Schizophrenia: A Lifelong Illness

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Objectives

- Appreciate the historical perspectives of schizophrenia
- Describe our current understanding of the etiology of schizophrenia
- Understand the current DSM-IV criteria for the diagnosis of schizophrenia
- Discuss the common co-morbidities of schizophrenia
- Review the basic treatment strategies for schizophrenia

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. 2004; 55: 401-430

Late 19th Century Europe

Most common etiology of psychosis was tertiary syphilis

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

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. 2004; 55: 401-430

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. 2004; 55: 401-430

Etiology of Schizophrenia

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 mania

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. 2004; 55: 401-430

Prenatal and Postnatal Factors

- Obstetrical complications
  - Toxemia and pre-eclampsia
  - Labor and deliver complications
- Maternal infection
- Maternal prenatal stress
  - Maternal stress hormones can disturb fetal neurodevelopment and fetal H-P-A axis
- Postnatal brain insults (head injury)

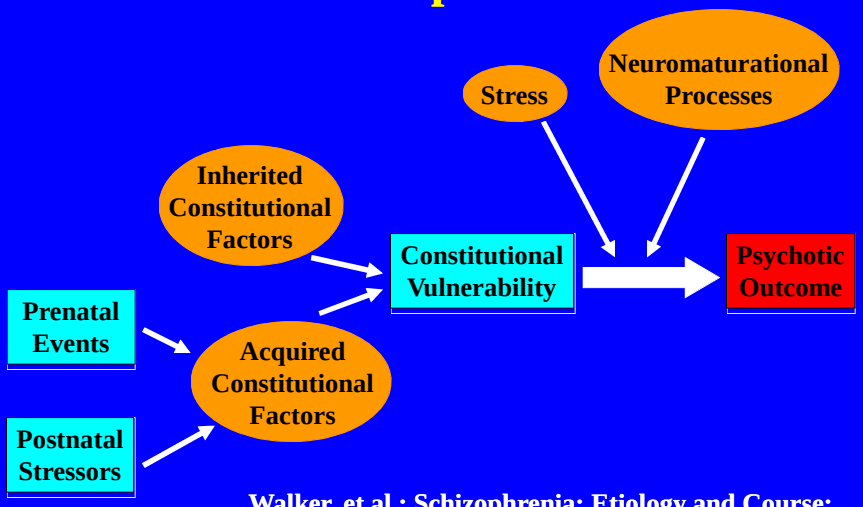
Walker, et al.; Schizophrenia: Etiology and Course; Annu. Rev. Psychol. 2004; 55: 401-430

Environmental Stressors

- Stressful events can worsen its course
- Stress reducing intervention programs improve course of illness
- 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

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

Diathesis-Stress Model of the etiology of schizophrenia



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

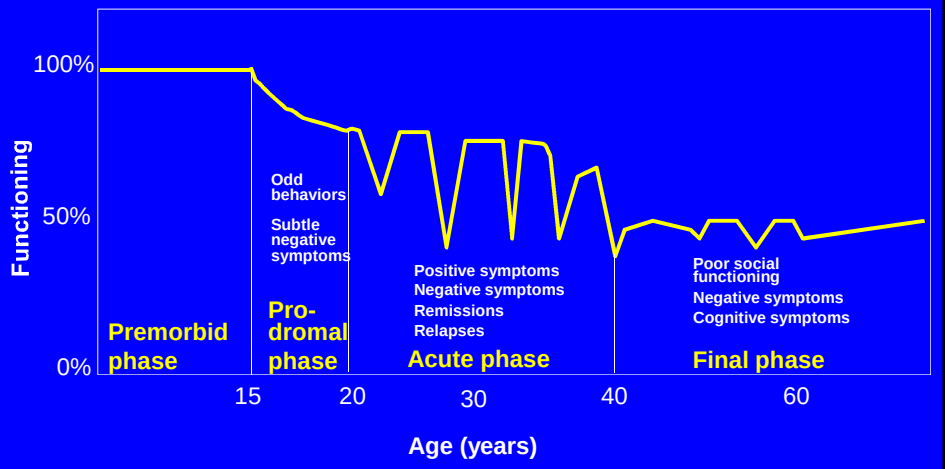
Diagnosis of Schizophrenia

Epidemiology of schizophrenia

- Schizophrenia affects an estimated 1% of the population
- Onset usually occurs between the early and late 20s
- Gender and race distribution are approximately equal
- High concentration in urban areas among lower socioeconomic populations

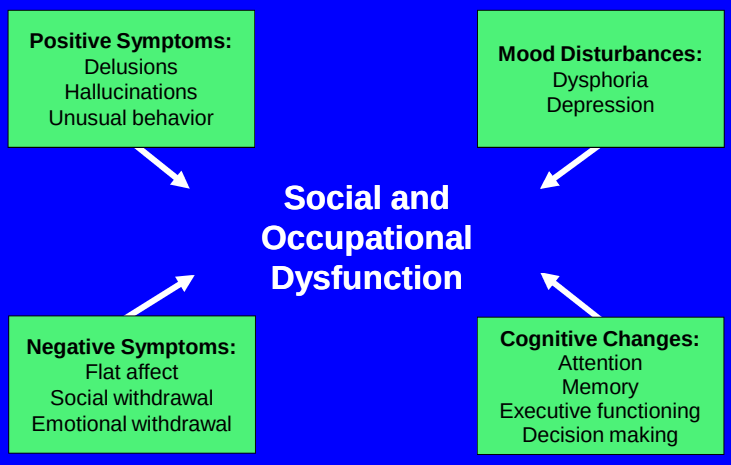
DSM-IV, 1994.
Kaplan HI et al. *Kaplan and Sadock's Synopsis of Psychiatry*. 7th ed.1994.

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-IV diagnostic criteria for schizophrenia

- Characteristic symptoms
  - 2 or more of the symptoms of schizophrenia: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, or negative symptoms
- Social/occupation dysfunction
  - dysfunction in 1 or more areas of functioning (such as work, interpersonal relations, or self-care) falls markedly below the level achieved prior to onset
- Duration
  - continuous signs of the illness persist for at least 6 months
- Schizoaffective and mood disorder exclusion
- Substance/general medical condition exclusion
- Prominent delusions or hallucinations present for at least 1 month in the presence of comorbid autistic disorder or other developmental disorders

DSM-IV,1994;273-315.

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.

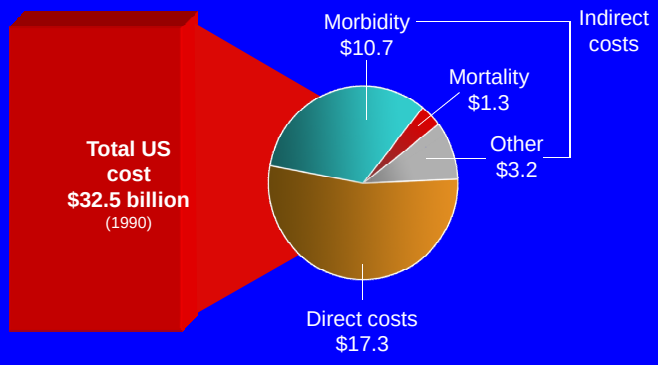
Issues in treating schizophrenia

- 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
  - 10%-15% 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.

Costs associated with schizophrenia

- One of the highest causes of disability in the world
- The most expensive psychiatric disorder to treat, despite its relatively low prevalence



Rice DP. *J Clin Psychiatry*. 1999;60(suppl 1):4-6.

Comorbidity in Schizophrenia

Psychiatric and medical comorbidities in schizophrenia

- High rates of psychiatric comorbidity
  - depression (approximately 25%)
  - suicidality (approximately 50%)
  - substance abuse (eg, alcohol, drugs) (up to 50%)
- High rates of medical comorbidity
  - underdiagnosis of physical illness
  - increased mortality
  - high lifetime rates of high blood pressure (34%), diabetes (15%), STDs (10%)

Kaplan HI et al. *Kaplan and Sadock's Synopsis of Psychiatry*. 7th ed.1994.
Siris SG. *Schizophrenia*. 1995;128-145.
Kane JM. *J Clin Psychopharmacol*. 1985;22S-27S.
Dixon L et al. *J Nerv Ment Dis*. 1990;490-502.

Mortality associated with schizophrenia

- High mortality rates in schizophrenia
  - 1.6 times higher all-cause mortality risk
  - 4.3 times higher risk from unnatural causes (eg, suicide, accidental death)
  - 1.4 times higher risk from natural causes (in particular from cardiovascular, infectious, respiratory, and endocrine disorders)
- Overall life expectancy is 20% shorter than that of the general population.

Dixon L et al. *J Nerv Ment Dis*. 1990;490-502.
Harris EC et al. *Br J Psychiatry*. 1998;11-43.
Newman SC et al. *Can J Psychiatry*. 1991;36:239-245.

Cardiovascular health status and mortality rates associated with schizophrenia

- Nearly 60% of patients are obese
- Risk of developing diabetes is more than 2 times higher than that for the general population
- 70%-80% of patients smoke vs 25% in the general population
- Approximately 2 times higher incidence of cardiovascular disease mortality than that for the general population

Theisen FM et al. *J Psychiatr Res*. 2001;35:339-345.
Herrán A et al. *Schizophr Res*. 2000;41:373-381.
Allebeck P. *Schizophr Bull*. 1989;15:81-89.
www.diabetic-lifestyle.com/articles/sep01_whats_1.htm.

Treatment of Schizophrenia

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, HIV status and Hepatitis C screen

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

Current Ideal Treatment of schizophrenia

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

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

Treatment goals in schizophrenia

Acute	Medium term	Long term
Control psychotic symptoms, including agitation and behavior Promote safety of patient/staff/society Choose appropriate treatment that: • Treats acute symptoms • Facilitates assessment • Fosters a therapeutic relationship	Stabilize positive, negative, depressive, and cognitive symptoms Establish appropriate drug and dose for maintenance treatment Provide psychosocial support: • Information/education • Compliance	Continue to improve symptoms, particularly negative and cognitive Improve global function • Social • Financial • Occupational • Practical Prevent relapse

APA Practice Guidelines for the Treatment of Psychiatric Disorders. 2000;301-356.
Schatzberg AF. *The American Psychiatric Press Textbook of Psychopharmacology*. 2nd ed. 1998;751-772.

Choice of medication in acute phase schizophrenia

- First line treatment
  - risperidone, olanzapine, quetiapine, ziprasidone or aripiprazole
- Persistent suicidal ideation/behavior, or persistent hostility and aggressive behavior
  - clozapine
- Repeated non-adherence to pharmacological treatment
  - Long-acting injectable antipsychotics: Haldol decanoate, Prolixin decanoate and Risperdal Consta

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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

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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 inerventions

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Typical Antipsychotics

- Potent Dopamine-2 Antagonists
- Benefits
  - Treat positive symptoms/psychosis
- Side effects
  - Significant EPS
  - Prolactin elevation
  - Increase in negative symptoms
  - Dose dependent risk of Tardive Dyskinesia
  - Variable weight gain

Considerations in prescribing atypical antipsychotics

- Efficacy in
  - positive symptoms
  - negative symptoms
  - depressive symptoms
  - cognitive symptoms
- Potential for side effects
  - weight gain
  - prolactin elevation
  - sedation
  - dyslipidemia
  - metabolic effects (glucose dysregulation)
- Potentially improved compliance rates
- Reduced incidence of EPS compared with conventional agents
- Potentially reduced TD liability

www.mesinc.com/education/monographs2/cme002/content/10.html.
Wirshing DA et al. *J Clin Psychiatry.* 2002;63:856-865.

Selected Side Effects of Commonly Used Antipsychotic Medications

Medication	EPS/TD	Prolactin elev	Weight Gain	Sedation
Thioridazine	+	++	+	++
Perphenazine	++	++	+	+
Haloperidol	+++	+++	+	++
Clozapine	0	0	+++	+++
Risperidone	+	+++	++	+
Olanzapine	0	0	+++	+
Quetiapine	0	0	++	++
Ziprasidone	0	+	0	0
Aripiprazole	0	0	0	+

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Selected Side Effects of Commonly Used Antipsychotic Medications

Medication	Glucose Abnorm	Lipid Abnorm	QTc Prolong	Hypotension
Thioridazine	+?	+?	+++	++
Perphenazine	+?	+?	0	+
Haloperidol	0	0	0	0
Clozapine	+++	+++	0	+++
Risperidone	++	++	+	+
Olanzapine	+++	+++	0	+
Quetiapine	++	++	0	++
Ziprasidone	0	0	++	0
Aripiprazole	0	0	0	0

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Recommended dosage range for "second-generation" antipsychotics

Atypical	Mg/day	Half-Life (hours)
Aripiprazole	10-30	75
Clozapine	150-600	12
Olanzapine	10-30	33
Quetiapine	300-800	6
Risperidone	2-8	24
Ziprasidone	120-200	7

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Receptor binding affinities of atypical antipsychotics

K_i (nM)

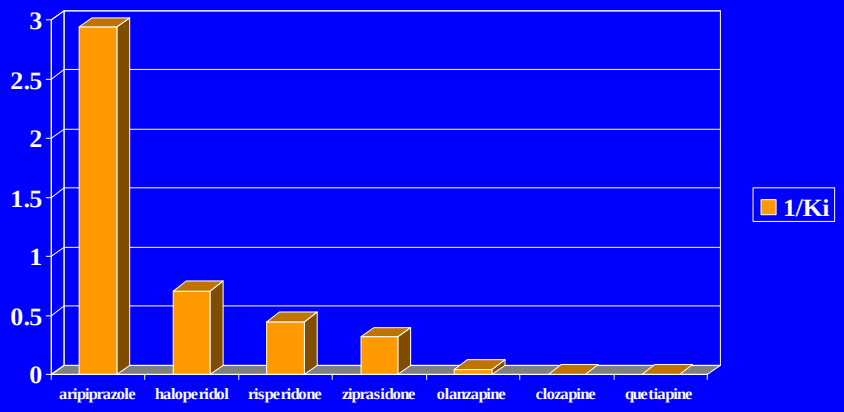
	Ziprasidone	Risperidone	Olanzapine	Quetiapine	Clozapine
D_2	3.1	2.2	20	180	130
5-HT_{2A}	0.39	0.29	3.3	220	8.9
5-HT_{2C}	0.72	10	10	1400	17
5-HT_{1A}	2.5	210	2100	230	140
5-HT_{1D}*	2.0	170	530	>5100	1700
α_1-adrenergic	13	1.4	54	15	4.0
M_1-muscarinic	5100	2800	4.7	100	1.8
H_1-histaminergic	47	19	2.8	8.7	1.8

K_i <1 nM — very high affinity; K_i = 1-10 nM — high; K_i = 11-100 nM — moderate; K_i =101-1000 nM — low; K_i >1000 nM — negligible.
*Bovine binding affinity; †rat synaptosomes; all other affinities human.

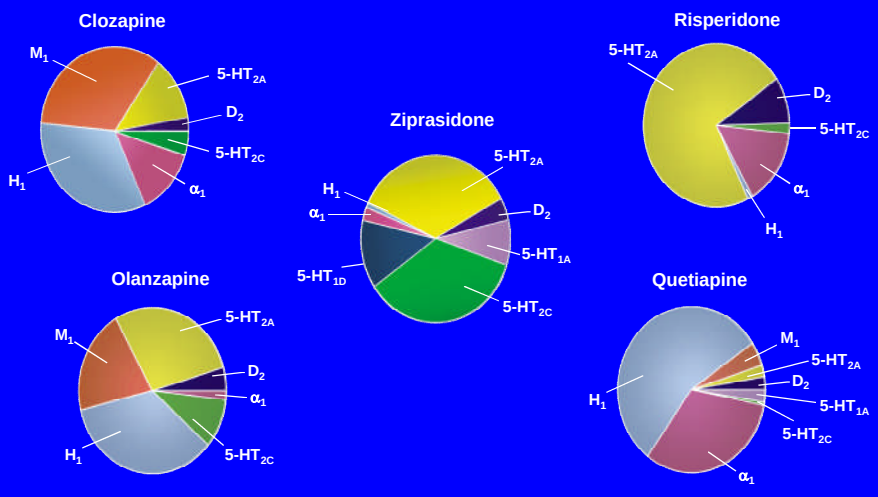
Zorn SH et al. *Interactive Monoaminergic Brain Disorders*. 1999;377-393.
Schmidt AW et al. *Eur J Pharmacol*. 2001;425:197-201.

Potency of antipsychotics at the Dopamine 2 Receptor

The larger the number, the stronger the affinity to D-2

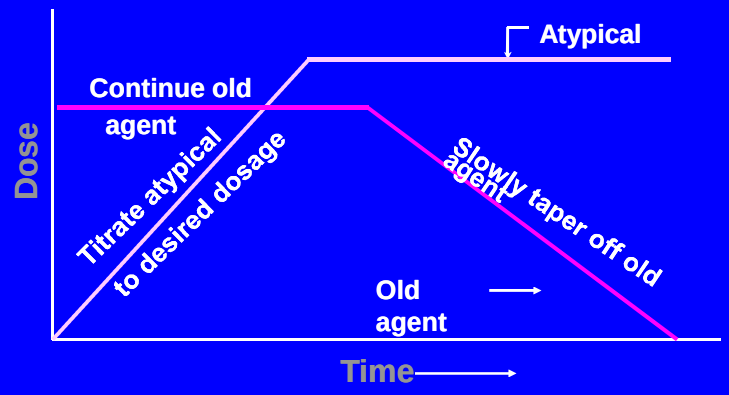


Pharmacology of atypical antipsychotics



Zorn SH et al. *Interactive Monoaminergic Brain Disorders*. 1999;377-393.
Schmidt AW et al. *Eur J Pharmacol*. 2001;425:197-201.

Switching Antipsychotics: Recommended Strategy



Long-term treatment

- "Indefinite maintenance antipsychotic medication is recommended for patients who have had multiple prior episodes or two episodes within 5 years."
- Psychosocial treatments
  - Family intervention
  - Supported employment
  - Assertive community treatment
  - Skills training
  - Cognitive behavior therapy

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