Overview of Clinical Symptoms and Treatment in Early Psychosis

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What is Psychosis?

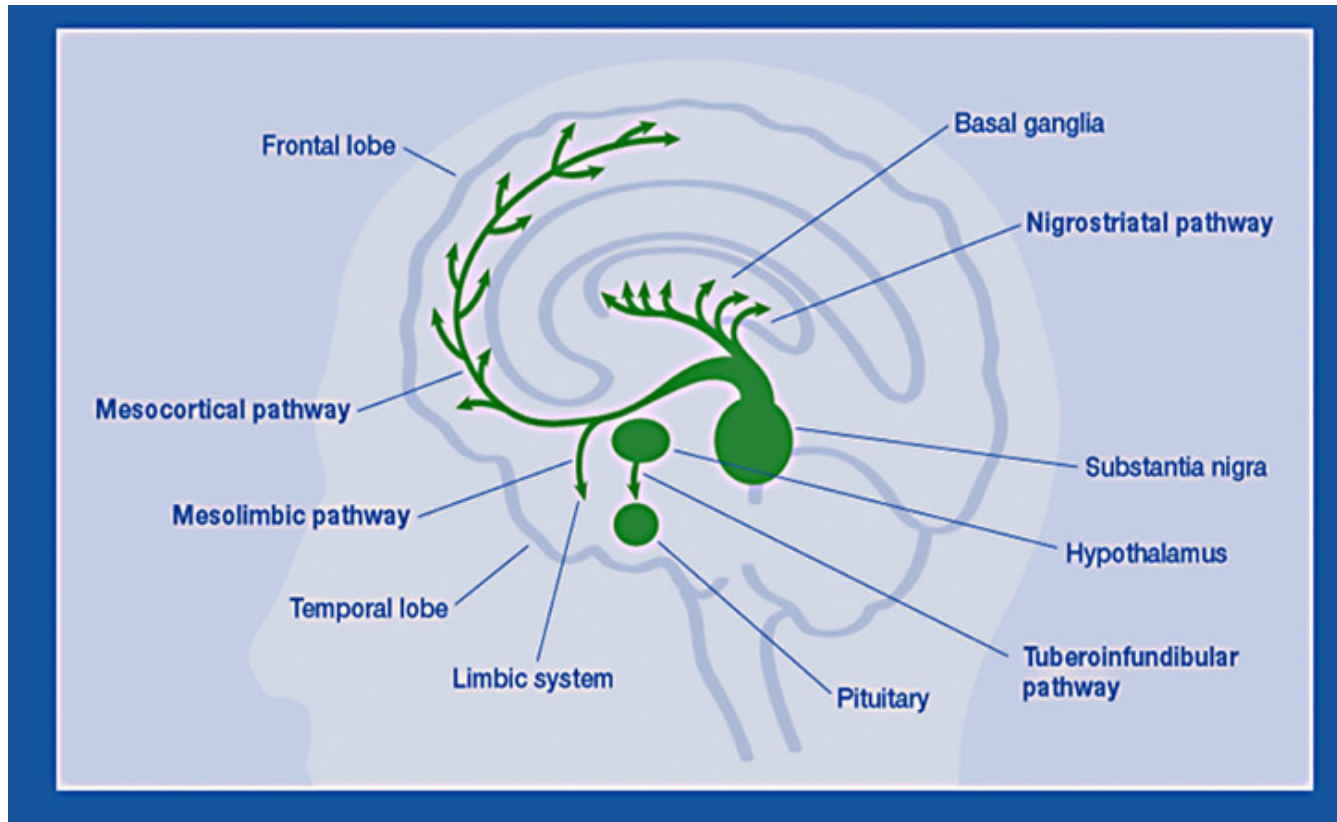**Alteration in reality testing manifested by either**

- Hallucinations

- Delusions

- Disorganized behavior
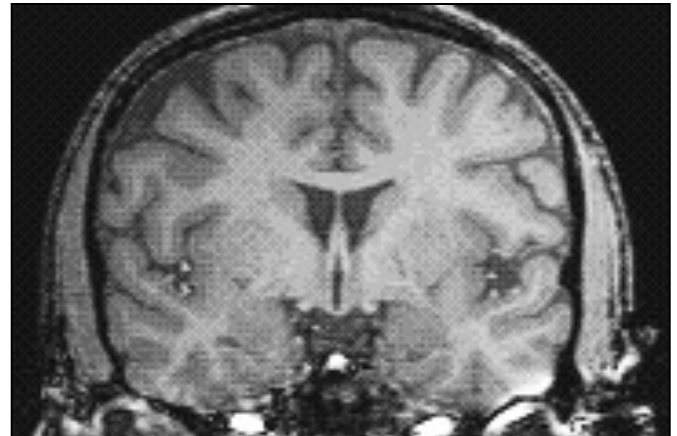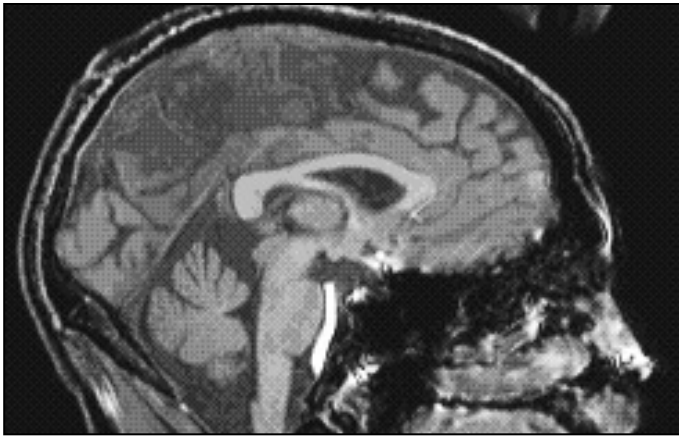
- Disorganized speech

Plus

- Impaired functioning

Dopamine Hypothesis: based on med effects, drugs, animal models
- **mesolimbic hyperactivity**
- mesocortical hypoactivity

Dopamine Hypothesis: based on med effects, drugs, animal models

Considerations in Early Psychosis

Diagram showing overlapping circles: Anxiety, Cognitive Problems, Drugs and Alcohol, Emotional Experience, Psychosis, Depression.
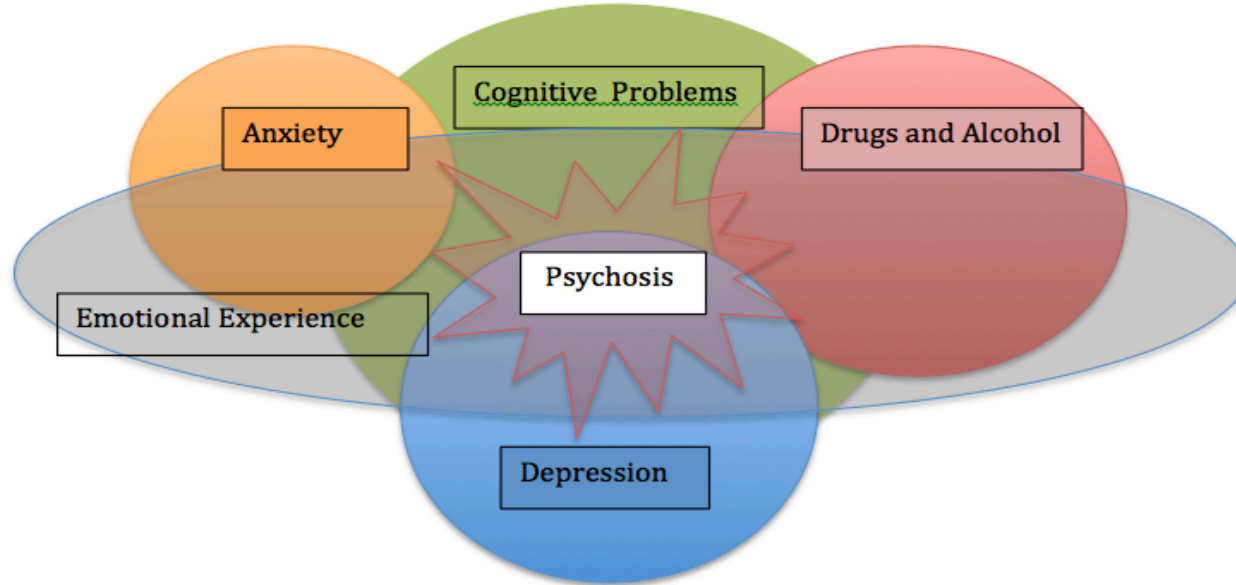
- Heterogeneity of Symptoms

- Medication Effects and Side-effects

- Insight/Willingness for Treatment

- Drug Use

- Effect of duration of untreated/persistent psychosis

- Family Unit

- Social-occupational Functioning

Identifying At-Risk Individuals (mild/warning signs of psychosis)
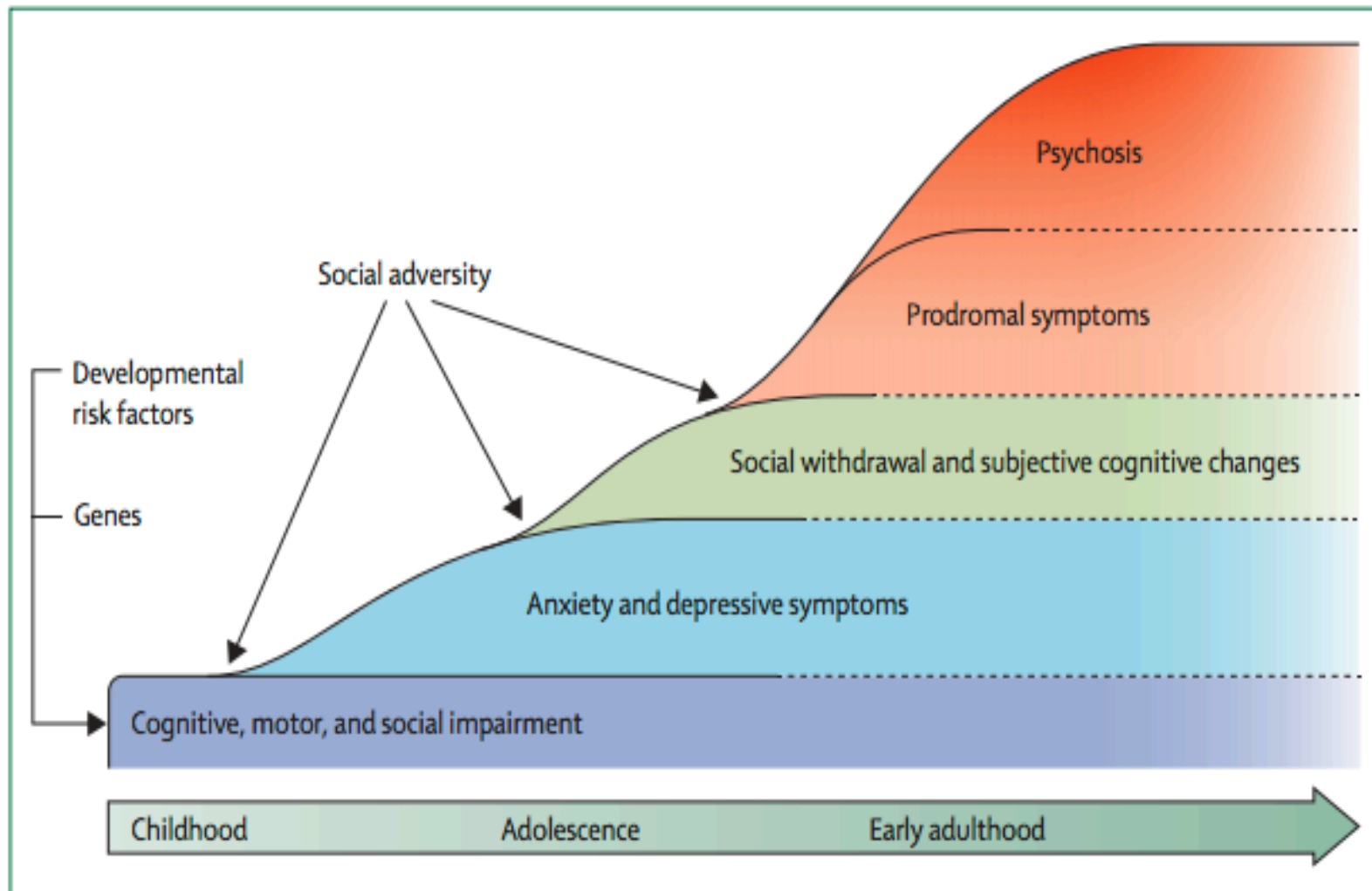
Figure 1: The trajectory to schizophrenia showing the evolution of symptoms and the main risk factors

Identifying At-Risk Individuals

Prevalence of mild signs of psychosis (Clinical Risk)
Childhood (ages 9-12) ~ 17%
Adolescence (ages 13-18) ~7.5%

Prodromal (Attenuated Psychosis Syndrome or Clinical High Risk)
Ages 16-30+ ~2-3%

Conversion rates from prodromal to psychosis
- ~20% over 1 year
- ~30% over 2 years
- ~35% remission over 5 years
- ~40% persistence

Psychiatric Disorders with Psychosis

Brief Psychotic Episode

Prodrome

Schizophrenia

Schizophreniform

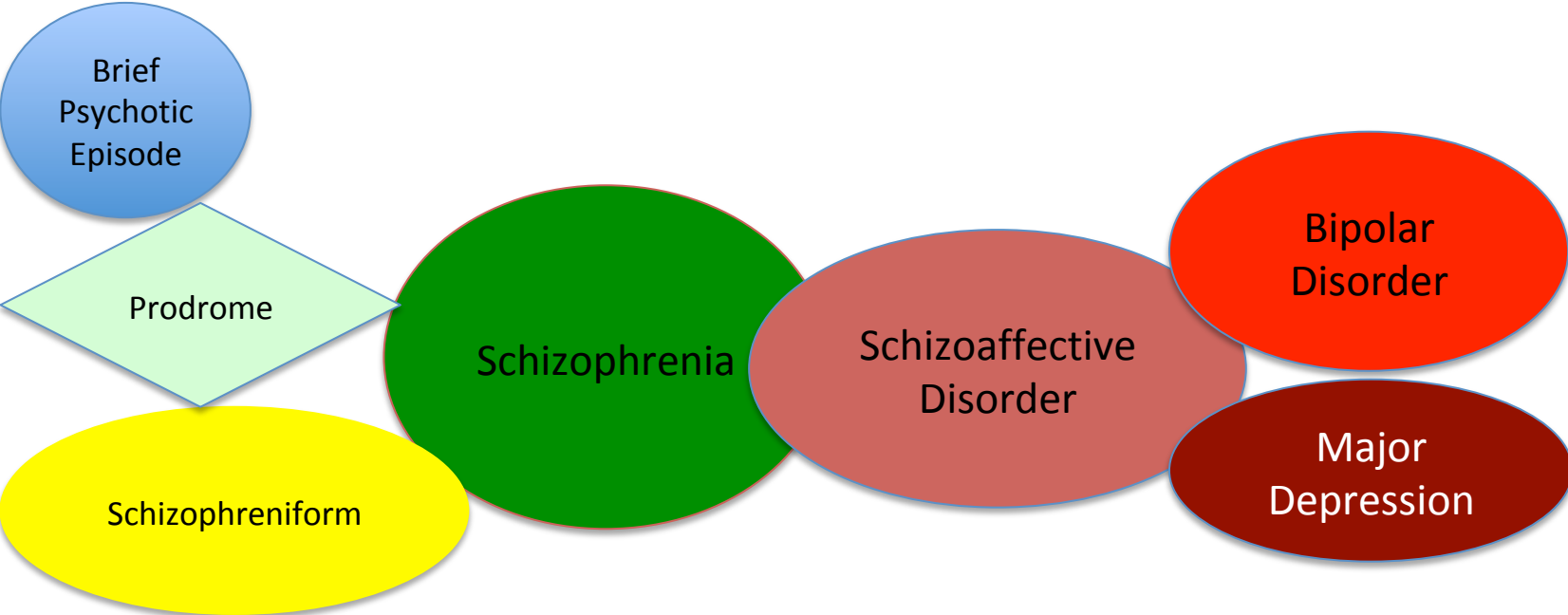Schizoaffective Disorder

Bipolar Disorder

Major Depression

Longer Duration Untreated Psychosis correlates with

- increased negative symptoms

- poorer medication response

- reduced symptomatic and functional recovery

WHO recommends DUP< 3months

Many young persons experience DUP of 1 year and longer before treatment

Remission in FEP: 40-60% over 1-2 years

Lack of significant clinical response within 1-2 years treatment associated with low chance of remission

What is at Stake?

~100,000 young Americans experience FEP each year

Lifetime prevalence of schizophrenia ~1%

Point prevalence ~0.8%

After FEP with Dx: schizophrenia

- <20% of individuals achieve full recovery with routine care
- 80-90% are unemployed
- 20% are homeless
- 23% are incarcerated
- ~10% complete suicide, often early in their illnesses

- Economic burden of schizophrenia in the United States estimated at $155 billion annually (2013)

- Estimated 23 million people worldwide

Causes: Genetic Risk

To Date: 108 risk genes for schizophrenia
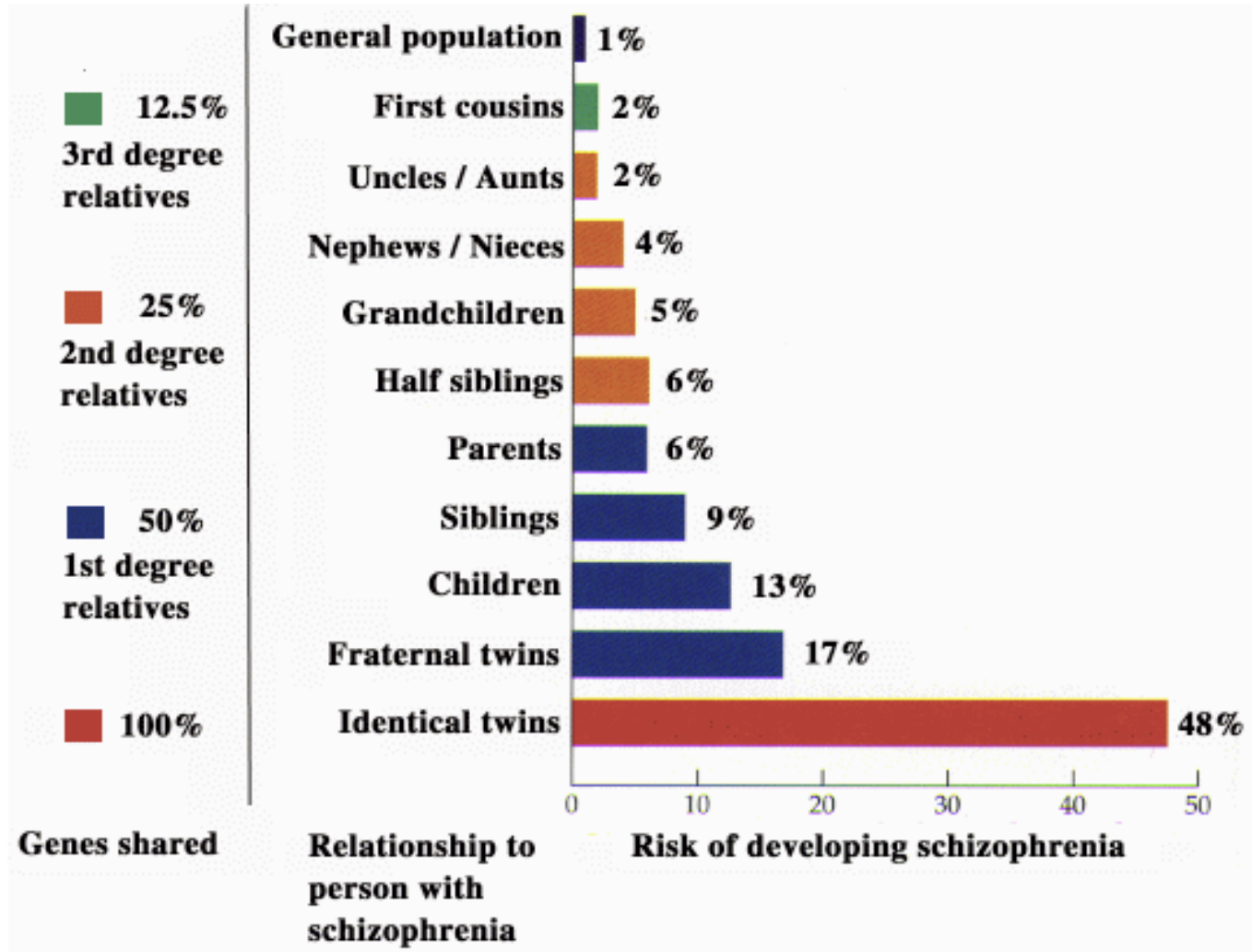
(Source: Gottesman, 1991)

Causes: Environmental Factors

Genetic vulnerability

Identified genes, such as neuregulin 1, dysbindin, and possibly COMT

- **Prenatal environment:**
  Obstetric complications
  Viral exposure
  Maternal stress and malnutrition

- **Childhood environment:**
  Child-rearing
  Child abuse
  Head injury

- **Later life environment:**
  Drug abuse
  Migration/ethnicity
  Urbanicity
  Social adversity/life events

- *Vulnerability for psychosis evident in markers of neurodevelopmental abnormality*

- *Childhood antecedents evident as a result of vulnerability interact with environment*

- *Interacts with maturational brain changes during adolescence*

Onset of schizophrenia

Phases of Illness
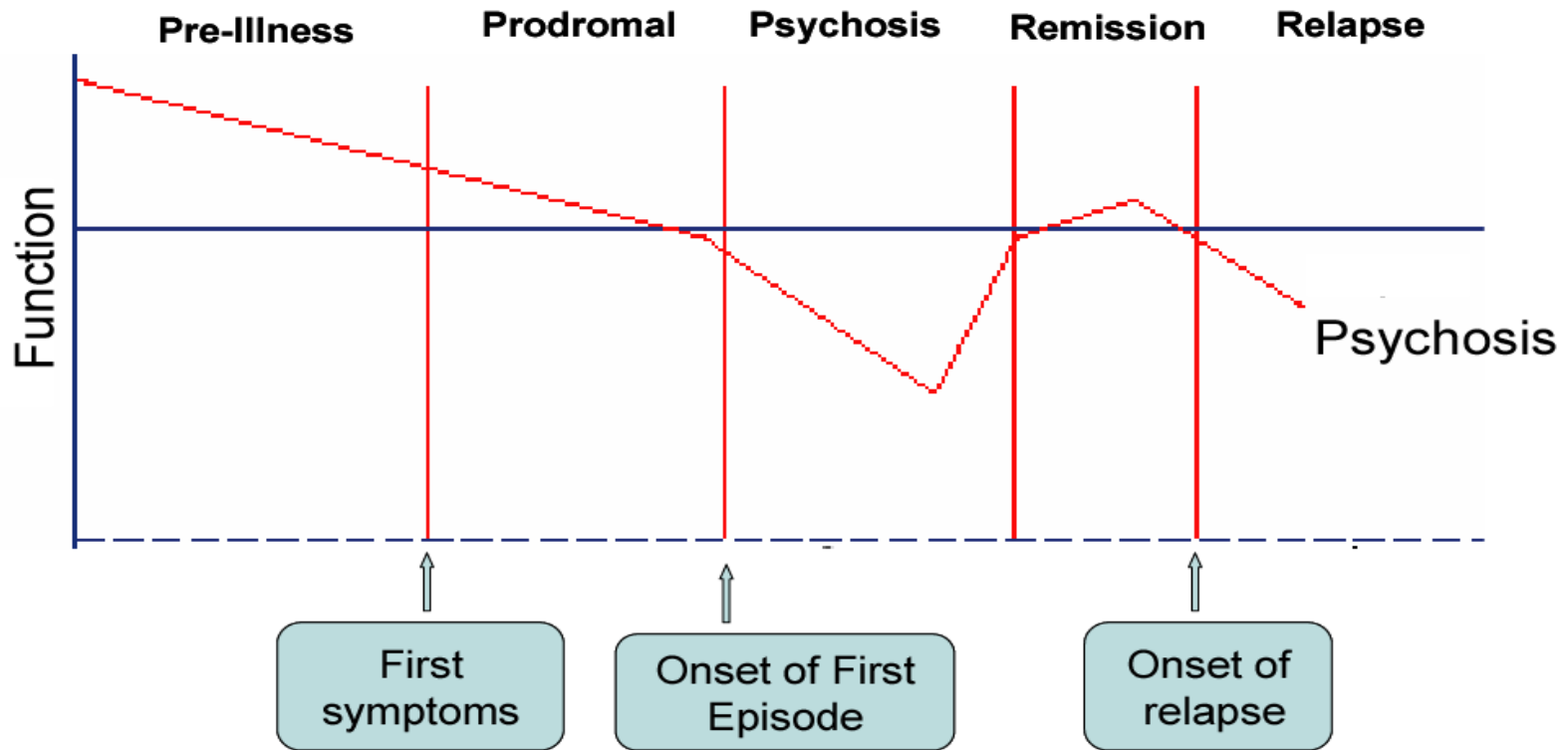
Adapted from Knowles, 2004

What are some common Differential Diagnoses to be considered?

Drugs:

temporary: cocaine, ecstasy, LSD, amphetamines, spice/K2
longer lasting: PCP, bath salts/synthetic cathinones
induction effect?: THC

differentiating factors
- shorter duration
- negative symptoms
- activation
- confusion

Comorbidity of schizophrenia and drug abuse
- 50% lifetime rate
- 30% over past 6 months (THC, cocaine, alcohol)

Neurological Disorders

- Epilepsy: TLE, primary generalized, Tuberous Sclerosis
- Space Occupying Lesions
- Dementias

Systemic Illnesses:

- Infections, e.g. syphilis, HIV, sarcoid/TB

- Hormonal, e.g. Thyroid, Cushing's disease

- Immune Disorders, e.g. SLE, paraneoplastic, NMDA-R antibody encephalitis, Hashimoto thyroiditis

- Genetic Disorders, e.g. velocardiofacial syndrome (22q11.2 deletion syndrome), Turner syndrome, hemochromatosis, BG calcifications, etc.

- Storage: Wilson's disease, juvenile/adult metachromatic leukodystrophy

What is a reasonable work-up to consider? (*Freudenreich 2007*)

Initial Medical Workup for First-Episode Schizophrenia[a]

Laboratory studies
- CBC
- Electrolytes
- BUN/creatinine
- Glucose
- Calcium and phosphorus
- TSH
- Liver function tests
- ESR
- Antinuclear antibodies
- Ceruloplasmin
- HIV screening[b]
- FTA-Abs for syphilis (rapid plasma reagin not sufficient)
- Vitamin B12 and folate
- Urinalysis
- Urine drug screen

Imaging studies: MRI to rule out demyelinating disease and brain tumor (e.g. meningioma)[c]

Electroencephalogram[‡]

[a]This list of tests is not exhaustive but represents merely one possible initial workup for first-episode psychosis. Other tests should be also considered if the clinical history and the clinical picture suggest that they might be useful diagnostically (e.g., chest X-ray, lumbar puncture, or karyotype).

[b]Recommended as part of routine care for all (hence including psychotic) patients. See Branson et al. (2006).[32]

[c]Controversial as yield is often considered low.

What is a reasonable work-up to consider?

Diagnostic Testing: MRIs in 152 FE patients (*Lubman 2002*)

2 cases of other medical condition

22% incidental abnormalities

76% normal

1400 youths (8-23 yrs) underwent MRIs through CHOP (*Gur 2013*)

10.6 % incidental findings

1% clinically significant

What is a reasonable work-up to consider?

Diagnostic Testing: EEG

Mayo Clinic Study: 122 FE patients (*Manchada 2005*)

39% normal

44% intermediate

17% clearly abnormal

Questionable diagnostic significance

Prognostic value for remission after 1 year

Normal EEG: 90% remission versus 55-60%

First-episode Psychosis Treatment

➢ Best chances of response/recovery

➢ Lack of effects of chronic illness

➢ Challenge of illness acceptance

Duration of untreated psychosis leads to increased

➢ Negative symptoms   ↘

➢ Cognitive dysfunction   ➔   associated with functional

impairment

First-episode Psychosis Treatment

➢ About 12 First-episode studies in the last 40 years

➢ 60-85% response rates based on positive symptoms

➢ Time to remission: mean=35 weeks, median 11 weeks

➢ No superiority of newer medications

➢ Relapse rates 60-80%

➢ 80% associated with medication nonadherence (Robinson 1999)

➢ Duration of Untreated Psychosis: worse outcome (Perkins 2005)

Development of Early Psychosis Programs

Mid-1980's
- England
- Australia

1990's
- Scandinavia
- Germany
- USA
- Canada

~2000
- Japan
- China
- South East Asia
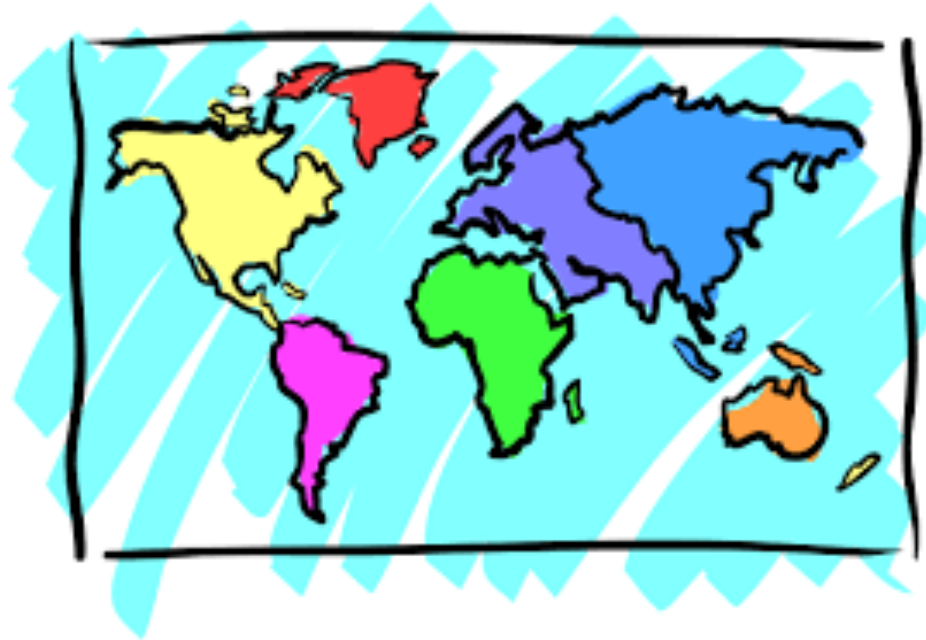
RAISE Trial (Recovery After Initial Schizophrenia Episode)

34 clinics in 21 States, recruited 2010-2012
First-episode psychosis regardless of duration

404 patients randomized to
Coordinated Specialty Care Model versus "Treatment as Usual"
➢ Personalized medication management
➢ Resilience based psychotherapy
➢ Family psychoeducation/therapy
➢ Supported employment

Ave age: 23 yrs
M:F=2.5:1
70% lived with family
Dx of schizophrenia or schizophreniform: 70%

NAVIGATE SITES

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┌──────────────────┐                    ┌─────────────────────────────────────────────┐
│ Screened[1]      │                    │ Reasons:                                    │
│ n = 512          │                    │ Not first episode.....................10     │
└──────────────────┘                    │ Does not meet age ..................8         │
        │                               │ More than 6mos. AP.............32            │
        ├───────────────┐               │ Exclusionary psych DX...........41           │
        ▼               ▼               │ Unable to consent....................9        │
┌──────────────┐  ┌──────────────┐      │ Lost contact........................40        │
│ Eligible[2]  │  │ Not eligible/│      │ Neurological or head trauma ... 14           │
│ n = 272      │  │ Not interested│     │ Does not want treatment ........11           │
└──────────────┘  │ n = 240      │      │ Does not want research..........36           │
        │         └──────────────┘      │ Does not want to leave provider 6           │
        ▼                               │ Unable to return to clinic..........12       │
┌──────────────┐                        │ Other.......................................21 │
│ Consented[3] │                        └─────────────────────────────────────────────┘
│ n = 272      │
└──────────────┘
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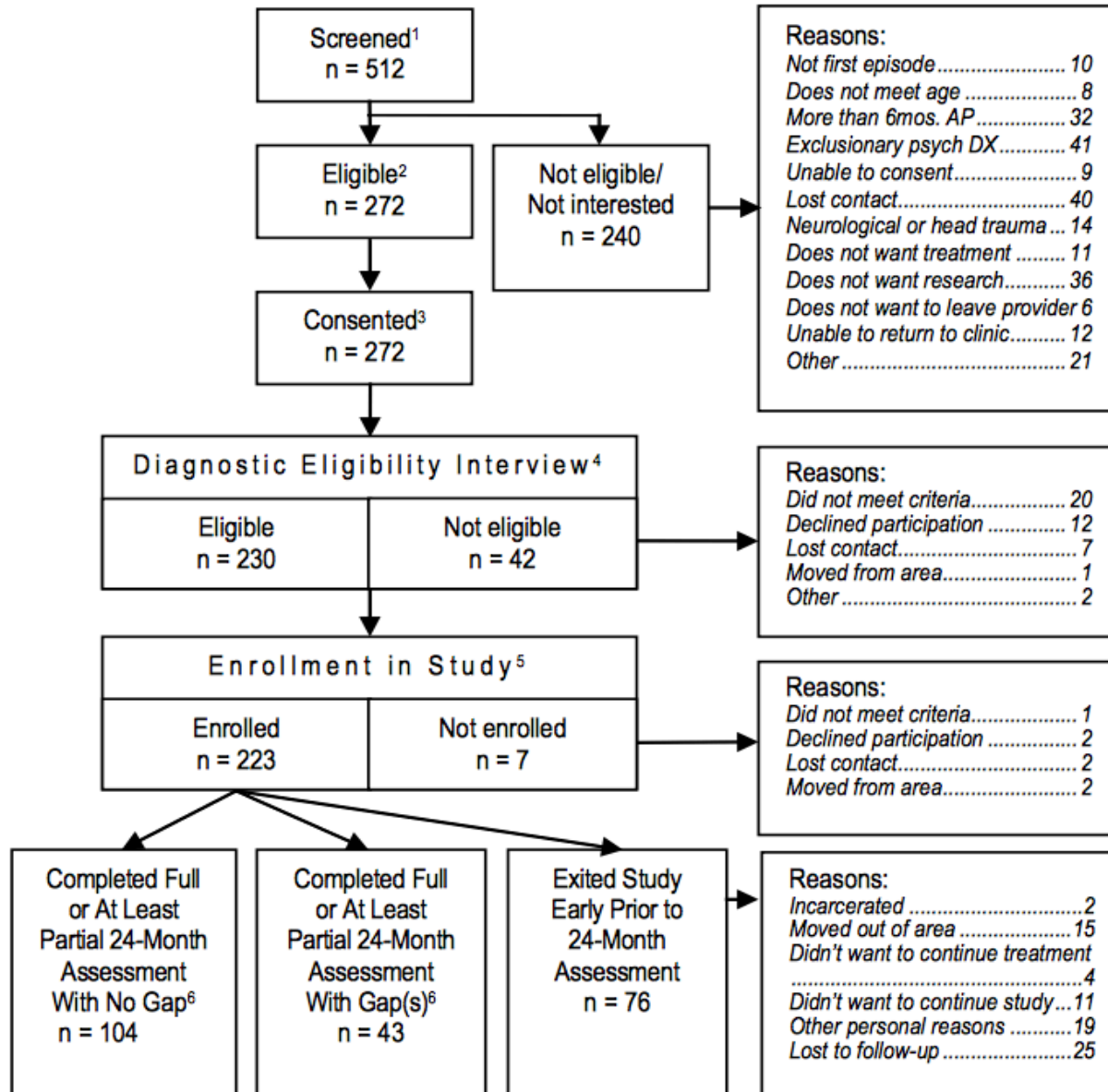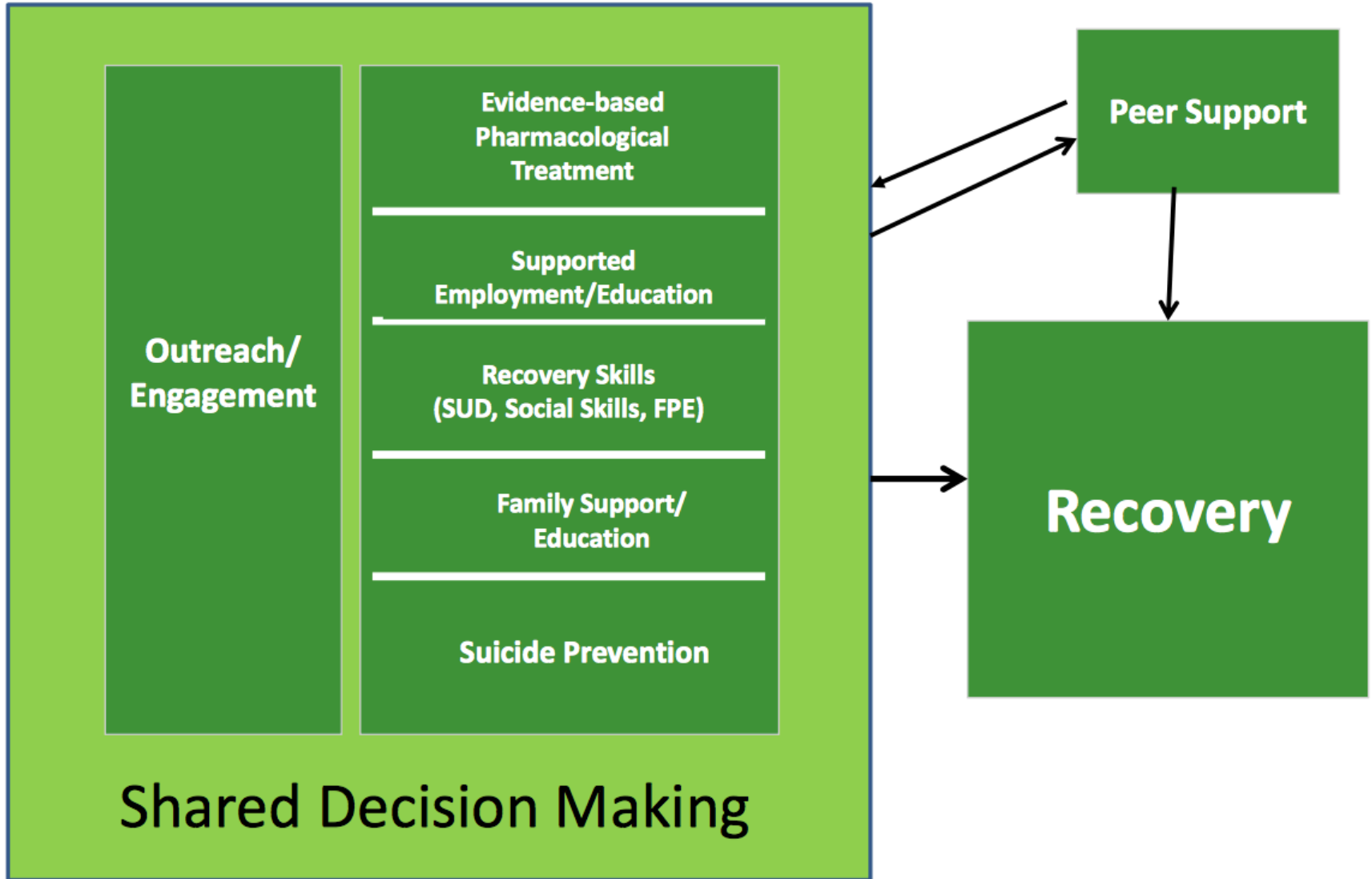
Diagnostic Eligibility Interview[4]

| Eligible n = 230 | Not eligible n = 42 |

Reasons:
Did not meet criteria.................20
Declined participation 12
Lost contact................................7
Moved from area.........................1
Other...2

Enrollment in Study[5]

| Enrolled n = 223 | Not enrolled n = 7 |

Reasons:
Did not meet criteria...................1
Declined participation 2
Lost contact..................................2
Moved from area..........................2

| Completed Full or At Least Partial 24-Month Assessment With No Gap[6] n = 104 | Completed Full or At Least Partial 24-Month Assessment With Gap(s)[6] n = 43 | Exited Study Early Prior to 24-Month Assessment n = 76 |

Reasons:
Incarcerated 2
Moved out of area 15
Didn't want to continue treatment 4
Didn't want to continue study...11
Other personal reasons 19
Lost to follow-up 25

RAISE Connection Team Interventions

Results: 223 patients in Coordinated Specialized Care (CSC)

65% completed 2-year treatment, 45% continuous care

Those in Coordinated Specialized Care

➤ experienced greater improvement in quality of life, including interpersonal relationships

➤ remained in treatment longer; lower doses of antipsychotics

➤ experienced greater relief from overall symptoms as well as depression

➤ better involvement in work and school

➤ duration of illness represents moderator of treatment response

Summary of 8 RCT (n=1200) of Early Psychosis Interventions comparing CSC versus TAU demonstrated

- 6 Studies: reduced psychotic symptom burden

- 4 Studies: higher retention in treatment with CSC

- 3 Studies: showed higher recovery rates

- 3 Studies: improved psychosocial functioning

- 3 Studies: cost effectiveness despite higher utilization

- 2 Studies: differential effects disappeared after completion of active treatment

Consequences

➢ Starting 2013 Congress allocated funds to be distributed through SAMSHA at the state level (5% MHBG) dedicated to treatment for those "with early serious mental illness"

➢ Evidence-Based Treatments for First Episode Psychosis: Components of Coordinated Specialty Care (CSC)

➢ Implemented in 28 States in 2015

➢ Increased funding for 2017 to 10% and dissemination in all 50 States
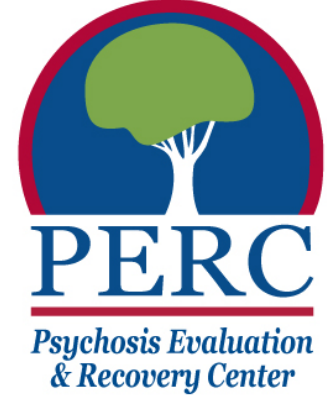
Existence since Spring 2015

Over 150 evaluations and enrolled

After intake evaluation
- Cognitive therapy for psychosis: recovery oriented
- Medication management
- Employment/scholastic support
- Cognitive remediation
- Family education

Cognitive therapy for psychosis: recovery oriented

Focus on

- Early experiences that she a person's belief system

- Reframing negative automatic thoughts

- Pursuing new behavior strategies to improve functioning

- Heavy focus on personal engagement (rapport building, activation)

Medication management

- Antipsychotic medications: oral or long acting injectibles
- Low dosages
- Time period 1-2 years
- Risk of relapse

Employment/Scholastic Support

- Career profile: past employment, schooling and interests
- Follow up about job searches
- Interact with academic settings about support
- Referral to Office of Vocational Rehabilitation
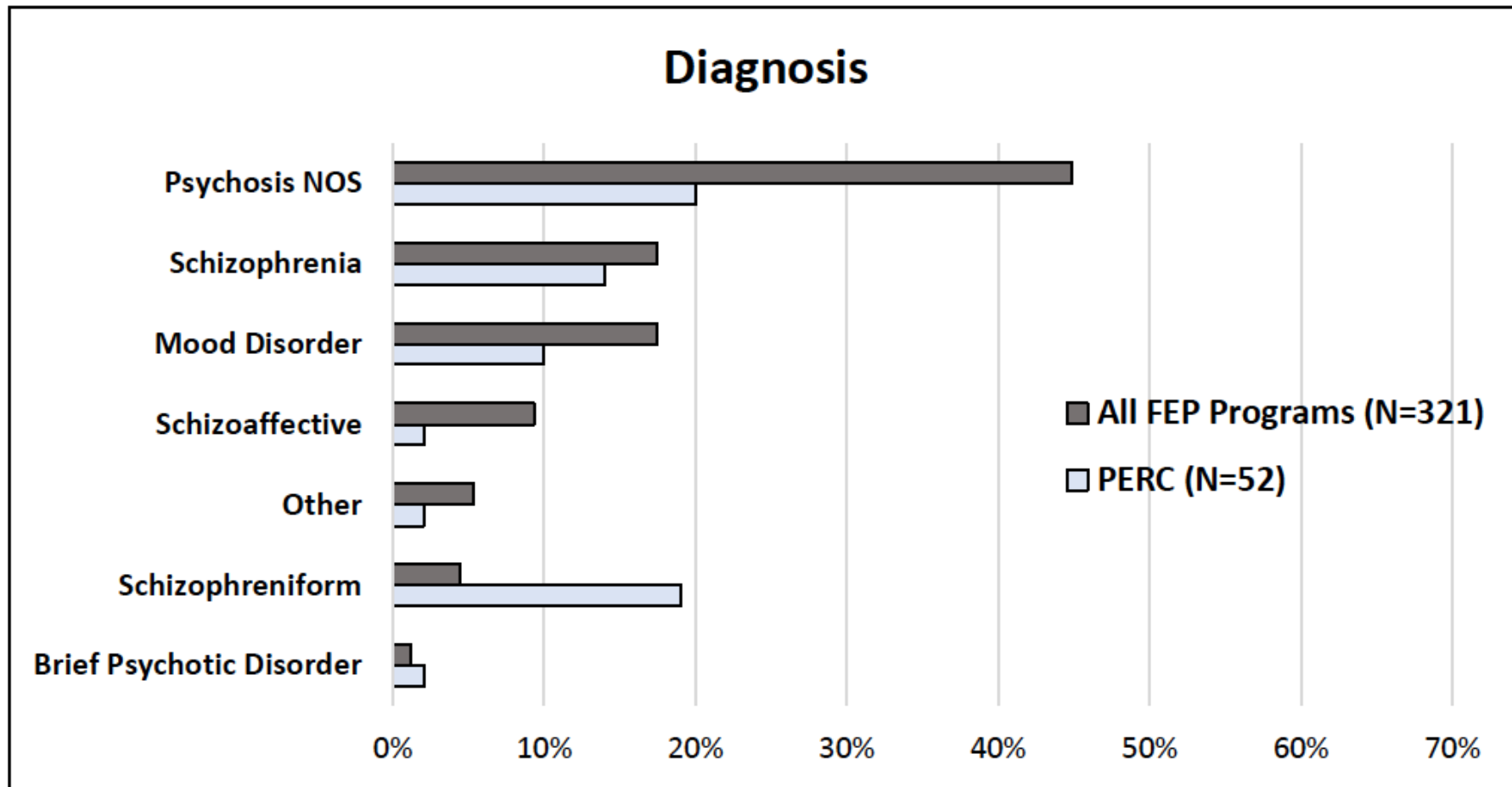
Clinical Characteristics

Diagnosis

Legend:
- ■ All FEP Programs (N=321)
- □ PERC (N=52)

X-axis: 0%, 10%, 20%, 30%, 40%, 50%, 60%, 70%

Categories (top to bottom): Psychosis NOS, Schizophrenia, Mood Disorder, Schizoaffective, Other, Schizophreniform, Brief Psychotic Disorder

Figure 10. Number of participants with primary qualifying diagnosis of Psychosis NOS (includes Unspecified and Other Specified Schizophrenia Spectrum and Other Psychotic Disorder), Schizophrenia, Mood Disorder with Psychotic Symptoms (includes Major Depressive and Bipolar Disorder), Other diagnosis not listed, Schizoaffective Disorder (includes Bipolar and Depressive Types), Unknown diagnosis, Schizophreniform and Brief Psychotic Disorder.

Pathways to Care and Hospitalizations

Pathways to Care	N	Mean	SD	Min	Max
Age (in years) at...					
Time of referral	44	21.82	4.44	14.33	33.83
Admission to FEP program	46	22.01	4.50	14.42	33.92
Onset of qualifying symptoms	45	21.34	4.44	13.50	33.83
1st MHT for Any Reason	31	21.44	3.89	15.50	33.83
1st MHT for Psychosis	39	21.97	4.40	14.17	33.83
Time (in months) from...					
Referral to Admission	44	0.48	0.66	0.00	3.00
1st MHT for any reason to Admission	31	15.48	34.5	0.00	155.00
Onset of Psychosis to Admission*	*45*	*6.73*	*7.83*	*0.00*	*44.00*
1st MHT for psychosis to Admission	39	4.90	7.70	0.00	44.00

Table 9. Summary of participant at different points of contact with Mental Health services. MHT = Mental Health Treatment. * Estimated onset of qualifying symptoms of psychosis for admission to FEP program.

Hospitalizations	Mean	Min	Max	SD
Age (in years) of First hospitalization (N=35)	22.58	17.00	33.83	4.53
Any Prior to Admission to FEP Program				
Number of Hospitalizations per participant (N=35)	1.31	1.00	3.00	0.68
Number of Nights in Hospital per participant (N=32)	15.38	1.00	73.00	15.69
90 Days Prior to Admission to FEP Program				
Number of Hospitalizations per participant (N=35)	1.69	0.00	21.00	3.61
Number of Nights spent per participant (N=31)	11.29	0.00	51.00	12.20

Table 10. Summary of psychiatric hospitalization history reported at the time of the admission.

- **70% of 50 participants had hospitalizations prior to enrollment in an FEP program.**
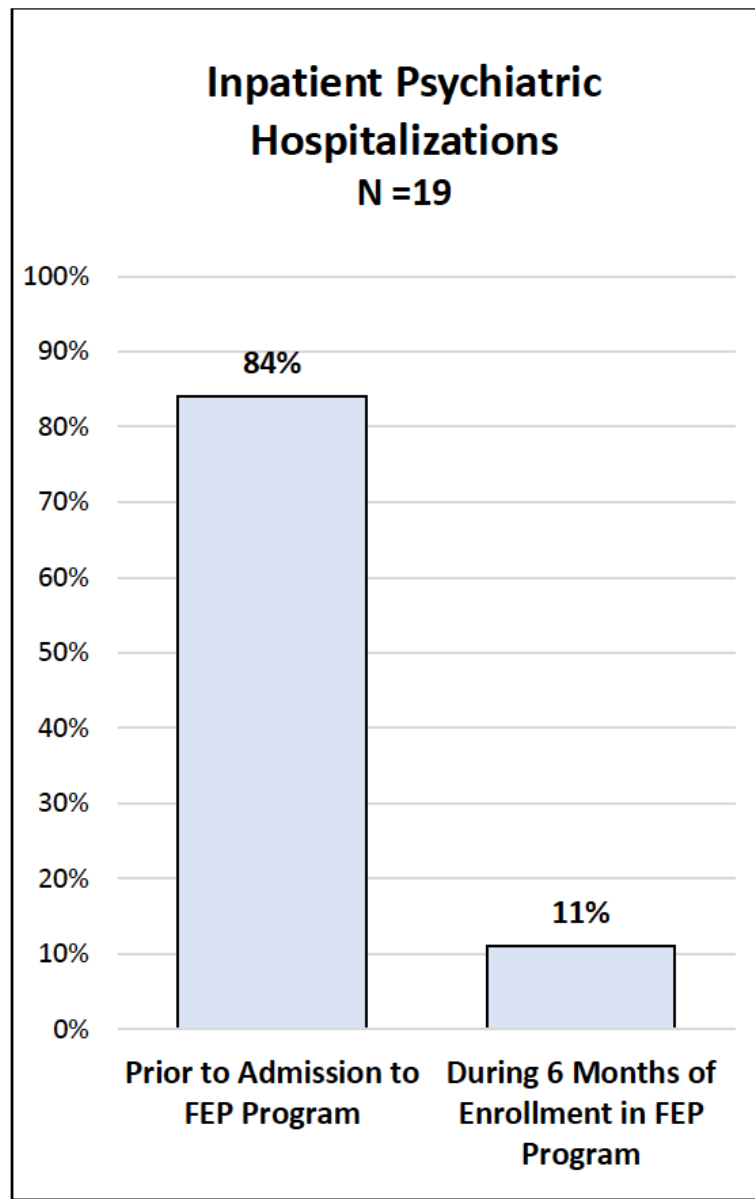
Inpatient Psychiatric Hospitalizations
N =19

Figure 8. Percent of participants with any hospitalization prior to enrollment in PERC and while enrolled in PERC for 6 months.

Average Number of Hospital Nights per Participant
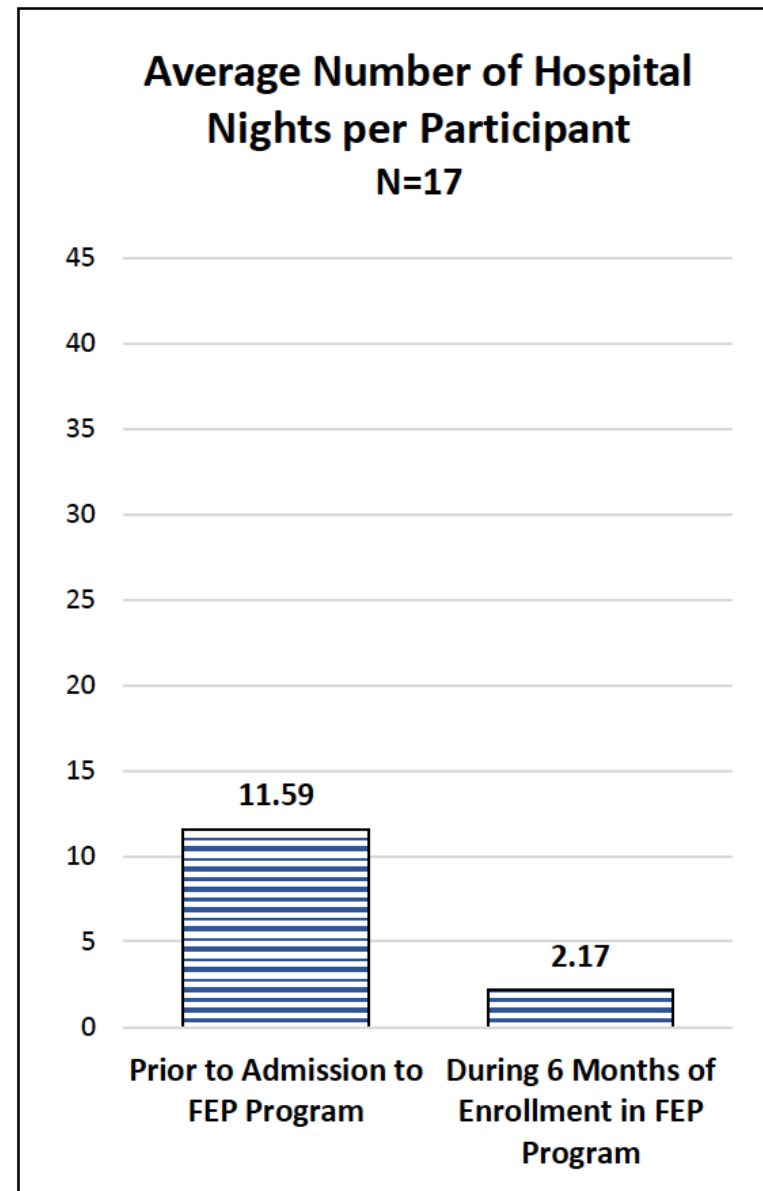### N=17

Figure 9. Average number of hospital nights per participant prior to enrollment in PERC and during first 6 months of enrollment in PERC.
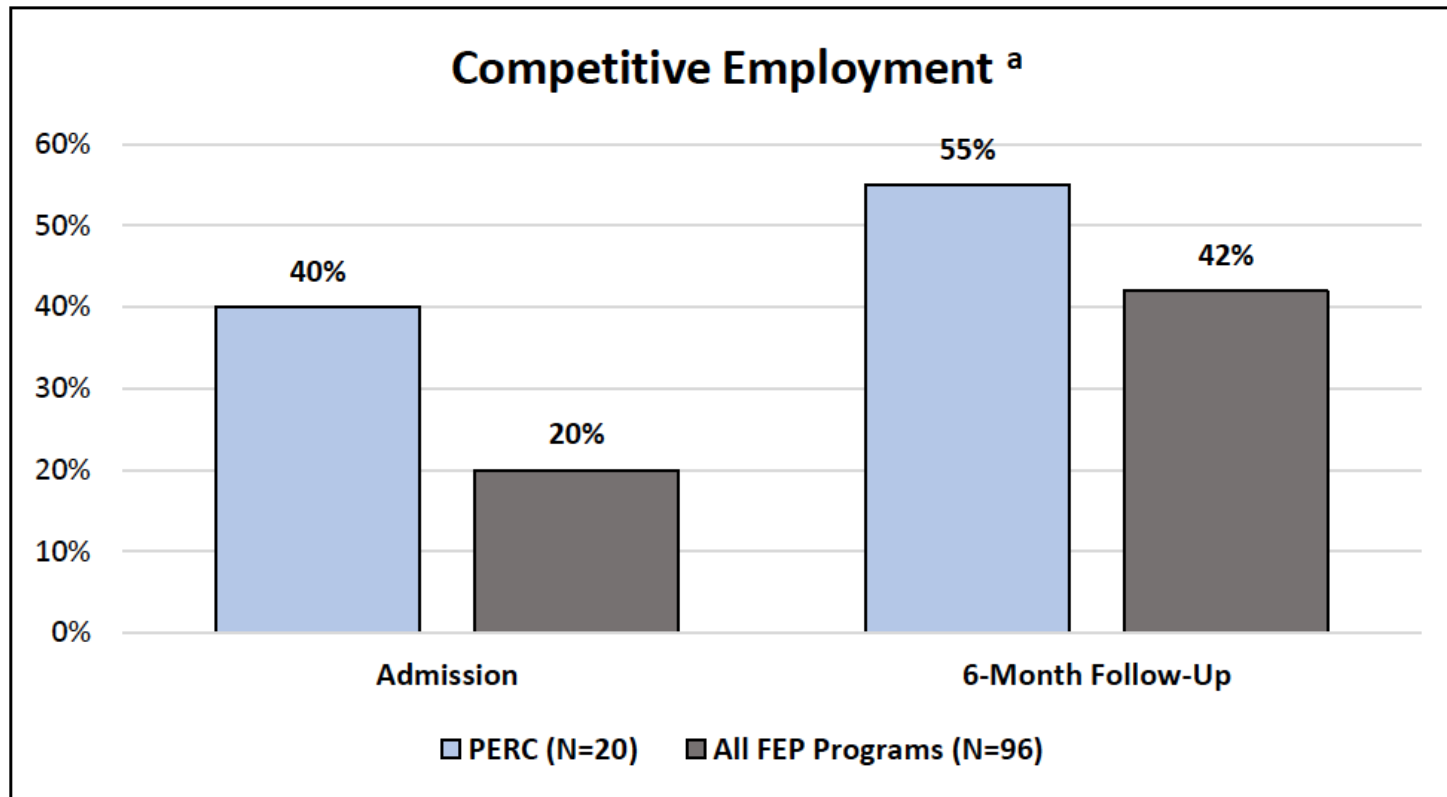
Figure 4. Percent of participants aged 15 years or older in competitive employment at admission and 6-month follow-up. [a] Competitive employment pays at least minimum wage, a paycheck was from employer and reported for tax purposes, is supervised by an employee of the place of work (not by an employee of an outside mental health agency or other 'sheltered' work situation), and the position was open to anyone rather than being reserved for people with behavioral health problems.

- 48% of participants who were unemployed at admission (N = 27) had previously been employed suggesting previously higher level than functioning than at admission.

- 9% of participants who were unemployed at admission (N=34) were looking for work.
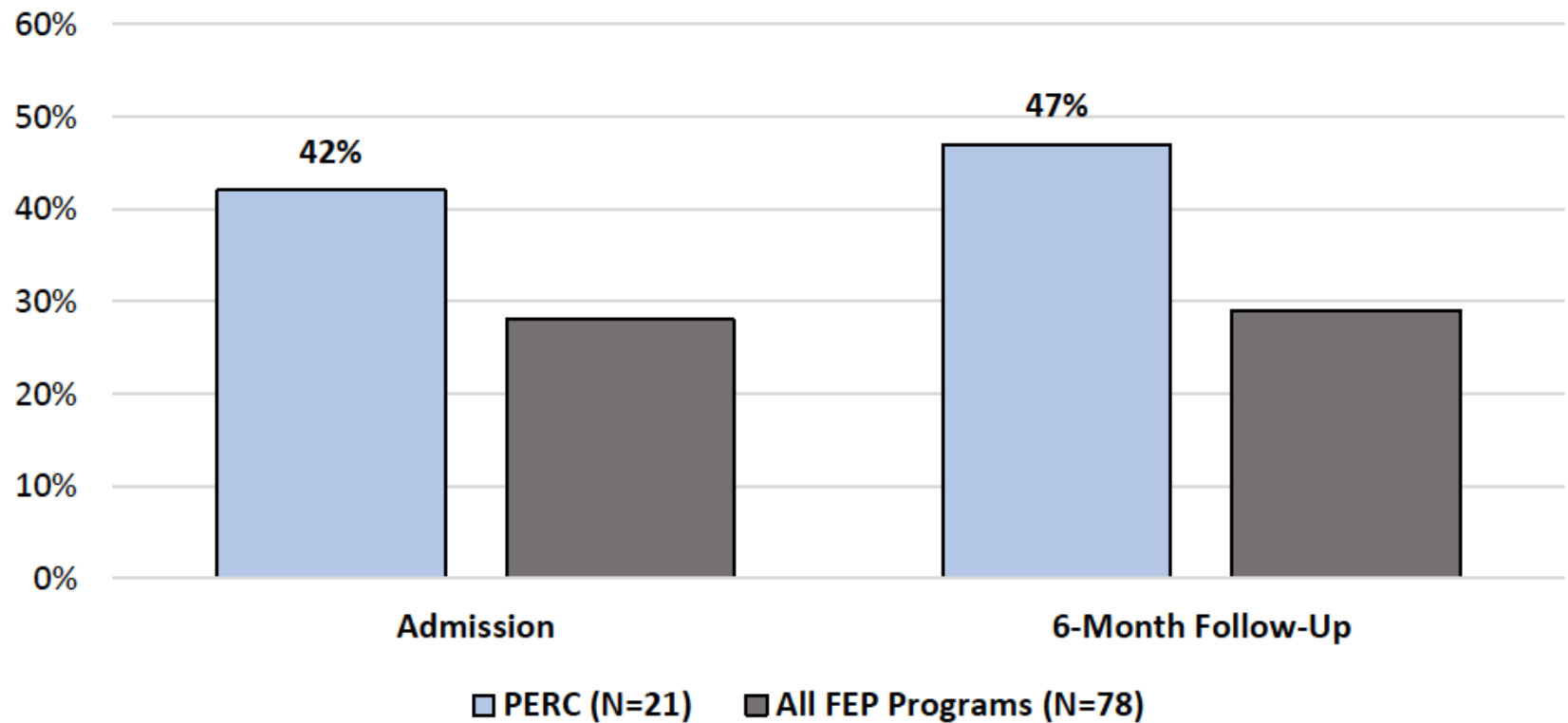
Figure 5. Percent of participants aged 18 years and older (*at the time of 6-month follow-up assessment) enrolled in school at admission or at 6-month follow-up.

Conclusions

Early psychosis presents as a unique opportunity for intervention

Decreasing duration of untreated psychosis is high priority
(Consensus statement: < 3 months)

Prevention of chronic illness and disability

Comprehensive Specialty Care: specialized intervention services
➢ may improve symptoms and clinical course

➢ increase retention in treatment program

➢ improve functional outcome

➢ are cost effective