Early Intervention in Schizophrenia: Targeting Metabolic Dysfunction

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Speaker Profiles

Christoph Correll, MD

Position: Dr. Correll is a Professor of Psychiatry at Hofstra Northwell School of Medicine, New York, NY, and Medical Director of the Recognition and Prevention (RAP) program at the Zucker Hillside Hospital, New York, NY.

Education: Dr. Correll completed his medical studies at the Free University of Berlin, Germany, and the Dundee University Medical School in Dundee, Scotland. He completed both his general psychiatry residency and child and adolescent psychiatry fellowship at the Zucker Hillside Hospital in New York, NY.

John Newcomer, MD

Position: Dr. Newcomer is a Professor of Integrated Medical Science at the Charles E. Schmidt College of Medicine at Florida Atlantic University (FAU) in Boca Raton, Florida. Dr. Newcomer has served as a principal investigator on research grants funded through the National Institutes of Health for more than 20 years, and has held a series of research leadership positions at Washington University in St. Louis, the University of Miami in Florida, and at FAU where he served as Vice Dean for Research and Innovation.

Education: Dr. Newcomer received his medical degree from Wayne State University School of Medicine in Detroit, Michigan. He completed his residency and research fellowship in psychiatry at Stanford University School of Medicine.
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Objectives

• Provide an overview of the potential importance of early intervention in psychosis

• Discuss possible metabolic effects of treatment

• Review challenges/barriers to implementing screening and explore integrated care approaches in overcoming such barriers

• Examine primary prevention/intervention for cardiometabolic disease
EARLY INTERVENTION
Developmental Model of Schizophrenia


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Early Intervention in Schizophrenia: Rationale and Challenges

• **Rationale**
  - The longer the untreated illness, the worse the outcome\(^1\)
  - Continuing cognitive decline early in the course of illness\(^2-4\)
  - Progressive gray-matter reductions during early course of illness\(^5\)

• **Challenges**
  - Current treatments are limited by efficacy and side effects\(^6\)
  - Unclear whether antipsychotics contribute to structural brain changes\(^7\)
  - Benefits of early intervention may not be sustained with longer follow-ups\(^8\)


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IRIS: Components of Early Intervention Programs

IRIS, Incident Response Improvement System.
NIMH Study: Recovery After an Initial Schizophrenia Episode (RAISE)

- N = 404
- Age: 15-40 years
- Diagnoses: schizophreniform disorder, schizophrenia, schizoaffective disorder, psychotic disorder NOS, acute psychotic disorder
- < 6 months antipsychotic treatment
- Cluster randomized assignment of 34 centers to integrated care (NAVIGATE) or community care
- Treatment and follow-up for >/=2 years
- Primary outcome: quality of life
- Secondary outcomes: service utilization, cost, subjective well-being, relapses, hospitalization, recovery, cardiometabolic health
RAISE: NAVIGATE Treatment Program

• Team based
  – Shared decision-making
  – Strength & resiliency focus
  – Psychoeducational teaching skills
  – Motivational enhancement teaching skills
  – Collaboration with natural supports

• Four components
  – Psychopharmacology – COMPASS*
  – Individual resiliency training (IRT)
  – Family psychoeducation
  – Supported employment/education

*A NAVIGATE developed computerized clinical decision making tool accessed via a secure web-based platform.

RAISE, Recovery After an Initial Schizophrenia Episode.
## RAISE Demographics: Adjusted for Cluster Design

<table>
<thead>
<tr>
<th></th>
<th>NAVIGATE</th>
<th>Community Care</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age and Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (mean)</td>
<td>23.18</td>
<td>23.08</td>
<td></td>
</tr>
<tr>
<td>Males (%)</td>
<td>78</td>
<td>66</td>
<td>.05</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White (%)</td>
<td>62</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>African American (%)</td>
<td>28</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Other (%)</td>
<td>7</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td><strong>Role Functioning</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In school (%)</td>
<td>16</td>
<td>26</td>
<td>.03</td>
</tr>
<tr>
<td>Working (%)</td>
<td>13</td>
<td>17</td>
<td></td>
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<tr>
<td><strong>Prior Hospitalization (%)</strong></td>
<td>76</td>
<td>81</td>
<td>.05</td>
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</table>

RAISE, Recovery After an Initial Schizophrenia Episode.
RAISE: PANSS Total Score Change Over 2 Years

Group by Time Interaction ($P = 0.016$)

DUP by Time Interaction ($P = 0.043$)

Cohen’s $d = -0.29$

PANSS Total Score

Median DUP = 74 weeks

CC, Community Care, DUP, duration of untreated psychosis; NAV, NAVIGATE; PANSS, Positive and Negative Syndrome Scale, RAISE, Recovery After an Initial Schizophrenia Episode.

Role of Antipsychotic Medications in Early Intervention

- Studies have demonstrated that first-episode patients may often respond to low doses of antipsychotic medications¹:
  - Some studies have shown that more than 80% of such patients who do not receive antipsychotic treatment may experience some recurrence of symptoms in the 5 years after remission¹
- APA guidelines recommend the use of antipsychotics in conjunction with psychosocial and vocational programs¹
- Metabolic side effects are of concern with these young patients because there is a risk for longer-term medical problems²

DISCUSSION
METABOLIC WELLNESS
Patients With Schizophrenia Have an Overall 3-fold Increased Risk of Death Versus the General Population

Reasons for Increased CVD Mortality Among Mentally Ill

- ↑ Modifiable health risk factors\(^1,2\)
  - ↑ Obesity
  - ↑ Lipid abnormalities (TC, LDL-C, TG, HDL)
  - ↑ Diabetes
  - ↑ Hypertension
  - ↑ Metabolic syndrome
  - ↑ Physical inactivity
  - ↑ Smoking
- ↓ Access to and/or utilization of medical care\(^1,2\)
- ↓ Adherence with therapies\(^3\)
- ↓ Economic capabilities\(^4\)
- ? Psychiatric disease-related risk\(^5\)

CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

Evidence suggests that the prevalence of metabolic syndrome in chronic antipsychotic-treated patients with schizophrenia is 2 to 3 fold higher than in first-episode or untreated patients, regardless of the syndrome definition used.

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<tbody>
<tr>
<td>Unmedicated patients, %</td>
<td>10.4%</td>
<td>12.9%</td>
<td>12.2%</td>
</tr>
<tr>
<td>First-episode patients, %</td>
<td>8.3%</td>
<td>11.8%</td>
<td>9.7%</td>
</tr>
<tr>
<td>Chronic medicated patients, %</td>
<td>33.8%</td>
<td>42.1%</td>
<td>41.7%</td>
</tr>
</tbody>
</table>

Distinguishing preexisting risk from treatment effects is important for understanding the source of metabolic abnormalities and can inform decisions regarding medication review and other interventions.

ATP III, Adult Treatment Panel III; ATP III-A, adapted Adult Treatment Panel; IDF, International Diabetes Federation; MetS, metabolic syndrome.

Reasons for Increased CVD Mortality in Serious Mental Illness

• In comparison to the general population, patients with severe mental illness are:
  • Less likely to be screened or treated for dyslipidemia, hyperglycemia, or hypertension
  • Less likely to receive angioplasty or CABG
  • Less likely to receive drug therapies of proven benefit (thrombolytics, beta-blockers, ACE inhibitors)
  • More likely to have premature mortality postmyocardial infarction

ACE, angiotensin-converting enzyme; CABG, coronary artery bypass grafting; CVD, cardiovascular disease.

Trends in Glucose and Lipid Testing Pre-, During-, and Post-FDA/ADA/APA Warnings*

Data from California, Missouri, and Oregon Medicaid programs, 2002-2005 (N = 33,213 propensity-matched pairs of bronchodilator and persistent SGA users).

*Data has been provided by the author
ADA, American Diabetes Association; APA, American Psychiatric Association; FDA, Food and Drug Administration; SGA, second-generation antipsychotics.
Overall Poor Adherence to Monitoring Guidelines

Patient characteristics\(^1\):
- Less likely to seek care
- Less likely to adhere to prescribed treatments
- Potential difficulty in communicating symptoms

Clinician behavior\(^1,2\):
- Primary care clinicians:
  - May lack the skills to treat this population
  - Time constraints
- Psychiatrists:
  - May not believe physical health is their responsibility
  - May lack physical medicine skills
  - Shortage of psychiatrists

Medical system\(^1\):
- Complex care systems may be difficult to navigate

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Control Chart of Monthly Glucose Testing Rates for CMHC-treated Adults

PCL indicates process center line of average testing rate for each intervention period; Square and circle around points indicates the point is outside control limits.

CMHC, community mental health center; LCL, lower control limit; PCL, process center line; UCL, upper control limit.

Integrating Mental and Physical Healthcare Services: Impact on Outcomes

- 10-year retrospective longitudinal study on the impact of delivering integrated mental and physical healthcare in team-based primary care vs traditional practices
  - Study included 113,452 adult patients, including 27 team-based medical practices and 75 traditional practices

- Compared to care in traditional practices, receipt of care in team-based practices was associated with:
  - Significantly higher rates of quality measures
  - Increased proportion of patients with an annual visit to PCP (OR, 1.09; 95% CI, 1.03 to 1.15; P = 0.002)
  - Lower rates of healthcare utilization
    - Emergency visits per 100 person-years: IRR, 0.77 [95% CI, 0.74 to 0.80], P < 0.001
    - Hospital admissions per 100 person-years: IRR, 0.89 [95% CI, 0.85 to 0.94], P < 0.001

Suggests the value of coordinated team relationships within a delivery system emphasizing the integration of physical and mental healthcare

CI, confidence interval; IRR, incidence rate ratio; OR, odds ratio; PCP, primary care physician.
Despite longer antipsychotic exposure, NAVIGATE patients as compared to community-care patients:

- Gained less weight ($P = 0.025$)
- Had lower BMI ($P = 0.025$)
- Experienced fewer side effects ($P = 0.002^a$)

The study also demonstrated that NAVIGATE patients received more guideline-adherent care (e.g., pharmacologic treatment) than community-care patients

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$^a$ The model included treatment condition, time, and the treatment-by-time interaction; treatment-by-time interaction, $F = 3.86$, df = 5, 1143, $P = 0.002$

BMI, body mass index.

Cardiometabolic Risk Management Strategies for Patients With Mental Illness

**Treatment Initiation**
- Baseline screening followed by regular monitoring
- Healthy lifestyle education/intervention to reduce risk
- Start with lower-risk psychotropic medication
- Treat emergent risk factors (e.g., obesity, dyslipidemia)

**If Cardiometabolic Disease Occurs (e.g., diabetes, CVD)**
- Coordinate care with CVD/diabetes medical team
- Monitor risk factors to prevent recurrence
- Healthy lifestyle intervention to reduce risk
- Switch to lower-risk psychotropics as appropriate

**Prevent Disease Progression and Complications**
- Coordinate care with CVD/diabetes medical team
- Monitor risk factors and disease indicators to prevent progression
- Healthy lifestyle intervention to reduce risk
- Switch to lower-risk psychotropics as appropriate

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CVD, cardiovascular disease.

Effect of Interventions to Reduce Coronary Heart Disease Risk

BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

Correll CU. CNS Spectr. 2007;12(10 suppl 17):12–20,35.
DISCUSSION
QUESTIONS
## Upcoming Virtual Forum

<table>
<thead>
<tr>
<th>Event</th>
<th>Speaker(s)</th>
<th>Date</th>
<th>Time</th>
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<tr>
<td>Tools to Assess and Address Medication Adherence in Patients With Serious Mental Illness</td>
<td>• Hayden Bosworth, PhD&lt;br&gt;• Michael Measom, MD</td>
<td>Wednesday, December 13, 2017</td>
<td>12:00 – 1:00pm EST</td>
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*Register for these programs at https://www.psychu.org/events/*
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