors) with quetiapine, risperidone and ziprasidone in which no causal relationship was established.
- For pts. taking antipsychotics who experience symptoms that could indicate the occurrence of TdP (dizziness, palpitations, or syncope), further evaluation like Holter monitoring may be useful.

EKG monitoring guidelines

- No need to routinely perform an EKG before initiating antipsychotic therapy in pts. without any risk factors for QTc prolongation.
- Obtain a baseline EKG in pts with risk factors for QTc prolongation or cardiac problems, including a hx of cardiac disease, HR < 50, hypokalemia, hypomagnesemia, or chronic alcohol abuse.
EKG monitoring guidelines (contd.)

- No need to perform an EKG when the doses of antipsychotic meds are increased, since changes in QTc do not appear to be dose-related in a clinically significant way at clinically relevant doses.
- Baseline EKG before initiating antipsychotics if: personal hx of heart disease or syncope; family hx of sudden death, or congenital long QT syndrome.
  - Weiden et al, 2002

In a nutshell

- Patients with severe mental illness have higher standardized mortality rates from cardiovascular disease than the general population.
- Certain cardiovascular adverse effects like orthostasis, tachycardia and lethal tachyarrhythmias from QTc prolongation are of less concern with atypical antipsychotics.
- Traditional risk factors for cardiovascular morbidity and mortality are of significant concern during atypical antipsychotic treatment particularly for olanzapine and clozapine.

Summary (contd.)

- Clozapine and olanzapine are associated with greatest risk of insulin resistance, or T2DM, but there are cases linked to exposure with other atypicals.
- Adiposity-independent mechanisms have also been shown increase the propensity of certain antipsychotics to cause insulin resistance.
- Myocarditis and QTc prolongation may result in fatal dysrhythmias, yet these events are exceedingly rare and contribute nominally to excessive CV mortality seen among patients with schizophrenia.
- Current practice guidelines suggest trials of metabolically more neutral agent like aripiprazole and ziprasidone when appropriate, and routine monitoring of weight, lipids and glucose for all patients receiving antipsychotic treatment.

Jerry’ s World

[Image of a building with the text Jerry’s World]