Early Signs of Psychosis in Youth

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Outline

1. Attenuated Psychosis Syndrome

2. Rationale Inclusion in DSM-5 Conditions for Further Study

3. Research Supporting Inclusion

4. Interventional Studies in High Risk Populations
Psychotic Disorders
Key Features

• Delusions - Fixed beliefs that are not true
• Hallucinations - Perceptions occurring without external stimulus.
• Disorganized Thinking (Speech) - Range from tangential to frank incoherence.
• Grossly Disorganized or Abnormal Motor Behavior
• Negative Symptoms – low emotional expressiveness & Avolition
Outline

1. Attenuated Psychosis Syndrome
DSM 5 Psychotic Disorders

- Schizophrenia & Schizotypenform Disorders
- Schizoaffective Disorder
- Brief Psychotic Disorder
- Delusional Disorder
- Catatonia
- Substance/Medication Induced Psychotic Disorder
- Psychotic Disorder Due to another Medical Condition
- Schizotypal Personality Disorder
- *Other Specified & Unspecified Psychotic Disorders
Attenuated Psychosis Syndrome

**Characteristic symptoms** - at least one of the following in attenuated form with intact reality testing:
- Delusions
- Hallucinations
- Disorganized Speech

**Frequency/Currency** - present in the past month and occur at an average frequency of at least once per week

**Progression** - symptoms must have begun in or significantly worsened in the past year

**Distress/Disability/Treatment Seeking** - symptoms are sufficiently distressing/disabling to patient/parent/guardian to lead them to seek help
Early Warning Signs

1. Marked changes in behavior, thoughts and emotions, such as:
   - Unusual perceptual experiences (sight/sounds)
   - Heightened perceptual sensitivity
   - Magical thinking
   - Unusual fears
   - Disorganized or unusual speech
   - Uncharacteristic or peculiar behavior
   - Reduced emotional or social responsiveness
Early Warning Signs

2. A significant deterioration in functioning:

- Unexplained decrease in work or school performance
- Decreased concentration and motivation
- Decrease in personal hygiene
- Decrease in the ability to cope with life events and stressors

3. Withdrawal from family and friends and activities
How can I tell whether it’s stress or the start of mental illness?

- Duration of symptoms
- Intensity of symptoms
- Degree of disruption...to what extent does it disrupt usual activities and responsibilities?
- Clustering (more than one) of the signs
Outline

2. Rationale Inclusion in DSM-5 Conditions for Further Study
Rationale for APS Inclusion in DSM-5

- Outcomes in Schizophrenia and Psychosis
- Duration of Untreated Psychosis (DUP) as a moderator of outcome
- Prodromal phase of schizophrenia
- Psychosis as a continuum
Schizophrenia Outcomes

• First Episode Psychosis (FEP) – 96% reach clinical remission with treatment
• 80% relapse within 5 years of first episode

Recurrences associated with
• Persistent residual psychotic symptoms
• Progressive loss of grey matter
• Less responsiveness to antipsychotic meds
• More social and vocational disability

(Stephenson et al, JAMA 2000; Penn et al, Am J Psychiatry 2005)
Functioning as an effect of repeated psychotic episodes
Psychosis – Implications

Psychosis confers more severe course of illness

Chicago Follow Up Study

• 15 year prospective study of 274 young (age 23) psychiatric inpatients (Index Admission)
• 64 with Schizophrenia / 12 Schizophreniform disorder
• 81 with other psychosis (46% Bipolar Disorder, 35% Unipolar Depressed)
• 117 non-psychotic patients (62% Depressive D/O’s)

(Harrow, Schizophr Bull 2005)
Periods of Recovery

(y-axis % with 1 year recovery in follow up period)
Any 1-Year Period of Recovery in 15 Year Follow Up

% Ever in Recovery

- Schizo: 41%
- SchiForm: 55%
- Other Psychotic: 67%
- Non Psychotic: 78%
Duration of Untreated Psychosis as Moderator of Outcome

DUP – time elapsed between onset of frank psychotic symptoms and initiation of treatment

Longer DUP associated with:

• Poorer response to antipsychotic medication
• Associated with severity of negative symptoms
• Reduced caudate, left temporal & orbital-frontal grey matter volume reduction
DUP as Moderator of Outcome

Shorter DUP Associated with:

• Better Social functioning in FEP patients at 1 and 2 year follow up.

So – Clinically we are very interested in shortening DUP
Prodromal Phase of Schizophrenia

- Prodromal Phase of Schizophrenia Course has long been recognized

- Significant negative social consequences of schizophrenia emerge in prodromal phase of the illness
Prodromal Phase of Schizophrenia

ABC Study of Schizophrenia

N = 232 FEP – 1st admission for Schizophrenia
Ages 15 to 55 at intake
Assessed prodromal phase of illness

• 73% started with non-specific or negative symptoms
• 20% started with positive and negative symptoms
• 7% started with positive symptoms only

(Hafner, Eur Arch Psych Clin Neuro 1999)
Prodromal Phase of Schizophrenia

Prodromal Time Course:

- A minority of subjects (18%) showed acute onset of prodromal symptoms within 1 month of index admission.

- A majority of subjects (68%) showed chronic onset of prodromal symptoms with 1st symptoms appearing > 1 year from time of 1st admission.

- Psychotic symptoms in prodrome averaged 1.1 years in length with peak of symptoms 2 months prior to index admission.

- Mean lapsed time from illness onset to 1st psychotic symptom was 5 years.
Prodromal Phase of Schizophrenia

Prodrome & Social Disability:

• Compared to controls – subjects with Schizophrenia had significantly impaired levels of social role functioning at index admission (education, occupation, employment, income, partnership & accommodation)

• Social role deficits appeared in prodromal phase 2 – 4 years before index admission

• The younger the subjects were at age of 1st symptoms in prodrome – the lower their social development at admission
Psychosis as a Continuum

View that psychosis phenotype is expressed at various levels in a population.

Assumption is that experiencing symptoms of psychosis – such as hallucinations and delusions is not inevitably associated with the presence of a psychotic disorder.

(van Os, Psychological Medicine 2009)
Psychosis as a Continuum

Meta-analysis of 35 cohorts investigating prevalence and incidence of psychotic phenotypes in community samples
(van Os, Psychological Medicine 2009)

- Psychotic Symptoms: 4%
- Psychotic Experiences: 8%
- Psychotic Disorder: 3%
Psychosis as a Continuum

Meta-analysis of 35 cohorts investigating prevalence and incidence of psychotic phenotypes in community samples

Summary
In incidence 3%
Prevalence 5%

Majority of psychotic experiences in the population are transitory and disappear in 75% - 90% of individual

(van Os, Psychological Medicine 2009)
Outline

3. Interventional Studies in High Risk Populations
High Risk for Psychosis Criteria

Researchers identify and study HR Individuals

High Risk State (HR) includes:

- Attenuated Psychotic Symptoms (APS) - > 1 week
- Brief Limited Intermittent Psychotic Episode (BLIP) - < 1 week
- Genetic Risk and Deterioration Syndrome (GRD)

Follow them to see who goes on to develop psychosis
Prodromal Risk Syndrome - NAPLS

North American Prodrome Longitudinal Study
(Woods, Schizophr Bull 2009)

Comparison Groups: (average age 18)

- Prodromal Risk \( N = 377 \)
- Normal Control \( N = 196 \)
- Help-Seeking Comparison \( N = 198 \)
Prodromal Risk Syndrome - NAPLS

- Individuals assessed at baseline and every 6 months up to 30 months
- Primary Outcome – time to conversion to psychosis
- Psychosis defined as
  - frank psychotic symptoms with serious disorganization or danger
  - Present for 1 month, at least ½ of days, > 1 hr/day
Prodromal Risk Syndrome - NAPLS

Outcomes – Conversion Rates at 2.5 Years

• Prodromal Risk Syndrome: 40% (N = 89)
• Normal Control: 0%
• Help-Seeking Comparison: 4% (N = 3)
Prodromal Risk Syndrome - NAPLS

Diagnosis of Converters:

• Prodromal Risk – Schizophrenia Spectrum 56%, Psychosis NOS 34%, Affective D/O 10%

• HSC – Bipolar Disorders 33%, Psychosis NOS 33%
Prodromal Risk Syndrome - NAPLS

Clinical Course of Non-Converters At 2-year follow up:

• 38% had anxiety disorder
• 15% depressive disorders
• Social & role functioning significantly lower than Normal Controls
• 40% still had a least 1 attenuated positive symptom
Transition to Psychosis of High Risk Individuals

Help-seeking patient populations
Bottom line – despite being at increased risk for conversion to psychosis – less than 40% will convert in a relatively short period of time.

Meta Analysis of conversion rates of 2500 HR individuals:
• 18% at 6-months
• 22% at 1 year
• 29% at 2 years
• 32% at 3 years
• 36% after 3 years

(Fusar-Poli et al. Arch Gen Psych 2012)
Outline

4. Interventional Studies in High Risk Populations
Personal Assessment and Crisis Evaluation (PACE)

- Prodromal Patients ages 14-28 (N = 59)
- Compared Needs Based Intervention (NBI) vs. Preventative Intervention (PI - which was NBI + Risperidone + CT)
- Treatment Duration was 6-months
- Mean Risperidone dose was 1.3 mg/day

12 month conversion rates (trend but not significant difference):
- NBI 10/28 (36%)
- PI 6/31 (19%)

(McGorry, Arch Gen Psych 2002)
Intervention Studies - Pharmacology

PRIME Study
N = 60 Prodromal Patients (age 12-45)
Olanzapine (N = 31) vs. Placebo (N = 29)
1 year treatment with additional 1 year no treatment follow up

Year 1 Conversion Rates:
• Olanzapine 5/31 (16%)
• Placebo 11/29 (38%)

Mean Olanzapine Dose 10.2 mg/day
Weight Gain in Treatment Year = 8.8 Kg

(McGlashan, Am J Psych 2006)
Intervention Studies - Neuroprotective

Omega-3 Fatty Acids (PUFA)

N = 81 Help Seeking Prodromal Patients (ages 12 to 25)

PUFA vs. Placebo (3 months treatment/9 additional months F/U)

12 month Conversion Rates:
• 2/41 (5%) PUFA
• 11/40 (28%) Placebo

(Amminger, Arch Gen Psych 2010)
Intervention Studies - Psychological

1 – Year Conversion Rates

1. Cognitive Therapy (N = 37) vs. Monitoring (N = 23)
   – Conversion Rates: 5.7% vs. 21.7%

2. Cognitive Behavior Therapy (N = 27) vs. Supportive Therapy (N = 24)
   – Conversion Rates: 0% vs. 12.5%

3. Integrated Psychological Intervention (N = 63) vs. Supportive Counseling (N = 65)
   – Conversion Rates: 3% vs. 16.9%

(Morrison Br J Psych 2004; Addington Schizophr Res 2011; Bechdolf Br J Psych 2012)
Intervention Studies - Combined

Meta-Analysis of RCT with 1 – Year Conversion Rates

• Significant effect of active treatments

• Risk Ratio of 0.34 (23% to 7%, P < .001)

• NNT = 6 for focused treatment versus control

(Fusar-Poli, JAMA Psychiatry 2013)
Cannabis & Psychosis

Cannabis associated with increased risk of developing psychosis in some individuals.

South London Study (Di Forti, Lancet 2015)

410 FEP Patients

370 Controls
### Cannabis & Psychosis

<table>
<thead>
<tr>
<th>Lifetime Cannabis Use</th>
<th>First Episode Psychosis N = 410</th>
<th>Controls N = 370</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>67%</td>
<td>63%</td>
</tr>
<tr>
<td>Never Used</td>
<td>33%</td>
<td>37%</td>
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</table>

### Frequency of Use

<table>
<thead>
<tr>
<th>Frequency of Use</th>
<th>First Episode Psychosis N = 410</th>
<th>Controls N = 370</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 per week</td>
<td>17%</td>
<td>35%</td>
</tr>
<tr>
<td>Weekends</td>
<td>20%</td>
<td>17%</td>
</tr>
<tr>
<td>Every Day</td>
<td>30%</td>
<td>11%</td>
</tr>
</tbody>
</table>

### Most Used Type of Cannabis

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<tr>
<th>Most Used Type of Cannabis</th>
<th>First Episode Psychosis N = 410</th>
<th>Controls N = 370</th>
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<tbody>
<tr>
<td>Hash-Like (low THC)</td>
<td>14%</td>
<td>44%</td>
</tr>
<tr>
<td>Skunk-Like (High THC)</td>
<td>53%</td>
<td>19%</td>
</tr>
</tbody>
</table>
Cannabis & Psychosis

< 1 use per week - Skunk Users:
• 2X more likely to have psychotic disorder than individuals who never used

Weekend use - Skunk Users:
• 3X more likely to have psychotic disorder than individuals who never used

Daily use - Skunk Users:
• 5X more likely to have psychotic disorder than individuals who never used

Users of Hash-Like Cannabis (no matter what frequency) no increase risk of psychosis compared to never-users
Attenuated Psychosis Syndrome

Summary

• Attenuated Psychosis Syndrome included in DSM-5

• Hope is to provide intervention for syndrome with active symptoms, distress and functional deficits and

• Alter trajectory of some psychotic illnesses
<table>
<thead>
<tr>
<th></th>
<th>Hallucinations</th>
<th>Delusions</th>
<th>Disorganization</th>
<th>Abnormal Psychomotor Behavior</th>
<th>Restricted Emotional Expression</th>
<th>Avolition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Not Present</td>
<td>Not Present</td>
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<td>Not Present</td>
<td>Not Present</td>
</tr>
<tr>
<td>1</td>
<td>Equivocal (severity or duration not sufficient to be considered psychosis)</td>
<td>Equivocal (severity or duration not sufficient to be considered psychosis)</td>
<td>Equivocal (severity or duration not sufficient to be considered disorganization)</td>
<td>Equivocal (severity or duration not sufficient to be considered abnormal psychomotor behavior)</td>
<td>Equivocal decrease in facial expressivity, prosody, or gestures</td>
<td>Equivocal decrease in self-initiated behavior</td>
</tr>
<tr>
<td>2</td>
<td>Present, but mild (little pressure to act upon voices, not very bothered by voices)</td>
<td>Present, but mild (delusions are not bizarre, or little pressure to act upon delusional beliefs, not very bothered by beliefs)</td>
<td>Present, but mild (some difficulty following speech and/or occasional bizarre behavior)</td>
<td>Present, but mild (occasional abnormal motor behavior)</td>
<td>Present, but mild decrease in facial expressivity, prosody, or gestures</td>
<td>Present, but mild in self-initiated behavior</td>
</tr>
<tr>
<td>3</td>
<td>Present and moderate (some pressure to respond to voices, or is somewhat bothered by voices)</td>
<td>Present and moderate (some pressure to act upon beliefs, or is somewhat bothered by beliefs)</td>
<td>Present and moderate (speech often difficult to follow and/or frequent bizarre behavior)</td>
<td>Present and moderate (frequent abnormal motor behavior)</td>
<td>Present and moderate decrease in facial expressivity, prosody, or gestures</td>
<td>Present and moderate in self-initiated behavior</td>
</tr>
<tr>
<td>4</td>
<td>Present and severe (severe pressure to respond to voices, or is very bothered by voices)</td>
<td>Present and severe (severe pressure to act upon beliefs, or is very bothered by beliefs)</td>
<td>Present and severe (speech almost impossible to follow and/or behavior almost always bizarre)</td>
<td>Present and severe (abnormal motor behavior almost constant)</td>
<td>Present and severe decrease in facial expressivity, prosody, or gestures</td>
<td>Present and severe in self-initiated behavior</td>
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Outline

Questions – Comments?

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