Schizophrenia and Antipsychotic Medications

Model Curriculum

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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

Outline

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

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

Negative Symptoms

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

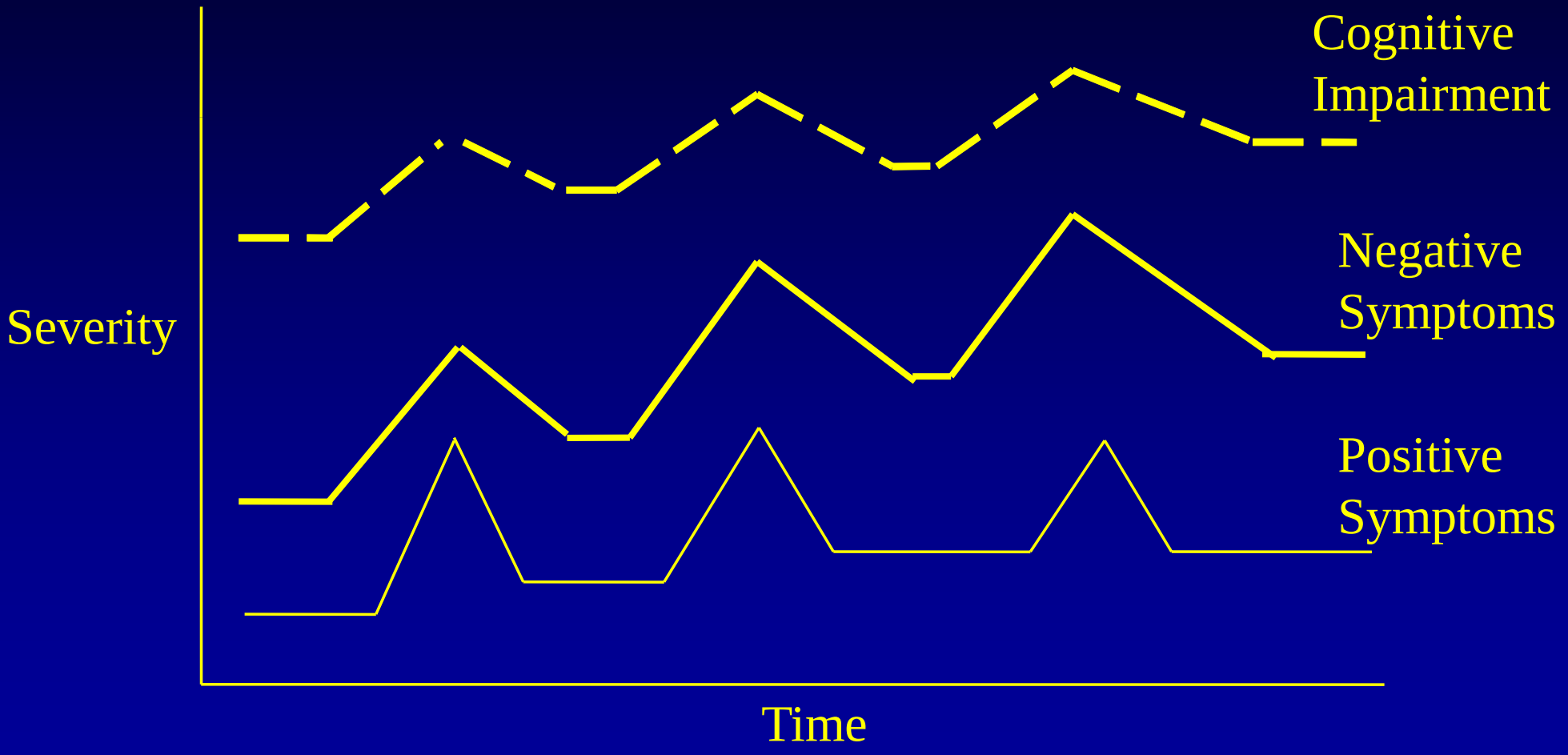
Cognitive Deficits

- Memory
- Attention
- Language
- Executive Function

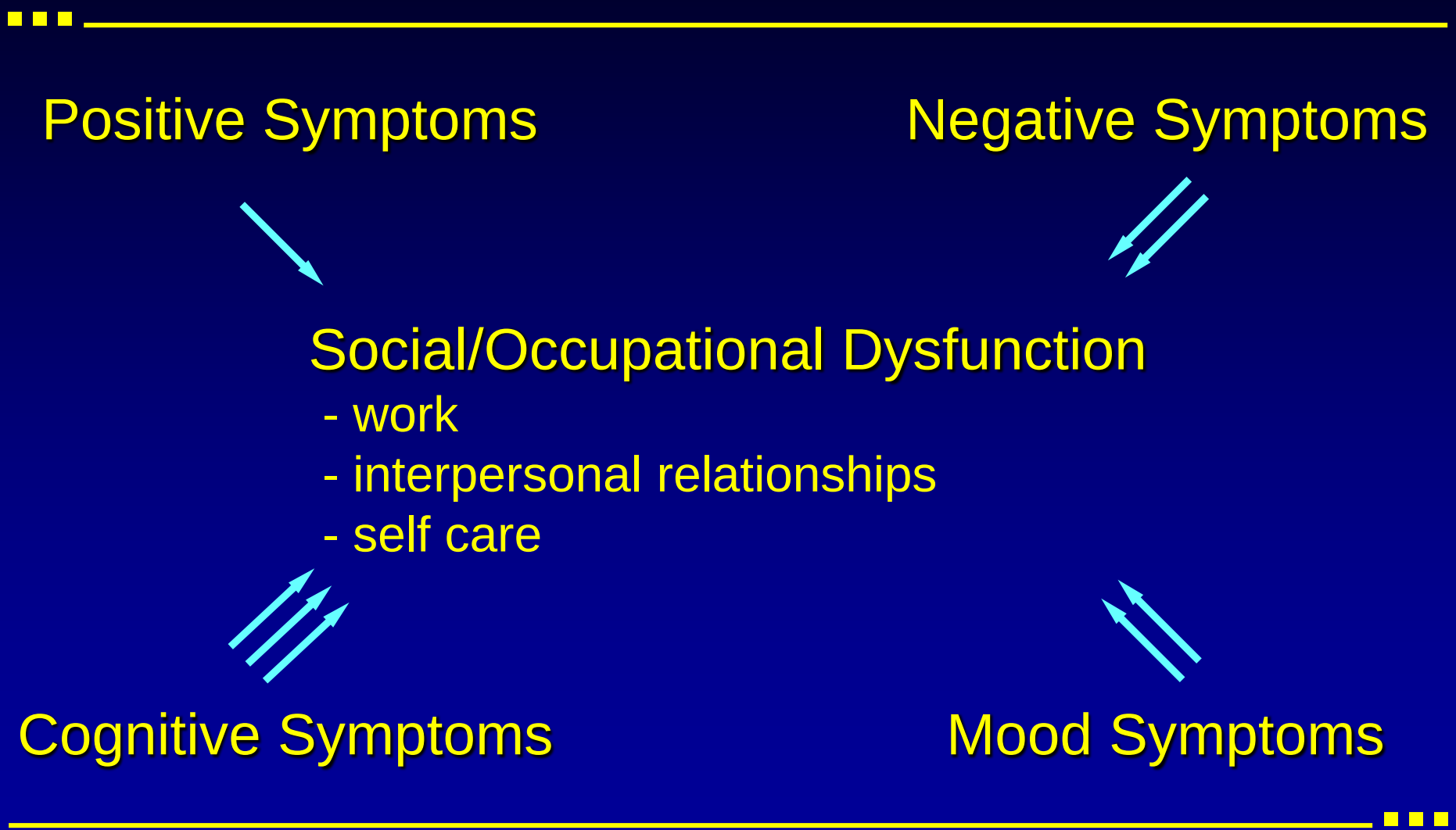
Mood Symptoms

- Depression
- Dysphoria
- Suicidality

Course of Symptom Subtypes

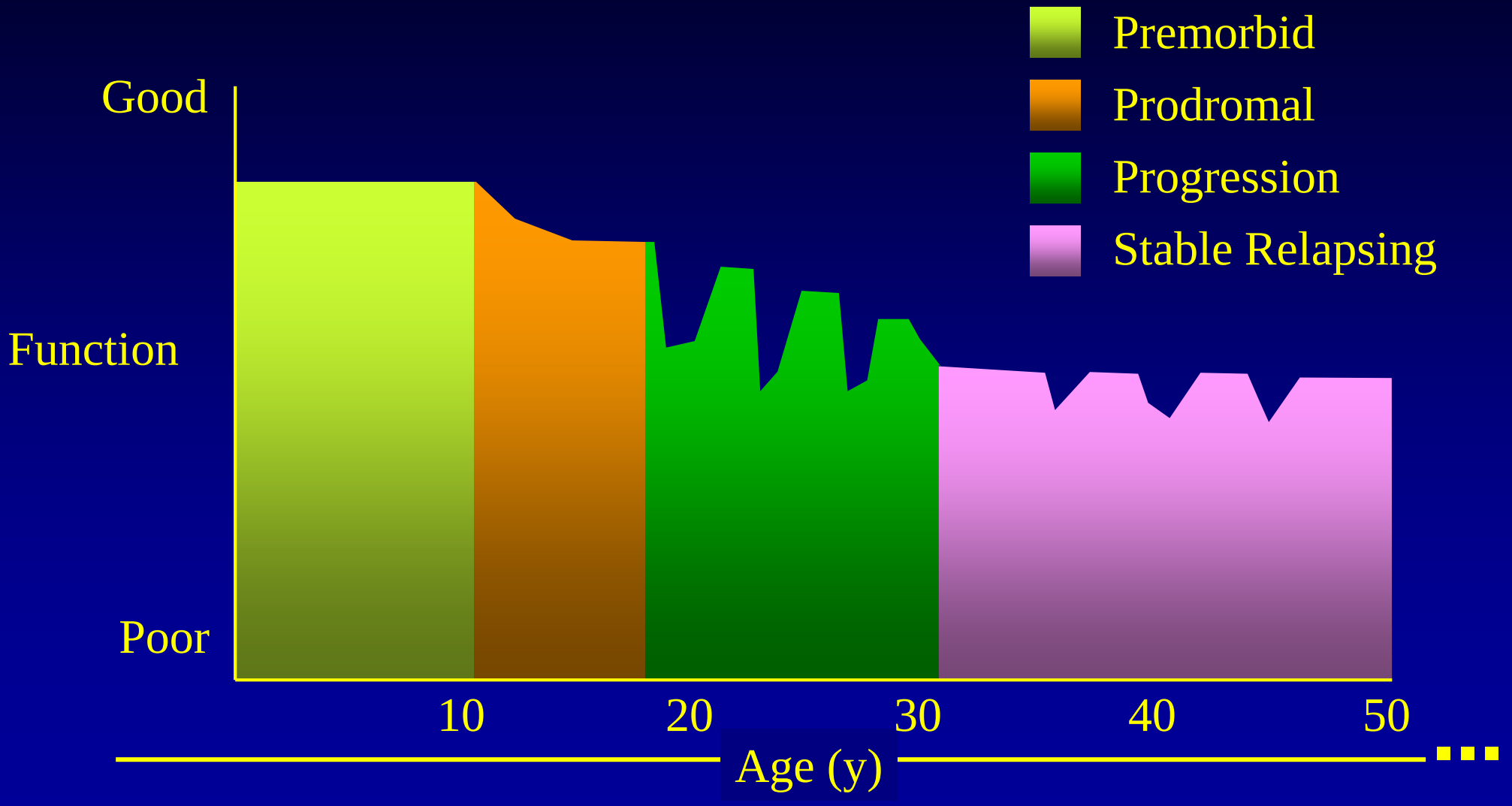


Contributions to Functional Impairment

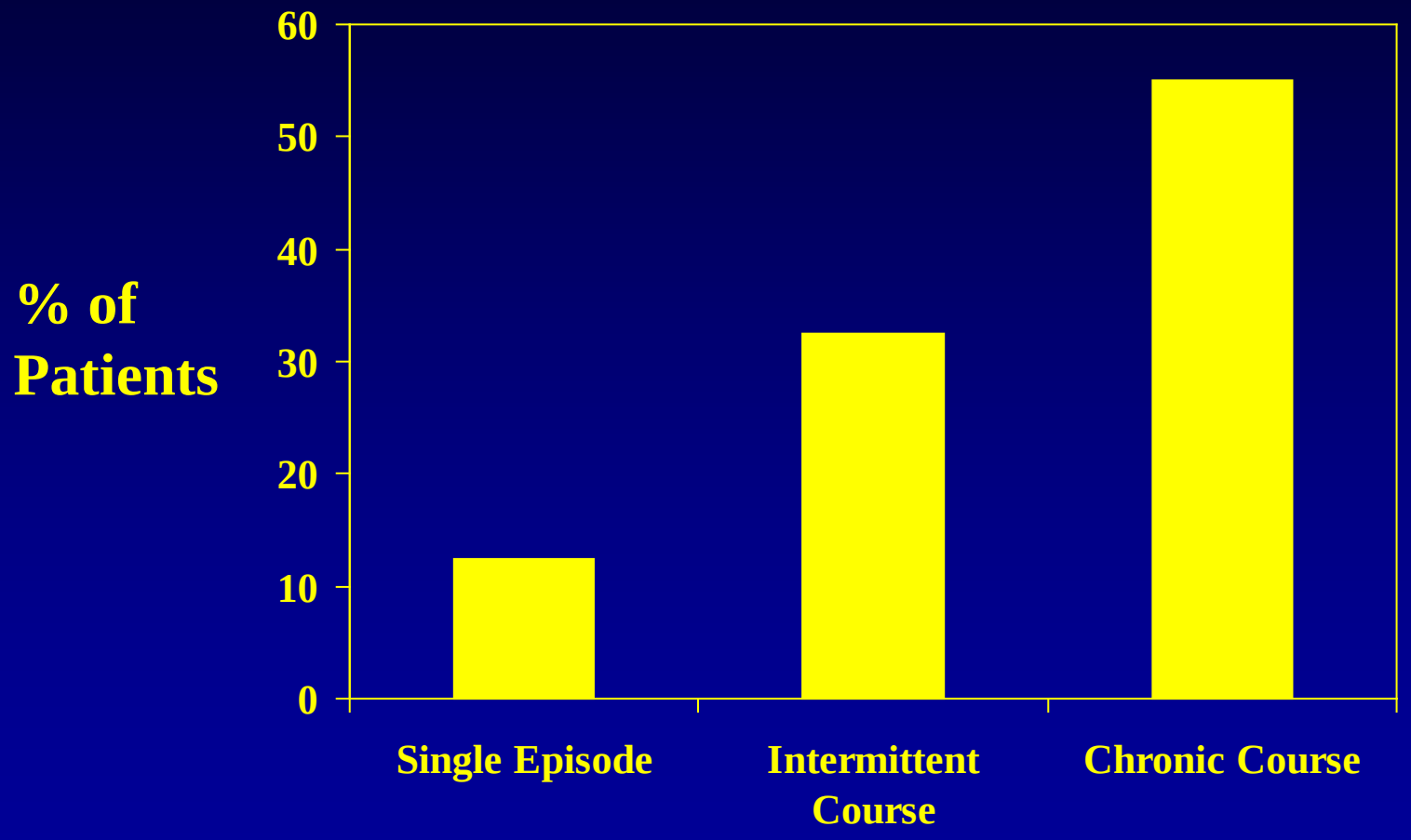


Adapted with permission from Michael F. Green, Ph.D.

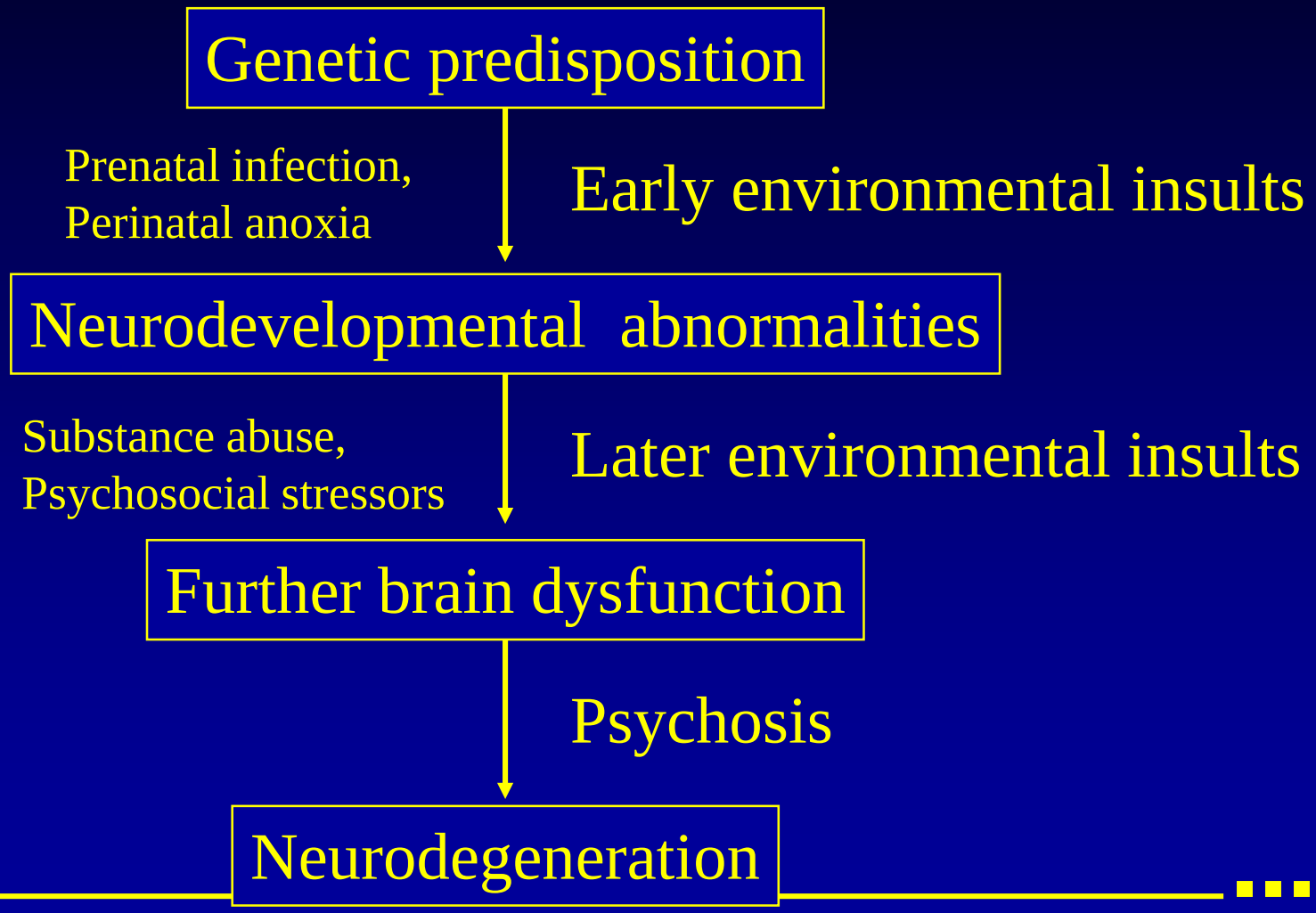
Natural History of Schizophrenia



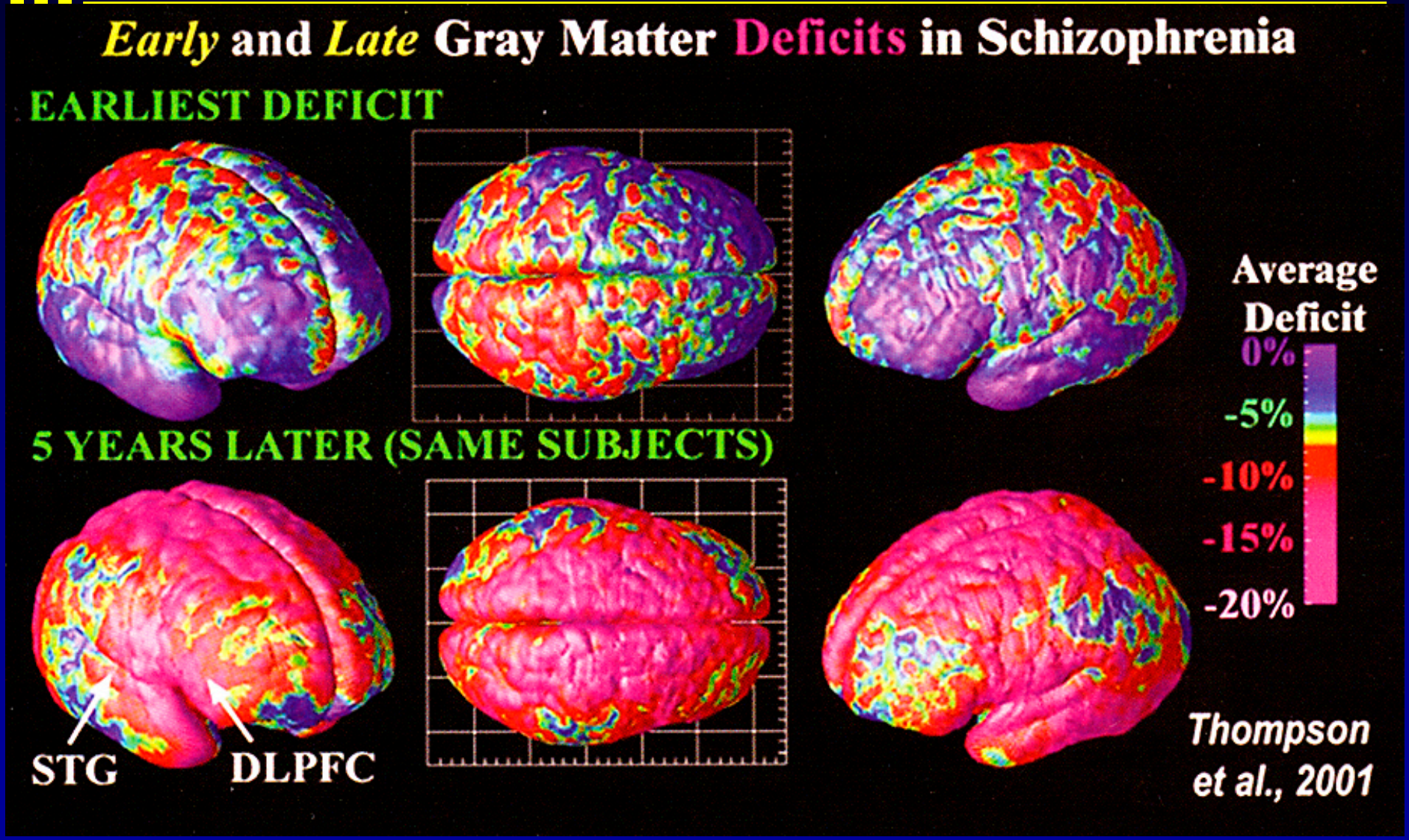
Natural History of Schizophrenia



Etiology of Schizophrenia



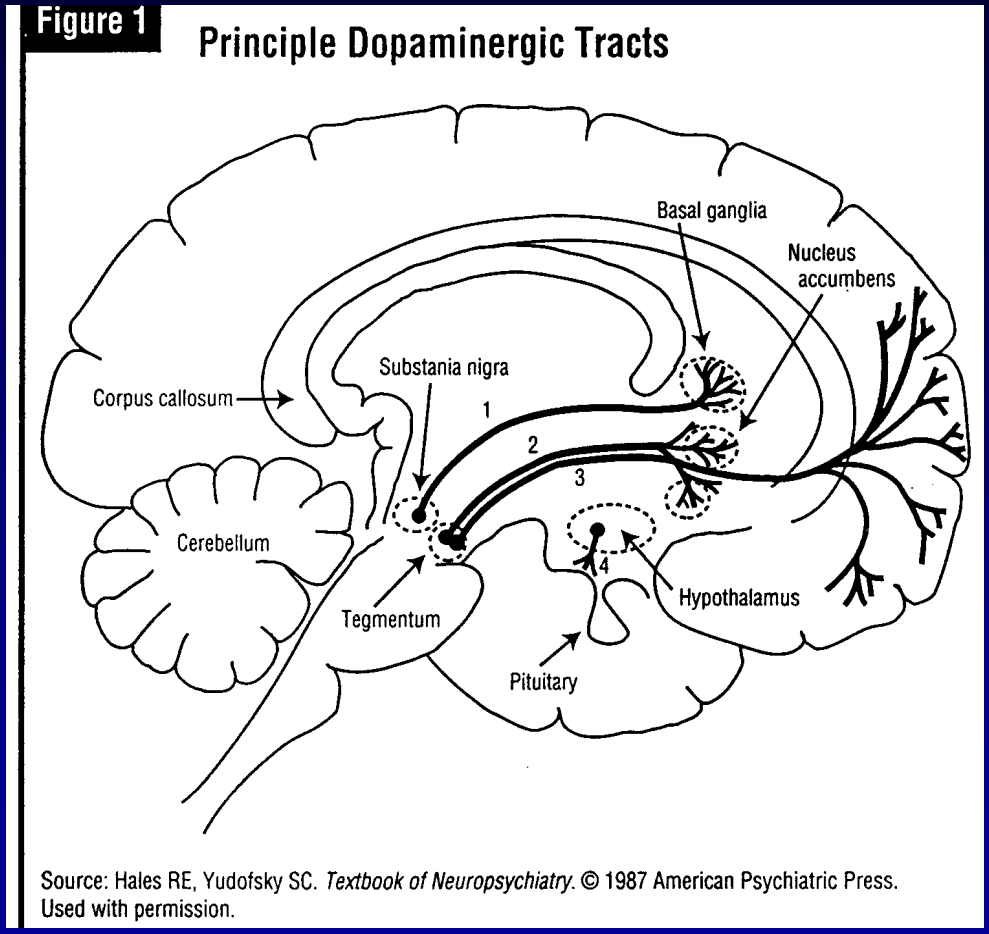
Structural Abnormalities in Schizophrenia



Dopamine Hypothesis of Schizophrenia

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

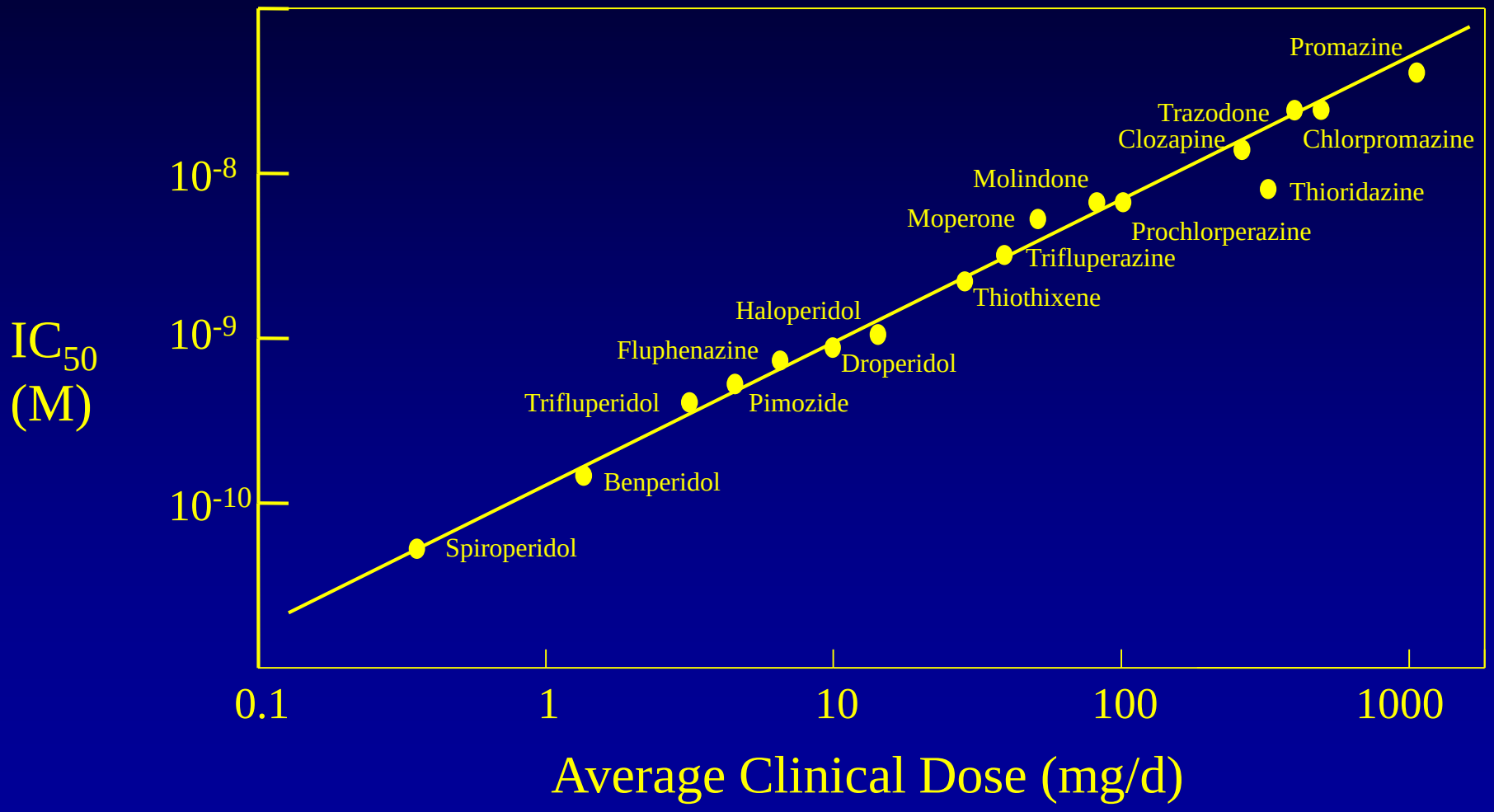


Dopamine Hypothesis

- Clinical efficacy of antipsychotics correlates with dopamine D_2 blockade
- Psychotic symptoms can be induced by dopamine agonists

Carlsson A, Am J Psychiatry 1978;135:164; Seeman P, Synapse 1987:1:133

Clinical Efficacy and Dopamine D_2 Blockade



Seeman P, Synapse 1987:1:133

Dopamine Hypothesis

- Normal subjects have 10% of dopamine receptors occupied at baseline
- Schizophrenic subjects have 20% of dopamine receptors occupied at baseline

Laruelle M, Quart J Nuc Med 1998;42:211

Dopamine Receptor Subtypes

D_1 Family

- D_1 and D_5 receptors
- Poor correlation with antipsychotic activity
- D_1 family may modulate effects of D_2 family

D_2 Family

- D_2, D_3, D_4 receptors
- High correlation with antipsychotic activity
- D_4 is prominent in limbic structures, but absent from extrapyramidal pathways
- Atypical antipsychotics have high D_4 affinity

Dopamine D_2 Effects

Possible Benefit	Possible Side Effects

• Antipsychotic effect	• EPS
	  • dystonia
	  • parkinsonism
	  • akathisia
	  • tardive dyskinesia
	• Endocrine changes:
	  • prolactin elevation
	  • galactorrhea
	  • gynecomastia
	  • menstrual changes
	  • sexual dysfunction

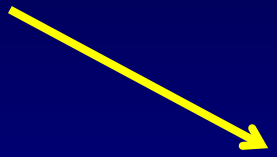
Dopamine and Antipsychotics

- 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

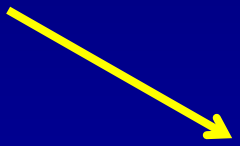
Kapur S & Remington G, Biol Psychiatry 2001;50:873

Dopamine Hypothesis

Subcortical Dopamine Excess



D_2 Hyperstimulation

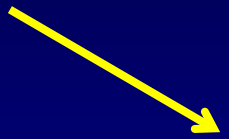


Positive Symptoms

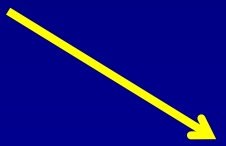
Bowers MB, Arch Gen Psychiatry 1974;31:50

Dopamine Hypothesis

Prefrontal Dopamine Deficit



D_1 & D_2 Hypostimulation



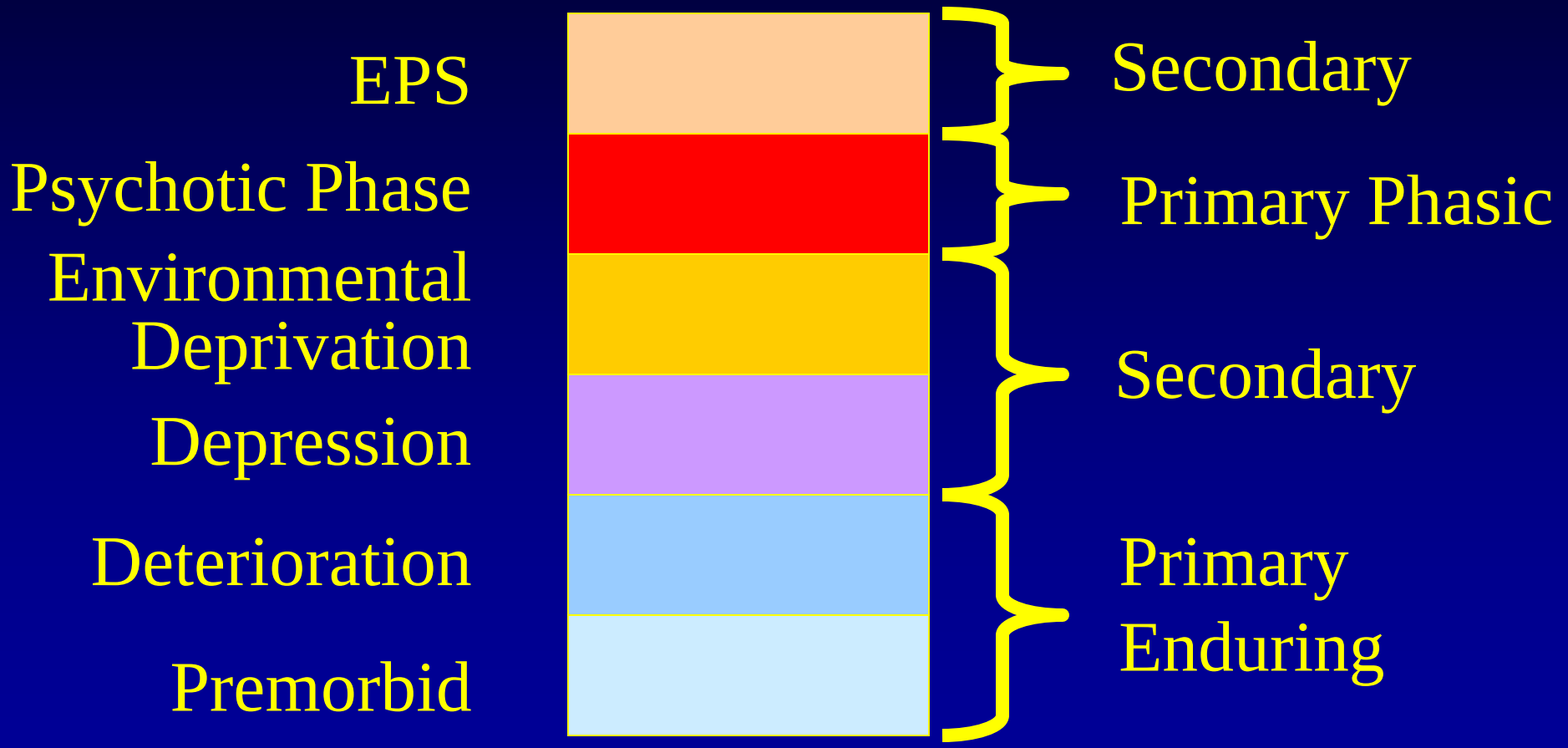
Cognitive & Negative Symptoms

Bowers MB, Arch Gen Psychiatry 1974;31:50

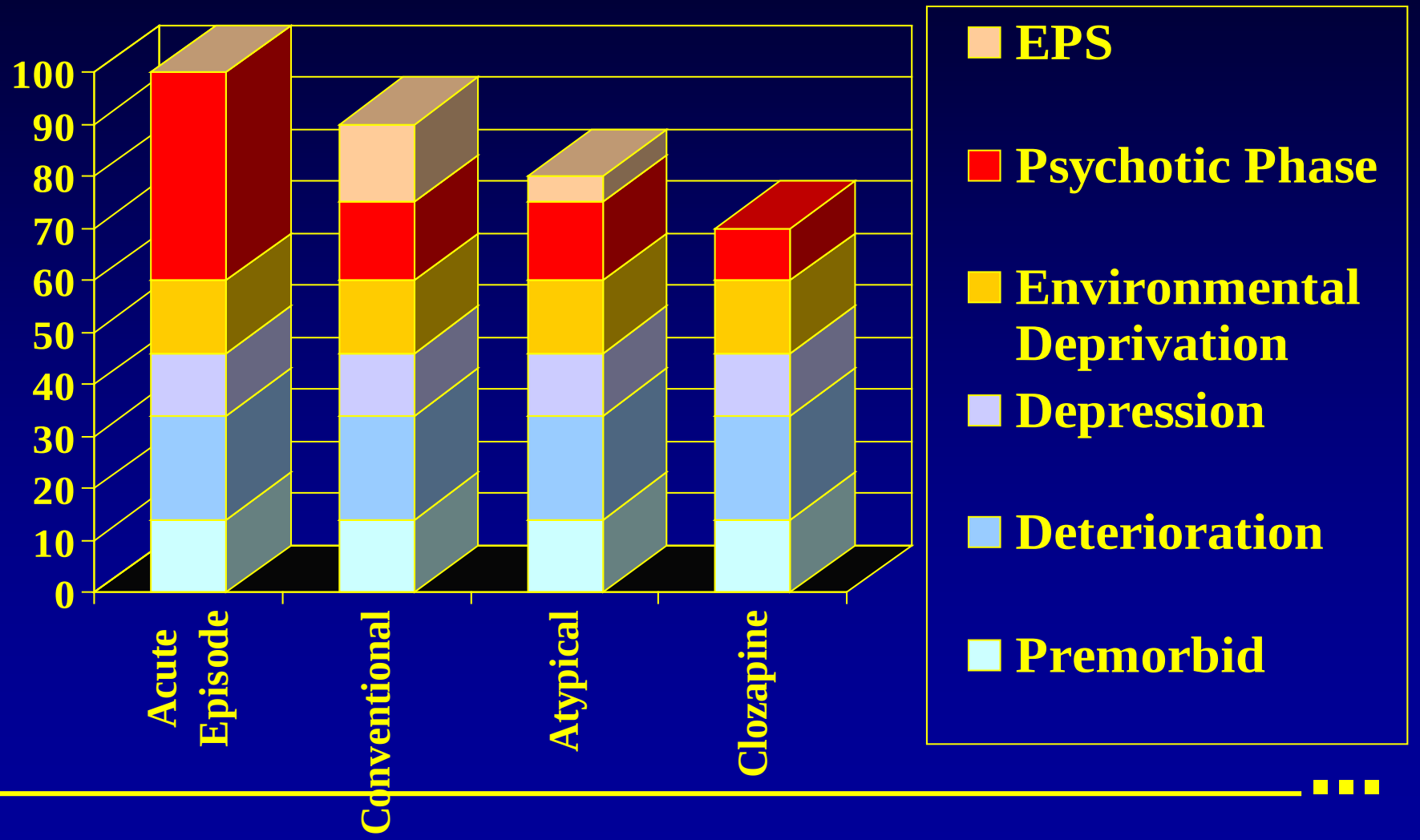
Negative Symptoms

How do antipsychotics improve negative symptoms?

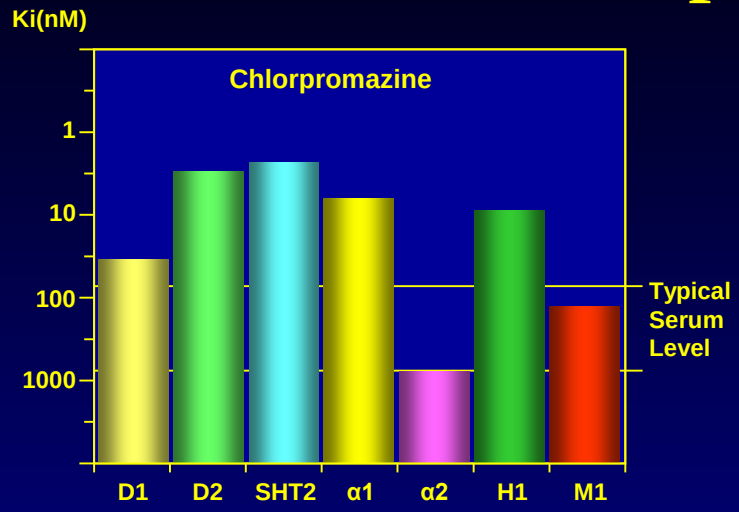
Negative Symptom Components

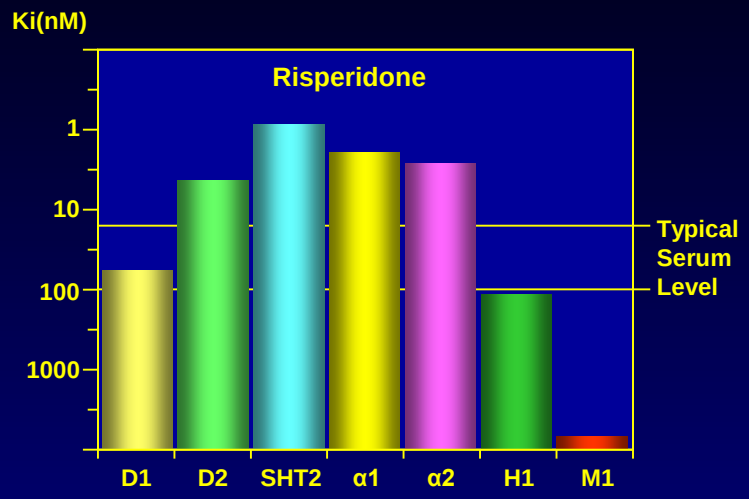


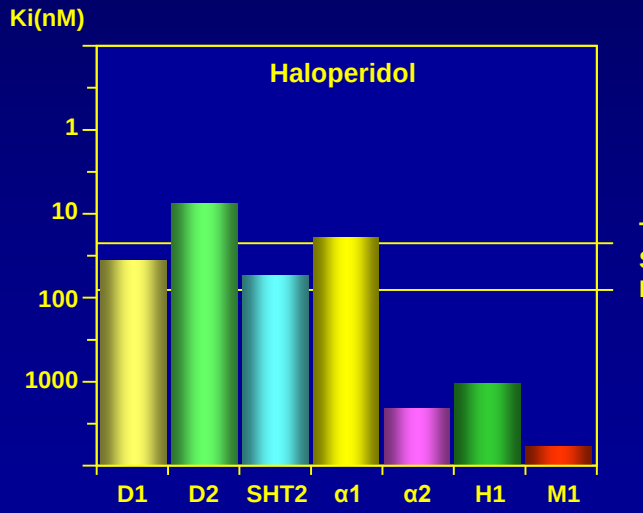
Negative Symptom Components

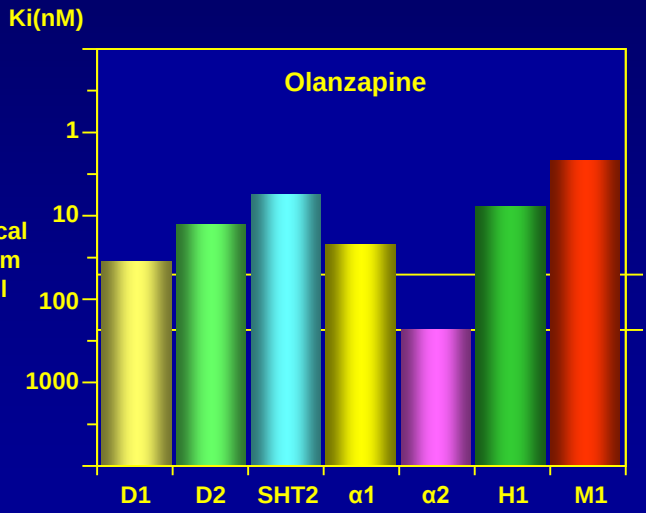


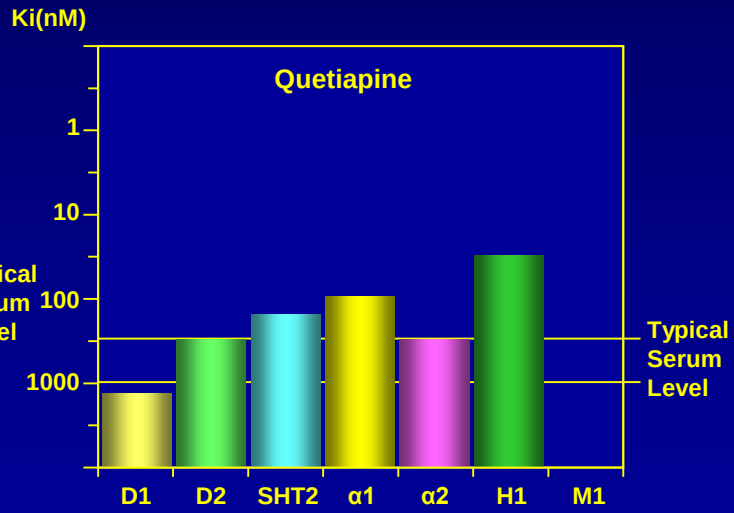
Receptor Profiles











Adapted from Jibson MD & Tandon R, J Psychiatric Res 1998;32, 215. Data from Beasley et al. (1996a, 1996b), Saller and Salama (1993), Seeger et al. (1995), Baldessarini and Frankenburg (1991), Thyrum et al. (1996), Dahl (1986), Heykants et al. (1994).

Serotonin

- Atypical antipsychotics are high in serotonin activity
- Serotonin agonists (e.g., LSD) produce psychotic symptoms
- Dopaminergic activity is modulated by serotonin

but

- Studies of serotonin in the brains of schizophrenic patients have been equivocal

Pharmacologic Treatment of Schizophrenia

Target Symptoms

- 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

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

Antipsychotic Medications

FDA Approved Indications for Antipsychotic Medications

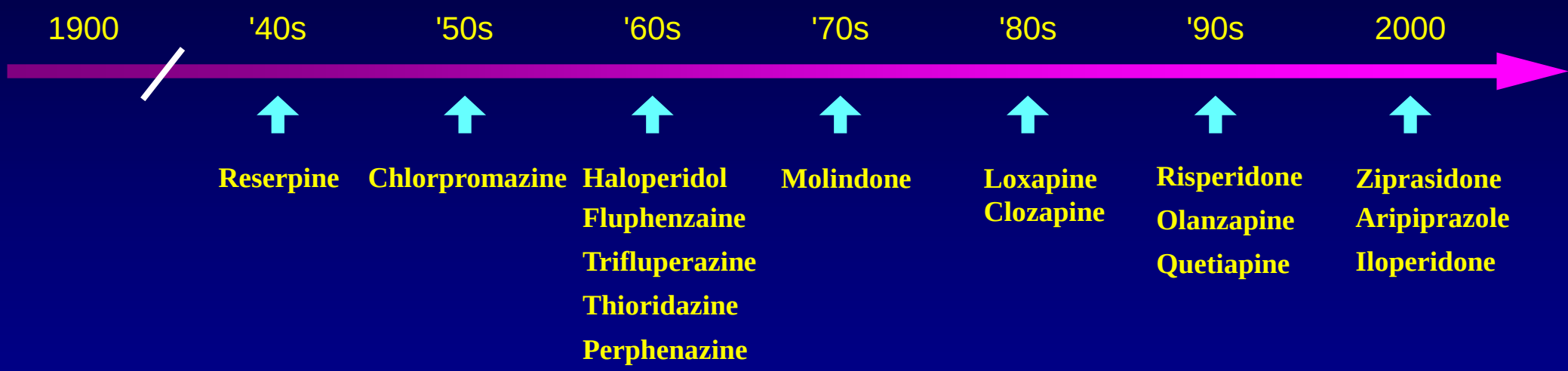
Adults

- Schizophrenia (acute and maintenance)
- Bipolar disorder (acute mania and maintenance)
- Agitation associated with schizophrenia or bipolar disorder

Children and Adolescents

- None

The Evolution of Antipsychotic Medications



Conventional, Typical Neuroleptics, or First Generation Antipsychotics

Atypical Antipsychotics

"Atypical Atypicals"

Second Generation Antipsychotics

Adapted from Lieberman J, et al., APA Annual Meeting, May 2001

Conventional Antipsychotic Medications (Neuroleptics)

- Chlorpromazine (Thorazine) introduced in 1952
- Several classes (phenothiazines, butyrophenones, thioxanthenes, indoles, benzamides, etc) introduced in the 1950s and 1960s
- Principal pharmacological activity is D_2 blockade
- Variable activity at H_1, M_1, and α_1 receptors
- High risk of EPS and tardive dyskinesia

Conventional Antipsychotic Medications (Neuroleptics)

High Potency

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

Conventional Antipsychotic Medications (Neuroleptics)

Low Potency

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

Conventional Antipsychotic Medications (Neuroleptics)

Advantages

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

Conventional Antipsychotic Medications (Neuroleptics)

Disadvantages

- High risk of EPS
- High risk of tardive dyskinesia

Atypical Antipsychotics (Second Generation Antipsychotics)

- Developed on the basis of receptor activity in addition to D_2 blockade
- Fewer EPS
- Decreased incidence of tardive dyskinesia

Atypical Antipsychotics

- Broader spectrum of activity
    - Some benefit for negative and cognitive symptoms
- Beneficial for treatment-refractory patients (clozapine only)

First-Line Atypical Antipsychotics

- Risperidone (Risperdal)
- Olanzapine (Zyprexa)
- Quetiapine (Seroquel)
- Ziprasidone (Geodon)
- Aripiprazole (Abilify)

Risperidone

- Advantages
  - Extensive clinical experience
  - Liquid, disintegrating tablet, and depot preparations
  - Relatively low cost
- Disadvantages
  - Dose-dependent EPS
  - Moderate risk of weight gain
  - Prolactin elevation

Olanzapine

- Advantages
  - Extensive clinical experience
  - Superior retention in maintenance treatment (CATIE)
  - Disintegrating tablet and injectable forms
- Disadvantages
  - High risk of weight gain and metabolic syndrome
  - High cost

Quetiapine

- Advantages
  - Lowest EPS risk
  - Rapid onset of action
  - Sedating
- Disadvantages
  - Longer dose titration
  - Moderate risk of weight gain
  - Moderate-high cost
  - Twice-daily dosing

Ziprasidone

- Advantages
  - Low risk of weight gain
  - Low risk of sexual dysfunction
  - Relatively low cost
  - Injectable formulation
- Disadvantages
  - Twice-daily dosing
  - qTc prolongation

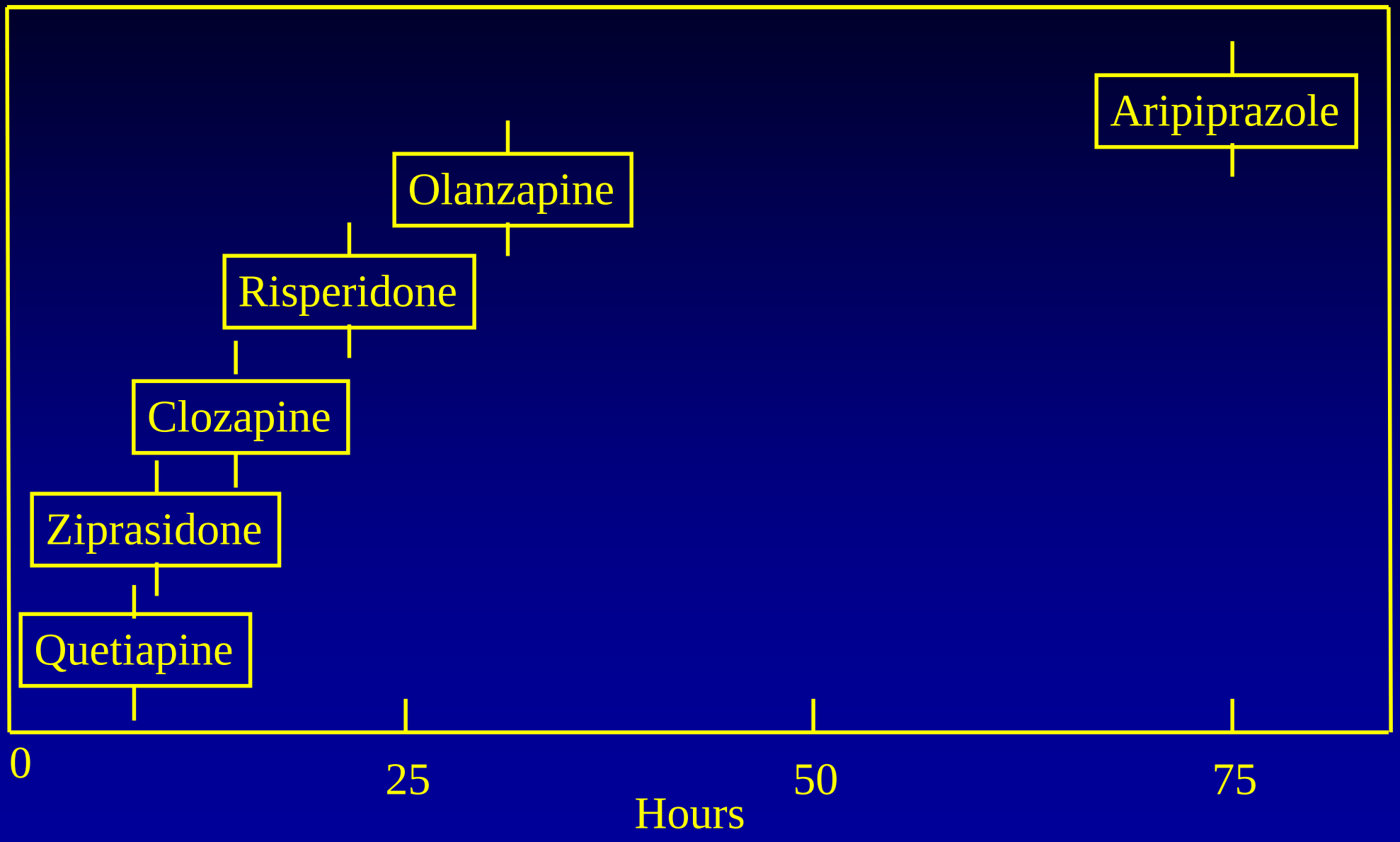
Aripiprazole

- Advantages
  - Unique pharmacology (partial agonist)
  - Relatively low cost
  - Long half-life
- Disadvantages
  - Less extensive clinical experience

Clozapine

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

Elimination Half-Times



Depot Antipsychotics

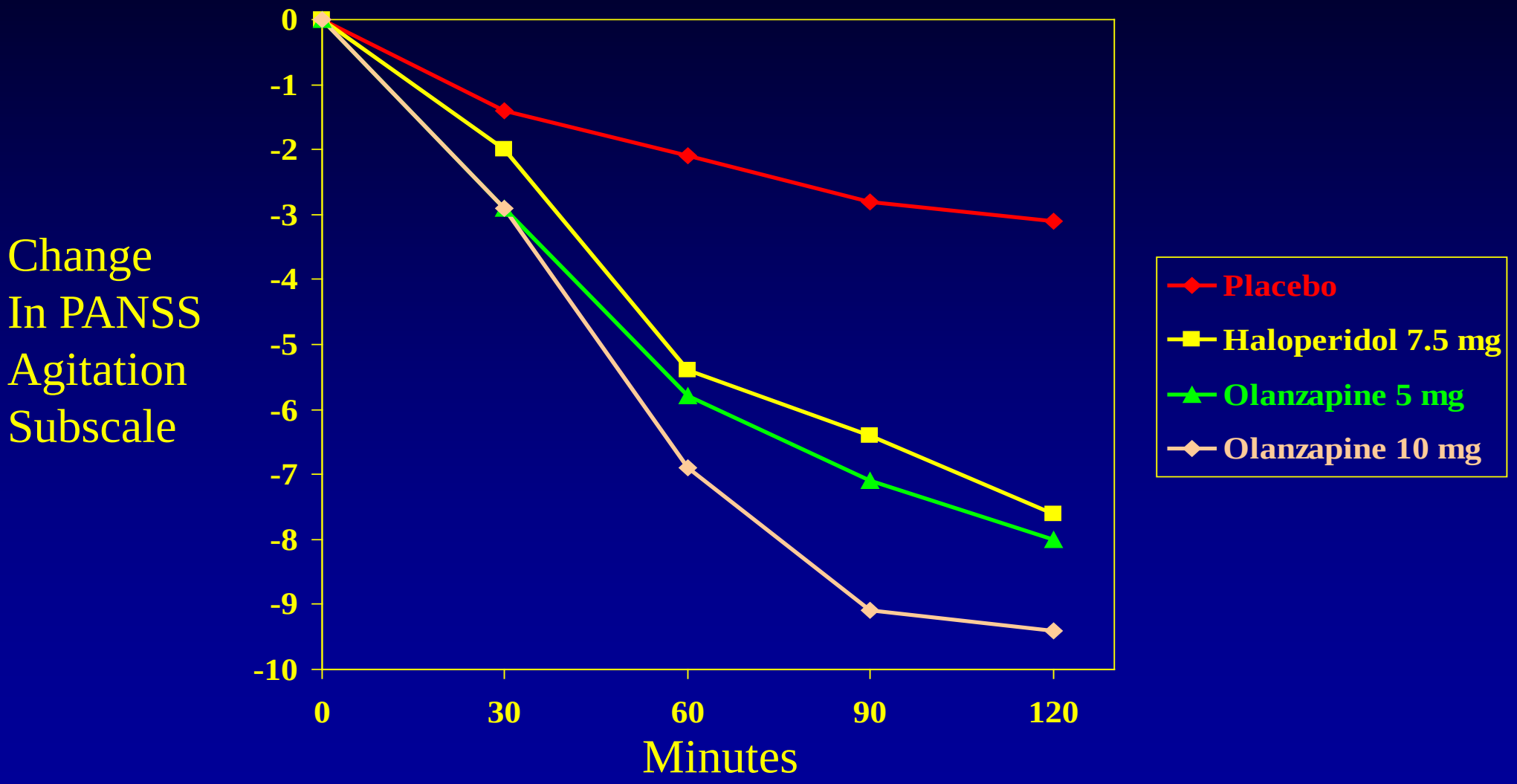
- Haloperidol (Haldol) decanoate
- Fluphenazine (Prolixin) decanoate
- Risperidone depot (Risperdal Consta)

Depot Antipsychotics

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

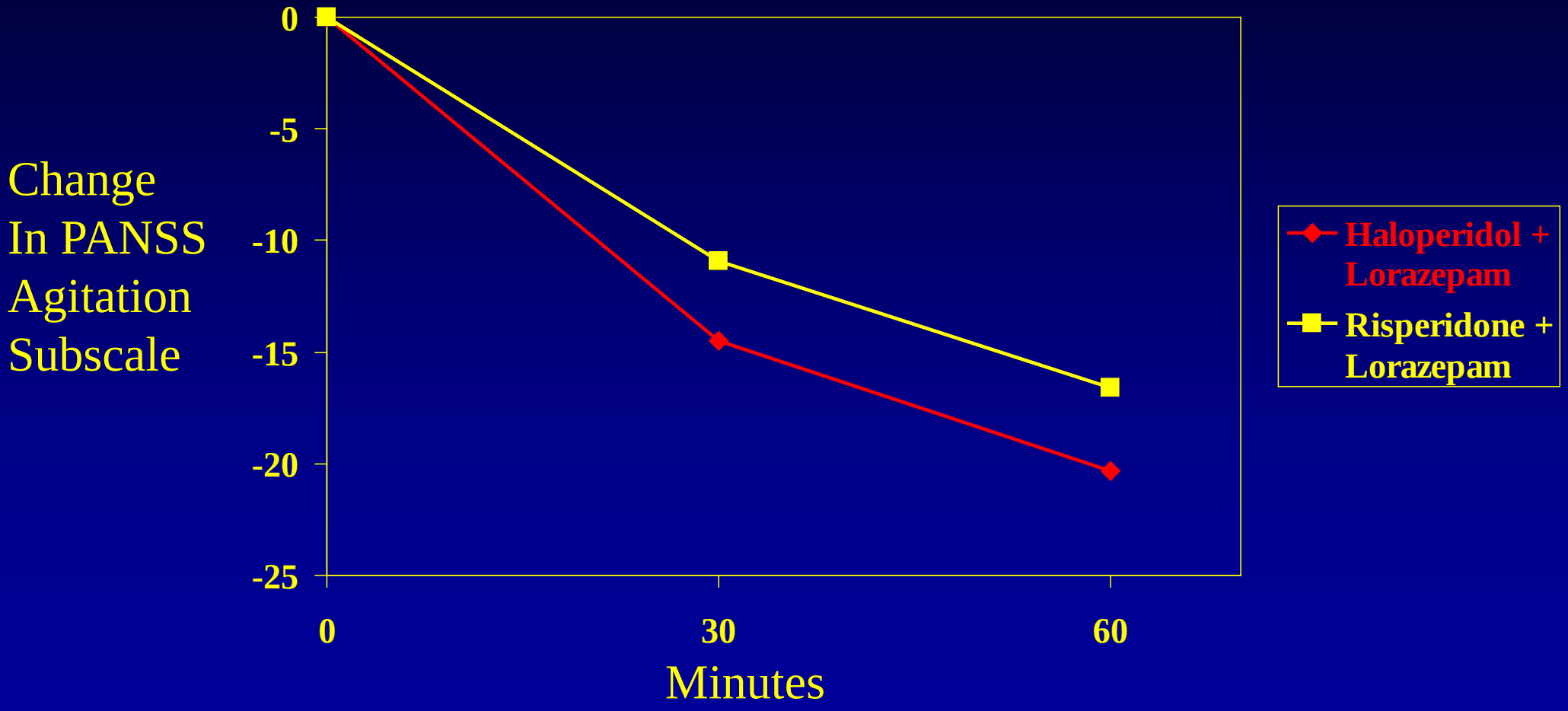
Efficacy of Antipsychotics

Injectable Olanzapine for Acute Agitation



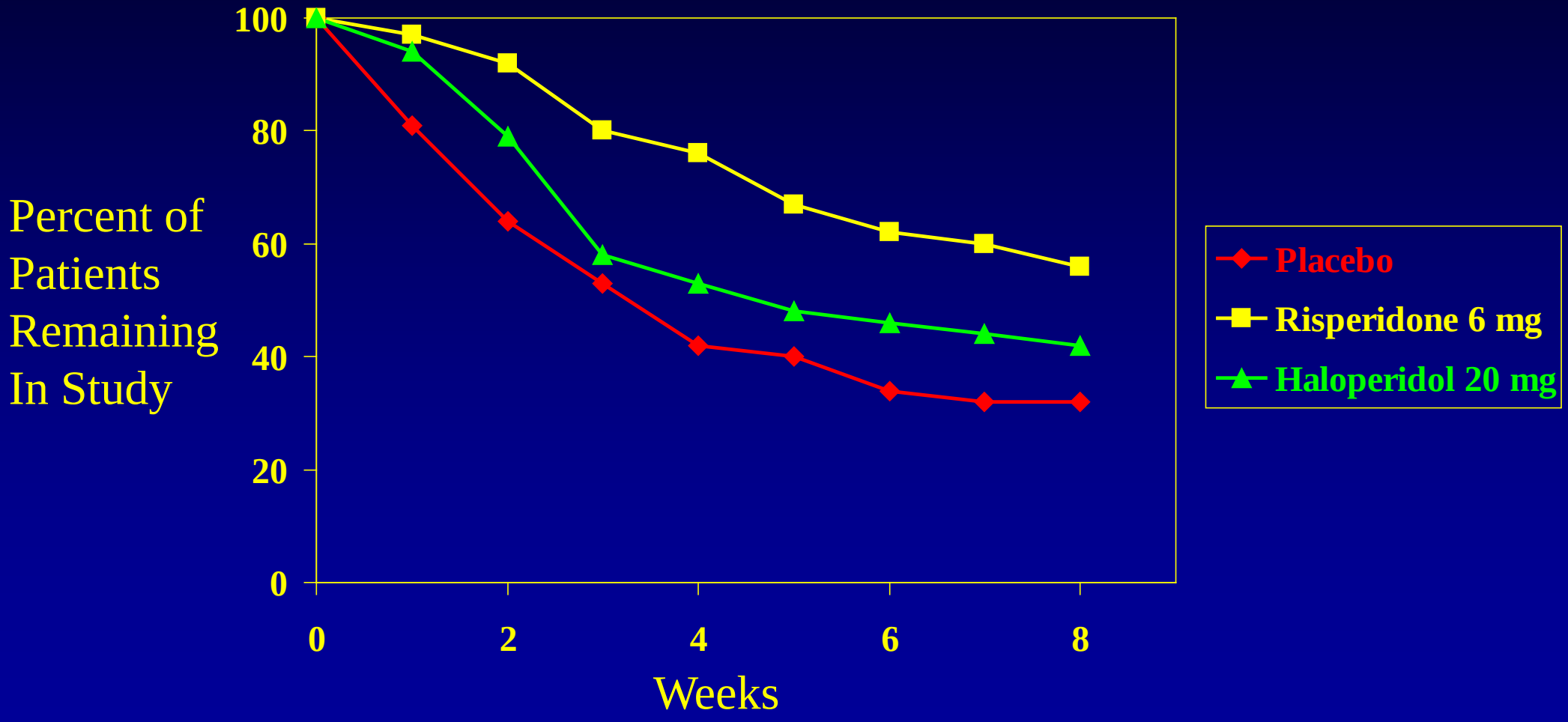
Breier A, et al., Arch Gen Psychiatry 2002;59:441

Oral Risperidone for Acute Agitation



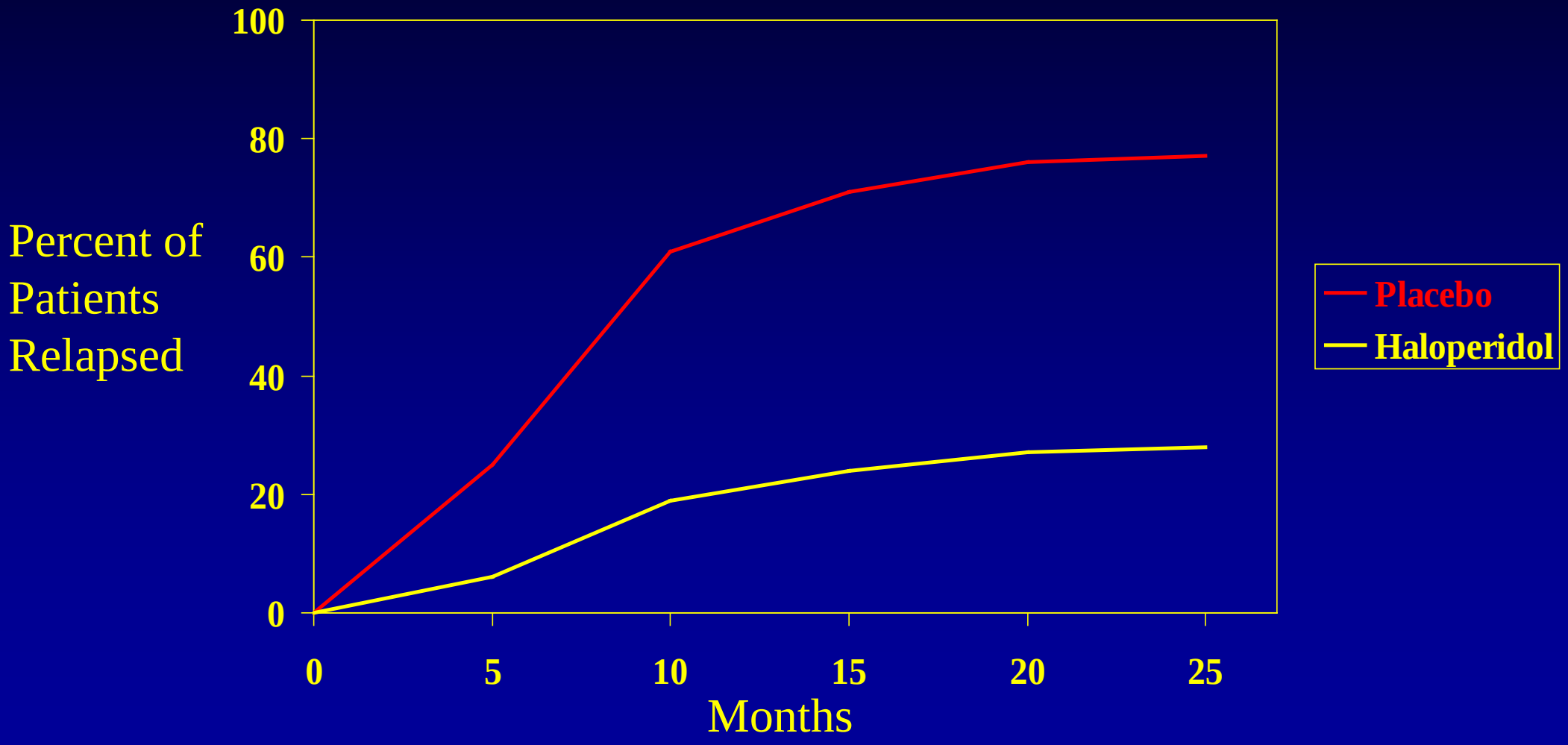
Currier GW & Simpson GM, J Clin Psychiatry 2001;62:153

Risperidone for Short-term Treatment



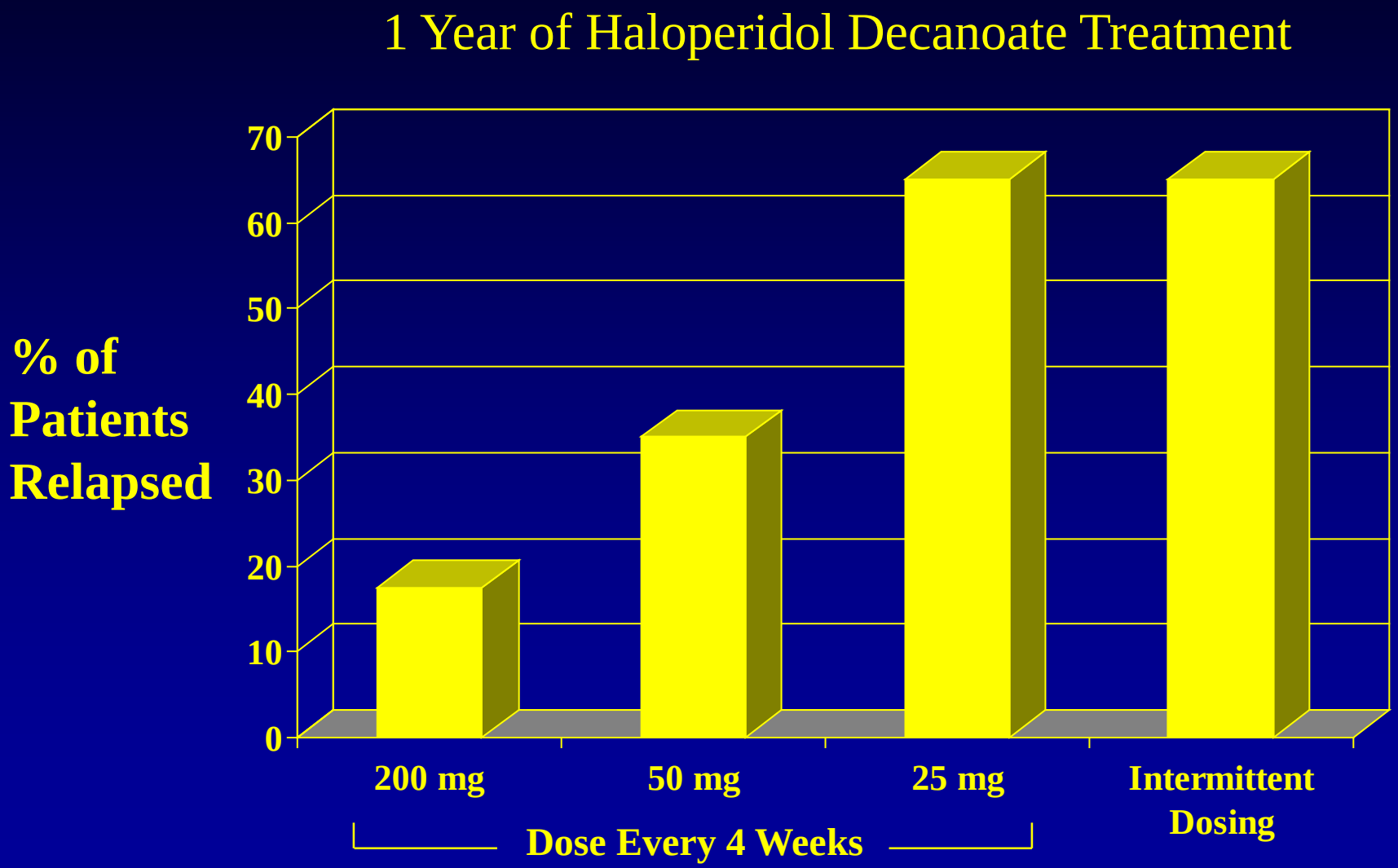
Marder SR & Meiback RC, Am J Psychiatry 1994;151:825

Haloperidol for Long-term Prevention of Relapse



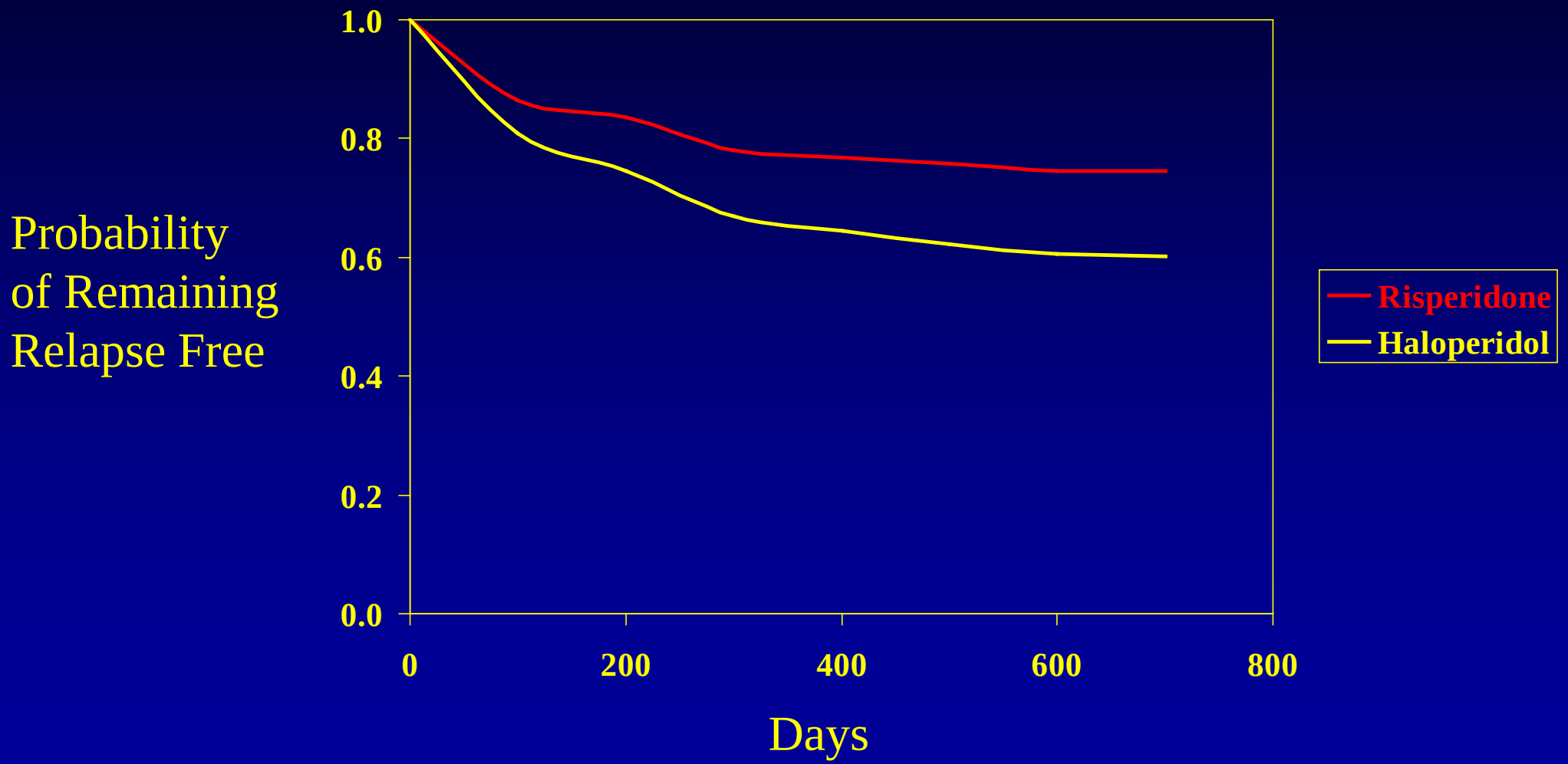
Hogarty GE & Goldberg, SC, Arch Gen Psychiatry 1973;28:54

Relationship between Medication Dose and Relapse



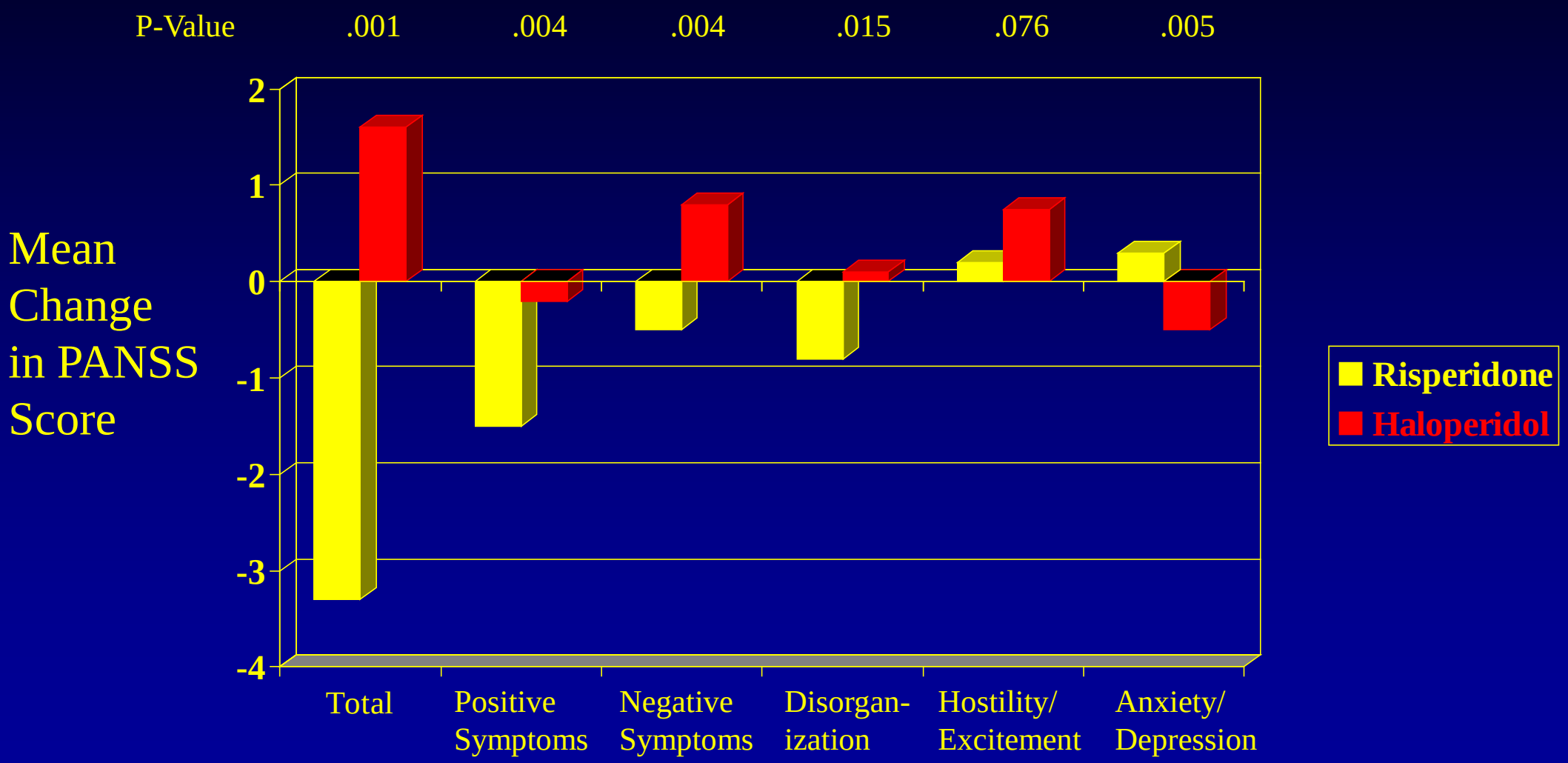
Davis JM, et al., J Clin Psychiatry 1993;54(Suppl):24

Risperidone for Long-term Prevention of Relapse



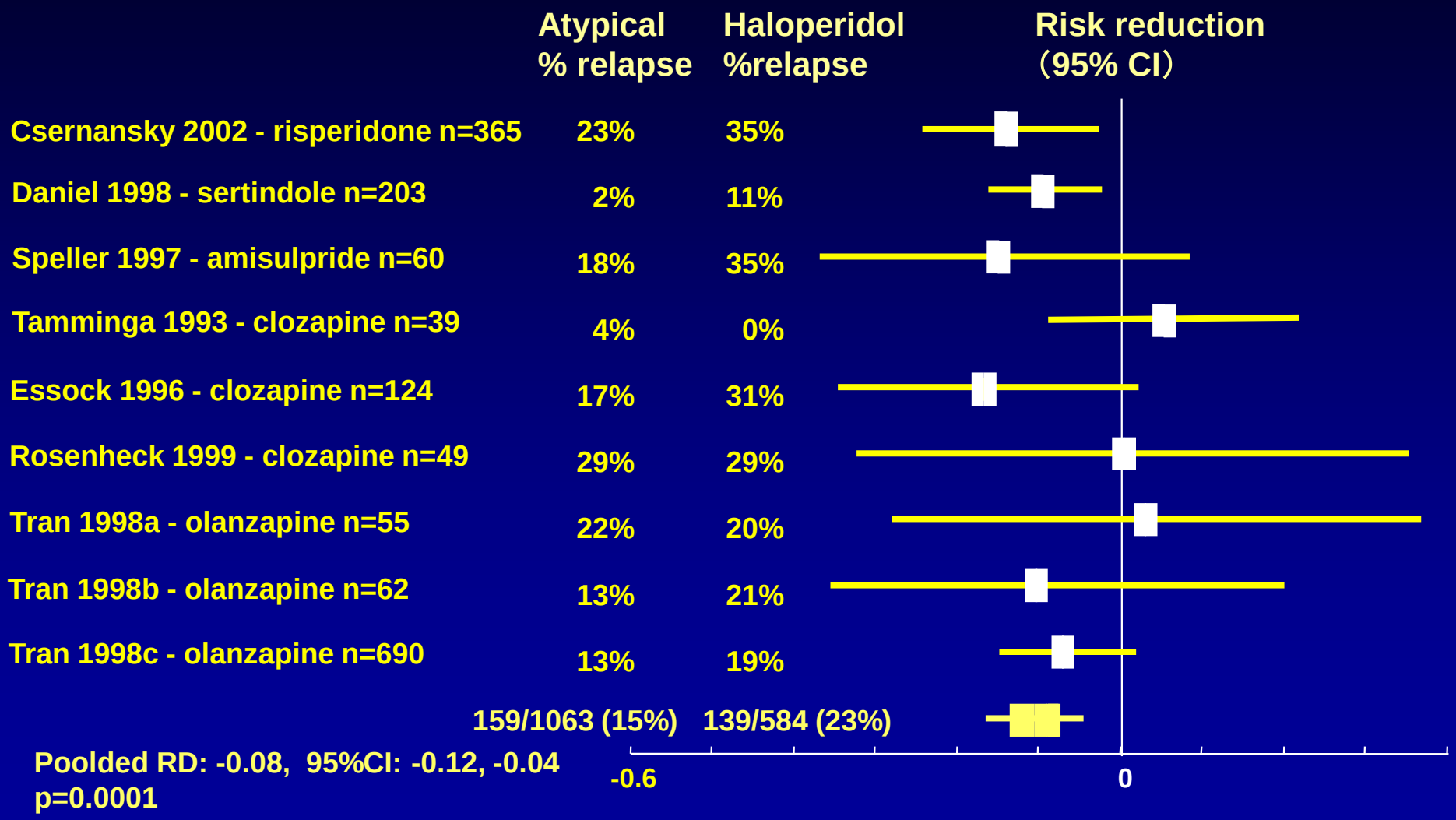
Csernansky JG, et al., NEJM 2002;346:16

Mean Change in PANSS Score at 2 Years



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

Meta-Analyses - Relapse

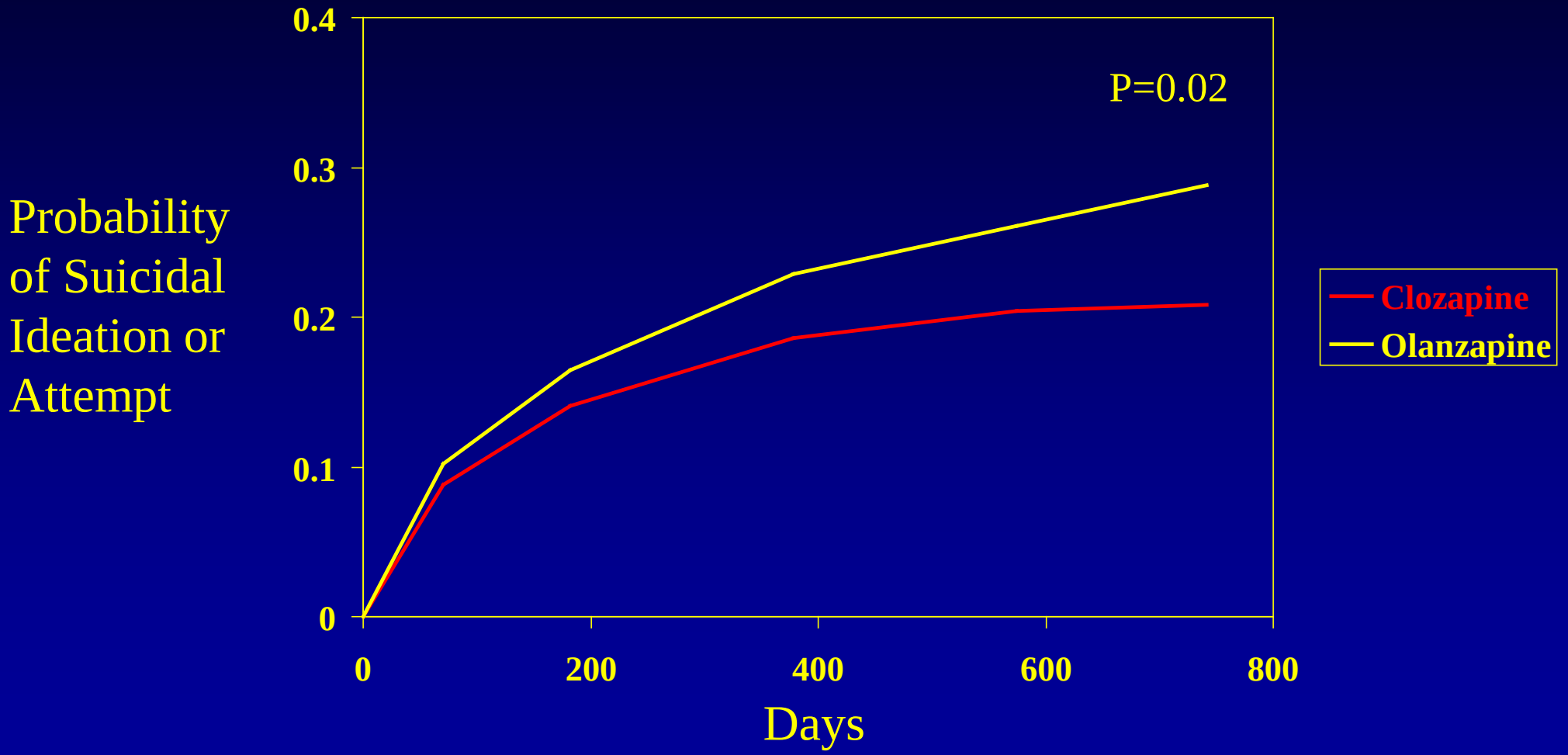


Leucht S, et al., Winter workshop on schizophrenia, 23 Feb-1 Mar, 2002, Davos

Neurocognitive Deficits

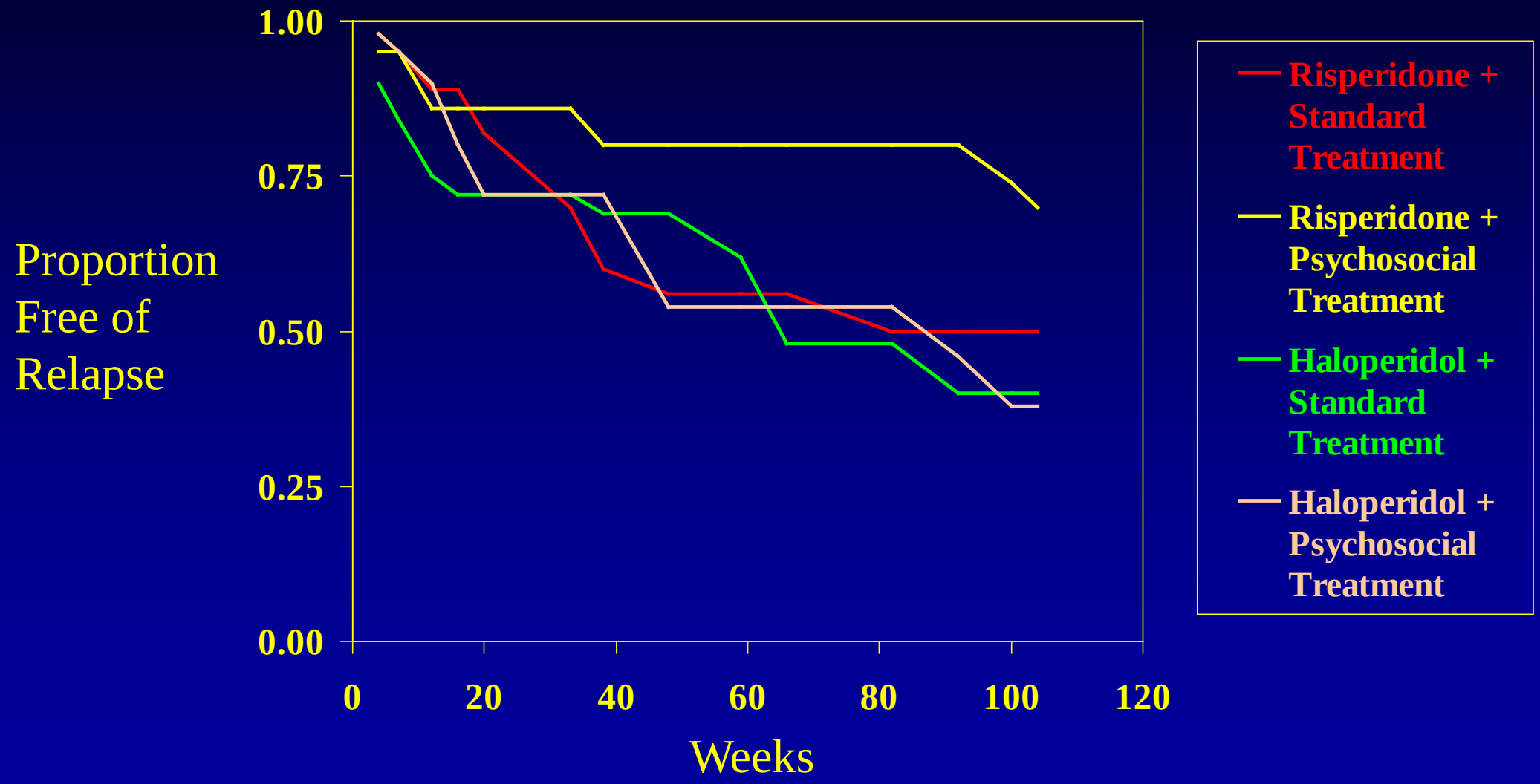
- Atypical antipsychotics have better cognitive profiles than conventional agents
- Atypical antipsychotics do not return cognitive functions to normal
- Neurocognitive benefits of atypical antipsychotics are of minor clinical significance

Prevention of Suicide



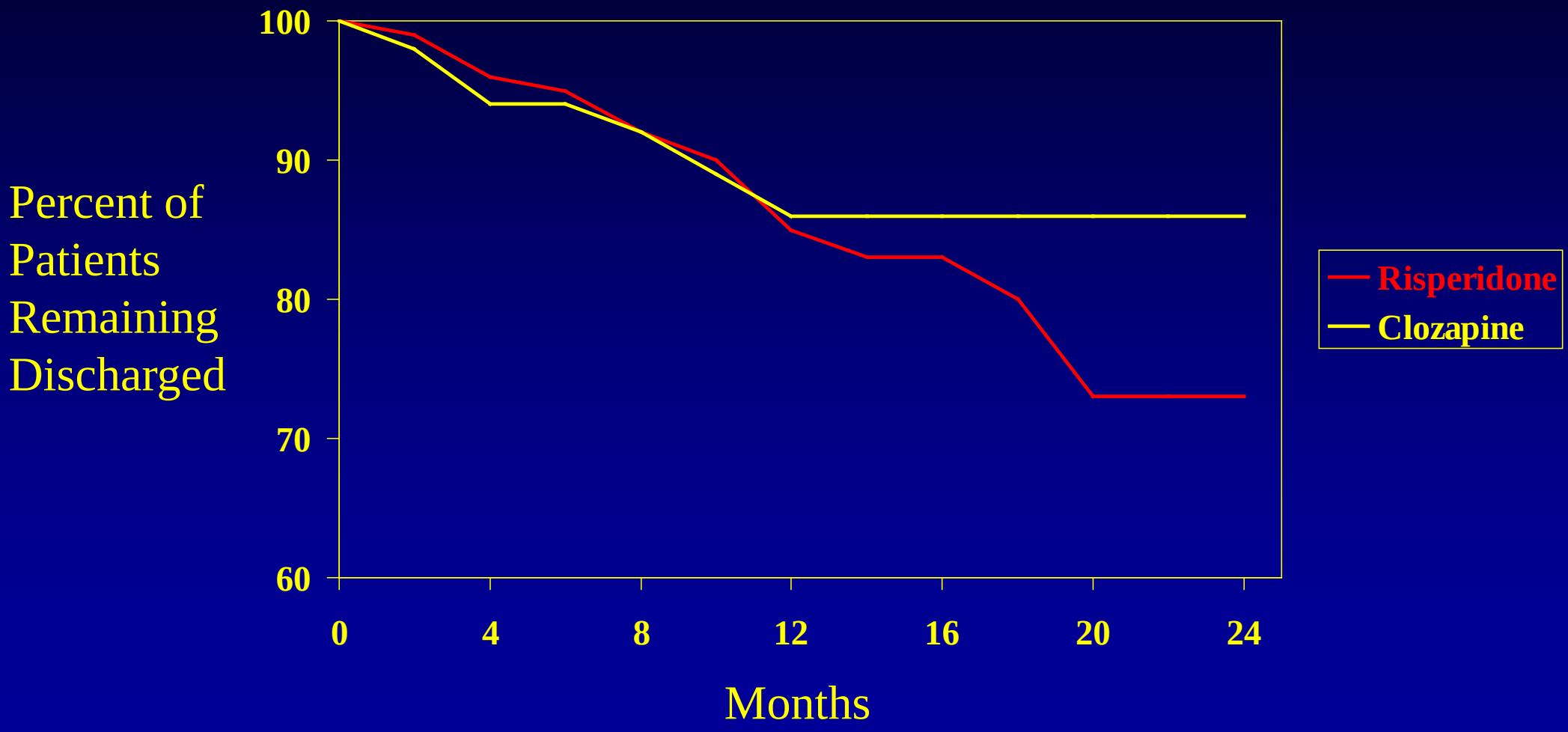
Meltzer HY, et al., Arch Gen Psychiatry 2003;60:82

Psychosocial Treatment



Glynn SM, et al., Am J Psychiatry 2002;159:829

Clozapine for Long-term Treatment



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

Side Effects

Side Effects - Overview

	EPS	Orthostatic Hypotension	Anticholinergic Symptoms	Prolactin Elevation
Aripiprazole	+/-	+/-	+/-	+/-
Clozapine	0	+++	+++	+/-
Haloperidol	+++	+	+/-	++
Olanzapine	+/-	+/-	+	+/-
Quetiapine	0	++	+/-	+/-
Risperidone	+	+	+/-	++
Ziprasidone	+/-	+/-	+/-	+/-

Side Effects - Overview

	qTc Prolongation	Sedation	Weight Gain*
Aripiprazole	+/-	+/-	+/-
Clozapine	+	+++	+++
Haloperidol	+/-	+	+
Olanzapine	+/-	++	+++
Quetiapine	+/-	+	++
Risperidone	+/-	+	++
Ziprasidone	+	+/-	+/-

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

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 conventional neuroleptic (20-40%)
- Low potency conventional neuroleptic
- Risperidone
- Aripiprazole/Olanzapine/Ziprasidone
- Quetiapine/Clozapine

Extrapyramidal Symptoms (EPS)

Treatment Options

- Reduce medication dose
- Slow down the rate of titration
- Consider alternative medication
- Adjunctive medication

Extrapyramidal Symptoms (EPS)

Treatment – Adjunctive Medication

- Anticholinergic
  - Benztropine 1-2 mg bid-qid
  - Trihexyphenidyl 2-5 mg bid-qid
- Antihistamine
  - Diphenhydramine 25-50 mg bid-qid
- Dopaminergic
  - Amantadine 100 mg bid-tid

Metabolic Syndrome

- Prevalence of obesity and diabetes in patients with schizophrenia is 1.5-2.0 times higher than the general population
- No studies on obesity and diabetes in drug-naïve schizophrenia patients are available

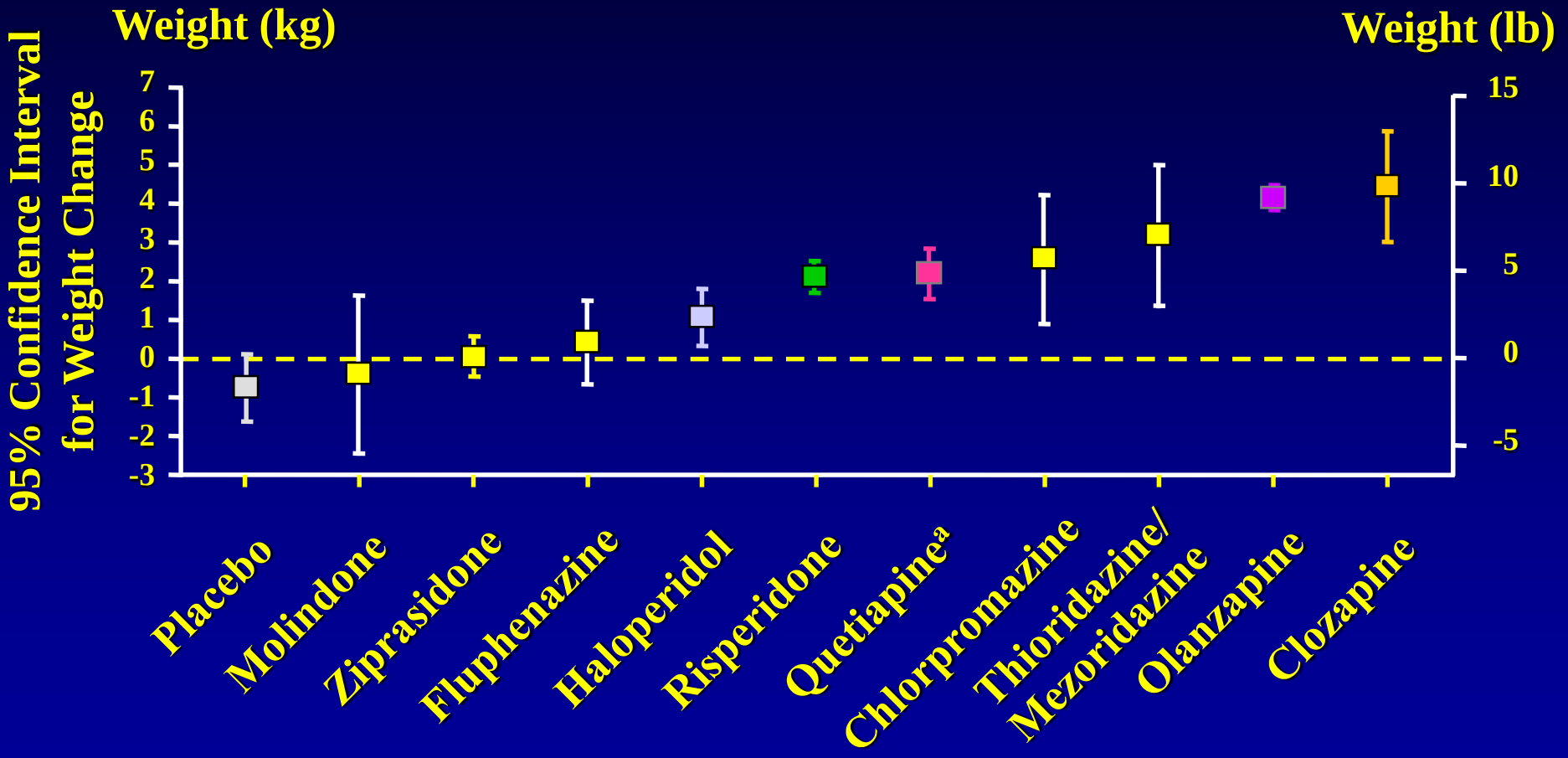
Metabolic Syndrome

Use of atypical antipsychotics is associated with metabolic dysregulation

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

Meta-analysis of Antipsychotic-related Weight Gain

Estimate at 10 Weeks[a]



[a] Quetiapine weight gain estimated at 6 weeks

Allison DB, et al., Am J Psychiatry 1999;156:1686

Risk of Metabolic Complications

Relative risk of medications

- Clozapine/Olanzapine
- Quetiapine/Risperidone
- Aripiprazole/Ziprasidone

Metabolic Syndrome

Recommended monitoring for patients on atypical antipsychotics

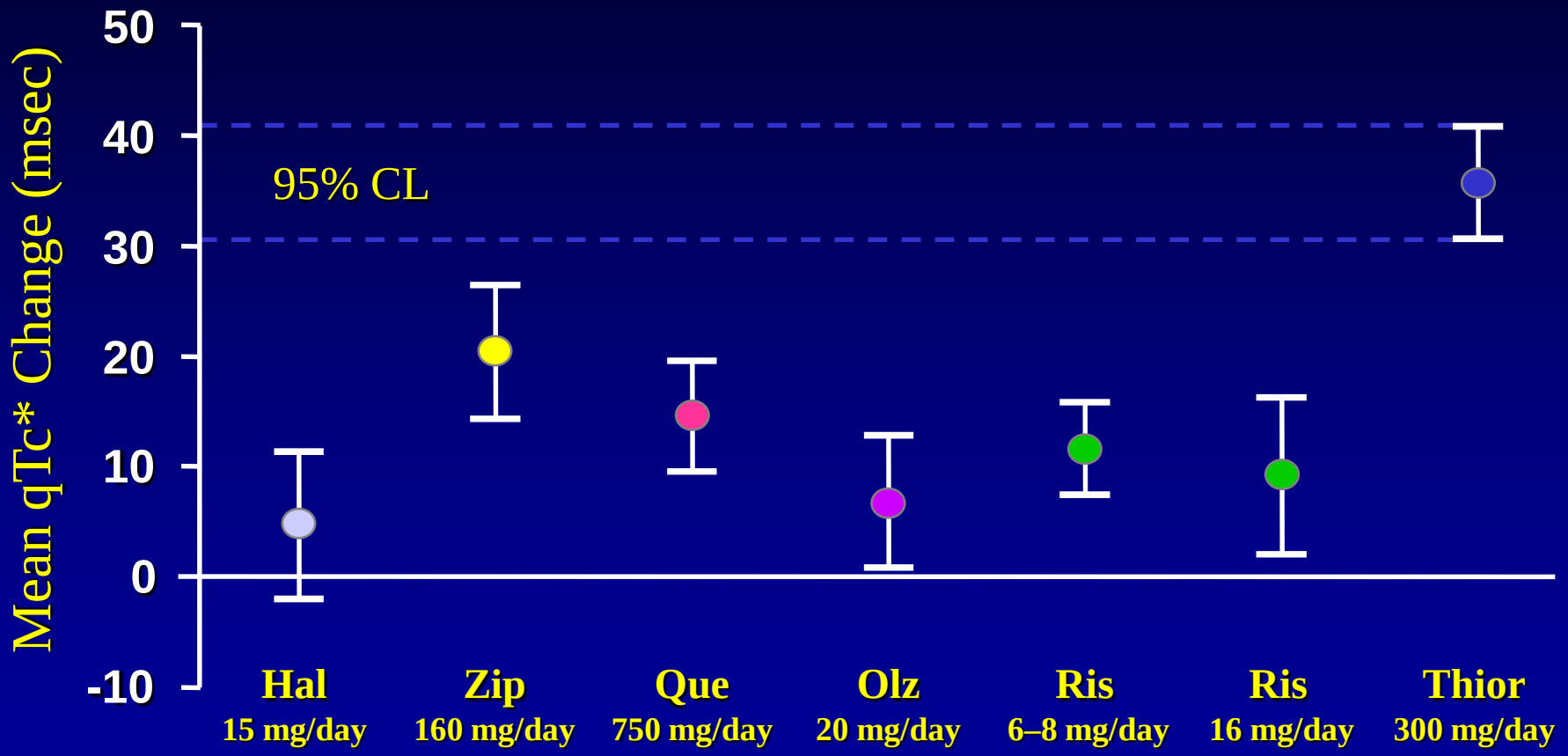
	Baseline	4 wks	8 wks	12 wks	Quarterly	Annual	5 yrs
Personal/family history	X					X	
Weight (BMI)	X	X	X	X	X		
Waist Circumference	X					X	
Blood pressure	X			X		X	
Fasting plasma glucose	X			X		X	
Fasting lipid profile	X			X			X

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

Cardiovascular Adverse Events

- Conventional low potency drugs thioridazine (Mellaril) and mesoridazine (Stelazine) are associated with qTc prolongation and increased risk of cardiac death
- Ziprasidone carries a “bold” warning regarding qTc prolongation and associated cardiac risk, but no increased incidence of cardiac mortality or morbidity has been detected with ziprasidone

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 atypical antipsychotics carry a “black box” warning of increased mortality in elderly patients with dementia-related psychosis
- Risk is comparable among all conventional and atypical antipsychotics

Increased Mortality

Meta-analysis of 15 studies of risk of typical and atypical antipsychotics in elderly patients

	Mortality	Odds Ratio
Controls	2.3%	
Atypical Antipsychotics	3.5%	1.54
Haloperidol	3.9%	1.68

Schneider LS, et al., JAMA 2005; 294:1934

Increased Mortality

Retrospective study of mortality in 22,890 elderly patients receiving antipsychotics

- Higher risk with conventional antipsychotics OR = 1.37
- Higher risk with recent initiation of medicine
- Higher risk with higher doses

Wang PS, et al., N Engl J Med 2005; 353:2335

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 Factors

- Class of medication:
  - High potency conventional neuroleptic (7%/yr)
  - Low potency conventional neuroleptic (5%/yr)
  - Risperidone/Olanzapine/Ziprasidone (0.5%/yr)
  - Quetiapine/Aripiprazole (uncertain)
  - Clozapine (not reported)

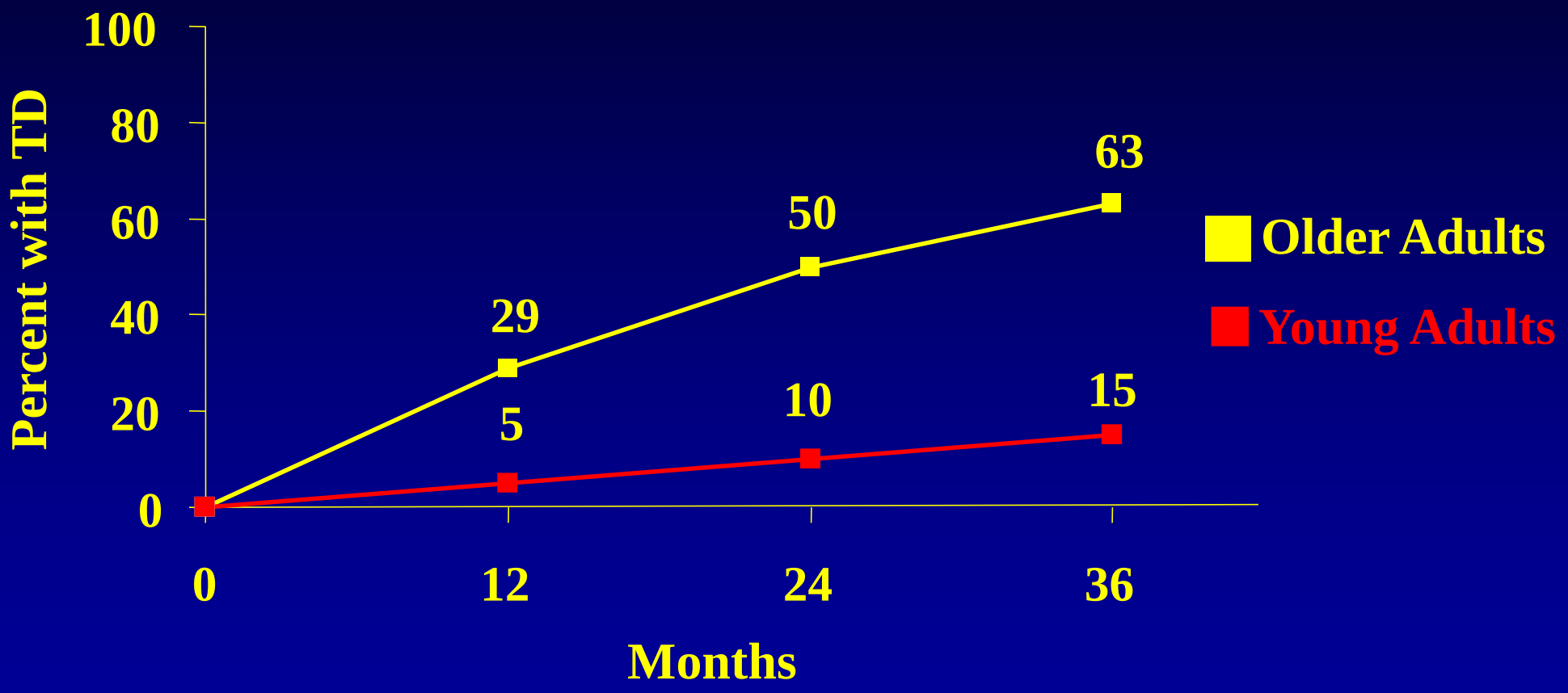
Tardive Dyskinesia

Cumulative Annual Risk of Tardive Dyskinesia

	Age 20	Age 70
Conventional Neuroleptic	5%	30%
Atypical Antipsychotic	0.5%	2.5-5%

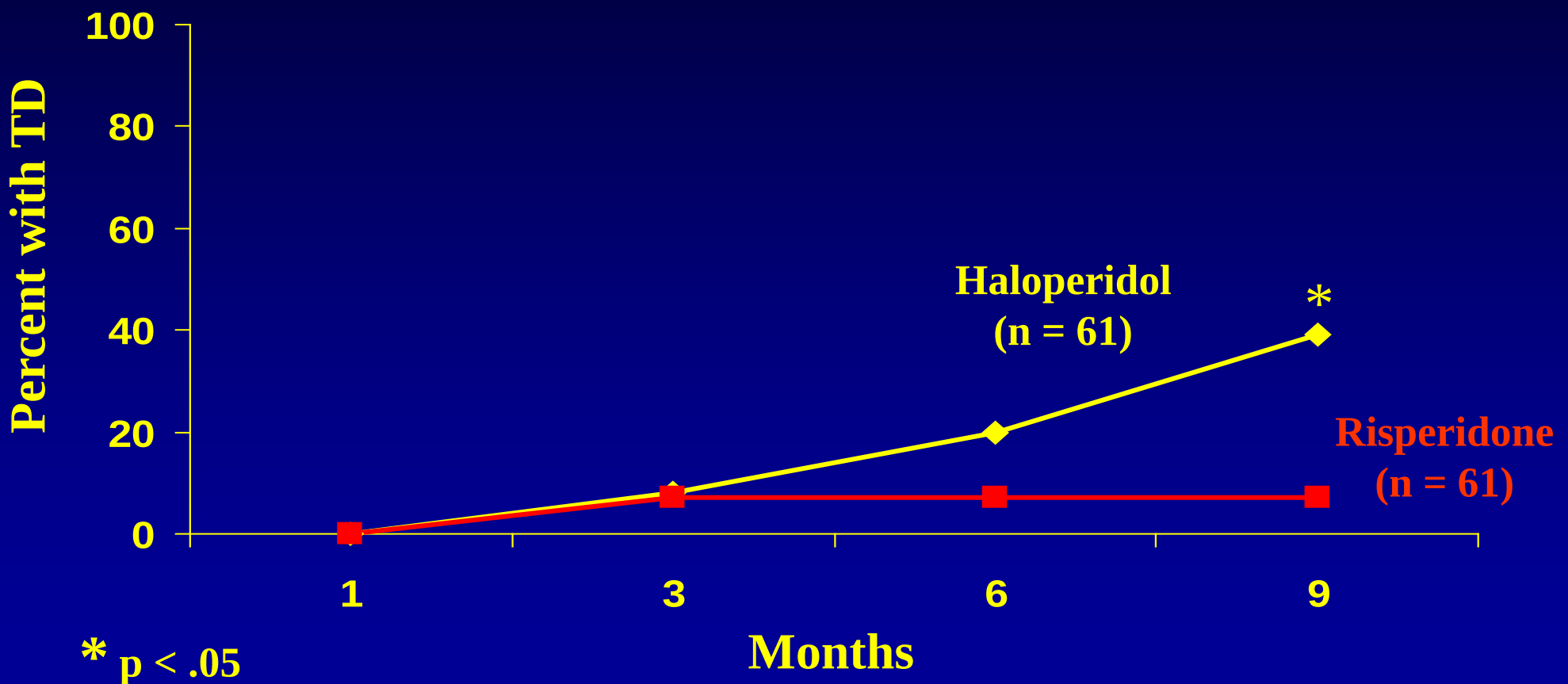
Kane JM, et al., J Clin Psychopharmacol 1988;8:52S. Chakos MH, et al., Arch Gen Psychiatry 1996;53:313. Woerner MG, et al., Am J Psychiatry 1998;155:1521. Correll CU, et al., Am J Psychiatry 2004; 161:414. Glazer WM, J Clin Psychiatry 2000; 61 suppl 4:21.

Cumulative Incidence of TD with Conventional Antipsychotics



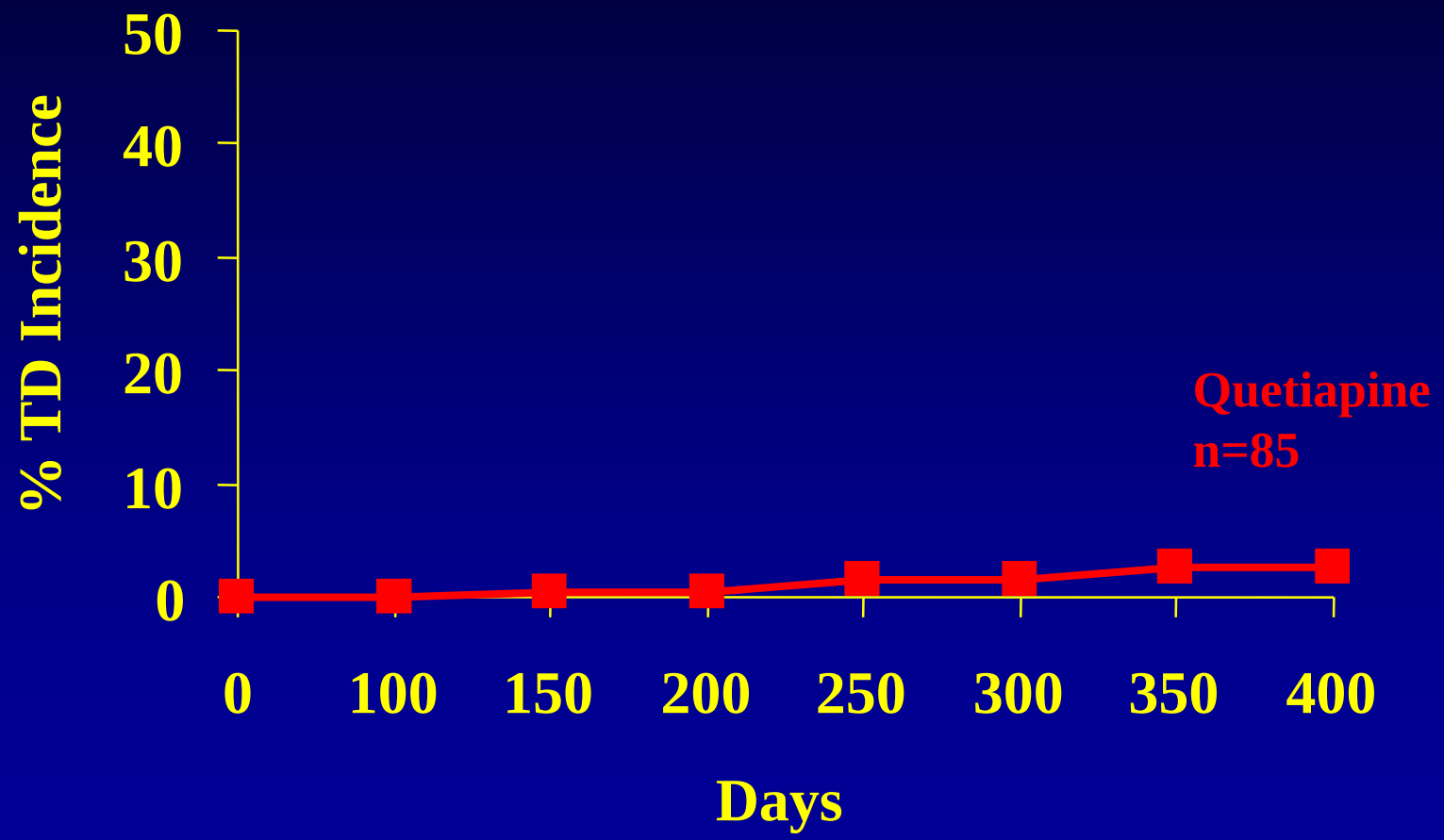
Kane JM, et al., J Clin Psychopharmacol 1988;8(4 Suppl):52S
Jeste D, et al., Am J Geriatric Psychiatry, 1999;7:70

TD Incidence in Older Patients: Haloperidol versus Risperidone (1mg/d)



Jeste DV, et al., J Am Geriatrics Soc 1999;47:716

Cumulative Incidence of Persistent TD With Quetiapine in Elderly Psychosis Patients



Jeste DV, et al., Am Assoc Geriatric Psychiatry poster, 2000

Tardive Dyskinesia

Natural History

- May spontaneously improve, remain static, or worsen
  - Static symptoms are most common
  - Spontaneous improvement is least common
- About half of patients experience relief of symptoms within 3 months of antipsychotic discontinuation

Tardive Dyskinesia

Acute Treatment

- Increase antipsychotic dose temporarily suppresses symptoms
- Benzodiazepine my bring about a modest reduction in symptoms

Tardive Dyskinesia

Maintenance Treatment

- Reduce antipsychotic dose and time of exposure
- Clozapine (standard dose)
  - 50% of patients show 50% reduction in movements
- Other treatments have not consistently been effective
  - Vitamin E
  - Dopaminergic agents
  - Benzodiazepine
  - Branched-chain amino acids

Antipsychotic Selection and Treatment Strategies

CATIE

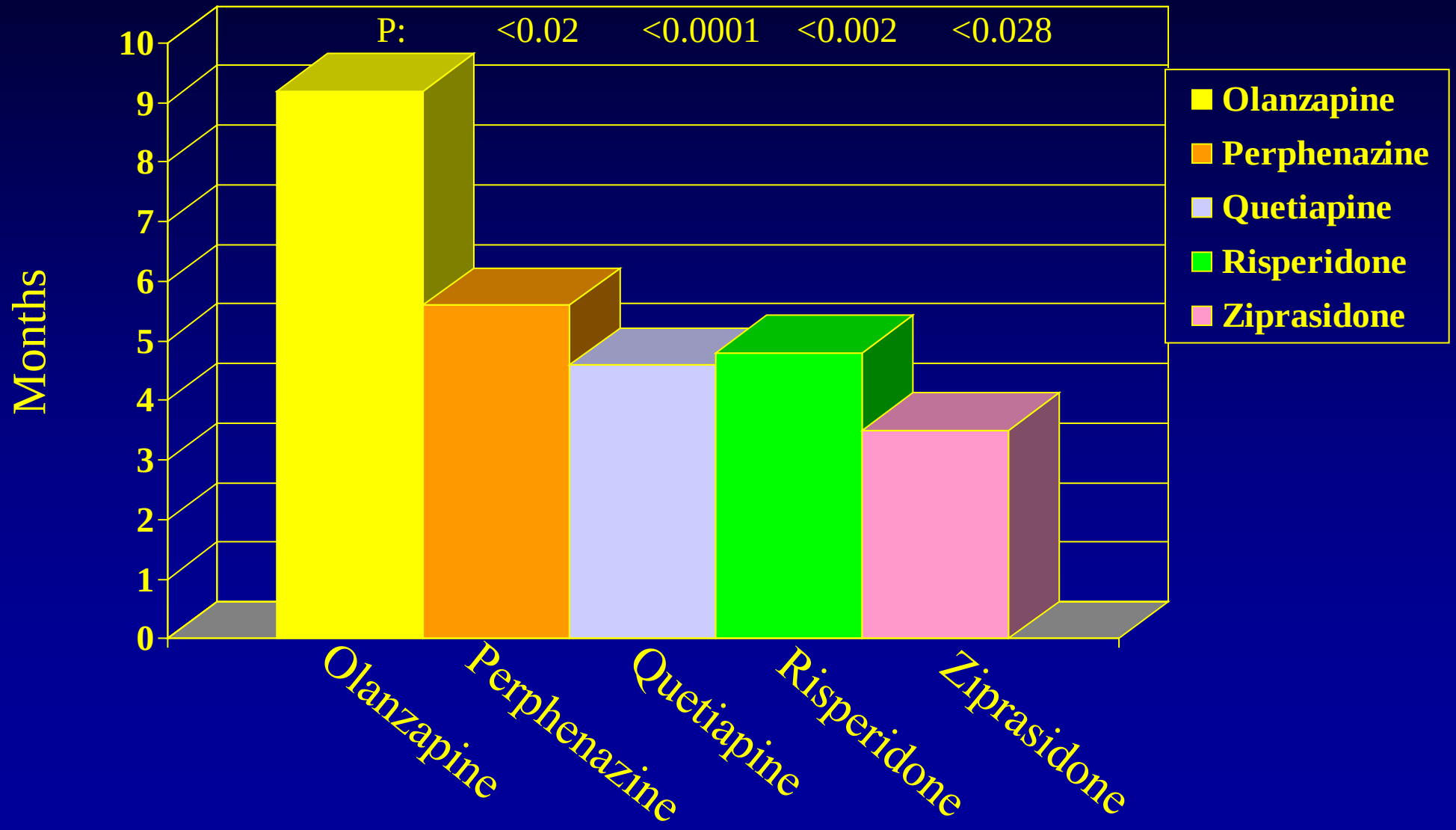
Clinical Antipsychotic Trials of Intervention Effectiveness

- 1493 outpatients with chronic schizophrenia
- Randomized, double-blind design
- NIMH sponsored
- 18 months
- Primary outcome was duration of treatment

Lieberman JA, et al., NEJM 2005; 353:1209

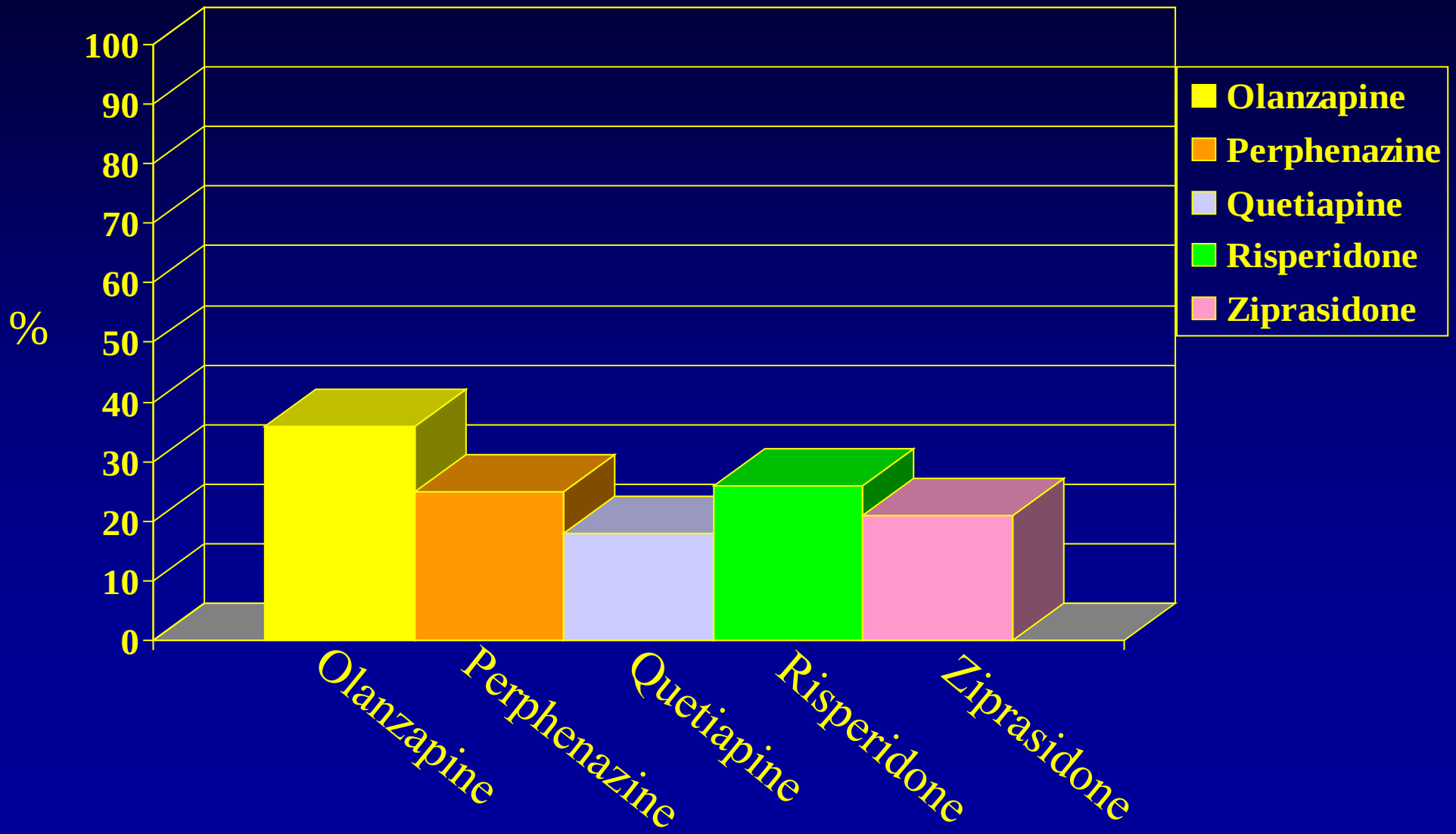
CATIE

Duration of Treatment



CATIE

Patients Completing 18 Months of Treatment



CATIE

Conclusions

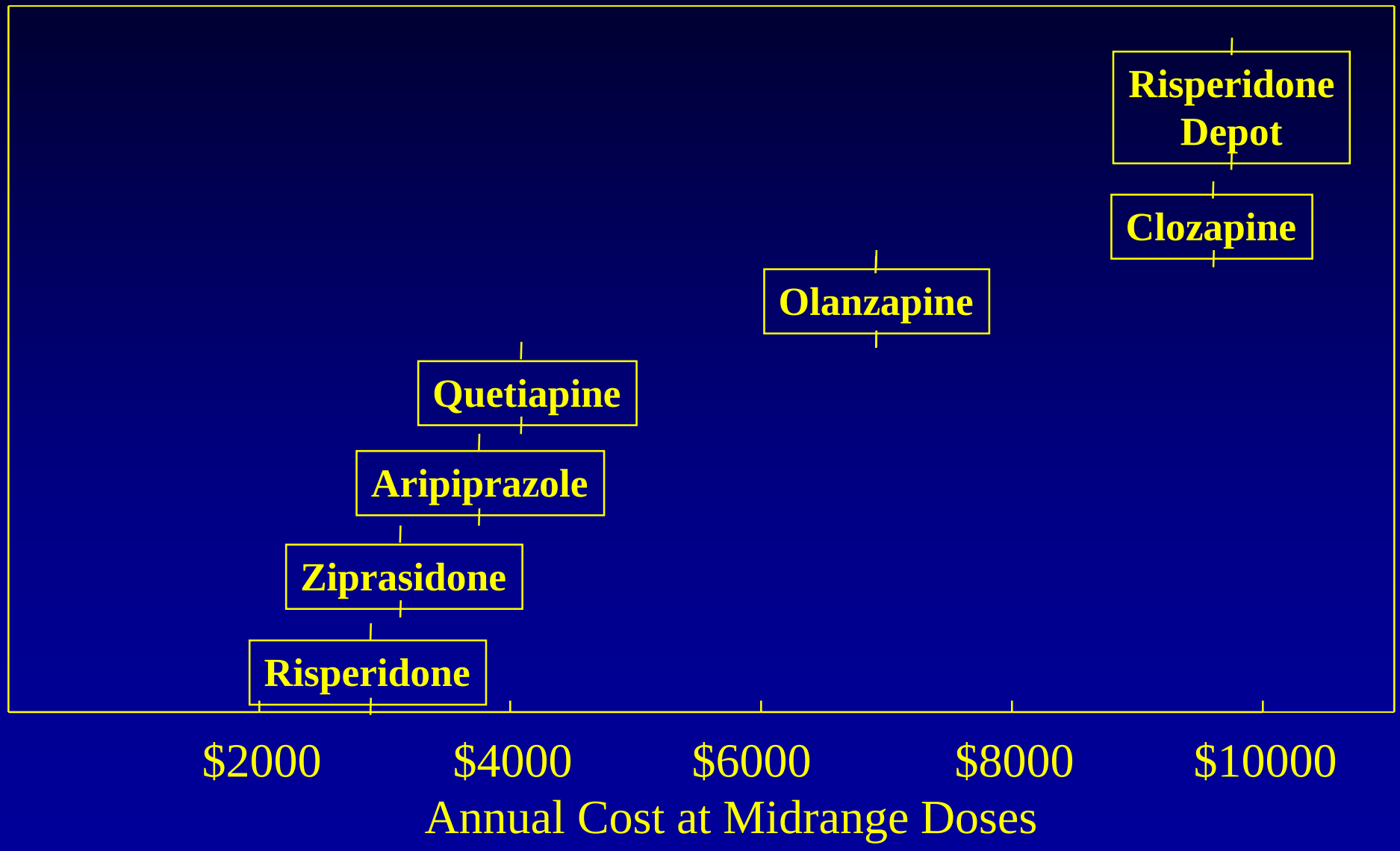
- Most patients discontinued treatment prior to 18 months, but duration of treatment differed among agents
- Tolerability of treatment was comparable among drugs, but specific side effects differed

CATIE

Conclusions

- Patients continued treatment with olanzapine longer than with other agents
- Olanzapine was associated with greater weight gain and metabolic problems
- Perphenazine was similar to quetiapine, risperidone, and ziprasidone in efficacy and side effects

Relative Costs of Atypical Antipsychotic Medications



Treatment Selection with Atypical Antipsychotics

- All first-line atypical antipsychotics are effective against psychotic symptoms
- All first-line atypical antipsychotics are equally well tolerated in large studies
- Each medication has unique side effects
- Each medication has unique pharmacokinetics
- Individual patients may respond preferentially to the medications

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 Augmentation Strategies

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

APA Practice Guideline, Am J Psychiatry 2004;161 (2:suppl):1

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

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