First-Episode Psychosis 2015: Risk, Prodrome, Treatment, and Outcome

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Learning Objectives

• Identify individuals early who are at high risk for, or who are entering, a first psychotic episode, in order to limit the duration of untreated psychosis

• Collaborate in novel practice teams that offer support for education and employment, social engagement, and independent housing, as well as psycho-education for patients and their family members

• Develop pharmacologic treatment strategies based upon principles of fewest medications, lowest effective doses, and scrupulous attention to avoidance of adverse effects
Section 1: Risk Factors and Unfolding Course

• Risk factors for the development of psychosis

• The primary process of psychotic disorders is manifest as deficits in cognition, motivation, and expression years before psychosis unfolds

• The unusual perceptual experiences and ideation that characterize the prodrome and the transition to psychosis reflect loss of control of dopamine tracts ramifying through the limbic system
Genetic and Environmental Risk Factors

- Genetic risk factors are not specific to subtypes of psychosis (affective or non-affective) and no single gene is known to have a major impact on risk status. Increasing paternal age increases risk.

- Prenatal (e.g., maternal influenza or starvation during the second trimester) and perinatal complications increase the risk for both affective and non-affective psychoses.

- Bioenvironmental risk factors (e.g., substance abuse, head injuries, adverse events/trauma) are linked with risk for the full spectrum of psychoses.
Cognitive Deficits Precede Psychosis

- Examination of school records suggests that children who will eventually develop schizophrenia begin school at a level of functioning that is a full grade behind their peers, with the gap increasing by the time they finish high school.
Premorbid Social Deficits

- Deficits in social functioning and impaired personal hygiene/social attentiveness predict later psychosis among clinical high risk subjects.

- Individuals experiencing FEP showed a reduced fertility rate (age-adjusted OR of having children .47 [95% CI = .39, .56]).

FEP = first-episode psychosis.
**Substance Use**

- Cannabis use is associated with earlier onset of the prodrome and greater risk of psychosis

- Among clinically high risk groups use of any illicit substance has been associated with increased risk of psychosis conversion

- Dual diagnosis patients were found to have a higher parental social class, better premorbid cognitive functioning, higher IQ, and better language skills

The Prodrome

- This period involves increasing symptoms (unusual perceptual experiences and ideation) and gradual functional decline (in cognitive and social functioning) that begin several months to years before the onset of frank psychosis.
Accelerating Cognitive Decline

- Cognitive impairments worsen over time, with those patients later in the developmental course of the prodrome displaying greater deficits than those in early phases.

- Those clinically high risk individuals who convert to psychosis have greater impairment than non-converters.

Accelerating Social Cognitive Decline

- Social cognition deficits are more pronounced in converters than non-converters, and predict faster conversion rates even when controlling for general cognitive functioning at baseline.

- Clinical high-risk patients are significantly disturbed by their illness.

Storms of Dopamine

- The major locus of dopaminergic dysfunction is presynaptic, characterized by elevated dopamine synthesis and release capacity.

- This is seen in the prodrome, is linked to symptom severity, and increases with the onset of frank symptoms.

- These findings suggest that presynaptic dopamine dysregulation underlies the onset of psychosis.

Aberrant Incentive Salience ("Limbic Chorea")

- Increased firing (chaotic or stress associated) of dopaminergic neurons in the striatum of schizophrenia patients attributes incentive salience to otherwise irrelevant stimuli

- Neuronal functions associated with dopaminergic signaling, such as the attribution of salience to reward-predicting stimuli and the computation of prediction errors, are altered in schizophrenia patients and this impairment contributes to delusion formation

Transition to Psychosis

- Current estimates suggest that only 20% to 40% of those who meet clinical high risk criteria convert to psychosis within 2 to 4 years

Pathways

Environmental risk + genetic risk factors → Basic symptoms → UHR → Early prodrome → Late prodrome → Schizophrenia, Other psychotic disorder, Other psychiatric disorder, No symptoms

Multiple pathways to schizophrenia + multiple pathways from UHR

UHR = ultra high risk.
Interventions to Delay or Prevent the Transition to Psychosis

• The criteria for identifying at risk individuals have low predictive value, which raises concern about unnecessary and potentially harmful interventions.

• Low doses of antipsychotic medication

• Cognitive-behavioral therapy

• Long-chain polyunsaturated fatty acids

• Compared to controls, the FEP group showed significant down-regulation of several n3 PUFAs, including 20:5n3, 22:5n3, and 22:6n3 within the phosphatidylcholine and phosphatidylethanolamine lipid classes.

• Differences between FE and controls were only observed in the n3 class PUFAs.

PUFAs = polyunsaturated fatty acids.
Omega-3, Long-Chain PUFAs

- 81 individuals at ultra high risk of psychotic disorder
- A 12-week intervention period of 1.2 g/day omega-3 PUFA or placebo was followed by a 40-week monitoring period; the total study period was 12 months
- By study’s end (12 months), 2 of 41 individuals (5%) in the omega-3 group and 11 of 40 (28%) in the placebo group had transitioned to psychotic disorder ($P = .007$)
- Omega-3 PUFAs also significantly reduced positive symptoms ($P = .01$), negative symptoms ($P = .02$), and general symptoms ($P = .01$), and improved functioning ($P = .002$) compared with placebo

Case 1

• An 18-year-old male is brought in by family concerned that he has stopped going out with his friends and stays in his room most of the time, sleeping during the day, and awake and wandering the house at night.

• He tells you that he is just fine. He denies hearing voices but sometimes follows “trails” on the internet. He knows that everything will be OK because he has “a shine” that will allow him to provide for himself whatever happens.

• Would you treat him? How?

• What should you be worried about?
Section 2: Early Detection and Engagement

- Duration of untreated psychosis (DUP) is a powerful predictor of outcome

- Early detection strategies: information dissemination and rapid action teams—the general public

- Engagement in a youth-friendly environment: stigma-free, education/employment support

- Family involvement
Duration of Untreated Psychosis

- Shorter DUP is associated with greater response to antipsychotic treatment

- At the time of treatment initiation, shorter DUP is associated with the reduced severity of negative symptoms

- DUP is a potentially modifiable prognostic factor

• A combination of easy-access detection teams (DTs) and a massive information campaign (IC) about the signs and symptoms of psychosis reduced the DUP in first-episode schizophrenia from 16 to 5 weeks

• “Teaching the general public about early signs of first psychosis, informing the public about the importance of getting help early, and educating the public about the existence of the DTs”

• “Newspaper advertisements, intensively used, have been the most important message carrier…we also produced brochures, posters, commercials on cinema, local TV, and local radio stations.”

• What happens to DUP in the same healthcare sector when the IC is stopped?
• In the no-IC period, DUP increased back up to 15 weeks (median) and fewer patients came to clinical attention through the DTs
• No-IC patients were diagnosed less frequently with schizophreniform disorder, and exhibited more positive and total symptoms, and poorer GAF scores

A 1-year community awareness program was implemented in a London EIS team, targeting staff in non-health service community organizations. The program comprised psychoeducational workshops and EIS link workers, and offered direct referral routes to EIS.

“Teachers, school counsellors, youth workers, housing or employment service staff, or leaders of faith groups or community organizations”

The community awareness program did not reduce treatment delays for people experiencing FEP.
What Do Young People Want?  
A Youth-Friendly Environment

• **Accessible**: including online (Facebook, Web site, etc), evenings, and weekends

• **Stigma-free**: “I wasn’t going to be judged, and the other young people around me would understand what I was going through.”

• **Recreational spaces**: Video game consoles, board games

• “Something to do, and good people to do it with.”  
  (Hemingway)
What Do Young People Want? A Job, School That Will Lead to a Job

• They prioritize work/school, independent living, and a social life. The 3 Cs: a cell phone, a car, and a condo

• A combined supported employment and education program for people with a first episode of psychosis led to higher rates of employment and class completion than usual services

Funding for Supported Employment

• The policy in Canada for funding vocational services for people with a serious mental illness changed from a fee-for-service model to an outcomes-based model, with reimbursement based on successful competitive job placement and retention.

• The results indicated increased rates of competitive work, mainly in entry-level jobs.

• This raised questions as to whether the narrow focus on job attainment may have been at the cost of less career development and ultimately less meaningful work for the consumers (Huh?)

Family Intervention

- Reduces relapse rates
- Increases cooperation with pharmacotherapy

- The burden of care may be reduced by psychosocial interventions, but the specific effects of interventions for caregivers themselves are not usually reported or are seen as secondary outcomes.

- Caregiver-focused interventions appear to improve the experience of caring and the quality of life of those caring for people with severe mental illness, and these benefits may be gained in FEP.

Cannabis and Stimulant Disorders and Readmission 2 Years after FEP

• Predictors of readmission were examined with Cox regression in 7269 people aged 15 to 29 years with a first psychosis admission

• Ongoing problem drug use predicted readmission

• The lowest rate of readmission occurred in people whose baseline drug problems were discontinued
Case 2

• The Mental Health Center you direct receives a $200,000 grant from SAMHSA, through the state, to upgrade programs for the treatment of FEP

• How will you utilize the money?
Section 3
Pharmacologic Treatments

• Low-dose antipsychotic medications
• Preemption and mitigation of adverse events

• Attention to affective psychopathology

• Medication non-adherence
• Long-acting injectable antipsychotic medications

• Clozapine
Low-Dose Antipsychotic Medication Discriminating Consumers

- Considerable evidence now indicates that low-dose antipsychotic treatment during the first episode is associated with symptomatic and functional improvement.

- Selection of antipsychotic medications that do not produce extrapyramidal side effects, weight gain/metabolic side effects, sedation, or sexual dysfunction at reasonable doses is now possible.

- “Succeed-first” strategy: very low-dose FGAs (haloperidol, perphenazine, loxapine)

FGA = first-generation antipsychotic.
Neuroleptic Threshold Doses of Haloperidol

- FEP patients tend to experience higher rates of extrapyramidal symptoms when treated with FGAs at doses recommended for chronic patients.
- The mean haloperidol doses at which multi-episode patients with chronic psychotic disorders developed mild bradykinesia-rigidity are 6 to 7 mg daily.
- FEP patients develop mild bradykinesia-rigidity at mean doses of 2 mg daily, and demonstrated excellent therapeutic response at these doses.
- At 1 to 2 mg daily, haloperidol is a highly effective antipsychotic that is well-tolerated in many patients with FEP.

• 400 patients with FEP were randomly assigned to olanzapine, quetiapine, or risperidone (the first 3 second-generation antipsychotic medications)

• Weight gain after 12 and 52 weeks of treatment was estimated as 15.6 (+/-1.1) and 24.2 (+/-1.9) lb for olanzapine, 8.6 (+/-1.1) and 14.0 (+/-1.9) lb with risperidone, and 7.9 (+/-1.1) and 12.1 (+/-1.8) lb for quetiapine, respectively

• By 52 weeks, treatment-emergent metabolic syndrome was reported in 51 individuals (13.4% of the total population), of whom 22 were receiving olanzapine, 18 quetiapine, and 11 risperidone
Affective Psychoses
Similarities to Non-Affective Psychoses

• Early intervention may improve both course and outcome
• Multiple prior episodes seems to be a risk factor for non-response to a variety of pharmacologic treatments
• Response to lithium has been found to decrease with the occurrence of multiple prior episodes (neuro-protective abilities)
• Patients may profit from psycho-education before potential cognitive disturbances occur during the long-term course of illness
• Appropriate use of mood stabilizing and antidepressant medications, spares the need for high antipsychotic doses

Long-Acting Injectable Antipsychotic Medication

• Key elements to take into account when offering an LAI in the early course of schizophrenia should include their potential superiority in allowing early detection of non-adherence and in reducing the number of re-hospitalizations and relapses

• Shared decision making works best if all parties share the same facts

• PRELAPSE Study: LAI aripiprazole vs TAU

LAI = long-acting injectable; TAU = treatment as usual.
“Trust but Verify”
Early Clozapine Trial Algorithm-Directed

• 76% responded to the first trial of an antipsychotic
• Only 7 (23%) of the remaining 30 patients responded to a second antipsychotic trial
• 13 of the remaining 23 individuals agreed to a trial of clozapine. The investigators compared the clozapine-treated group with a group of 9 patients who refused clozapine
• Patients who received clozapine experienced a mean BPRS change of 19 points (from 53.5 to 34.5) and a change in the CGI severity rating from 5.4 to 3.5 (from severely ill to mildly ill); those who refused clozapine had a 2-point increase in mean BPRS (from 53 to 55) and a .6-point increase in the mean CGI severity rating from 5.4 to 6 (remaining markedly to severely ill)

BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impression.
Should Treatment Be Stopped? Actually, No!

• Systematic review to determine the risk of experiencing a recurrence of psychotic symptoms in individuals who have discontinued antipsychotic medications after achieving symptomatic remission from a first episode of non-affective psychosis (FEP)

• 6 studies were identified that met criteria and these reported a weighted mean 1-year recurrence rate of 77% following discontinuation of antipsychotic medication

• By 2 years, the risk of recurrence had increased to over 90%. By comparison, we estimated the 1-year recurrence rate for patients who continued antipsychotic medication to be 3%

• A trial off of antipsychotic medications is associated with a very high risk of symptom recurrence and should thus not be recommended

Case 3

• A 22-year-old woman who experienced FEP failed to respond to low-dose haloperidol or asenapine. Her auditory hallucinations and suspiciousness have decreased substantially over 4 weeks of treatment with olanzapine, but she has gained 15 pounds and is hungry all the time.

• What can you do?
Section 4: Successes and Disappointments

• FEP Programs, now 10 years out: remission, recovery, relapse

• DUP, negative psychopathology at baseline, substance misuse, criminality, suicide

• Waning benefit

• Where do we go from here?
60% to 70% of patients will achieve remission (key positive and negative features rated “mild” or less) at some point during follow-up in FEP programs, but the numbers for sustained remission are substantially lower.

10% to 20% of patients will achieve recovery (good social and occupational functioning in the community) at some point during follow-up in FEP programs, but the numbers for sustained recovery are lower.
Relapse Rates Are High Even with Continued Treatment

- In an FEP program in Spain, 21% relapsed by the end of year 1, 41% by the end of year 2, and 65% by the end of year 3

- In an FEP program in New York, 5 years after initial recovery, the cumulative first relapse rate was 82%

- Discontinuing antipsychotic drug therapy increased the risk of relapse by almost 5 times (hazard ratio for an initial relapse, 4.89 [99% CI = 2.49-9.60]

Duration of Untreated Psychosis

- Shorter DUP, longer treatment time, higher baseline PANSS positive score, and higher PANSS general pathological scores predicted response (China, 1 year)
- Shorter DUP was associated with higher C-GAF at 2 years, greater increase in C-GAF, and higher rates of clinical remission in early-onset FEP (Spain, 2 years)
- Short DUP predicted both 3-month and 2-year remission rates in FEP (Denmark, 2 years)
- Shorter DUP and early symptom resolution predicted symptomatic remission at the end of follow-up (Hong Kong, 3 years)

PANSS = Positive and Negative Syndrome Scale.
• DUP predicted remission, positive symptoms, and social functioning at 8 years (Ireland, 8 years)
• The short DUP group experienced a significantly higher remission rate over the course of the illness. DUP had a specific impact on negative symptom remission (Hong Kong, 10 years)
• A significantly higher percentage of early-detection patients had recovered at the 10-year follow-up relative to usual-detection patients. Early-detection recovery rates were higher largely because of higher employment rates for patients in this group (Norway, 10 years)
Baseline Negative Psychopathology

- High levels of apathy, poor verbal memory, and being male were the baseline variables that best predicted poor functioning at 1-year follow-up, explaining 34% of the variance in GAF-F (Norway, 1 year)

- Prominent negative symptoms were associated with earlier onset, lower premorbid functioning, worse executive functioning and attention at baseline, and lower rates of working/studying during the 2-year follow-up (Turkey, 2 years)

- Higher severity of negative symptoms at baseline predicted less likelihood of recovery (Denmark, 10 years)

Substance Misuse

- Individuals with persistent substance misuse had more severe depression, more positive symptoms, poorer functional outcome, and greater rates of relapse at 1 year than those who stopped and those who had never misused substances (United Kingdom, 1 year).

- Continuous cannabis use was associated with higher levels of psychotic symptoms after 5 years, and this association was only partly explained by insufficient antipsychotic medication (Denmark, 5 years).

Violent Offending, Criminality (Denmark, 5 years)

- No significant reduction in violent offending or any offending was found in the assertive specialized treatment group (adjusted hazard ratio = 1.06; 95% CI = .72-1.56) compared with the control group. Prevalence of offending was low and had often commenced prior to inclusion in the trial.
Suicide Attempts

- 22% made a suicide attempt over the follow-up period, including 12 successful suicides (5%). The following baseline risk factors increased the risk of any suicide attempts: history of self-harm (OR = 4.27; P < .001), suicidal tendencies (OR = 2.30; P = .022), being depressed for >50% of the initial psychotic episode (OR = 2.49; P = .045), and hopelessness (OR = 2.03; P = .030) (Australia, 7 years).

- Results suggested that early intervention patients had reduced suicide rate, fewer number and shorter duration of hospitalization, longer employment periods, and fewer suicide attempts over 10 years (Hong Kong, 10 years).

Sweden, 5-Year Uh Oh!

- Naturalistic cohort study between 1995 and 2000 of all FEP patients (n = 144) in Uppsala County, Sweden, compared a 3-year period before (non-mACT) and after the introduction of a mACT program in 1998.

- The implementation of a modified assertive community treatment was not followed by subsequent improvements of 5-year outcome on a group level for patients with FEP.

mACT = modified assertive community treatment.
Results suggested that Early Intervention patients had reduced suicide rate, fewer number and shorter duration of hospitalization, longer employment periods, and fewer suicide attempts over 10 years.

At 10 years, no difference was found in psychotic symptoms, symptomatic remission, and functional recovery.

The short-term benefits of the Early Intervention service on number of hospitalizations and employment was sustained after service termination, but the differences narrowed down.

10-Year Follow-Up of the OPUS Specialized Early Intervention Trial for FEP

• To examine the effect of 2 years of OPUS vs TAU within an FEP cohort, 10 years after inclusion into the OPUS trial
• While there was evidence of a differential 10-year course in the development of negative symptoms, psychiatric bed days, and possibly psychotic symptoms in favor of OPUS treatment, differences were driven by effects at earlier follow-ups and had diminished over time
• There were no differences between OPUS and TAU regarding income, work-related outcomes, or marital status

Disease/Course Alteration or Prosthesis
Disease/Course Alteration or Prosthesis
When the FEP Program is Stopped…
Case 4

• A 24-year-old woman has had an excellent outcome of treatment for an FEP. She is taking lurasidone 40 mg daily and has no adverse effects. She has a job as an aide in a veterinary clinic and is highly regarded there. She is engaged to be married. Her 2 years of participation in your grant-supported FEP program is coming to an end

• What will you do?
Section 5: RAISE

• Recovery After an Initial Schizophrenia Episode
• “Coordinated Specialty Care (CSC) is a team-based, multi-element approach to treating FEP that has been broadly implemented in Australia, the United Kingdom, Scandinavia, and Canada. Component interventions include assertive case management, individual or group psychotherapy, supported employment and education services, family education and support, and low doses of select antipsychotic agents.”

Specified Aims of RAISE Determined by NIMH

• Develop a comprehensive and integrated intervention to
  – Promote symptomatic recovery
  – Minimize disability
  – Maximize social, academic, and vocational functioning
  – Be capable of being delivered in real world settings utilizing current funding mechanisms

Key Study Inclusion Criteria

• Ages 15 to 40 years

• The following diagnoses are included in the clinical differential: schizophreniform disorder, schizophrenia, schizoaffective disorder, psychotic disorder NOS, brief psychotic disorder

• Less than 6 months of treatment with antipsychotic medications
NAVIGATE

• 4 components
  – Psychopharmacology - COMPASS
  – Individual Resiliency Training (IRT)
  – Family Psycho-education
  – Supported Employment/Education

Outcome Assessments

- Primary Outcome Measure: Heinrichs-Carpenter Quality of Life Scale
- Key Secondary Outcome Measures
  - PANSS, Calgary Depression Rating Scale
  - Service Utilization Rating Scale, Treatment Received, Employment and School, Cost
  - Self assessments by patients
  - Cognition – BACS
  - Physical Assessments

BACS = Brief Assessment of Cognition in Schizophrenia.
Duration of Untreated Psychosis
The Real World

• Participants were 404 individuals (ages 15-40 years) who presented for treatment for FEP at 34 nonacademic clinics in 21 states.

• Median DUP was 74 weeks (mean = 193.5±262.2 weeks; 68% of participants had DUP of >6 months).

• Correlates of longer DUP included earlier age at first psychotic symptoms, substance use disorder, positive and general symptom severity, poorer functioning, and referral from outpatient treatment settings.

Cardiometabolic Risk in Patients with FEP: Baseline Results from the RAISE-ETP Study

- 48% were obese or overweight, 51% smoked, 57% had dyslipidemia, 10% had hypertension, and 13% had metabolic syndrome
- Total psychiatric illness duration correlated significantly with higher body mass index, fat mass, fat percentage, and waist circumference
- Antipsychotic treatment duration correlated significantly with higher non-HDL-C, triglycerides, and triglycerides to HDL-C ratio and lower HDL-C and systolic blood pressure (all \( P \leq .01 \))
- Olanzapine was significantly associated with higher triglycerides, insulin, and insulin resistance, whereas quetiapine was associated with significantly higher triglycerides to HDL-C ratio (all \( P \leq .02 \))
Compared with Community Care Patients, Patients in NAVIGATE Had Better

- Retention in treatment

- Quality of Life Scores

- PANSS Total Scores

- Calgary Depression Scale Scores
Section 5: Overview

• Psychosis is one manifestation of a broader disease process that results in (at present) irreversible loss of cognitive and social cognitive abilities

• Early identification and treatment limits the functional loss

• Individuals with the disease process are more likely to continue in treatment if they assign it value

• Psychosocial treatment may be prosthetic and, like pharmacologic treatment may need to be continued indefinitely
Q&A Session