Early Intervention in Psychosis: Benefits, Barriers, and Best Practices

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EARLY INTERVENTION IN FIRST-EPIPODE SCHIZOPHRENIA:
RATIONALE AND CHALLENGES

Matcheri S Keshavan MD

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Early Intervention in Schizophrenia: Rationale and Challenges

• Rationale
  – Longer the untreated illness, worse the outcome\(^1\)
  – Continuing cognitive decline early in 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\(^8\)

Rationale for Early Intervention:
1. Clinical Evidence: Long Untreated Psychosis Is Negatively Correlated With Outcome

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Correlation (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General symptomatic outcome (n = 15)</td>
<td>-0.15 (-0.22 to -0.09)</td>
</tr>
<tr>
<td>Positive symptoms (n = 8)</td>
<td>-0.14 (-0.22 to -0.07)</td>
</tr>
<tr>
<td>Negative symptoms (n = 18)</td>
<td>-0.13 (-0.21 to -0.05)</td>
</tr>
<tr>
<td>Hospital treatments (n = 11)</td>
<td>-0.09 (-0.22 to 0.04)</td>
</tr>
<tr>
<td>Social functioning (n = 14)</td>
<td>-0.18 (-0.27 to -0.09)</td>
</tr>
<tr>
<td>Employment (n = 7)</td>
<td>-0.05 (-0.16 to 0.06)</td>
</tr>
<tr>
<td>Global outcome (n = 19)</td>
<td>-0.17 (-0.26 to -0.07)</td>
</tr>
<tr>
<td>Quality of life (n = 7)</td>
<td>-0.10 (-0.22 to 0.01)</td>
</tr>
<tr>
<td>Remission (n = 10)</td>
<td>-0.14 (-0.23 to -0.06)</td>
</tr>
</tbody>
</table>

Rationale for Early Intervention: 2. Neuropsychological Evidence

Effect sizes from 4 meta-analyses on cross-sectional IQ impairment in individuals with psychosis or at risk for psychosis compared to controls (Cohen’s $d$)


IQ, intelligence quotient; PRE, premorbid; PRO-C, prodrome converter; FE, first-episode schizophrenia; CSZ, chronic schizophrenia.
Rationale for Early Intervention: 3. Evidence From Neuroimaging

Continuing Gray Matter Loss After Illness Onset

Normal Adolescents Adolescents With Schizophrenia


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Challenge 1: Current Antipsychotics May Have Limited Efficacy and Lead to Side Effects

Discontinuation of Antipsychotics

- 74% of CATIE participants discontinued their assigned antipsychotic before completing 18 months of treatment due to intolerable side effects, inadequate symptom control, or other reasons.
- Effectiveness (as measured by treatment continuation) was generally similar across antipsychotics.

CATIE, Clinical Antipsychotic Trials of Intervention Effectiveness.
Challenge 2: Do Antipsychotics Cause Gray Matter Loss? Some Confusing Data

- Long-term antipsychotic use is associated with gray matter reductions\(^1\)
- Monkeys treated with antipsychotics have reductions in neurons and glia\(^2\)
- Brain-tissue loss in schizophrenia may be related to relapse duration\(^3\)

Challenge 3: Initial Improvements With Early Intervention May Not Be Sustained in Long-term Follow-up

Symptom scores and level of functioning of recipients of OPUS versus treatment as usual from inclusion and 10-years forward

GAF, Global Assessment of Functioning Scale; OPUS, Cognitive training plus a comprehensive psychosocial programme [Danish]; SAPS/SANS, Scale for the Assessment of Positive/Negative Symptoms.

Discussion Questions

• Question 1: Most of these early intervention clinical programs are time-limited and gains are lost to some extent when people discontinue the intervention. Why are the gains lost? What can be done to minimize these losses?

• Question 2: What is the clinical relevance of grey matter loss in these patients?

The following responses represent the presenters’ opinions based on their clinical experience.
MEDICAL MANAGEMENT OF EARLY PSYCHOSIS

Diana O. Perkins, MD, MPH
Medical Director, OASIS
Professor, Department of Psychiatry
University of North Carolina at Chapel Hill
What We Knew in 2008

Variable Outcomes

- Most patients will have symptomatic recovery from a first episode\(^1\)
- Most patients elect for a trial period off of antipsychotics; most experience multiple relapses*:
  - Interferes with normal psychosocial development
  - Interferes with educational and vocational achievements
  - Risk of harm to self, others, or property is higher during active psychosis
  - Risk of involuntary hospitalization increases
  - Prognosis may be negatively impacted

- Some people have a worse course of schizophrenia than others\(^2\):
  - 10% to 15% highly treatment resistant
  - 10% to 15% benign course

- Long-term outcomes: variable, but most reports show < 20% have full recovery\(^3\):
  - Almost all Veterans Health Administration patients with schizophrenia are disabled\(^2\)

- Risk of suicide is high (~5% to 6%)\(^4\)

\(^*\)Presenter’s clinical experience.

Most, But Not All, Patients Have a Recurrent Illness

- 207 Persons with first-episode schizophrenia\(^1\):
  - 24 Had had only a single episode in 7.5 years\(^1\)
- Predictors\(^*\) of a single episode included shorter duration of untreated psychosis and more rapid time-to-response to medication\(^1\)
- Single-episode patients all stopped taking antipsychotic medication during follow-up period\(^**\)

\(^*\)Including only predictors that survived adjustment for multiple testing.

\(^**\)Personal communication from Dr. Alvarez-Jimenez.

**Environment Impacts Prognosis**

Symptomatic and Functional Prognosis at 2 Years After a First Episode of Schizophrenia

![Bar chart showing remitting, complete remissions and continuous or episodic, no complete remissions in Developed Countries (n=603) and Developing Countries (n=467).](chart)

*Developed Countries* (n=603)
*Developing Countries* (n=467)

- Remitting, complete remissions
- Continuous or episodic, no complete remissions

*Czech Republic, Denmark, Ireland, Japan, Russia, UK, USA.

**Colombia, India, Nigeria.


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Outreach and Support Intervention Services (OASIS)

• Developed by the Department of Psychiatry at University of North Carolina – Chapel Hill School of Medicine
• Began 2005
• Emphasizes early identification and treatment of young people and their families at the start of a psychotic disorder
• Intention is “to help young people who experience psychosis recover and get their lives back on track”
• Comprehensive team approach

Percent of OASIS Patients With Good and Excellent Functioning, as Measured by the GAF Score

GAF, Global Assessment of Function; OASIS, Outreach and Support Intervention Services. OASIS data on file.
OASIS Patient Outcomes

• 23% of patients were on Disability and Medicaid:
  – 41% of those on disability were working or in college
  – Over half applied for disability in order to qualify for Medicaid

• 2 people committed suicide

OASIS data on file.
Health and Wellness

- Patients with schizophrenia die prematurely from cardiovascular disease,\(^1\) breast cancer,\(^2\) and respiratory diseases\(^2\)
- Emphasis on monitoring and prevention
- 100% of patients receive health and wellness counseling:
  - Daily exercise
  - Healthy diet*
  - Smoking cessation
- Weight gain prevention:
  - Monitor closely (weekly intervals)
  - Medication to prevent antipsychotic-related weight gain (eg, metformin)\(^3\)

Exercise and Schizophrenia

• Exercise in persons with schizophrenia:
  – Mood and positive and negative symptom scores improve\(^1\)
  – Cognition improves\(^2\)
  – Quality-of-life measures improve\(^{1,2}\)
  – Health measures improve\(^1\)

• Why?
  – In MK-801 “induced schizophrenia” mice, treadmill exercise improved biomarkers* of brain pathology NMDA receptor and brain-derived neurotrophic factor expression\(^3\)

* NMDA receptor expression and BDNF expression.

Cardiometabolic Risk Factors

*OASIS data “snapshot” as of 6 November 2014. OASIS data on file.
N.C., North Carolina; RAISE, Recovery After an Initial Schizophrenia Episode; OASIS, Outreach and Support Intervention Services; CATIE, Clinical Antipsychotic Trials of Intervention Effectiveness.
Discussion Question

• What recommendations do you make regarding stopping antipsychotic medication?

The following responses represent the presenters’ opinions based on their clinical experience.
COGNITIVE IMPAIRMENT: IMPORTANCE AND TREATMENT IN FIRST-EPIISODE PSYCHOSIS

Richard Keefe, PhD
Professor of Psychiatry & Behavioral Sciences and Psychology & Neuroscience
Duke University Medical Center
• Criterion A. Characteristic symptoms: 2 (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated)\(^1\)
At least 1 of these should include 1–3:
   1. Delusions
   2. Hallucinations
   3. Disorganized speech
   4. Grossly disorganized or catatonic behavior
   5. Negative symptoms (i.e., diminished emotional expression or avolition)

• But here is the first sentence of the description (DSM-5): “The characteristic symptoms of schizophrenia involve a range of cognitive, behavioral, and emotional dysfunctions, but no single symptom is pathognomonic of the disorder”\(^1\)

• Cognitive impairment may be the core of the illness and is becoming accepted as a domain that needs to be assessed in patients with schizophrenia

Neurocognitive Profile for Drug-naïve, First-episode and Previously Treated Patients

ABS, abstraction-flexibility; ATT, attention-vigilance; MOT, fine manual motor functions; SEM, standard error of the mean; SPT, spatial organization; VBL, verbal intelligence and language function; VBM, verbal memory and learning; VIM, visual memory; VSM, speeded visual-motor processing and attention.

Cognitive Impairment Is Not Related to Positive Symptoms in Chronic Schizophrenia

CATIE Trial: Correlations Between Symptom Dimensions and Neurocognitive Domains

PANSS

Positive Symptoms

Negative Symptoms

No relationship

Small to medium correlations

PANSS

CATIE, Clinical Antipsychotic Trials of Intervention Effectiveness; PANSS, Positive and Negative Syndrome Scale.

Figure based on Keefe RS, et al. *Neuropsychopharmacol.* 2006;31(9):2033-2046.
Relationship First Clearly Identified in Seminal Reviews and Meta-analyses

Neurocognitive Deficits

- Community Functioning
- Instrumental and Problem-solving Skills
- Psychosocial Rehabilitation Programs

Neurocognitive Deficits

- Verbal Memory
- Immediate Memory
- Executive Functions
- Attention/Vigilance

Correlation With Outcome, Pooled Estimated $r$

- Large
- Medium
- Small

$P < .0001$

$r$ Estimates weighted by sample size.
Change in the Cognitive Composite Score From Baseline to 6 Months in First-episode Psychosis

Using Neuroplasticity-Based Auditory Training to Improve Verbal Memory in Schizophrenia

Change in Cognitive Performance in Patients With Schizophrenia After 50 Hours of Computerized Auditory Training or 50 Hours of Computer Games

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Change in Age-Adjusted z-Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global Cognition</td>
<td></td>
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<tr>
<td>Speed of Processing</td>
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<tr>
<td>Verbal Working Memory</td>
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<td>Verbal Learning</td>
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<tr>
<td>Verbal Memory</td>
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<tr>
<td>Problem Solving</td>
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<tr>
<td>Nonverbal Working Memory</td>
<td></td>
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<tr>
<td>Visual Learning</td>
<td></td>
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<tr>
<td>Visual Memory</td>
<td></td>
</tr>
<tr>
<td>Social Cognition</td>
<td></td>
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</tbody>
</table>

- Significant difference between groups (p<0.01, repeated-measures ANOVA).
- Significant difference between groups (p<0.05, repeated-measures ANOVA).
- Nonsignificant difference between groups (p=0.10, repeated-measures ANOVA).


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Over 38 studies, cognitive remediation was found to have a significant benefit to patients with schizophrenia.

“Interventions that include an aggressive focus on cognition along with family support may prove surprisingly effective for preempting or forestalling psychosis. Although a ‘statin-like’ medication would be an unambiguous breakthrough, we should not assume that a medication will be more effective than harnessing the developing brain’s intrinsic plasticity for reversing the neural trajectory that leads from risk to prodrome.”
Cognitive Development in Schizophrenia: Follow-back From the First Episode

• Significant differences in academic achievement tests as early as the first grade were seen
  – Scores from participants who would later develop schizophrenia (n = 59) lagged behind their healthy peers (n = 26) by 0.8 to 1.1 grade equivalents

• This gap widened resulting in a difference between groups of 1.5 to 1.8 grade equivalents by the twelfth grade

• In the subset of patients for whom SAT scores were available, we found that WAIS-R Full Scale IQ was 11.5 points lower than predicted from earlier SAT scores, suggesting a substantial decline in cognitive ability accompanying the initial episode of illness

• These findings suggest that schizophrenia is marked by substantial cognitive deficits in the first grade, that there may be additional subtle decline preceding the overt onset of psychotic symptoms, and that the initial episode of illness is marked by additional decline

Verbal “Deficit” in Young Subjects Who Later Developed Schizophrenia

- Similar results for picture completion

- The dependence upon verbal learning throughout early education, may be particularly important in the development of later cognitive skill
Processing Speed “Lag” in Young Subjects Who Later Develop Schizophrenia

Reichenberg A et al. 

- Similar results for block design
- Average correlation between tests showing lag and deficit in schizophrenia subjects who later developed schizophrenia: $r = 0.61$ versus $r = 0.43$ in controls ($p = 0.06$)

<table>
<thead>
<tr>
<th>Cognitive Measure: Freedom from Distractibility Subtests</th>
<th>Group Comparison</th>
<th>Test for Developmental Deficit and Lag:</th>
</tr>
</thead>
</table>
| Arithmetic                                              | Schizophrenia vs. Comparison | Deficit estimate=$-0.29$, $t=1.38$, $p=0.17$  
Lag estimate=$-0.26$, $t=2.69$, $p=0.007$ |
| Depression vs. Comparison                               |                 | Deficit estimate=$-0.11$, $t=0.92$, $p=0.36$  
Lag estimate=$-0.14$, $t=2.58$, $p=0.01$ |
| Digit Symbol                                            | Schizophrenia vs. Comparison | Deficit estimate=$0.04$, $t=0.19$, $p=0.85$  
Lag estimate=$-0.17$, $t=2.15$, $p=0.03$ |
| Depression vs. Comparison                               |                 | Deficit estimate=$-0.06$, $t=0.53$, $p=0.60$  
Lag estimate=$0.07$, $t=1.58$, $p=0.11$ |
Discussion Question

• Is first-episode intervention for cognition too late?

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QUESTIONS
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