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Beyond Early Intervention

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DISCLOSURE

RESEARCH, EDUCATION & TRAVEL GRANT. SPEAKERS GROUP & ADVISORY PANELS

- Janssen Cilag
- Janssen Ortho
- Astra zeneca.Canada & UK
- Pfizer
- Ashoka Innovators for Public
- Prerana Charitable Trust and Mental health Foundation, India
- Roche pharmaceuticals
- Nicolus Pharmaceuticals
- SUN Pharma
- Prempharma

WHO: 2010
10 facts about mental disorders

"There is more to early intervention than merely intervening early"

Program, Prediction and Prevention

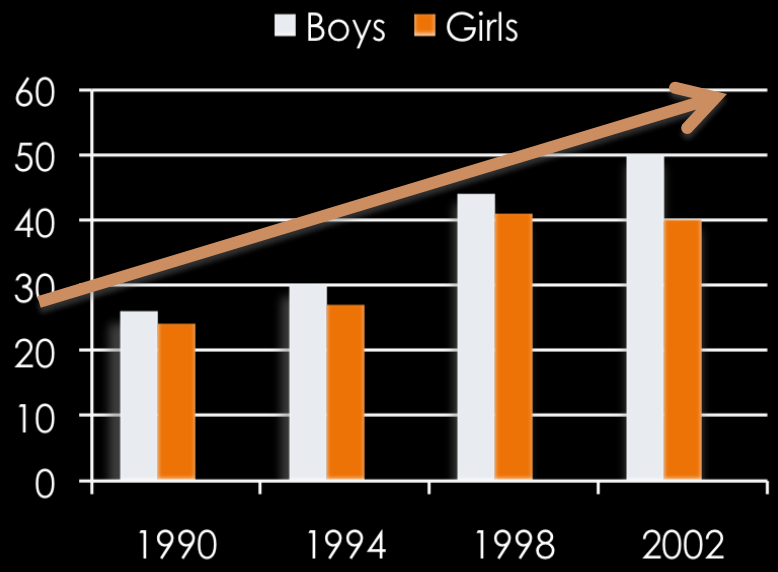
Malla AM, Norman RMTreating psychosis: is there more to early intervention than intervening early?.Can J Psychiatry. 2001 Sep;46(7):645-8

McGorry P, Johanessen JO, Lewis S, Birchwood M, Malla A, Nordentoft M, Addington J, Yung A. Early intervention in psychosis: keeping faith with evidence-based health care. Psychol Med. 2010 Mar;40(3):399-40

Adolescent's mental health

Suicide. Substance abuse. Major mental disorder

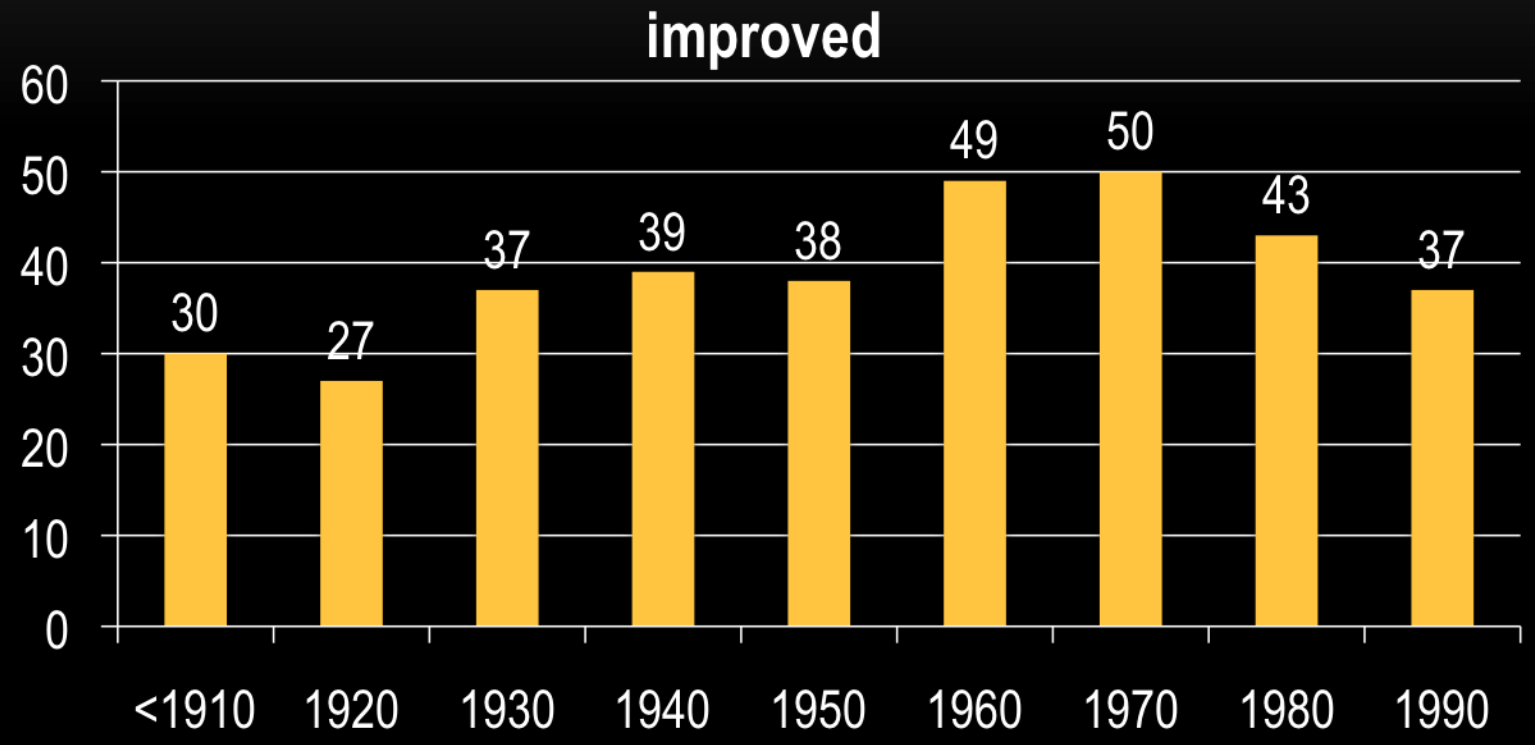
- Schizophrenia – 51 Million
- 1 million suicide every years
- 10% below the age 16
- Suicide in Canada 3400 per year
- 170 below the age of 19



Grade 10 students who have tried Marijuana, by year of survey (%)
(Public health agency of Canada (http://www.phac-aspc.gc.ca/dca-dea/publications/hbsc-2004/chapter_6_e.html)

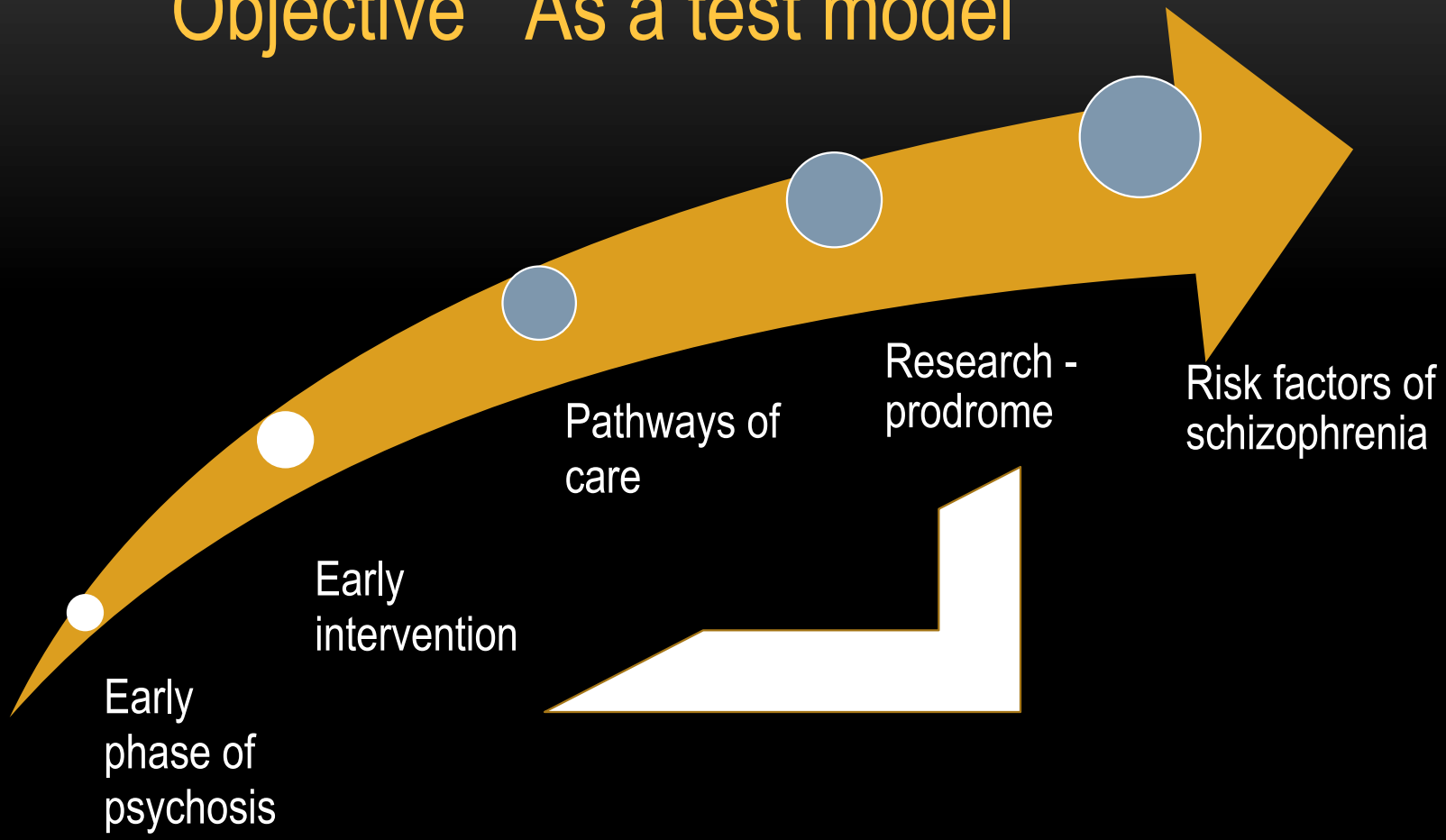
WHO
Health Canada 2003

Outcome of schizophrenia- Hundred years:



Hegarty JD, Baldessarini RJ, Tohen M, Waternaux C, Oepen G.
One hundred years of schizophrenia: a meta-analysis of the outcome literature. Am J Psychiatry. 1994 Oct;151(10):1409-16.

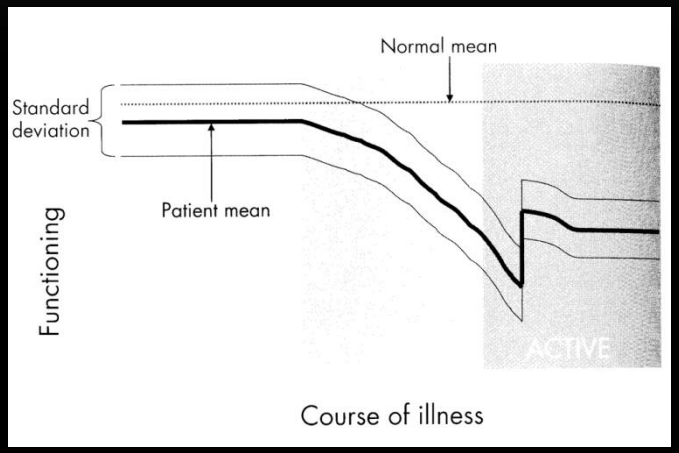
Objective ‘As a test model’



Liu P et al. An evidence map of interventions across premorbid, ultra-high risk and first episode phases of psychosis. Schizophr Res. 2010 Oct;123(1):37-44

If this is true, EI could halt or slow the progression of brain abnormalities in schizophrenia and related psychoses.

1. 80-85% at risk subjects report symptoms .. For several years
    1. Functional decline
    2. Impaired perception
    3. Thought processes
    4. Cognitive dysfunctions
    5. Mood symptoms



Direct evidence suggests that continued loss of gray matter occurs during the first few years after the onset of psychosis

Active disease process may be taking place in the brain during the transition to psychosis in prodrome phase.

The optimism ?

1. Psychosis is toxic
2. There are neurobiological changes in the brain
3. Hope that ‘at-risk’ individuals can be successfully identified
4. Those who are symptomatic and ‘help-seeking’ can be treated to prevent conversion to psychosis

Venkatasubramanian G et al Reduced Caudate Volume in Never-Treated Schizophrenia : Evidence for Neuro developmental Etiopathogenesis. . Indian J Psychiatry. 2003 Apr;45(2):20-6.
Keshavan MS, Amirsadri A Early intervention in schizophrenia: current and future perspectives.Curr Psychiatry Rep. 2007 Aug;9(4):325-8

What has been the achievement of Early intervention initiative ?

- Treatment delay is main pathological factor
- Program based intervention is better and cost effective
- Utilizing Community resources to tailor intervention
- Formulating Best clinical practice and standard of care
- Conceptual reorganization of schizophrenia from categorical to dimensional
- Staging model
- Argument for addressing subthreshold illness

Keshavan MSSchizophrenia, "just the facts": what we know in 2008 Part 3: neurobiology.Schizophr Res. 2008 Dec;106(2-3):89-107.

What has been the achievement of Early intervention initiative ?

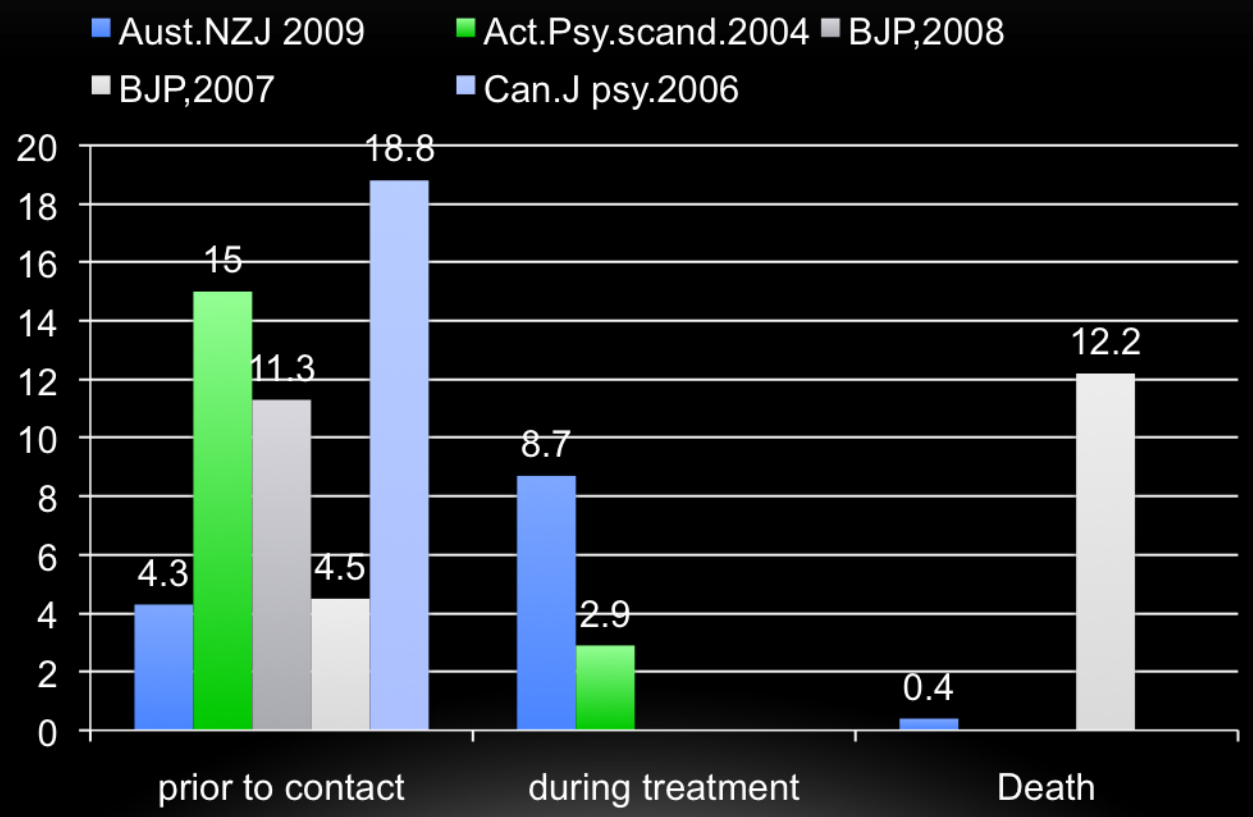
- Duration of untreated psychosis is a marker for
  - Outcome
  - Progression and relapse
  - Level of functioning
- ‘Critical period’ is most important treatment success
- Community and family in therapy
- Neurobiological changes appear early and may even prior to the onset of psychosis
- Feasible across regions with similar success
- Risk factors for schizophrenia and their mechanism of action

Duration of untreated psychosis

- Association with outcome
  - Moderately strong association with outcome at 6 and 12 month and weak at 24 months follow up.
  - Moderately stronger - who ‘did not achieve remission’
  - Neuro-imaging abnormalities - gray matter volume reductions in orbital-frontal regions
  - Cognitive dysfunction
    - Executive function is predictive parameter
- Some studies – ‘No association’

Yamasawa R. et al.Clinical significance of early intervention for patients with schizophrenia--duration of untreated psychosis and prognosis. 2009;111(3):274-7
Amresh Shrivastava, Nilesh Shah, Megan Johnston, Larry Stitt, Meghana Thakar, Gurusamy Chinnasamy
Indian Journal of Psychiatry, Year 2010, Volume 52, Issue 2 [p. 164-167]

Rates of suicide in early psychosis



Key elements (EPIC model) of Early Intervention in schizophrenic illness. 'R [5]'

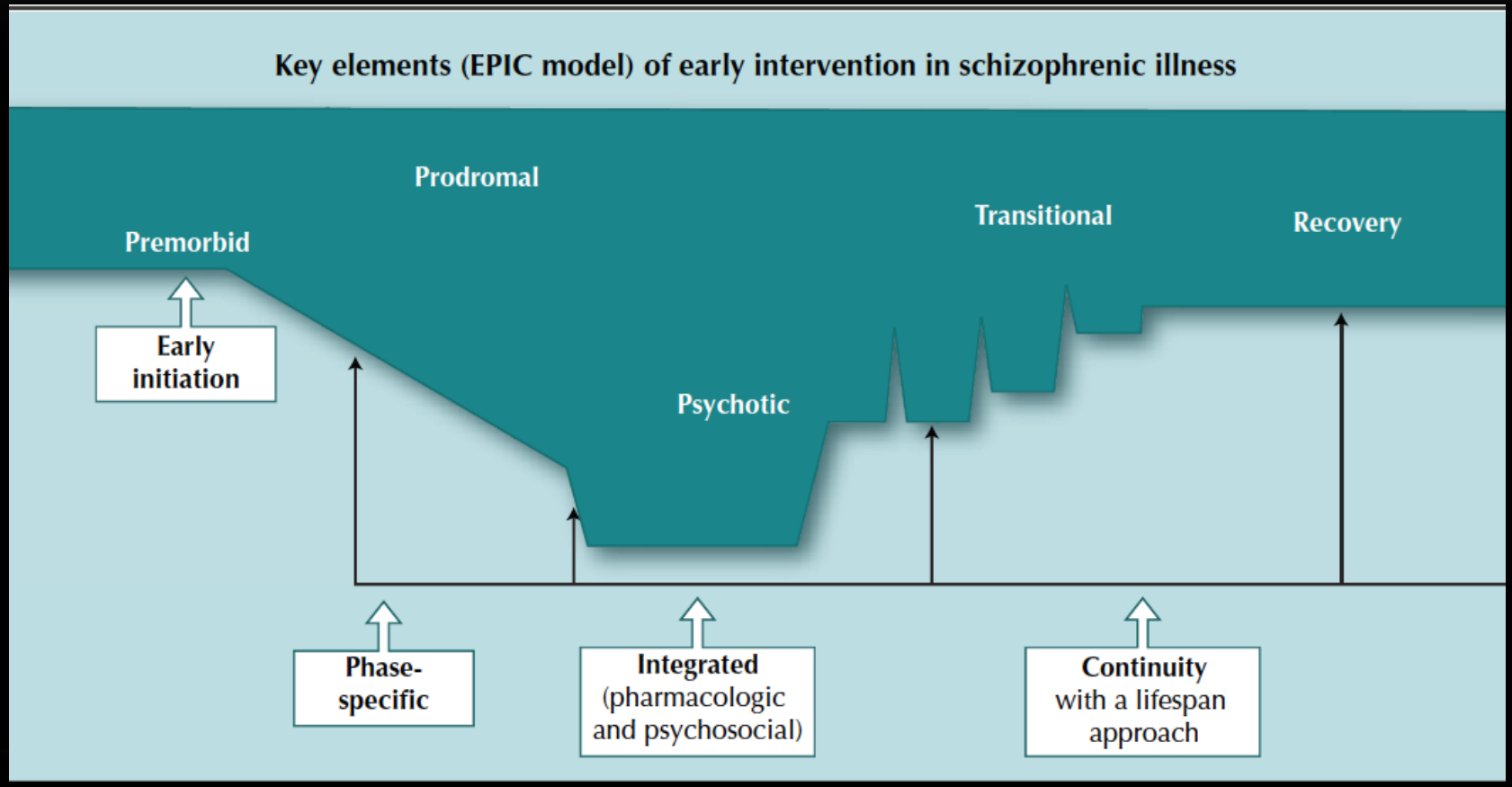
Recognition
Of early symptoms

Reduction of
Untreated illness
duration

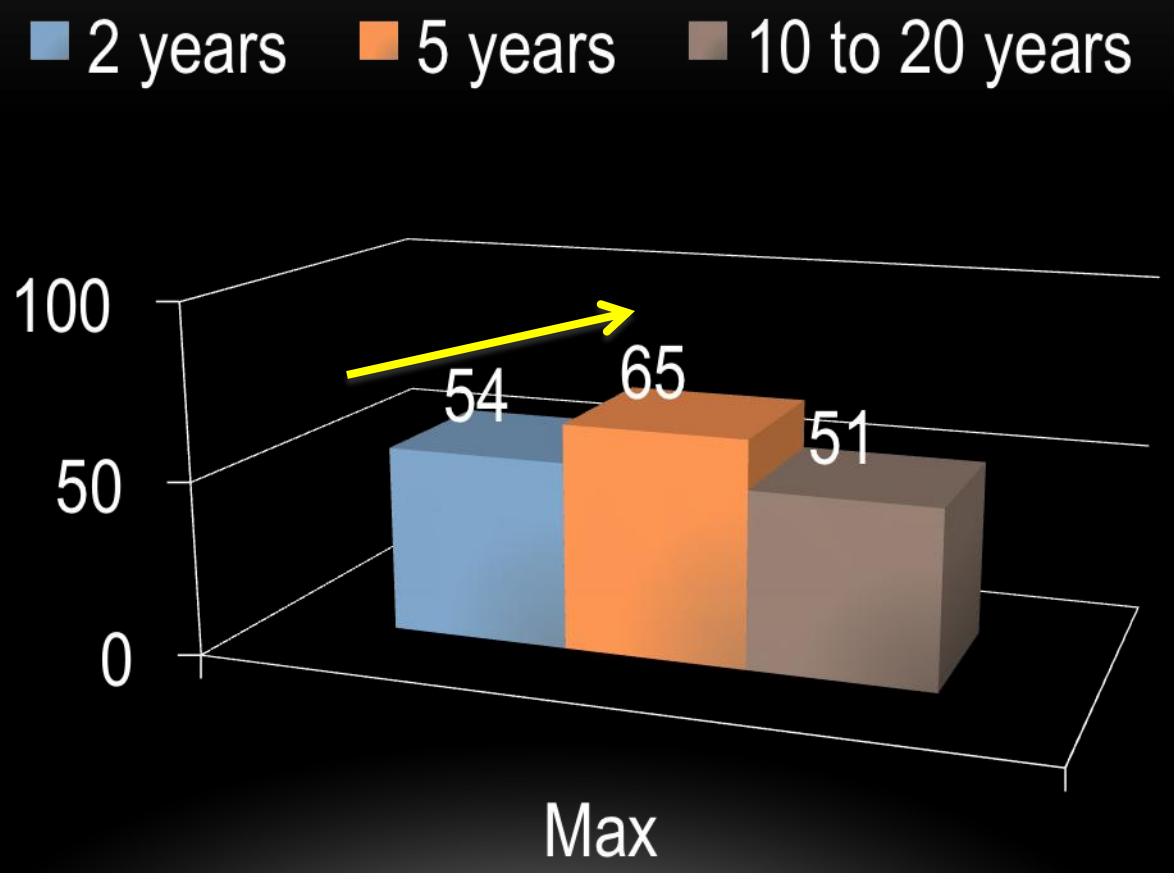
Remediation
Of psychosis

Relapse
prevention

Rehabilitation

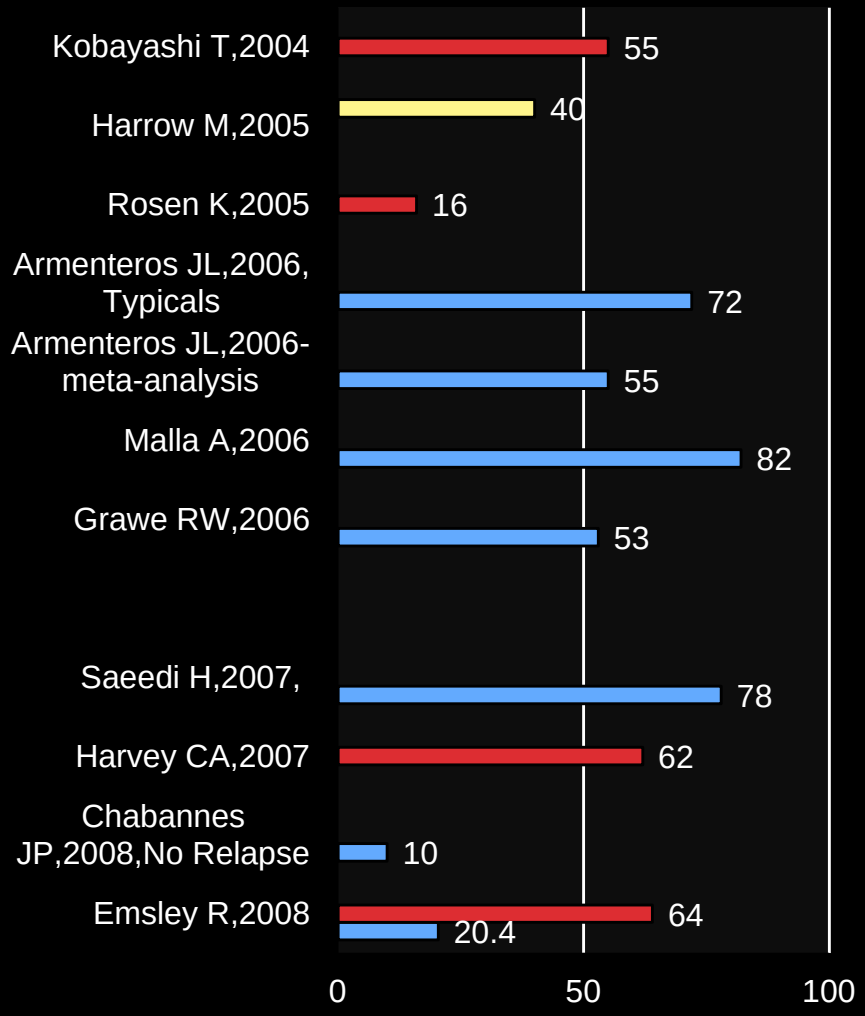


Complete Remission as Outcome status in Schizophrenia: Maximum value - Treatment As usual



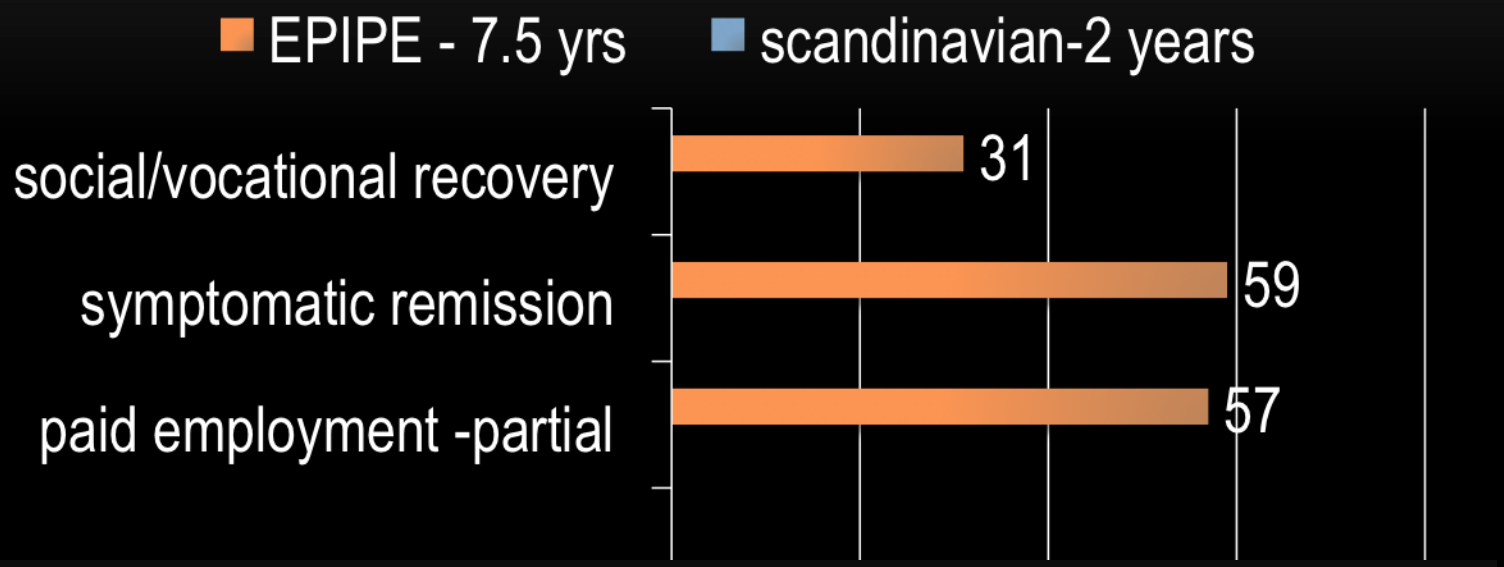
This trend is in contrast to EI possibly because of criteria used

Early intervention program: short and long term outcome



Depends upon the criteria used for remission and recovery

Outcome first episode : Recovery , 2010



Is it cost effective??

McCrone P, Craig TK, Power P, Garety PA.Cost-effectiveness of an early intervention service for people with psychosis. Br J Psychiatry. 2010 May;196(5):377-82

Early intervention in rural regions : Services, funding, local resources, networking

- The problems: referrals:
- Acceptability, accessibility, availability
- Urban models may not be suitable

- DUP : rural settings
  Minimum 10 weeks [Netherlands 1998]
  - Max 796 weeks – India Rural, Bangalore, 44 weeks, Mumbai—urban]
  - EI and Community-based strategies Mental health promotion can reduce DUP

•Shrivastava A, et al **Effects of duration of untreated psychosis on long-term outcome of people hospitalized with first episode schizophrenia.** Indian J Psychiatry. 2010 Apr;52(2):164-7.

•Alvarez-Jimenez M et all **Prediction of a single psychotic episode: A 7.5-year, prospective study in first-episode psychosis.** Schizophr Res. 2010 Nov 15.

•**Malla A et al, Duration of untreated psychosis is associated with orbital-frontal grey matter volume reductions in first episode psychosis.** Schizophr Res. 2011 Jan;125(1):13-20. Epub 2010 Nov 6. [Tirupathi, 2004]–[Norman & Malla London, and other studies.]

Clinical course and outcome of FEP in rural settings

- Follow up of Predominantly treatment-naive cohort in rural Ethiopia for 3.4 years, N= 321 cases 89.6% treatment naive
- 54% were in psychotic episode, 17.6% were in partial remission and 27.4% were in complete remission for at least the month preceding the follow-up assessment.
- OCCUPATIONAL FUNCTIONING in a rural Chinese community
  - Better—at 2 years – and Reduced at 10 years
  - More benign form of the illness and higher levels of social capital.

Ran M, Br J Psychiatry. 2001 Feb;178:154-8.
Chatterjee S, Pillai A, Jain S Cohen A, Patel V. Br J Psychiatry. 2009 Nov;195(5):433-9. ,
Tirupati S, Conrad A, Frost B Johnston S. Aust J Rural Health. 2010 Apr;18(2):66-71.

Alem A, Kebede D Fekadu A, Shibre T, Fekadu D, Beyero T, Medhin G, Negash A, Kullgren G. Schizophr Bull. 2009 May;35(3):646-54

Beyond Early Intervention

- Paradigm shift in service delivery
- Prevention
  - Individual
  - Community
- Prediction for development, response and outcome
  - Candidate factor for a risk prediction
- Health policy

Amresh Shrivastava. Indian Journal of Psychiatry, Year 2010, Volume 52, Issue 1 [p. 13-16]

McGorry PD. Early intervention in psychotic disorders: beyond debate to solving problems. Br J Psychiatry Suppl. 2005 Aug;48:s108-10

Yung AR et al. The prevention of schizophrenia. Int Rev Psychiatry. 2007 Dec;19(6):633-46.

Prevention

- Universal strategies- towards general population: dealing with risk factor, public health e.g. Substance abuse
- Selective : those at high risk without any signs
  - Services- child and adolescents
  - Evidence of effectiveness
  - Detecting prodrome [full blown syndrome]
  - Identification of UHR- mental health promotion

Ongoing Initiatives for prevention

- Research in prodrome and ARMS
- Community experiments in case identification
- Pharmacological and behavioral treatments for management of those at risk with symptoms
- ‘open-the-door’ – dealing with stigma
- Research in the field of risk factors

Yung AR, Nelson B, Thompson A, Wood SJ.The psychosis threshold in Ultra High Risk (prodromal) research: is it valid? Schizophr Res. 2010 Jul;120(1-3):1-6.

‘At-risk for psychosis’: challenges

- Identification,
- Consensus in Definitions & Measurements
- Validation - Specificity in Non-specific symptoms
- Predictive validity of symptoms
- Biomarkers & behavioral markers of regional brain dysfunction
- Argument for Intervention: when & how ?
- Is their a neurobiological basis for ARMS ?

Amresh Shrivastava, PD McGorry, Ming Tsuang, Scott W Woods, Barbara A Cornblatt, Cheryl Corcoran, William Carpenter."Attenuated psychotic symptoms syndrome" as a risk syndrome of psychosis, diagnosis in DSM-...5 .Indian Journal of Psychiatry, Year 2011, Volume 53, Issue 1 [p. 57-65]

.

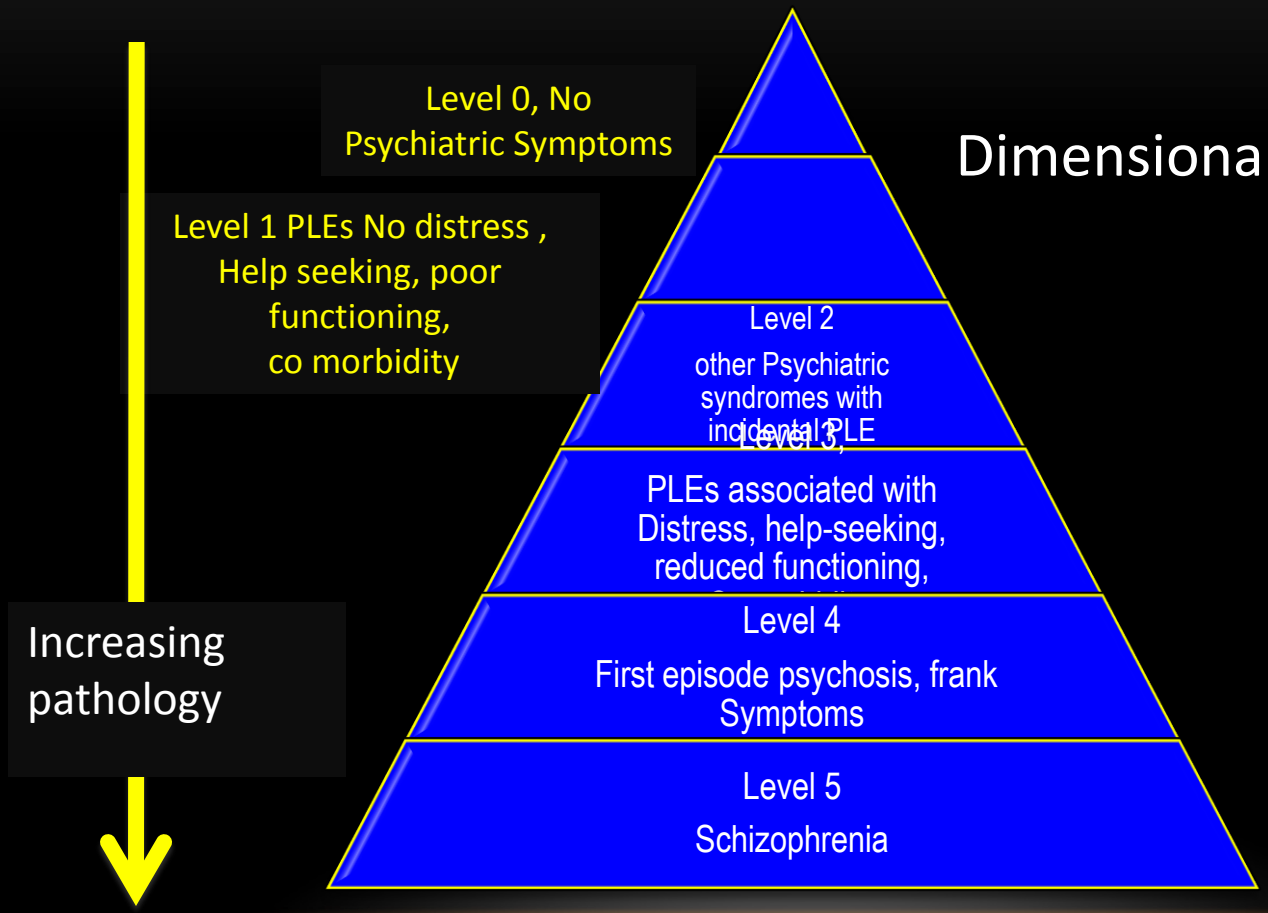
Woods SW, Walsh BC, Saksa JR, McGlashan TH. The case for including Attenuated Psychotic Symptoms Syndrome in DSM-5 as a psychosis risk syndrome Schizophr Res. 2010 Nov;123(2-3):199-207

1. PRODROMAL SYNDROME ASSESSMENT TOOLS

- Identification by a structured interview
  - Structured interview for prodromal syndrome (SIPS)
  - Comprehensive Assessment of At Risk mental state (CAARMS)
  - Bonn scale for assessment of basic symptoms (BSABS)
- Syndromes
  - Attenuated positive symptom syndrome
  - Brief intermittent psychotic syndrome
  - Genetic risk + deterioration syndrome

Attenuated Symptom Syndrome of UHR as a diagnosis in DSM V

2. conceptual reorganization of schizophrenia
Staging Model :Detect sub threshold symptoms Psychotic-like-experiences (PLE)



Dimensional approach

3. CONVERSION TO THE FIRST EPISODE OF PSYCHOSIS

Q.3 for how long the onset of psychosis can be predicted? 6 M, 12 M, 2 yr. ..>

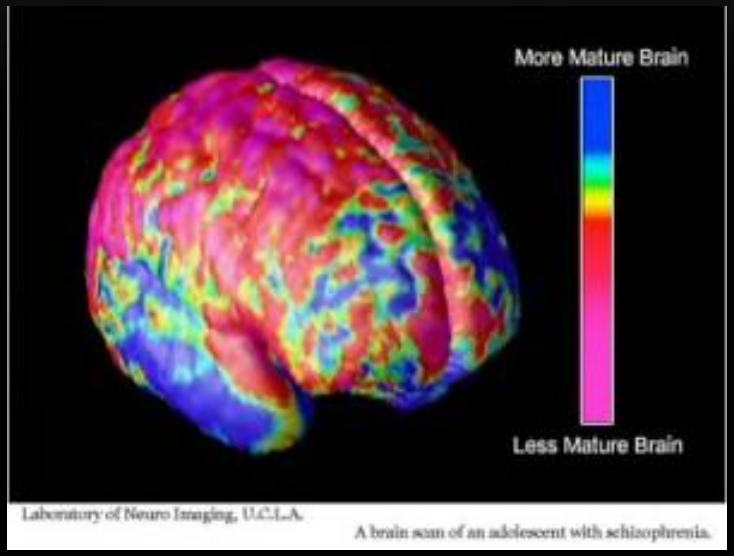
Study	Assessment Tool	Subject Number	Age at baseline	F/U Dx	Drug Treatment	Annual Conversion Rate *
Klosterkotter, et al, 2001	BSABS	77	29	N	Unknown - naturalistic?	8%
Yung, McGorry, et al, 2004	CAARMS	49	19	B	None	41%
Lencz, Cornblatt, et al, 2003	SIPS	34	16	B	Unknown - naturalistic?	13%
McGlashan, et al, 2005	SIPS	60	18	N	Randomized to OLAN vs PCB	17%
Haroun, et al, 2006	SIPS	50	19	B	Unknown - naturalistic?	13%

* Actual length of F/U varied - assumed risk of conversion was linear over time.
F/U Dx - B - broad, N - narrow

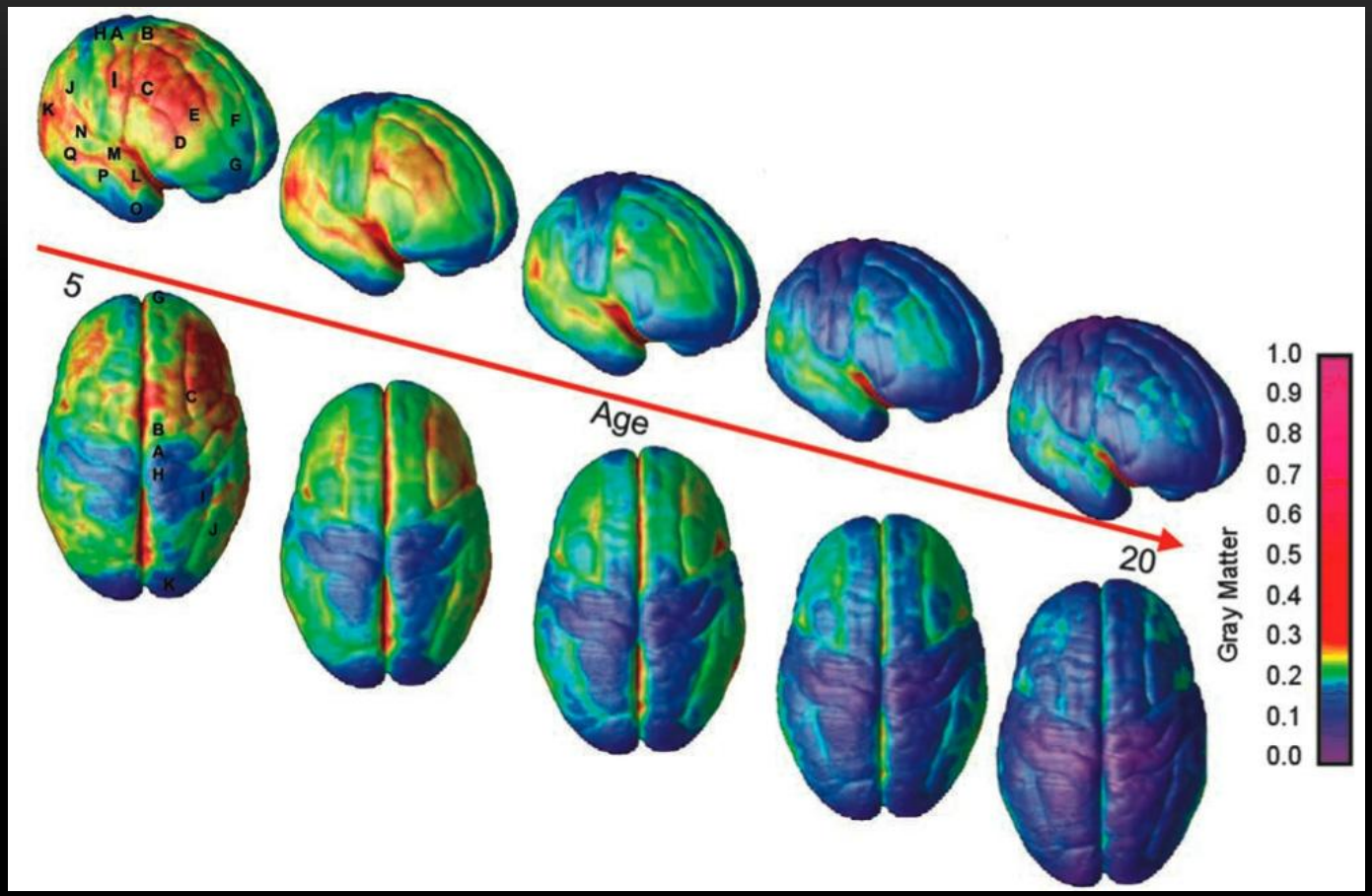
Modified from: Haroun, Dunn, Haroun, and Cadenhead, Schiz Bull 32:166-178, 2006.

4. Pathogenesis

- Neurobiology
- Cognition
- Risk factors
- Neuroprotection
- Gene-Environment interplay



1.Brain Changes



The relative failure of neuroimaging measures to predict transition to psychosis suggests that standard techniques are incapable of capturing the subtle differences

NEUROIMAGING STUDIES IN UHR:: CONSENSUS FINDINGS

1. Dysfunction maturational processes
2. loss of gray matter in DPFC , lateral and medial temporal region and cingulate gyras
3. Aberrant mechanisms for brain maturation,
4. Subtle regionally and temporally specific changes through the course of psychosis,

   (1) Early (pre- and perinatal) anomalies,

   (2) *around the time of transition*

   (3) Late (post-pubertal) changes soon after the onset of psychosis,

5. The relative failure of neuroimaging measures to predict transition to psychosis

2.Neurocognitive impairment in UHR

1.Working memory, 2.Executive functioning

strongest predictor for conversion to psychosis

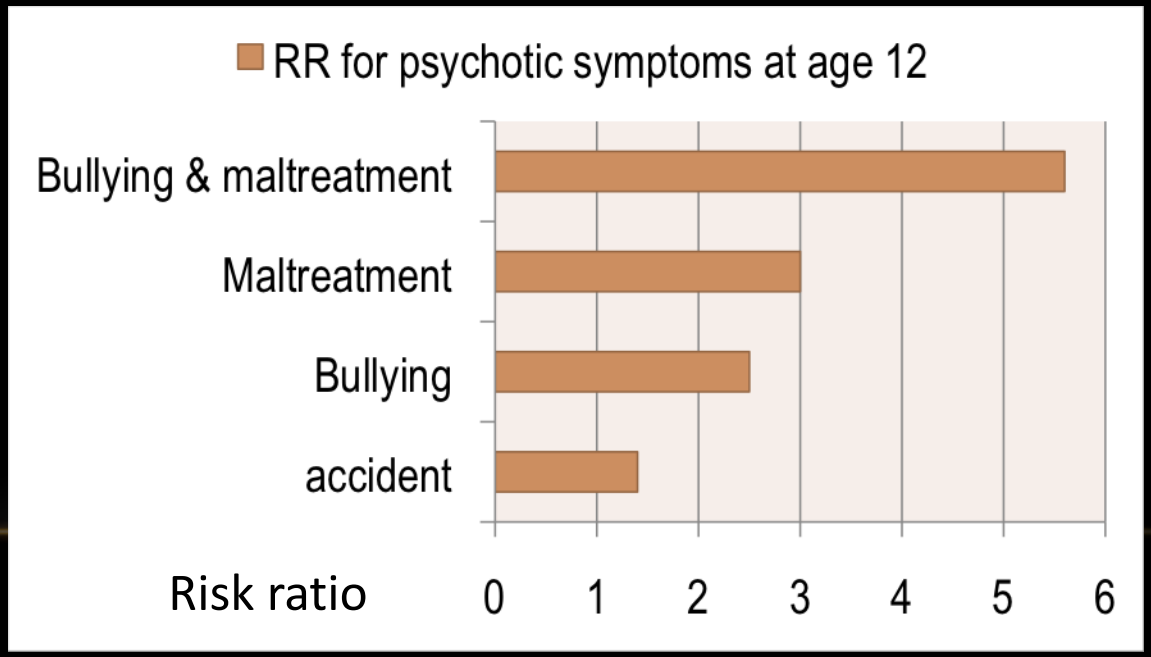
- Core feature of established psychotic illnesses.
- The association is less understood.
- Some evidence - CI present prior to the onset of psychosis,
- Findings -- not consistent.

Cognition declines as psychosis progresses

Brewer WJ, Wood SJ, Generalized and specific cognitive performance in clinical high-risk cohorts: a review highlighting potential vulnerability markers for psychosis. Schizophr Bull. 2006 Jul;32(3):538-

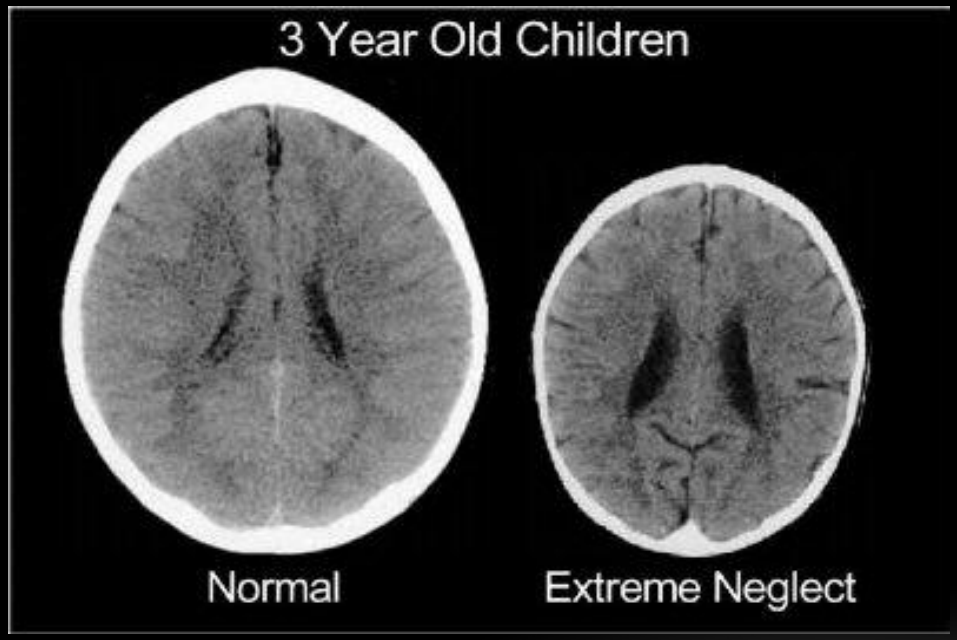
3.Risk factors. Childhood trauma and sex abuse

- Increased risk of psychosis amongst people exposed to CSA [Archive of gen Psyhciatry. 2010 Nov.]
- Later onset psychotic symptoms associated with bullying and abuse [AJP,2011 January]



Risk for Schizophrenia

Childhood Experience & the Expression of Genetic Potential: What Childhood Neglect Tells Us About Nature and Nurture? [1, 2]



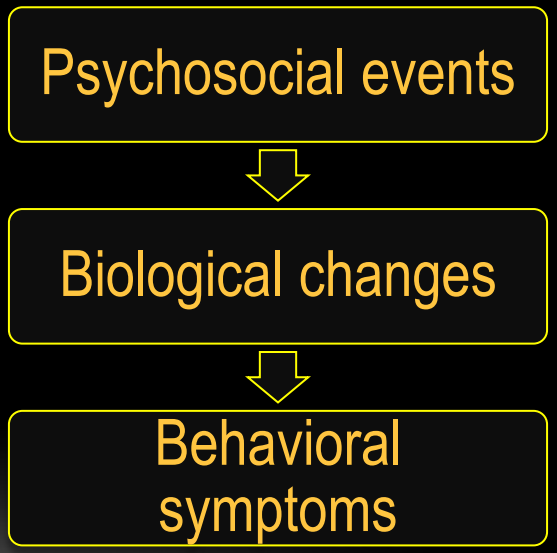
NEURONAL DEVELOPMENT & CHILD ABUSE

1.Chen TJ, Med Hypotheses. 2006;66(5):1043-4.
2.Anda RF,Eur Arch Psychiatry Clin Neurosci. 2006 Apr;256(3):174-86. 2005

4.Impaired neuroprotection and Neuroplasticity

- Dendrites
- BDNF and NGF
- Membrane abnormality
- Phospholipids
- Synaptic connectivity.
- Neuronal integrity

Understanding about gene-environment interplay



Five Key Predictors

1.Predicting onset, 2.Predicting progression, 3. Both

- Genetic risk with recent deterioration in function.
- Higher levels of unusual thoughts
- Higher level of suspicion or paranoia.
- Greater social impairment
- History of substance abuse

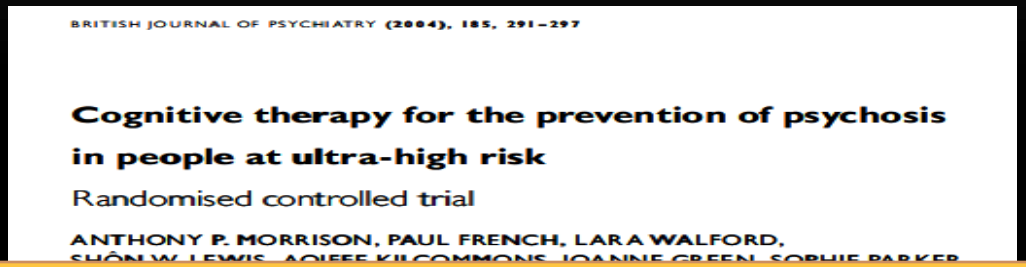
Emerging cognitive, imaging and neurochemical predictors

Argument for intervention

- Early psychosis researchers suspected that pushing the point of intervention back to the prodromal phase of psychotic disorders may result in even better outcomes.
- Ethical aspects - more salient given the recently observed declining transition rate in ultra-high-risk samples.
- Further controlled intervention trials with larger sample sizes are required in order to confirm and extend these findings

IMcGorry PD,et al Intervention in individuals at ultra-high risk for psychosis: a review and future directions.J Clin Psychiatry. 2009 Sep;70(9):1206-12

Non pharmacological treatments
CBT, assertive community treatment and case management



BRITISH JOURNAL OF PSYCHIATRY (2004), 185, 291–297

Cognitive therapy for the prevention of psychosis in people at ultra-high risk

Randomised controlled trial

ANTHONY P. MORRISON, PAUL FRENCH, LARA WALFORD,

Treatment Group	Follow-up Rate N (%)	PANNS Transition N (%)	Antipsychotic Medication N (%)	DSM-IV Psychotic Diagnosis N (%)
Cognitive Therapy (N = 35)	17 (49%)	7 (20%)	5 (14%)	7 (20%)
Monitoring (N = 23)	10 (43%)	5 (22%)	8 (35%)	7 (30%)

Morrison et al, 2004

Article

Randomized, Double-Blind Trial of Olanzapine Versus Placebo in Patients Prodromally Symptomatic for Psychosis

Thomas H. McGlashan, M.D.

Robert B. Zipursky, M.D.

Diana Perkins, M.D.

Jean Addington, Ph.D.

Tandy Miller, Ph.D.

Scott W. Woods, M.D.

Keith A. Hawkins, Psy.D.

Ralph E. Hoffman, M.D.

Adrian Preda, M.D.

Irvin Epstein, M.D., F.R.C.P.C.

2009
Fish Oil :
strongest outcome data
Ziprasidone –
Placebo controlled trial

symptoms in people with prodromal symptoms of schizophrenia.

Method: This randomized trial occurred at four North American clinics in the Prevention Through Risk Identification, Management, and Education project. Outpatients received olanzapine (5–15 mg/day, N=31) or placebo (N=29) during a 1-year double-blind treatment period and no treatment during a 1-year follow-up period. Efficacy measures included the conversion-to-psychosis rate and Scale of Prodromal Symptoms scores.

Results: During the treatment year, 16.1% of olanzapine patients and 37.9% of placebo patients experienced a conversion and 28 with olanzapine. The olanzapine patients gained significantly more weight (mean=8.79 kg, SD=9.05, versus mean=0.30 kg, SD=4.24).

Conclusions: A significant treatment difference in the conversion-to-psychosis rate was not demonstrated. However, these results may be influenced by low power. The nearly significant differences suggest that olanzapine might reduce the conversion rate and delay onset of psychosis. Olanzapine was efficacious for positive prodromal symptoms but induced weight gain. Further treatment research in this phase of illness is warranted.

(Am J Psychiatry 2006; 163:790–799)

Future

- The hope is that this research will help facilitate intervention at earlier stages that may in turn
  - minimize functional deterioration, and
  - delay, attenuate or even prevent transition to psychosis.
- Predict those most likely to transition to psychosis;
  - At the initial FEP stage,
  - To predict those likely to develop schizophrenia;
  - in established schizophrenia to inform on outcome.

SUMMARY

- Early psychosis and early intervention initiative is a ‘testing model’ for future services.
- Treatment model is program based
- It has built-in research initiative
- Opens of possibilities of attempts for prevention
- ATMS is a growing area of research which forms central core for argument to invest in preventive efforts
- Challenge is to translate research to services, particularly for rural and underserviced regions