Human Behavior Course
2004

Schizophrenia & Psychosis Three
Therapeutics

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HUMAN BEHAVIOR COURSE 2004
SCHIZOPHRENIA & PSYCHOSIS THREE – SLIDES

LEARNING OBJECTIVES AND STUDY QUESTIONS FOR DISCUSSION.

1. **What do twin studies suggest about genetic versus environmental causation of schizophrenia?**
2. **Know the rates of schizophrenia among relatives of an individual with schizophrenia.**
3. **List the most consistent anatomic findings in schizophrenia from autopsy and structural neuroimaging?**
4. **How are neuroimaging results correlated with symptoms and prognosis?**
5. **What do functional neuroimaging studies of patients with schizophrenia show? What happens with cognitive challenge to executive functioning?**
6. **What is "sensory gating" and how does it related to EEG findings in patients with schizophrenia?**
7. **Describe the dopamine theory of schizophrenia? What are the major lines of evidence that support it? What are the suspected mechanisms of dopamine over activity in schizophrenia?**
8. **Which dopamine receptor is thought to be involved in schizophrenia?**
9. **What are the limitations of the dopamine hypothesis of schizophrenia?**
10. **What other neurotransmitter systems may be involved in schizophrenia?**
11. **What are the four major D2 pathways with clinical implications in schizophrenia? What symptoms and medication side effects does each pathway mediate?**
12. **Know which antipsychotic agents are "conventional" and where each conventional agent lies along the spectrum of "low potency" versus "high potency" agents.**
13. **What is the general side effect profile associated with low-potency agents? Which side effects are associated with what receptor mechanisms?**
14. **What is the general side effect profile associated with high potency agents? Which side effects are associated with what receptor mechanisms?**
15. **List the extrapyramidal symptoms? Describe their mechanism. How are extrapyramidal symptoms managed in patients who experience them?**
16. **What is the difference between acute dystonia and tardive dystonia?**
17. **What are the signs of tardive dyskinesia? What is the mechanism thought to be?**
18. **What is the approximate risk each year of tardive dyskinesia in someone taking conventional antipsychotics?**
19. **What are the risk factors for developing tardive dyskinesia among patients receiving conventional antipsychotics?**
20. **What is the differential diagnosis of tardive dyskinesia?**
21. **How is tardive dyskinesia managed in patients that have it?**
22. **What are the signs of neuroleptic malignant syndrome?**
23. **What are the risk factors for neuroleptic malignant syndrome? What is the prognosis?**
24. **What is the management for neuroleptic malignant syndrome?**
25. **What positive symptoms of schizophrenia respond worst to antipsychotics?**
26. **What types of symptoms overall respond best to conventional antipsychotics?**
27. **Name the "atypical" antipsychotic agents. Know the unique risks and benefits of each.**
28. **Know table 8-10 (page 237) in Cohen. Don't worry about knowing the specific cytochromes that metabolize each drug.**

Slide 1

Psychosis & Schizophrenia Three – Terms & Concepts

- ★ stress diathesis model
- ★ twin studies
- ★ family studies
- ★ adoption studies
- ★ linkage studies
- ★ polygenic transmission
- ★ incomplete phenotypic penetrance
- ★ smooth pursuit eye movements
- ★ conventional antipsychotic agents
- ★ parkinsonism
- ★ extrapyramidal symptoms
- ★ akathisia
- ★ acute dystonia
- ★ tardive dystonia
- ★ tardive dyskinesia
- ★ neuroleptic malignant syndrome
- ★ malignant catatonia
- ★ benztropine (Cogentin)
- ★ trihexyphenidyl (Artane)
- ★ chlorpromazine (Thorazine)
- ★ thioridazine (Mellaril)
- ★ haloperidol (Haldol)
- ★ fluphenazine (Prolixin)
- ★ trifluoperazine (Stelazine)
- ★ perphenazine (Trilafon)
- ★ bromocriptine
- ★ dantrolene
- ★ electroconvulsive therapy
- ★ glutamate
- ★ GABA
- ★ serotonin
- ★ lysergic acid diethylamide (LSD)

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Slide 2

Psychosis & Schizophrenia Three – Terms & Concepts

- ★ atypical antipsychotic agents (see table 8-10 in Cohen)
- ★ clozapine (Clozaril)
- ★ agranulocytosis
- ★ olanzapine (Zyprexa)
- ★ risperidone (Risperdal)
- ★ quetiapine (Seroquel)
- ★ ziprasidone (Geodon)
- ★ torsades de pointe

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Table 8–1. *DSM-IV-TR* Classification of Psychotic Disorders

SCHIZOPHRENIA

Symptoms persist for at least 6 months, including at least 1 month of active-phase symptoms, including hallucinations, delusions, thought disorder, disorganized or catatonic behavior, or "negative" symptoms (more on the latter momentarily), along with evidence of a decline in social or occupational functioning

SCHIZOPHRENIFORM DISORDER

Same criteria as schizophrenia except for its duration (1 to 6 months) and (given its shorter time span) the absence of a requirement that there be evidence of a decline in functioning

BRIEF PSYCHOTIC DISORDER

A psychotic disturbance lasting more than 1 day but remitting by 1 month

SCHIZOAFFECTIVE DISORDER

The patient meets criteria for both schizophrenia and mood disorder. There are acute episodes in which the patient demonstrates evidence of both mood disorder and active-phase symptoms of schizophrenia, but these are preceded or followed by at least 2 weeks of delusions or hallucinations *without* prominent mood symptoms (which is what distinguishes this from major depressive disorder or bipolar disorder with psychotic symptoms)

DELUSIONAL DISORDER

Nonbizarre delusions in the absence of other active-phase symptoms of schizophrenia, lasting for at least 1 month

SHARED PSYCHOTIC DISORDER (*FOLIE A DEUX*)

The disturbance develops in an individual who is strongly influenced by someone else who has an established delusion with similar content

PSYCHOTIC DISORDER DUE TO A GENERAL MEDICAL CONDITION

The psychotic symptoms are judged to be a direct physiological consequence of a general medical condition

SUBSTANCE-INDUCED PSYCHOTIC DISORDER

The psychotic symptoms are judged to be a direct physiological consequence of a drug of abuse, a medication, or toxin exposure.

PSYCHOTIC DISORDER NOT OTHERWISE SPECIFIED

The patient demonstrates either a presentation with psychotic symptoms that don't meet the criteria for any of the specific psychotic disorders or there is currently inadequate or contradictory information preventing a more specific diagnosis from being made

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Psychosis & Antipsychotics Overview

- ★ Psychosis – some basics
- ★ Antipsychotics
  - Indications & Target Symptoms
  - Important Adverse Effects
  - Drug Selection & Administration
  - Newer Agents
- ★ Neuroleptic Malignant Syndrome
- ★ Tardive Dyskinesia

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Psychosis
'Thought Disorder' ~ Positive Symptoms

- ★ Thought content symptoms
  - 'Impaired reality testing'
  - Delusions
  - Hallucinations (auditory and others)
- ★ Thought process symptoms
  - Loosening of associations
  - Tangentiality
  - 'Derailed' or disorganized

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Psychosis
Signs & Symptoms

- ★ Behavioral symptoms
  - Agitation
  - Impulsivity
  - Catatonia
- ★ 'Negative symptoms'
  - Ambivalence, unmotivated
  - Social withdrawal
  - Impoverished speech

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Table 8–2. Distinctions between Type I and Type II Schizophrenia

Type I Schizophrenia	*Type II Schizophrenia*
Prominent positive symptoms	Positive symptoms less prominent
Good premorbid functioning	Poor (schizotypal) premorbid functioning
Acute onset	Insidious decline
Remissions and exacerbations	Chronic deterioration
Better response to traditional antipsychotics	Poor response to traditional antipsychotics
Good cognition between episodes	Prominent cognitive impairment
Normal findings on routine neuroimaging	Atrophy and enlarged ventricles on neuroimaging

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Psychosis
Differential Diagnosis

Psychosis Due to General Medical Condition

- ★ Delirium
- ★ Dementia
- ★ Psychoactive Substance-Induced
- ★ Fluent Aphasia

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Idiopathic (Functional) Psychosis
Differential Diagnosis

acute

Brief Reactive Psychosis
Acute Mania
Schizophreniform Disorder
Psychotic Disorder NOS

one month or more

Major Depression
Schizoaffective Disorder
Delusional Disorder

six months or more

Schizophrenia

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Table 8–3. *DSM-IV-TR* Criteria for Schizophrenia

A. *Characteristic symptoms*: Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):
   1. Delusions
   2. Hallucinations
   3. Disorganized speech (e.g., frequent derailment or incoherence)
   4. Grossly disorganized or catatonic behavior
   5. Negative symptoms, i.e., affective flattening, alogia, or avolition

   Note: Only one criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behavior or thoughts, or two or more voices conversing with each other

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

C. *Duration*: 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 two or more symptoms listed in criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences)

D. *Schizoaffective and mood disorder exclusion*: Schizoaffective disorder and mood disorder with psychotic features have been ruled out because either (1) no major depressive, manic, or mixed episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods

E. *Substance/general medical condition exclusion*: The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition

F. *Relationship to a pervasive developmental disorder*: If there is a history of autistic disorder or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated)

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Table 8–4. *DSM-IV-TR* Criteria for Schizophrenia Diagnostic Subtypes

PARANOID TYPE

A type of schizophrenia in which the following criteria are met:
- A. Preoccupation with one or more delusions or frequent auditory hallucinations
- B. None of the following is prominent: disorganized speech, disorganized or catatonic behavior, or flat or inappropriate affect

DISORGANIZED TYPE

A type of schizophrenia in which the following criteria are met:
- A. All of the following are prominent:
  1. Disorganized speech
  2. Disorganized behavior
  3. Flat or inappropriate affect
- B. The criteria are not met for catatonic type

CATATONIC TYPE

A type of schizophrenia in which the clinical picture is dominated by at least two of the following:
1. Motoric immobility as evidenced by catalepsy (including waxy flexibility) or stupor
2. Excessive motor activity (that is apparently purposeless and not influenced by external stimuli)
3. Extreme negativism (an apparently motiveless resistance to all instructions or maintenance of a rigid posture against attempts to be moved) or mutism
4. Peculiarities of voluntary movement as evidenced by posturing (voluntary assumption of inappropriate or bizarre postures), stereotyped movements, prominent mannerisms, or prominent grimacing
5. Echolalia or echopraxia

UNDIFFERENTIATED TYPE

A type of schizophrenia in which symptoms that meet criterion A are present, but the criteria are not met for the paranoid, disorganized, or catatonic type

RESIDUAL TYPE

A type of schizophrenia in which the following criteria are met:
- A. Absence of prominent delusions, hallucinations, disorganized speech, and grossly disorganized or catatonic behavior
- B. There is continuing evidence of the disturbance, as indicated by the presence of negative symptoms or two or more symptoms listed in criterion A for schizophrenia, present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences)

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Table 8–7. Risk of Developing Schizophrenia by Relationship to Schizophrenic Proband

Relationship to Proband	*Risk of Schizophrenia*
No relationship (general population)	1%
One parent	5–6%
One sibling	10%
One sibling and one parent	17%
Two parents	46%

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Table 8–8. Conventional Antipsychotic Classes and Agents

Class	*Examples*
Phenothiazines	Chlorpromazine (Thorazine)
	Fluphenazine (Prolixin)
	Trifluoperazine (Stelazine)
	Perphenazine (Trilafon)
	Thioridazine (Mellaril)
Butyrophenones	Haloperidol (Haldol)
Thioxanthenes	Thiothixene (Navane)
Dihydroindolones	Molindone (Moban)
Dibenzoxazepines	Loxapine (Loxitane)

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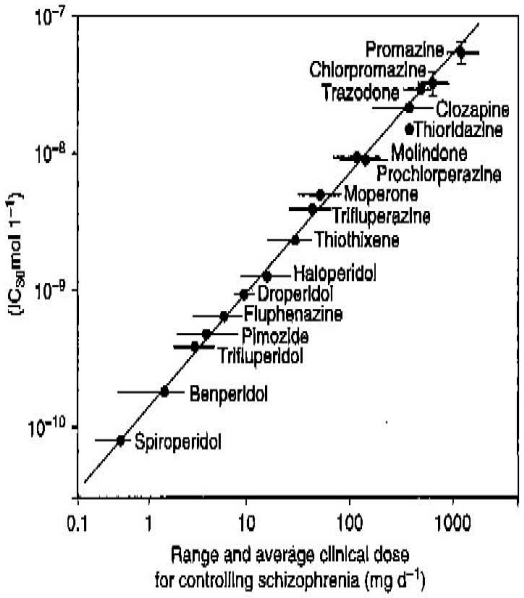

Figure 8–1. Potency and receptor affinity of typical antipsychotic medications. Reproduced with permission from Seeman P, Lee T: "Antipsychotic Drugs: Direct Correlation Between Clinical Potency and Presynaptic Action on Dopamine Neurons." *Science* 188:1217, 1975.

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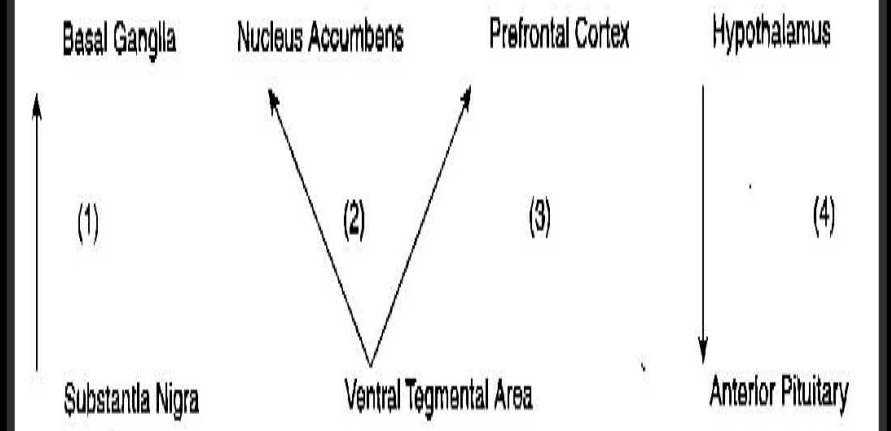

Figure 8–2. Four primary dopamine D_2 pathways: (1) the nigrostriatal tract, (2) the mesolimbic tract, (3) the mesocortical tract, and (4) the tuberoinfundibular tract.

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Table 8–9. Conventional Antipsychotic Drug Potency and Relationship to Side Effects

Drug	*Equivalent Dose (mg)*	*Sedation*	*Autonomic*	*Extrapyramidal*
Fluphenazine (Prolixin)	2	1+	1+	3+
Haloperidol (Haldol)	2	1+	1+	3+
Thiothixene (Navane)	4	1+	1+	3+
Trifluoperazine (Stelazine)	5	2+	1+	3+
Perphenazine (Trilafon)	10	2+	1+	2+/3+
Molindone (Moban)	10	2+	1+	1+
Loxapine (Loxitane)	15	2+	1+/2+	2+/3+
Mesoridazine (Serentil)	50	3+	2+	1+
Chlorpromazine (Thorazine)	100	3+	3+	1+/2+
Thioridazine (Mellaril)	100	3+	3+	1+

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Antipsychotic Agents
Mechanism of Action

- ★ Dopamine (D2) receptor blockade
  - Close correlation between receptor binding and clinical efficacy
- ★ Mesolimbic and Mesocortical pathways
  - mesolimbic ‘positive symptoms’
  - mesocortical ‘negative symptoms’
- ★ Responsible for dopamine hypothesis of psychosis
  - PET studies show increased D2 receptor density in psychotic patients prior to any neuroleptics

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Antipsychotic Agents
Indications

Short-term Use	Long-term Use
schizophrenia (exacerbation)	schizophrenia (chronic)
acute mania	Tourette’s syndrome
depression with psychosis	tx-resistant bipolar disorder
other acute psychoses	Huntington’s chorea
acute delirium	chronic organic psychoses
dementia with psychosis	delusional disorders (?)
drug-induced psychosis	childhood psychoses (?)
nausea & vomiting	
intractable hiccups	
behavioral dyscontrol (?)	
borderline personality disorder (?)	

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Antipsychotic Agents
Predictors of Response

- ★ Late onset
- ★ Acute onset (versus insidious over > 4 weeks)
- ★ Good premorbid function
- ★ Family history of mood disorder (versus schizophrenia)
- ★ Normal cognition & memory
- ★ Normal ventricle size (versus enlarged)
- ★ Absence of flat or blunted affect

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Antipsychotic Agents
Choosing a Medicine

- ★ Response to previous agents
- ★ Avoid polypharmacy
  - one agent at a time
  - toxicities are additive
- ★ Presenting problem
- ★ Optimize tolerance & side-effect profile
  - age
  - medical status

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Antipsychotic Agents
High versus Low-Potency

Potency	Drug	Dose
High	haloperidol, fluphenazine	2 mg
↓	thiothixene	4 mg
	trifluoperazine	6 mg
	perfenazine	8 mg
Low	chlorpromazine, thioridazine	100 mg

- ★ High Potency: haloperidol, fluphenazine
  - low in anticholinergic, sedative, orthostatic effects
  - high incidence of extrapyramidal signs
- ★ Low Potency: chlorpromazine, thioridazine
  - high in anticholinergic, sedative, orthostatic effects
  - low incidence of extrapyramidal signs

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"Atypical" (Newer) Agents
see table 8-10 in Cohen

Common theme: mixed anti-$5HT_2$ & anti-D_2 effects

- ★ Clozapine (Clozaril) – agranulocytosis, seizures
- ★ Olanzapine (Zyprexa) – EPS, sedation, weight gain
- ★ Risperidone (Risperdal) – weight gain, QT_c prolongation
- ★ Quetiapine (Seroquel) - cataracts in beagles
- ★ Ziprasidone (Geodon) – QT_c prolongation

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Antipsychotic Agents
Agents for Selected Patients

CONDITION	RECOMMENDATION
Cardiac problems	Avoid low-potency agents
Elderly	Use low doses of high-potency agents
Hx of EPS	Avoid high-potency agents
Parkinson's Disease	Use low doses of low-potency agents
Suicidal Patients	Avoid thioridazine or mesoridazine
Delirium	Avoid anticholinergic agents
Seizure Disorder	Use high potency agents
Catatonia	Avoid high-potency agents
Antiemetic	Use perphenazine or chlorpromazine
Tourette's	Use haloperidol or pimozide
Borderline PD	Use low dose, high-potency agents
Tx-resist Schizophrenia	Consider newer agents

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Antipsychotic Agents
Target Symptoms

★ Respond in hours to weeks
- Agitation
- Impulsivity
- Confusion

★ Respond in weeks
- Auditory hallucinations
- Visual hallucinations

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Antipsychotic Agents
Target Symptoms

★ May not respond
- Delusions
- Social withdrawal
- Lack of motivation
- Flat affect
- Impoverished speech

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Antipsychotic Agents
Phases of Administration

★ Pharmacolysis (acute) phase: e.g., haloperidol 5 mg QID
- First 3-10 days
- Goal is acute symptom reduction
- Gradual upward dose titration
- Lorazepam 1-2 mg / 5 mg haloperidol for sedation

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Antipsychotic Agents
Phases of Administration

- ★ Stabilization phase
  - Lasts from 1-3 weeks
  - Slow taper of antipsychotic & antiparkinsonian to maintenance levels
- ★ Maintenance phase: e.g., haloperidol 1-5 mg daily
  - Lowest dose to maintain symptom-free, maximize adherence, facilitate return to independent function
  - Depot haloperidol or fluphenazine

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Neuroleptic Malignant Syndrome

- ★ Mortality near 20%
- ★ Symptoms & signs
  - Muscular rigidity (may cause rhabdomyolysis)
  - Diminished level of consciousness
  - Autonomic instability (MT, MNBP, MHR, diaphoresis)

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Neuroleptic Malignant Syndrome

- ★ Complications: seizures, coma, dysrhythmias
- ★ Lab findings: MCPK, LDH, SGOT/PT, WBC
- ★ Treatment
  - Supportive (often ICU) care
  - DC antipsychotic
  - Bromocriptine, amantadine, or dantrolene
  - IV hydration to prevent rhabdomyolysis/renal failure

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