Physical Health in Schizophrenia

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What are some factors that affect the physical health of people with schizophrenia?

- Smoking
- Lack of exercise
- Poor eating habits
- Poor hygiene
- Medication side effects
- Stress
Low Levels of Physical Fitness

• Cardiovascular diseases (CVD)
• Metabolic syndrome (MetS)
• Independent risk factor for all-cause mortality
Metabolic Syndrome

3 or more of the following:

- Abdominal obesity (waist circumference >40” for men or >35” for women)
- Elevated triglyceride levels (>150 mg/dL)
- Reduced HDL cholesterol (<40 mg/dL for men or <50 mg/dL for women)
- Elevated fasting glucose (>100 mg/dL)
- Elevated blood pressure (> 130/85 mm Hg)

AHA, NHLBI 2004
CATIE Study (N=1460)

• Overall Metabolic Syndrome
  – 43% (AHA criteria)
  – 138% higher prevalence in males compared to general population
  – 251% higher prevalence in females compared to the general population

• Untreated Comorbidities
  – 30% diabetes
  – 62% hypertension
  – 88% dyslipidemia

Physical Fitness in Schizophrenia

• Reduced
  • whole body balance,
  • leg muscle strength,
  • abdominal muscular endurance
  • running speed

• Low physical fitness is associated with
  • illness duration,
  • smoking,
  • the presence of MetS
  • more severe negative, depressive, and cognitive sx's.

## Metabolic Disturbance in Schizophrenia

<table>
<thead>
<tr>
<th></th>
<th>Schizophrenia</th>
<th>General Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of Obesity</td>
<td>40-62%</td>
<td>30%</td>
</tr>
<tr>
<td>Prevalence of Diabetes</td>
<td>2-3x higher</td>
<td></td>
</tr>
<tr>
<td>Mortality Risk</td>
<td>5x higher</td>
<td></td>
</tr>
<tr>
<td>Life Expectancy</td>
<td>61 years</td>
<td>76 years</td>
</tr>
<tr>
<td>Metabolic Syndrome</td>
<td>30-60%</td>
<td>22%</td>
</tr>
</tbody>
</table>

Kelly, Boggs, Conley PCNA 2007
# Obesity in Schizophrenia

- **BMI** = \( \frac{Wt(kg)}{Ht(m^2)} \)

<table>
<thead>
<tr>
<th></th>
<th>BMI</th>
<th>WHO classification</th>
<th>Popular description</th>
<th>Population</th>
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</thead>
<tbody>
<tr>
<td><strong>Prevalence of Obesity</strong></td>
<td>&lt; 18.0</td>
<td>Underweight</td>
<td>Thin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18.5-24.9</td>
<td>------</td>
<td>“Normal” weight</td>
<td></td>
</tr>
<tr>
<td><strong>Prevalence of Diabetes</strong></td>
<td>25.0-29.9</td>
<td>Grade 1 overweight</td>
<td>Overweight</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30.0-39.9</td>
<td>Grade 2 overweight</td>
<td>Obesity</td>
<td></td>
</tr>
<tr>
<td><strong>Mortality Risk</strong></td>
<td>40.0</td>
<td>Grade 3 overweight</td>
<td>Morbid obesity</td>
<td></td>
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<tr>
<td><strong>Life Expectancy</strong></td>
<td>61</td>
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Kelly, Boggs, Conley PCNA 2007
What causes Obesity?

Fundamentals of Energy Balance Regulation

Environment and Lifestyle

- Taste & Smell “Palatability”
- Availability & Cost/Reward Optimization
- Clock

Homeostatic Regulator
Hypothalamus & Brainstem

Cortico-Limbic and other Systems

Energy Intake

Nutrient Sensing

Cumulative error of 1% (~25 kcal/day)

Energy Expenditure

> 60 Kg weight gain over adult lifespan (60 tons of food)

Internal Milieu

Nutrient Partitioning

Genetic

Individual Predisposition / ‘Wiring’

Early life events

What causes Obesity?

Lenard & Berthoud Obesity, 2008

“Hyperphagia” Baltimore June 4/5, 2009
Risk Factors for Obesity in People with Schizophrenia

• Sedentary lifestyle
• Lack motivation
• Limited resources for nutritional and educational services.
• Possible genetic link to diabetes
• Medication side effects
What are the Consequences of Obesity?

- Lowered self image and decreased social interactions
- Non-adherence to medication
- Medical problems
  - hypertension
  - dyslipidemia
  - non-insulin dependent diabetes
  - others (osteoarthritis, cancers, gout, gallbladder disease, respiratory dysfunction, possible hepatic complications)
  - Cardiovascular disease and increased mortality
Antipsychotic-Induced Weight Gain

- 40 - 80% of patients taking an antipsychotic medication experience weight gain resulting in body weight that exceeds ideal levels by ≥20%.

After only six months….

- Over one-quarter (26.3%) developed a metabolic syndrome
- Abdominal perimeter increased by 14.6 cm
- Triglyceride levels increased by 48.99 mg/dl
- Fasting blood glucose levels increased by 10.72 mg/dl

Estimated Mean Weight Gain at 10 wks Meta-analysis Using Random Effects Regression

Follow-up meta-analysis by same group 10 years later (Parsons et al., 2009)
Mechanisms of Weight Gain/Obesity

• Hyperphagia and increased meal size have been implicated as possible significant contributors to the problem.

• Clozapine and olanzapine have both been associated with food craving and binge eating in people with schizophrenia.

Disruption in Satiety Signaling in People with Schizophrenia: A Comparison of Antipsychotics

Kimberly R. Warren, M. Patricia Ball, Laura M. Rowland, Robert W. Buchanan, Robert P. McMahon, Zoe S. Warwick

in manuscript preparation
Measuring Hunger/Satiety

• Self-report
  – Visual analogue scale (VAS)
  – Likert scale

• Behavioral
  – Preload-test meal paradigm
Test Meal Intake

Test Meal Consumption

![Bar chart showing kcal intake under different conditions and with different medications.](chart)

- Olanzapine
- Clozapine
- Controls

- Condition: Ensure vs. Water

- Kcals consumed: 0 to 500

The chart illustrates the difference in kcal intake between conditions and medications, with Olanzapine and Clozapine showing a higher intake compared to controls.
Hunger Ratings: Change from Baseline

Control: t(10) = -2.834, p < 0.05

Olanzapine: t(11) = 0.378, p = 0.713

Clozapine: t(12) = -2.105, p = 0.057

Conventional: t(5) = -0.772, p = 0.48
Waist to Hip Ratios

![Graph showing waist to hip ratios for Olanzapine, Clozapine, Conventional, and Control groups. The graph includes error bars and indicates a statistically significant result with an F(3,33) = 5.378, p < 0.01.]}
Conclusions

• Ppl with SCZ tend to consume more than controls in a preload-test meal investigation.
• Ppl on olanzapine appear to have a greater disconnect between hunger ratings and the amount consumed than the other groups.
• Disruption in satiety signaling is a potential mechanism for the weight gain associated with SGAs.
• There are other factors involved in the eating behavior of ppl with SCZ.
Effects of the Cannabinoid-1 Receptor Antagonist/Inverse Agonist Rimonabant on Satiety Signaling In Overweight People with Schizophrenia: A Randomized, Double-Blind Pilot Study

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3. Chemistry and Drug Metabolism Section, Intramural Research Program, National Institute on Drug Abuse, NIH, Baltimore, MD

Funded, in part, from an NIMH R34 (PI: Buchanan) and NIDA contract (PI: Kelly)
Rimonabant

- Cannabinoid-1 (CB-1) receptor antagonist that promotes weight loss in the general population
- Approved for use in 46 countries worldwide prior to 2008; not approved in US
- Pulled from European Union in Oct 2008
Implications of CB$_1$ Receptor Activation

**Central Nervous System**

- Hypothalamus
- Limbic system

↑Appetite
↑Motivation to eat/smoke

**Peripheral Tissue**

- Liver
- GI tract
- Skeletal muscle

↑Lipogenesis
Altered glucose metabolism

Study Design Overview

- 16-week double-blind treatment with rimonabant (20 mg/day) or placebo added to current antipsychotic treatment
- Target N=60

- **Aim**
  - Does rimonabant enhance satiety signaling relative to placebo?
    - Weight and waist circumference baseline and every 4 weeks

- **Methods**
  - Fasting glucose, insulin and lipid panel at baseline, 8 and 16 weeks
  - HbA1C, Adiponectin, Satiety baseline and endpoint
    - Adiponectin is a protein hormone that modulates a number of metabolic processes, including glucose regulation and fatty acid catabolism. It is secreted from adipose tissue.
  - Study had a weekly psychosocial and exercise program for all participants (adapted from Ganguli and Brar 2002)
## Changes in Satiety over 16-week Trial (Behavioral)

One person from placebo group did not participate in satiety paradigm.

<table>
<thead>
<tr>
<th></th>
<th>Rimonabant (N=7 BL, N=4 EOS)</th>
<th>Placebo (N=7 BL, N=4 EOS)</th>
<th>Mixed model treatment difference estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weeks</td>
<td>Assessment</td>
<td>Weeks</td>
</tr>
<tr>
<td>Total (kcal)</td>
<td>0</td>
<td>64.4 ± 68.0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>53.3 ± 50.2</td>
<td>16</td>
</tr>
<tr>
<td>Wheat Thins ® (kcal)</td>
<td>0</td>
<td>40.6 ± 53.1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>38.3 ± 52.2</td>
<td>16</td>
</tr>
<tr>
<td>Nilla Wafers ® (kcal)</td>
<td>0</td>
<td>23.9 ± 35.2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>15.0 ± 20.9</td>
<td>16</td>
</tr>
</tbody>
</table>
Conclusions

• kcal consumption tended to decrease with rimonabant, though not statistically significant

• Implications for CB-1 receptor targeting to improve metabolic parameters in people with schizophrenia.
Chief Brain Pathways involved in Eating Behavior

Figure 2  A schematic representation of the chief brain pathways involved in the regulation of eating behavior. ARC, arcuate nucleus; NTS, nucleus of the solitary tract; CCK, cholecystokinin; GLP-1, glucagon-like peptide 1; PYY, peptide YY. PVN, paraventricular nucleus; LHA, lateral hypothalamic area; PFA, perifornical area; NPY, neuropeptide Y; AGRP, Agouti-related peptide; POMC, pro-opiomelanocortin; CART, cocaine- and amphetamine-regulated transcript; CRH, corticotropin-releasing hormone; TRH, thyrotropin-releasing hormone; OX, oxytocin; MCH, melanin-concentrating hormone.

OT in Prader-Willi Syndrome

- Decreased numbers of PVN OT neurons have been found in Prader-Willi syndrome and correlate with the hyperphagia and obesity of this illness.

Body weight and fat mass. Body weight curves of Oxt<sup>-/-</sup> (n = 10) and Oxt<sup>+/+</sup> (n = 10) male and female mice. No body weight difference between control and knockout mice until 2nd month of age has been observed. Differences in the body weight between Oxt<sup>-/-</sup> and wild-type mice were observed at 3rd month of age. No differences between gender were observed within Oxt<sup>-/-</sup> or Oxt<sup>+/+</sup> mice. *Significantly different with respect to Oxt<sup>+/+</sup> with $P < 0.005$ (a). Weight of abdominal fat pad in 6 months old Oxt<sup>-/-</sup> and Oxt<sup>+/+</sup> males and females mice. *Significantly different with respect to Oxt<sup>+/+</sup> with $P < 0.05$ (b).

• The hyperphagia experienced during pregnancy has been shown to be likely due to the brain adapting to the high levels of OT secreted, and, therefore becoming less responsive.

  

• Abnormal values of OT have been found in the hypothalamic PVN, internal pallidal segment and substantia nigra of post-mortem brains of people with schizophrenia.

  
Design

Double-blind, randomized study with two, counterbalanced testing occasions involving a single dose of 1) oxytocin nasal spray and 2) a placebo.

**Aim 1:** To determine the effect of intranasal oxytocin on satiety signaling in people with schizophrenia.

**Hypothesis 1:** Participants will have greater satiety signaling, indicated by less consumption, during the oxytocin condition relative to placebo.

**Aim 2:** To determine the effect of intranasal oxytocin on appetite hormone levels.

**Hypothesis 2:** Participants will show a slower and less dramatic drop of postprandial leptin, and lower levels of postprandial insulin in the oxytocin condition relative to placebo.

![Testing Day Timeline](image)
Strategies for Weight Prevention and Weight Loss

• Treatments for weight gain and obesity include:
  – Behavioral modifications such as diet and exercise
  – Possible pharmacological treatment

• Schizophrenia PORT has no pharmacologic evidence-based recommendations.
Exercise

- **Benefits**
  - Neurocognition
    - Pajonk et al., 2010
    - Friedman et al., 2010
  - Symptoms
  - Inflammation
  - CV mortality

- **Challenges**
  - Motivation
  - Access
  - Motivation?
Study Overview

• 10-week training session
  – 3 supervised walking/jogging sessions weekly
  – once weekly educational group on healthy behaviors

• Onsite 5K event

• Laboratory and psychological measures at baseline and end of study
Participation

- 14 of 17 (82%) participated in the training sessions and completed the 5K
- 11 of 17 (64.7%) participated in all training sessions
- 14 of 17 (82.4%) participated in 50% or more of the sessions
- 17 (100%) participated in 25% or more of the sessions
Conclusions

• Exercise sessions and the 5K were a means for ppl with schizophrenia to interact with others in a de-stigmatizing manner

• Training for and completing a 5K event is feasible in a population with chronic schizophrenia

• It is possible to achieve a high rate of adherence in ppl with schizophrenia to an exercise program conducted in preparation for a 5K event
Hippocampal Plasticity in Response to Exercise in Schizophrenia


Figure 3. T1-weighted magnetic resonance images in the sagittal and coronal plane, with the right hippocampus marked in blue, comparing baseline (A and B) and end point (C and D) of the patient in the schizophrenia exercise group with the largest increase in hippocampal volume (from 3.898 cm$^3$ to 4.667 cm$^3$; +19.7%).
Both HTN and BMI $>25$ exert negative effects on neurocognition

Effects of Aerobic Exercise on Neurocognition in Schizophrenia

Primary Aim:

Aim 1: To assess the effects of 12 weeks of aerobic exercise on neurocognition (MATRICS Consensus Cognitive Battery (MCCB) and Serial Reaction Time Test (SRTT) in men and women with schizophrenia compared to control group.
Effects of Aerobic Exercise on Neurocognition in Schizophrenia

Secondary Aims:

Aim 2: To determine the effects of 12-weeks of aerobic exercise on physical fitness ($VO_2$ max), body fat (whole body by dual energy x-ray absorptiometry and regional fat by computed tomography), and blood pressure and the effects of those changes on neurocognition in men and women with schizophrenia compared to control group.

Aim 3: To examine the effects of aerobic exercise on insulin resistance (HOMA-IR), glucose tolerance, glucose and insulin area under curve during an oral glucose tolerance test, lipid profiles, and endothelial (intercellular and vascular adhesion molecules) and inflammatory markers (c-reactive protein, cytokines and serum amyloid alpha), and adipokines (adiponectin and leptin) in relation to neurocognitive performance.
Genetic Link between Schizophrenia and Abnormal Glucose Metabolism?

- N=26 drug-naïve first-episode and N=26 healthy controls
  - >15% of patients had impaired fasting glucose tolerance (0% controls)
  - Patients had higher FBG, insulin and cortisol

- N=160 drug-naïve first-episode and N=200 controls
  - Though weight and BMI was higher in controls,
  - Diabetes higher in patients (8%) than controls (1%) and FBG significantly higher in patients

- Suggests a genetic link between schizophrenia and abnormal glucose metabolism which is exacerbated by medications

Ryan et al 2003, Verma et al 2009
Conclusions

- Ppl with SCZ tend to live 25 years less than the general population, mainly do to preventable diseases.
- Obesity and its consequences affect ppl with SCZ more than the general population.
- Antipsychotics are partially responsible.
- The mechanisms are not known.
- Future work involving physiological mechanisms and behavioral interventions needs to be done.
- Prevention and early treatment of weight gain are critical to improving the long-term health of ppl with SCZ.