First Episode Psychosis: Assessing and Treating

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Objectives

- Provide an overview of the many divergent risk factors that may individually or collectively synergize to unleash an individual's first psychotic episode, with a focus on those episodes that will progress to schizophrenia.
- Review the comprehensive differential diagnoses of the many possible etiologies to a first psychotic episode.
- Discuss the treatment options that exist, and how determining the primary etiology to the psychotic episode will significantly inform treatment planning.
- Explore likely future prognostic variations, depending again on the cause of the first psychotic episode.

Historical Overview

Historical Descriptions of Psychosis

- Ancient Mesopotamia
- Ancient India
- Ancient Greece
- Ancient Rome
- The Middle Ages
- 16th Century Europe

Walker, et al.; Schizophrenia: Etiology and Course;
Annu. Rev. Psychol. 55: 401-430 (2004).

Late 19th Century Europe

Most common etiology of psychosis was tertiary syphilis

Walker, et al.; Schizophrenia: Etiology and Course; *Annu. Rev. Psychol.* 55: 401-430 (2004).

Emil Kraepelin (1856-1926)

- Differentiated bipolar psychosis from schizophrenia
- Called schizophrenia "dementia praecox" (dementia of the young)

Walker, et al.; Schizophrenia: Etiology and Course; *Annu. Rev. Psychol.* 55: 401-430 (2004).

Eugen Bleuler (1857-1939)

- Coined the term "schizophrenia"
- Derived from two Greek words:
  - "schizo" = "to tear" or "to split"
  - "phren" = "the intellect" or "the mind"

Walker, et al.; Schizophrenia: Etiology and Course; *Annu. Rev. Psychol.* 55: 401-430 (2004).

Etiology of Schizophrenia

Sigmund Freud

- "Sigmund Freud himself was wary of treating psychotic patients, believing them to be beyond his methods, though he did hazard a wild guess that paranoid schizophrenia was the result of suppressed homosexual impulses."

Ridley, M. The Agile Gene. Chapter 4: The madness of causes. HarperCollins Publishers Inc. (2003).

Schizophrenogenic mother

In 1935, a refugee analyst from Germany, Frieda Fromm-Reichmann, arrived at Chestnut Lodge in Rockville, Maryland. She wrote in 1948:

"The schizophrenic is painfully distrustful and resentful of other people due to the severe early warp and rejection he encountered in important people of his infancy and childhood, as a rule, mainly in a schizophrenogenic mother."

Fromm-Reichmann, F. 1948. Notes on the development of treatment of schizophrenics by psychoanalytic psychotherapy. *Psychiatry* 11:263:73.

Schizophrenogenic father

Age of father as a risk factor for schizophrenia

Recent Swedish record-linkage studies were reviewed.

Over 700,000 subjects born between 1973 and 1980 were followed from birth to 2002.

In fully adjusted analyses, the risk of schizophrenia in offspring was 4.62 times higher when fathers were >/=50 years old at time of conception compared to fathers that were 21-24 years old.

De novo mutations in the germ cells of older fathers may play a causal role in the etiology of some cases of schizophrenia.

Rasmussen F; Paternal age, size at birth, and size in young adulthood - risk factors for schizophrenia. *Eur J Endocrinol.* 155 Suppl 1:S65-9; 2006.

Strong genetic component

Quantitative genetic techniques with large twin samples have demonstrated a significant overlap in the genes that contribute to schizophrenia, schizoaffective disorder, and bipolar disorder.

Genetic vulnerability seems to be towards psychosis as a general inherited phenomena, with other inherited and acquired factors directing this vulnerability towards schizophrenia or affective psychosis.

Walker, et al.; Schizophrenia: Etiology and Course; *Annu. Rev. Psychol.* 55: 401-430 (2004).

Genetic risk

- No relative = 1%
- First cousin = 2%
- Aunt/Uncle or ½ sibling = 6%
- Full sibling = 9%
- Non-identical twin = 16%
- Both parents = 40%
- Identical twin = 50%

Over 100 different genes are currently believed to contribute to the risk of schizophrenia. Current research has identified almost a gene on each of our 23 chromosomes.

Could the increased risk be from "nurture"?
In individual's with schizophrenia that are adopted at birth:

Biological relatives are 10Xs more likely to have schizophrenia than their adoptive families.

Kety, S.S. & Ingraham, L.J. Genetic transmission and improved diagnosis of schizophrenia from pedigrees of adoptees. *J. Psychiatric Research*. 26:247-55 (1992).

Neurotransmitter dysfunction

Chlorpromazine, shown to block the dopamine-2 receptor, was widely used in 1955 as the first drug to treat psychotic symptoms. This led to the Dopamine hypothesis of psychosis.

There are (5) five dopamine receptor families:

Dopamine receptors 1 and 5 are structurally similar.

Dopamine receptors 2, 3 and 4 are structurally similar.

All effective antipsychotics block dopamine 2 (D-2) receptors.

Clozapine, our "gold standard" binds tightest at D-4.

Recent interest in D-3 agonism for reward and as antidepressant.

Neurotransmitter dysfunction

Glutamate has emerged as an important neurotransmitter in understanding psychosis. NMDA-glutamate antagonists induce both positive and negative schizophrenia-like symptoms in animal models:

Ketamine
Phencyclidine (PCP).

Serotonin is a complex and ubiquitous neurotransmitter system in the brain that includes 7 serotonin receptor families, and receptor sub-families totaling over 20.

The serotonin 5HT-2A receptor is agonized by hallucinogens:
LSD, psilocybin, and mescaline.

Infections *in utero*

- Influenza virus
- Herpes virus
- Protozoan toxoplasmosis (cat scratch fever)
  – Toxoplasma can cross the placenta and cause blindness and intellectual impairment in the fetus.

Walker, et al.; Schizophrenia: Etiology and Course;
Annu. Rev. Psychol. 55: 401-430 (2004).

Influenza viral infection in utero

More individuals with schizophrenia are born in the winter than summer.

True in both the northern and southern hemisphere.

Sarnoff Mednick reviewed medical records in Helsinki Mental Hospital. He found an increased risk of schizophrenia in the children of women who had an Influenza infection during pregnancy, especially in the second trimester.

Mednick, S.A., Machon, R.A., Huttunen, M.O. and Bonett, D.; Adult schizophrenia following prenatal exposure to an influenza epidemic. *Archives of General Psychiatry*. 45:189-92 (1988).

Munk-Jorgensen, P. and Ewald, H. Epidemiology in neurobiological Research: Exemplified by the influenza-schizophrenia theory. *British Journal of Psychiatry*. 178 (supplement 40): s30-s32.) (2001).

Obstetrical complications

Severe maternal malnutrition.

Abnormal maternal thyroid functioning.

Labor and deliver complications.

Hypoxic insults during delivery.

Preeclampsia causing fetal hypoxia increases the risk of schizophrenia 9X.

Significant events from birth to the onset of the first psychotic episode

Postnatal brain insults (head injury)

History of significant trauma

Environmental toxins

Brain infections

Substance abuse

Symptoms predating first psychotic episode

Retrospective review of individuals who developed schizophrenia revealed a history of :

Anxiety

Slow to walk

Poor at verbal comprehension

Cannon, M., Caspi, A., Moffitt, T.E., et al. Evidence for early childhood, pan-developmental impairment specific to schizophreniform disorder: Results from a longitudinal birth cohort. *Archives of General Psychiatry.* 59:449-56 (2002).

Heavy cannabis use:
a well established risk factor for psychosis

Onset of psychosis 2.7 years earlier in cannabis users compared to non-users.

Onset of psychosis NOT significantly earlier in alcohol users compared to non-users (earlier by 0.3 years).

One third of patients that develop first episode psychosis are cannabis users.

Andrade C; Cannabis and Neuropsychiatry, 2: The Longitudinal Risk of Psychosis as an Adverse Outcome. *J Clin Psychiatry*. 77(6):e739-e742. 2016

Heavy cannabis use:
a well established risk factor for psychosis

Increasing cannabis use increases risk of psychosis:

Ten studies showed a dose-dependent increase in the risk of developing psychosis.

Median level of cannabis use doubled the risk of psychosis (OR = 1.97).

Cannabis users in top 20% of amount used increased risk 3.4 times.

Highest level cannabis users increased risk 3.9 times.

Andrade C; Cannabis and Neuropsychiatry, 2: The Longitudinal Risk of Psychosis as an Adverse Outcome. *J Clin Psychiatry*. 77(6):e739-e742. 2016

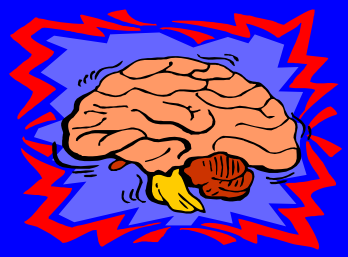
Neurodevelopmental Model:
Schizophrenia as a disease of the Fourth Dimension = time.

Daniel Weinberger in 1987:
The cause of schizophrenia is no longer present when the symptoms appear.

Neuroplasticity of the brain:
3 stages of extensive pruning (ages 2, 12 and 22)
This pruning may unmask symptoms.

One clue: Complement Component 4 gene mutations

The Wiring of the Brain



- **There are approximately 100 billion neurons in the human brain**
- **There are from 1,000 to 10,000 synapses/neuron**
- **Hence, there are up to 1,000 trillion synapses in the human brain – *an amazing quadrillion synapses!!***

Schizophrenia risk from complex variation of complement component 4

Researchers at Harvard Medical School in Boston, MA identified a gene that may explain neurodevelopmental brain changes in adolescents that for some individuals may lead to schizophrenia. The complement component 4 (C4) gene codes for proteins that "tag" neurons for synaptic pruning. Variations in the sequence of this C4 gene may "tag" the wrong neuronal synapses for pruning during brain development (which continues until age 25), resulting in the removal of critical pathways that may increase the vulnerability of developing schizophrenia.

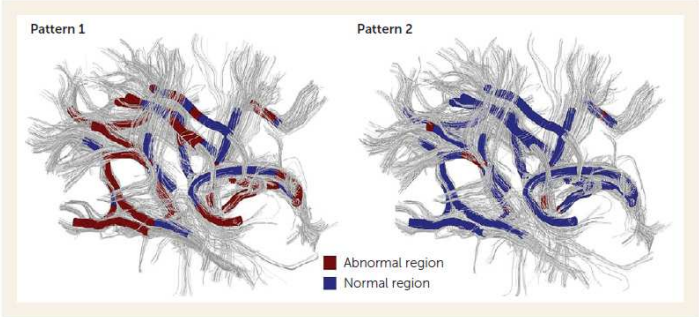
Sekar, A., Bialas, A., Rivera, H., Davis, A., et al. Schizophrenia risk from complex variation of complement component 4. *Nature*. Published online January 27, 2016.

Environmental Stressors

- Stressful events can increase propensity of psychotic episodes.
- Stress reducing intervention programs improve course of illness, and may delay onset of first episode psychosis.
- Stress exposure impacts brain function:
  - Activation of HPA axis releases cortisol from the adrenal gland.
  - Cortisol can alter neurotransmitter activity.
  - Chronic elevation of cortisol reduces hippocampal volume, and is linked with more severe symptoms and cognitive deficits in schizophrenia.

Brain scans of individuals dx with schizophrenia

FIGURE 3. Two Different Patterns of White Matter Deficits in 113 Drug-Naive First-Episode Schizophrenia Patients, Identified by Diffusion Tensor Imaging With a Fully Data-Driven Method[a]

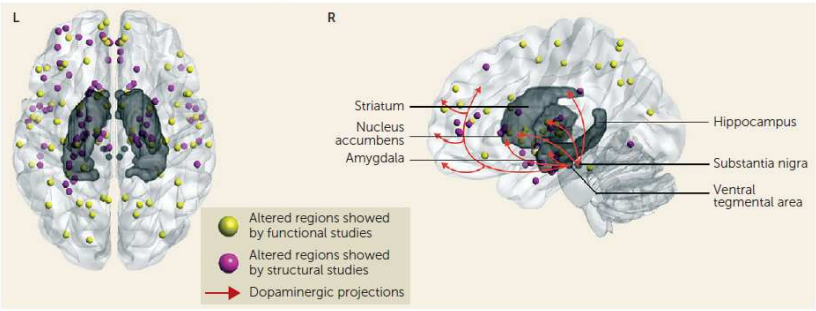


[a] The red regions are tracts with significantly decreased fractional anisotropy and increased mean diffusivity, and the blue regions indicate normal tracts. The existence of the two different patterns of white matter deficits in first-episode schizophrenia suggests qualitatively distinct genetic influences or neurodevelopmental alterations and may explain the inconsistent findings among studies. This is one step forward in the use of such measures to identify and classify patient subgroups based on neurobiological parameters rather than symptoms and clinical history. (Adapted from reference 27. Copyright 2015 American Medical Association. All rights reserved.)

Gong Q, Lui S, Sweeney JA. A Selective Review of Cerebral Abnormalities in Patients With First-Episode Schizophrenia Before and After Treatment. ***Am J Psychiatry.*** **173:232–243; 2016.**

Brain scans of individuals dx with schizophrenia

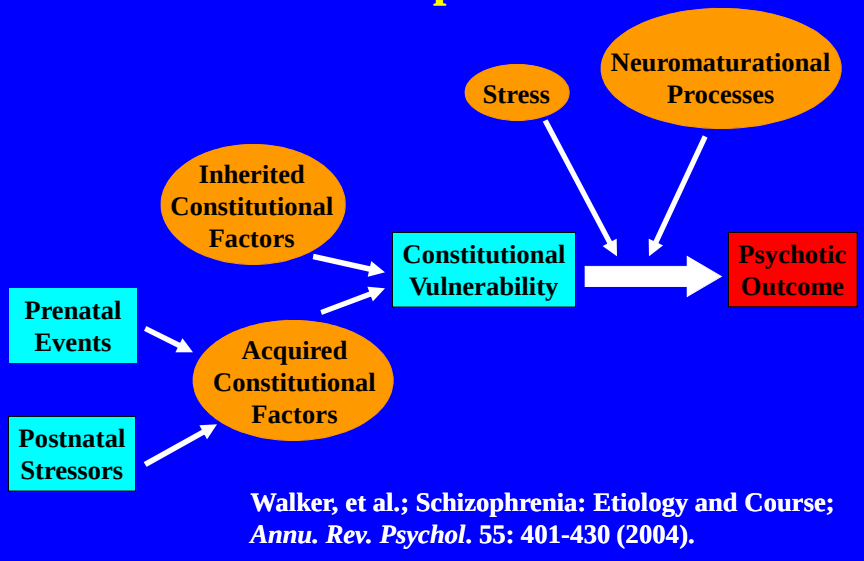
FIGURE 1. Altered Brain Regions Demonstrated by Structural and Functional MRI Studies of First-Episode Schizophrenia Before Treatment and Innervation of Brain Regions by Dopaminergic Projections[a]



[a] The color-coded nodes represent the coordinates of the altered gray matter volume reported by structural studies and of the altered function reported by functional studies (the studies are listed in Table S1 in the online data supplement).

Gong Q, Lui S, Sweeney JA. A Selective Review of Cerebral Abnormalities in Patients With First-Episode Schizophrenia Before and After Treatment. ***Am J Psychiatry.*** **173:232–243; 2016.**

Diathesis-Stress Model of the etiology of schizophrenia



Walker, et al.; Schizophrenia: Etiology and Course; *Annu. Rev. Psychol.* 55: 401-430 (2004).

Evaluation of a First Psychotic Episode

Initial Evaluation

- Medical, neurological, psychiatric and substance abuse history
- Comprehensive mental status exam
- Heart rate, BP and temperature
- Body weight, height and Body Mass Index (BMI)
- Routine laboratory testing (next slide)
- ECG
- Brain MRI (preferred) or Brain CT
- EEG
- Heavy metal toxicology

Practice Guidelines for the Treatment of Patients with Schizophrenia; Second Edition; Am J Psychiatry; Volume 161, Number 2; February 2004 Supplement.

Initial Evaluation (continued) Laboratory testing

- Toxicology screen (urine and +/- blood)
- Complete blood count
- Serum electrolytes
- Serum glucose, cholesterol and triglycerides
- Liver, renal and thyroid function
- Pregnancy test
- Prolactin level
- Syphilis test, Lyme Disease test
- HIV status, Hepatitis C screen

Practice Guidelines for the Treatment of Patients with Schizophrenia; Second Edition; Am J Psychiatry; Volume 161, Number 2; February 2004 Supplement.

Differential Diagnoses of First Episode Psychosis

- **Medical etiologies:**
  - **Brain tumors**
  - **Head trauma**
  - **Multiple sclerosis**
  - **Huntington's disease**
  - **Wilson's disease**
  - **NMDA-receptor autoimmune encephalitis**
  - **Lyme disease (Borrelia burgdorferi)**
  - **Tertiary syphilis**
  - **Seizures**

Lieberman JA, Stroup TS & Perkins DO, Essentials of Schizophrenia, American Psychiatric Publishing, Inc. 2012. And others.

NMDA-receptor autoimmune encephalitis

In 2009 in NYC a young New York Post journalist developed the abrupt onset of symptoms that included manic, psychotic, delusional, and paraniod symptoms. After significant rapidly progressive deterioration she was ultimately diagnosed as the 217th person ever diagnosed with anti-NMDA - glutamate receptor autoimmune encephalitis.

She rapidly recovered after aggressive treatment with :

steroids
plasmapheresis
IVIG (intravenous immunoglobulin)

Cahalan S. Brain On Fire: My Month of Madness. Simon & Schuster . 2012.

NMDA-receptor autoimmune encephalitis

Fortunately, her treating neurologist had read a paper by neuro-oncologist Dr. Josep Dalmau at the University of PA that had been published in the Annals of Neurology in 2005.

In this publication, Dr. Dalmau described for the first time a rare condition called Glutamate NMDA-receptor autoimmune encephalitis, which mimics common serious psychiatric diagnoses, including mania and psychosis. He described four young woman who developed prominent psychiatric symptoms and encephalitis. Symptoms included hallucinations, delusions, and confusion. All 4 also had teratomas in their ovaries (not always present). All 4 had the exact same antibodies, which attacked the glutamate NMDA-receptors in their brains, especially their hippocampus.

Cahalan S. Brain On Fire: My Month of Madness. Simon & Schuster . 2012.

Differential Diagnoses of First Episode Psychosis

- **Medication side effect:**
  - L-dopa (and other anti-parkinson's disease medications)
  - Amantadine
  - Psychostimulants (methylphenidate, amphetamine)
  - Anticholinergic medications
  - Corticosteroids
  - Ketamine
  - Medication overdose
  - Medication toxicity due to drug-drug interactions
  - Rare side effect of many prescription drugs

Lieberman JA, Stroup TS & Perkins DO, Essentials of Schizophrenia, American Psychiatric Publishing, Inc. 2012. And others.

Differential Diagnoses of First Episode Psychosis

- Substance induced psychosis – can be from drug intoxication or withdrawal:
  - Hallucinogens (LSD, psilocybin, and mescaline)
  - Stimulants (cocaine, methamphetamine)
  - PCP and ketamine
  - Heavy cannabis abuse
  - Alcohol withdrawal delirium
  - Sedative/hypnotic withdrawal
  - Bath salts
  - Spice, K2 and other synthetic cannabinoids
  - Inhalent abuse

Lieberman JA, Stroup TS & Perkins DO, Essentials of Schizophrenia, American Psychiatric Publishing, Inc. 2012. And others.

Differential Diagnoses of First Episode Psychosis

- Psychiatric Disorders:
  - Brief Psychotic Disorder
  - Schizophreniform Disorder
  - Schizophrenia
  - Delusional Disorder
  - Schizoaffective Disorder
  - Psychosis in Major Depression
  - Psychosis in Bipolar I Disorder

DSM-5, American Psychiatric Association, 2013.

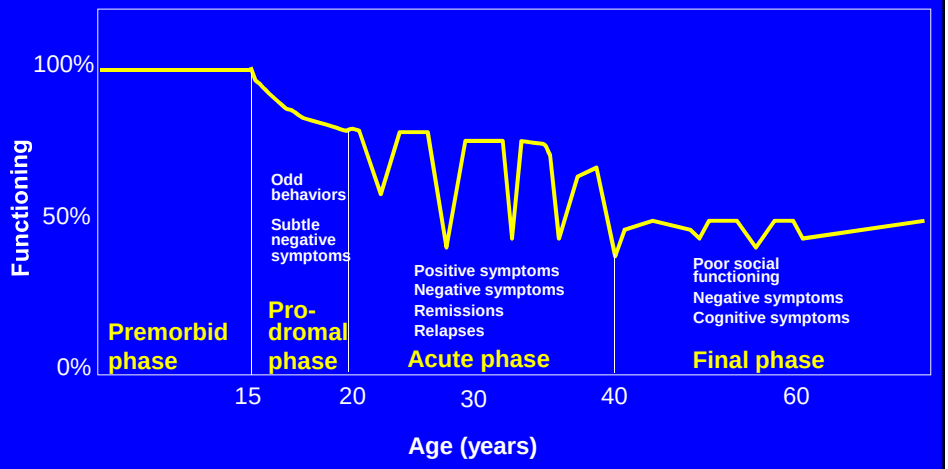
Diagnosis of Schizophrenia

Epidemiology of schizophrenia

- Schizophrenia affects an estimated 1% of the population
- Onset usually occurs between the late teens and late 20s
  - Median age of onset = 23 years in men & 28 years in women
- 1.4 times more common in males than females.
- Onset can be acute (weeks) or insidious.
- Urban birth/residence versus nonurban populations:
  - 1.9-fold increased risk in males
  - 1.3-fold increased risk in females

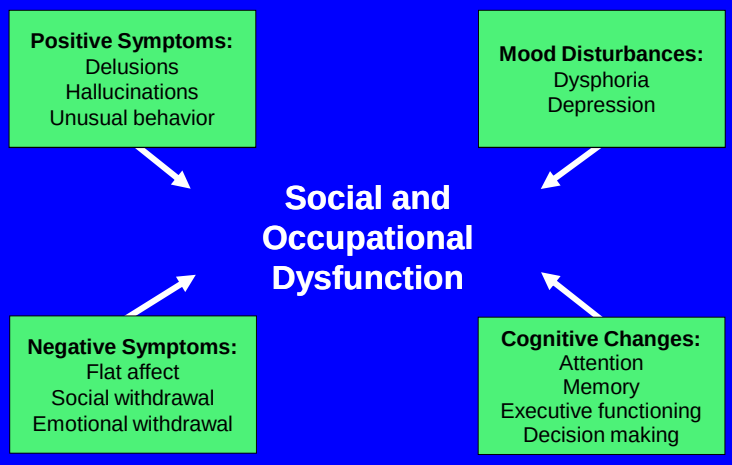
Lieberman JA, Stroup TS & Perkins DO, Essentials of Schizophrenia, American Psychiatric Publishing, Inc. 2012.

Course of illness in schizophrenia



Black DW et al. *Introductory Textbook of Psychiatry.* 2001;204-228.

Symptoms of schizophrenia



Black DW et al. *Introductory Textbook of Psychiatry.* 2001;204-228.
Siris SG. *Schizophrenia.* 1995;128-145.
Harvey PD et al. *Am J Psych.* 2001;158:176-184.
Stahl SM. *Essential Psychopharmacology.* 2nd ed. 2000;385-386.

DSM-5 diagnostic criteria for schizophrenia (295.90) F20.9

Diagnostic Criteria:

A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2), or (3):

1. Delusions.
2. Hallucinations.
3. Disorganized speech (e.g., frequent derailment or incoherence).
4. Grossly disorganized or catatonic behavior.
5. Negative symptoms (i.e., diminished emotional expression or avolition).

DSM-5, American Psychiatric Association, 2013.

DSM-5 diagnostic criteria for schizophrenia (295.90) F20.9

Diagnostic Criteria:

B. For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).

DSM-5, American Psychiatric Association, 2013.

DSM-5 diagnostic criteria for schizophrenia (295.90) F20.9

Diagnostic Criteria:

C. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

DSM-5, American Psychiatric Association, 2013.

DSM-5 diagnostic criteria for schizophrenia (295.90) F20.9

Diagnostic Criteria:

D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either 1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or 2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.

DSM-5, American Psychiatric Association, 2013.

DSM-5 diagnostic criteria for schizophrenia (295.90) F20.9

Diagnostic Criteria:

E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

F. If there is a history of autism spectrum disorder or communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to other required symptoms of schizophrenia, are also present for at least one month (or less if successfully treated).

DSM-5, American Psychiatric Association, 2013.

Cognitive symptoms of schizophrenia

- Thought disorder
- Odd use of language
  - incoherence
  - loose associations
  - neologisms
- Impaired attention and information processing
- Inability to produce spontaneous speech
- Problems with serial learning
- Impaired executive functioning

Harvey PD et al. *Am J Psychiatry*. 2001;158:176-184.
Stahl SM. *Essential Psychopharmacology*. 2nd ed. 2000;385-386.

Treatment of Schizophrenia

Issues in treating schizophrenia

- Schizophrenia is progressive and chronic, with frequent exacerbations
  - requires lifelong drug therapy
- Estimated noncompliance rates of 50% are common among patients within 1 year of discharge
- High relapse rate
  - up to 50% of those who relapse are noncompliant
- Up to 50% of patients with schizophrenia meet criteria for alcohol abuse
- Approximately 50% of patients attempt suicide at least once
  - 5%-10% commit suicide

Kaplan HI et al. *Kaplan and Sadock's Synopsis of Psychiatry*. 7th ed.1994.
Black DW et al. *Introductory Textbook of Psychiatry*. 2001;204-228.
Kane JM. *J Clin Psychopharmacol*. 1985;22S-27S.
Weiden PJ et al. *J Prac Psychol Behav Health*. 1997;106-109.

Clinical features associated with a poor prognosis

Poor premorbid social and school functioning

Insidious onset

Earlier age at onset

Prominent negative symptoms

More severe cognitive impairments

Male sex

Lieberman JA, Stroup TS & Perkins DO; Essentials of Schizophrenia, American Psychiatric Publishing, Inc. Page 5; 2012.

Current Ideal Treatment of schizophrenia

- Medication
- Psychosocial interventions
  - Family therapy
  - Social skills training
  - Psycho-education
  - Vocational training
  - Cognitive Behavioral Therapy
  - Stress management
- Community support
  - Assertive Community Treatment (ACT) - multidisciplinary team = nurse, case manager, general physician and psychiatrist

RAISE

Recovery After an Initial Schizophrenia Episode

- Began in 2009 by the NIMH.
- 100,000 adolescents and young adults in the USA have a First Psychotic Episode (FEP) every year.
- Peak onset between ages 15 – 25.
- Research has shown that comprehensive early intervention for FEP improves symptoms and functioning superior to the usual standard care models.

Heinssen RK, Goldstein AB and Azrin ST; Evidence-Based Treatments for First Episode Psychosis: Components of Coordinated Specialty Care. RAISE Monograph. April 14, 2014

RAISE

Recovery After an Initial Schizophrenia Episode

- Delivered in specialized early intervention programs.
- Two year period of intensive recovery-oriented services.
- Best outcomes with intervention early after onset of first episode psychosis.
- Four pillars of treatment:
  - Antipsychotic medication.
  - Cognitive Behavioral Therapy.
  - Family education and support.
  - Educational and vocational rehabilitation.

Heinssen RK, Goldstein AB and Azrin ST; Evidence-Based Treatments for First Episode Psychosis: Components of Coordinated Specialty Care. RAISE Monograph. April 14, 2014

Comprehensive Versus Usual Community Care for First-Episode Psychosis: 2-Year Outcomes From the NIMH RAISE Early Treatment Program

Objective: The primary aim of this study was to compare the impact of NAVIGATE, a comprehensive, multidisciplinary, team-based treatment approach for first-episode psychosis designed for implementation in the U.S. health care system, with community care on quality of life.

Method: Thirty-four clinics in 21 states were randomly assigned to NAVIGATE or community care. Diagnosis, duration of untreated psychosis, and clinical outcomes were assessed via live, two-way video by remote, centralized raters masked to study design and treatment. Participants (mean age, 23) with schizophrenia and related disorders and ≤6 months of antipsychotic treatment (N=404) were enrolled and followed for ≥2 years. The primary outcome was the total score of the Heinrichs-Carpenter Quality of Life Scale, a measure that includes sense of purpose, motivation, emotional and social interactions, role functioning, and engagement in regular activities.

Results: The 223 recipients of NAVIGATE remained in treatment longer, experienced greater improvement in quality of life and psychopathology, and experienced greater involvement in work and school compared with 181 participants in community care. The median duration of untreated psychosis was 74 weeks. NAVIGATE participants with duration of untreated psychosis of <74 weeks had greater improvement in quality of life and psychopathology compared with those with longer duration of untreated psychosis and those in community care. Rates of hospitalization were relatively low compared with other first-episode psychosis clinical trials and did not differ between groups.

Conclusions: Comprehensive care for first-episode psychosis can be implemented in U.S. community clinics and improves functional and clinical outcomes. Effects are more pronounced for those with shorter duration of untreated psychosis.

Am J Psychiatry 2016; 173:362–372; doi: 10.1176/appi.ajp.2015.15050632

Kane JM, Robinson DG, Schooler NR, et al. Comprehensive Versus Usual Community Care for First-Episode Psychosis: 2-Year Outcomes From the NIMH RAISE Early Treatment Program. Am J Psychiatry. 173:362-372; 2016.

Criteria to enter study

- **DSM-IV diagnoses of schizophrenia, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder or psychotic disorder NOS.**
- **Subjects took <= 6 months of lifetime antipsychotic medication.**
- **Intervention = NAVIGATE: personalized medication management, family psychoeducation, resilience-focused individual therapy, and supported employment and education.**
- **Treatment was provided approximately 5 hours/week.**
- **Weekly team meetings.**

Kane JM, Robinson DG, Schooler NR, et al. Comprehensive Versus Usual Community Care for First-Episode Psychosis: 2-Year Outcomes From the NIMH RAISE Early Treatment Program. Am J Psychiatry. 173:362-372; 2016.

Additional study details

- NAVIGATE group = 223 patients.
- Community care as usual = 181 patients.
- Median duration of untreated psychosis = 74 weeks.
- 71% of patients lived with their families.
- NAVIGATE participants remained in treatment a median of 23 months
- Community care as usual remained in treatment a median of 17 months.

Kane JM, Robinson DG, Schooler NR, et al. Comprehensive Versus Usual Community Care for First-Episode Psychosis: 2-Year Outcomes From the NIMH RAISE Early Treatment Program. Am J Psychiatry. 173:362-372; 2016.

Results

"NAVIGATE improved outcomes for patients over 24 months, with effects seen in length of time in treatment, quality of life, participation in work and school, and symptoms. These are outcomes of importance to service users, family members, and clinicians."

"There was a substantial difference in effect sizes comparing the change between treatments for participants with a duration of untreated psychosis of <=74 weeks and those with a duration of untreated psychosis of >74 weeks: 0.54 compared with 0.07 for Quality of Life Scale, and 0.42 compared with 0.13 for PANSS scores, respectively."

Kane JM, Robinson DG, Schooler NR, et al. Comprehensive Versus Usual Community Care for First-Episode Psychosis: 2-Year Outcomes From the NIMH RAISE Early Treatment Program. Am J Psychiatry. 173:362-372; 2016.

Choice of medication in acute phase schizophrenia

- First line treatment
  - Many antipsychotics classified as first, second or third generation drugs depending on the mechanism of action.
- Treatment failure of at least 2 adequate trials of first line treatments. AND/OR Persistent suicidal ideation/behavior, or persistent hostility and aggressive behavior
  - clozapine
- Repeated non-adherence to pharmacological treatment
  - Long-acting injectable antipsychotics: many.

Practice Guidelines for the Treatment of Patients with Schizophrenia; Second Edition; Am J Psychiatry; Volume 161, Number 2; February 2004 Supplement.

Considerations in acute non-response

- Medication non-adherence
- Rapid medication metabolism
- Re-institution or increase in cigarette smoking (clozapine and olanzapine)
- Poor absorption
- Check plasma concentration 12 hour trough for clozapine and haloperidol (serum levels available for most antipsychotics).

Practice Guidelines for the Treatment of Patients with Schizophrenia; Second Edition; Am J Psychiatry; Volume 161, Number 2; February 2004 Supplement.

Common contributors to symptom relapse: acute and long-term

- Non-adherence to antipsychotic medication
  - Side effects
  - Denial of illness
  - Lack of resources
- Substance abuse
- Stressful life events
- Natural course of illness
- Lack of psychosocial interventions

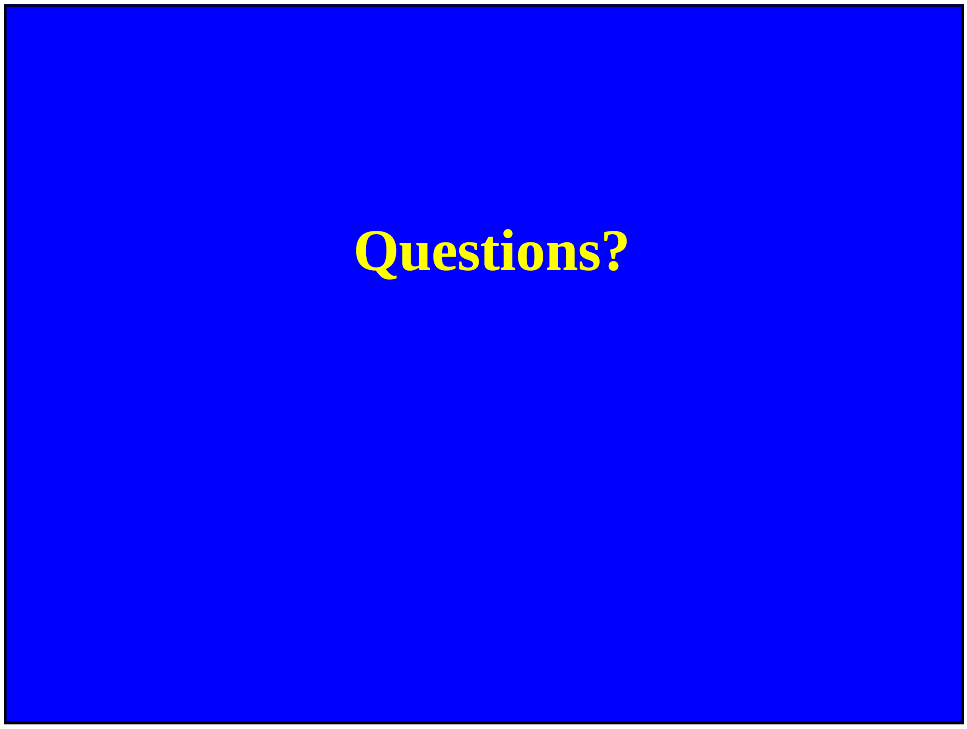
Practice Guidelines for the Treatment of Patients with Schizophrenia; Second Edition; Am J Psychiatry; Volume 161, Number 2; February 2004 Supplement.

Long-term treatment

- "Indefinite maintenance antipsychotic medication is recommended for patients who have had multiple prior psychotic episodes or two episodes within 5 years."

- Psychosocial treatments
  - Family intervention
  - Supported employment
  - Assertive community treatment
  - Skills training (social skills and stress management)
  - Cognitive behavior therapy
  - Psycho-education

Practice Guidelines for the Treatment of Patients with Schizophrenia; Second Edition; Am J Psychiatry; Volume 161, Number 2; February 2004 Supplement.


Questions?