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Antipsychotic Medications

Model Curriculum

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Learning Objectives

- Students will identify the major target symptoms of schizophrenia treatment
- Students will become familiar with first and second generation antipsychotic medications
- Students will recognize the major side effects of antipsychotic medications
- Students will recognize the unique features of clozapine and depot antipsychotics

Pretest



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1. Negative symptoms of schizophrenia include:
 - a. Auditory hallucinations
 - b. Blunted affect
 - c. Depressed mood
 - d. Persecutory delusions
 - e. Thought disorganization



Pretest

-
2. Clinical efficacy of antipsychotic medications is highly correlated with:
- Dopamine D1 binding
 - Dopamine D2 binding
 - Serotonin binding
 - The ratio of D1/D2 binding
 - The ratio of D2/serotonin binding
-

Pretest

-
3. Clozapine is unique among antipsychotics in that it:
- a. Has greater efficacy
 - b. Has fewer side effects
 - c. Is a dopamine D2 partial agonist
 - d. Is FDA approved for treatment of bipolar mania
 - e. Has a more favorable safety profile
-

Pretest

-
4. Which of the following antipsychotics has the lowest risk of extrapyramidal side effects?
- a. Aripiprazole
 - b. Olanzapine
 - c. Quetiapine
 - d. Risperidone
 - e. Ziprasidone
-

Pretest

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5. Which of the following antipsychotics has the lowest risk of metabolic complications?
- a. Clozapine
 - b. Olanzapine
 - c. Quetiapine
 - d. Risperidone
 - e. Ziprasidone
-

Schizophrenia and Its Treatment

Definition



Schizophrenia is a chronic or recurrent disorder characterized by

- Periods of psychosis
- Long-term functional deterioration



Symptom Subtypes in Schizophrenia

Positive Symptoms

- Delusions
- Hallucinations
- Thought Disorganization
- Catatonia

Cognitive Deficits

- Memory
- Attention
- Language
- Executive Function

Negative Symptoms

- Blunted Affect
- Anhedonia/Asociality
- Alogia
- Inattention
- Avolition/Apathy

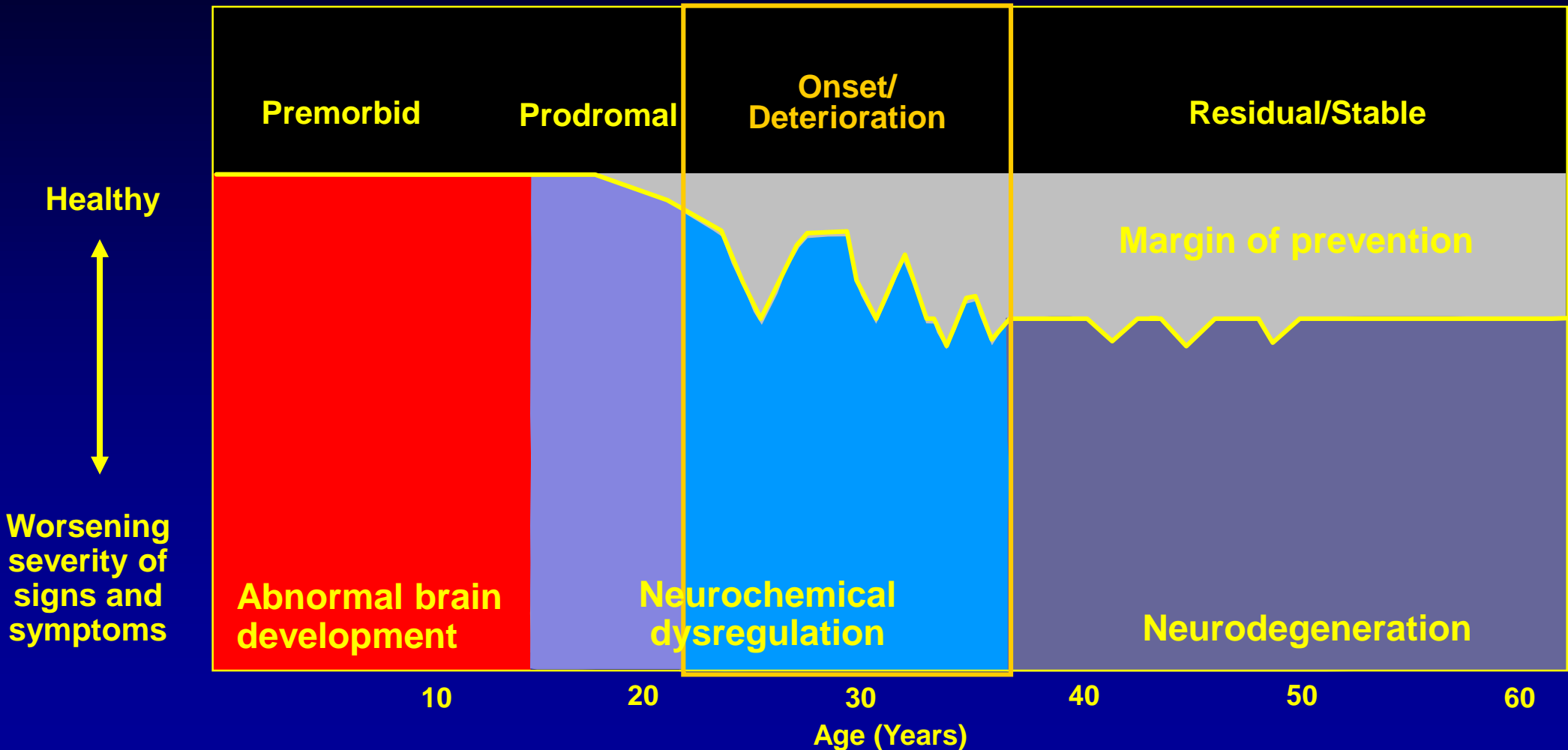
Mood Symptoms

- Depression
 - Dysphoria
 - Suicidality
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Contributions to Functional Impairment



Progressive Stages of Illness in Schizophrenia



Adapted from: Lieberman JA, et al. Biol Psychiatry 2001;50(11):884-97.

Dopamine Hypothesis

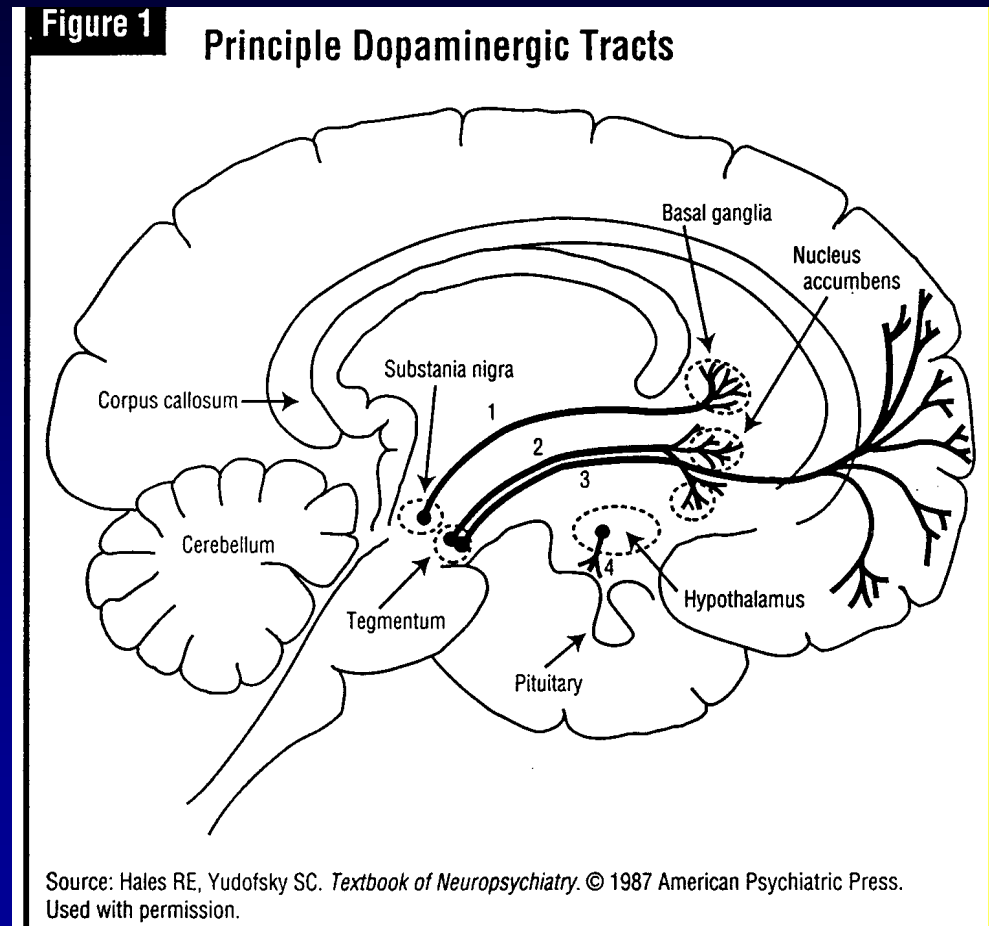
- Clinical efficacy of antipsychotics correlates with dopamine D₂ blockade
- Psychotic symptoms can be induced by dopamine agonists
- Normal subjects have 10% of dopamine receptors occupied at baseline
- Schizophrenic subjects have 20% of dopamine receptors occupied at baseline

Dopamine and Antipsychotics

- 65% D₂ receptor occupancy is required for efficacy
- 80% D₂ receptor occupancy is correlated with EPS
- Shorter time of D₂ receptor occupancy is correlated with lower EPS

Major Dopamine Pathways

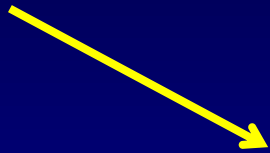
1. Nigrostriatal tract- (extrapyramidal pathway) begins in the substantia nigra and ends in the caudate nucleus and putamen of the basal ganglia
2. Mesolimbic tract - originates in the midbrain tegmentum and innervates the nucleus accumbens and adjacent limbic structures
3. Mesocortical tract - originates in the midbrain tegmentum and innervates anterior cortical areas
4. Tuberoinfundibular tract - projects from the arcuate and periventricular nuclei of the hypothalamus to the pituitary



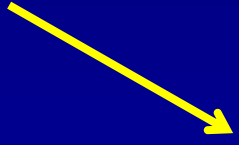
Dopamine Hypothesis



Subcortical
Dopamine
Excess



D₂
Hyperstimulation



Positive
Symptoms



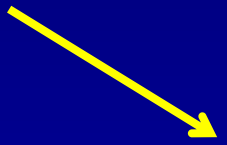
Dopamine Hypothesis



Prefrontal
Dopamine
Deficit



D₁ & D₂
Hypostimulation



Cognitive
& Negative
Symptoms





Pharmacologic Treatment of Schizophrenia



Target Symptoms



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- Active psychosis
 - most common reason for hospitalization
 - most responsive to medications
 - Negative symptoms
 - poor response to medication
 - progress most rapidly during early acute phases of illness



Target Symptoms



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- Cognitive impairment
 - Minimal improvement with medications
 - Functional deterioration
 - Highly correlated with cognitive symptoms
 - Moderately correlated with negative symptoms
 - Occurs mostly during acute episodes, which can be prevented by medications



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FDA Approved Indications for Antipsychotic Medications

■ ■ ■ Adults

- Schizophrenia (acute and maintenance)
- Bipolar disorder (acute mania, maintenance, bipolar depression)
- Agitation associated psychotic disorders
- Antidepressant augmentation

Children and Adolescents

- Schizophrenia
 - Autism
-



* First Generation Antipsychotics

(Conventional Antipsychotics, Neuroleptics)

- Chlorpromazine (Thorazine) introduced in 1952
 - Several classes (phenothiazines, butyrophenones, thioxanthenes, indoles, benzamides, etc) introduced in the 1950s and 1960s
 - Principal pharmacological activity is D₂ blockade
 - Variable activity at H₁, M₁, and α₁ receptors
 - High risk of EPS and tardive dyskinesia
-

* First Generation Antipsychotics (FGA)

High Potency

- High extrapyramidal side effect (EPS) risk
 - Weaker anticholinergic effects
 - Most common agents
 - Haloperidol (Haldol)
 - Fluphenazine (Prolixin)
 - Perphenazine (Trilafon)
 - Thiothixene (Navane)
-

* First Generation Antipsychotics (FGA)

■■■ Low Potency

- Lower EPS risk
 - Stronger anticholinergic effects
 - Most common agents
 - Chlorpromazine (Thorazine)
 - Thioridazine (Mellaril)
-



* First Generation Antipsychotics (FGA)

- Advantages

- Injectable formulations (including IV)
- Depot formulations
- Inexpensive

- Disadvantages

- High risk of EPS
 - High risk of tardive dyskinesia
-

* Second Generation Antipsychotics (Atypical Antipsychotics)

- Developed on the basis of receptor activity in addition to D₂ blockade
 - Fewer EPS
 - Decreased risk of tardive dyskinesia
 - Beneficial for treatment-refractory patients (clozapine only)
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Second Generation Antipsychotics (SGA)

- Aripiprazole (Abilify)
 - Asenapine (Saphris)
 - Brexpiprazole (Rexulti)
 - Iloperidone (Fanapt)
 - Cariprazine (Vraylar)
 - Olanzapine (Zyprexa)
 - Paliperidone (Invega)
 - Quetiapine (Seroquel)
 - Risperidone (Risperdal)
 - Ziprasidone (Geodon)
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- Clozapine (Clozaril) – Second-line use only

Clozapine

- Advantages

- Effective for 30-50% of treatment-refractory patients
- Most effective for negative symptoms
- Only proven treatment for TD

- Disadvantages

- Risk of severe leukocytopenia
 - Weekly, biweekly, or monthly blood draws
 - Unfavorable side effect profile
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Depot Antipsychotics

Medication	Dosing Frequency
Aripiprazole LA	4-6 wks
Fluphenazine decanoate	1-2 wks
Haloperidol decanoate	2-4 wks
Olanzapine LA	4 wks
Paliperidone palmitate	4 wks
Paliperidone palmitate ER	12 wks
Risperidone LA	2 wks

Depot Antipsychotics



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- Advantages
 - Ensured compliance
 - Lower total doses compared with oral medication may reduce side effects
 - Disadvantages
 - Poor patient acceptance
 - Minimal flexibility in dosing
 - Higher cost





Side Effects - Overview

By Class

	EPS	Orthostatic Hypotension	Anticholinergic Symptoms	Prolactin Elevation
High-potency FGA	+++	+	+/-	++
Low-potency FGA	++	+++	+++	++
SGA (1 st line)	+/- to +	+/- to ++	+/- to ++	+/- to ++
Clozapine	0	+++	+++	+/-



Side Effects - Overview

By Class

	qTc Prolongation	Sedation	Weight Gain
High-potency FGA	+/-	+	+
Low-potency FGA	++	+++	+++
SGA (1 st line)	+/- to +	+/- to +++	+/- to +++
Clozapine	+/- to +	+++	+++

Side Effects - Overview

Second Generation Antipsychotics

	EPS	Orthostatic Hypotension	Anticholinergic Symptoms	Prolactin Elevation
Aripiprazole	+	+/-	+/-	+/-
Asenapine	+	+/-	+/-	+/-
Brexpiprazole	+	++	+	+/-
Cariprazine	++	+/-	+	+/-
Iloperidone	+/-	+/-	+	+
Lurasidone	++	+	+/-	+/-
Olanzapine	+/-	+/-	+	+/-
Paliperidone	+	+	+/-	++
Quetiapine	+/-	++	++	+/-
Risperidone	+	+	+/-	++
Ziprasidone	+/-	+/-	+/-	+/-



Side Effects - Overview

Second Generation Antipsychotics


	qTc Prolongation	Sedation	Weight Gain
Aripiprazole	+/-	+/-	+/-
Asenapine	+/-	+	+
Brexpiprazole	-	++	+
Cariprazine	-	+	+/-
Iloperidone	+	+	++
Lurasidone	+/-	++	+/-
Olanzapine	+/-	+++	+++
Paliperidone	+/-	+	++
Quetiapine	+/-	+++	++
Risperidone	+/-	+	++
Ziprasidone	+	+/-	+/-

* Extrapyramidal Symptoms (EPS)

- Akathisia (subjective sense of restlessness)
 - Stiff, rigid muscles
 - Bradykinesia (slow movements)
 - Dystonia (muscle spasms)
 - Tremor
 - Cognitive dysfunction
-

Extrapyramidal Symptoms (EPS)

Risk by class of medication

- 
- High-potency first generation antipsychotic (20-40%)
 - Low-potency first generation antipsychotic
 - Paliperidone/Risperidone
 - Aripiprazole/Asenapine/Brexpiprazole/Cariprazine/
Iloperidone/Lurasidone/Olanzapine/Ziprasidone
 - Quetiapine/Clozapine (rare)

Metabolic Syndrome


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Use of atypical antipsychotics is associated with metabolic dysregulation

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- Weight gain
 - Type 2 diabetes
 - Elevated LDL cholesterol
 - Elevated triglycerides
 - Decreased HDL cholesterol
 - Diabetic ketoacidosis

Risk of Metabolic Complications

Relative risk of medications

- 
- Clozapine/Olanzapine/Low Potency FGA
 - Iloperidone/Paliperidone/Quetiapine/
Risperidone/High Potency FGA
 - Asenapine/Brexpiprazole/Iloperidone/
 - Aripiprazole/Cariprazine/Lurasidone/
Ziprasidone

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Metabolic Syndrome

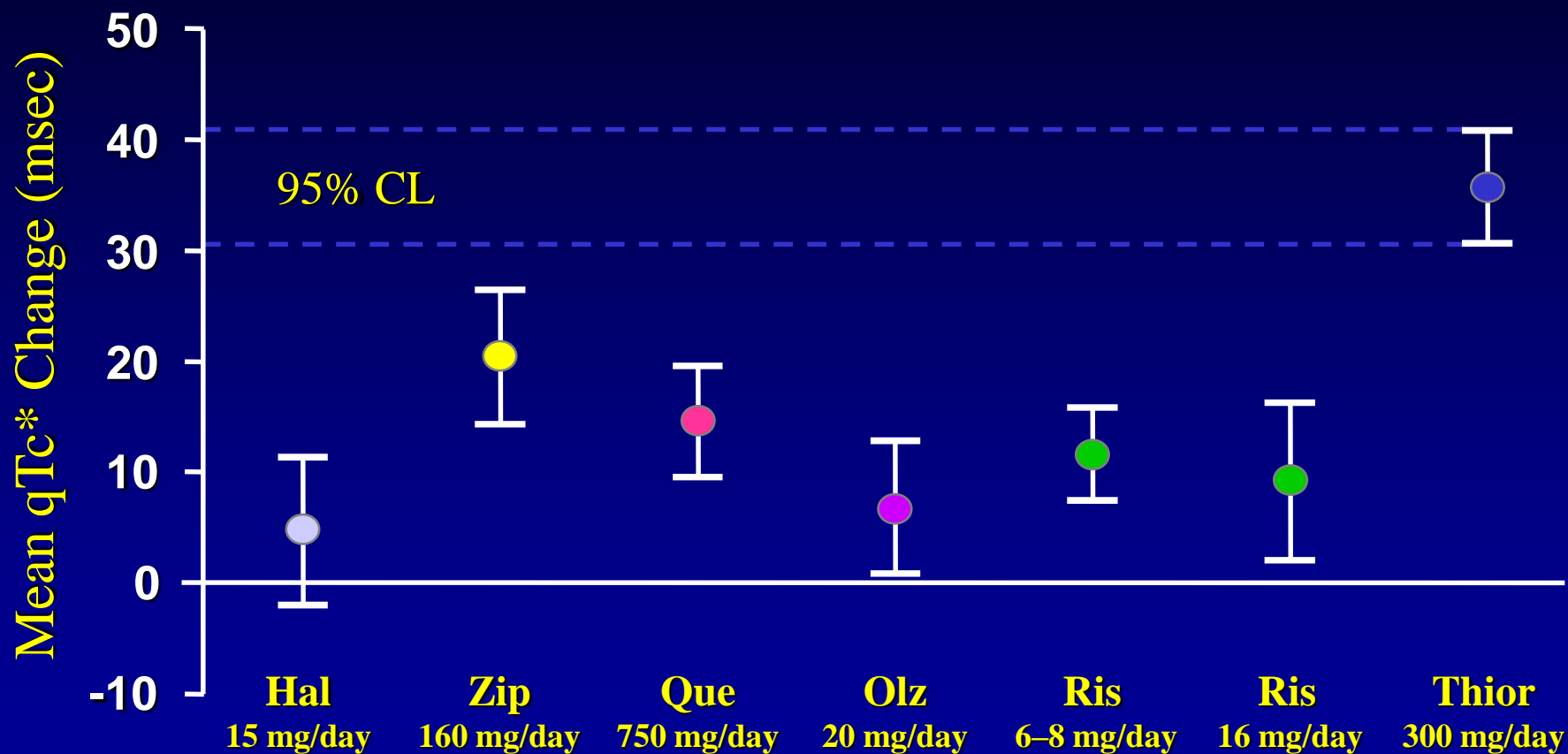
Recommended monitoring for patients on atypical antipsychotics

	Baseline	4 wks	8 wks	12 wks	Quarterly	Annual	5 yrs
Personal/family history	X					X	
Weight (BMI)	X	X	X	X	X		
Waist Circumference	X					X	
Blood pressure	X			X		X	
Fasting plasma glucose	X			X		X	
Fasting lipid profile	X			X			X

Cardiovascular Adverse Events

- Low potency FGA thioridazine (Mellaril) is associated with qTc prolongation and increased risk of cardiac death
- Ziprasidone and iloperidone carry a “bold” warning regarding qTc prolongation and associated cardiac risk, but no increased incidence of cardiac mortality or morbidity has been detected

Mean qTc Change at Steady-state C_{max}



*Bazett correction

Metabolic inhibition did not prolong the QTc interval with any drug studied

Data on file, Pfizer Inc. (Study 054)

Increased Mortality

- All antipsychotics carry a “black box” warning of increased mortality in elderly patients with dementia-related psychosis
- Risk is comparable among all first and second generation antipsychotics
- Risk is not associated with diagnosis
- Risk is present at all ages

Increased Mortality

Meta-analysis of 15 studies of risk of antipsychotics in elderly patients


	Mortality	Odds Ratio
Controls	2.3%	
All SGAs	3.5%	1.54
Haloperidol	3.9%	1.68

Tardive Dyskinesia

- Adverse reaction to antipsychotic medications
- Irregular, choreoathetotic movements
 - Chorea - irregular, spasmodic movements
 - Athetosis - slow writhing movements
- May occur in any muscle group
- Most common in facial, oral, and truncal muscles

Tardive Dyskinesia

Risk by class of medication:

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- High potency FGAs (7%/yr)
 - Low potency FGAs (5%/yr)
 - SGAs (0.5%/yr)
 - Clozapine (none reported)

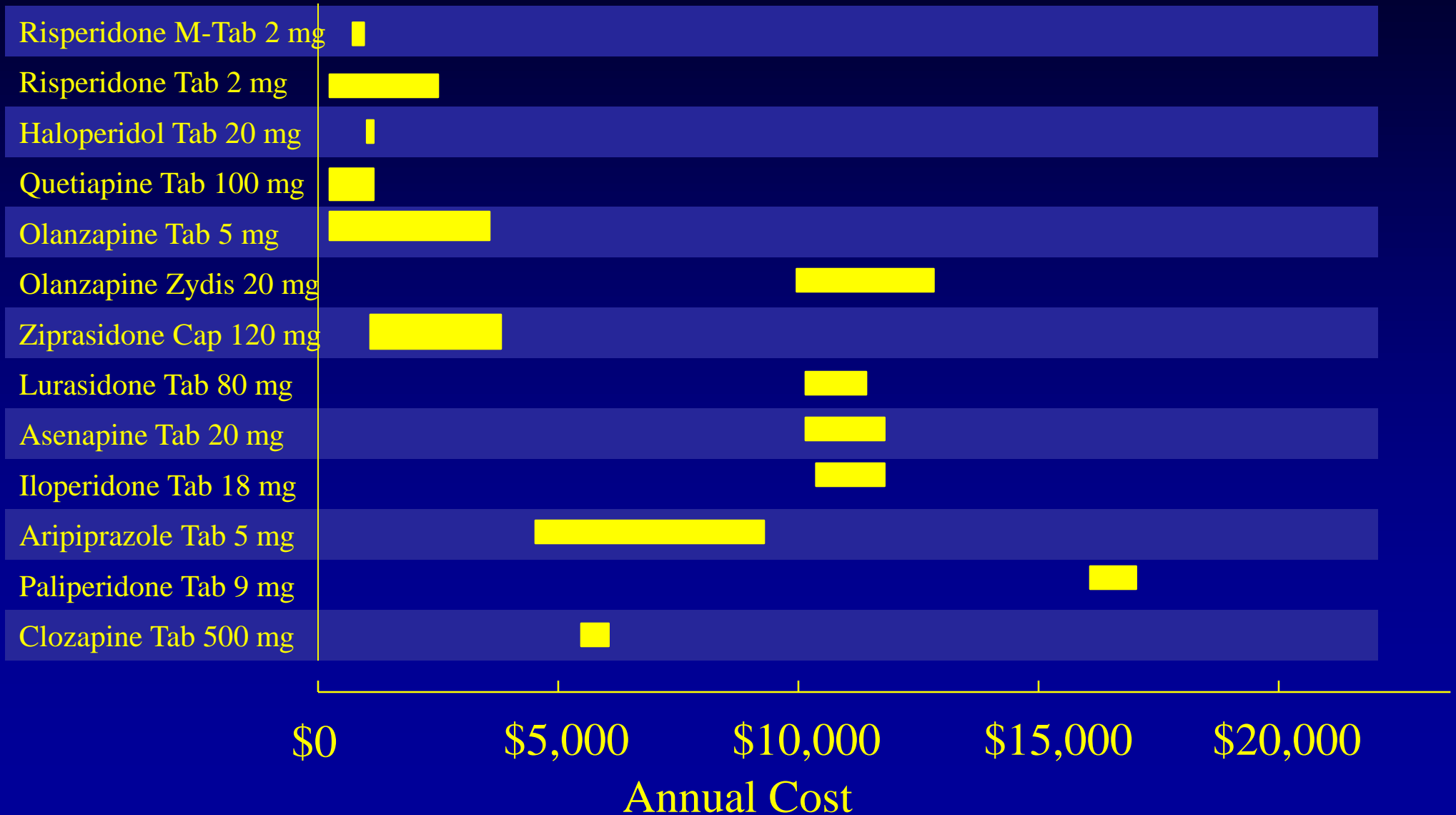
Tardive Dyskinesia

Cumulative Annual Risk of Tardive Dyskinesia

	Age 20	Age 70
FGAs	5%	30%
SGAs	0.5%	2.5-5%

Kane JM, et al., J Clin Psychopharmacol 1988;8:52S. Chakos MH, et al., Arch Gen Psychiatry 1996;53:313. Woerner MG, et al., Am J Psychiatry 1998;155:1521. Correll CU, et al., Am J Psychiatry 2004; 161:414. Glazer WM, J Clin Psychiatry 2000; 61 suppl 4:21.

Relative Costs of Antipsychotic Medications



Treatment Selection with Antipsychotics

- All antipsychotics are effective against psychotic symptoms
 - Second generation antipsychotics have lower risk of EPS and TD than first generation drugs
 - Each medication has unique side effects
 - Each medication has unique pharmacokinetics
 - Individual patients may respond preferentially to different medications
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Treatment Recommendations



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- Continuous, full-dose antipsychotic treatment is the key to good outcome in schizophrenia
 - “Lowest effective dose” strategies are associated with higher relapse rates and poorer outcomes
 - Antipsychotic polypharmacy is rarely justified
 - Frequent medication changes are associated with poorer outcomes



Treatment Recommendations



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- Long-acting injectable antipsychotics ensure treatment adherence
 - Clozapine should be considered for patients not responding to trials of at least 2-3 antipsychotics
 - Psychosocial treatment is essential to good outcome



Post-test



-
1. Negative symptoms of schizophrenia include:
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Post-test

-
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Post-test

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 - c. Quetiapine
 - d. Risperidone
 - e. Ziprasidone
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Post-test



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5. Which of the following antipsychotics has the lowest risk of metabolic complications?
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 - c. Quetiapine
 - d. Risperidone
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Answer Key



1. b

2. b

3. a

4. c

5. e

