Weight Gain in Psychiatric Treatment: Risks, Implications, and Strategies for Prevention and Management

Amresh Srivastava, *University of Western Ontario*
Megan Johnston, *University of Toronto*
Disclosure
Research, education & travel grant.
Speakers group & advisory panels

- Janssen Cilag
- Janssen Ortho
- AstraZeneca Canada & UK
- Pfizer
- Roche Pharmaceuticals
- Nicolus Pharmaceuticals
- SUN Pharma
- Prempharma
Six RCTs assessed the effects of cognitive behavioural therapy (CBT), three assessed nutritional counselling and one assessed a combination of nutritional counselling and exercise. Non-pharmacological interventions significantly reduced weight and BMI compared with treatment as usual (WMD in weight 22.56 kg, 95% CI 23.2 to 21.9 kg; p,0.001; I² = 28.9%; WMD in BMI 20.91 kg/m², 95% CI 21.1 to 20.7 kg/m²; p,0.001; I² = 28.9%). The reduction in weight with non-pharmacological interventions was maintained at 2–3 months of follow-up (three RCTs; WMD 24.1 kg, 95% CI 25.8 to 22.5 kg; p,0.001). Analyses of subgroups found no statistically significant differences in the treatment effect sizes between trials that aimed to prevent weight gain (four trials) and those that aimed to produce weight loss (six trials); between group (five trials) and individual (five trials) forms of intervention;
Meta-Analysis of Antipsychotic-Related Weight Gain: Estimate at 10 Weeks

† 4-6 week pooled data (Marder SR et al. Schizophr Res 2003;1;61:123-136).
Ziprasidone vs. Placebo (ZEUS Study): Median Body Weight at Baseline and Endpoint

Incidence of Clinically Significant (≥7%) Weight Gain in Short-Term Studies

Zyprexa USPI.
Risperdal USPI.
Seroquel USPI.
Ziprasidone Safety and Tolerability (6-Month Continuation Study): Demonstrated a Favourable Effect on Weight vs. Olanzapine

† *p* < 0.001 between groups
‡ *p* < 0.05 vs. baseline


**Mean Dose**
- Ziprasidone 135.2 mg/d
- Olanzapine 12.6 mg/d
Ziprasidone Safety and Tolerability (6-Month Continuation Study): Demonstrated Favourable Effects on Lipids and Insulin vs. Olanzapine

† p=NS vs. baseline
‡ p<0.05 vs. baseline
p=NS between treatment groups


Mean Dose
Ziprasidone 135.2 mg/d
Olanzapine 12.6 mg/d
Ziprasidone Safety and Tolerability (1-Year Switch Extension Studies): Change in Weight from Baseline
58 Weeks After Switching to Ziprasidone

MMRM = Mixed-model repeated measures
OC = Observed cases
BL = Baseline
† p<0.05; ‡ p<0.01; § p<0.0001; ¶ Core baseline – 6-week trial.
Antipsychotics and Weight Gain After 10 Weeks of Treatment

**Mean change from baseline at 6 months (lb)**

<table>
<thead>
<tr>
<th></th>
<th>Mean Modal Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziprasidone</td>
<td>135.2 mg/d</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>12.6 mg/d</td>
</tr>
</tbody>
</table>

*P*<0.05 vs baseline

***P*<0.001 vs between groups

Distribution of Weight Change in Double-blind, Comparative, Short-term (4-12 wk) Studies

<table>
<thead>
<tr>
<th>Mean change (lb)</th>
<th>N=187</th>
<th>N=1067</th>
<th>N=230</th>
<th>N=112</th>
<th>N=55</th>
<th>N=92</th>
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<tbody>
<tr>
<td></td>
<td>-0.7</td>
<td>1.3</td>
<td>-0.02</td>
<td>4.2</td>
<td>2.9</td>
<td>11.2</td>
</tr>
</tbody>
</table>

**P<0.01, ***P<0.001, ****P<0.0001 (vs placebo for distribution of weight change from baseline).

Parsons B et al. APA. May 2006.
Ziprasidone (1-year Switch Extension Studies)

Safety and Tolerability: Sustained Decrease in Weight After Switching

Mean Body Weight Change Over 58 Weeks

Weeks

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Switched to ziprasidone from conventionals (n=71)</th>
<th>Switched to ziprasidone from risperidone (n=43)</th>
<th>Switched to ziprasidone from olanzapine (n=71)</th>
</tr>
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<tbody>
<tr>
<td>6</td>
<td>*</td>
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<td>58</td>
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</tr>
</tbody>
</table>

LS mean change from core baseline at end point (lb)

15-lb (6.8-kg) loss after switching from risperidone
22-lb (10-kg) loss after switching from olanzapine

*P<0.05, **P<0.001 ***P<0.0001.
†Core baseline—6-week trial. ‡Mixed-model analysis.
Weiden PJ, et al. APA 2004
Does weight gain matter?

- **Psychological effects**
  - low self esteem, depression, sleeping poorly
- **Social effects**
  - Isolation, reluctance to participate in activities
- **Financial Effects**
  - unemployment, additional purchases

- **Physical symptoms**
  - tiredness, sweating, back pain, arthritis, shortness of breath, stress incontinence, snoring

- **Metabolic problems**
  - hypertension, hyperlipidaemia, ischemic heart disease, diabetes, major cancers, menstrual problems
Weight gain and atypical APD

- haloperidol
- sertindol
- risperidone
- olanzapine
- clozapine

Weight change categories:
- no change
- <10% gain
- >10% gain
Weight gain and Quetiapine

- “Drug was associated with weight gains of approx. 2.1; 3.5; and 5.6 kg after treatment for 4 to 6 weeks, 18 to 26 weeks and 1 year respectively”

- “Clinically significant weight gain [>7% increase in body weight] occurred in up to 25% of quetiapine recipients in some clinical trials”

- There is evidence to indicate that weight gain may be more common with Quetiapine than with classical antipsychotics

- In multiple fixed dose comparative trial 10 to 16% of patients receiving Quetiapine had clinically significant weight gain compared to 4% receiving haloperidol

- Mean weight gain in 6 weeks study ranged between 0.9 to 2.9 kg in Quetiapine patients compared with 0.3 kg receiving haloperidol, and a reduction of 0.8 kg in placebo

- In CPZ trial, 27% of Quetiapine-treated patients had significant weight gain compared to 18% in CPZ group
Long-term weight change - differences between atypical antipsychotics

Quetiapine 475 mg/day†
(n=455)

Olanzapine 15 mg/day
(n=69)

Mean change from baseline weight (kg)

Time (weeks)

†Mean dose at completion of trial

Kasper & Müller-Spahn 2000

Adapted from Nemeroff 1997
Incidence of type 2 diabetes associated with antipsychotic use in schizophrenia

Cross-sectional study (n=396)  Zoler and Ganguli 1999; Canadian Guidelines on the Treatment of Diabetes 1999
New onset diabetes Mellitus and diabetic ketoacidosis: analysis of 45 cases

Jim, H.; Meyer JM; Jeste DV; Ann. Cl. Psy March 2002

- Clozapine 20 cases
- Olananzapine 19
- Quetiapine 03
- Risperidone 03
- NS for duration, weight gain, family history of DM, exposure to drug
- 87% were male
- 84% were over-weight at base
- 42% presented with DKA
- DKA was seen in young, female, less weight
Differences are expected on efficacy & side effect

Absence of side effects

Symptom Remission

Social Recovery

QOL

ADL

Side Effects

EPS

Vitals

Sedation

Weight

Metabolic

Cardiac

Blood count

seizure

Symptom Remission

Social Recovery

Absence of side effects
Atypical antipsychotics:
SDA: Ratio- D2/5HT$_{2A}$

**Does Receptor occupancy correlate with symptom control?**

---

### Comparative Receptor Binding Profiles

- **Haloperidol**
  - D2
  - 5HT2A
  - α1

- **Clozapine**
  - H1
  - M
  - 5HT2A
  - α1
  - D2

- **Olanzapine**
  - M1
  - 5HT2A
  - α1
  - H1
  - D2

- **Risperidone**
  - H1
  - D2
  - α1
  - 5HT2A

- **Ziprasidone**
  - α1
  - D2
  - 5HT2A

- **Quetiapine**
  - D2
  - 5HT2A
  - H1
  - α1

---

*Arndt J, Skarsfeldt T. Neuropsychopharmacology 1998; Goldstein et al.*
Weight Gain and AAPD

One subject likely to gain >7% weight out of

- Clozarine
- Olanzapine
- Risperidone
- Ziprasidone
- Fluphenazine
- Aripiprazole
Early Weight gain persists
Short (N=1717, 4-12 wks) & Long-term (N=1649, 52 wks),

Bruce, P et al, Weight effects associated with antipsychotics: A comparative database analysis, Schizophrenia research 110 (2009) 103-110
What We Should Be Doing

<table>
<thead>
<tr>
<th>Inquiry</th>
<th>Measure</th>
<th>Lab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal or family history:</td>
<td>• Height</td>
<td>• Fasting Glucose</td>
</tr>
<tr>
<td>- Diabetes</td>
<td>• Weight</td>
<td>• Fasting Lipids</td>
</tr>
<tr>
<td>- Hypertension</td>
<td>• Waist circumference</td>
<td></td>
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<tr>
<td>- CHD (MI or Stroke)</td>
<td>• Blood Pressure</td>
<td></td>
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<tr>
<td>- Cigarette smoking</td>
<td></td>
<td></td>
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<tr>
<td>- Diet</td>
<td></td>
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<tr>
<td>- Physical Activity</td>
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</tr>
</tbody>
</table>

And - trying to use medications which have fewer metabolic side effects!
### ADA/APA Consensus Conference on Antipsychotic Drugs and Obesity and Diabetes

#### Summary

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight Gain</th>
<th>Risk for Diabetes</th>
<th>Worsening Lipid Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine (Clozaril)</td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa)</td>
<td>+++</td>
<td>++</td>
<td>++</td>
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<tr>
<td>Risperidone (Risperdal)</td>
<td>++</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Paliperidone (Invega)</td>
<td>++</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Quetiapine (Seroquel)</td>
<td>++</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Aripiprazole* (Abilify)</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ziprasidone* (Geodon)</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

+ = increase effect; - = no effect; D = discrepant results. *Newer drugs with limited long-term data.
Change in Body Weight Following Switch to Aripiprazole-8 Wk Study

*n p<0.001; †p=0.077
LOCF analysis.
Estimated Weight Change (lb) After Switch to Ziprasidone†

Repeated measures analysis

Switched from

- Conventionals
- Olanzapine
- Risperidone

Weeks

LS Mean Change, lb

*P<0.05
**P<0.001
***P<0.0001

Presented at APA 2004, New York, NY
Change in Body Weight Following Switch to Ariniprazole-8 Wk Study

* $p<0.001$; † $p=0.077$

LOCF analysis.

Estimated Weight Change (lb) After Switch to Ziprasidone†

Repeated measures analysis

<table>
<thead>
<tr>
<th>Switched from</th>
<th>Olanzapine</th>
<th>Conventional</th>
<th>Risperidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS Mean Change, lb</td>
<td>-25</td>
<td>-20</td>
<td>-15</td>
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<td>-10</td>
<td>-5</td>
<td>0</td>
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<td>55</td>
<td>58</td>
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</tbody>
</table>

*P<0.05
**P<0.001
***P<0.0001

Switched from

Presented at APA 2004, New York, NY

†Repeated measures analysis
What’s New?
Newer Antipsychotics

- Paliperidone (Invega®) - Risperdal metabolite
  - Very similar side effect profile to Risperdal
  - Very similar effectiveness to Risperdal
- Bifeprunox - similar in mechanism to Abilify
  - More nausea than Abilify -> Long titration (8 days) - not for acute use
  - Questions about effectiveness - awaiting FDA decision
- Asenapine - another atypical antipsychotic
  - No major efficacy or safety benefits - awaiting FDA decision
- Iloperidone - another atypical antipsychotic
  - No major efficacy benefits, QTc concerns - awaiting FDA decision
- Long-Acting Injectables (Not Yet Approved)
  - Olanzapine Pamoate: 2-4 wks, effective, major safety concerns
  - Paliperidone Palmitate: 4 wks, not yet filed with FDA (?2009)
On the Horizon

- Some features of schizophrenia may be due to decreased levels of activity at a certain type of receptor (NMDA glutamate receptors)
- Glycine can stimulate those receptors and might prove useful as a treatment for schizophrenia
- Glycine Transport Inhibitors (GlyT1 Blockers)
  - The GlyT1 transporter is localized to important areas of the brain
  - Interesting data in animal models of psychosis induced by PCP
How A Reuptake Inhibitor Works

Presynaptic Nerve Ending

Glycine Reuptake Pump

Postsynaptic Neuron

Synaptic vesicles with Glycine

Glycine

NMDA Receptors
Conclusions

• Except for clozapine, most of the currently available agents, and those on the horizon, are more alike than different in terms of effectiveness

• Safety and avoidance of metabolic side effects are major reasons to choose certain medications

• Providers have a duty to monitor weight, blood pressure, blood sugar and cholesterol (lipids)

• Long-acting injectable medications are useful, will have more options in the next few years

• Ongoing research may help identify newer classes of medications
Case

1. Why did he develop diabetes and diabetic ketoacidosis?
   
   *Do 2nd Generation (Atypical) antipsychotics have adverse metabolic effects?*

2. Could this metabolic decompensation have been predicted and prevented?

3. How should his psychotic symptoms be treated now?
<table>
<thead>
<tr>
<th>Table 3: Etiologic classification of diabetes mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 1 diabetes mellitus</strong> (beta-cell destruction, usually leading to absolute insulin deficiency)</td>
</tr>
<tr>
<td>• Immune mediated</td>
</tr>
<tr>
<td>• Idiopathic</td>
</tr>
<tr>
<td><strong>Type 2 diabetes mellitus</strong> (may range from predominantly insulin resistance with relative insulin deficiency to predominantly secretory defect with insulin resistance)</td>
</tr>
<tr>
<td><strong>Gestational diabetes mellitus</strong> (onset or recognition of glucose intolerance in pregnancy)</td>
</tr>
<tr>
<td><strong>Other specific types</strong></td>
</tr>
<tr>
<td><strong>Genetic defects of beta-cell function</strong></td>
</tr>
<tr>
<td>• Chromosome 12, HNF-1α (formerly MODY 3)</td>
</tr>
<tr>
<td>• Chromosome 7, glucokinase (formerly MODY 2)</td>
</tr>
<tr>
<td>• Chromosome 20, HNF-4α (formerly MODY 1)</td>
</tr>
<tr>
<td>• Mitochondrial DNA</td>
</tr>
<tr>
<td>• Others</td>
</tr>
<tr>
<td><strong>Genetic defects in insulin action</strong></td>
</tr>
<tr>
<td>• Type A insulin resistance</td>
</tr>
<tr>
<td>• Leprechaunism</td>
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<tr>
<td>• Rabson-Mendenhall syndrome</td>
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<td>• Lipoatrophic diabetes</td>
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<td>• Others</td>
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<td><strong>Diseases of the endocrine pancreas</strong></td>
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<tr>
<td>• Pancreatitis</td>
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<td>• Trauma pancreatectomy</td>
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<td>• Neoplasia</td>
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<td>• Cystic fibrosis</td>
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<td>• Fibrocalculous pancreaticoy</td>
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<td>• Others</td>
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<tr>
<td><strong>Endocrinopathies</strong></td>
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<td>• Acromegaly</td>
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<td>• Cushing's syndrome</td>
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<td>• Glucagonoma</td>
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<td>• Pheochromocytoma</td>
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<td>• Hyperthyroidism</td>
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<td>• Somatostatinoma</td>
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<td>• Aldosteronoma</td>
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<td>• Others</td>
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<tr>
<td><strong>Infections</strong></td>
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<tr>
<td>• Congenital rubella</td>
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<tr>
<td>• Cytomegalovirus</td>
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<td>• Others</td>
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<td><strong>Uncommon forms of immune-mediated diabetes</strong></td>
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<tr>
<td>• “Stiff-man” syndrome</td>
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<td>• Anti-insulin receptor antibodies</td>
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<td>• Others</td>
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<td><strong>Drug or chemical induced</strong></td>
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<td>• Vacor</td>
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<td>• Pentamidine</td>
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<td>• Nicotine acid</td>
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<td>• Glucocorticoids</td>
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<td>• Diazoide</td>
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<td>• Beta-adrenergic agonists</td>
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<tr>
<td>• Thiazide</td>
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<td>• Dilantin</td>
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<tr>
<td>• Alpha-interferon</td>
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<tr>
<td>• Others</td>
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<tr>
<td><strong>Other genetic syndromes sometimes associated with diabetes</strong></td>
</tr>
<tr>
<td>• Down's syndrome</td>
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<tr>
<td>• Klinefelter's syndrome</td>
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<tr>
<td>• Turner's syndrome</td>
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<tr>
<td>• Wolfram's syndrome</td>
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<tr>
<td>• Friedreich's ataxia</td>
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<tr>
<td>• Huntington's chorea</td>
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<tr>
<td>• Laurence–Biedel syndrome</td>
</tr>
<tr>
<td>• Myotonic dystrophy</td>
</tr>
<tr>
<td>• Porphyria</td>
</tr>
<tr>
<td>• Prader–Willi syndrome</td>
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<tr>
<td>• Others</td>
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</tbody>
</table>
DKA risk factors

- **T1DM**
  - 1<sup>st</sup> presentation
  - Acute-illness
  - Insulin omission (inappropriate sick-day management, noncompliance, Eating Disorders)

- **T2DM**
  - During stress
  - Ethnicity: African-American, Hispanic

- Extremes of age
- Poor glycemic control
- CSII
Natural History of Type 2 Diabetes

## Antipsychotic Agents That Decrease Neuronal Response in the Cerebral Cortex to Incoming Stimuli

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Type of Agent</th>
<th>Result</th>
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<tbody>
<tr>
<td>Dopamine D2 antagonism</td>
<td>First-generation (haloperidol)</td>
<td>Blockade of dopamine facilitation of pyramidal-neuron response</td>
</tr>
<tr>
<td>D2 and 5-HT₂₄ antagonism</td>
<td>Second-generation (olanzapine, risperidone, quetiapine, ziprasidone)</td>
<td>Blockade of dopamine facilitation of pyramidal-neuron response and serotonin facilitation of glutamate release</td>
</tr>
<tr>
<td>Multiple actions</td>
<td>Clozapine</td>
<td>D1, D2, and 5-HT₂₃ antagonism, leading to decreased pyramidal-neuron responses; increased acetylcholine release and norepinephrine antagonism, leading to increased interneuron regulation of pyramidal neurons</td>
</tr>
<tr>
<td>Mixed dopaminergic agonism and antagonism</td>
<td>Aripiprazole</td>
<td>Facilitation of low-level stimulation of dopamine receptors, blockade of higher levels of stimulation</td>
</tr>
<tr>
<td>Dopamine D2 and D3 antagonism</td>
<td>Amisulpride</td>
<td>Blockade of cortical dopamine receptors, but not those in basal ganglia</td>
</tr>
</tbody>
</table>
Schizophrenia & Diabetes Mellitus

- Many studies shown ↑ risk in schizophrenia:
  - IGT, Insulin resistance
  - Type 2 Diabetes mellitus
    - 10% Schizophrenia > 6–8% general population
- Studies over several decades, predating both typical & atypical neuroleptics
- Many recent case reports/series:
  - Treatment emergent DM (sometimes severe with DKA)
  - Atypical > 1st Generation Antipsychotics
- Alternative hypothesis:
  - Worsening DM phenotype in schizophrenia population mirrors general population
# Diabetes Mellitus (DM) in Canada

## Magnitude of the Problem

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of People</th>
<th>% of Population</th>
<th>Cardiovascular Hospitalization</th>
<th>Lower Limb Amputation</th>
<th>New Dialysis/Yr</th>
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</thead>
<tbody>
<tr>
<td>1996</td>
<td>1.2 mill.</td>
<td>4</td>
<td>80,000</td>
<td>6,000</td>
<td>1,500</td>
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<tr>
<td>2006</td>
<td>1.9 mill.</td>
<td>6</td>
<td>158,000</td>
<td>10,000</td>
<td>2,500</td>
</tr>
<tr>
<td>2016</td>
<td>2.7 mill.</td>
<td>7</td>
<td>228,000</td>
<td>15,000</td>
<td>3,500</td>
</tr>
</tbody>
</table>

Based on diagnosed diabetes.

*Blanchard et al.*
Rising DM Prevalence (Diagnosed)

<table>
<thead>
<tr>
<th>Year</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>5.9</td>
</tr>
<tr>
<td>2005</td>
<td>6.2</td>
</tr>
<tr>
<td>2010</td>
<td>7.6</td>
</tr>
</tbody>
</table>

(Decimal Numbers = Percent of the population affected)
RCT Data

- 1 study (Pubmed “Antipsychotics & Diabetes”)
- 157 inpatients: schizophrenia or schizoaffective dx
- Randomized to:
  - clozapine, olanzapine, risperidone, or haloperidol
- 2 Periods: 8 week fixed dose → 6 week variable dose
- FBG, fasting cholesterol (Baseline, 8 wk, 14 wk)
RCT Data

● 157 patients to start:
  • 49 failed to complete 1\textsuperscript{st} 8 wk period (initial 31\% loss to F/up)
    – Breakdown of f/up as per Rx group not reported
  • 28 failed to complete 2\textsuperscript{nd} 6 wk period (18\% loss to F/up)
  • Overall 49\% loss to F/up

● Baseline Characteristics:
  • Only statistical difference between groups FBS:
    • clozapine, risperidone > haloperidol (P < 0.05)
RCT Data

● 7 (4.4%) patients had DM at baseline
  • Rx with OHA
  • BS dropped despite antipsychotic Rx (haloperidol, olanzapine, risperidone)

● 14 (8.9%) developed new DM over course of study
  • 6 clozapine, 4 olanzapine, 3 risperidone, 1 haloperidol  (NS)

● Effect of Antipsychotics on FBS:
  • Clozapine  ↑ 0.9 mM (P < 0.01)
  • Olanzapine  ↑ 0.8 mM (P < 0.02)
  • Haloperidol  ↑ 0.5 mM (P < 0.03)
  • Risperidone  NS
RCT Data

- **Effect of Antipsychotics on Fasting cholesterol:**
  - Clozapine $\uparrow 0.4$ mM ($P < 0.02$)
  - Olanzapine $\uparrow 0.5$ mM ($P < 0.04$)
  - Haloperidol NS
  - Risperidone NS

- **Weight Gain:**
  - Olanzapine 7.3 Kg ($P < 0.0001$)
  - Clozapine 4.8 Kg ($P < 0.0003$)
  - Risperidone 2.4 Kg ($P = 0.09$)
  - Haloperidol NS
RCT Data - Summary

- Only 1 RCT Study
- Study Flaws:
  - 49% loss to F/up
  - Very short F/up to P/up Adverse Metabolic Rxns
  - Baseline: higher FBS clozapine, risperidone groups
  - Fatal Flaws?

- Results:
  - 9% of all patients Rx with antipsyhotics developed new DM
  - clozapine, olanzapine, haloperidol ↑ FBS
  - clozapine, olanzapine ↑ Fasting Cholesterol
  - No correlation between weight gain and FBS in this study
Cohort Data

- Regie de l’Assurance Maladie du Quebec database
- 33,946 patients
  - Prescription for olanzapine or risperidone
- Development of DM:
  - Determined by censoring
  - Greater risk with olanzapine
  - Crude OR 1.08 (95% CI 0.89-1.31, P = 0.43)
  - Adjusted OR 1.20 (95% CI 1.0-1.43, P = 0.05)
    » Adjusted for age, sex, haloperidol use
- Their conclusion: ↑ DM risk olanzapine > risperidone
- Reality: Negative study
**Cohort Data**

*Buse et al:*

- Risk increased with all antipsychotics
- Risk increased with schizophrenia in general?

### Table 3

<table>
<thead>
<tr>
<th>Cohort</th>
<th>New cases (n)</th>
<th>Patients (n)</th>
<th>Patient-years</th>
<th>Incidence (per 1000 patient-years)</th>
<th>HRc Ratio 95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conventional antipsychotics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All combined</td>
<td>307</td>
<td>19,782</td>
<td>3645.57</td>
<td>84</td>
<td>3.5</td>
<td>3.1–3.9</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>133</td>
<td>8476</td>
<td>1568.39</td>
<td>85</td>
<td>3.1</td>
<td>2.6–3.7</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>62</td>
<td>3133</td>
<td>654.28</td>
<td>95</td>
<td>4.2</td>
<td>3.2–5.5</td>
</tr>
<tr>
<td><strong>Atypical antipsychotics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All combined</td>
<td>641</td>
<td>38,969</td>
<td>9571.18</td>
<td>67</td>
<td>3.1</td>
<td>2.9–3.4</td>
</tr>
<tr>
<td>Clozapine</td>
<td>7</td>
<td>277</td>
<td>103.95</td>
<td>67</td>
<td>3.3</td>
<td>1.4–8.0</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>194</td>
<td>13,863</td>
<td>3374.57</td>
<td>58</td>
<td>3.0</td>
<td>2.6–3.5</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>40</td>
<td>4196</td>
<td>1025.75</td>
<td>39</td>
<td>1.7</td>
<td>1.2–2.4</td>
</tr>
<tr>
<td>Risperidone</td>
<td>400</td>
<td>20,633</td>
<td>5066.90</td>
<td>79</td>
<td>3.4</td>
<td>3.1–3.8</td>
</tr>
<tr>
<td><strong>General patient population</strong></td>
<td>45,513</td>
<td>5,816,473</td>
<td>2,908,236.5</td>
<td>15.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Cohort Data

- Claims data for 2.5 million psychotic patients within health plans, analyzed retrospectively
- Increased risk of new DM:
  - conventional low-potency antipsychotics (OR 4.16)
  - conventional hi-potency antipsychotics (OR 2.13)
  - clozapine (OR 7.44), olanzapine (3.10)
- No increased risk with risperidone (OR 0.88)
**Case Series Data: DKA**

- 19 reported cases of DKA associated with atypical antipsychotics
- **Increased risk: women, younger age, lower weight**

<table>
<thead>
<tr>
<th>Variables</th>
<th>DM only, N = 26 (%)</th>
<th>DKA, N = 19 (%)</th>
<th>t test or $\chi^2$</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (female)</td>
<td>3.8</td>
<td>26.3</td>
<td>4.79</td>
<td>0.029</td>
</tr>
<tr>
<td>Race (African American)</td>
<td>42.3</td>
<td>52.6</td>
<td>1.07</td>
<td>0.585</td>
</tr>
<tr>
<td>Adjunctive medications</td>
<td>81.8</td>
<td>69.2</td>
<td>0.73</td>
<td>0.392</td>
</tr>
<tr>
<td>Overweight at baseline</td>
<td>100</td>
<td>58.3</td>
<td>9.44</td>
<td>0.002</td>
</tr>
<tr>
<td>Weight gain</td>
<td>47.6</td>
<td>36.4</td>
<td>0.372</td>
<td>0.542</td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td>36.0</td>
<td>38.9</td>
<td>0.039</td>
<td>0.981</td>
</tr>
<tr>
<td><strong>Mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>43 (6.8)</td>
<td>37 (8.9)</td>
<td>2.712</td>
<td>0.010</td>
</tr>
<tr>
<td>Weeks on atypical</td>
<td>20.9 (27.2)</td>
<td>18.0 (20.5)</td>
<td>0.385</td>
<td>0.702</td>
</tr>
<tr>
<td>Blood glucose (mg/dL)</td>
<td>481 (360)</td>
<td>750 (396)</td>
<td>2.34</td>
<td>0.024</td>
</tr>
</tbody>
</table>
Fig. 1. Time to presentation with diabetes mellitus or diabetic ketoacidosis after instituting atypical antipsychotic therapy ($N = 45$).
### TABLE 3. Baseline to end point changes in steady state glucose infusion rate, insulin levels, and insulin sensitivity index

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Change in M [mmol/min·kg (\times 10^{-3})]</th>
<th>Change in I [pmol/liter]</th>
<th>Change in M/I [(\times 10^{-5})]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine</td>
<td>-2.4 (16.0)</td>
<td>111.0 (266.4)</td>
<td>-4.63 (11.0)(^a)</td>
</tr>
<tr>
<td>Risperidone</td>
<td>-7.8 (11.6)</td>
<td>81.6 (266.4)</td>
<td>-3.7 (7.4)</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.3 (16.0)</td>
<td>-112.8 (260.4)</td>
<td>0.92 (7.4)</td>
</tr>
</tbody>
</table>

Data collected during the final hour of the clamps were used to calculate the steady state glucose infusion rate (M; millimoles per kg BW/min), steady state insulin level (I; picomoles per liter), and an insulin sensitivity index (M/I). Results are shown as the group mean change from baseline in M, I, and M/I. SDs are shown in parentheses. 

\(^a\) \(P < 0.05\) within a group.
Basic Science


Summary:

- Olanzapine and risperidone caused 3 Kg wt. Gain
- No evidence of reduced insulin secretion/β-Cell function
- Increased insulin resistance
  - Only statistically significant with olanzapine
  - Became nonsignificant when multivariate analysis controlled for weight gain
Do Atypical antipsychotics cause DM?

● 1 flawed RCT
  - 9% of patients Rx with any antipsyhotic developed new DM
  - clozapine, olanzapine, haloperidol ↑ FBS
  - clozapine, olanzapine ↑ Fasting Cholesterol
  - Less DM risk with Risperidone?

● Cohort Studies
  - Increased risk of DM due to schizophrenia itself or Rx with any antipsychotic (atypical or conventional)
  - Some studies suggest less DM risk with risperidone

● Case Reports/Studies
  - DKA, ? Positive de-challenge and re-challenge

● Basic Science
  - Normal insulin secretion, ↓ insulin sensitivity with ↑ weight
Why did this patient develop DKA?

- clozapine? quetiapine?
- Type 2 DM related to schizophrenia?
  - Underlying precipitant(s): pancreatitis, ileus, esophageal tear, pneumonia
- Pancreatitis with endocrine dysfn?
  - GB stone, EtOH, Triglycerides
  - Psychiatric co-interventions: Valproate
Could this have been predicted or prevented?

- **Risk factors for T2DM**
  - Obese, older, ethnic groups, FHx DM, etc.

- **Risk factors for DKA**
  - Thin, younger, female?

- **CDA 2003 Guidelines:**
  - Schizophrenia: “more frequent (than q3y) testing with either FPG or OGTT”
  - My suggestion: baseline and q6mos FBS, HbA1c, lipid profile
    - Not Evidence Based Suggestion!
  - Ideal screening/surveillance method needs to be investigated
Need for more Research…

- **Better RCTs, Cohort Studies**
  - Is there a risk or not with atypical antipsychotics?
  - Are some safer than others: risperidone?
  - Can DM complications be prevented if started on a new antipsychotic?
    - Screening/Surveillance
    - Exercise/diet
    - Prophylactic anti-diabetic Rx: metformin, acarbose, orlistat, TZD’s, sulfonylureas, insulin glargine

- **Basic Science**
  - Mechanisms?
Weight Gain Comparision of Atypical Antipsychotics

Incidence of ≥7% Increase in Body Weight in Short-Term Trials*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Percent of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole**</td>
<td>5.1</td>
</tr>
<tr>
<td>Paliperidone ER***</td>
<td>7.9</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>9.8</td>
</tr>
<tr>
<td>Risperidone</td>
<td>18.0</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>23.0</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>29.0</td>
</tr>
</tbody>
</table>

*Based on United States Product Inserts
**Error bars reflect reporting of weight gain in PI by baseline BMI
***confirmation of US PI
Many studies shown ↑ risk in schizophrenia:
  • IGT, Insulin resistance
  • Type 2 Diabetes mellitus
    – 10% Schizophrenia > 6–8% general population

Studies over several decades, predating both typical & atypical neuroleptics

Many recent case reports/series:
  • Treatment emergent DM (sometimes severe with DKA)
  • Atypical > 1st Generation Antipsychotics

Alternative hypothesis:
  • Worsening DM phenotype in schizophrenia population mirrors general population
RCT Data - Summary

- Only 1 RCT Study
- Study Flaws:
  - 49% loss to F/up
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  - Baseline: higher FBS clozapine, risperidone groups
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Diabetes and Antipsychotics

- **Schizophrenia & Diabetes Mellitus:**
  - Many studies shown ↑ risk in schizophrenia:
    - IGT, Insulin resistance
    - Type 2 Diabetes mellitus
      - 10% Schizophrenia > 6–8% general population
  - Studies over several decades, predating both typical & atypical neuroleptics

- **RCT Data – Summary:**
  - **Results:**
    - 9% of all patients Rx with antipsyhotics developed new DM
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- **1 flawed RCT, Cohort Studies, Case Reports/Studies**
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