Behavioral Health is Essential To Health

Prevention Works

Treatment is Effective

People Recover
Schizophrenia: Treating The Whole Person

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Doug Noordsy:
Research Funding: Janssen
Consulting: Pear Therapeutics
• What is Metabolic Dysregulation?
• Prevalence in Early Psychosis Population
• Impacts of Medication
• Guidelines for Testing/Monitoring
• Treatment Strategies
Metabolic syndrome occurs when a person has three or more of the following measurements:

- Abdominal obesity (Waist circumference > 40” in men, > 35” in women)
- Triglycerides >150 mg/dL
- HDL <40 mg/dL in men or <50 mg/dL in women
- Systolic >130 mmHg or diastolic >85 mmHg
- Fasting glucose >100 mg/dL

(About Metabolic Syndrome, 2016)
Life Span

• 10-25 year shortened life span
  ➢ Lifestyle
    • Smoking
    • Sedentary
  ➢ Medical Comorbidities
    • Cardiovascular disease
    • Diabetes
  ➢ Medication effects
  ➢ Suicide

(Laursen, 2012)
- Hypothalamus
  - Appetite Regulation/Satiety
  - Control of hepatic glucose production
- Liver
  - Hepatic Glucose production
  - De Novo lipogenesis
- Pancreas
  - Insulin/Glucagon secretion
- Gut
  - Insulin/Glucagon regulation
- Muscle
  - Glucose uptake
- Fat
  - Glucose uptake
  - Inflammatory state
  - Adipokine action
Schizophrenia

• Core Symptoms
  • Delusions
  • Hallucinations
  • Negative Symptoms
  • Cognitive Symptoms
  • Metabolic Symptoms?
Pre-Antipsychotic Era

Fig. 1.—Changes in true blood glucose concentration after ingestion of 100 gm. of glucose. Open circles refer to patients improved after treatment. Lines indicate average changes, the broken line indicating average changes in patients improved after treatment.

(Henneman, 1954)
## Drug-Naive

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Patients</th>
<th>Control Subjects</th>
<th>Relatives</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fasting Glucose</strong> (mmol/L)</td>
<td>4.7 ± 0.54</td>
<td>4.5 ± 0.48</td>
<td>3.3 ± 0.57</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Two-Hour Glucose</strong> (mmol/L)</td>
<td>6.0 ± 1.69</td>
<td>4.5 ± 0.81</td>
<td>5.7 ± 1.77</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td><strong>HbA1c (%)</strong></td>
<td>5.3 ± 0.4</td>
<td>5.2 ± 0.3</td>
<td>5.3 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Fasting Insulin</strong> (pmol/L)</td>
<td>38.8 ± 20.1</td>
<td>27.3 ± 12.2</td>
<td>40.2 ± 23.9</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td><strong>Two-Hour Insulin</strong> (pmol/L)</td>
<td>205.2 ± 124.8</td>
<td>77.5 ± 36.6</td>
<td>160.0 ± 116.2</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td><strong>HOMA-IR</strong></td>
<td>1.15 ± 0.7</td>
<td>0.78 ± 0.3</td>
<td>1.15 ± 0.8</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td><strong>Leptin (nmol/L)</strong></td>
<td>3.7 ± 2.3</td>
<td>3.6 ± 3.2</td>
<td>3.5 ± 1.6</td>
<td>NS</td>
</tr>
</tbody>
</table>

(Spelman, 2006)
Meta-Analysis – Fasting Glucose

(Schizophrenia Research, 2017)
Meta-Analysis – Insulin Resistance

![Graph showing meta-analysis results for insulin resistance in schizophrenia]

(Schizophrenia Research, 2017)
# Danish Cohort

## TABLE 2. Age-Specific Incidence Rates of Diabetes Mellitus in People With and Without Schizophrenia in a Population Cohort

<table>
<thead>
<tr>
<th>Group and Age</th>
<th>Person-Years</th>
<th>Incident Diabetes</th>
<th>Incidence Rate&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Difference From People Without Schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>People without schizophrenia</strong>&lt;br&gt;(N=2,727,565)</td>
<td>Person-Years (millions)</td>
<td>N</td>
<td>Rate</td>
<td>95% CI</td>
</tr>
<tr>
<td>0–9 years</td>
<td>23.66</td>
<td>3,449</td>
<td>0.15</td>
<td>0.14–0.15</td>
</tr>
<tr>
<td>10–14 years</td>
<td>9.16</td>
<td>2,654</td>
<td>0.29</td>
<td>0.28–0.30</td>
</tr>
<tr>
<td>15–19 years</td>
<td>7.34</td>
<td>2,462</td>
<td>0.33</td>
<td>0.32–0.35</td>
</tr>
<tr>
<td>20–24 years</td>
<td>5.15</td>
<td>1,776</td>
<td>0.35</td>
<td>0.33–0.36</td>
</tr>
<tr>
<td>25–29 years</td>
<td>2.98</td>
<td>2,100</td>
<td>0.70</td>
<td>0.67–0.75</td>
</tr>
<tr>
<td>30–36 years</td>
<td>1.24</td>
<td>1,474</td>
<td>1.18</td>
<td>1.12–1.25</td>
</tr>
<tr>
<td>0–36 years</td>
<td>49.53</td>
<td>13,915</td>
<td>0.28</td>
<td>0.28–0.29</td>
</tr>
<tr>
<td><strong>People with schizophrenia</strong>&lt;br&gt;(N=8,945)</td>
<td>Person-Years</td>
<td>N</td>
<td>Rate</td>
<td>95% CI</td>
</tr>
<tr>
<td>0–9 years</td>
<td>29.12</td>
<td>0</td>
<td>0.00</td>
<td>–</td>
</tr>
<tr>
<td>10–14 years</td>
<td>269.44</td>
<td>0</td>
<td>0.00</td>
<td>–</td>
</tr>
<tr>
<td>15–19 years</td>
<td>4,824.17</td>
<td>13</td>
<td>2.69</td>
<td>1.56–4.64</td>
</tr>
<tr>
<td>20–24 years</td>
<td>16,263.53</td>
<td>59</td>
<td>3.63</td>
<td>2.81–4.68</td>
</tr>
<tr>
<td>25–29 years</td>
<td>16,941.88</td>
<td>75</td>
<td>4.43</td>
<td>3.53–5.55</td>
</tr>
<tr>
<td>30–36 years</td>
<td>8,987.59</td>
<td>56</td>
<td>6.23</td>
<td>4.80–8.10</td>
</tr>
<tr>
<td>0–36 years</td>
<td>47,315.73</td>
<td>203</td>
<td>4.29</td>
<td>3.74–4.92</td>
</tr>
</tbody>
</table>

<sup>a</sup> Incidence rate of diabetes mellitus per 1,000 person-years.

<sup>b</sup> Two-sided exact test.
# Danish Cohort (cont.)

## TABLE 3. Endogenous Risk for Diabetes Mellitus in Antipsychotic-Naive People With Schizophrenia in a Population Cohort

<table>
<thead>
<tr>
<th>Group</th>
<th>Incidence Rate&lt;sup&gt;a&lt;/sup&gt;</th>
<th>95% CI&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Adjusted Hazard Ratio</th>
<th>95% CI</th>
<th>Number Needed to Harm&lt;sup&gt;b&lt;/sup&gt;</th>
<th>95% CI&lt;sup&gt;b&lt;/sup&gt;</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up censored at first antipsychotic prescription&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>People without schizophrenia (N=2,736,510)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.27</td>
<td>0.27–0.28</td>
<td>1.00&lt;sup&gt;e&lt;/sup&gt;</td>
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<td></td>
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<tr>
<td>People with schizophrenia (N=4,322)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2&lt;sup&gt;g&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No use of antipsychotics during the entire follow-up&lt;sup&gt;h&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>People without schizophrenia (N=2,673,114)</td>
<td>0.27</td>
<td>0.27–0.28</td>
<td>1.00&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>People with schizophrenia (N=1,154)</td>
<td></td>
<td></td>
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<tr>
<td>Model 1&lt;sup&gt;f&lt;/sup&gt;</td>
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<tr>
<td>Model 2&lt;sup&gt;g&lt;/sup&gt;</td>
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</tbody>
</table>

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<sup>a</sup> Incidence Rate and 95% CI are estimated from the Cox proportional hazards model.  
<sup>b</sup> Number Needed to Harm (NNH) is calculated as 1/Attributable Risk Difference (AR).  
<sup>c</sup> Follow-up censored at first antipsychotic prescription.  
<sup>d</sup> People without schizophrenia.  
<sup>e</sup> Adjusted for age, sex, and calendar year.  
<sup>f</sup> Model 1 adjusted for age, sex, and calendar year.  
<sup>g</sup> Model 2 adjusted for age, sex, calendar year, and baseline body mass index (BMI).  
<sup>h</sup> No use of antipsychotics during the entire follow-up.
Microbiome in Early Psychosis

• Higher rates of antibiotic treatment prior to onset

• Gut bacterial colonies differ from general population
Challenges for Studying Medication Impact

• First exposure is fleeting
  Changes occur rapidly

• Diagnostic Imprecision
  Heterogeneity of APD effects
  Heterogeneity of schizophrenia

• Comorbidities
  Lifestyle factors
  Substances
  Previous exposures
Findings: Animals

- Hypothalamic changes from olanzapine
  - Primary effect on gene expression

- Increased food intake
  - Slowed metabolism

- Hyperglycemia within one hour of 1st dose
  - Marked hepatic insulin resistance
EUFEST

EUFEST - Gain >7% weight gain from baseline

- Olanzapine
- Quetiapine
- Amisulpride
- Haloperidol
- Ziprasidone

EUFEST: Weight Change from Baseline (Kg)

(Fleischhacker, 2013)
Findings in Schizophrenia

• Clinical Conundrum

• Obesity and Impaired Glucose Metabolism
  1. Which comes first?
  2. Separate mechanisms?
  3. Central or peripheral?
Antipsychotic Signaling Pathway(s)
Dopamine Receptors

- Best studied in the CNS
  - Putative target of APD therapy
  
  However...

- Dopamine receptors are also expressed outside the CNS
  - Pancreas

  - $D_1R-D_5R$ expressed in insulin-secreting beta cells
Dopamine’s Role in the Pancreas?

- L-DOPA triggers hyperglycemia
- Dopamine inhibits glucose-stimulated insulin release
  - D₂R-dependent
- Unclear if these effects are primarily modulated in the pancreas, CNS or both
What Role(s) APDs Play in the Pancreas?

(Rubí & Maechler, 2010)
Clinical Relevance: Hyperinsulinemia

(Mehran et al., 2012)
Take Home - Pancreas

• Pancreatic beta cells express DA signaling machinery.

• Glucose stimulation increases beta cell DA secretion.

• Blockade of D2R and D3R by APDs blocks DA’s inhibition of insulin secretion (increases insulin).
People in Early Psychosis

People in Early Psychosis at Highest Risk for Metabolic Side Effects of Antipsychotics

• Often underweight at baseline
• First exposure to antipsychotic medications
• Age/stage of life
  – May still be growing
Genetic Correlations to Schizophrenia

Duncan et al, Genetic correlation analysis reveals transdiagnostic...Schiz Bull, in press
Guidelines for Monitoring

• Lab Testing
  – Baseline
  – 3 months after initiation
  – Annual

(American Diabetes Association, 2004)
Guidelines for Monitoring (cont.)

- Tests:
  - Lipids
    - Triglycerides
  - Hemoglobin A1c
  - Fasting Glucose

(American Diabetes Association, 2004)
• At each visit
  – Vital signs
    • BP
    • Weight
      – Review weight trends with patient
• Initiate and maintain relationship with PCP

(American Diabetes Association, 2004)
Treatment Options

• Lifestyle/Behavioral Management
• Diet
  – microbiome
• Physical Exercise
• Medication
  – Metformin or other metabolic medications
• Integrated healthcare
Diet

• Modified Mediterranean diet
• Fish & nut oils
• Leafy greens
• Citrus
• Microbiota Accessible Carbos
Medication Options

• Antipsychotic medications
  – Relative risks for weight gain, insulin resistance

• Metabolic medications
  – Appetite suppression
  – Glucose regulation
  – Lipid regulation
FIGURE 1. 95% Confidence Intervals for Weight Change After 10 Weeks on Standard Drug Doses, Estimated From a Random Effects Model

Allison, 1999
## Antipsychotic Side Effects

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>CPZ</th>
<th>HAL</th>
<th>CLZ</th>
<th>RSP/PPD</th>
<th>OLZ</th>
<th>QTP</th>
<th>ZPS</th>
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<tbody>
<tr>
<td>↑QTc</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Sedation</td>
<td>++++</td>
<td>+</td>
<td>++++</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
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<td>TD</td>
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<td>0</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Wt gain</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>+/-</td>
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<tr>
<td>Glucose</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>0</td>
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# Antipsychotic Side Effects (cont.)

<table>
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<tr>
<th></th>
<th>EPS</th>
<th>PRO</th>
<th>QTc</th>
<th>Sedation</th>
<th>TD</th>
<th>Wt gain</th>
<th>Glu</th>
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<tr>
<td>ARI</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
<td>?/++</td>
<td>+</td>
<td>0</td>
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<tr>
<td>ANP</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>+++</td>
<td>?</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>ILO</td>
<td>0</td>
<td>++</td>
<td>++</td>
<td>++</td>
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<td>LUR</td>
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<td>+</td>
<td>0</td>
<td>+/-</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
“Will I still be able to not exercise?”
Dendritic Spine Reduction in Schizophrenia

- Dendritic spines: area 46
- Non-schizophrenic individual
- Schizophrenic individual #1
- Schizophrenic individual #2

(Glantz, 2000)
Aerobic Exercise Improves Cognitive Functioning in People with Schizophrenia

- Cognitive deficits pervasive, treatment options limited
- 10 controlled trials, 385 patients
- 20-60” 2-4x/week, 4-24 weeks aerobic or mixed
- Exercise significantly improved global cognition
- Effect size = 0.43
- Greater exercise → greater cognitive gain
- Exercise trainer → greater efficacy
- Working memory: $g = 0.39$
- Social cognition: $g = 0.71$
- Attention/vigilance: $g = 0.66$
- Processing speed, verbal memory, visual memory, problem solving = NS

(Firth et al, 2016)
How Does Exercise Exert Beneficial Effects?

- **Neurotransmitter effects**
  - Endorphins, endocannabinoids (AEA)\(^1\)
  - Norepinephrine, serotonin, dopamine\(^2\)

- **Neurotrophic effects**
  - *Brain Derived Neurotrophic Factor* (BDNF)\(^1\)

- **Glycogen storage in astrocytes**
  - Frontal cortex + hippocampus\(^3\)

- **Tighter glucose regulation\(^4\)**

(Meeusen, 1995)
(Matsui, 2012)
Jensen, 2011)
Exercise Recommendations for Managing Psychiatric Disorders

- Consider current capacity
- 30 to 60 min, 3 to 7 days/week
- More is better, to a point (3 hours/week)
- Mix aerobic + strength training (150 + 2)
- Intensity: 60% to 85% HRmax (220 - age)
- Have client choose activity
  - Access, cost, familiarity, enjoyment
  - Variation vs. repetition

HRmax, maximum heart rate
Assessing Response to Exercise

- Adherence to plan
- Changes in core symptoms
- Changes in sleep, appetite, energy, well-being
- Refinement of plan
- Triggers to lapse
- Goals
Take Home - Exercise

• Metabolic risks are greatest at onset of treatment
• Exercise is a potent and important treatment for mind and body
• Discuss diet and exercise at every visit
Take Home

• Links between psychosis and metabolic disease
• Consider metabolic risks of antipsychotic medication choice
  – Shared Decision Making
• Monitor metabolic outcomes closely
• Intervene early and often
Resources

- PEPPNET: https://med.stanford.edu/peppnet.html
- Psychosis Summit: http://www.psychosisissummit.com
QUESTIONS?