6-19-2007

Early Psychosis: A Bridge to Future

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

Western

Schulich
MEDICINE & DENTISTRY

Schulich School of Medicine & Dentistry

Shaping the Future of Health Care

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

1 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).

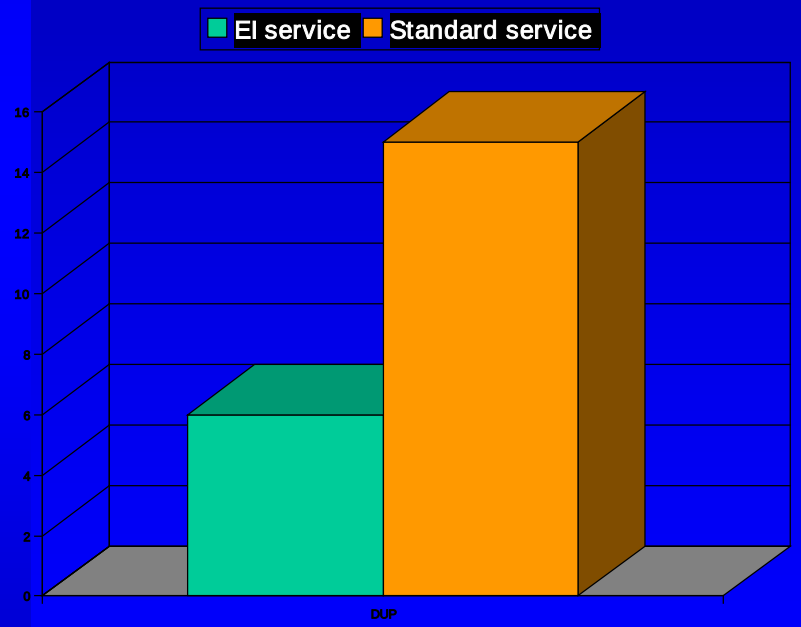
Does it make a difference to treat in early phase

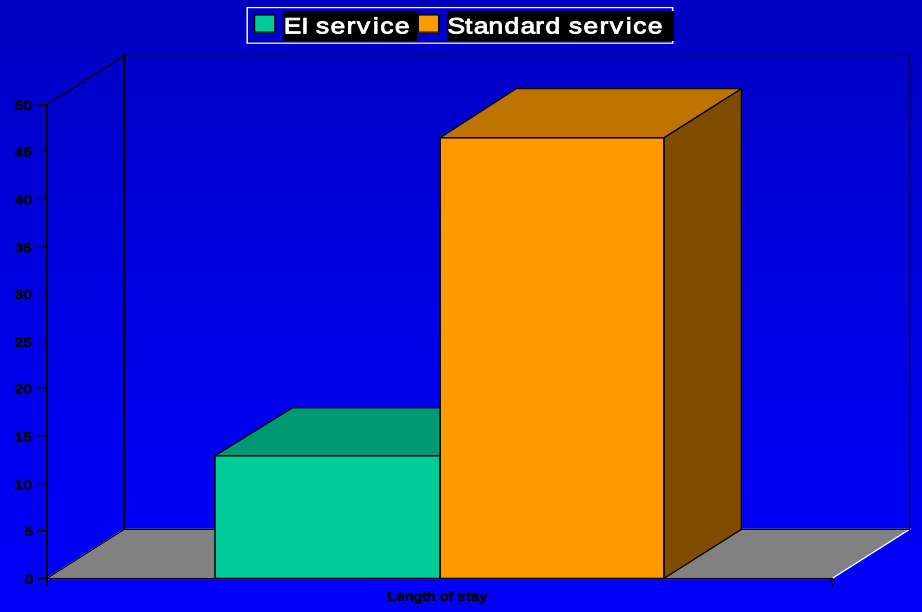
Benefits of Early Treatment

- 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

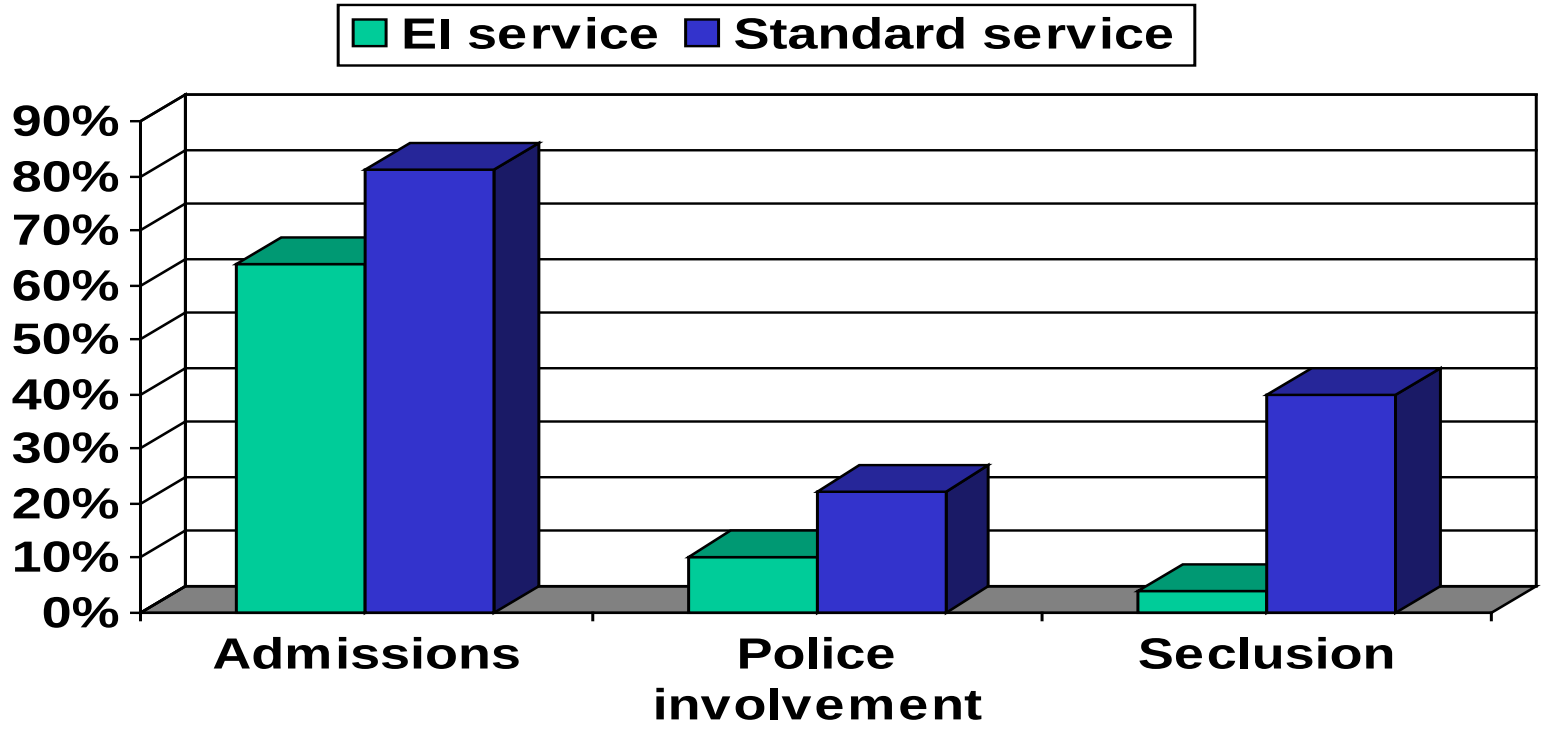
Yung AR, Organ BA, Harris MG. Aust N Z J Psychiatry. 2003 Aug;37(4):429-36.





Models of early intervention service

Yung AR, Organ BA, Harris MG. Aust N Z J Psychiatry. 2003 Aug;37(4):429-36.



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

Newfoundland

- N&L EPP

Nova Scotia:

- NSEPP
- Halifax -

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 SMIs
- 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
- Characteristics
- What is the pathology
- What is the management
- Research questions

Cannabis and Early Psychosis

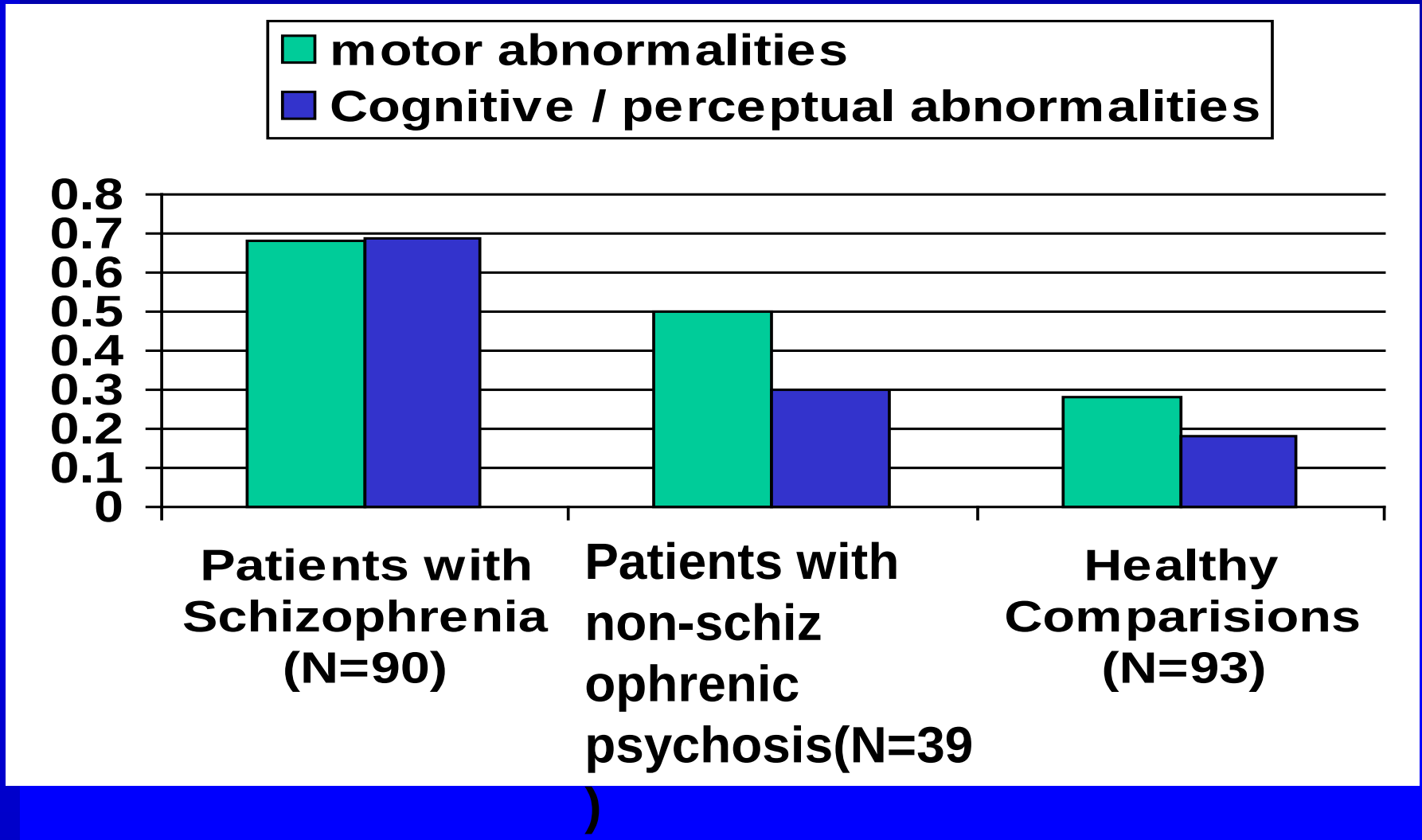
- It is widely known that patients with schizophrenia, including first-episode patients, have much higher rates of cannabis use compared with their counterparts in the general population.

- 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.

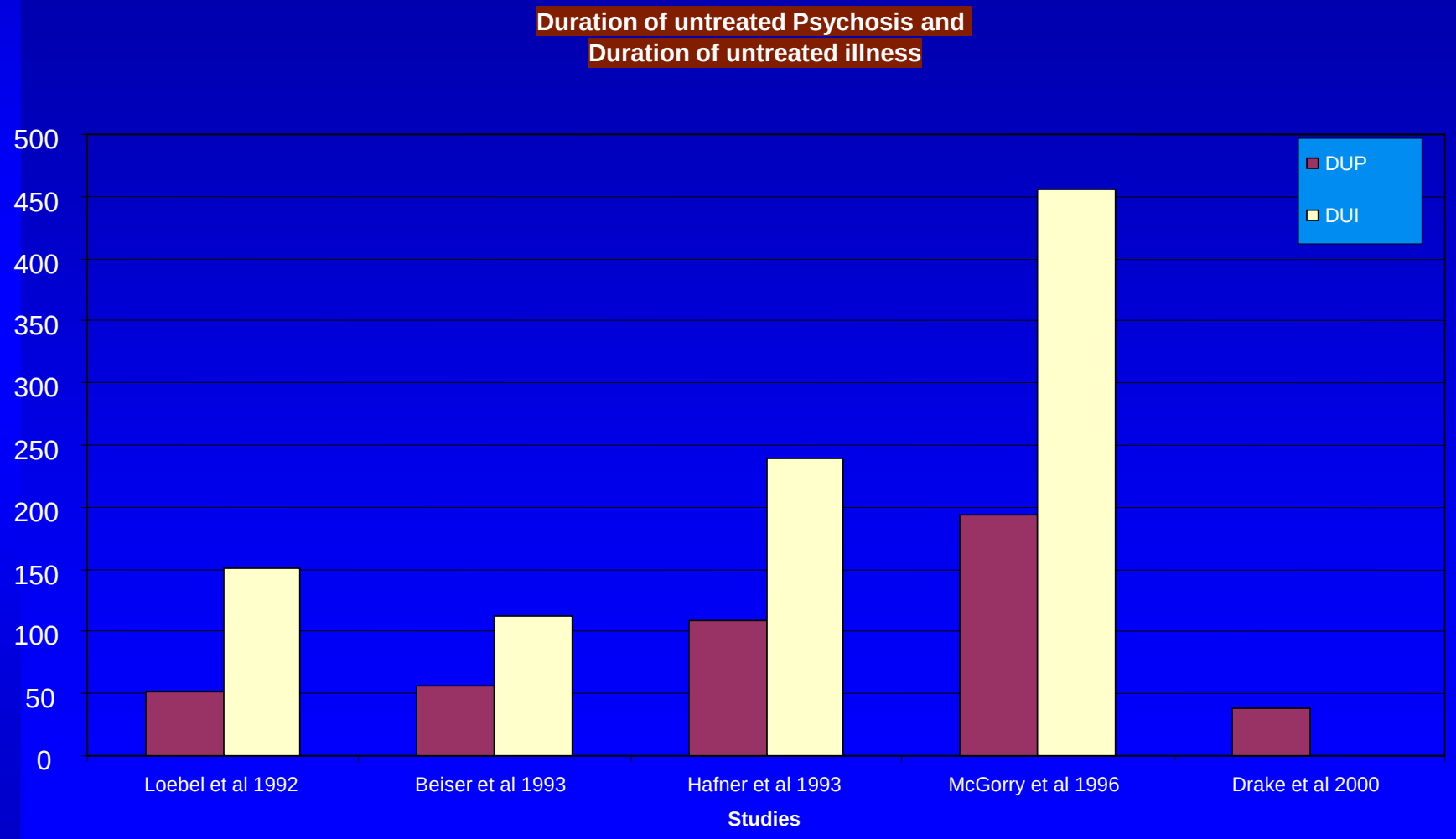
Motor and cognitive Factors of Neurological Evaluation Scale of FEP,



Post-FEP: the Critical Phase of Psychosis

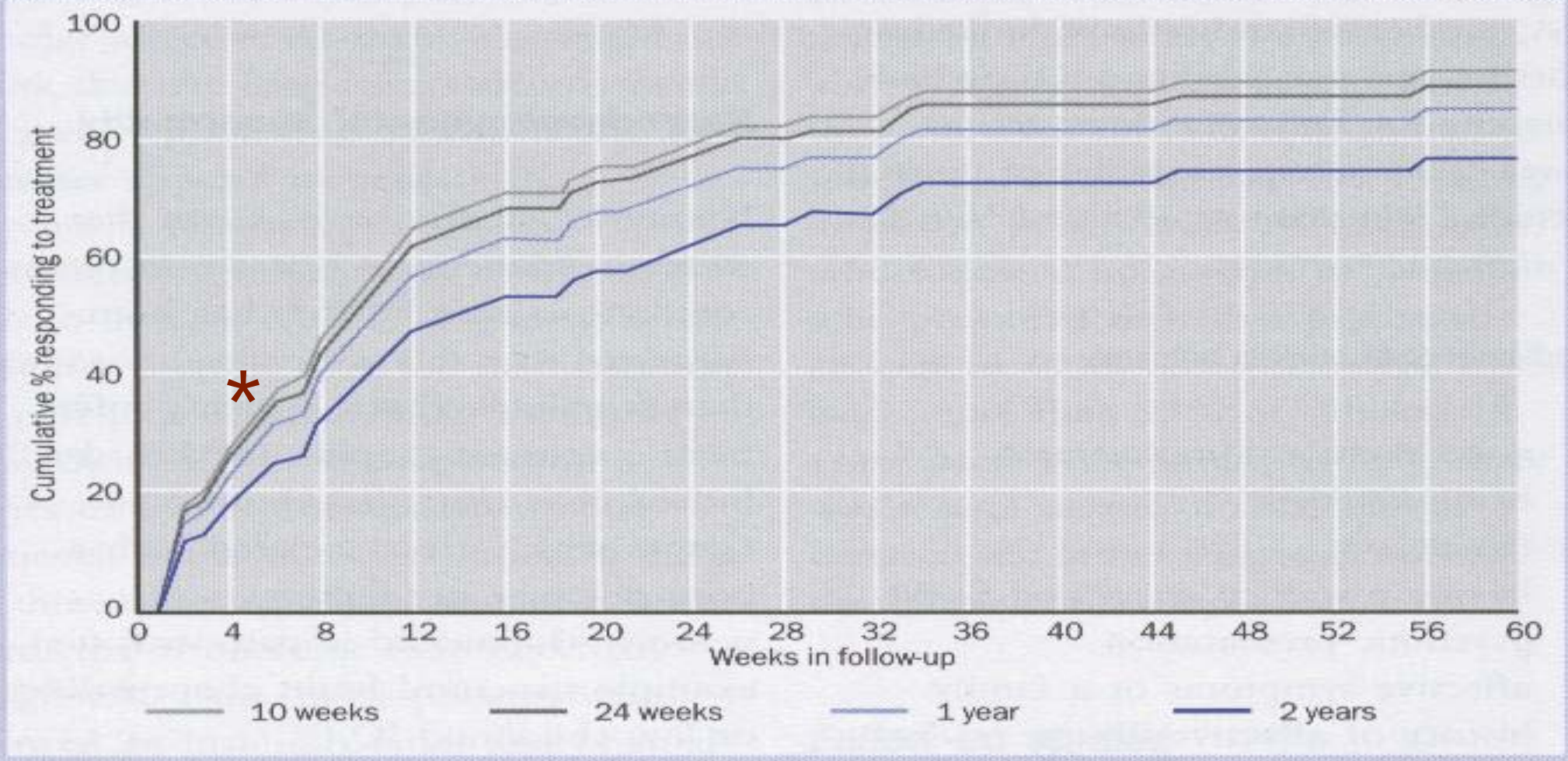
- Individual is vulnerable to negative influence because of a combination of factors:-
- Coping up with return of insight and depression
- A realization of having developed a mental illness/brain disorder
- Question about future functioning
- Ideas of faith, trust and mistrust
- ‘why me’
- Why medication,
- Negative EE
- Attitude of family members
- persisting psychotic symptoms in remission

Duration of Untreated Psychosis



Response Vs DUP

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.[163] With permission from Elsevier Science.



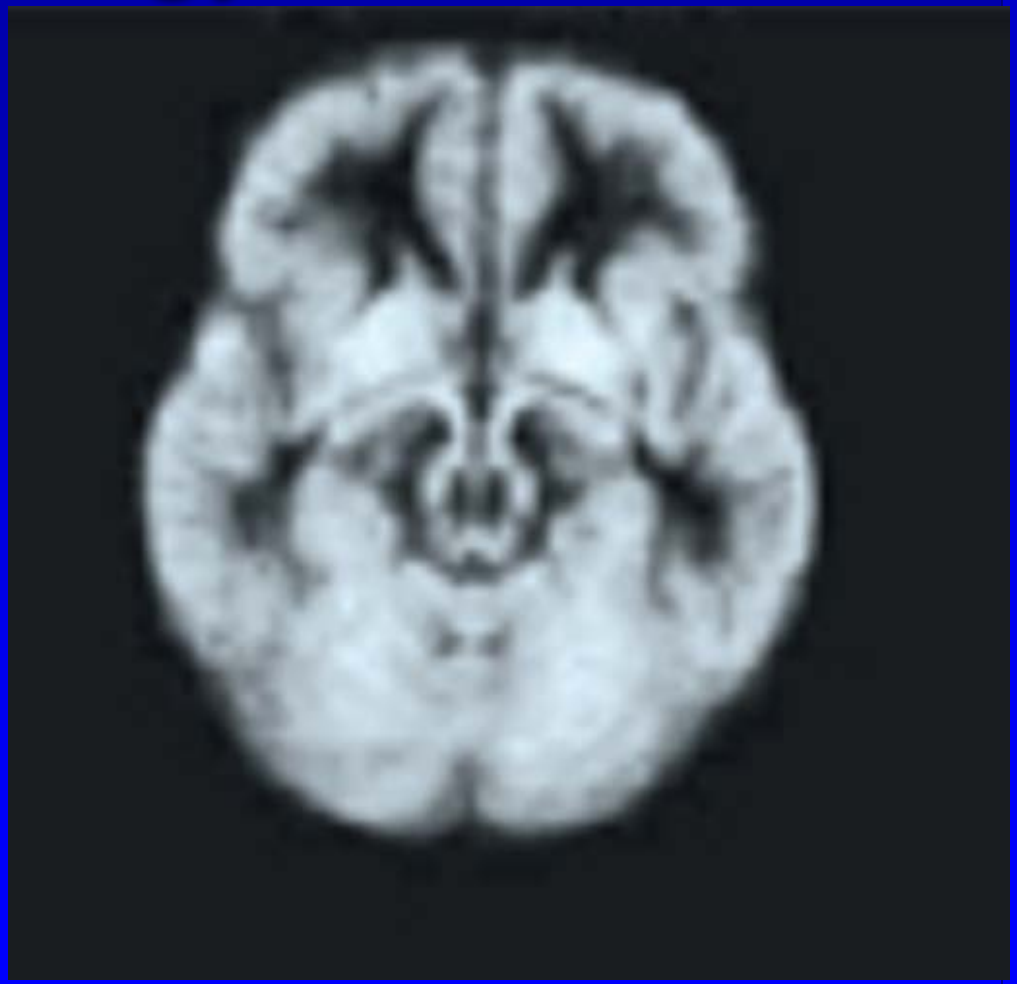
3

- What is EP
- Characteristics
- What is the pathology
- What is the management
- Research questions

What is The pathology

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

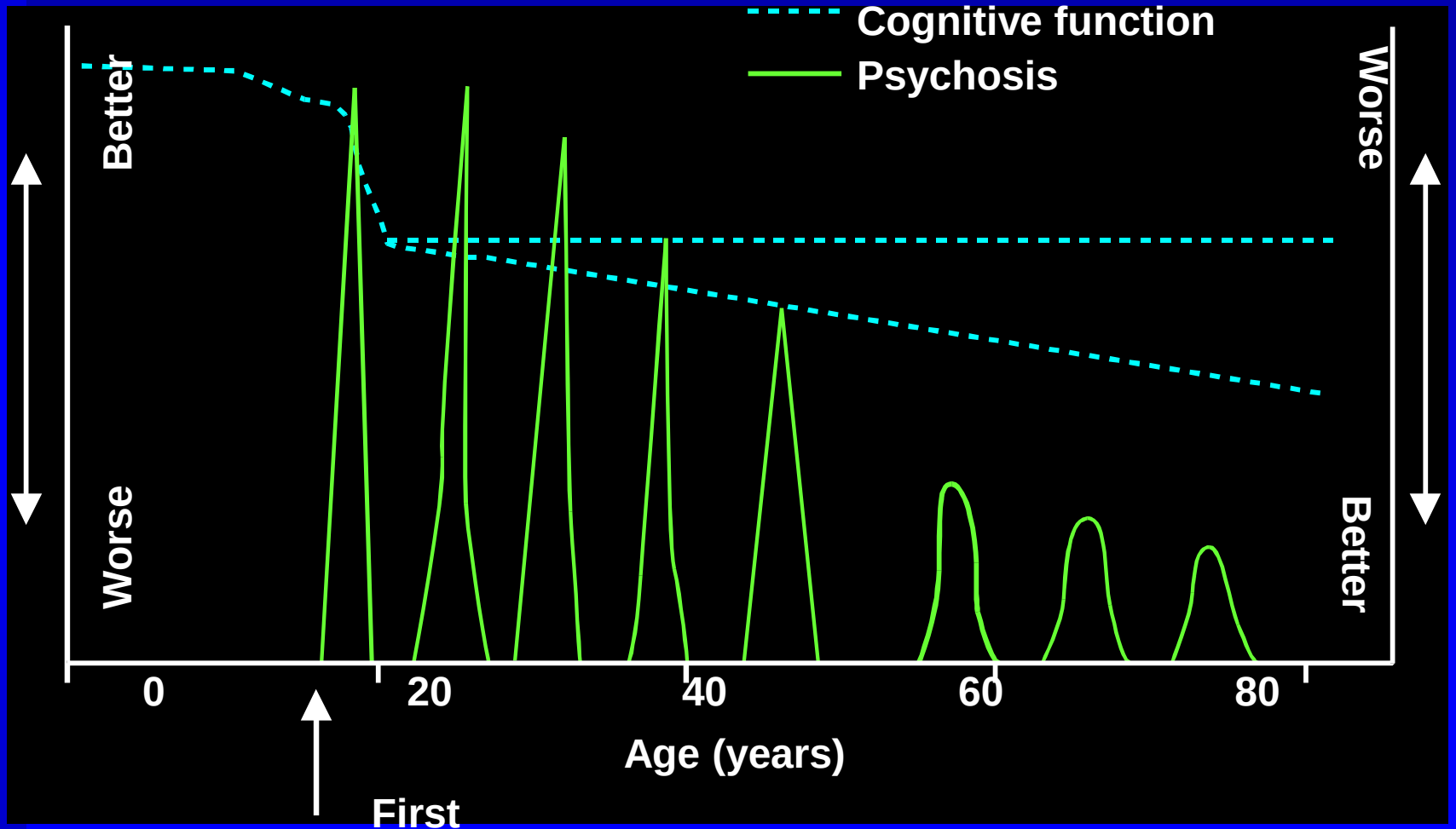
- # Heredity is the best established risk factor;
- # Premorbid neurocognitive alterations clearly exist;
- # Prodromal symptoms often precede psychosis;
- # Onset of psychosis is typically in late adolescence; and
- # Cognitive deficits are central to the illness

Keshavan MS, Pittsburgh & Detroit

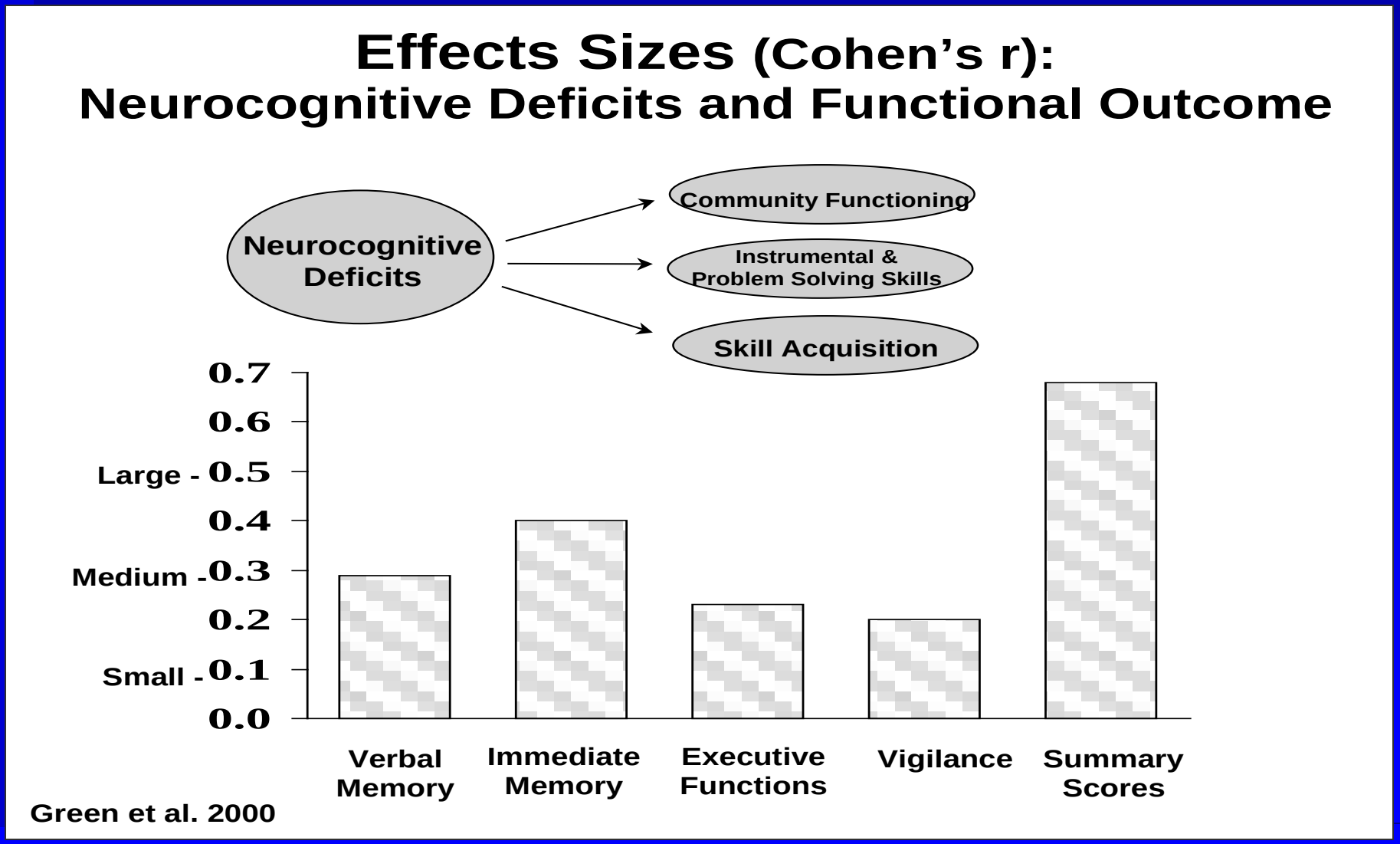
Cognitive impairment in schizophrenia: prevalence

- 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

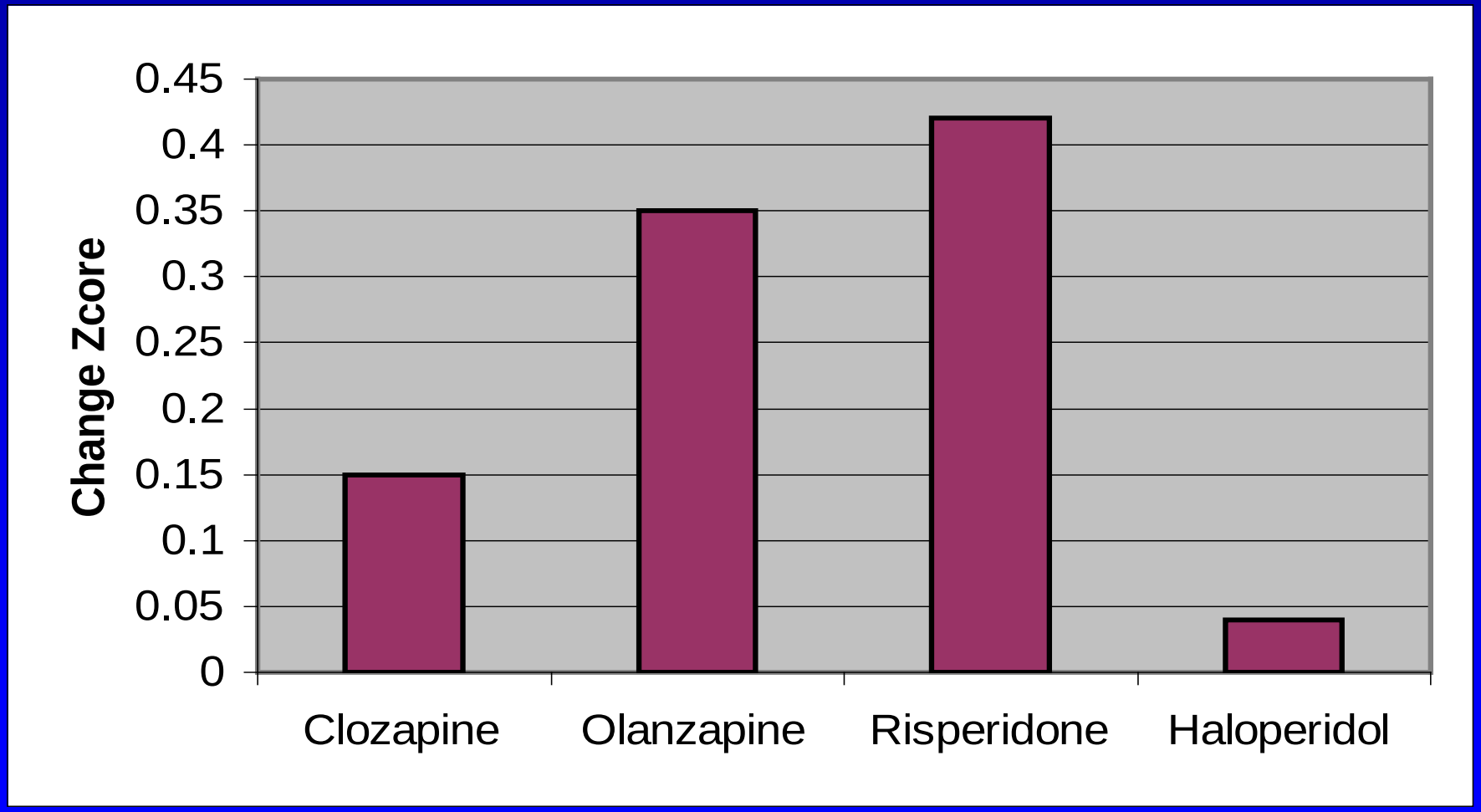
Cognitive dysfunction is a lasting feature of schizophrenia



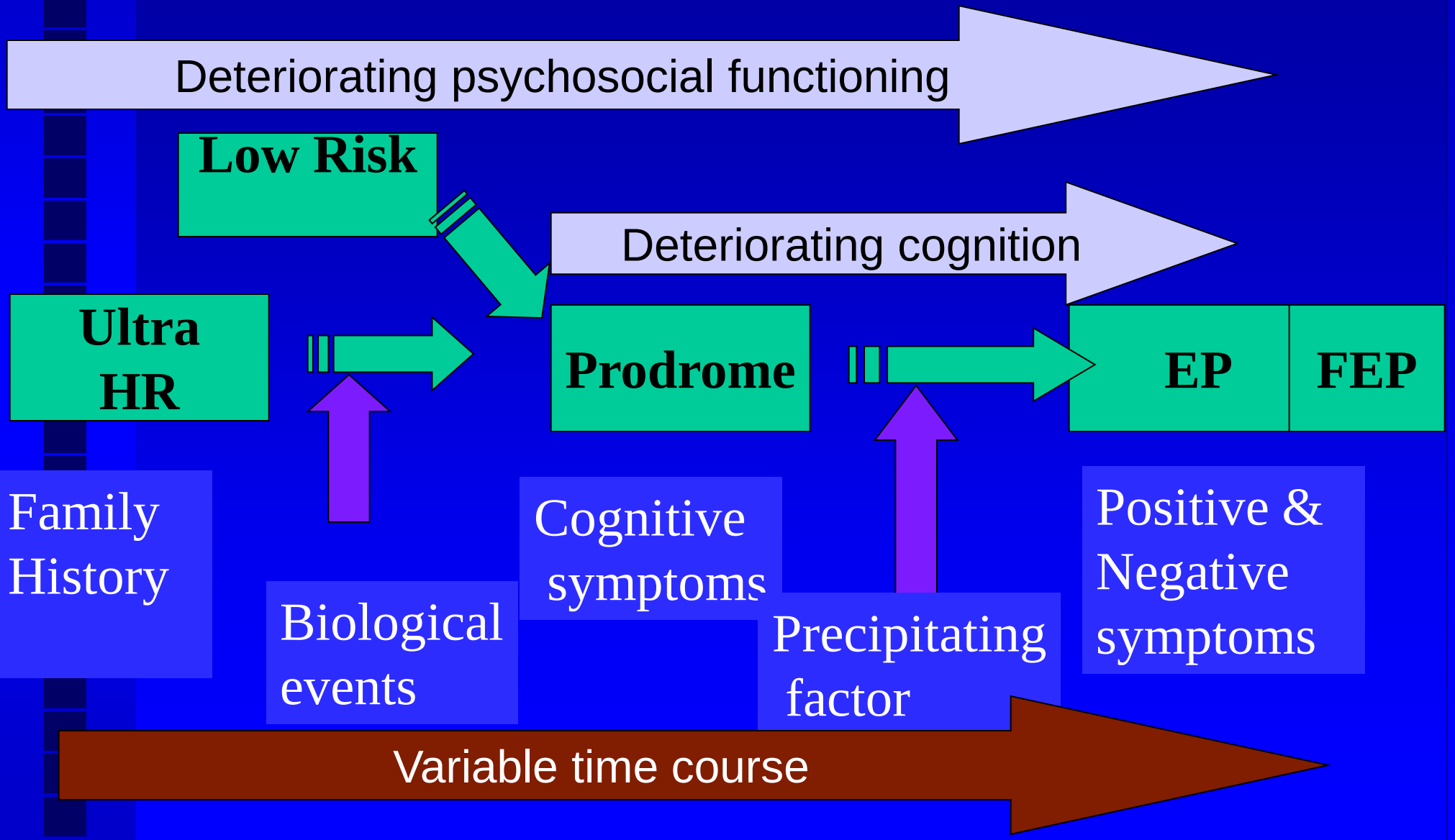
Cognitive deficits are the best predictors of functional outcome



Atypicals and cognition: comparison of effects Bilder et al Am J Psychiatry 2002

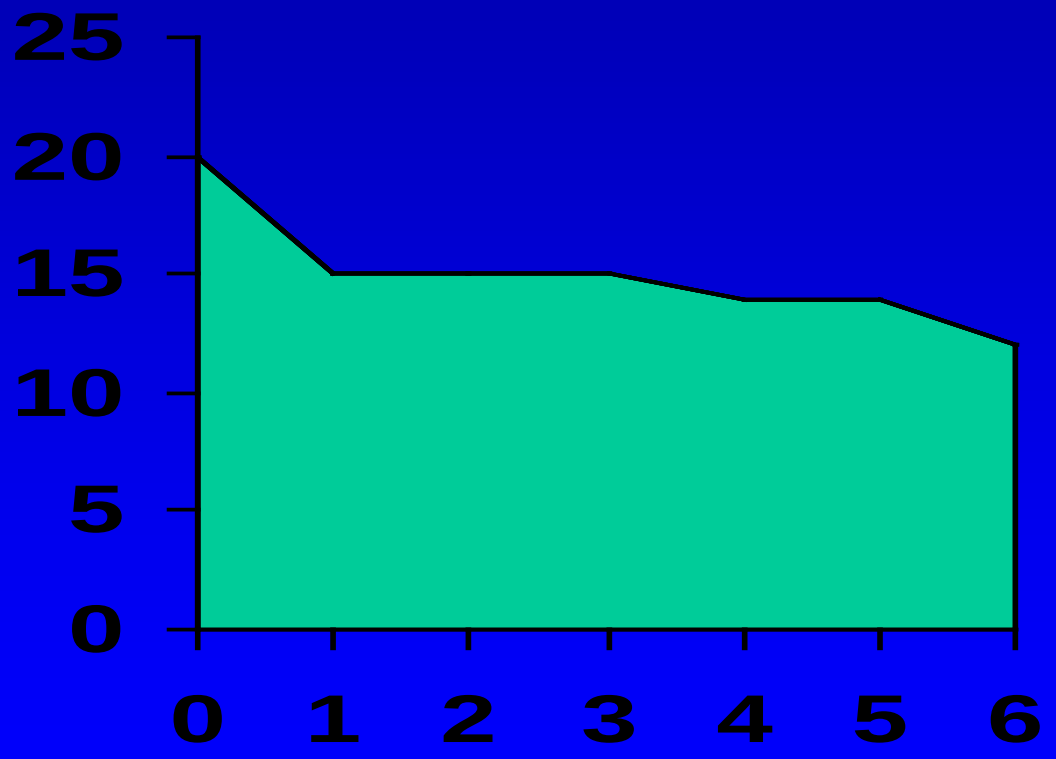


Conversion to psychosis and time course



Prediction of Psychosis

Yung et al 1998 British Journal of Psychiatry



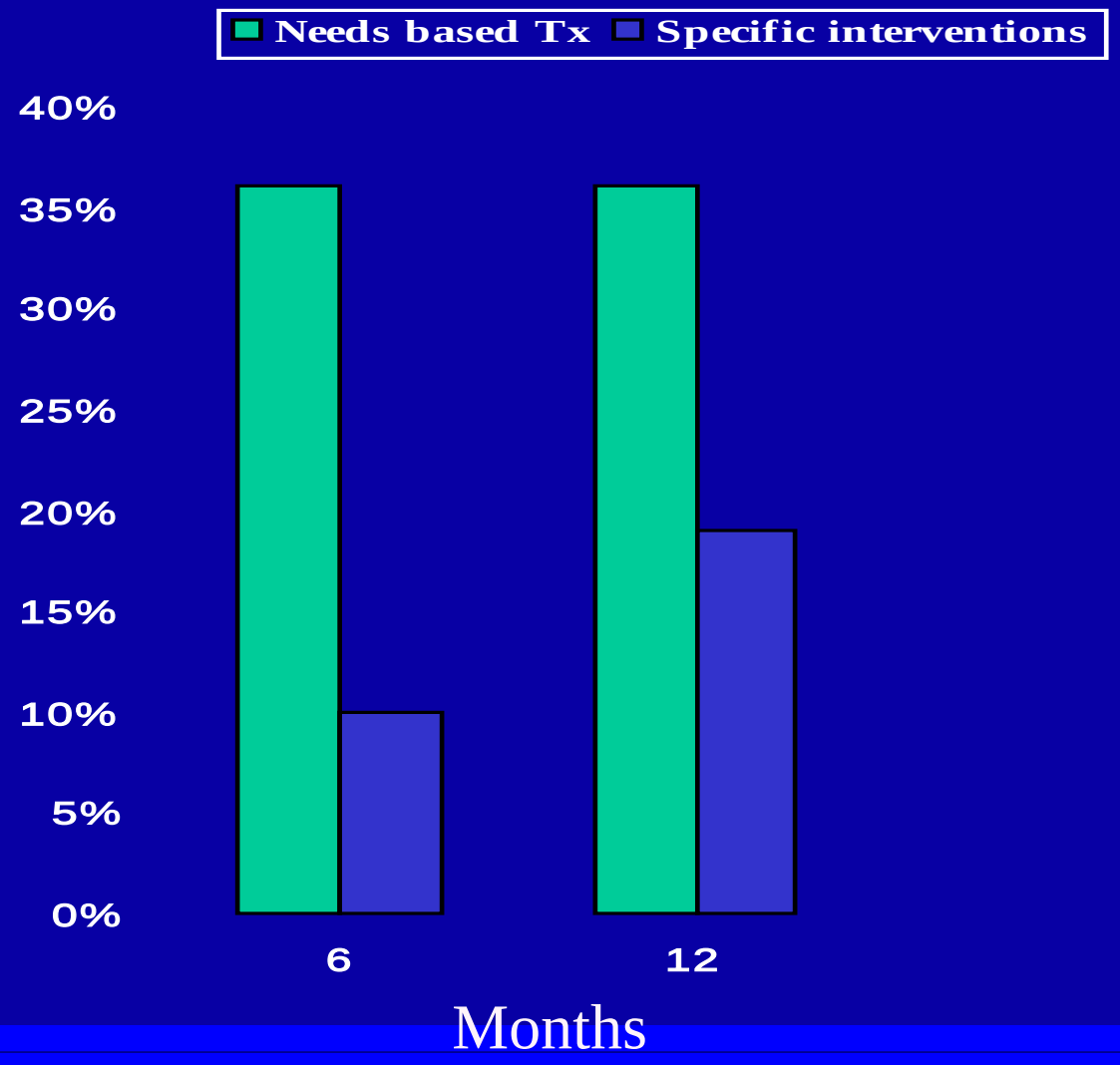
Number not psychotic

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

Prevention of psychosis

McGorry et al 2002 Archives of General Psychiatry

% making transition to psychosis



Predicting onset of psychosis:PACE

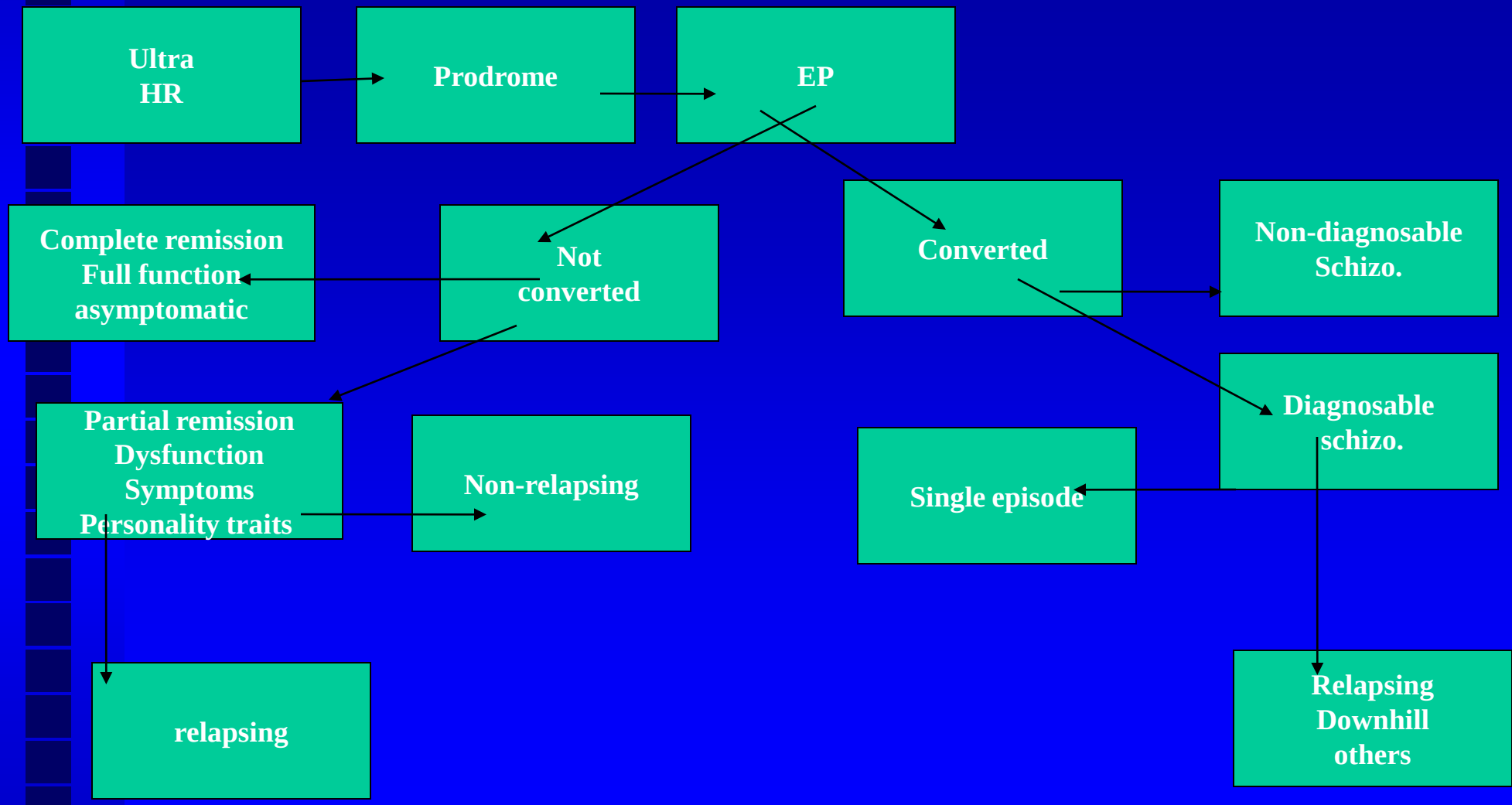
What features predict onset of first-episode within an ultra-high risk group?

- 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

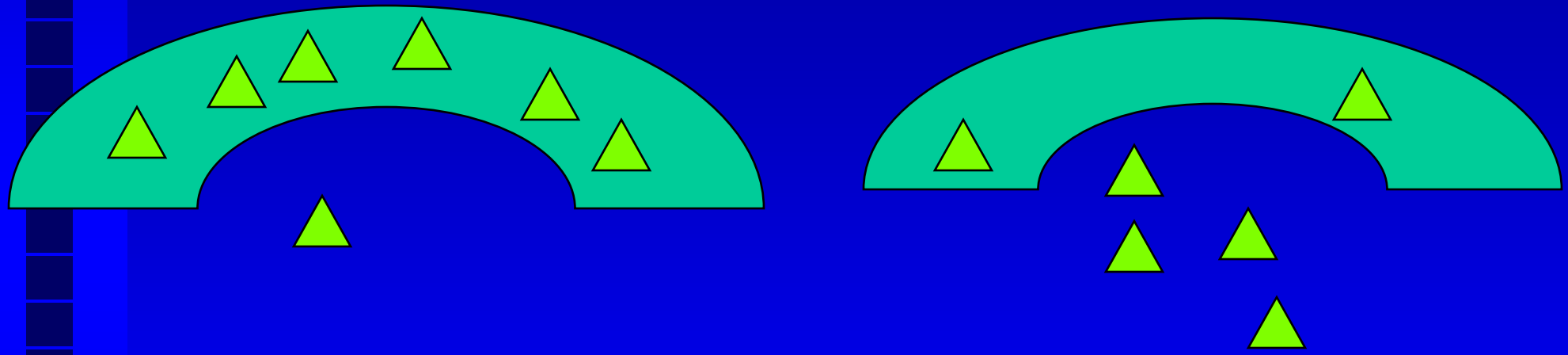
- Reduced concentration, attention
- Reduced drive, motivation, anergia
- Depressed mood
- Sleep disturbance
- Anxiety
- Social withdrawal
- Suspiciousness
- Deterioration in role functioning
- Irritability

Natural consequence or outcome in phenomenology EP



AN " EARLY" DEVELOPMENT THEORY: impaired neural migration in schizophrenia?

Akbarian 1993



Normal

Schizophrenia

4

- What is EP
- Characteristics
- What is the pathology
- What is the management
- Research questions

What is The management

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

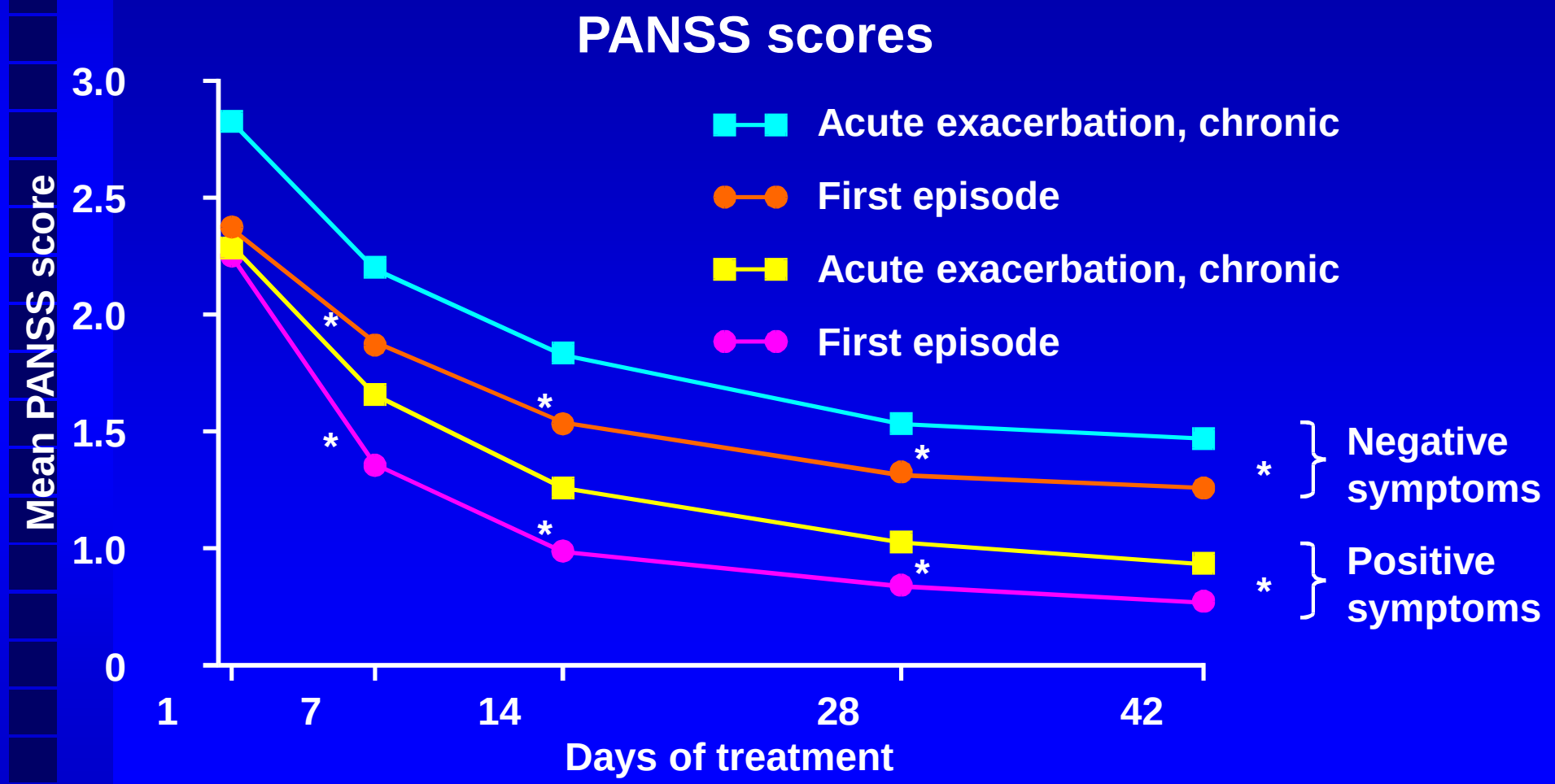
Recommendation for pharmacotherapy of first episode psychosis

- 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

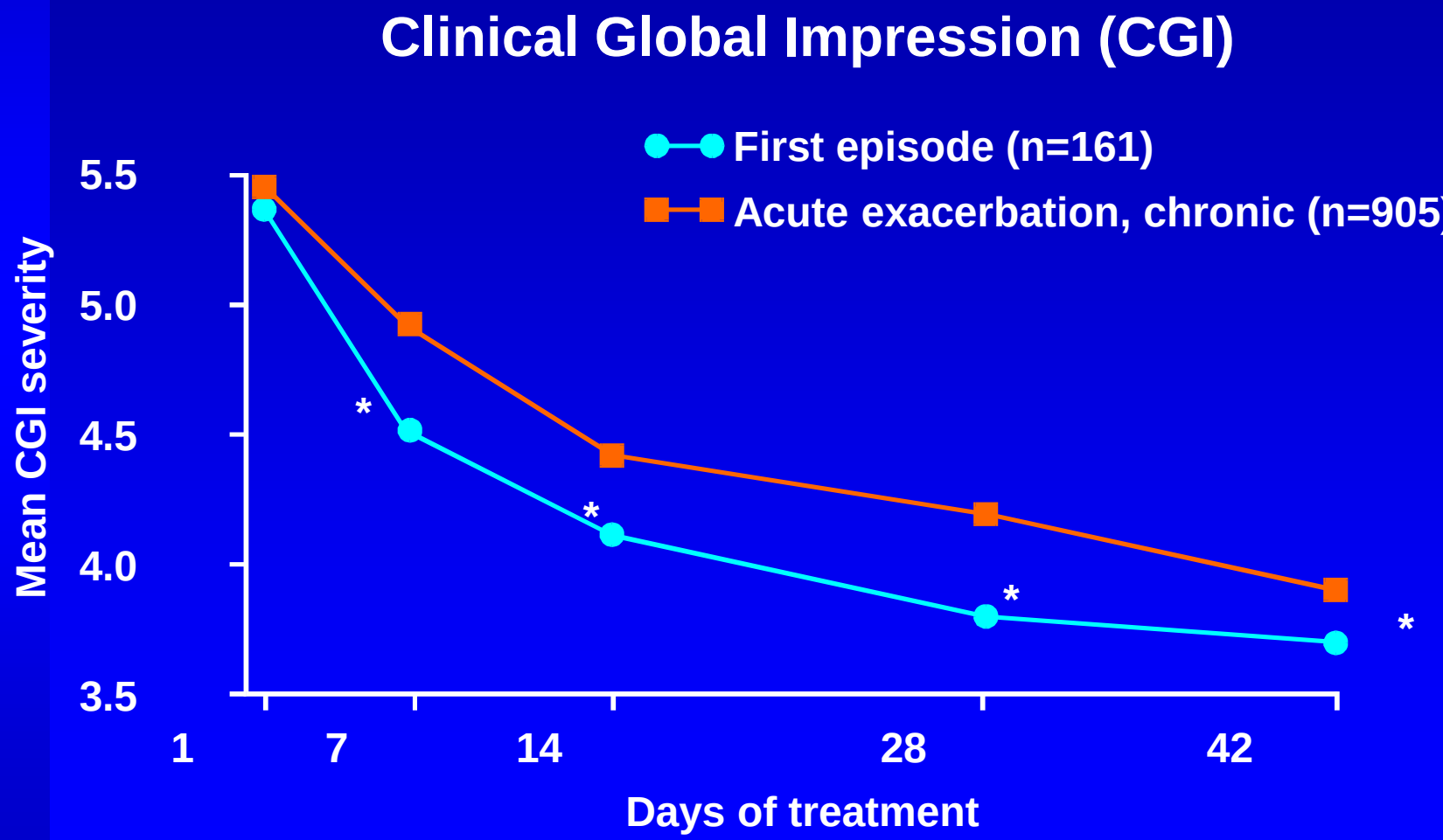
First-episode schizophrenia versus chronic schizophrenia treated with risperidone (1)



*p<0.005

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

First-episode schizophrenia versus chronic schizophrenia treated with risperidone (2)

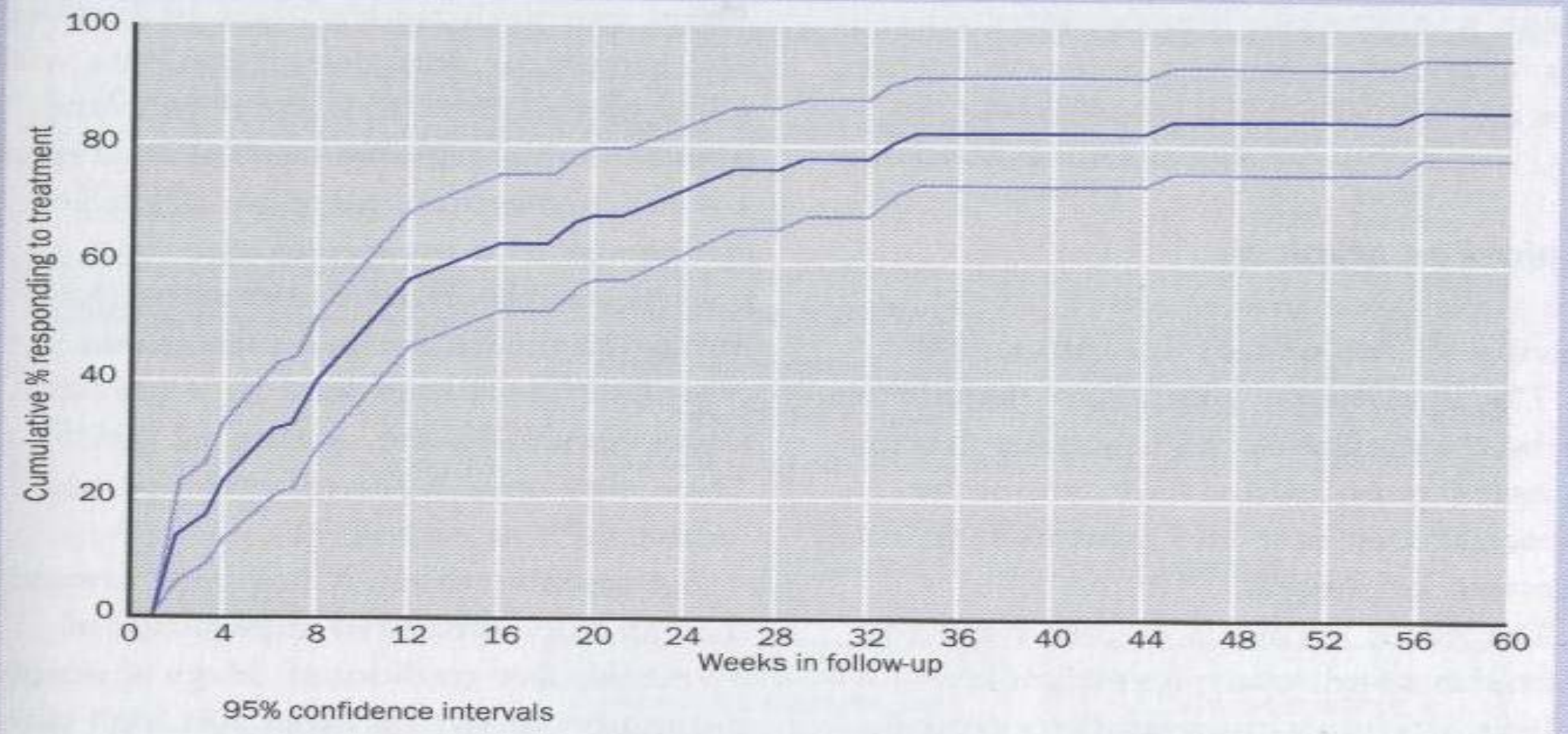


*p<0.05

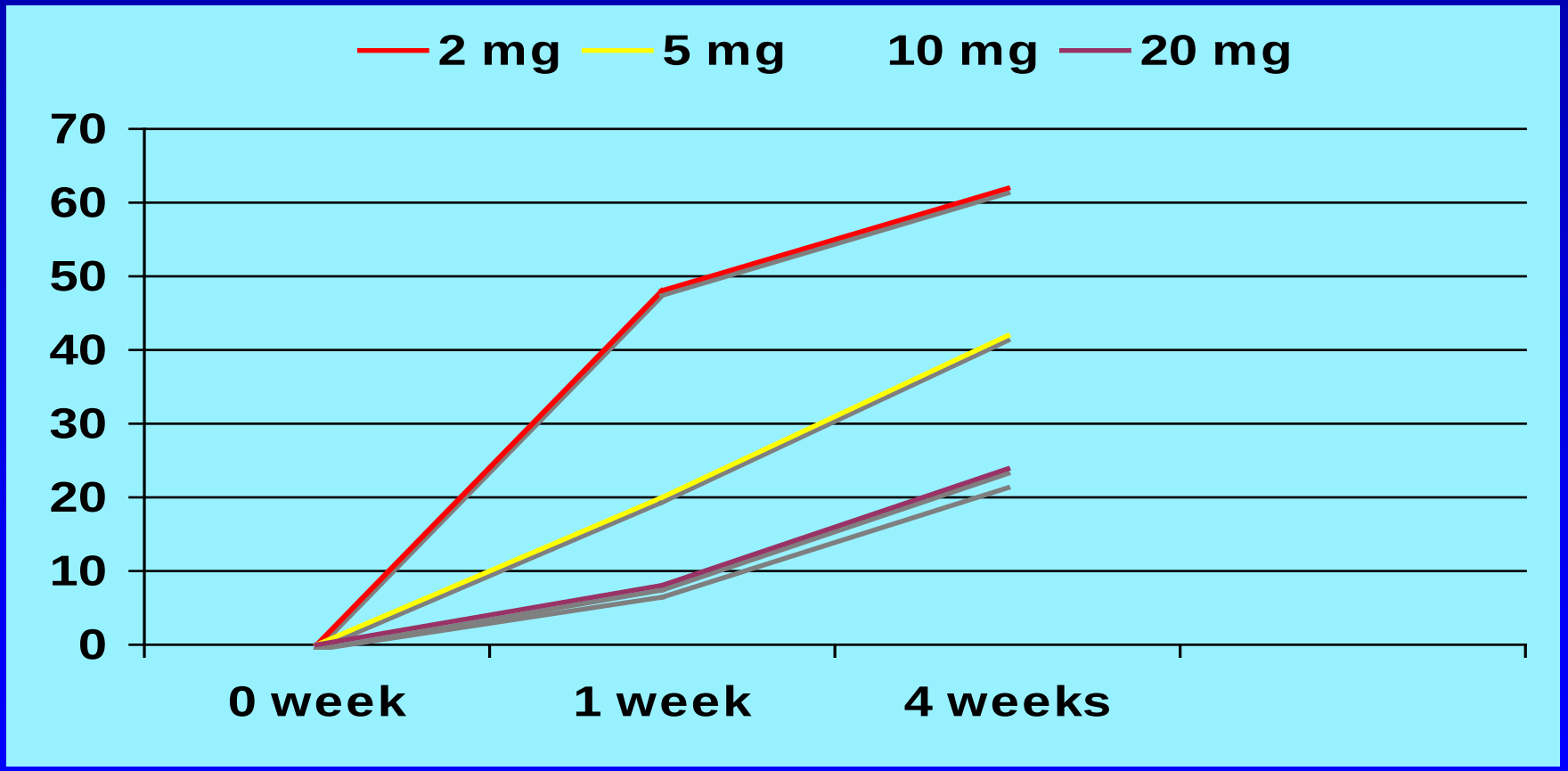
Rüther E, Klauder A. WCP, Hamburg, August 1999

Response rate in FES

Figure 2
Cumulative percentage of first-episode patients responding to treatment. Adapted from Lieberman JA et al.[163] With permission from Elsevier Science.

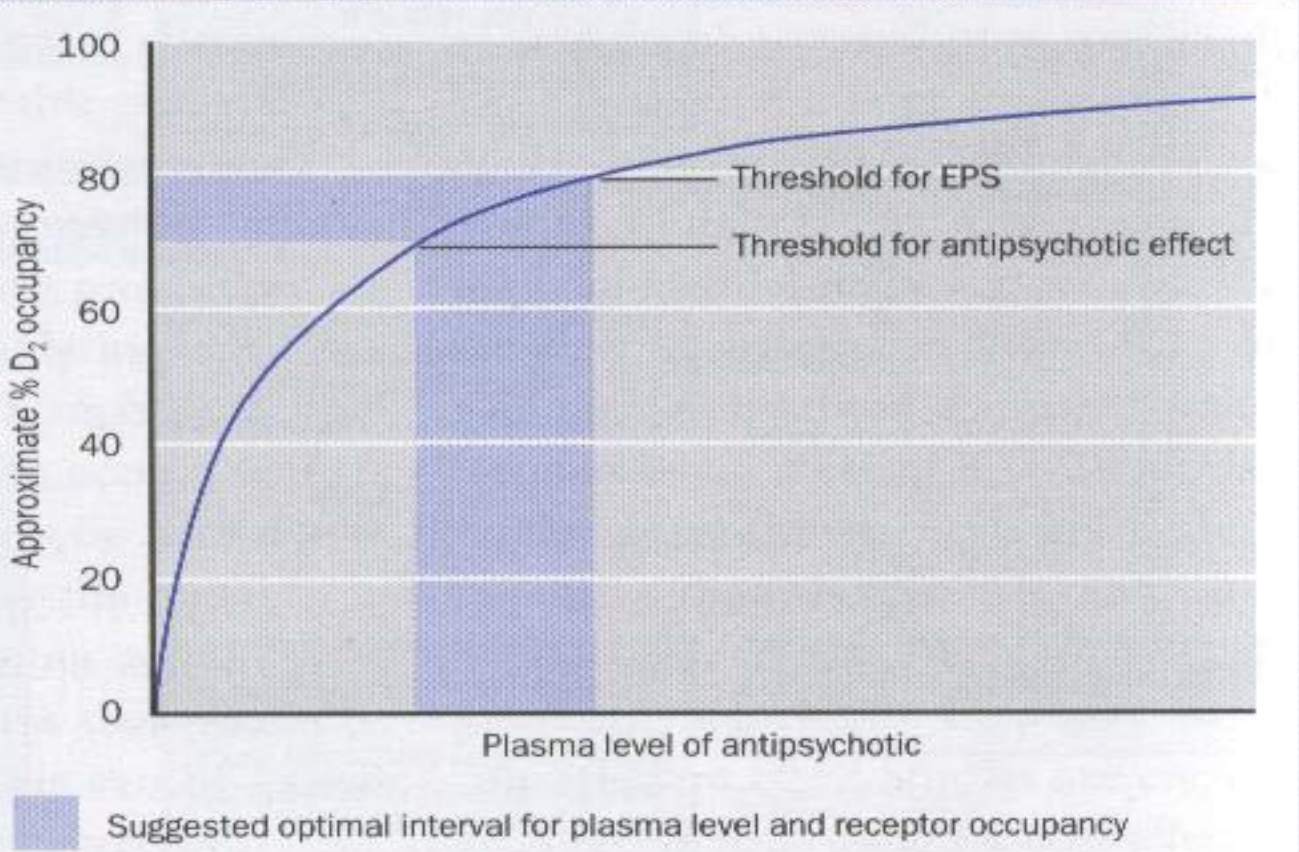


How much antipsychotic



Optimum D2 occupancy 65% at 2 and 10 mg dosage

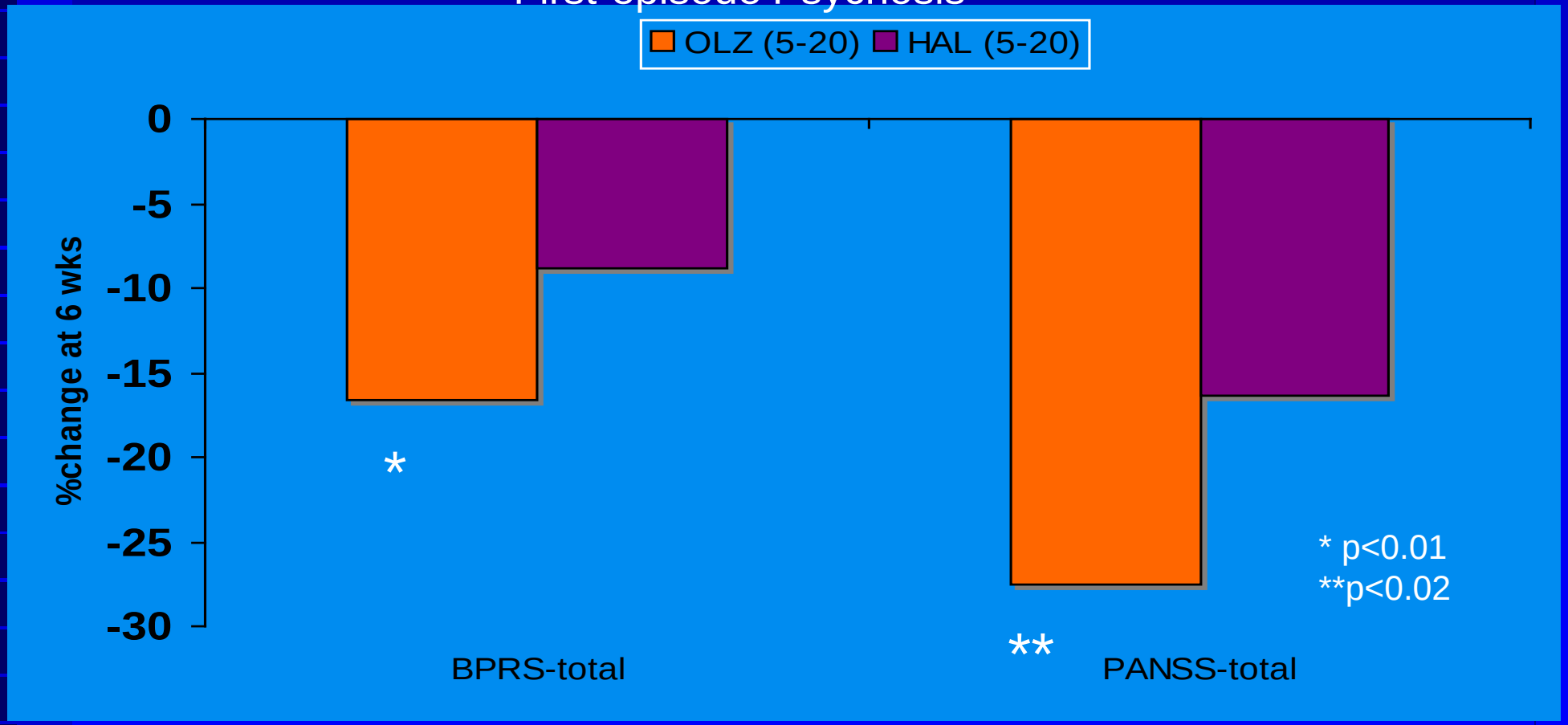
Figure 4
Hyperbolic relationship between D_2-receptor occupancy and plasma level for antipsychotics with significant D_2-receptor affinity. [The approximate thresholds for antipsychotic effect and EPS are shown.[168]



Should AATPD be used

Olanzapine vs. Haloperidol

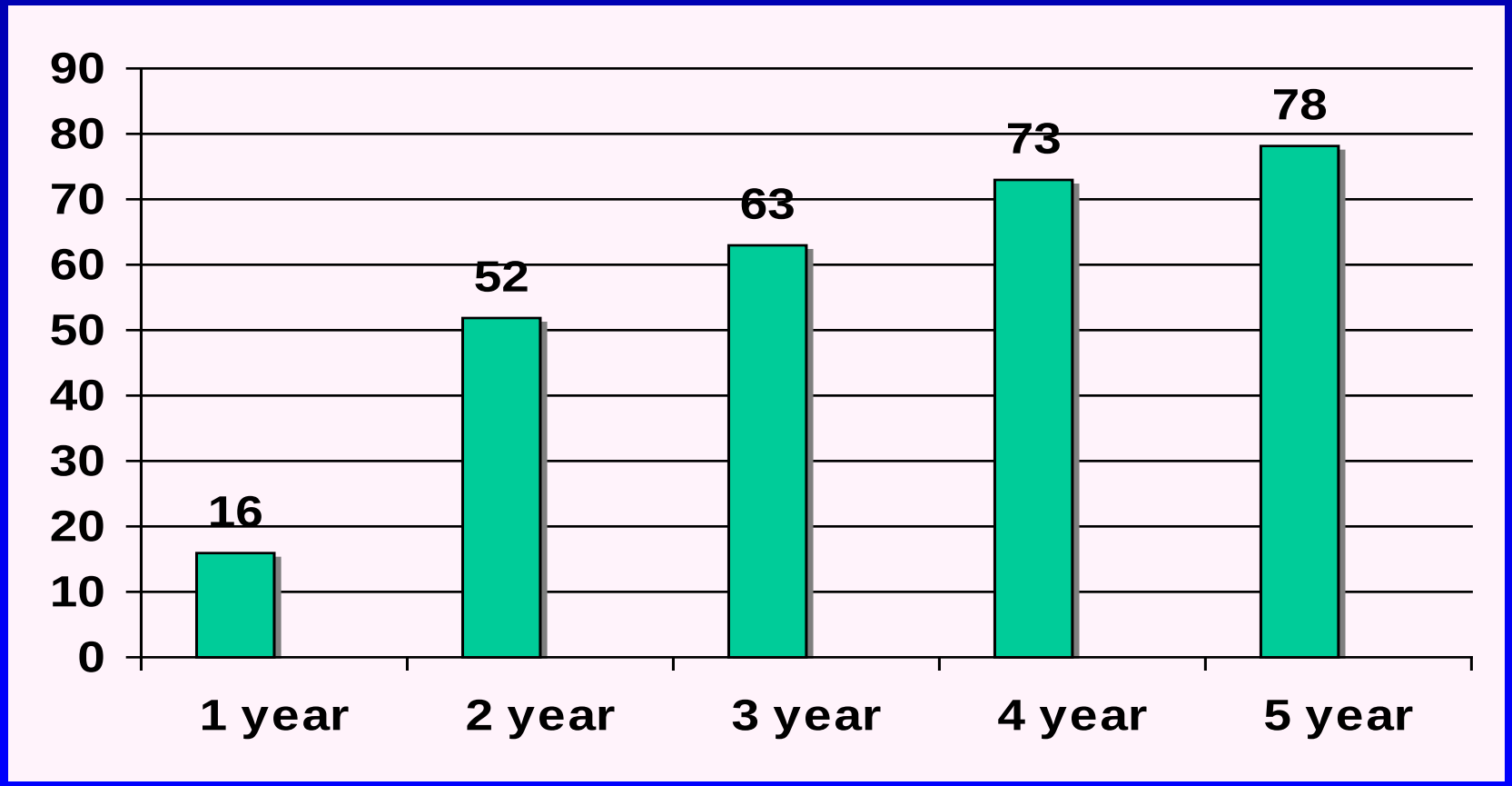
First-episode Psychosis



Sanger TM. Am J Psychiatry 1999;156:79-87.

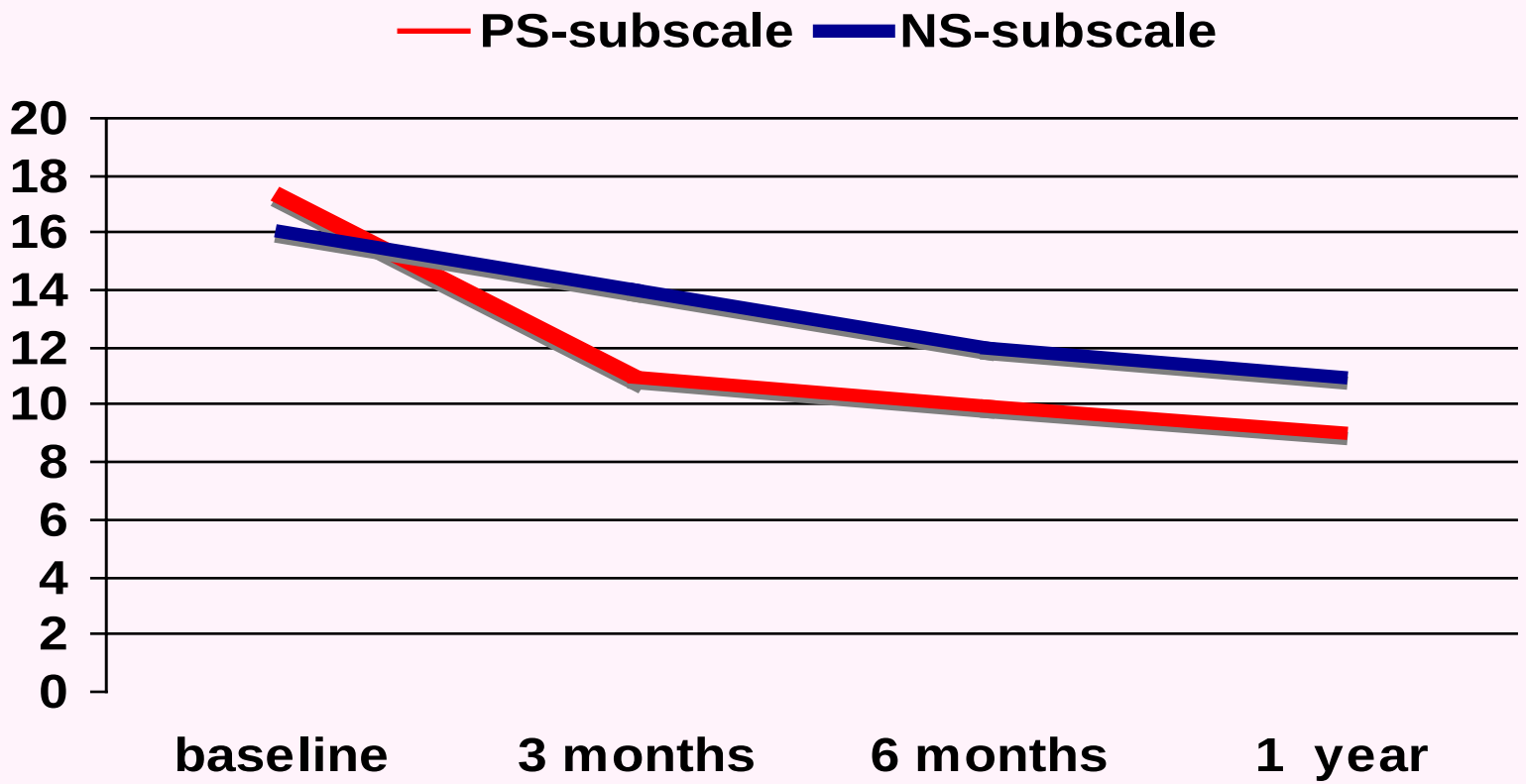
First episode psychosis: Relapses

Antipsychotics for how long?



Quetiapine in FEP

Improvement in Symptoms and cognitive tests



On continuous performance test improvement was noted at 3months

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
- Nondefecit 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 1Year
- 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