6-19-2007

Early Psychosis: A Bridge to Future

Amresh Srivastava
University of Western Ontario, amresh.srivastava@sjhc.london.on.ca

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Early Psychosis: A bridge to future

Amresh Srivastava
Assistant Professor of Psychiatry & Physician Team Leader, Early Psychosis Program, RMHC-St.Thomas
19 June 2007
• What is EP
• Characteristics
• What is the pathology
• What is the management
• Research questions

What is early psychosis
Why discuss EP? - the Evidence

The philosophy is to identify earliest and treat to ensure full remission and function.

- Does it make a difference to treat in early phase?
- If so what should be the optimal treatment?
- Does it make a difference to treat in a specialized way? Does a program make any difference?
- What is the state of psychopathology in early stages?

What is the natural outcome in EI
- What is appropriate Pharmacological therapy
- How and why to Integrate psychosocial and pharmacological therapies
- What is adequate Maintenance treatment
- What are the pertinent issues in Long term perspective
What Is Early Psychosis?

- the first episode of psychosis involves poor performance in multiple cognitive domains, including affective psychoses.
- A meta-analysis of 12 functional MRI studies revealed decreased dorsolateral prefrontal cortex activation in first-episode psychosis.
- Neuropathologic studies have found decreased somal size and dendritic spine density in pyramidal neurons of the dorsolateral prefrontal cortex.
When Does the First Episode of Psychosis Occur?

• A long-standing question relates to whether the neuropathology of psychosis begins in adolescence or long before.

• A study from the Pittsburgh High Risk Study, which included 76 high-risk offspring of parents with schizophrenia, reported gray matter reductions in the high-risk group and even greater reductions among those with schizotypy.
When Does the First Episode of Psychosis Occur?

- Furthermore, scores on attention and executive functioning (measured with the Continuous Performance Task and the Wisconsin Cart Sorting Test) declined in the high-risk group during the premorbid phase whereas these cognitive scores increased in the control group.

- Other groups have found gray matter losses during the premorbid and prodromal phases.

- In summary, the "when" of first-episode psychosis can be described as a sequential, cascading process from childhood to early adolescence to later adolescence, with cognitive and imaging findings present before the onset of psychosis.
Why Does Early Psychosis Occur?

• The "why" of first-episode psychosis is also an area of intensive research.
• Both genetic and environmental factors are important to the etiology of the illness.
• Genes of interest to schizophrenia researchers appear to relate to the glutamatergic system (for example, the "disrupted in schizophrenia-1" [DISC-1] gene or the regulator of G-protein signaling 4 [RGS4] gene).
Does it make a difference to treat in early phase

Benefits of Early Treatment

- More rapid effect
- Lower dose required
- Increased effects on positive symptoms
- Fewer residual symptoms
- Fewer deficit symptoms
- Fewer future relapses
- Better social integration
Models of early intervention service

Models of early intervention service

Canada’s Early Intervention Services

**British Columbia:**
- EP Initiative of British Columbia
- EPIVMHC, Victoria
- Vancouver
- EPIP, White Rock

**Alberta:**
- EPT&PP, Calgary (930,000)

**Saskatchewan:**
- EIPP, Saskatoon

**Ontario:**
- PEPP, London
- FEPP, Toronto
- Psychotic Disorders U., Hamilton
- Ottawa FEPP
- KPP&TP, Kingston

**Quebec:**
- Levis
- Montreal
- Quebec City

**Nova Scotia:**
- N&L EPP

**Newfoundland:**
- N&EPP

**Key figures:**
- Jean Addington
- Bob Zipursky
- Ashok Malla
- Lili Kopala
Early intervention Program

- Essentially a political agenda
- Welfare
- Targets prevention
- Initially has high investment
- But in long run it will cut mental health spending or at least will
- Optimize the usage of funds
- Expected to minimize spending on chronic patients
Early Intervention is a Public health initiative

- SMI utilizes >90% of Budget globally
- Bipolar Disorder and schizophrenia are main SMI s
- Bipolar Disorder < schizophrenia : epidemiologically, possibly because of better outcome of affective disorders.
- In schizophrenia we need to find avenues of innovation.
- That has been ‘Early intervention’
Schizophrenia-Economic Cost

- Direct cost in USA 19 billion and indirect 46 b.
- Cost of schizophrenia care was 837 M Pounds in UK; 94% being spent on SMI and inpatients care
- Active psychosis was third most disabling condition ahead of paraplegia and blindness. Point prevalence 0.4%
- GBD of schizophrenia was 1.1% of total DALY and 2.8% of YLD.
- Even after recovery residual symptoms are disabling and lead to poor QOL.
Schizophrenia- unmet needs

- 30-50% patients attempt suicide sometimes in life time,
- 10% patients die due to suicide
- A schizophrenia patient has life span 10-20 years lesser.
- Not more than 10% patients have access to treatment
- Not more than 10% receive care
- Not more than 10% emergencies receive treatment
Schizophrenia- Early Intervention

- A disease of late-childhood and early adolescence.
- Investment for early treatment is far more lesser than expenditure on delayed (increased DUP) treatment.
- Thus EI is a sensible and manageable economic agenda.
What are the Characteristics

- What is EP
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Cannabis and Early Psychosis

- It is widely known that patients with schizophrenia, including first-episode patients, have much higher rates of cannabis use compared with their counterparts in the general population.
- Recent epidemiologic research has discovered that cannabis is likely a component cause of psychosis,
  - meaning that cannabis use in combination with genetic and/or environmental factors exerts a causal influence on the onset of psychosis in individuals at risk.
Cannabis may reduce the age of onset of psychosis.

- Institute of Psychiatry at the Maudsley, London, UK, -- preliminary data from the Genetics and Psychosis (GAP) study
- With a goal to recruit 1000 first-episode patients, the research project currently has 278 participants (72% male; mean age of 25 years; 51.3% black/African English, 37.7% white).
- 56% had used cannabis and 19% had used other drugs.
- There were no significant differences in substance abuse prevalence rates across ethnic groups.
- Preliminary data from this ongoing study suggest that cannabis may reduce the age of onset of psychosis.
Motor and cognitive Factors of Neurological Evaluation Scale of FEP,

Patients with Schizophrenia (N=90)

Patients with non-schizophrenic psychosis (N=39)

Healthy Comparisions (N=93)
Post-FEP: the Critical Phase of Psychosis

- Individual is vulnerable to negative influence because of a combination of factors:
  - Coping up with return of insight and depression
  - A realization of having developed a mental illness/brain disorder
  - Question about future functioning
  - Ideas of faith, trust and mistrust
  - ‘why me’
  - Why medication,
  - Negative EE
  - Attitude of family members
  - Persisting psychotic symptoms in remission
**Figure 6**
Cumulative percentage of first-episode patients responding to treatment by duration of illness prior to study entry. Adapted from Lieberman JA et al. With permission from Elsevier Science.
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Neurobiology of EP

- Brain structure and function alteration, present early and pre-date onset of symptoms,
- Changes in frontal and temporal lobes.
- Functional and neurochemical brain abnormalities are seen in premorbid and early phase.
- Some can be trait like.
- Others might progress.
An Overview of the Neurobiology of Early Psychosis

- Heredity is the best established risk factor;
- Premorbid neurocognitive alterations clearly exist;
- Prodromal symptoms often precede psychosis;
- Onset of psychosis is typically in late adolescence; and
- Cognitive deficits are central to the illness.

Keshavan MS, Pittsburgh & Detroit
Cognitive impairment in schizophrenia: prevalence

- 85% of stable outpatients with minimal psychotic symptoms show significant cognitive impairment

- In contrast, specific delusions and hallucinations are present in as few as 25 to 40% of patients
Cognitive dysfunction is a lasting feature of schizophrenia
Cognitive deficits are the best predictors of functional outcome

**Effects Sizes (Cohen’s r): Neurocognitive Deficits and Functional Outcome**

- **Neurocognitive Deficits**
  - Community Functioning
  - Instrumental & Problem Solving Skills
  - Skill Acquisition

**Scores**

- **Large** - 0.5
- **Medium** - 0.3
- **Small** - 0.1

- **Verbal Memory**
- **Immediate Memory**
- **Executive Functions**
- **Vigilance**
- **Summary Scores**

*Green et al. 2000*

![Bar chart showing change z-scores for different medications](chart.png)

- Clozapine
- Olanzapine
- Risperidone
- Haloperidol
Conversion to psychosis and time course

Deteriorating psychosocial functioning

Low Risk

Ultra HR

Deteriorating cognition

Prodrome

EP

FEP

Family History

Biological events

Cognitive symptoms

Precipitating factor

Positive & Negative symptoms

Variable time course
Prediction of Psychosis

Yung et al 1998 British Journal of Psychiatry

40% made transition at six months, 50% at one year

Number not psychotic

Months of assessment
Prevention of psychosis
McGorry et al 2002 Archives of General Psychiatry

% making transition to psychosis

Needs based Tx
Specific interventions

Months

0% 5% 10% 15% 20% 25% 30% 35% 40%

6 12
Predicting onset of psychosis: PACE

What features predict onset of first-episode within an ultra-high risk group?

- Duration of symptoms more than 900 days
- GAF less than 51
- BPRS total score greater than 15
- BPRS-Psychotic scale more than 2
- SANS attention score more than 1
- HDRS more than 18
- Normal left hippocampal volume
- Cannabis dependence
- Maternal age more than 30 years
Prodromal features in first-episode psychosis most commonly described in first-episode studies

- Reduced concentration, attention
- Reduced drive, motivation, anergia
- Depressed mood
- Sleep disturbance
- Anxiety
- Social withdrawal
- Suspiciousness
- Deterioration in role functioning
- Irritability
Natural consequence or outcome in phenomenology EP

Ultra HR

Prodrome

EP

Complete remission
Full function
asymptomatic

Not converted

Converted

Non-diagnosable Schizo.

Partial remission
Dysfunction
Symptoms
Personality traits

Non-relapsing

Single episode

Diagnosable schizo.

Relapsing Downhill others

relapsing
AN “EARLY” DEVELOPMENT THEORY: impaired neural migration in schizophrenia?

Akbarian 1993

[Diagram showing normal and schizophrenia germinal zones]
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Aim of management in FEP
EI Services in many countries developed based on the evidence
Germany, Australia, UK, Canada, USA, Sweden, Denmark

- To reduce the time between onset of psychotic symptom and effective treatment
- To accelerate remission through effective biological and psychosocial interventions.
- To reduce individual’s adverse reaction to the experience of psychosis and to maximize social and work functioning
- To prevent relapse and treatment resistance
Principles of best practice management

• A strategy for early detection and assessment of frank psychosis.
• A specific focus on therapeutic engagement
• A comprehensive assessment
• An embracing of diagnostic uncertainty
• Treatment in least restrictive setting using low-dose medication
Recommendation for pharmacotherapy of first episode psychosis

- An antipsychotic free observation period
- A low threshold for use of atypical antipsychotic medications
- The use of low dose antipsychotic plus benzodiazepines.
- The aim of remission
- Early assessment of treatment resistance
- Maintenance of medication for at least 1-2 years in non-affective psychosis (except in case with short DUP)
Early Intervention

- Focus on psychological adjustment and maintenance of social roles
- Focus of entire family
- Prevention of relapse and resistance to treatment
- Now the practices of the EI services are gearing up to Prodrome of First episode psychosis
First-episode schizophrenia versus chronic schizophrenia treated with risperidone (1)

PANSS scores

Days of treatment

Mean PANSS score

Acute exacerbation, chronic
First episode
Acute exacerbation, chronic
First episode

Negative symptoms
Positive symptoms

*p<0.005

Rüther E, Klauder A. WCP, Hamburg, August 1999
First-episode schizophrenia versus chronic schizophrenia treated with risperidone (2)

Clinical Global Impression (CGI)

- First episode (n=161)
- Acute exacerbation, chronic (n=905)

Rüther E, Klauder A. WCP, Hamburg, August 1999

*p<0.05
Response rate in FES

Figure 2
Cumulative percentage of first-episode patients responding to treatment. Adapted from Lieberman JA et al. With permission from Elsevier Science.
How much antipsychotic

![Graph showing the increase in antipsychotic dosage over weeks for different mg levels.](image)
Optimum D2 occupancy 65% at 2 and 10 mg dosage

**Figure 4**
Hyperbolic relationship between $D_2$-receptor occupancy and plasma level for antipsychotics with significant $D_2$-receptor affinity. The approximate thresholds for antipsychotic effect and EPS are shown.  

- Threshold for EPS
- Threshold for antipsychotic effect

Suggested optimal interval for plasma level and receptor occupancy
Should AATPD be used

Olanzapine vs. Haloperidol
First-episode Psychosis

First episode psychosis: Relapses

Antipsychotics for how long?
Quetiapine in FEP

Improvement in Symptoms and cognitive tests

On continuous performance test improvement was noted at 3 months
Aripiprazole in Teen-Schizophrenia
San Diego; APA, May, 2007

- Six week, double-blind, randomized placebo-controlled trial was conducted at 101 centers in 13 countries, A total of 302 adolescents, ranging in age from 13 to 17 (mean age 15.5),
- DSM-IV diagnosis of schizophrenia, and a Positive and Negative Syndrome Scale total score of 70 or greater.
- More than 85% of the patients completed the study.
- The mean baseline Positive and Negative Syndrome score was 94.5.
- After one week on the full drug dose, patients in the 30-mg group had a significant improvement compared with placebo in total PANSS score (-10.42 compared with -7.2, LOCF, P<0.05).
- Both the 10-mg and 30-mg doses showed significant differences
Predictor of response

Not related to response
- Diagnosis
- Baseline disorganization
- NS
- Akathesia
- Dystonia
- Psychosis activation by methylphenidate
- Baseline motor function
- N-P test
- Severe hallucination and delusions
- Level of depression

Related to response
- Higher premorbid functioning
- More acute onset
- Shorter duration of illness
- Lower baseline PS NS
- Nondeficit state status
- Absence of parkinsons sign during APD Tx
Limitations of pharmacological treatment in FEP

• Remission of psychotic symptoms only in 50% individuals within first 3 months; 75% within first 6 months and Up to 80% in 1 Year

• Benefits are tampered by Side effects

• Medication adherence, with 6-12 Mths, 33-50%

• Persistent psychosis up to 20%

• Significant depression and anxiety secondary to traumatic experience of psychosis, up to 50%
Limitations of pharmacological treatment in FEP-2

• Poor functional recovery (79% of 75% remitted were non-functional; Tohen et al 2000, Biol.Psych, Harvard FE Project)

• Impairment of General social Functioning, QOL, & Occupational Functioning despite clinical recovery. This prevails up to 5 years after onset even with optimal pharmacological treatment
Psychosocial Intervention

- Pharmacotherapy alone is not enough.
- Means facilitating recovery from an initial episode of psychosis and reducing the long-term disability associated with schizophrenia.
- Research is growing
- Treatment guidelines for FEP based on clinical experience not research includes: therapeutic engagement, targeting psychological and social adjustment, developing an active relapse prevention plan, and identifying barriers to treatment,
Issues for psychosocial therapy “breaking-the-barriers”

- Goals
- Short term
- Long term

- Factors causing disengagement
- Factors Interfering continuation &
- Compliance
- Factors interfering with personal growth