

#NAMIcon16

Research Update on Schizophrenia

Robert Freedman MD

Professor and Chair, Department of Psychiatry

University of Colorado

Editor, American Journal of Psychiatry



Disclosures

- No financial conflicts of interest from the pharmaceutical industry.
- I am employed by the University of Colorado and the American Psychiatric Association.
- My research is support by NIMH, the Anschutz Foundation, and the Institute for Children's Mental Disorders



Two themes of research in schizophrenia

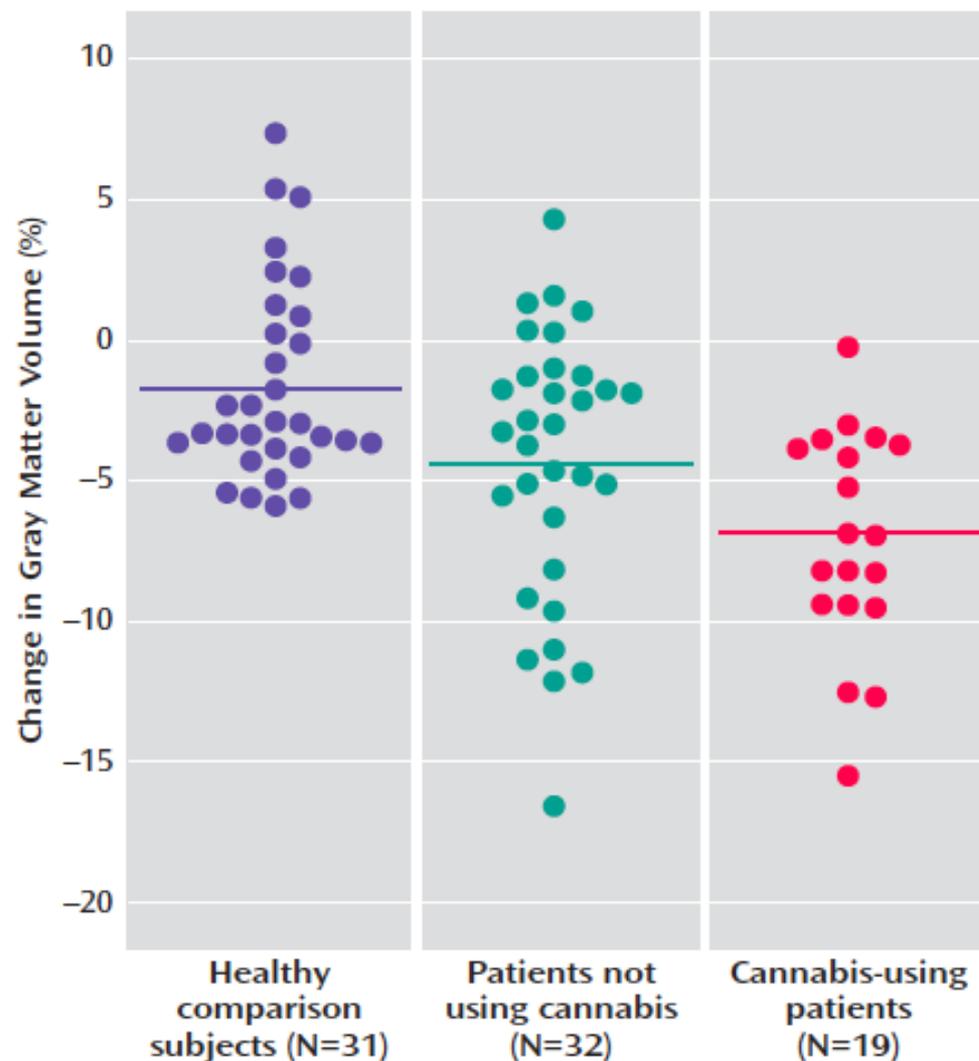
- The course of schizophrenia in the first ten years: the benefits of treatment, changes in diagnosis and the effects of marijuana.
- The prevention of schizophrenia in future generations: can you protect your grandchildren?



What effect does marijuana have?

Accelerated loss of brain volume in patients who use cannabis.

FIGURE 1. Brain Volume Changes Over Time in Schizophrenia Patients and Healthy Comparison Subjects: Gray Matter Volume^a



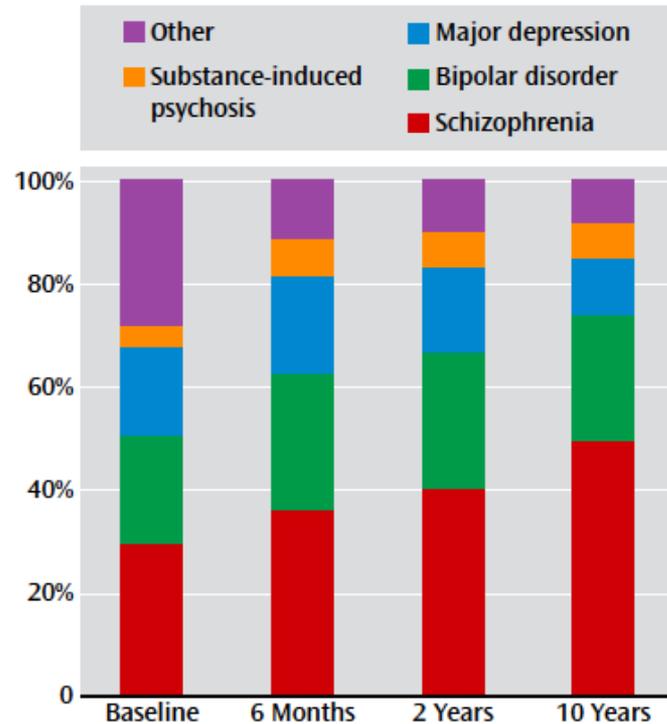
(Am J Psychiatry 2008; 165:490-496)



Why does the diagnosis change?

Myth—The first doctor told me that my son had schizoaffective disorder, but the new doctors think it's schizophrenia.

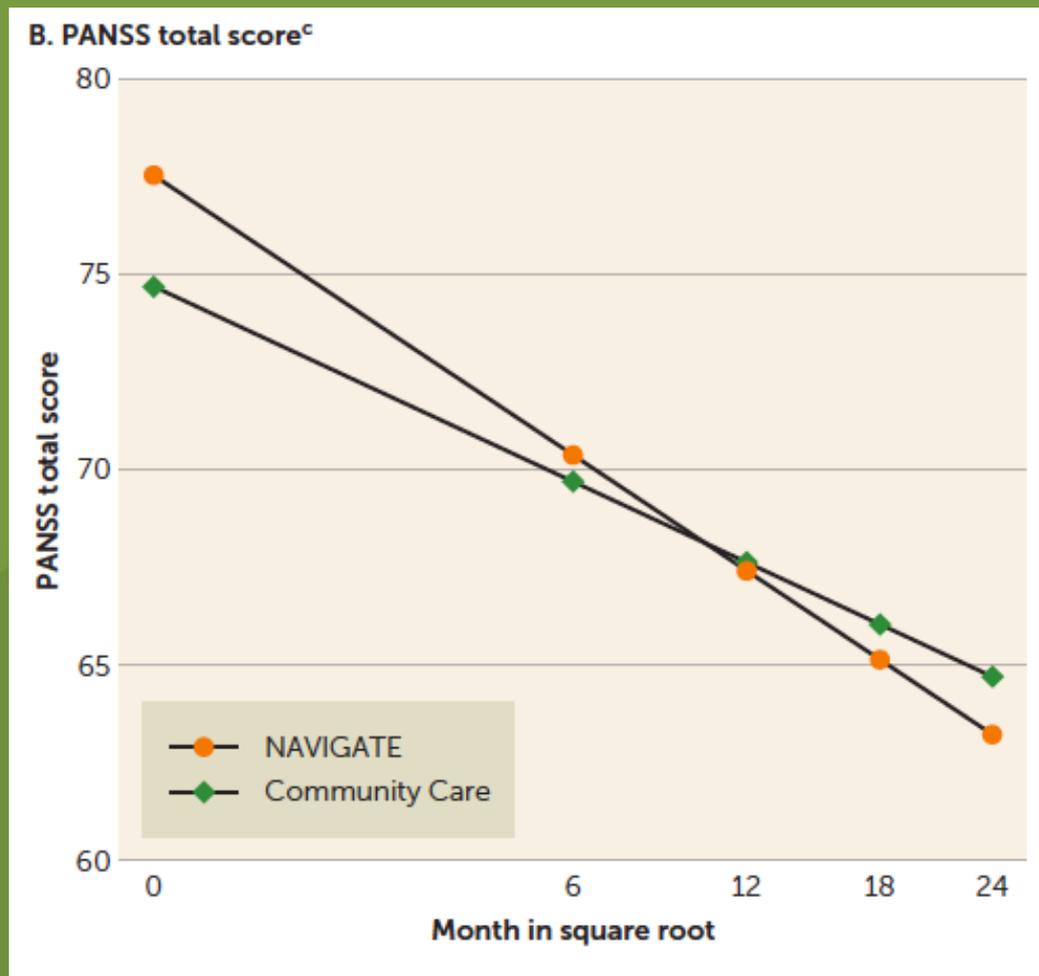
FIGURE 1. Cross-Sectional Distributions of Research Diagnoses at Baseline and Follow-Up Assessments for First-Admission Patients With Psychosis^a



^a N=470 at baseline and 10 years; N=438 at 6 months; N=459 at 2 years.



How much difference do services in the community make?



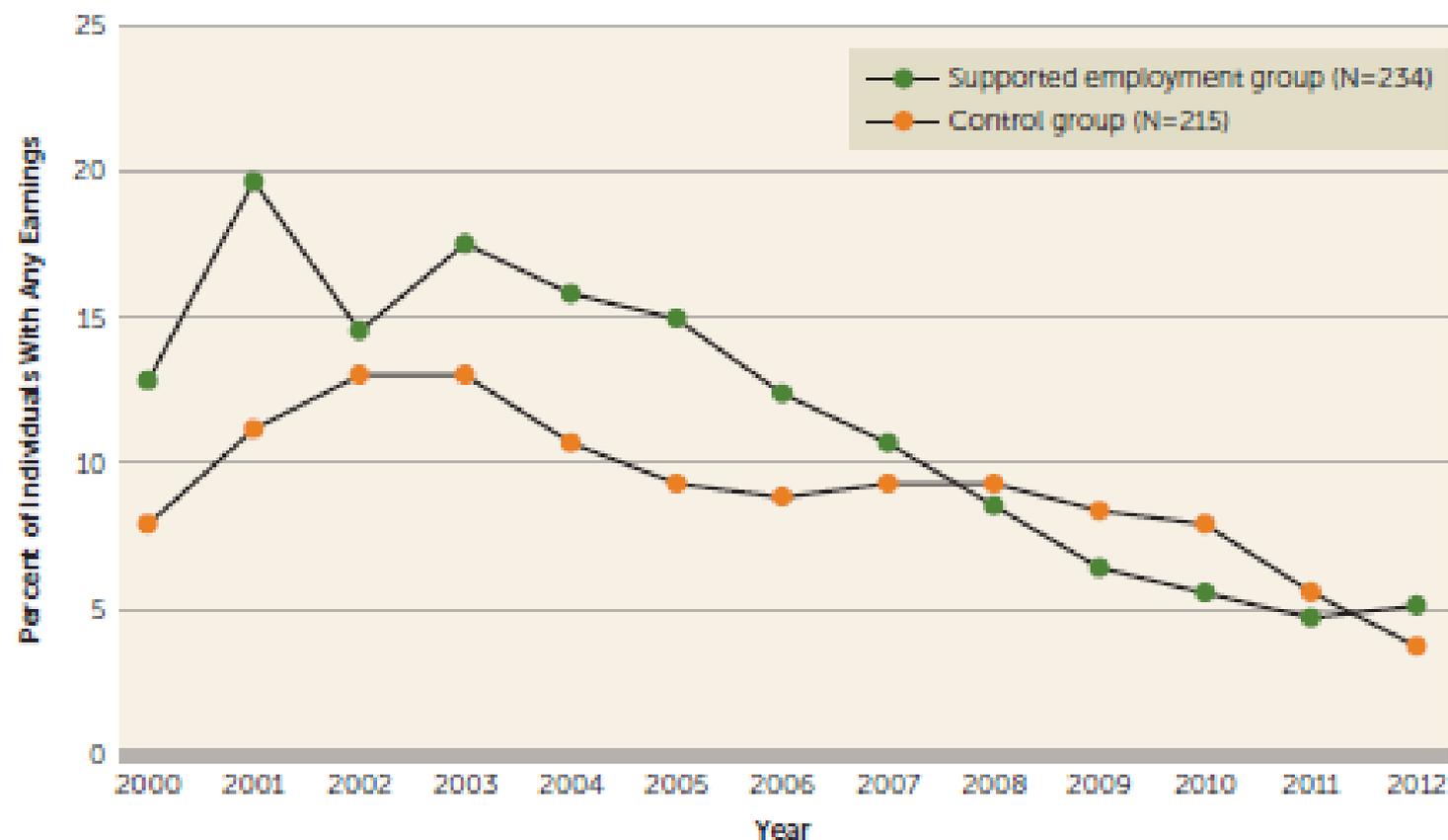
Better participation leads to better compliance with medication and lower doses.

Am J Psychiatry 2016; 173:362–372;



Will there be a job?

FIGURE 1. Percentage of Individuals With Psychiatric Disabilities Who Received or Did Not Receive Supported Employment Services Who Had Any Earned Income (2000–2012)^a



^aIn multivariable longitudinal random logistic regression models, supported employment participants were significantly more likely to have any earned income than control group participants (odds ratio=2.89, $p=0.022$).

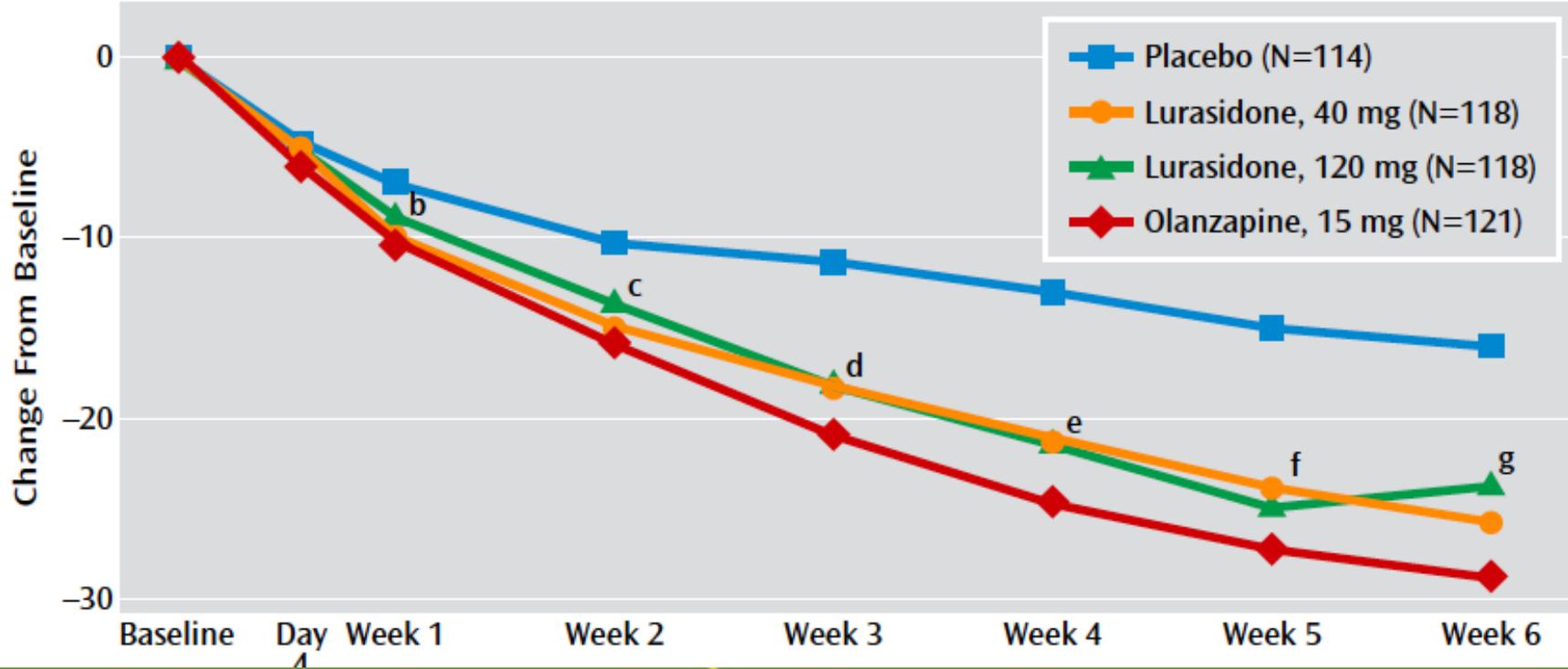
Cook
JA
AJP
2016,
in
press



Are the newest drugs the best drugs?

Myth: My doctor tried everything, but then she finally found something that works.

FIGURE 2. Change From Baseline in PANSS Total Score in a Randomized, Double-Blind, Placebo- and Olanzapine-Controlled Study of Lurasidone^a



(Am J Psychiatry 2011; 168:957-967)

Schizophrenia 2016: Summary

1. People are getting better.
2. Diagnoses are not the issue they seem to be.
3. New medications are not improving outcome (although they decrease side effects).
4. There are benefits of early treatment: better outcomes and fewer suicides.
5. Marijuana adds to the loss of cognitive function.
6. Fewer than 1 of 10 people return to long term, full time employment.
7. Don't overlook clozapine.



Schizophrenia 2016: Summary: A Ceiling on Effectiveness

1. New medications are not improving outcome.
2. There are some benefits of early treatment: better outcomes and fewer suicides, but these benefits are small.
3. Marijuana adds to the loss of cognitive function.
4. Fewer than 1 of 10 people return to long term, full time employment.
5. 10% commit suicide or other violent acts, including mass shootings.



Are we seeing the real problem?
James Craik MD worries about his fatal bleeding
of Washington for a sore throat in 1799, a
condition that has been routinely cured by
penicillin since 1950.



A clue: People with schizophrenia smoke more heavily than any other group. They activate alpha 7 nicotinic receptors, which are genetically abnormal in schizophrenia. How can we do better than give patients cigarettes?



“Very soon, being without a pack of cigarettes made me very uneasy.”

Elyn R. Saks, *The Center Cannot Hold*. 2007.



If schizophrenia is a genetic illness, and... genes are the blueprint that builds the brain before birth, why don't we intervene then?



Early brain dysfunction in newborns who will later develop schizophrenia has long been known

VOL. 20, No. 3, 1994

Neuromotor Precursors of Schizophrenia

441

by Elaine F. Walker, Tammy
Savole, and Dana Davis

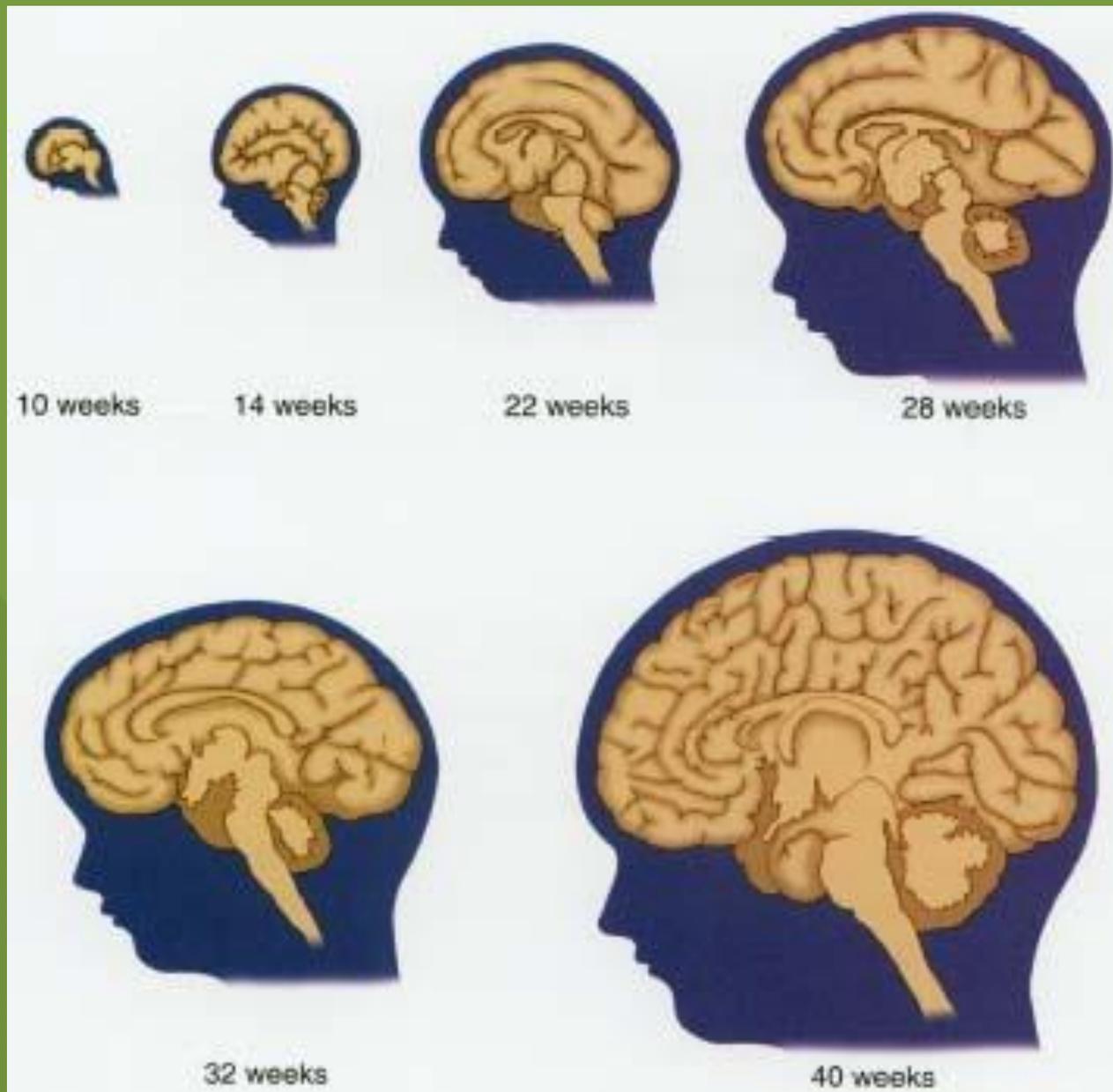
Abstract

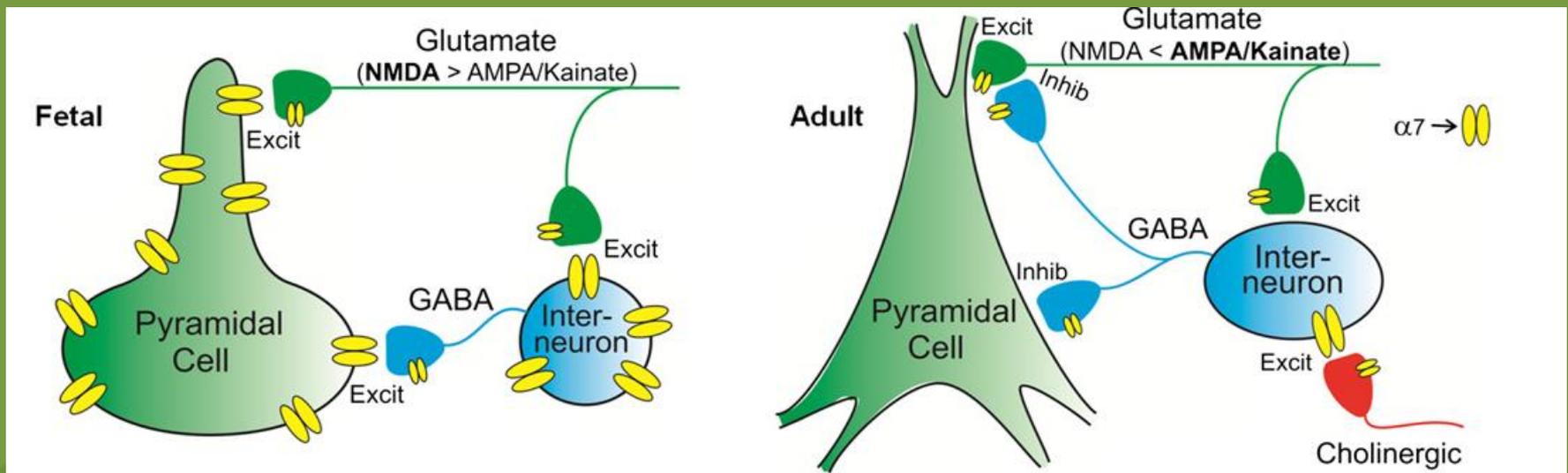
also discussed.
Schizophrenia Bulletin, 20(3):



The brain develops before birth using a series of neurotransmitter “operating systems.”

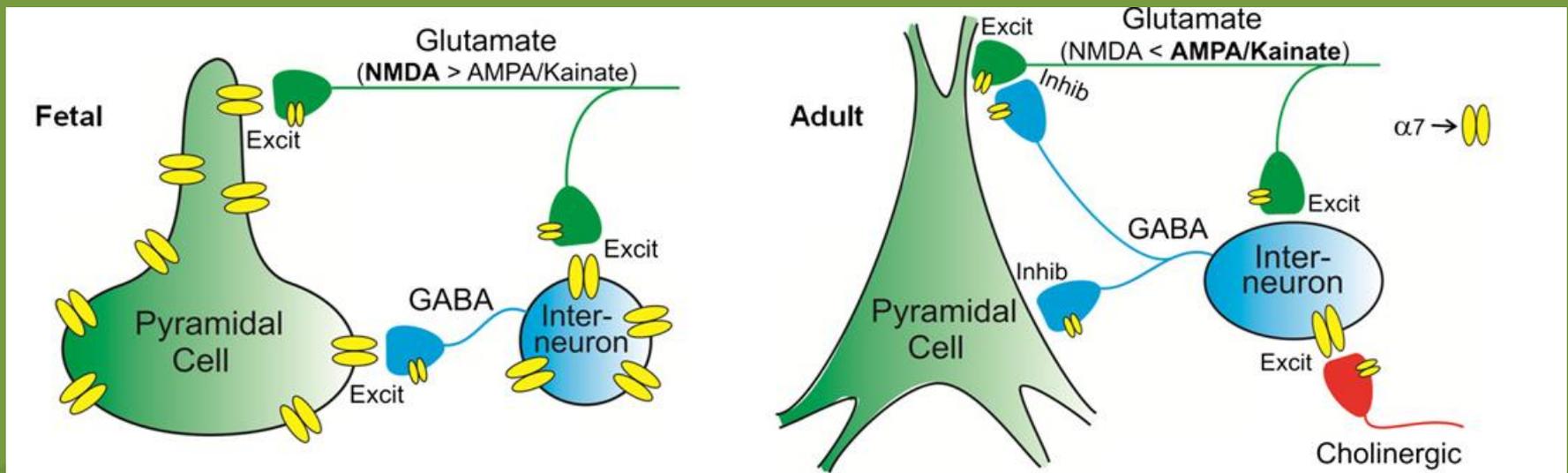
Alpha7 nicotinic receptors, one of the receptors abnormal in schizophrenia, help install the new systems.





In the fetal brain, alpha 7 nicotinic receptors are more widely distributed than in adults, consistent with their greater activity then.





In the fetal hippocampus, alpha 7 nicotinic receptors are more widely distributed
but how are they activated?



Choline activates nicotinic receptors before birth

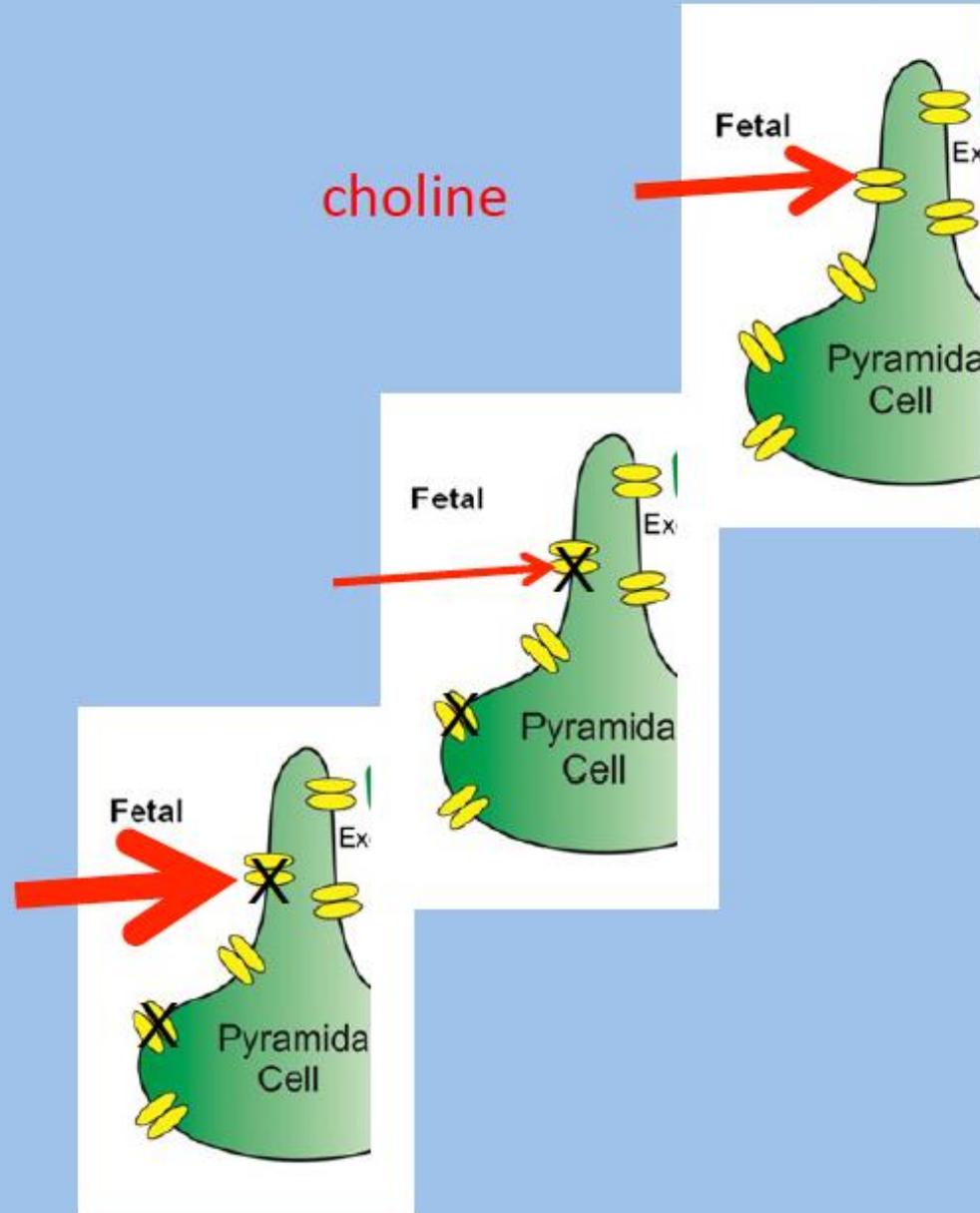
- Normal ingredient in liver, eggs, and meats.
- Pregnant women often cannot keep up with the demands of the baby
- Stress, anxiety, depression, infection, and nicotine use during pregnancy all increase the risk for mental illness in the baby and may be overcome by increasing choline.
- The single greatest risk factor, genetic risk, may be overcome by increasing choline as well. Phosphatidylcholine is available as a natural vitamin.



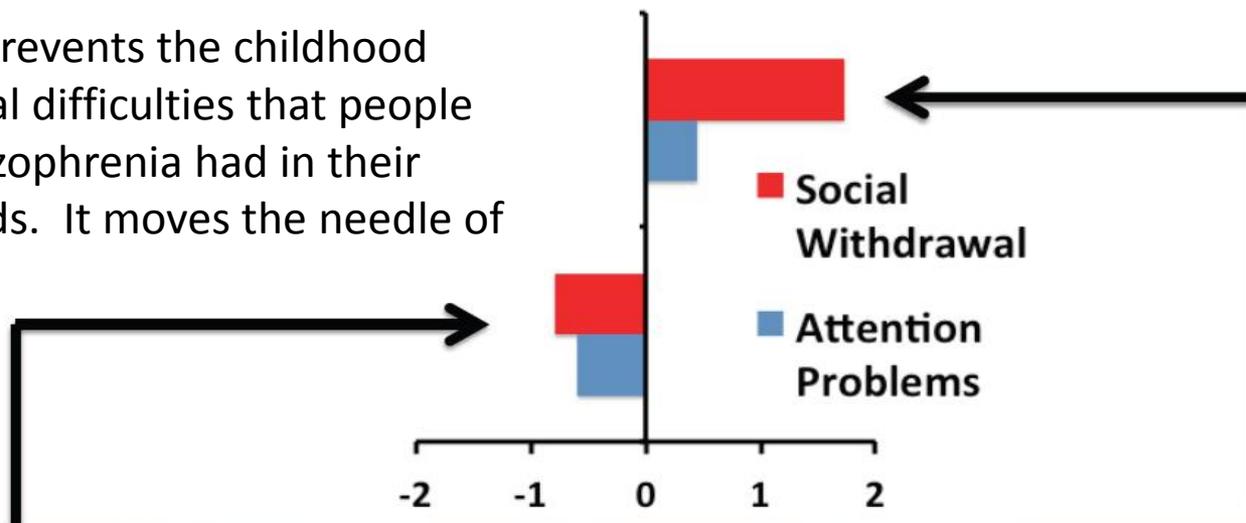
Normal genes
and nutrition

Genetic and
nutritional
deficiencies

Can choline
supplements
overcome
deficiencies?



Choline prevents the childhood behavioral difficulties that people with schizophrenia had in their childhoods. It moves the needle of risk back.



Perinatal
choline



3-4 year
old

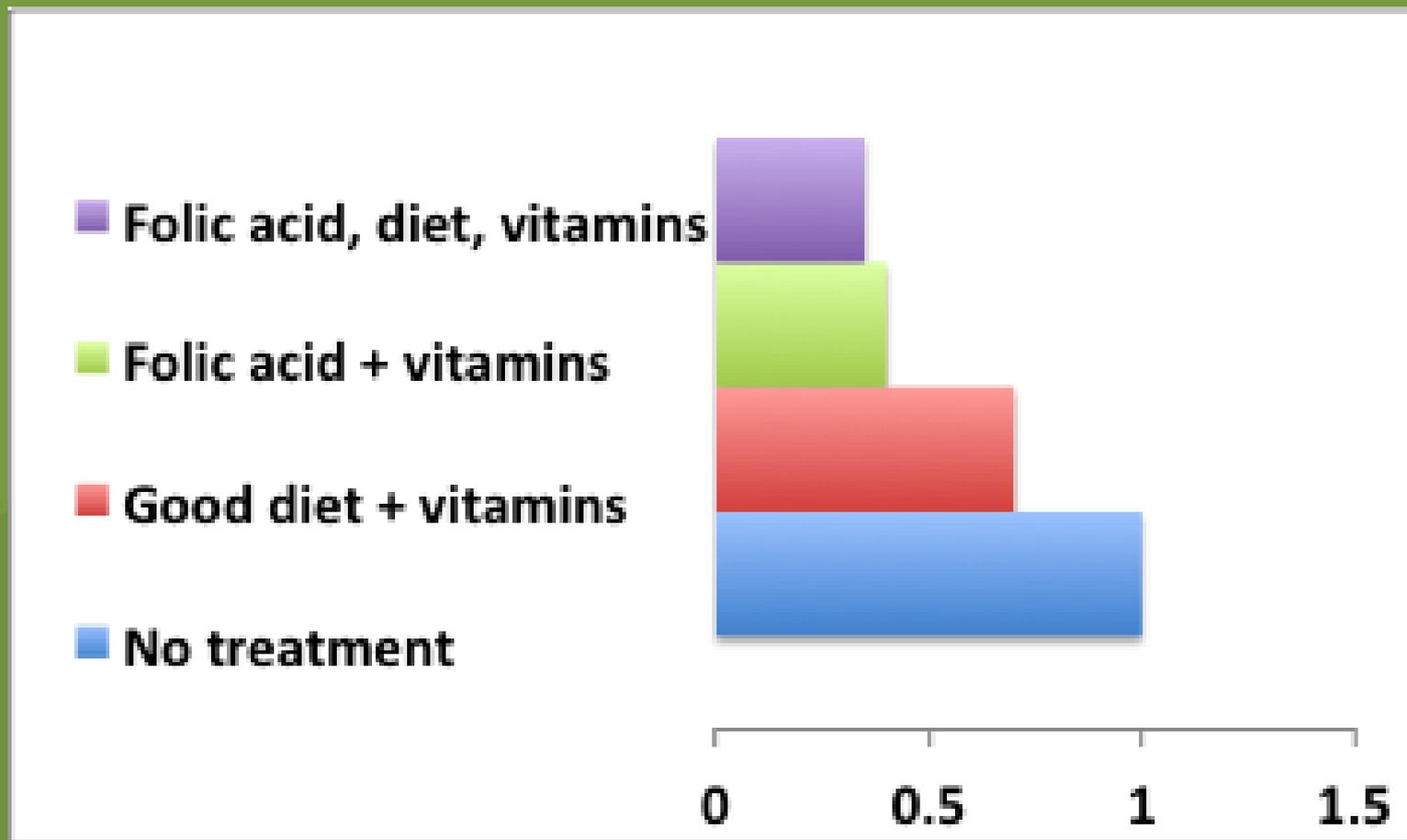


Adult
Schizophrenia

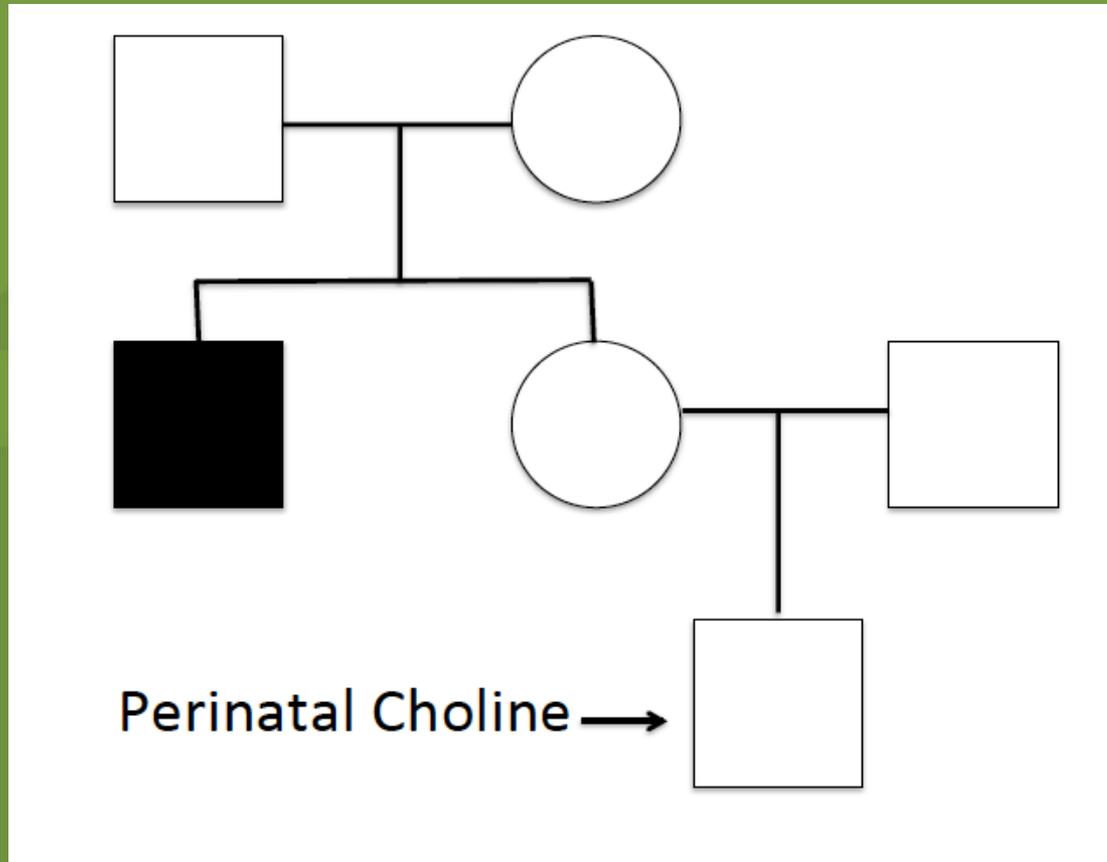
Am J Psychiatry 2016; 173:509–516



Folic acid is an example of a nutrient that prevents the developmental abnormality cleft palate before birth (Wilcox 2007)



Like folic acid, choline is effective only before birth; you cannot wait until later when you are already ill.

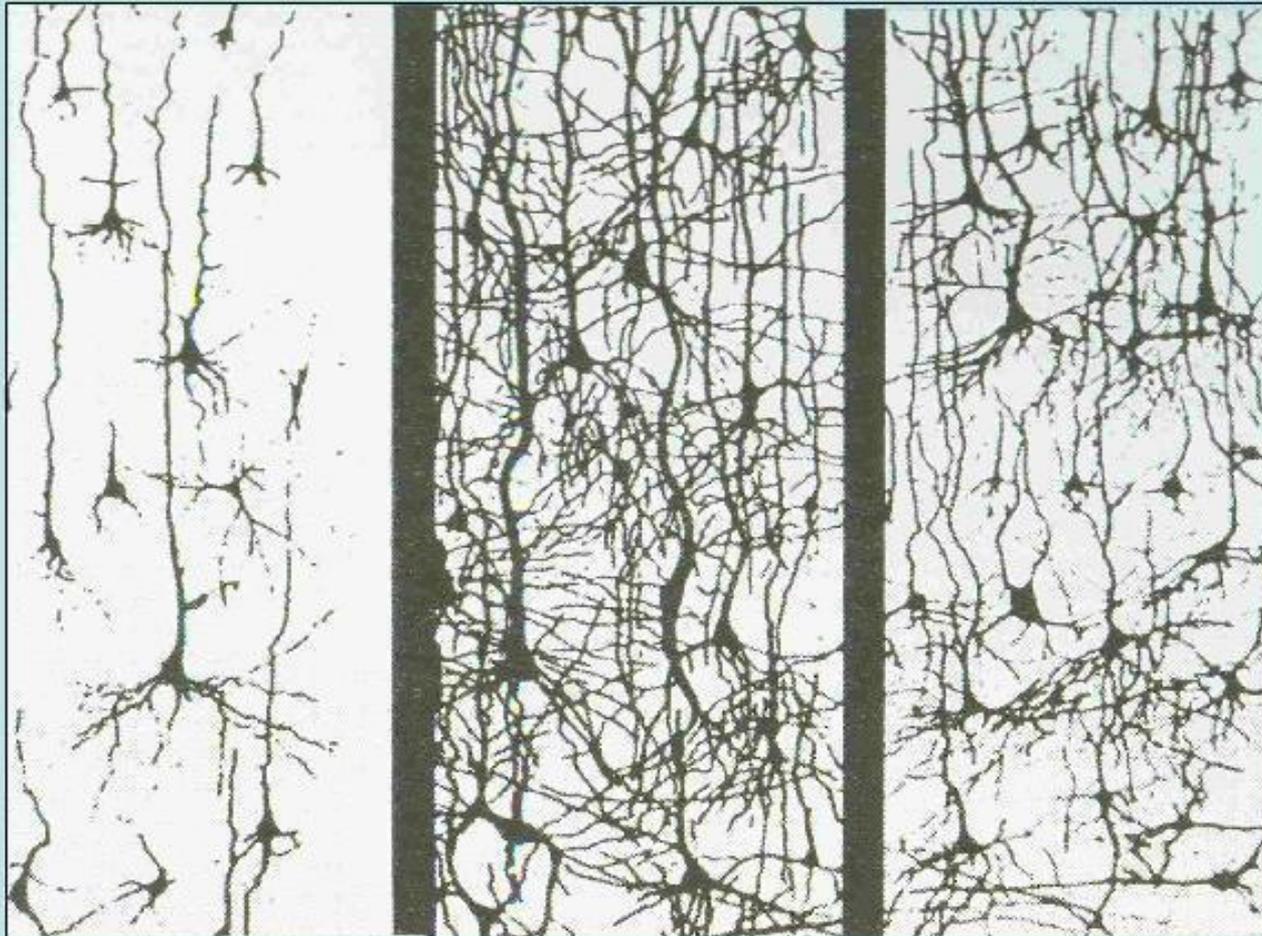


Synaptic Density

At birth

6 years old

14 years old



Source: Rethinking the Brain, Families and Work Institute, Rima Shore, 1997; Founders Network slide

Fetal life is only Step 1 in brain development. Each step is part of the risk for future mental illness.



Better treatment for schizophrenia now and in the future

- Now: Maximize support services in the community, try clozapine before switching to newer drugs (it's more effective), and avoid marijuana (easier said than done).
- In the future: Interventions from before birth to prevent the illness.

