Treatment of Acute Schizophrenia

Model Curriculum

Michael Jibson, M.D., Ph.D.
Ira Glick, M.D.

American Society for Clinical Psychopharmacology

Disclosure

Jibson: In the past 12 months I received $3,500 in royalties from *Up-to-Date* for chapters on antipsychotics and psychosis.

Glick: No writing assistance or external financial support was utilized in the production of this lecture. I am a consultant for, have received honoraria from, or have conducted clinical research supported by, the following: Abbott Laboratories, AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, Eli Lilly and Company, Forest Research Institute, GlaxoSmighKline, Janssen Pharmaceuticals, Jazz Pharmaceuticals, Merck, Novartis, Pfizer Inc., Sunovion, Takeda, and Vanda Pharmaceuticals.

I have equity in Johnson & Johnson

*

Learning Objectives

- Residents will identify the major target symptoms of schizophrenia treatment
- Residents will become familiar with first and second generation antipsychotic medications
- Residents will recognize the major side effects of antipsychotic medications
- Residents will identify the elements of effective schizophrenia treatment

Outline

- Schizophrenia and Its Treatment
  - Clinical description, course, and target symptoms
  - Dopamine hypothesis
- Antipsychotic medications
- Efficacy of antipsychotics
- Side effects of antipsychotics
  - Extrapyramidal symptoms
  - Metabolic syndrome
  - Cardiovascular
  - Tardive dyskinesia
  - Mortality
- Antipsychotic selection and treatment strategies

Pretest

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:
   a. Dopamine D1 binding
   b. Dopamine D2 binding
   c. Serotonin binding
   d. The ratio of D1/D2 binding
   e. 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 first-line atypical antipsychotic has the lowest risk of extrapyramidal side effects?
   a. Aripiprazole
   b. Olanzapine
   c. Quetiapine
   d. Risperidone
   e. Ziprasidone

Pretest

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

*

Schizophrenia and Its Treatment

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

Negative Symptoms

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

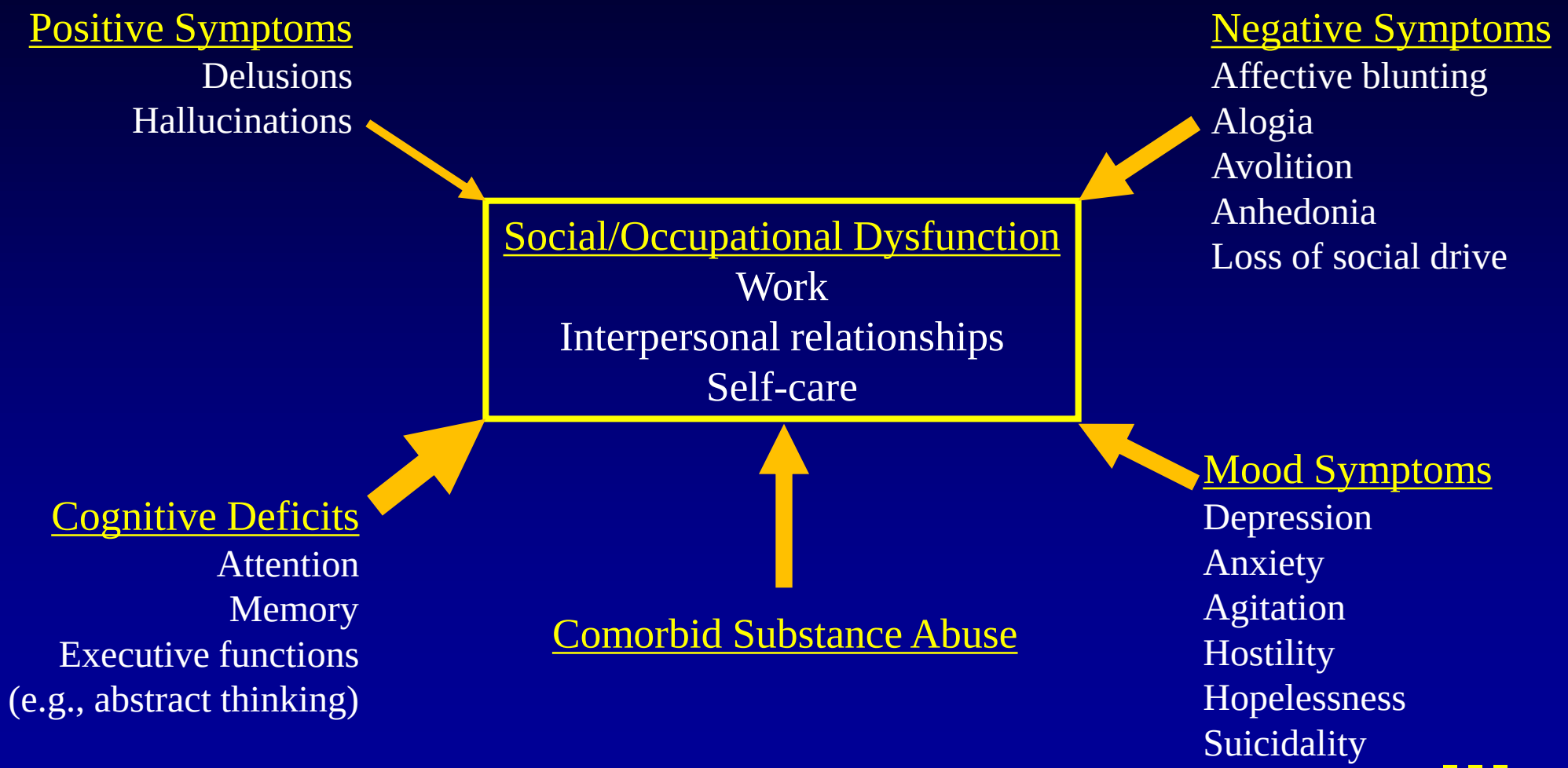
Cognitive Deficits

- Memory
- Attention
- Language
- Executive Function

Mood Symptoms

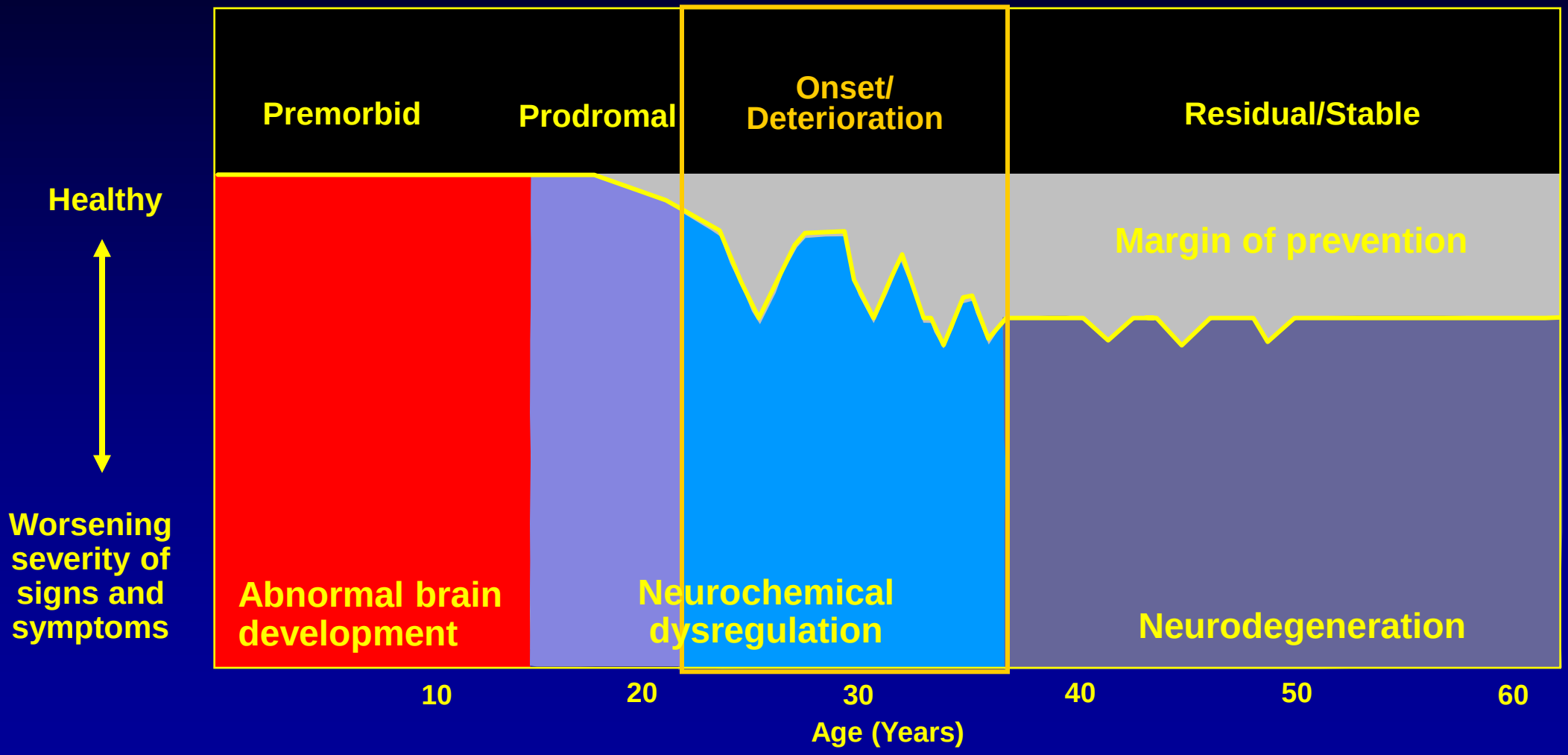
- Depression
- Dysphoria
- Suicidality

Functional Deficits



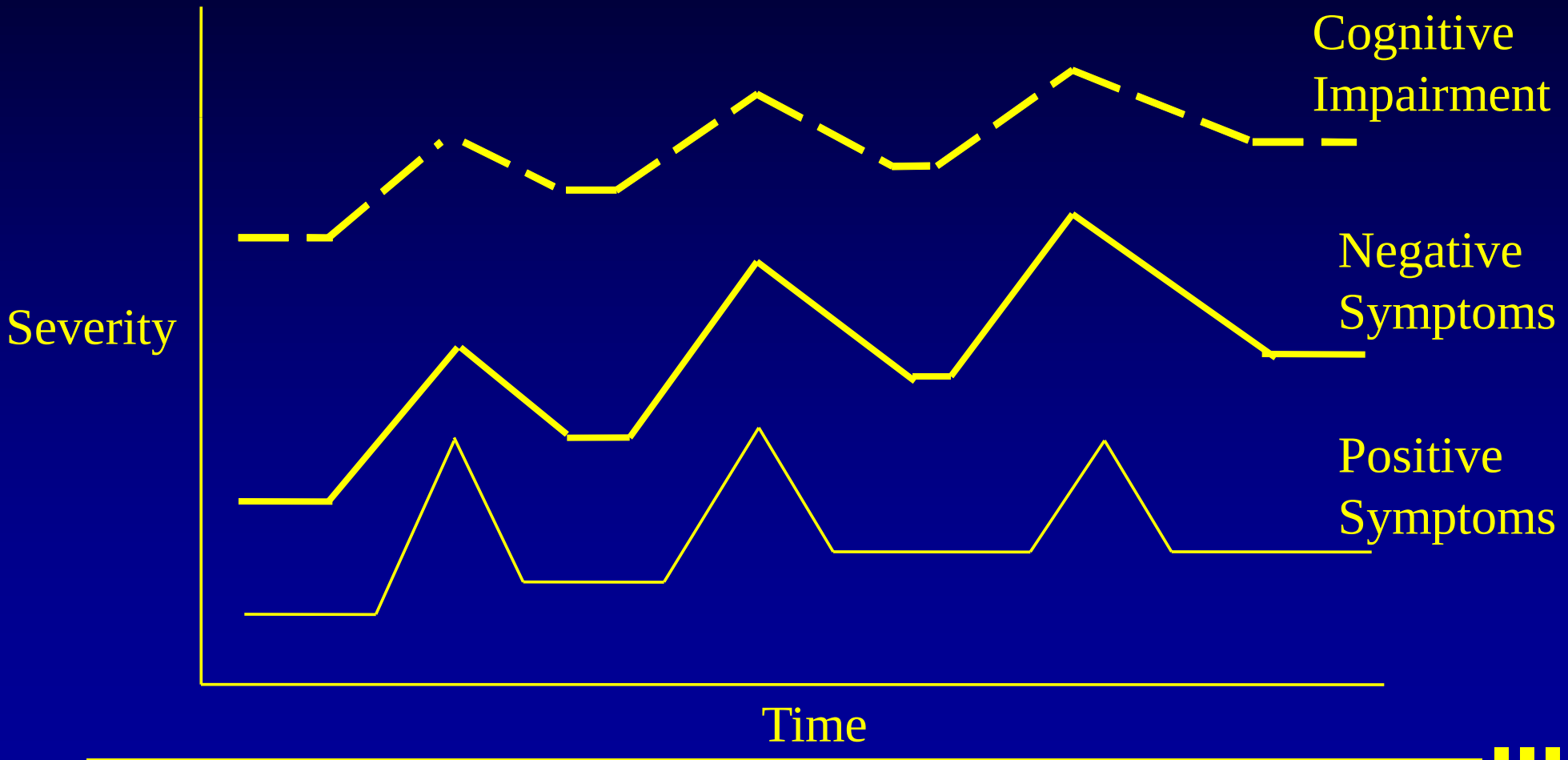
1. APA. DSM-IV-TR. 4th edition. Washington, D.C: American Psychiatric Association; 2000.
2. Goghari VM, Sponheim SR, MacDonald AW 3rd. Neurosci Biobehav Rev 2010;34(3):468-86.

Progressive Stages of Illness in Schizophrenia

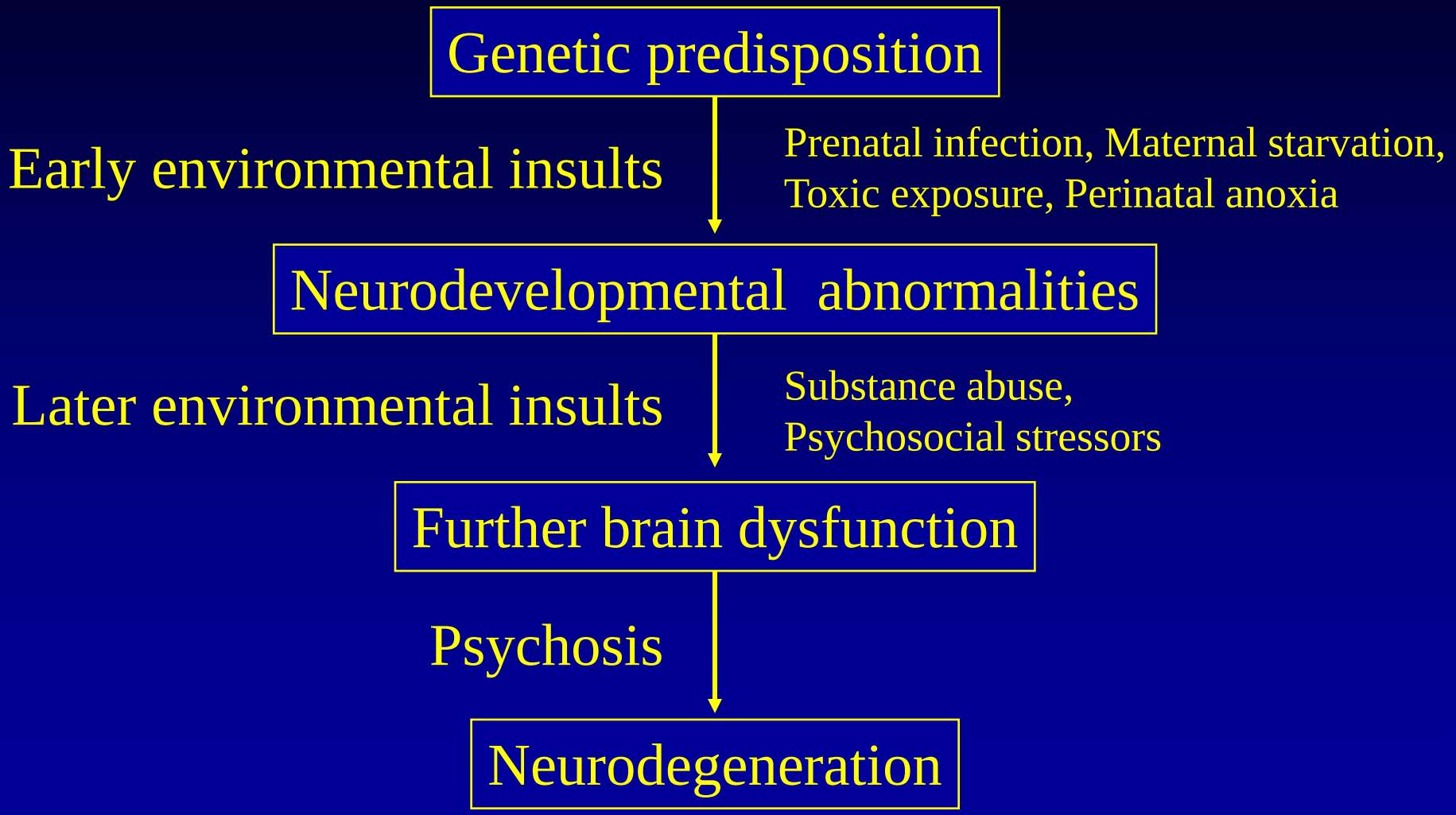


Adapted from: Lieberman JA, et al. Biol Psychiatry 2001;50(11):884-97.

Course of Symptom Subtypes



Etiology of Schizophrenia



Neurochemistry

Dopamine Hypothesis

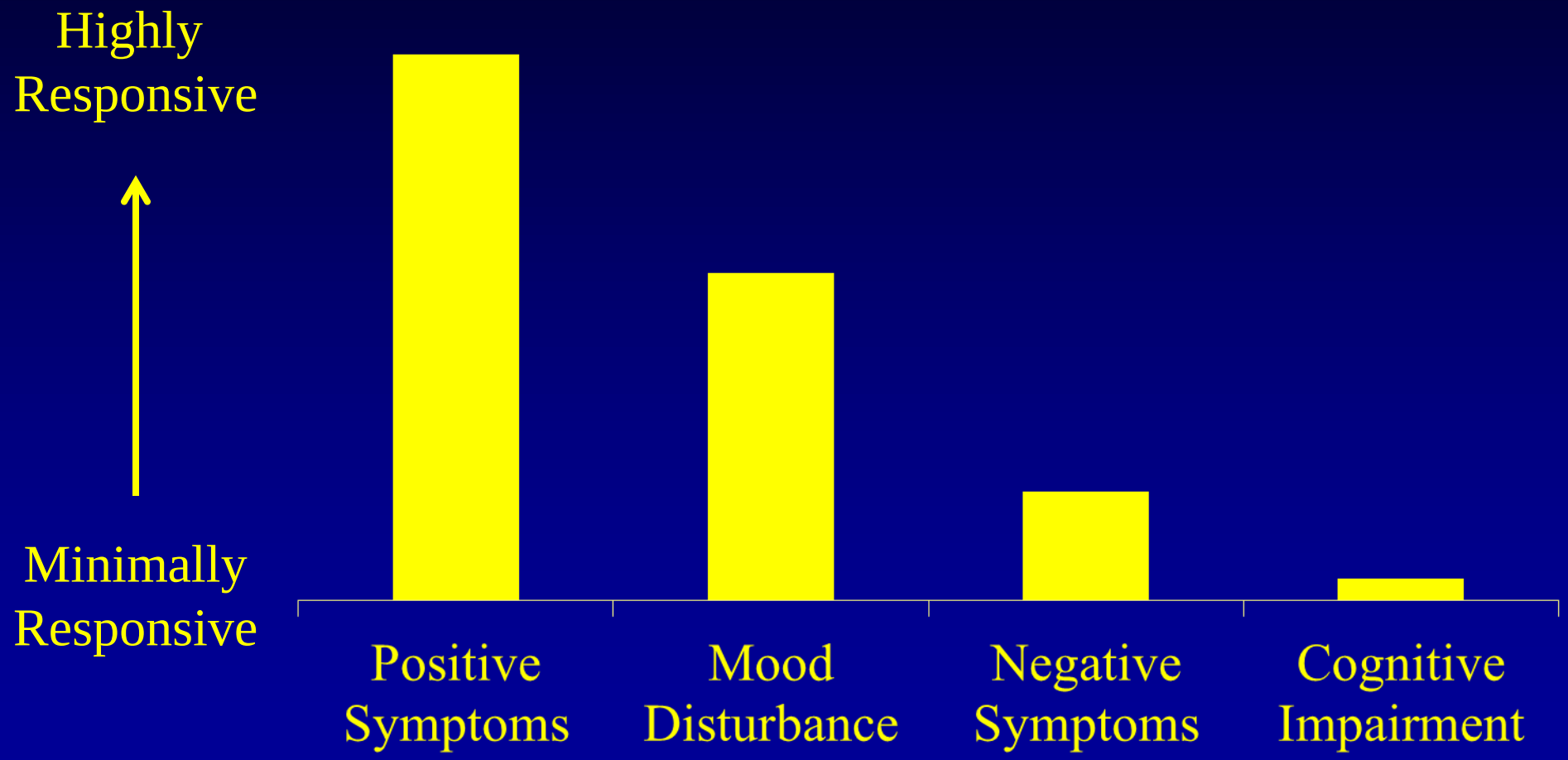
- High pretreatment dopamine activity in schizophrenia patients compared to population
- High correlation between D_2 receptor occupancy and antipsychotic efficacy
- Increased D_2 receptors and dopamine metabolites in post-mortum studies of schizophrenia patients

*

Dopamine and Antipsychotics

- All antipsychotics appear to work primarily via D_2 receptors
- 65% D_2 receptor occupancy is required for efficacy
- 80% D_2 receptor occupancy is correlated with EPS
- Shorter time of D_2 receptor occupancy is correlated with lower EPS

Symptom Response to Antipsychotics



Symptom Response to Other Treatments

- Antidepressants
  - May be helpful in cases of sustained depression
  - No benefit for negative symptoms
- Acetylcholinesterase inhibitors
  - Minimal efficacy for cognitive impairment
- Cognitive remediation
  - Anecdotal evidence of efficacy for cognition

Goals of Treatment

- Control active psychosis and mood symptoms
- Prevent future acute episodes
- Minimize progression of negative and cognitive symptoms
- Maximize functional capacity

*

Goals of Treatment

Functional Deficits

- Overall decline may be improved by medication impact on symptom progression
- Control of acute symptoms and avoidance of future acute episodes are the key to good outcome

*

First Generation Antipsychotics (FGA)

High Potency

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

First Generation Antipsychotics (FGA) High Potency

- Advantages
  - Injectable formulations (including IV)
  - Depot formulations
  - Inexpensive
- Disadvantages
  - High risk of EPS
  - High risk of tardive dyskinesia

*

First Generation Antipsychotics (FGA)

Low Potency

- Lower EPS risk
- Stronger anticholinergic effects
- More sedating
- Most common agents
  - Chlorpromazine (Thorazine)
  - Loxapine (Adasuve; Loxitane)
  - Thioridazine (Mellaril)

First Generation Antipsychotics (FGA) Low Potency

- Advantages
  - Highly sedating
  - Injectable formulations (including IV)
  - Inexpensive
- Disadvantages
  - High risk of qTc prolongation
  - High risk of tardive dyskinesia

Second Generation Antipsychotics (SGA)

- Aripiprazole (Abilify)
- Asenapine (Saphris)
- Iloperidone (Fanapt)
- Lurasidone (Latuda)
- Olanzapine* (Zyprexa)
- Paliperidone (Invega)
- Quetiapine* (Seroquel)
- Risperidone* (Risperdal)
- Ziprasidone* (Geodon)
- Clozapine* (Clozaril) - Second-line use only

*Generic available

Second Generation Antipsychotics (SGA) (Atypical Antipsychotics)

- Advantages
  - Fewer EPS
  - Decreased risk of tardive dyskinesia
- Disadvantages
  - Higher cost
  - No IV formulation

*

Clozapine

- Advantages
  - Effective for 30-50% of treatment-refractory patients
  - Most effective for negative symptoms
  - Only proven treatment for tardive dyskinisia
- Disadvantages
  - Risk of agranulocytosis
  - Weekly, biweekly, or monthly blood draws
  - Unfavorable side effect profile

*

Depot Antipsychotics

- Aripiprazole long acting (Abilify Maintena)
- Fluphenazine (Prolixin) decanoate
- Haloperidol (Haldol) decanoate
- Olanzapine pamoate (Relprevv)*
- Paliperidone palmitate (Invega Sustenna)
- Risperidone long acting (Risperdal Consta)

*Requires administration in qualified setting due to postinjection delirium/sedation syndrome

Depot Antipsychotics

	Loading Protocol	Onset of Action	Usual Dosing Interval
Aripiprazole	No	5 days	4 weeks
Fluphenazine	No	1 day	2 weeks
Haloperidol	Yes	1 day	4 weeks
Olanzapine	Yes	1 day	2-4 weeks
Paliperidone	Yes	1 day	4 weeks
Risperidone	No	3-4 weeks	2 weeks

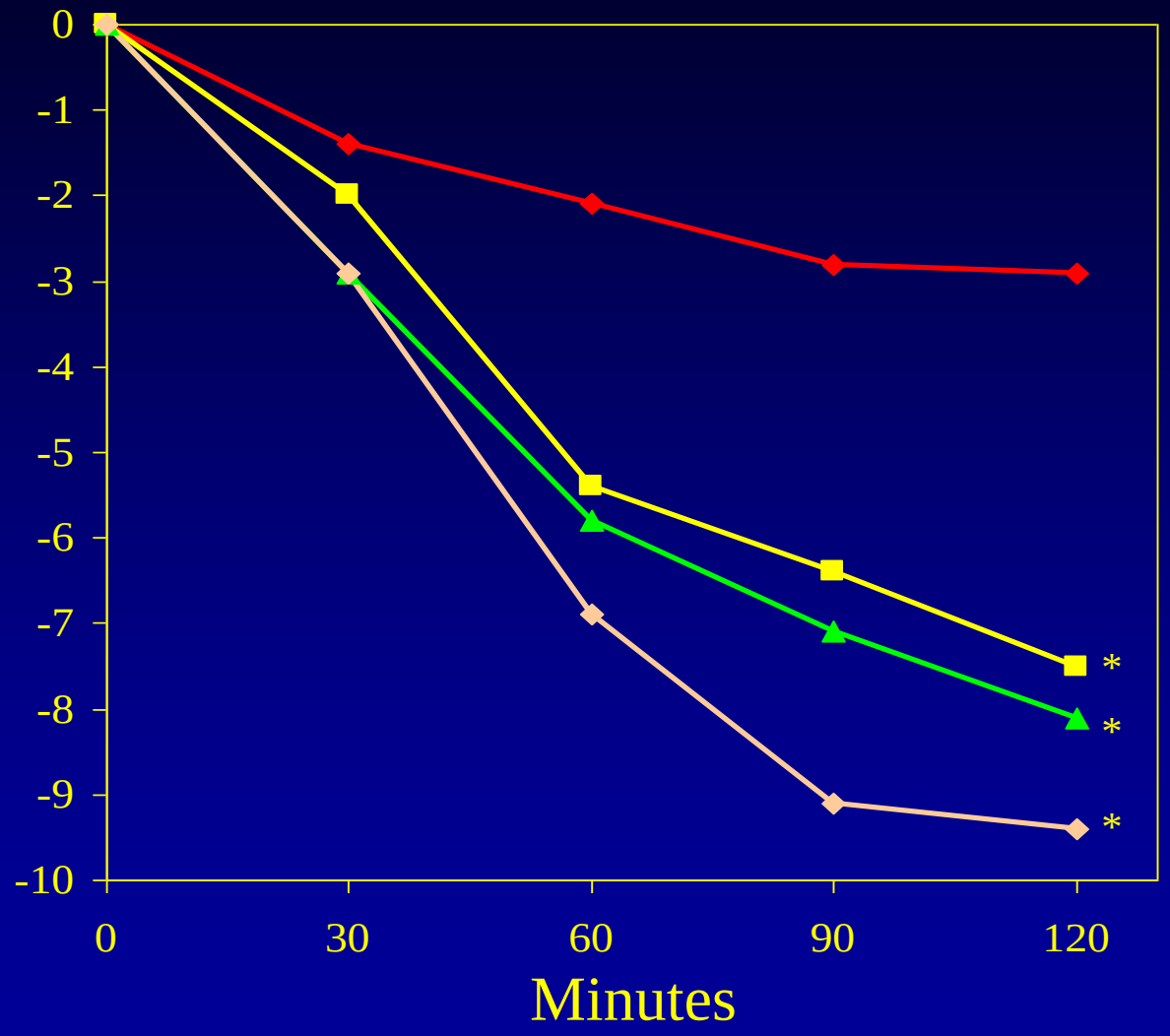
*

Depot Antipsychotics

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

*

Efficacy of Antipsychotics for Acute Agitation



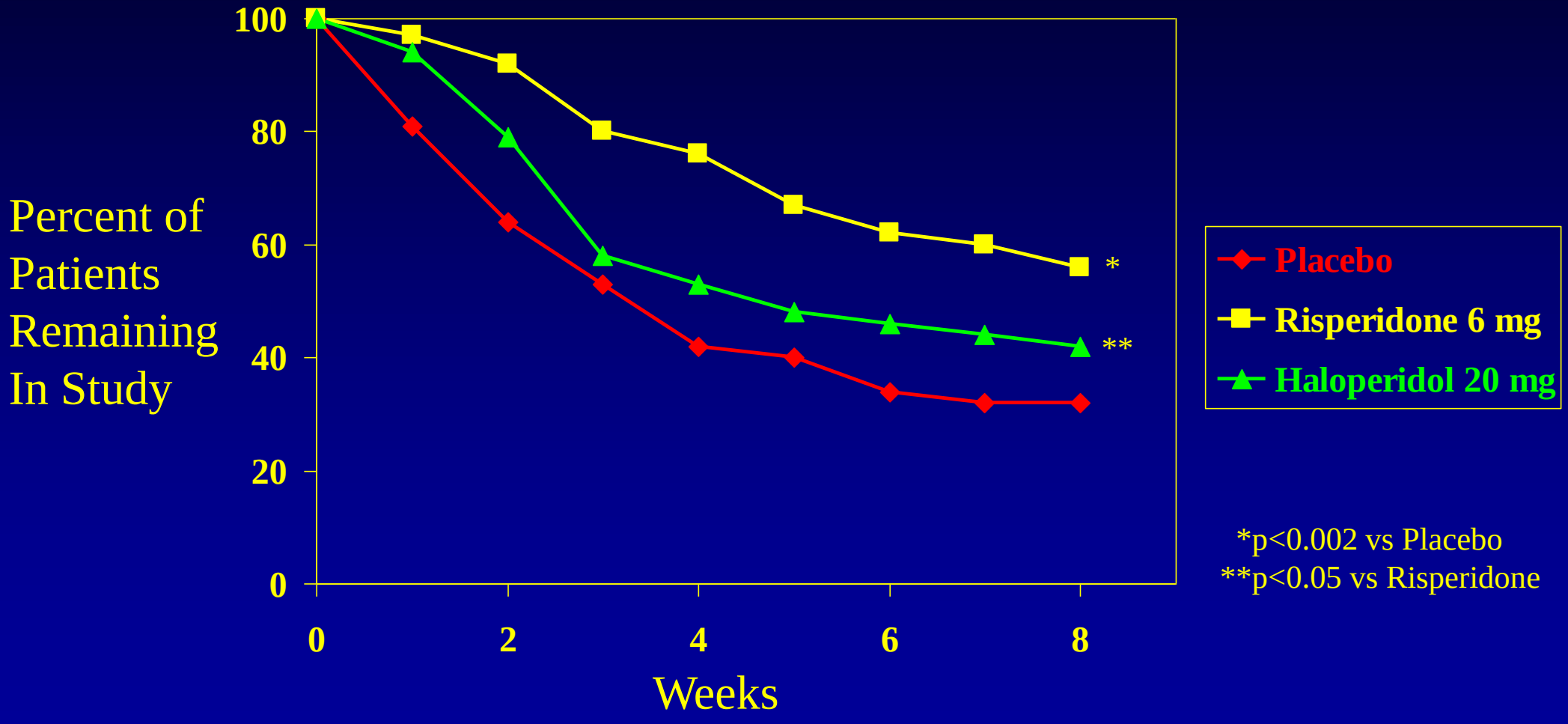
*p<0.001 vs Placebo

Olanzapine vs Haloperidol not significant

Breier A, et al., Arch Gen Psychiatry 2002;59:441

*

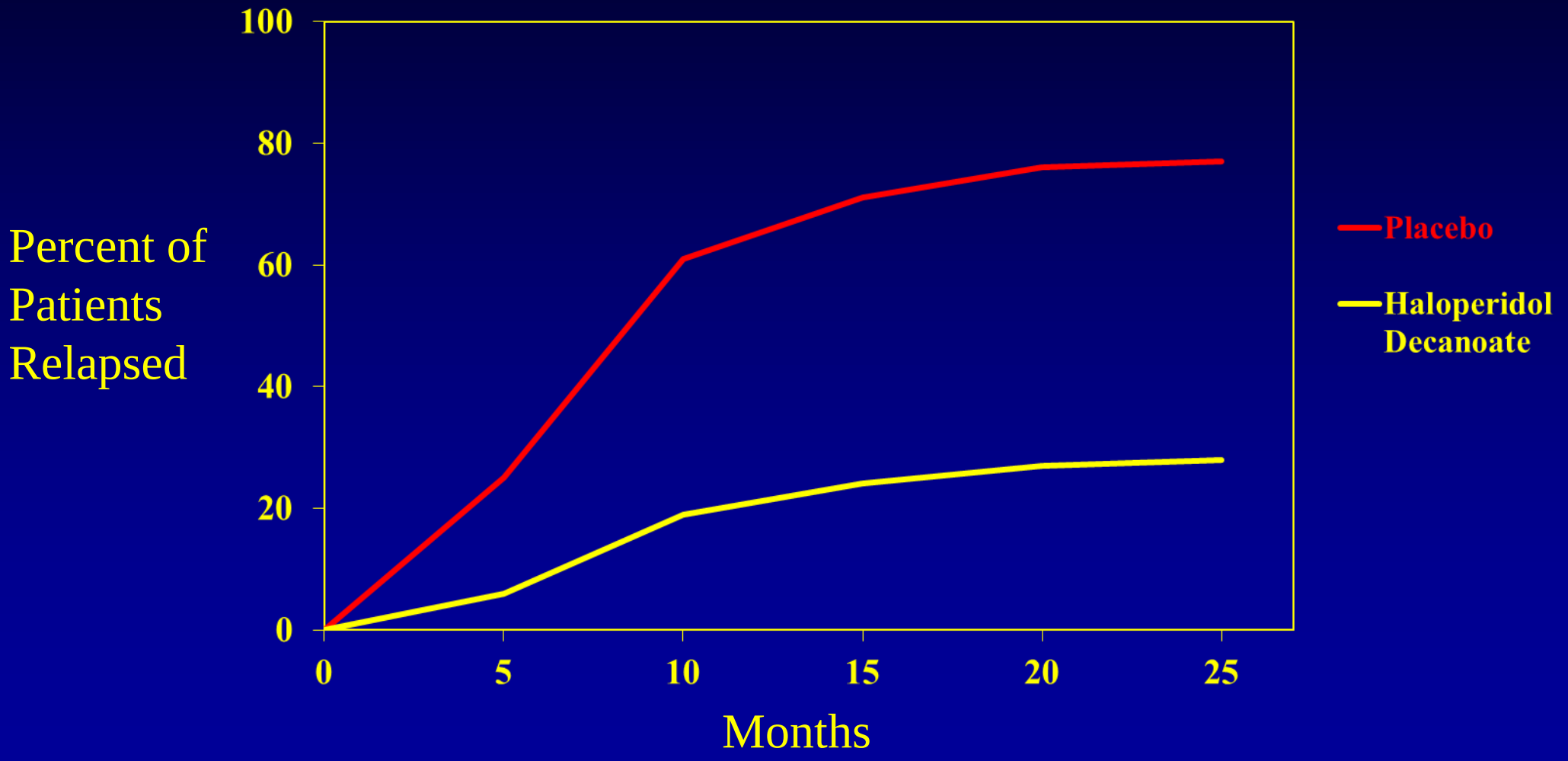
Efficacy of Antipsychotics for Short-term Treatment of Schizophrenia



Marder SR & Meiback RC, Am J Psychiatry 1994;151:825

*

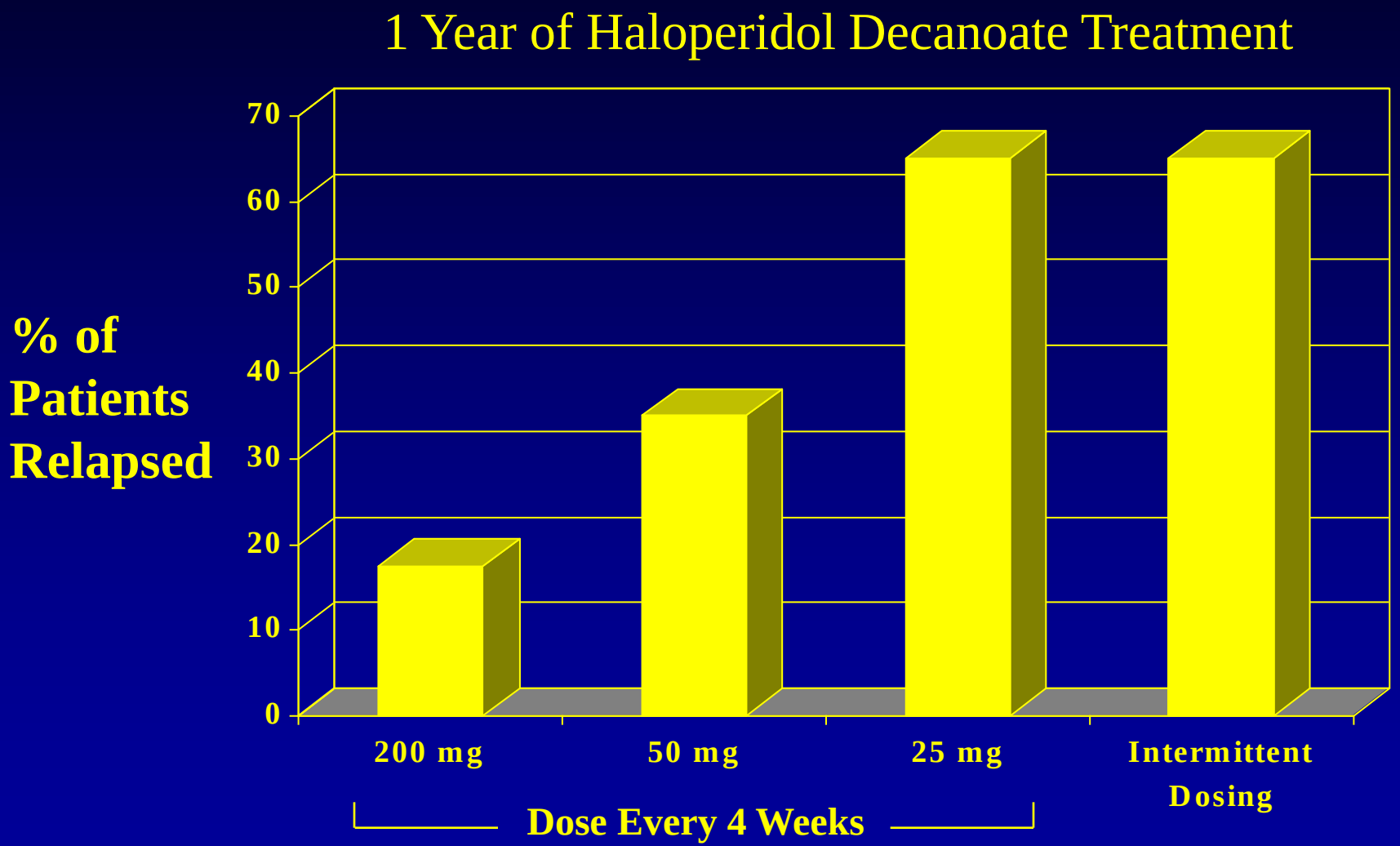
Efficacy of Antipsychotics for Long-term Prevention of Schizophrenia Relapse



Hogarty GE & Goldberg, SC, Arch Gen Psychiatry 1973;28:54

*

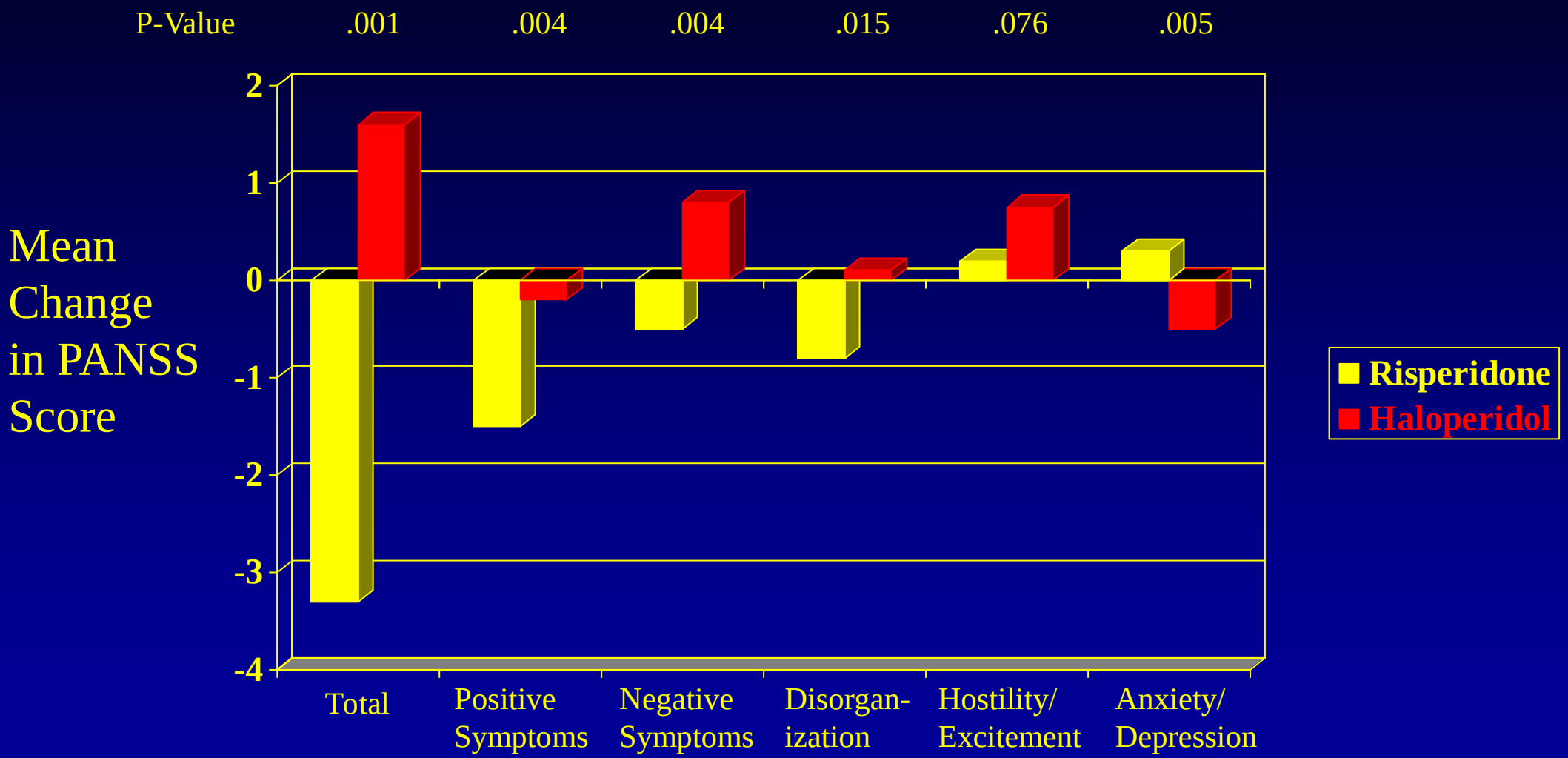
Relationship between Medication Dose and Relapse in Schizophrenia



Davis JM, et al., J Clin Psychiatry 1993;54(Suppl):24

*

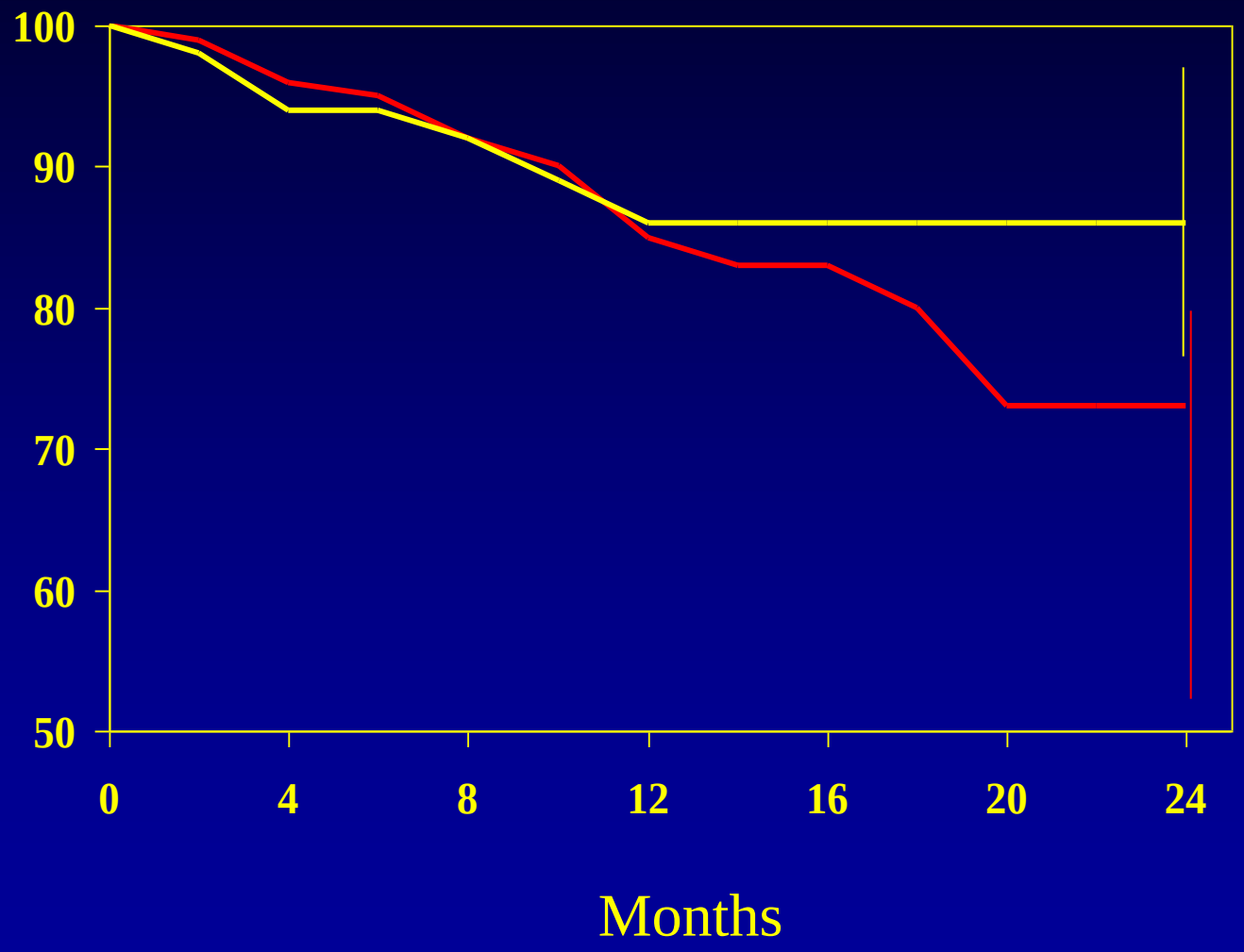
Efficacy of Antipsychotics for Schizophrenia Symptoms at 2 Years



Csernansky JG, et al., NEJM 2002;346:16

*

Clozapine for Long-term Schizophrenia Treatment



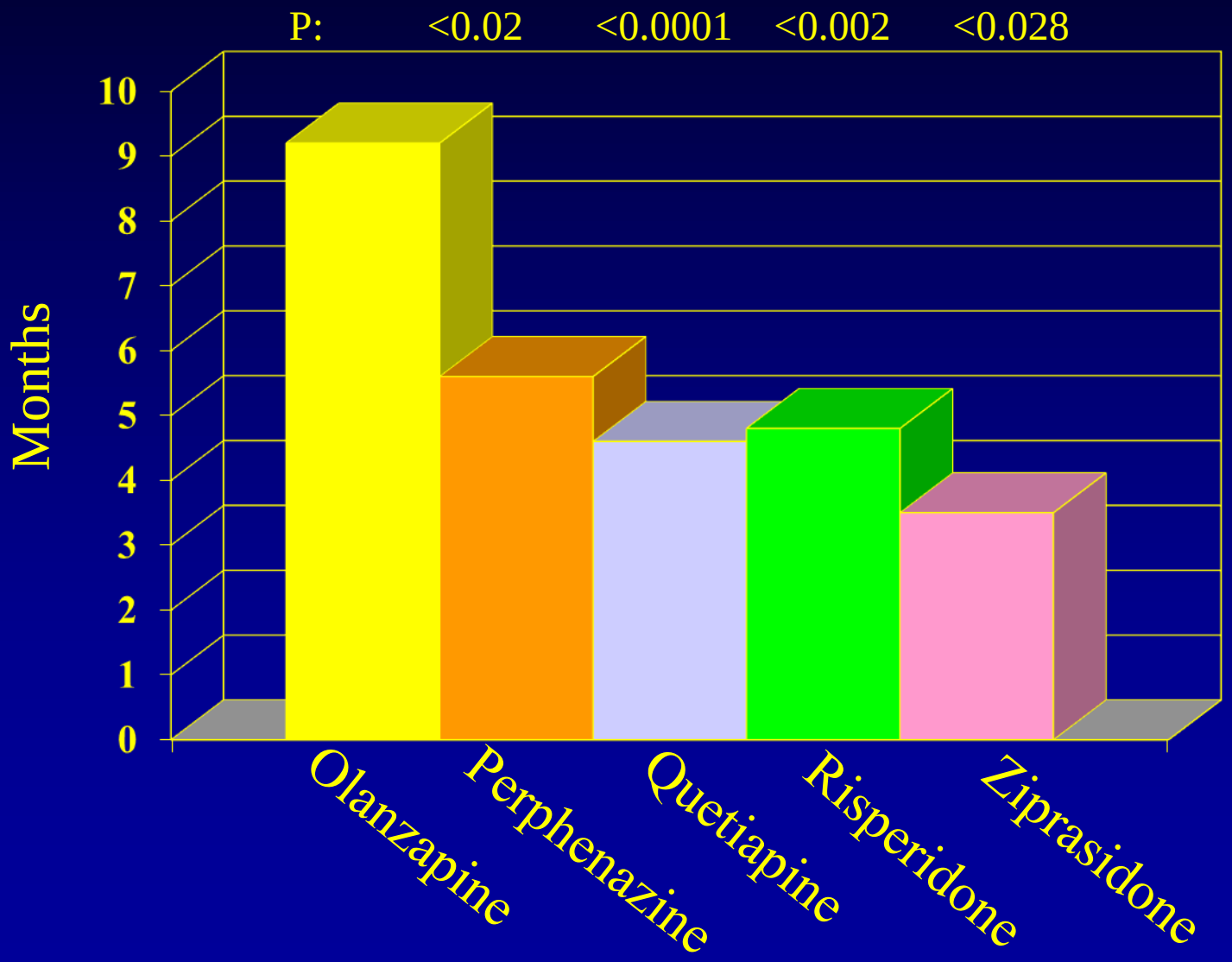
95% CI:
Clozapine 77-97
Risperidone 52-80

Conley RR, et al., Am J Psychiatry 1999;156:863

*

CATIE

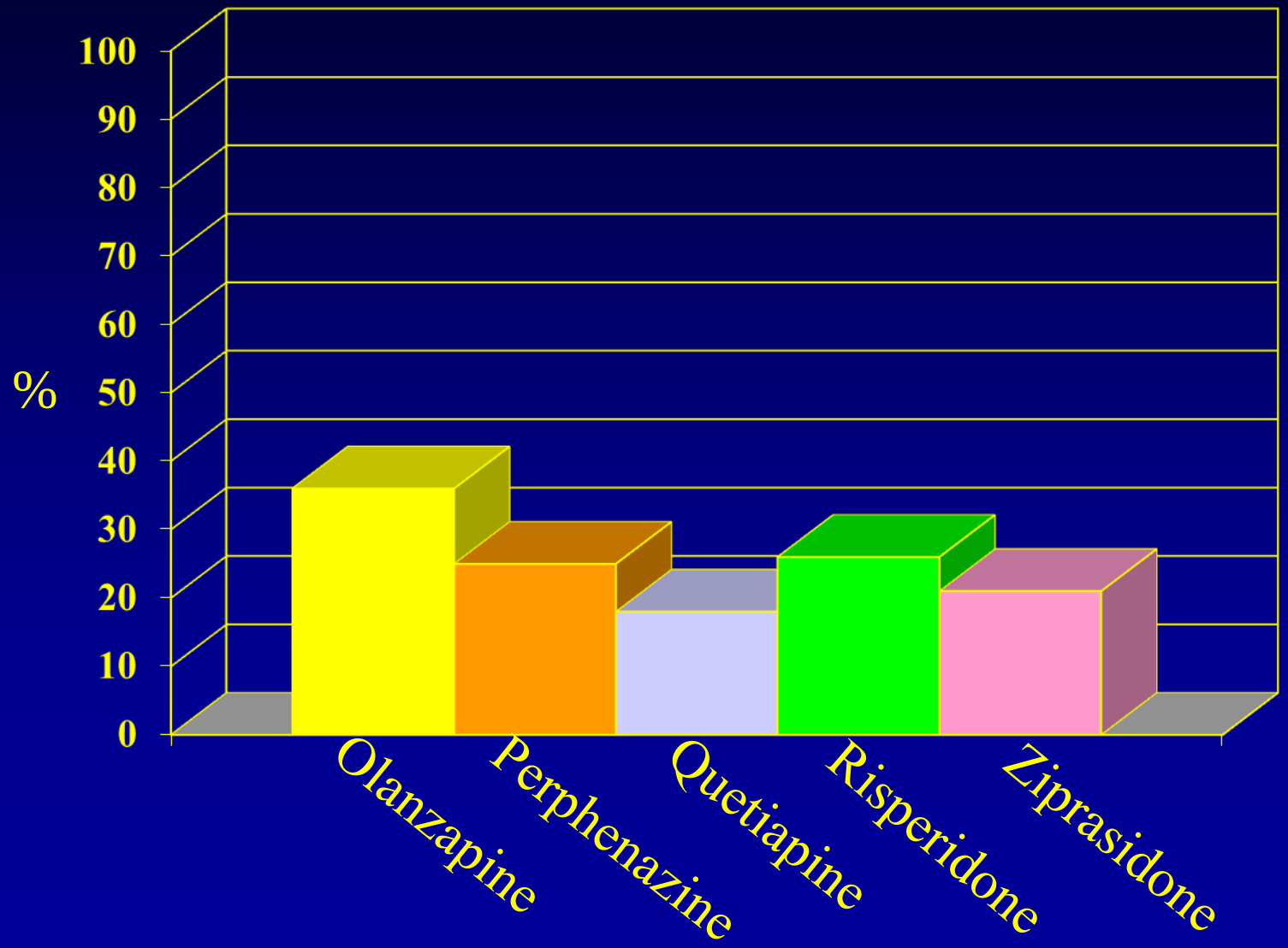
Duration of Treatment



*

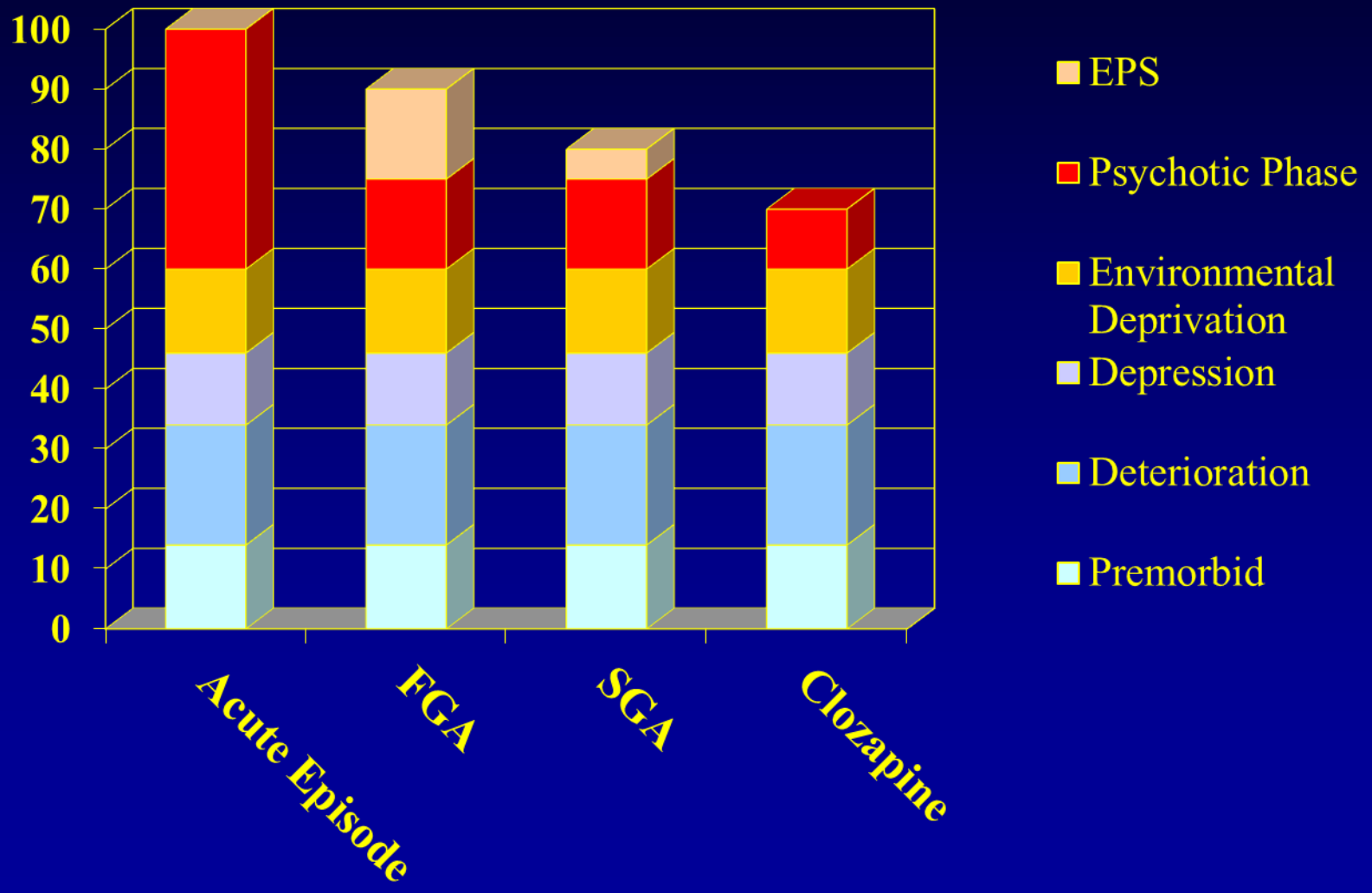
CATIE

Patients Completing 18 Months of Treatment



*

Treatment of Negative Symptoms



*

Treatment of Neurocognitive Deficits

- Atypical antipsychotics have better cognitive profiles than conventional agents
- Atypical antipsychotics do not return cognitive functions to normal
- Neurocognitive benefits of atypical antipsychotics are of minor clinical significance

Antipsychotic Treatment Selection

- All antipsychotics are effective for:
  - Acute agitation
  - Acute psychosis
  - Acute bipolar mania
  - Maintenance treatment of schizophrenia

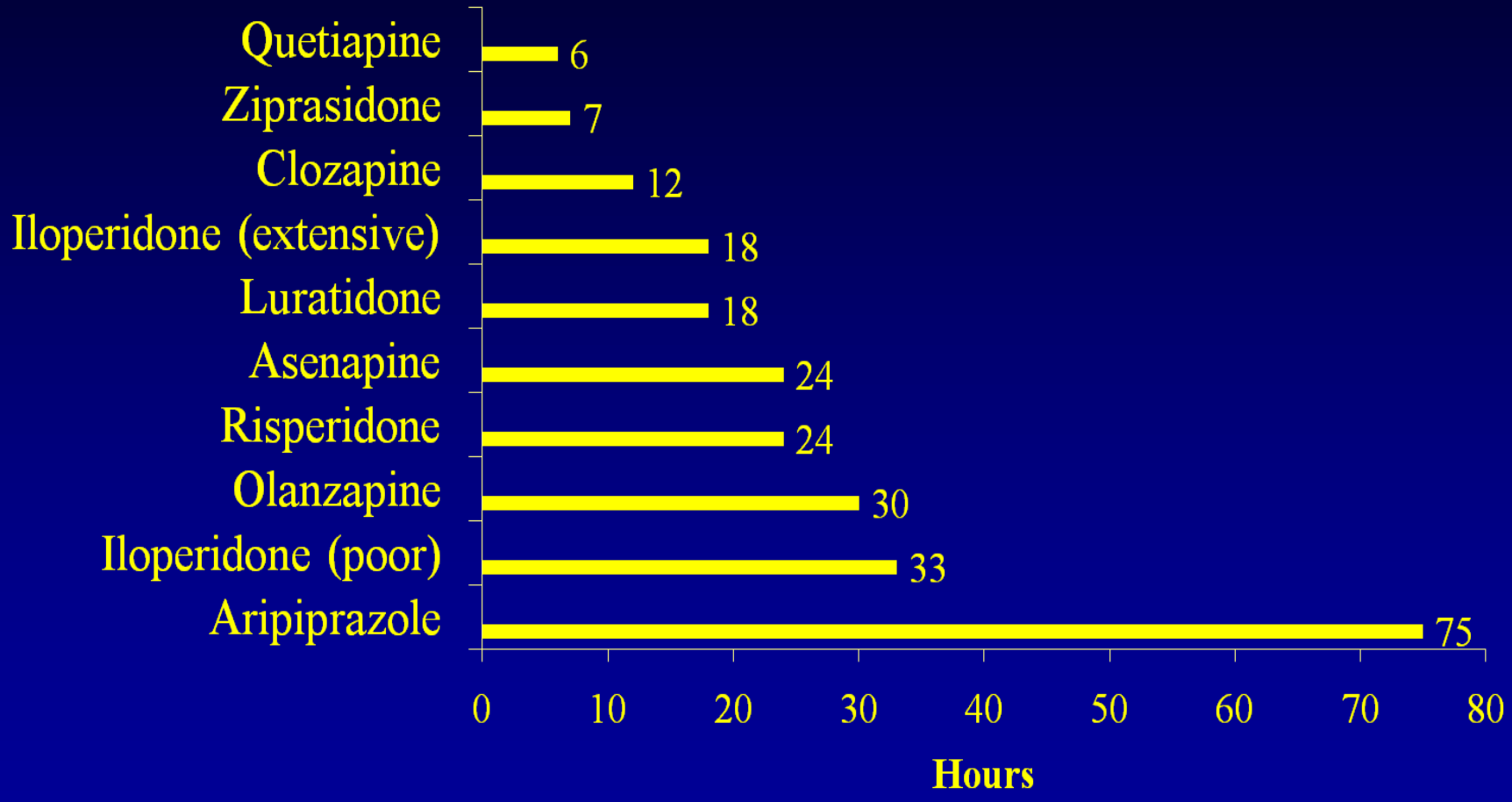
Antipsychotic Treatment Selection

- Differences in efficacy among most antipsychotics tend to be small in large studies
- Individual patients often respond preferentially to specific medications
- Olanzapine provides modest benefit for continuity of treatment
- Clozapine provides clear benefit for treatment refractory patients

Antipsychotic Treatment Selection

- Antipsychotics differ greatly across classes and even within class in:
  - Formulation (eg, oral disintegrating tablets, short-acting injectable, long-acting injectable)
  - Pharmacokinetics (rate of absorption, clearance rate, route of metabolism)
  - Side effect profile (EPS, weight gain, cardiac effects)
  - Cost

Elimination Half-Times



Side Effects of SGAs

	Olanz	Quet	Risp	Asen	Iloper	Luras	Paliper	Aripip	Zipras	Cloz
EPS	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	-
Dose Related EPS	+	+/-	++	+	+/-	+	++	+	+	-
Anticholin-ergic Effects	+	++	+/-	+/-	+	-	+/-	+/-	+/-	+++
Orthostatic Hypoten-sion	+	++	++	+/-	+++	+	++	+	+	+++
Sedation	++	+++	+	++	+	++	+	+	+	+++
Weight Gain	+++	++	++	++	++	+/-	++	+	+	+++
QT Changes	+/-	+	+	+	++	-	+	+/-	++	+
Prolactin Elevation	+/-	+/-	++	++	-	+	++	+/-	+/-	-
Tardive dyskinesia	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	-

*

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 Medication

- High-potency FGA
- Low-potency FGA
- Paliperidone/Risperidone
- Aripiprazole/Asenapine/Iloperidone/Lurasidone/ Olanzapine/Ziprasidone
- Quetiapine/Clozapine

*

Extrapyramidal Symptoms (EPS)

Treatment

- Benztropine (Cogentin) 0.5-2 mg q6hr prn
- Trihexyphenidyl (Artane) 2-5 mg q6hr prn
- Amantadine 100 mg bid-tid prn
- To avoid unnecessary long-term exposure to anticholinergics, prn use is preferred to scheduled dosing

*

Metabolic Syndrome

Use of atypical antipsychotics is associated with metabolic dysregulation

- 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 FGAs
- Iloperidone/Paliperidone/Quetiapine/ Risperidone/High Potency FGAs
- Asenapine
- Aripiprazole/Lurasidone/Ziprasidone

*

Metabolic Syndrome

Recommended monitoring for patients on 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

ADA et al., Diabetes Care 2004; 27:596

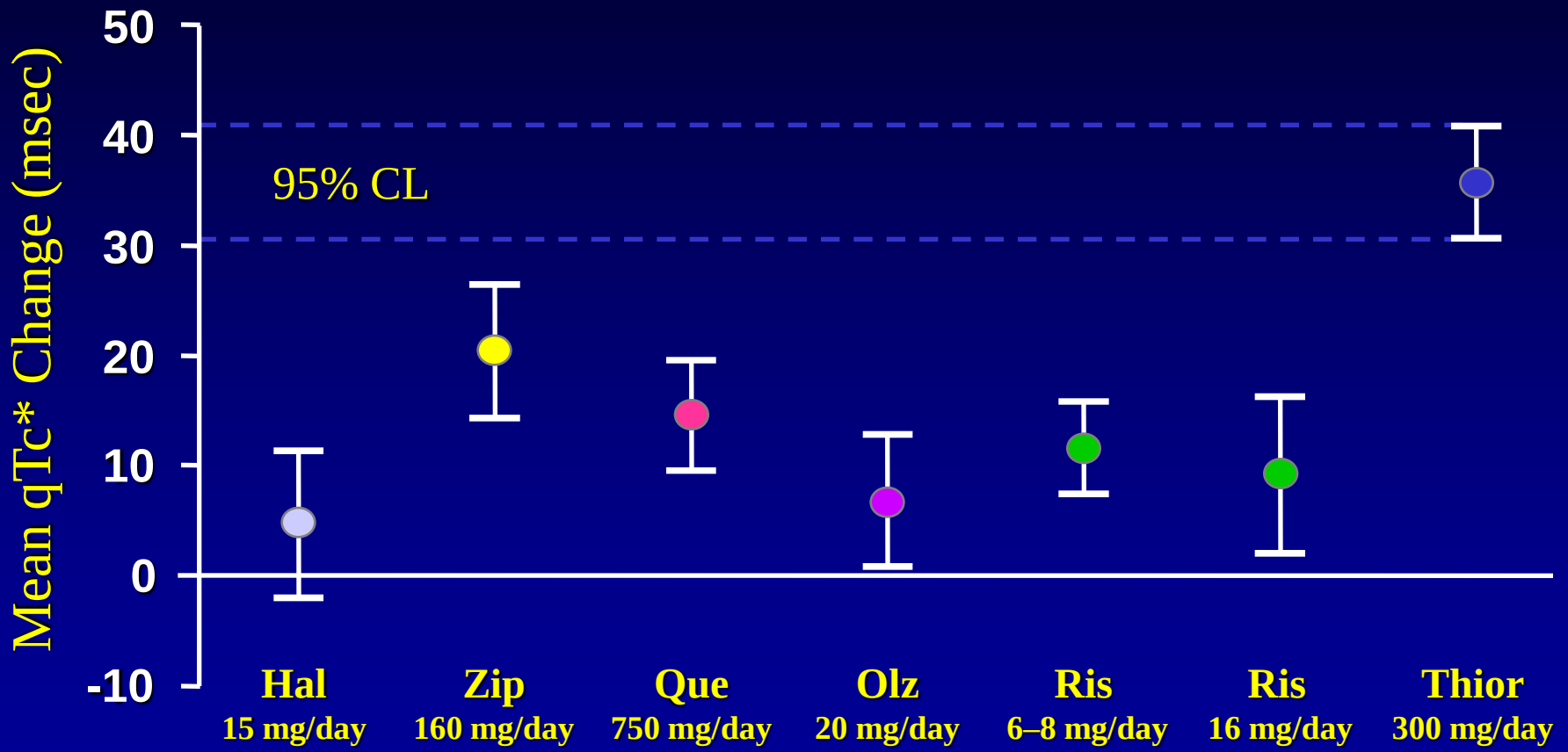
*

Cardiovascular Adverse Events

- Thioridazine (Mellaril) carries a “black box” warning of qT prolongation and increased risk of cardiac death
- Ziprasidone (Geodon) carries a “bold” warning regarding qT 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

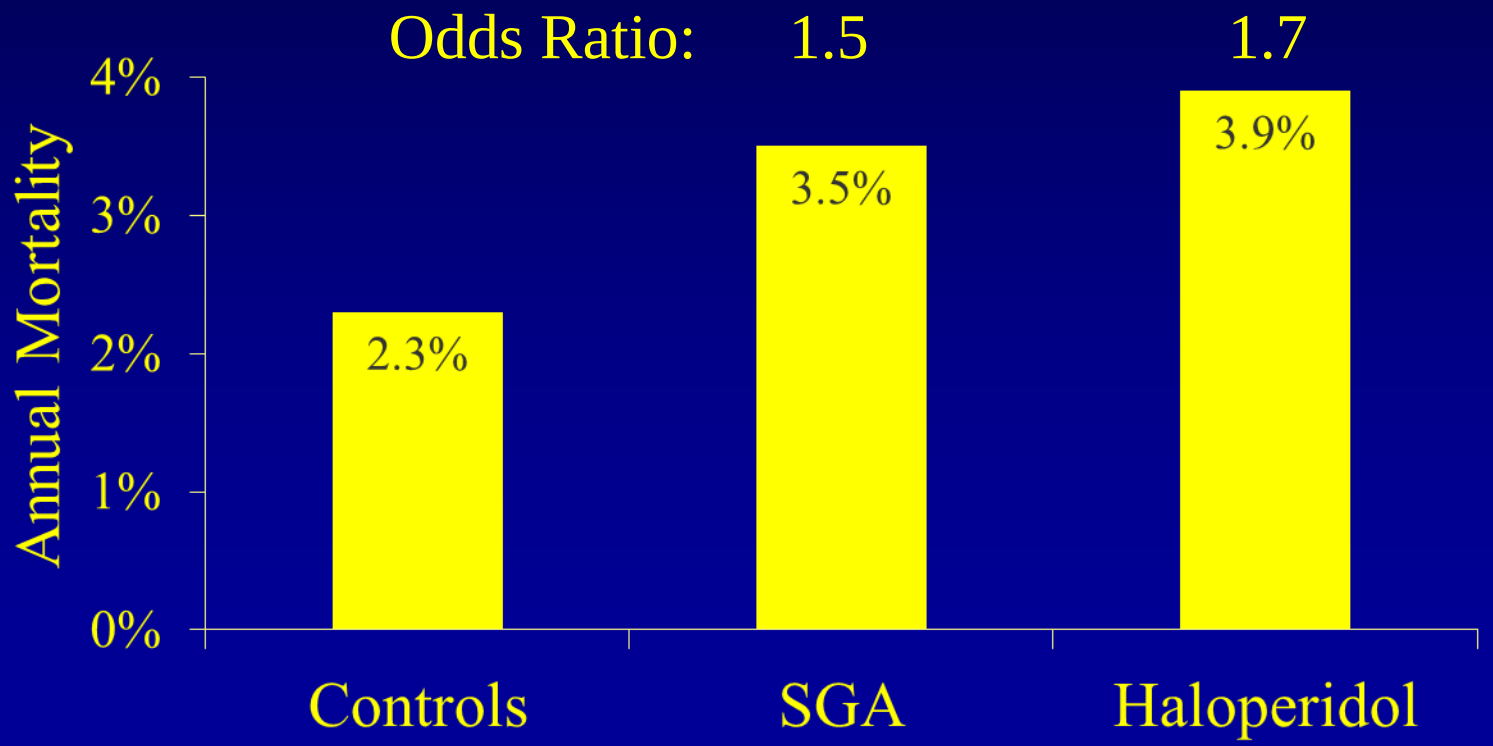
- All antipsychotics carry a “black box” warning of increased mortality in elderly patients with dementia-related psychosis
- Risk is comparable among all FGAs and SGAs
- Risk is related to age, not diagnosis

*

Increased Mortality

Risk of FGAs and SGAs in elderly patients

(Meta-analysis of 15 studies)



*

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

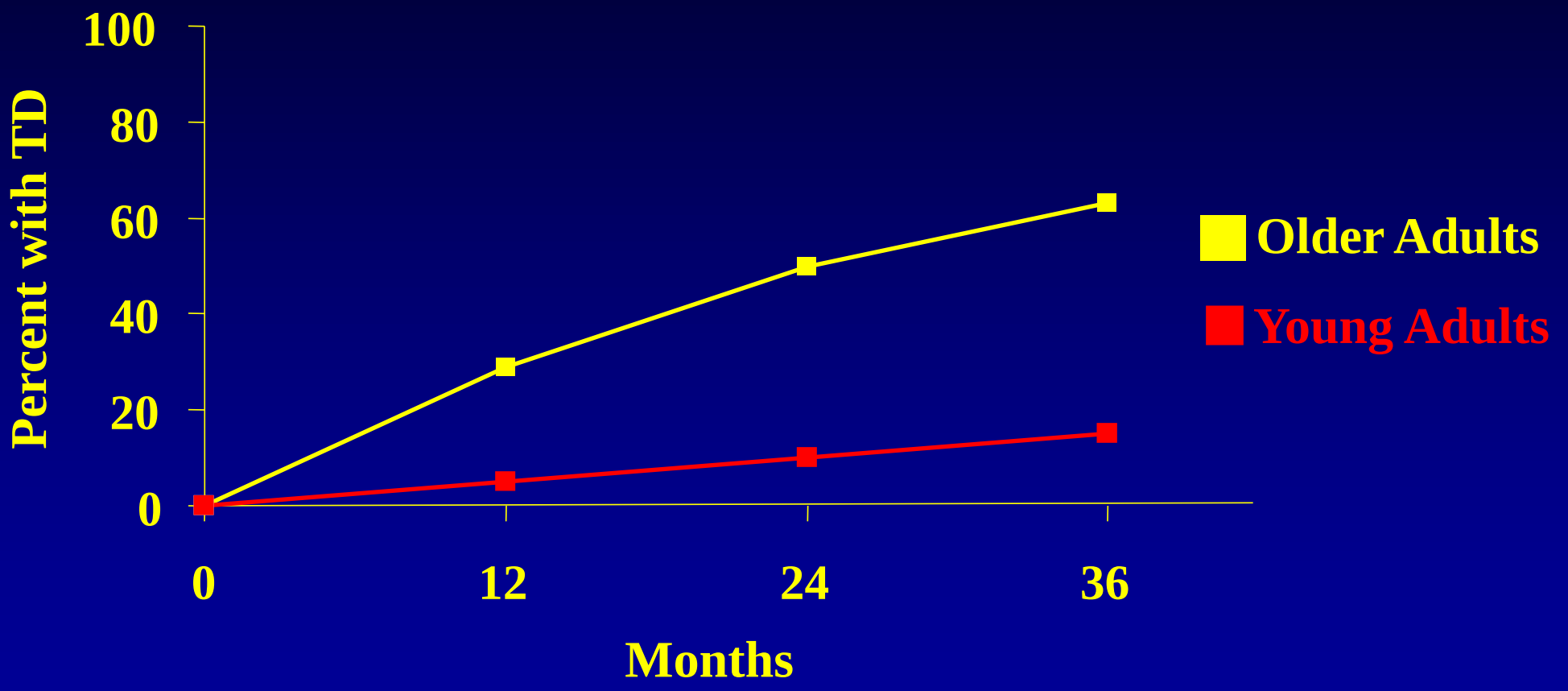
*

Tardive Dyskinesia

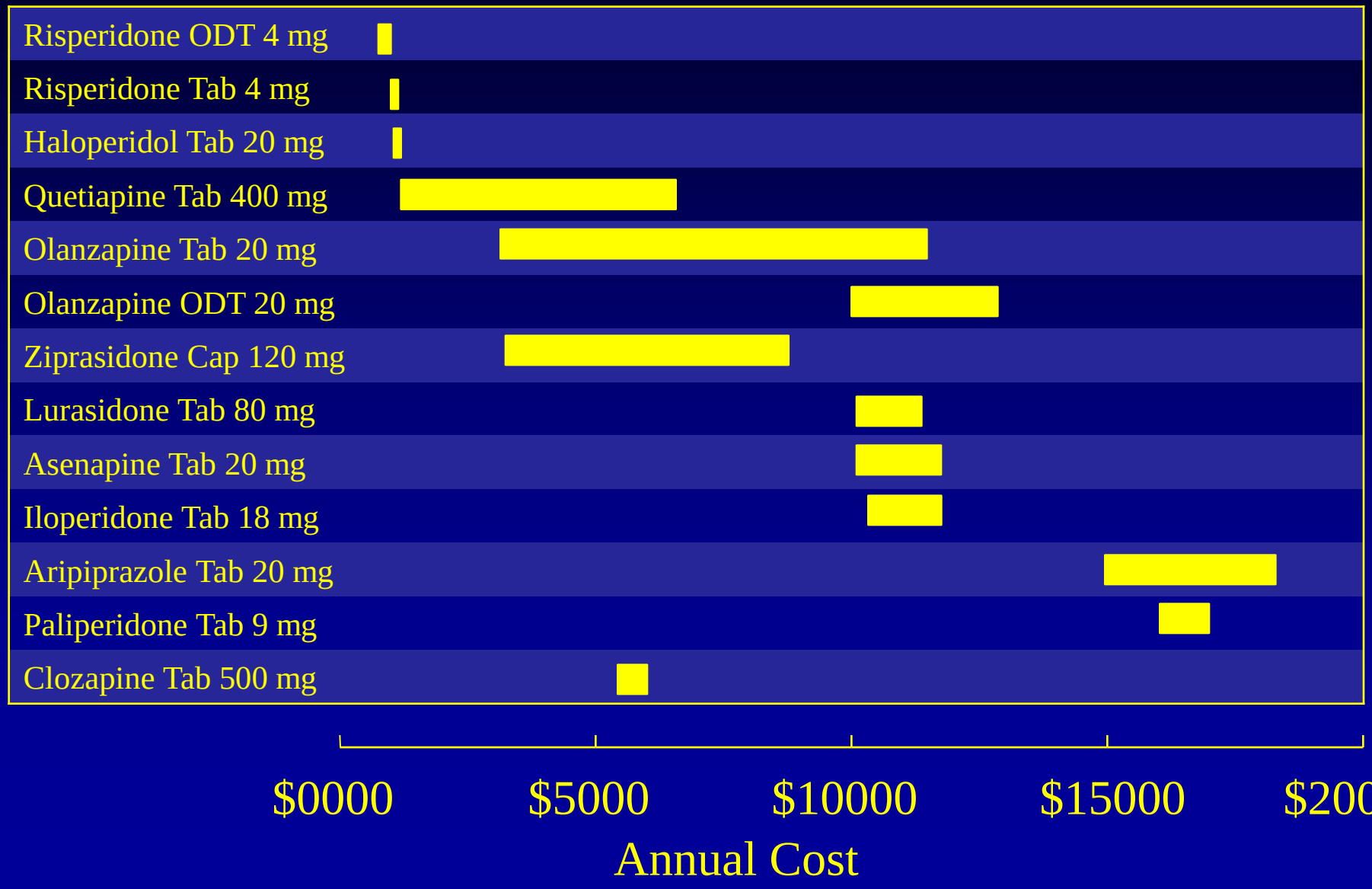
Risk by class of medication:

- High potency FGA (7%/yr)
- Low potency FGA (5%/yr)
- SGA (0.5%/yr)
- Clozapine (none reported)

Risk by Age with FGAs



Relative Costs of Oral Antipsychotic Medications



Antipsychotic Augmentation Strategies

- Augmentation strategies have generally shown modest results
- No one strategy is generally accepted
  - Mood stabilizers
  - Benzodiazepines
  - Antidepressants
  - Antipsychotic combinations
  - ECT

Antipsychotic Combinations

- 20-25% of patients receive more than one antipsychotic
- Few data are available on efficacy and safety of antipsychotic combinations
- Anecdotal accounts of specific combinations have not been supported by formal studies
- Pharmacologic justification is weak
- Side effects tend to be additive
- Costs are always additive

Psychosocial Interventions

WHO International Pilot Study on Schizophrenia and Determinants of Outcome

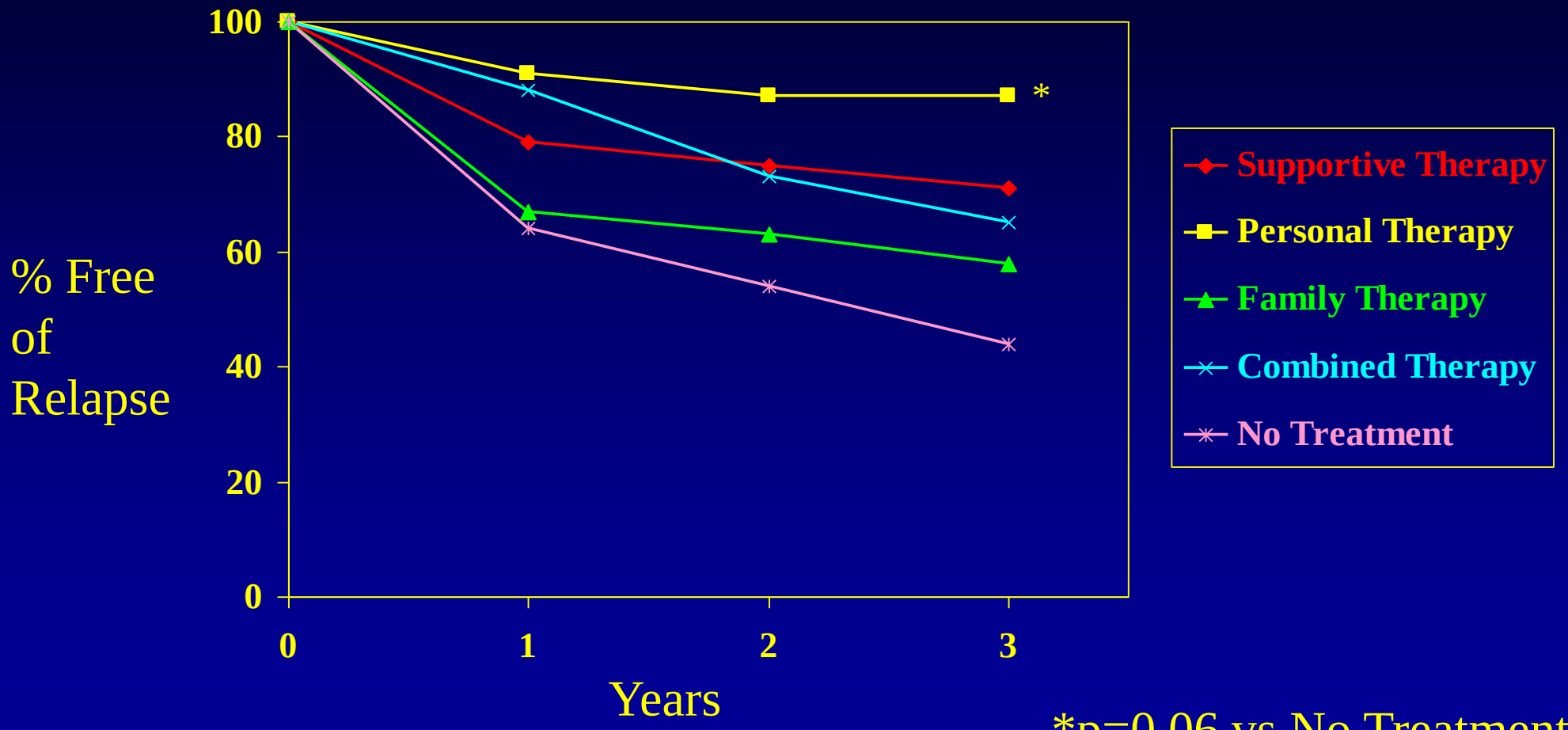
- Outcomes for schizophrenia are better in developing than industrialized countries
- Possible factors in developing countries:
  - Intact families
  - Greater community support network
  - Fewer social and occupational demands
  - Greater acceptance of psychotic behavior

Psychosocial Treatments

- Case management
- Assertive community treatment (ACT)
- Family interventions
- Social skills training
- Vocational rehabilitation
- CBT
- Supportive psychotherapy

*

Psychosocial Treatment



*p=0.06 vs No Treatment

*

Treatment Recommendations

- 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

- Depot 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:
    a. Auditory hallucinations
    b. Blunted affect
    c. Depressed mood
    d. Persecutory delusions
    e. Thought disorganization

Post-test

2. Clinical efficacy of antipsychotic medications is highly correlated with:
   a. Dopamine D1 binding
   b. Dopamine D2 binding
   c. Serotonin binding
   d. The ratio of D1/D2 binding
   e. The ratio of D2/serotonin binding

Post-test

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

Post-test

4. Which first-line atypical antipsychotic has the lowest risk of extrapyramidal side effects?
   a. Aripiprazole
   b. Olanzapine
   c. Quetiapine
   d. Risperidone
   e. Ziprasidone

Post-test

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

Answer Key

1. b
2. b
3. a
4. c
5. e