Antipsychotic Medications

Model Curriculum

American Society for Clinical Psychopharmacology

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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 recognize the unique features of clozapine and depot antipsychotics

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

Pretest

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

Schizophrenia and Its Treatment

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Definition

Schizophrenia is a chronic or recurrent disorder characterized by

- Periods of psychosis
- Long-term functional deterioration

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Symptom Subtypes in Schizophrenia

Positive Symptoms

- Delusions
- Hallucinations
- Thought Disorganization
- Catatonia

Cognitive Deficits

- Memory
- Attention
- Language
- Executive Function

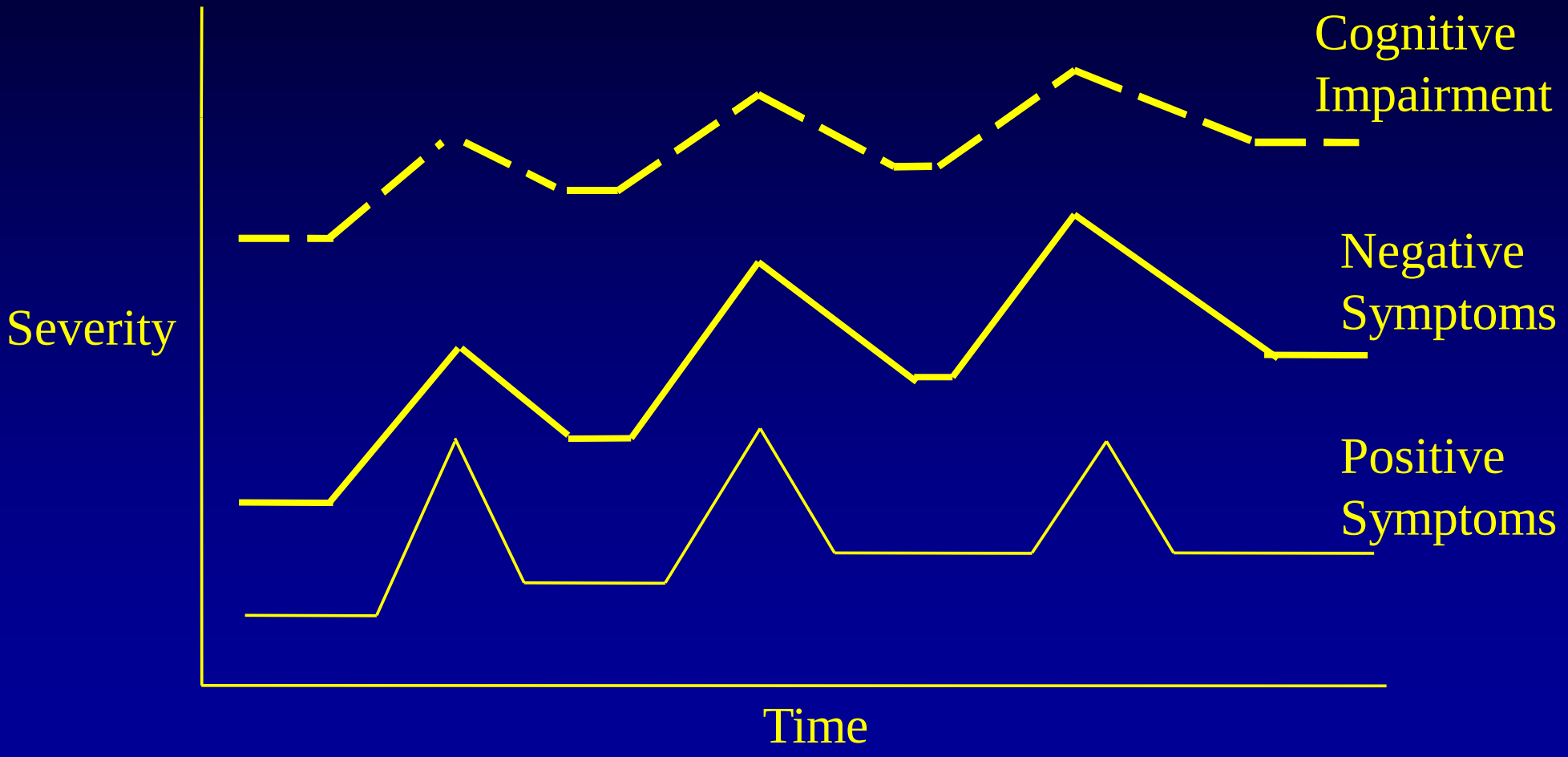
Negative Symptoms

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

Mood Symptoms

- Depression
- Dysphoria
- Suicidality

Course of Symptom Subtypes



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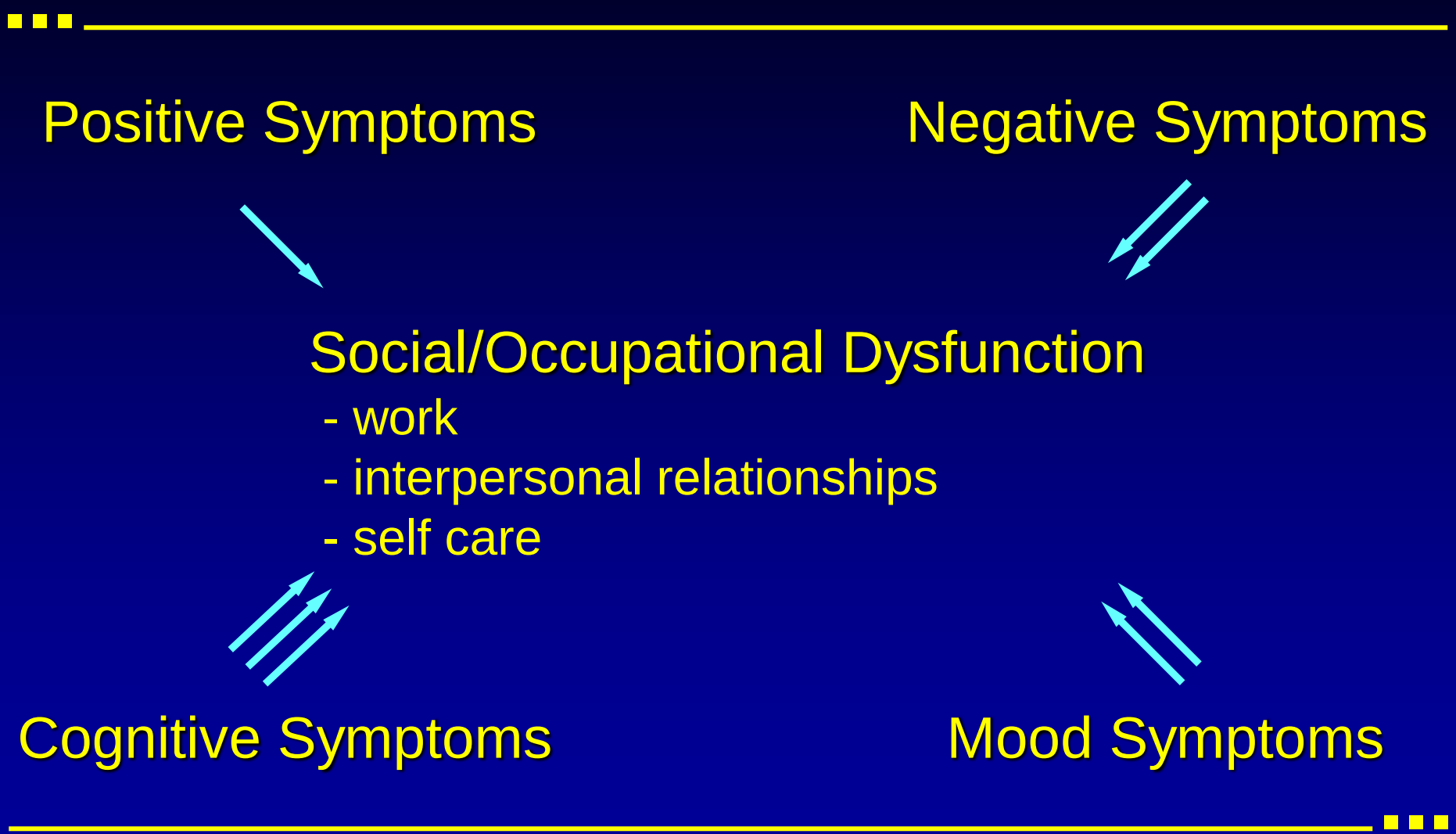
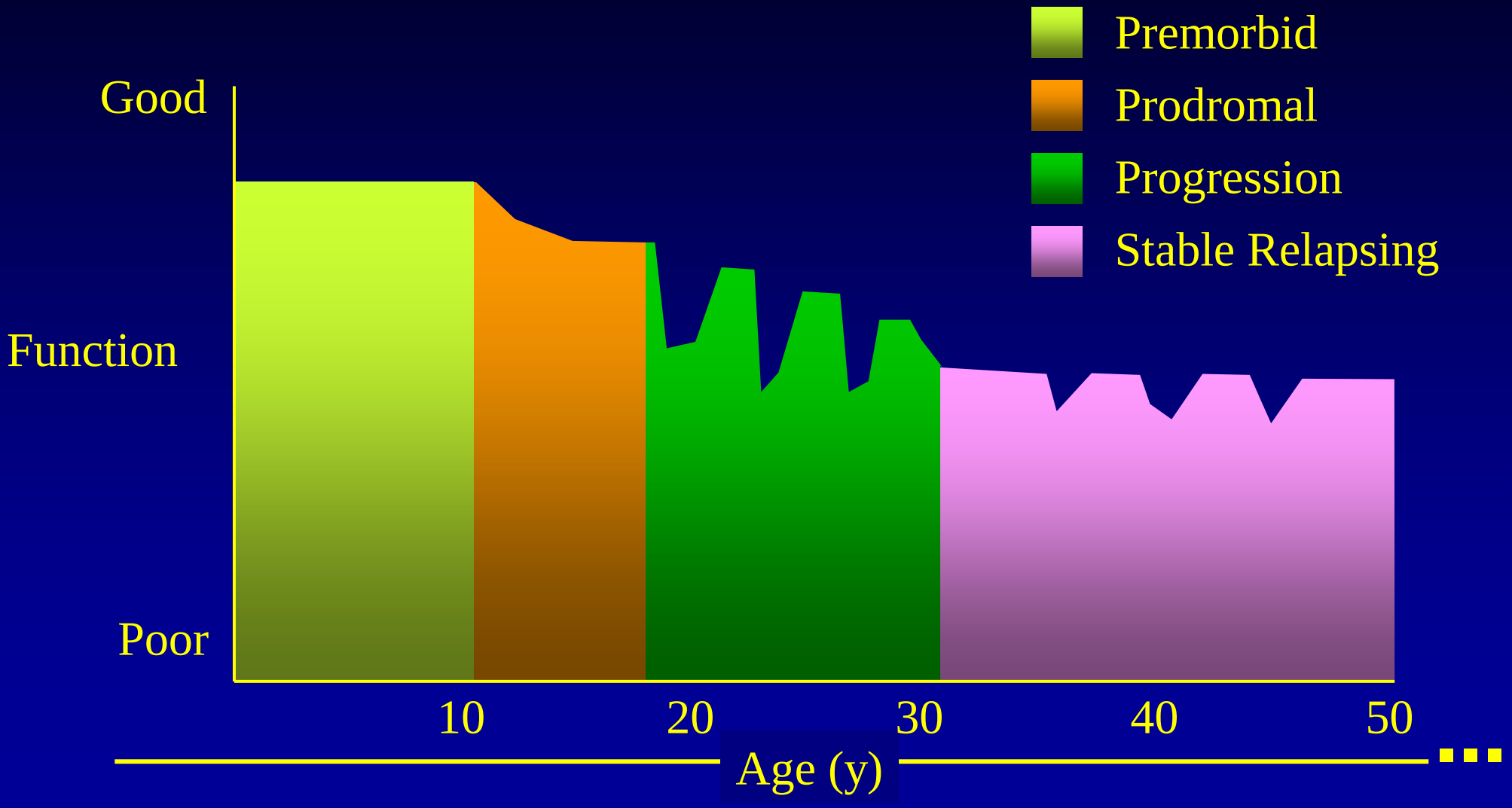
Contributions to Functional Impairment



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

Natural History of Schizophrenia



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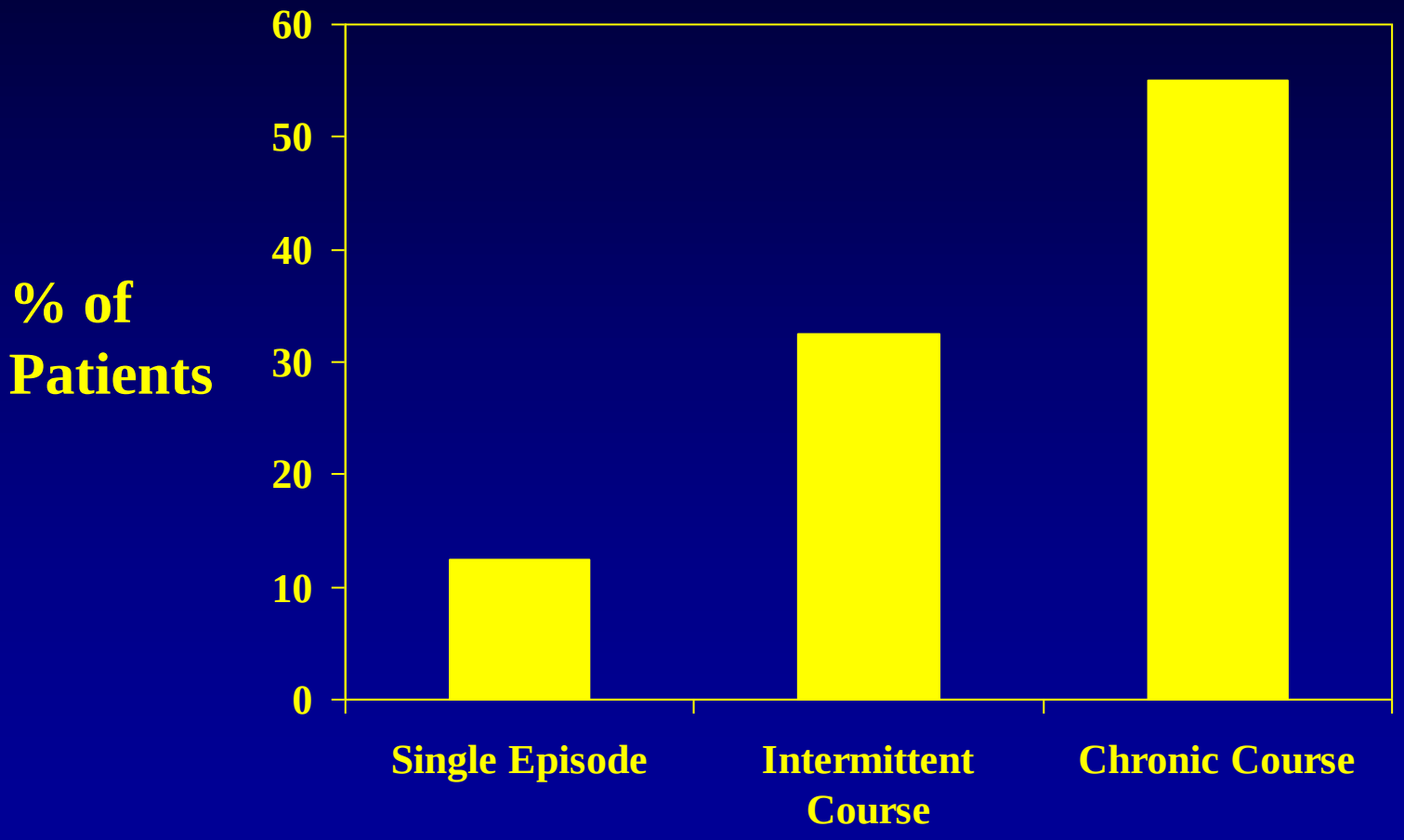
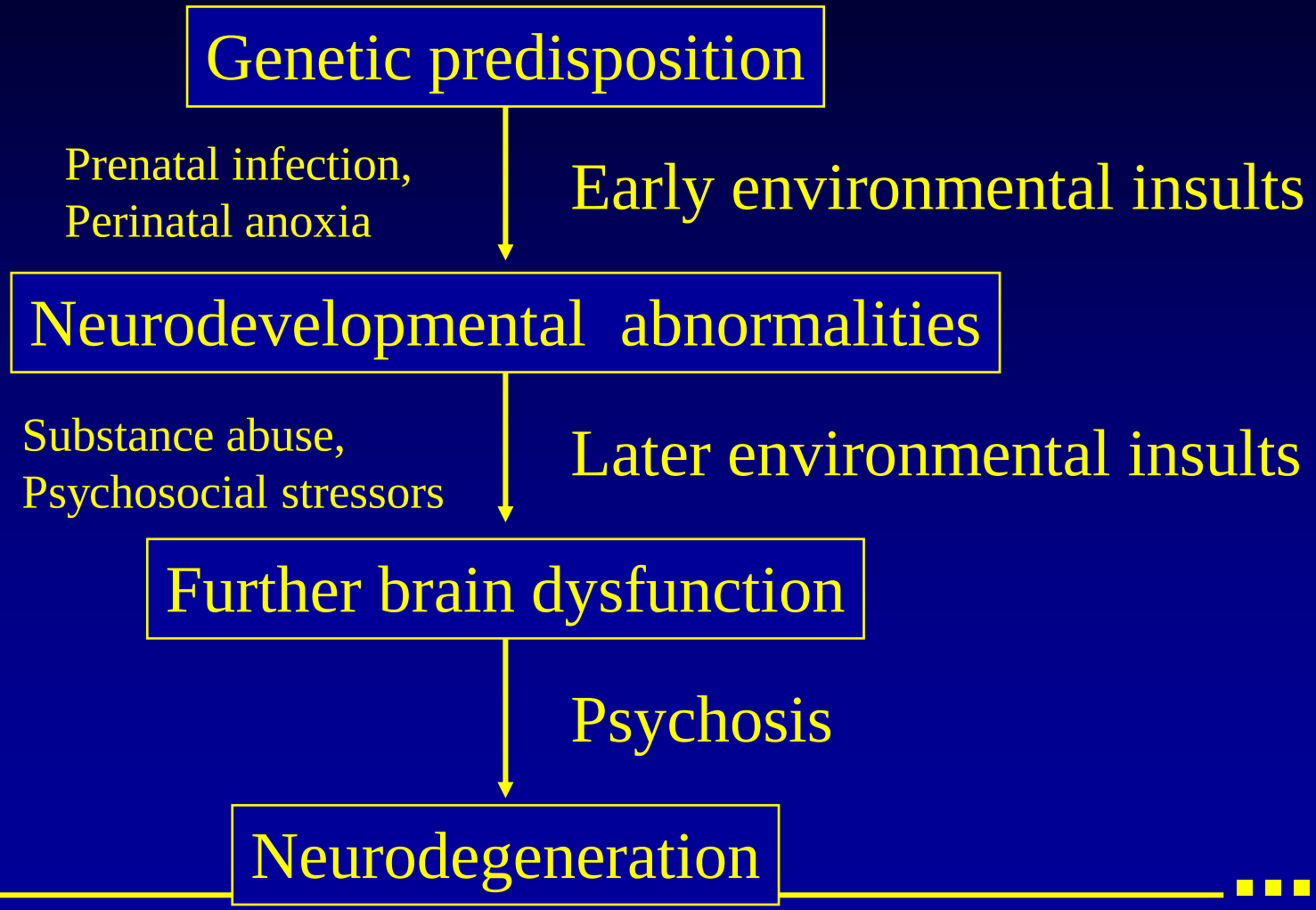
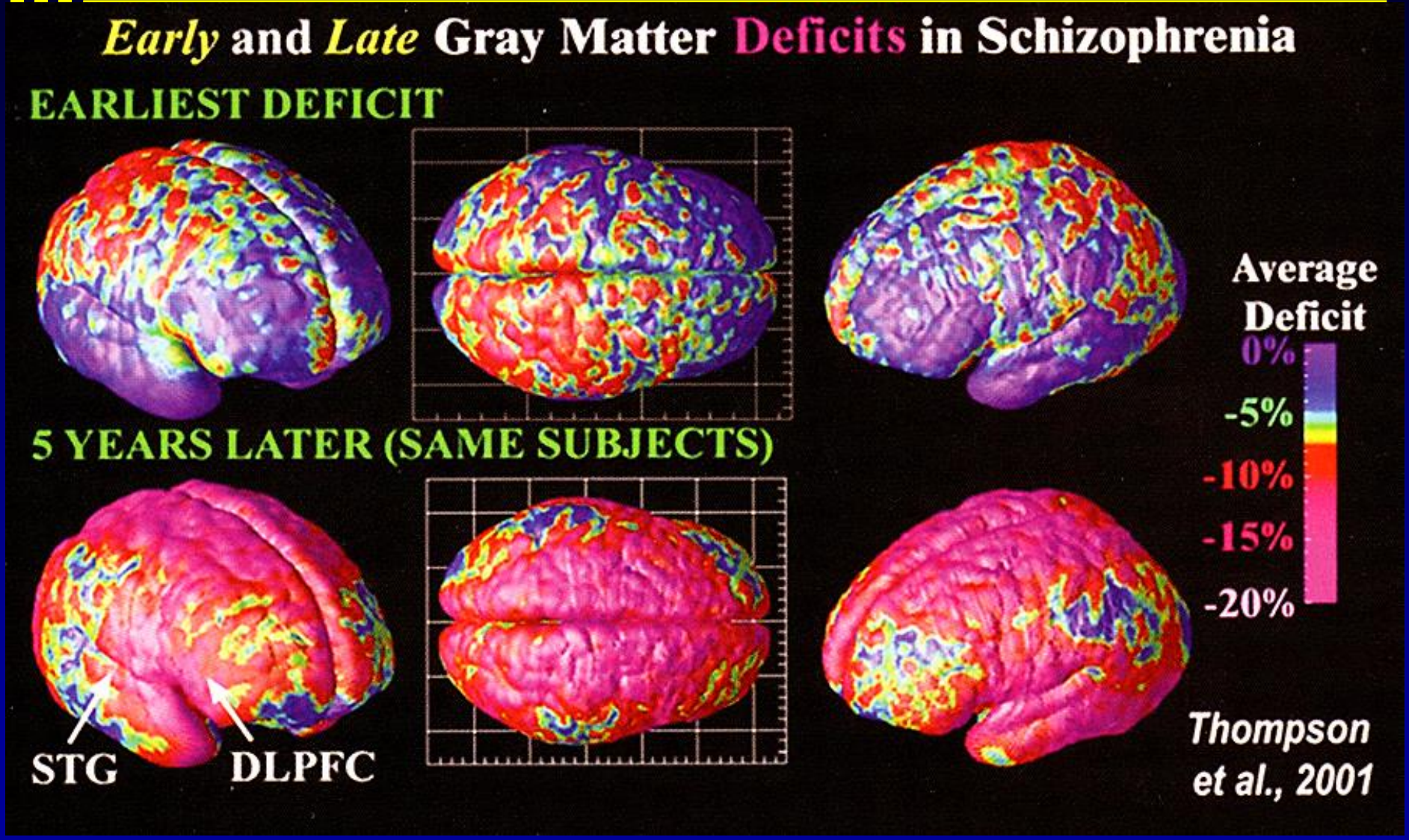
Natural History of Schizophrenia



Etiology of Schizophrenia



Structural Abnormalities in Schizophrenia



Dopamine Hypothesis of Schizophrenia

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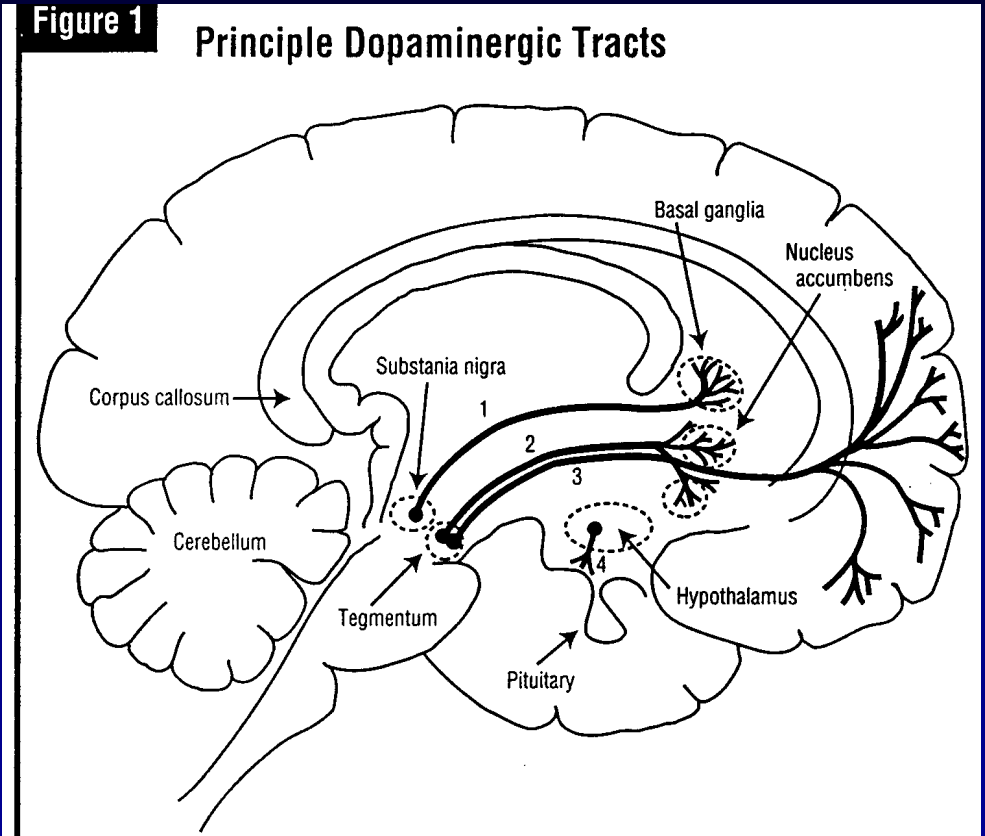
Major Dopamine Pathways

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



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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

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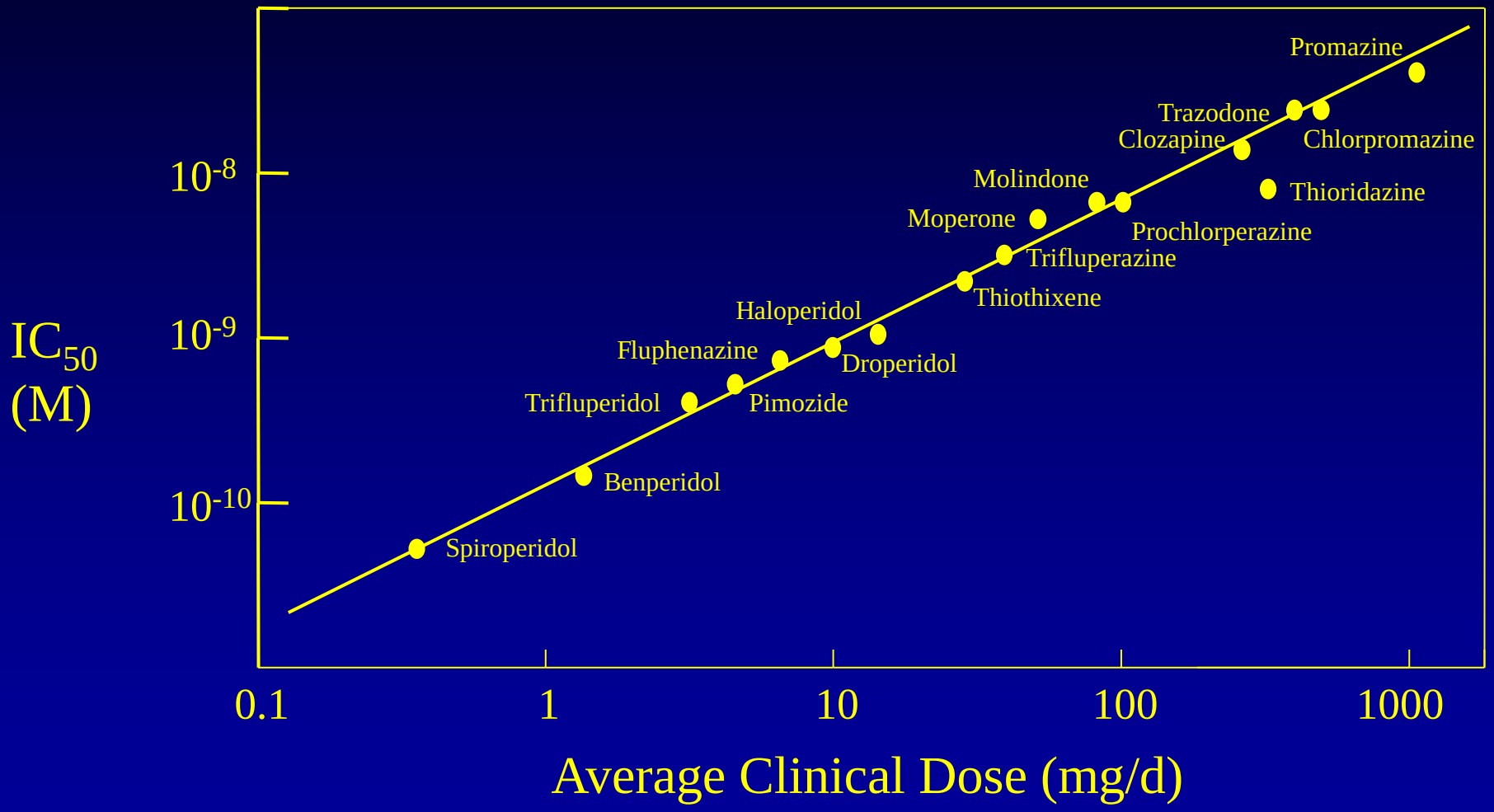
Clinical Efficacy and Dopamine D_2 Blockade



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

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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

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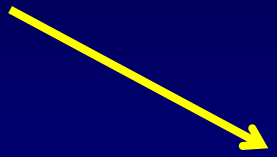
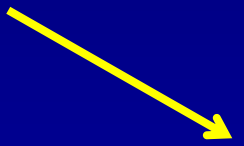
Dopamine Hypothesis

Subcortical Dopamine Excess



D_2 Hyperstimulation



Positive Symptoms

Bowers MB, Arch Gen Psychiatry 1974;31:50

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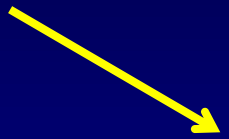
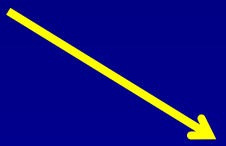
Dopamine Hypothesis

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?

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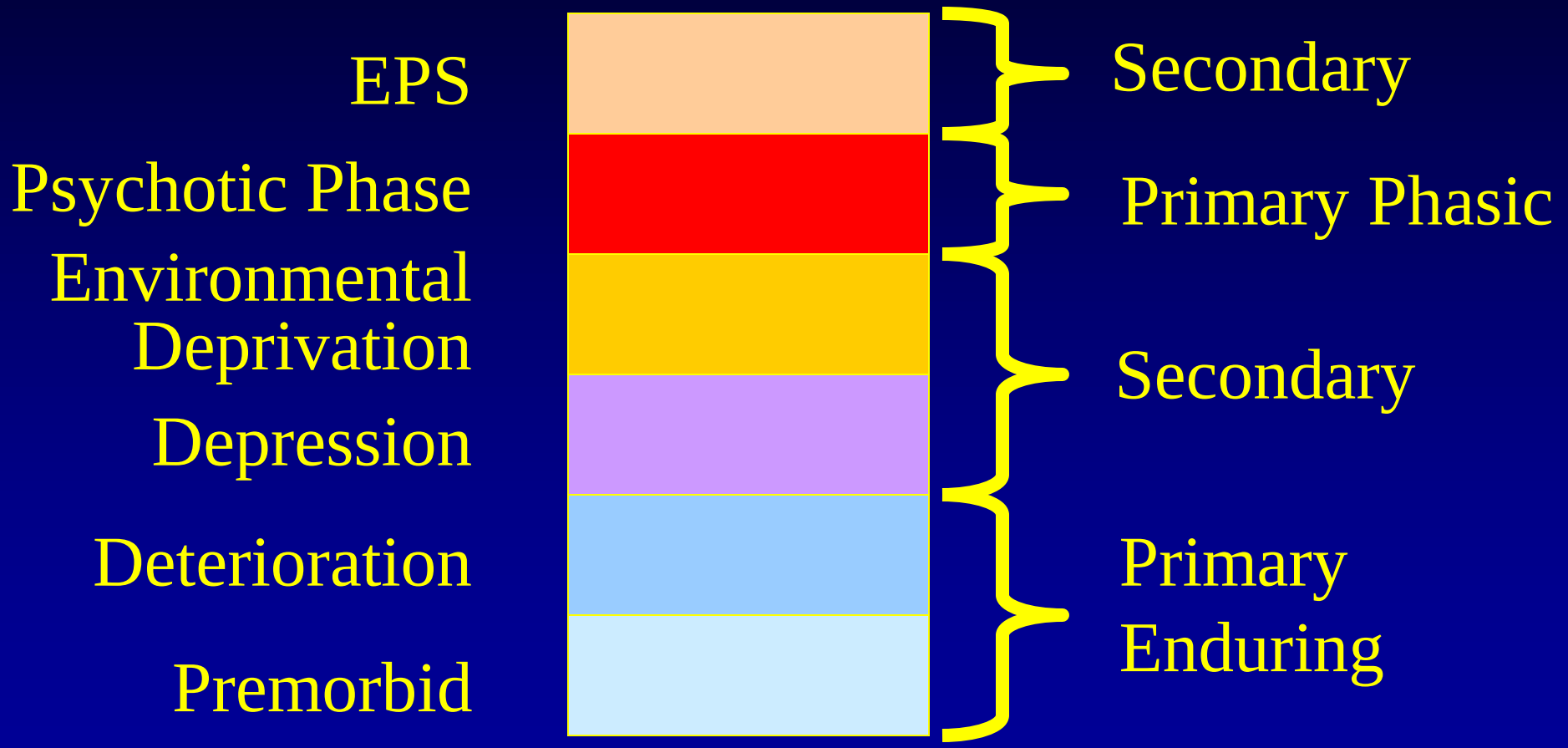
Negative Symptom Components



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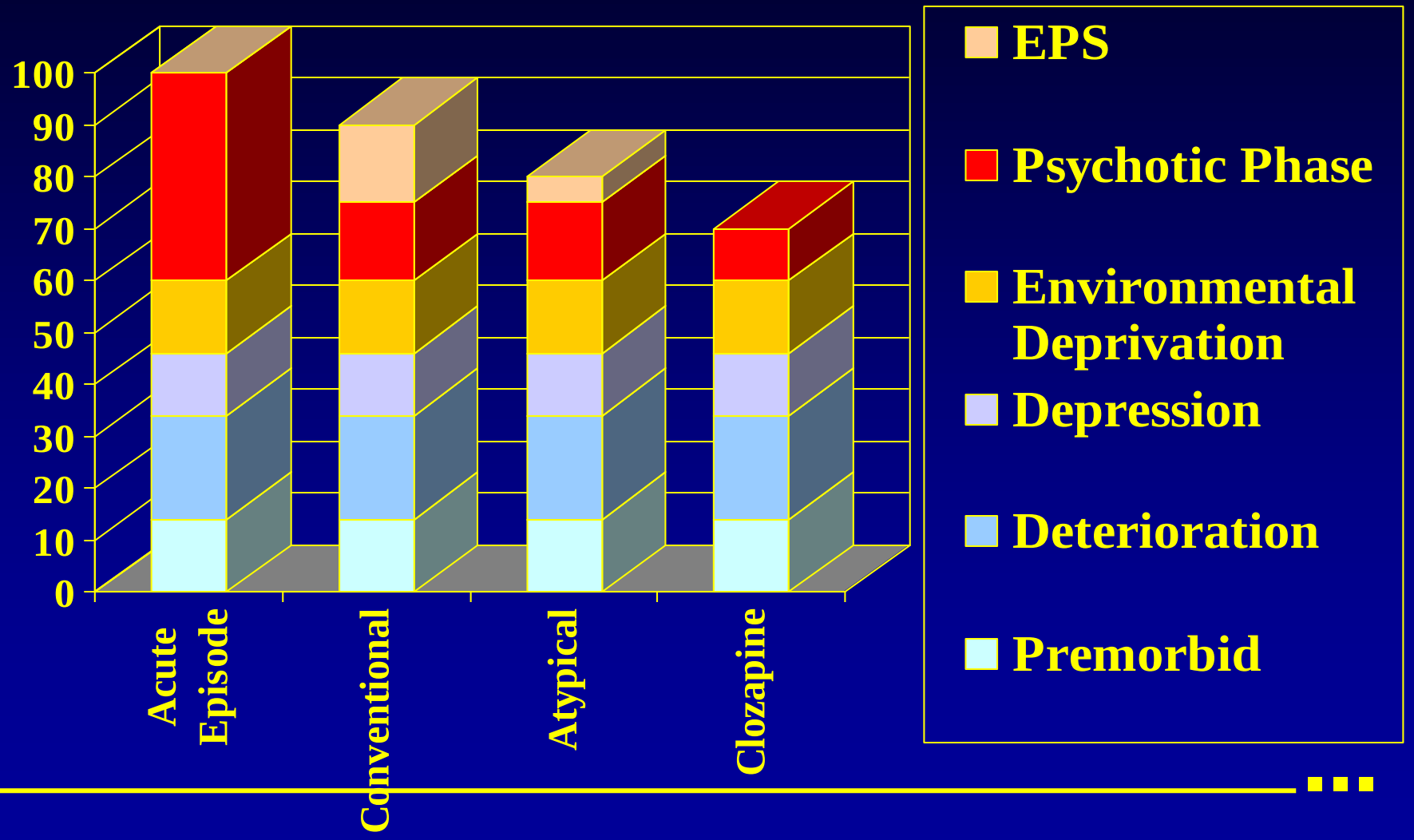
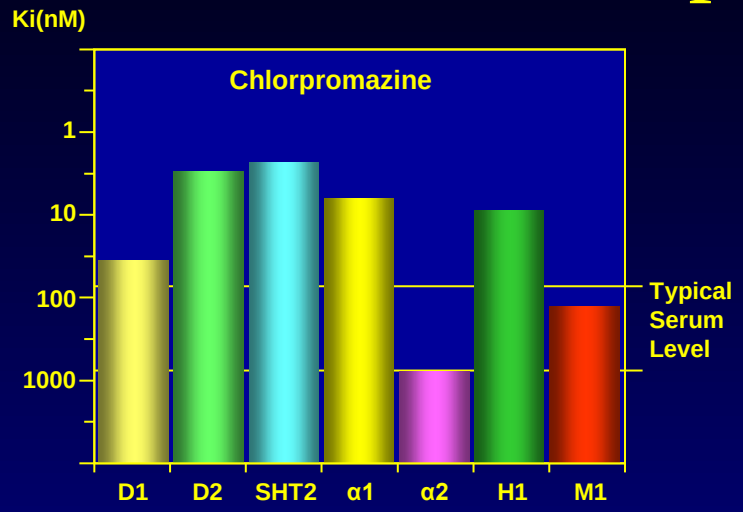
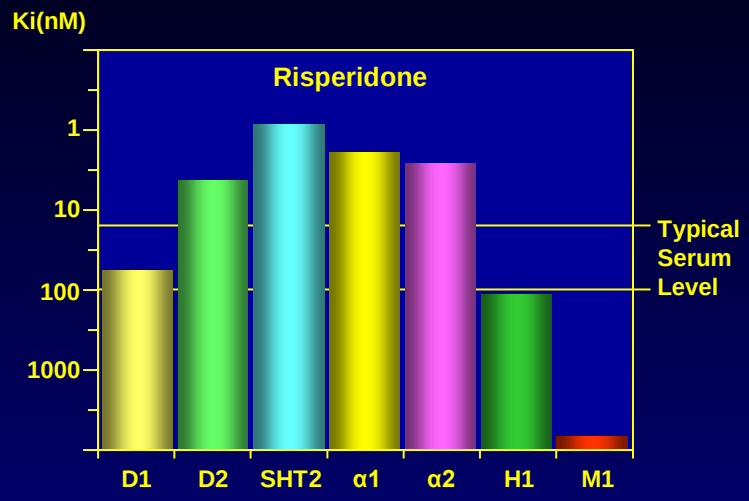
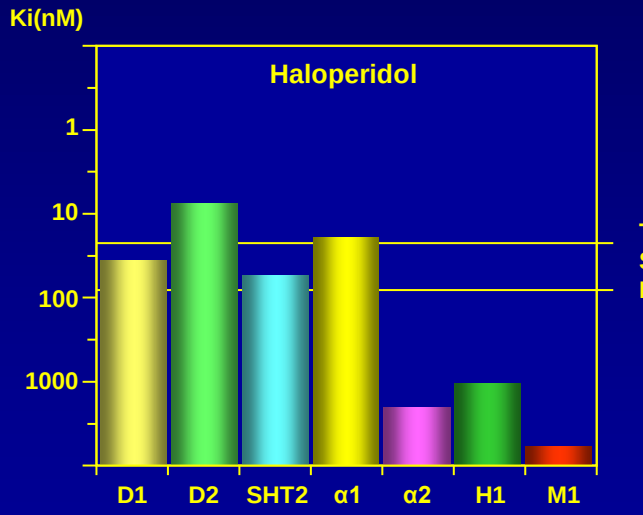
Negative Symptom Components

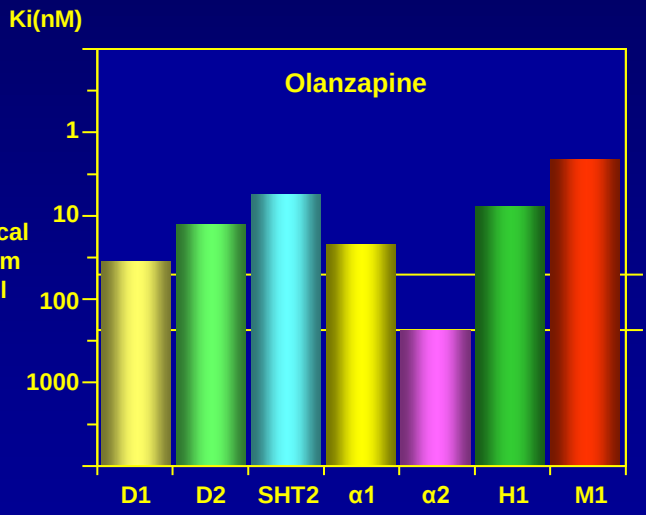


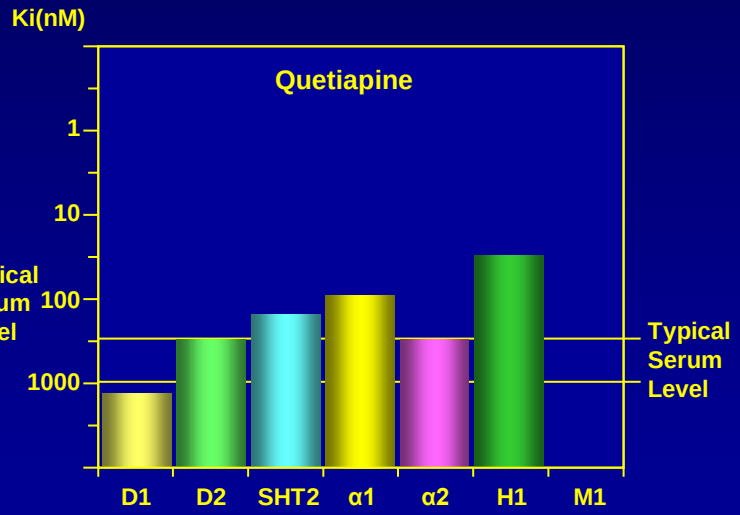
Receptor Profiles











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

- Second generation 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

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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

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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

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FDA Approved Indications for Antipsychotic Medications

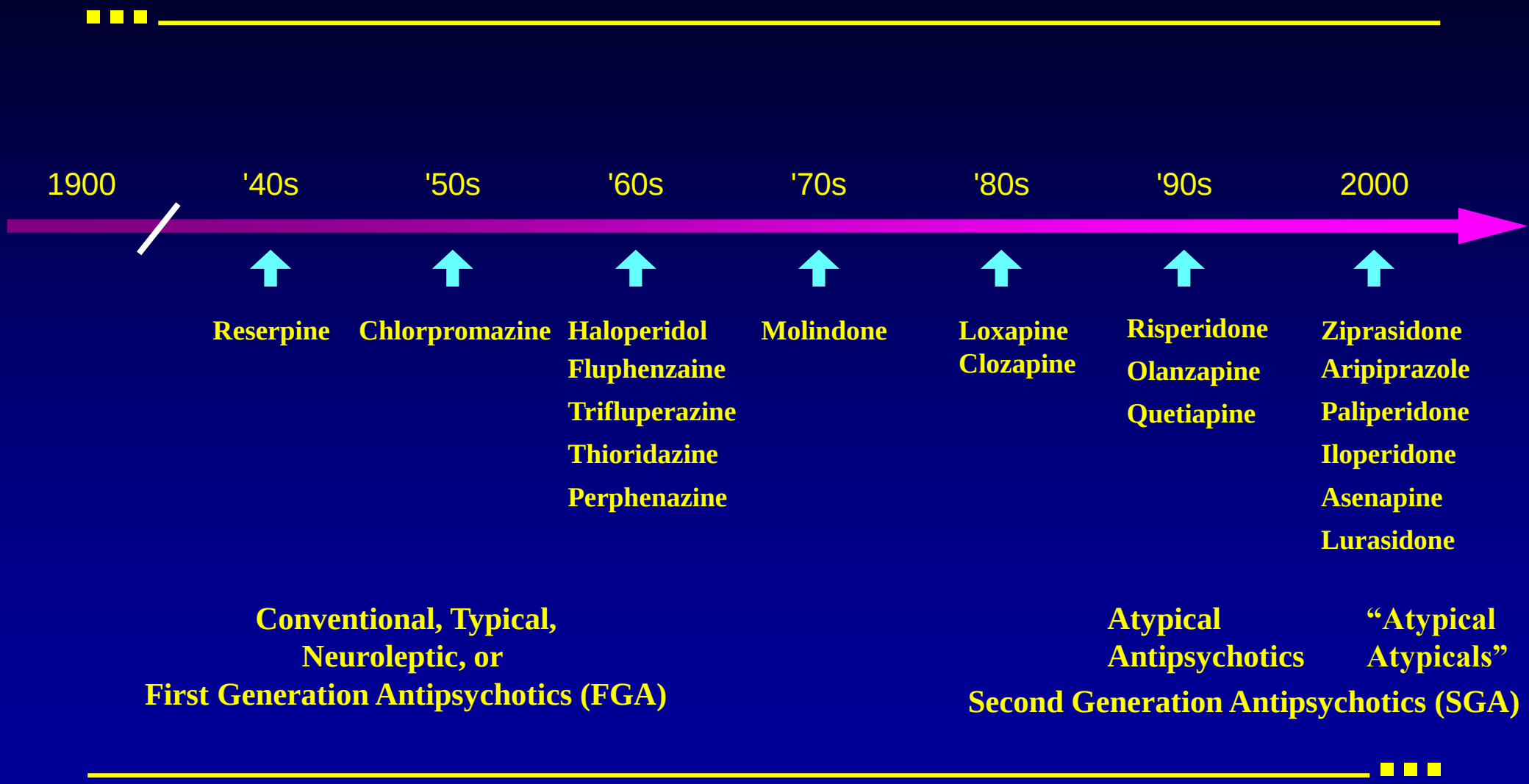
Adults

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

Children and Adolescents

- Schizophrenia
- Autism

The Evolution of Antipsychotic Medications



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

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First Generation Antipsychotics (FGA)

- 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

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First Generation Antipsychotics (FGA)

High Potency

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

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First Generation Antipsychotics (FGA)

Low Potency

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

First Generation Antipsychotics (FGA) Low Potency

- Advantages
  - Highly sedating
  - Injectable formulations
  - Inexpensive
- Disadvantages
  - High risk of qTc prolongation
  - High risk of tardive dyskinesia

Second Generation Antipsychotics (SGA) (Atypical Antipsychotics)

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

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Second Generation Antipsychotics (SGA)

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

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

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Aripiprazole

- Advantages
  - Unique pharmacology (partial agonist)
  - Disintegrating tablet and injectable formulations
  - Long clearance half-time
- Disadvantages
  - Unpredictable response when combined with dopamine antagonists
  - Moderate-high cost

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Asenapine

- Advantages
  - Sublingual administration
  - Newly approved
- Disadvantages
  - Limited clinical experience
  - Twice-daily dosing
  - Moderate-high cost

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Iloperidone

- Advantages
  - Newly approved
- Disadvantages
  - Limited clinical experience
  - Twice-daily dosing
  - Moderate-high cost

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Olanzapine

- Advantages
  - Extensive clinical experience
  - Long clearance half-time
  - Disintegrating tablet and injectable forms
- Disadvantages
  - High risk of weight gain and metabolic syndrome
  - Moderate-high cost

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Lurasidone

- Advantages
  - Newly approved
  - Low risk of weight gain and metabolic syndrome
- Disadvantages
  - Limited clinical experience
  - Moderate-high cost

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Paliperidone

- Advantages
  - Does not require hepatic metabolism
  - Depot formulation
- Disadvantages
  - Dose-dependent EPS
  - Moderate risk of weight gain
  - Prolactin elevation
  - Moderate-high cost

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Quetiapine

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

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Risperidone

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

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Ziprasidone

- Advantages
  - Low risk of weight gain
  - Low risk of sexual dysfunction
  - Injectable formulation
- Disadvantages
  - Twice-daily dosing
  - Dosing with meals recommended
  - qT prolongation

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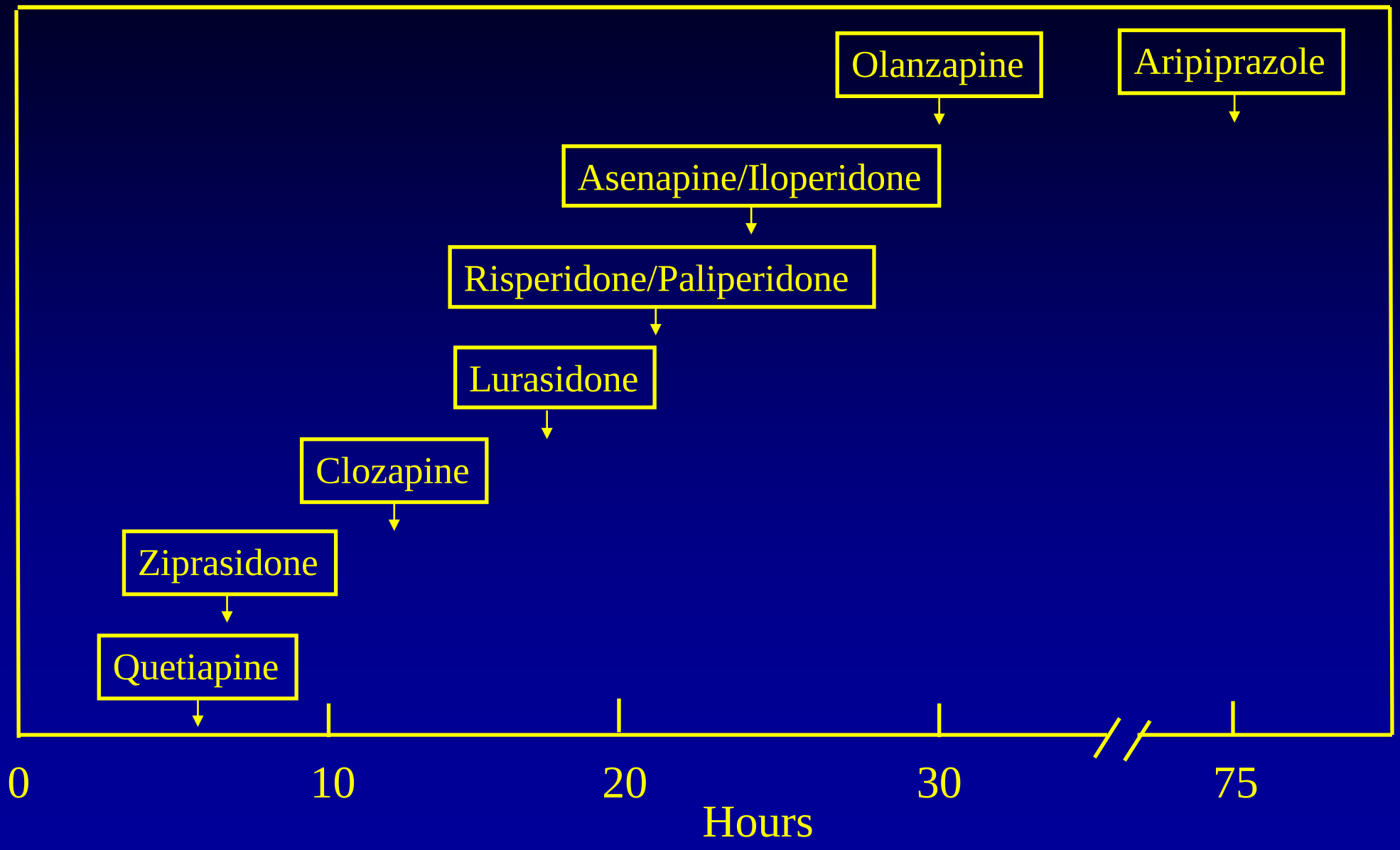
Clozapine

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

SGA Elimination Half-Times



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Depot Antipsychotics

- Fluphenazine (Prolixin) decanoate
- Haloperidol (Haldol) decanoate
- Olanzapine pamoate (Zyprexa Relprevv)
- Paliperidone palmitate (Invega Sustenna)
- Risperidone depot (Risperdal Consta)

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Depot Antipsychotics

Medication	Dosing Frequency
Fluphenazine decanoate	1-2 wks
Haloperidol decanoate	2-4 wks
Olanzapine pamoate	2-4 wks
Paliperidone palmitate	4 wks
Risperidone depot	2 wks

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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

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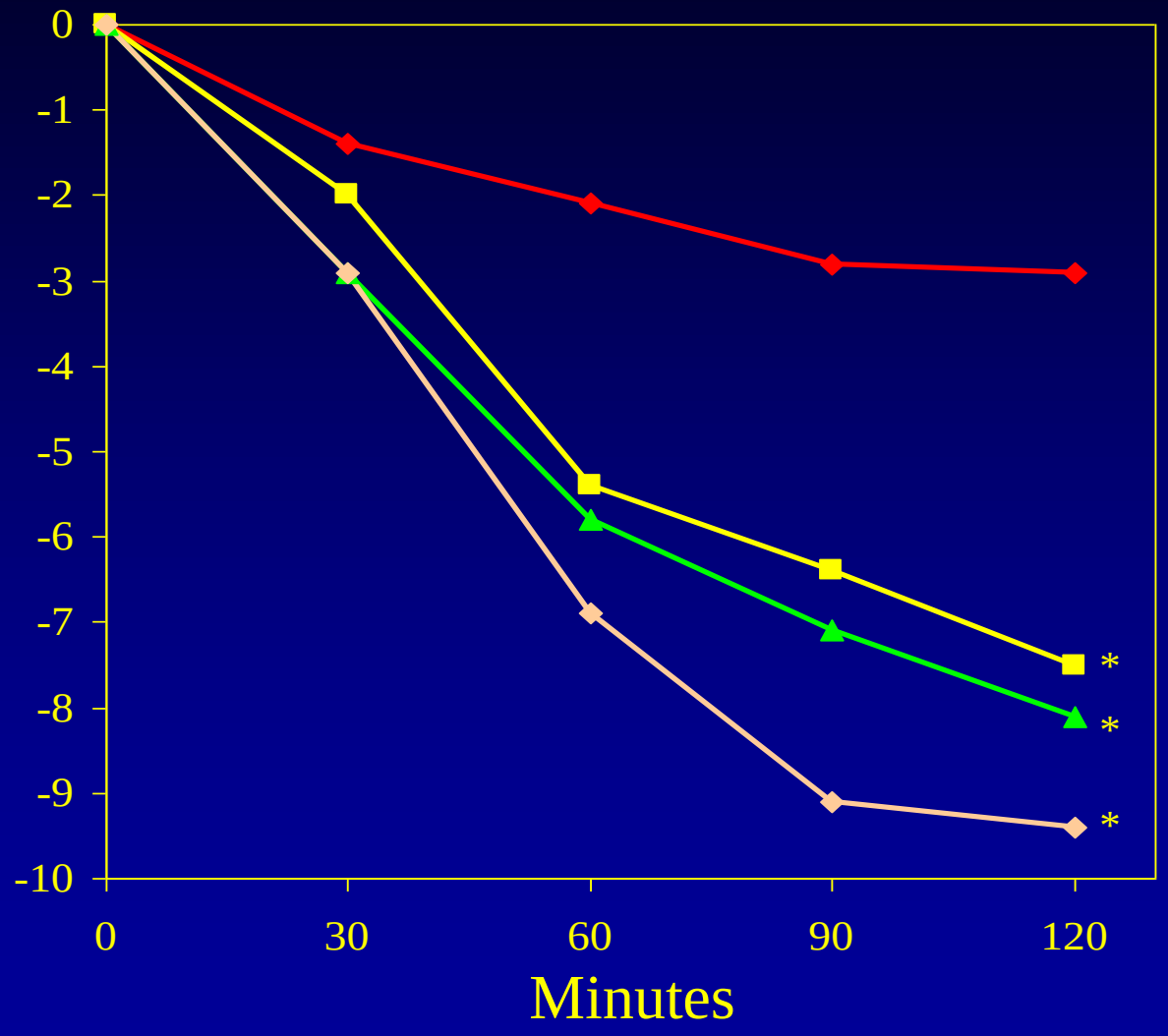
Injectable Olanzapine for Acute Agitation

Change In PANSS Agitation Subscale



*p<0.001 vs Placebo

Olanzapine vs Haloperidol not significant

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

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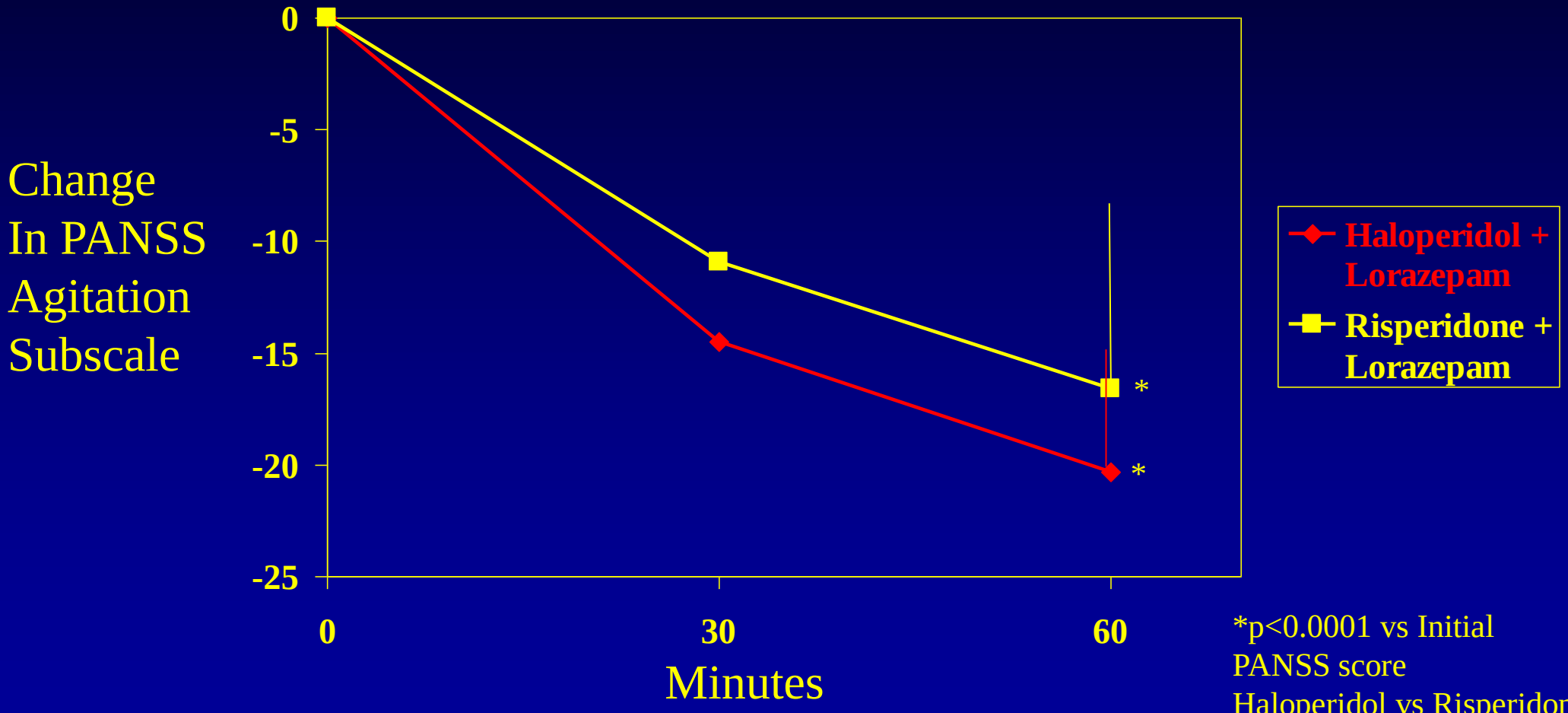
Oral Risperidone vs IM Haloperidol for Acute Agitation



*p<0.0001 vs Initial PANSS score
Haloperidol vs Risperidone not significant

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

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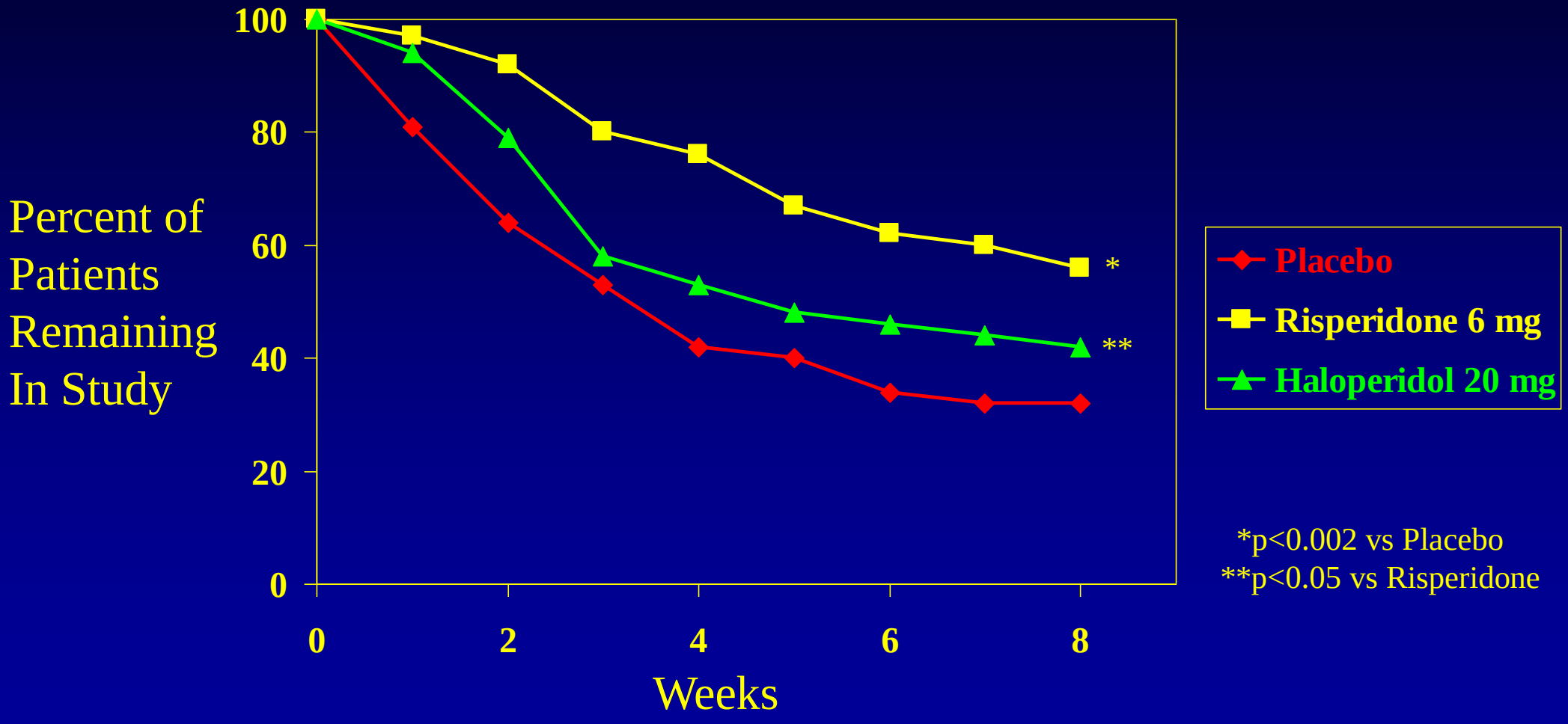
Risperidone for Short-term Treatment



*p<0.002 vs Placebo
**p<0.05 vs Risperidone

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

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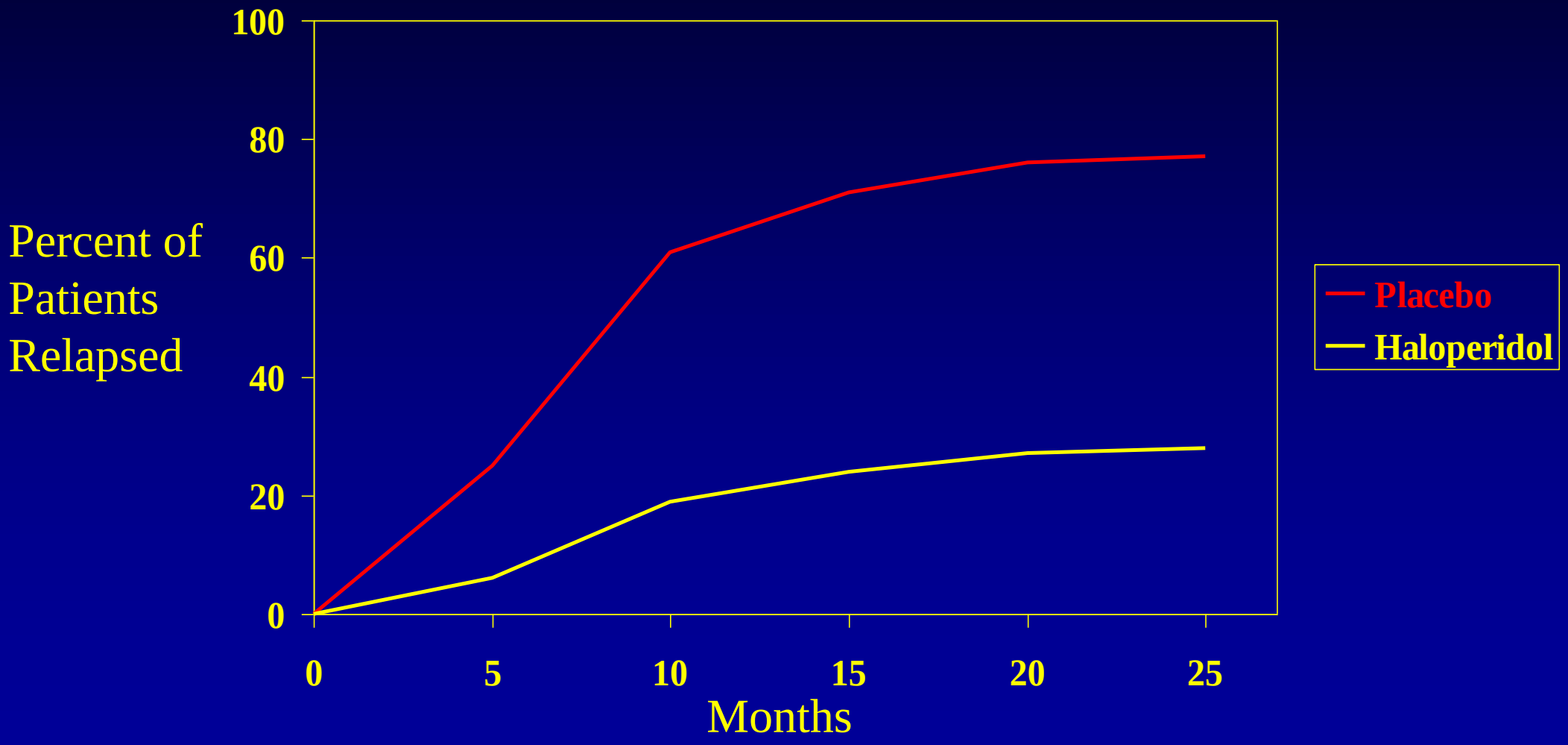
Haloperidol for Long-term Prevention of Relapse



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

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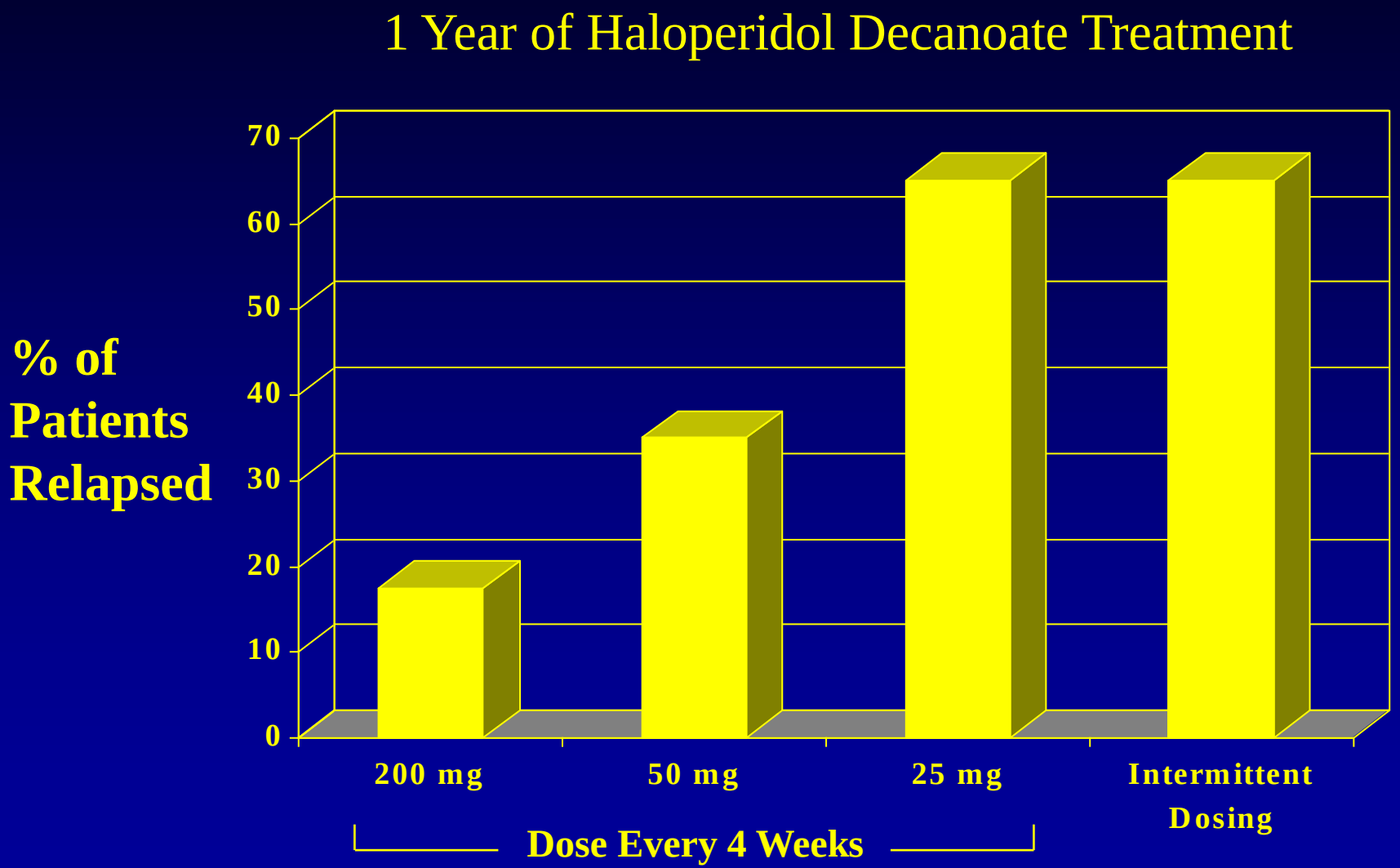
Relationship between Medication Dose and Relapse



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

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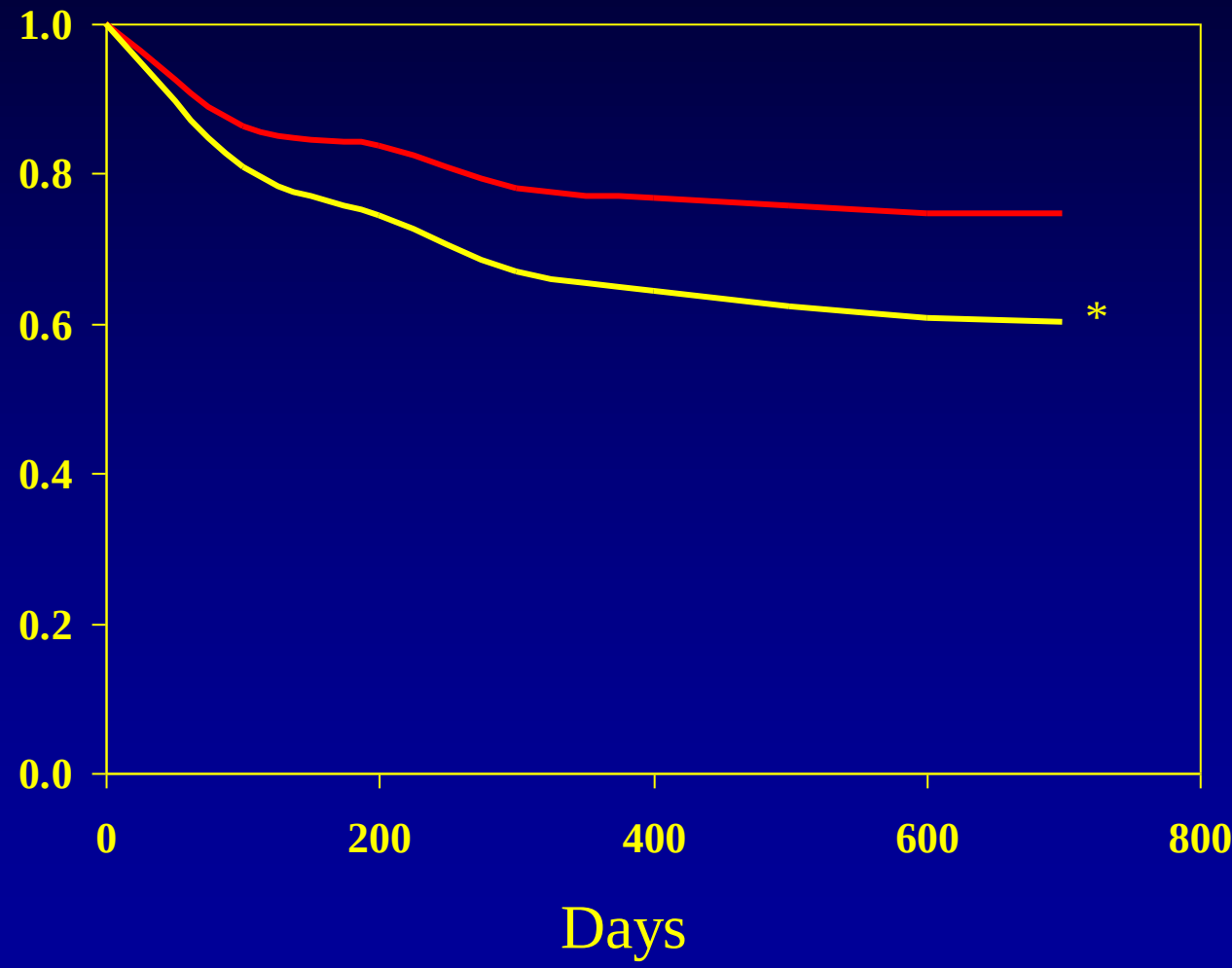
Risperidone for Long-term Prevention of Relapse



* p<0.001 for risperidone vs haloperidol

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

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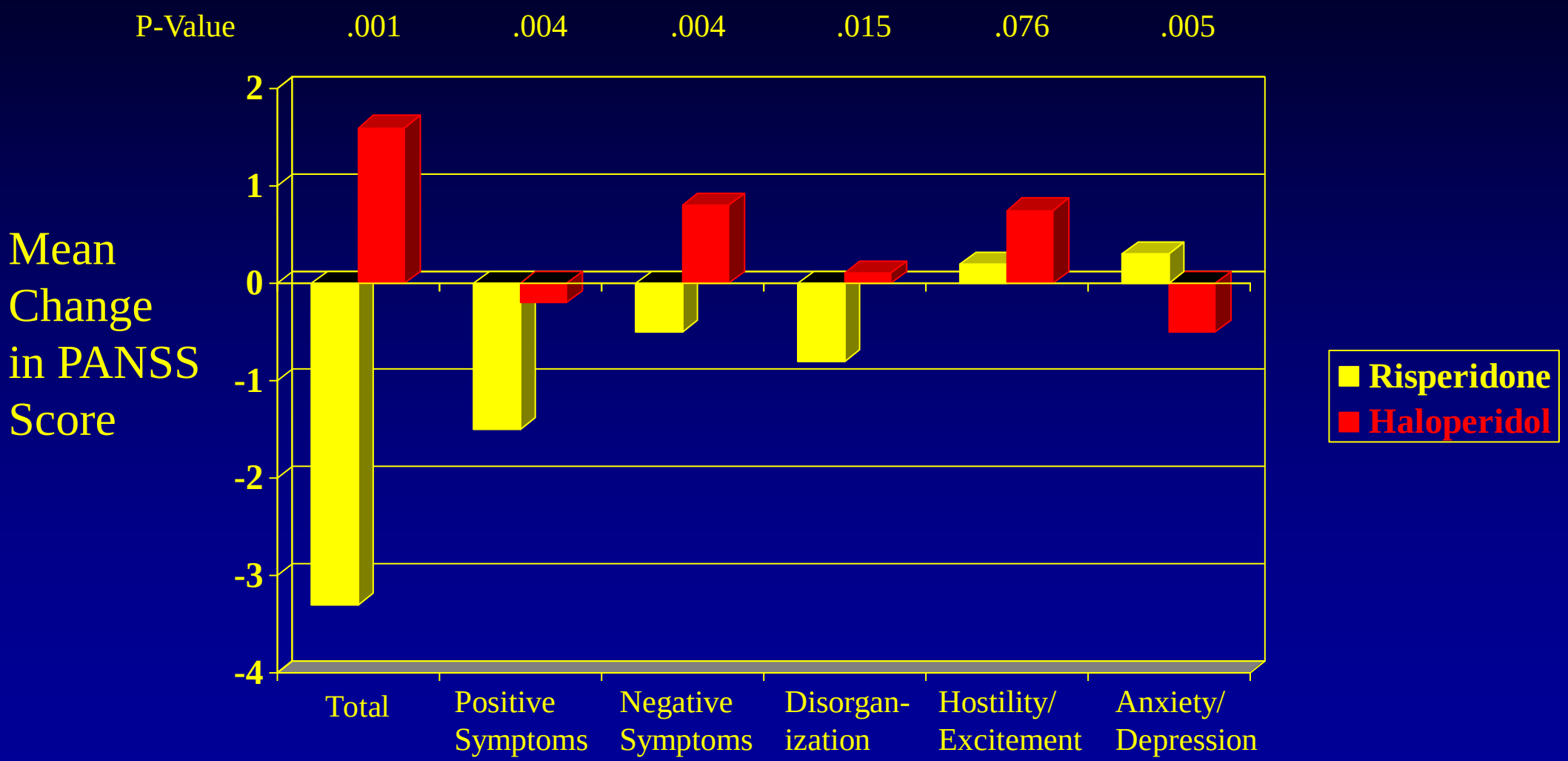
Mean Change in PANSS Score at 2 Years



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

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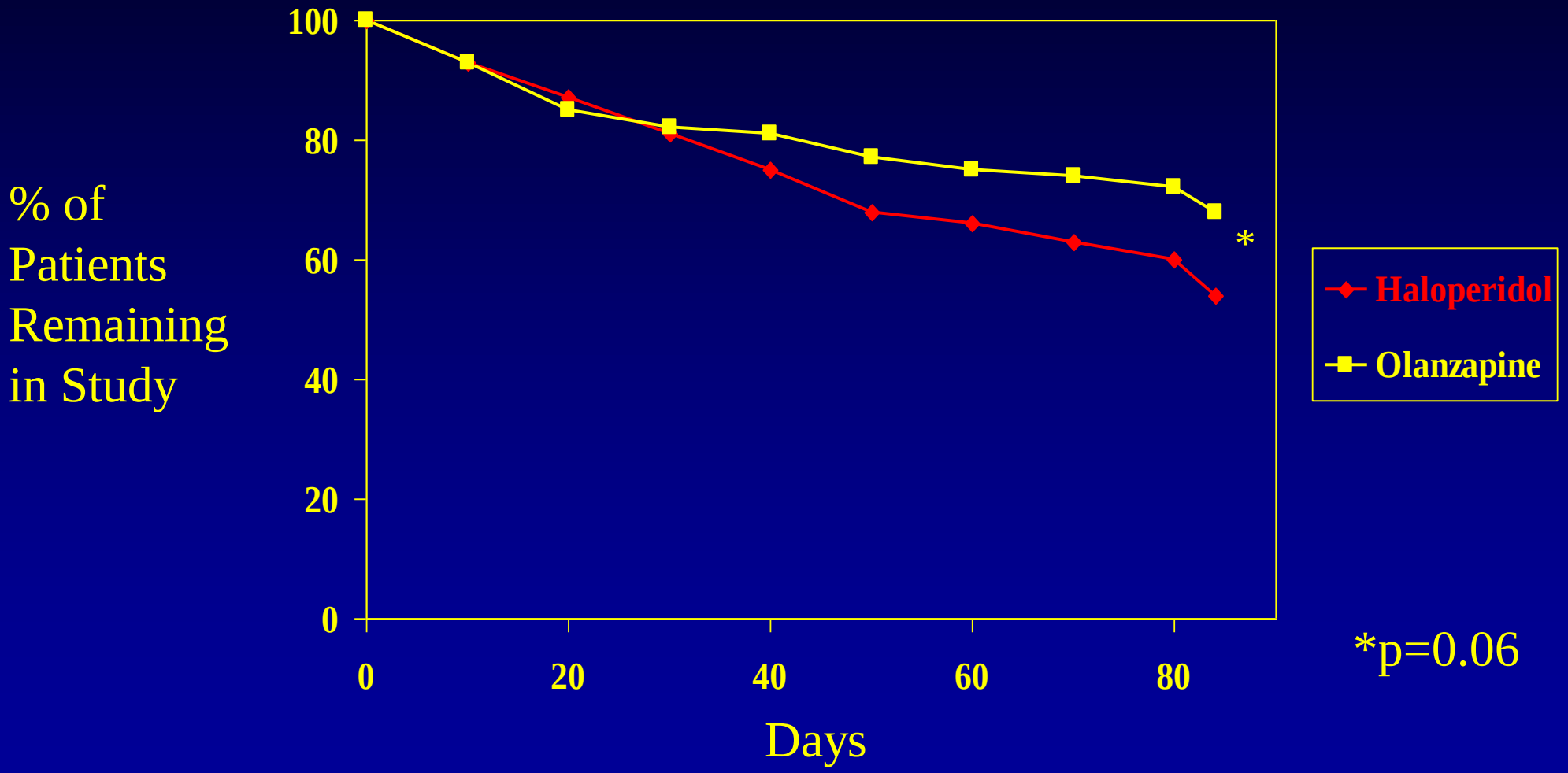
Olanzapine for Prevention of Relapse



*p=0.06

Lieberman JA, et al. Am J Psychiatry 2003; 160:1396

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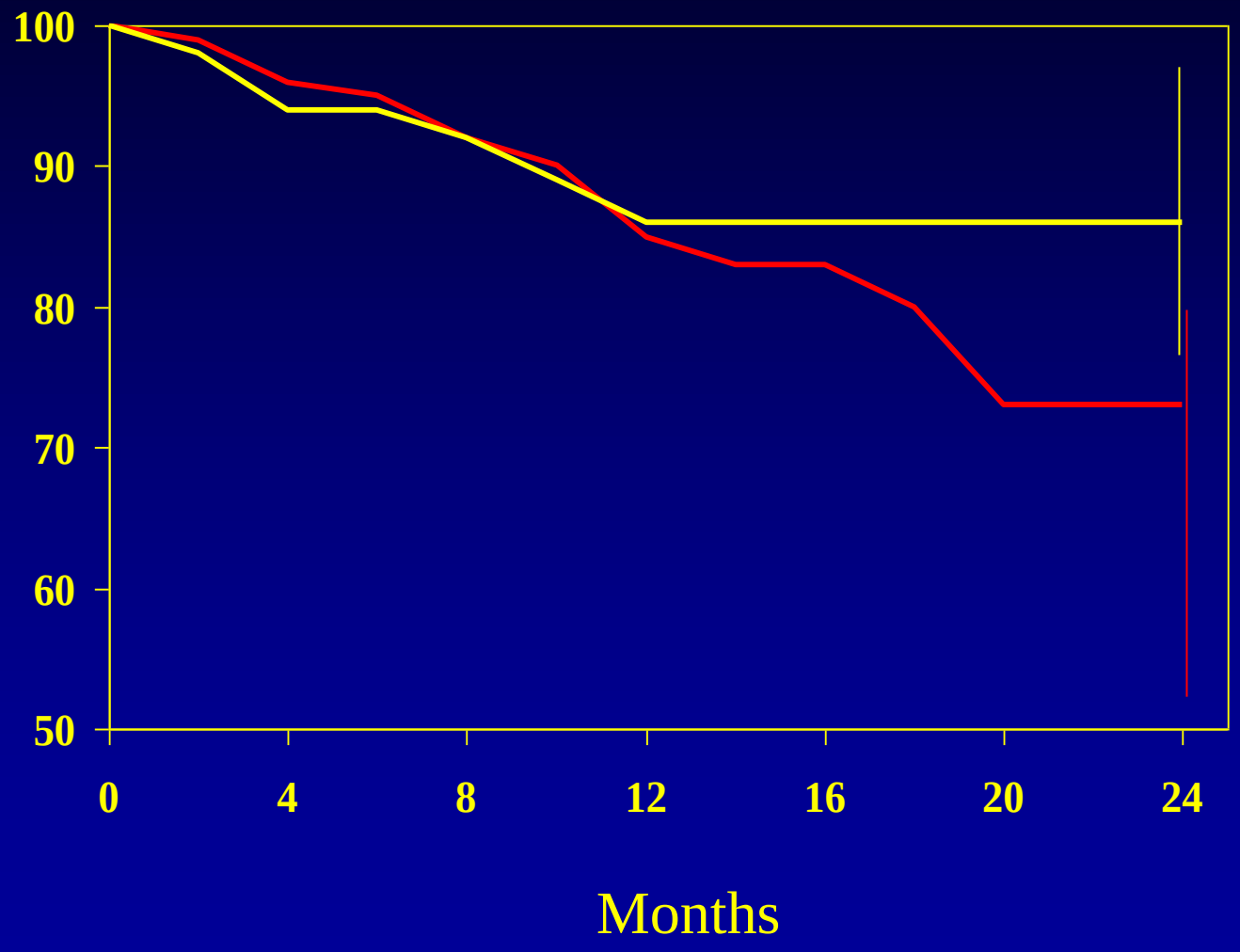
Clozapine for Long-term Treatment



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

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

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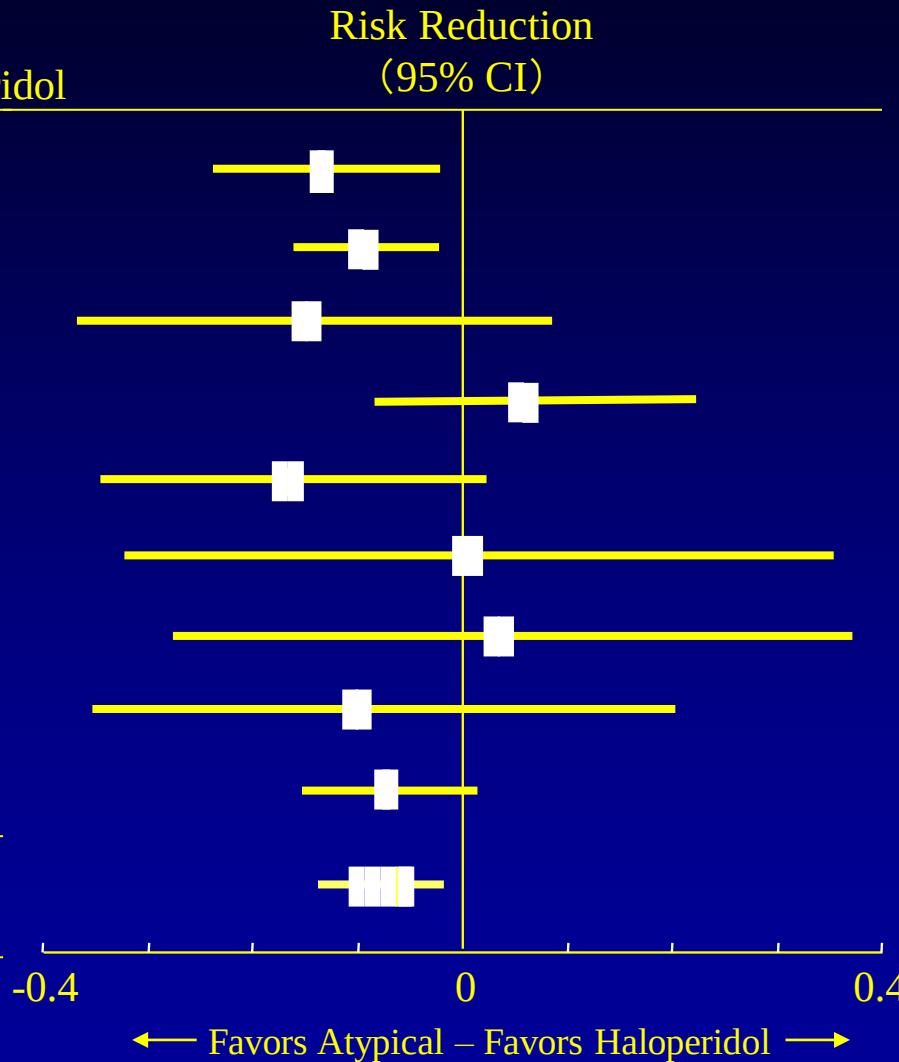
Meta-Analyses – Relapse Risk

Author	Medication	n	% Relapse Atypical	% Relapse Haloperidol
Csernansky 2002	Risperidone	365	23%	35%
Daniel 1998	Sertindole	203	2%	11%
Speller 1997	Amisulpride	60	18%	35%
Tamminga 1993	Clozapine	39	4%	0%
Essock 1996	Clozapine	124	17%	31%
Rosenheck 1999	Clozapine	49	29%	29%
Tran 1998a	Olanzapine	55	22%	20%
Tran 1998b	Olanzapine	62	13%	21%
Tran 1998c	Olanzapine	690	13%	19%
Average	Atypical	1063	15%	23%
	Haloperidol	584		



Pooled RD: -0.08, 95% CI: -0.12, -0.04; p=0.0001

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

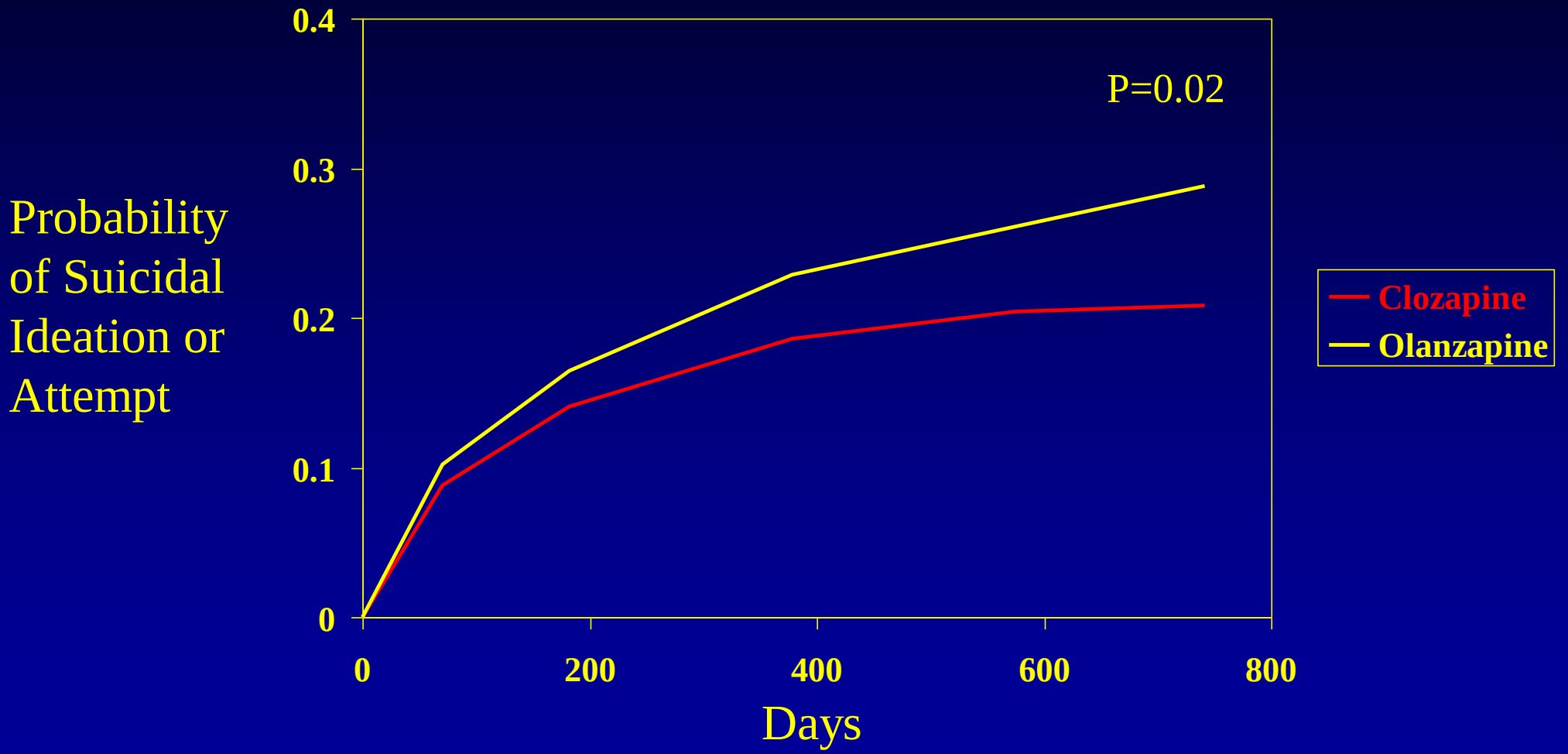
*

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

Prodromal Treatment

- Olanzapine[1] and risperidone[2] have been studied for prodromal treatment
- Relative risk of psychosis was 2.5-3.5 without treatment
- Benefits were less dramatic with longer treatment
- Benefits of treatment were lost within 1 year of discontinuation
- Medication may delay, rather than prevent, psychosis

1. McGlashan TH, Am J Psychiatry 2006; 163:790
2. McGorry PD, Arch Gen psychiatry 2002; 59:921

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
- Supportive psychotherapy
- CBT

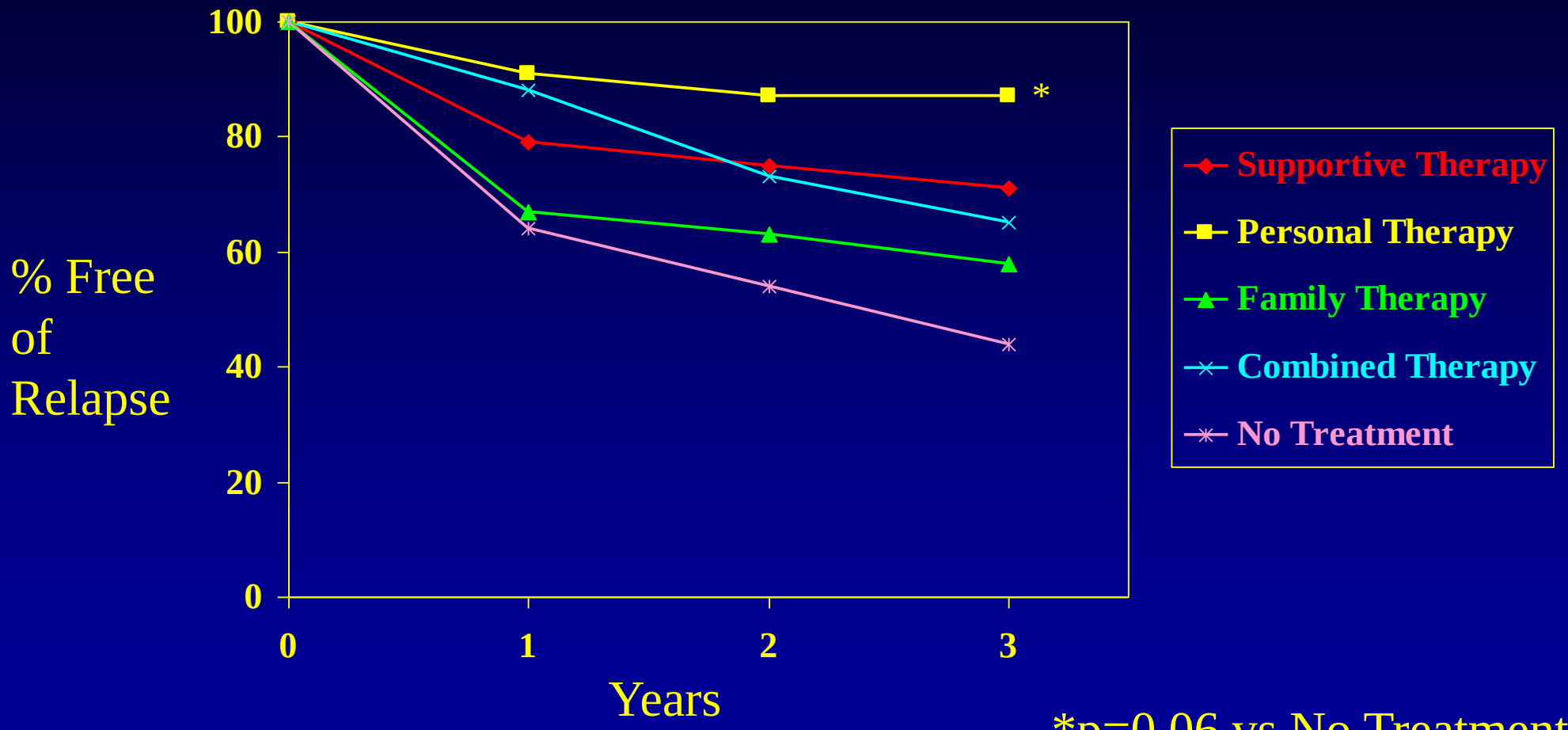
Psychotherapy

What Works	What Doesn't
• Supportive groups	• Insight oriented Tx
• Individual supportive Tx	• Milieu Tx
• CBT*	

*Evidence is mixed. CBT is recommended in APA Practice Guidelines (2004) and PORT recommendations (Dixon LB, et al. Schiz Bull 2010; 36,48), but a recent review found no evidence of efficacy (Jones C, et al. Cochrane Database Syst Rev 1, 2009).

*

Psychosocial Treatment



*p=0.06 vs No Treatment

Hogarty GE, et al. Am J Psychiatry 1997; 154:1504

Side Effects

*

Side Effects - Overview

By Class

	EPS	Orthostatic Hypotension	Anticholinergic Symptoms	Prolactin Elevation
High-potency FGA	+++	+	+/-	++
Low-potency FGA	++	+++	+++	++
First-line SGA	+/- to +	+/- to ++	+/- to ++	+/- to ++
Clozapine	0	+++	+++	+/-

*

Side Effects - Overview

By Class

	qTc Prolongation	Sedation	Weight Gain
High-potency FGA	+/-	+	+
Low-potency FGA	++	+++	+++
First-line SGA	+/- to +	+/- to +++	+/- to +++
Clozapine	+/- to +	+++	+++

*

Side Effects - Overview

Second Generation Antipsychotics

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

*

Side Effects - Overview

Second Generation Antipsychotics

	qTc Prolongation	Sedation	Weight Gain
Aripiprazole	+/-	+/-	+/-
Asenapine	+/-	+	+
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 FGA (20-40%)
- Low-potency FGA
- Paliperidone/Risperidone
- Aripiprazole/Asenapine/Iloperidone/Lurasidone/ 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 any antipsychotic is associated with metabolic dysregulation

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

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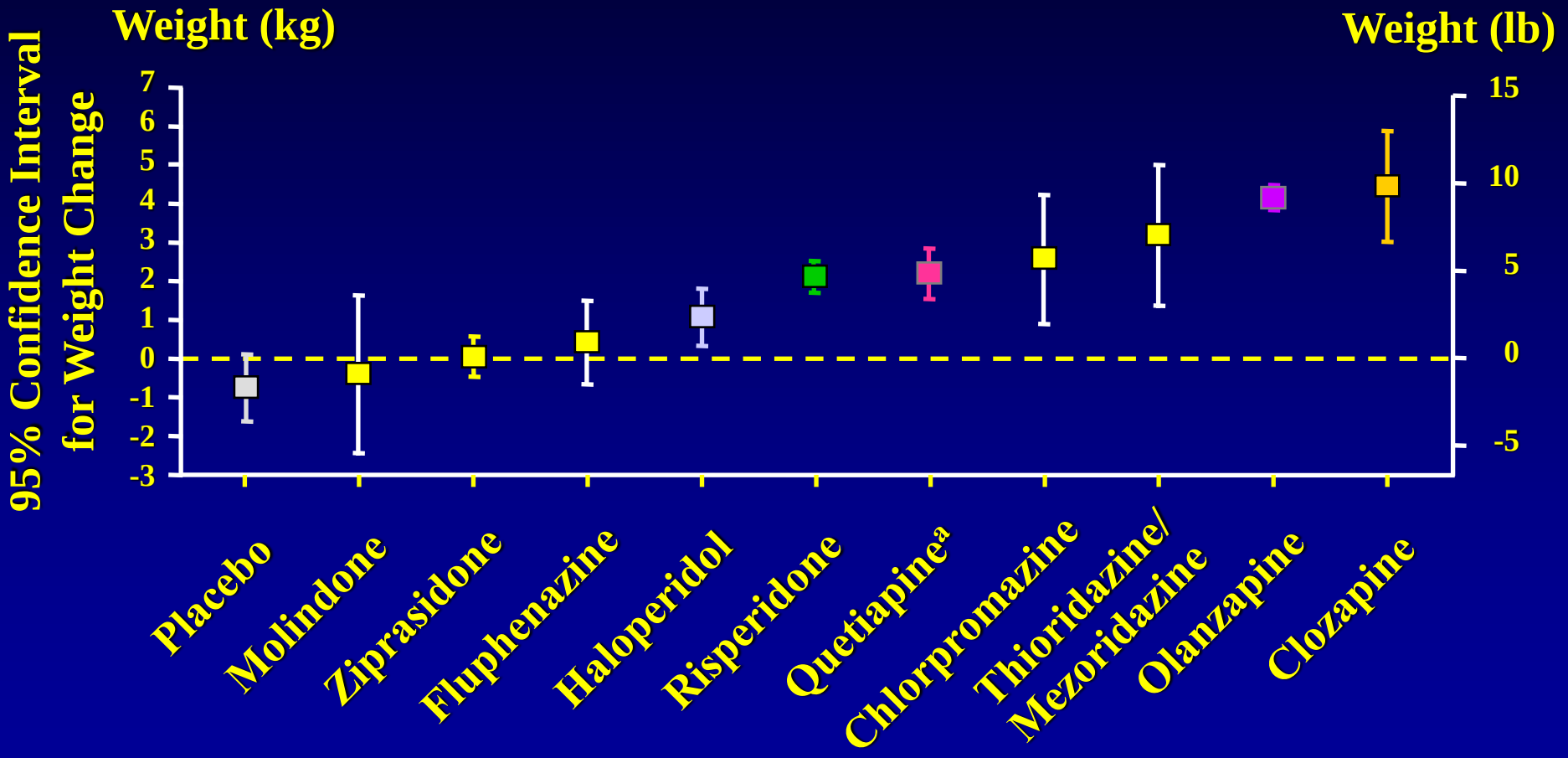
Meta-analysis of Antipsychotic-related Weight Gain

Estimate at 10 Weeks[a]



[a] Quetiapine weight gain estimated at 6 weeks

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

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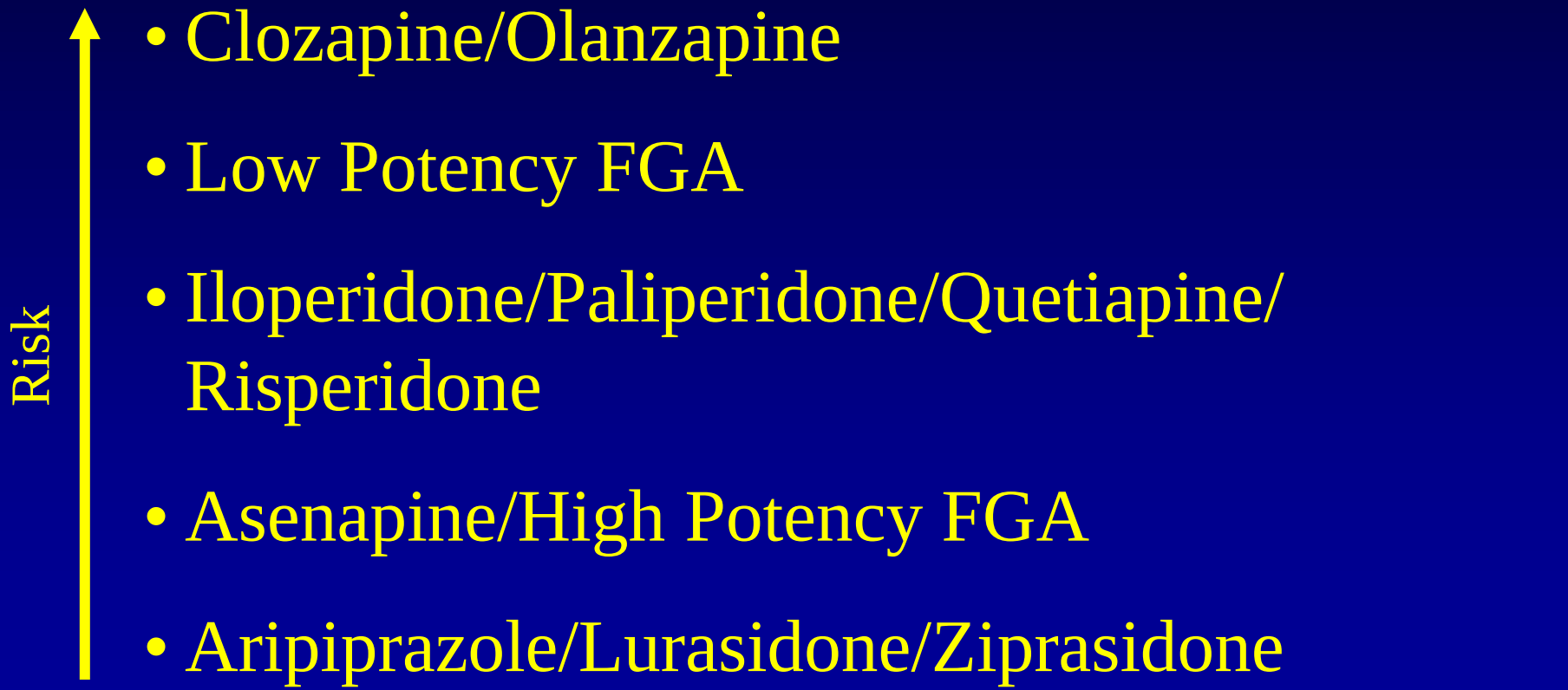
Risk of Metabolic Complications

Relative risk of medications



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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

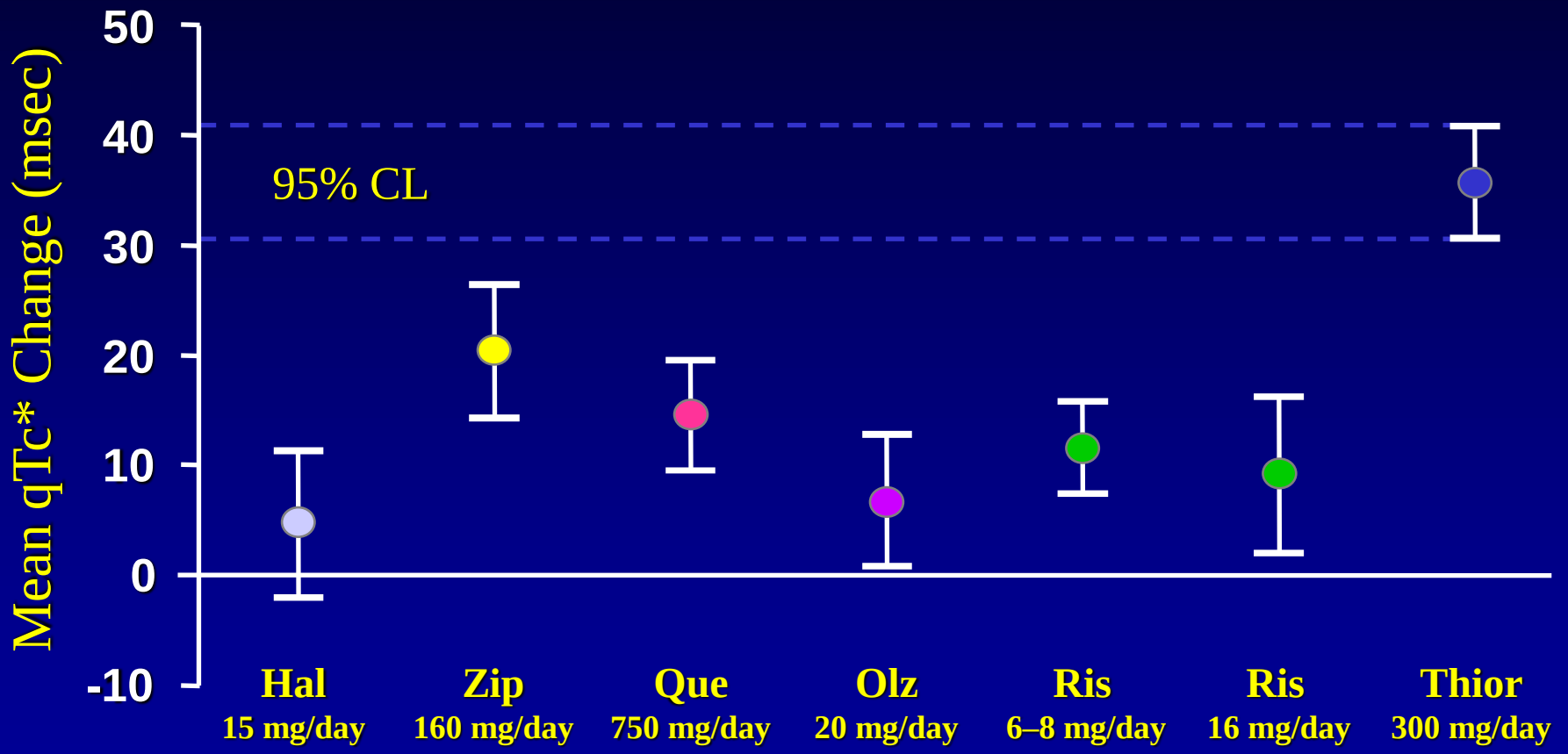
*

Cardiovascular Adverse Events

- Low potency FGAs 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 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

*

Increased Mortality

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

	Mortality	Odds Ratio
Controls	2.3%	
SGAs	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 FGA: 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 by class of medication:

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

*

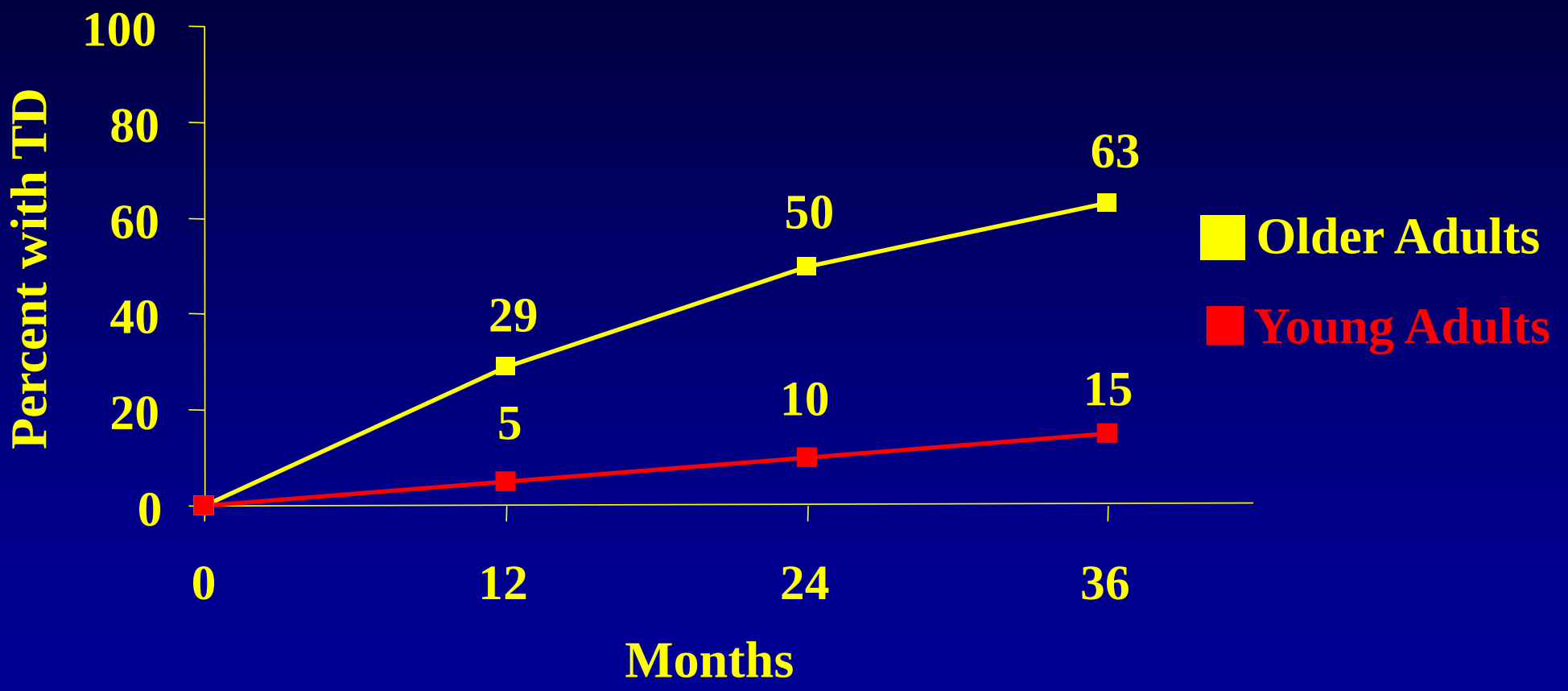
Tardive Dyskinesia

Cumulative Annual Risk of Tardive Dyskinesia

	Age 20	Age 70
FGA	5%	30%
SGA	0.5%	2.5-5%

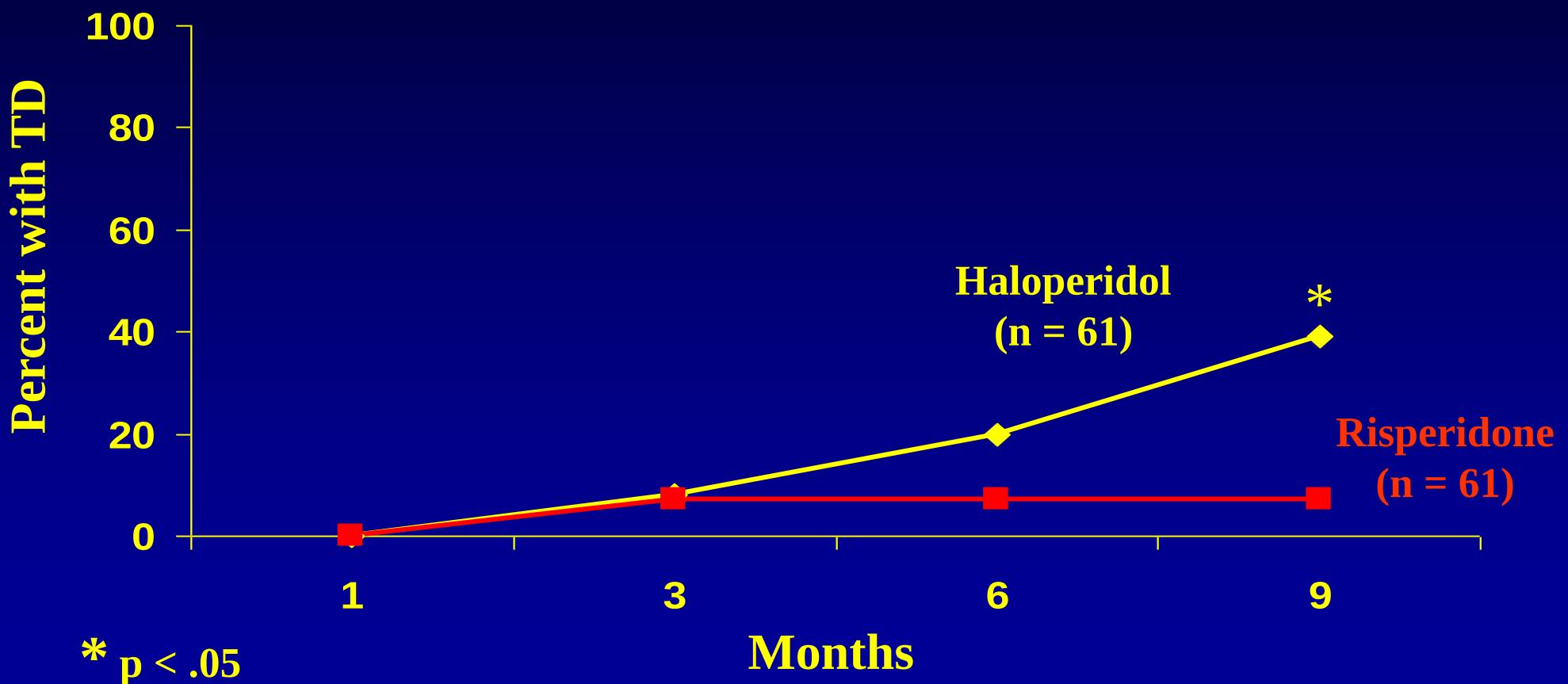
Kane JM, et al., J Clin Psychopharmacol 1988;8:52S. Chakos MH, et al., Arch Gen Psychiatry 1996;53:313. Woerner MG, et al., Am J Psychiatry 1998;155:1521. Correll CU, et al., Am J Psychiatry 2004; 161:414. Glazer WM, J Clin Psychiatry 2000; 61 suppl 4:21.

Cumulative Incidence of TD with FGAs



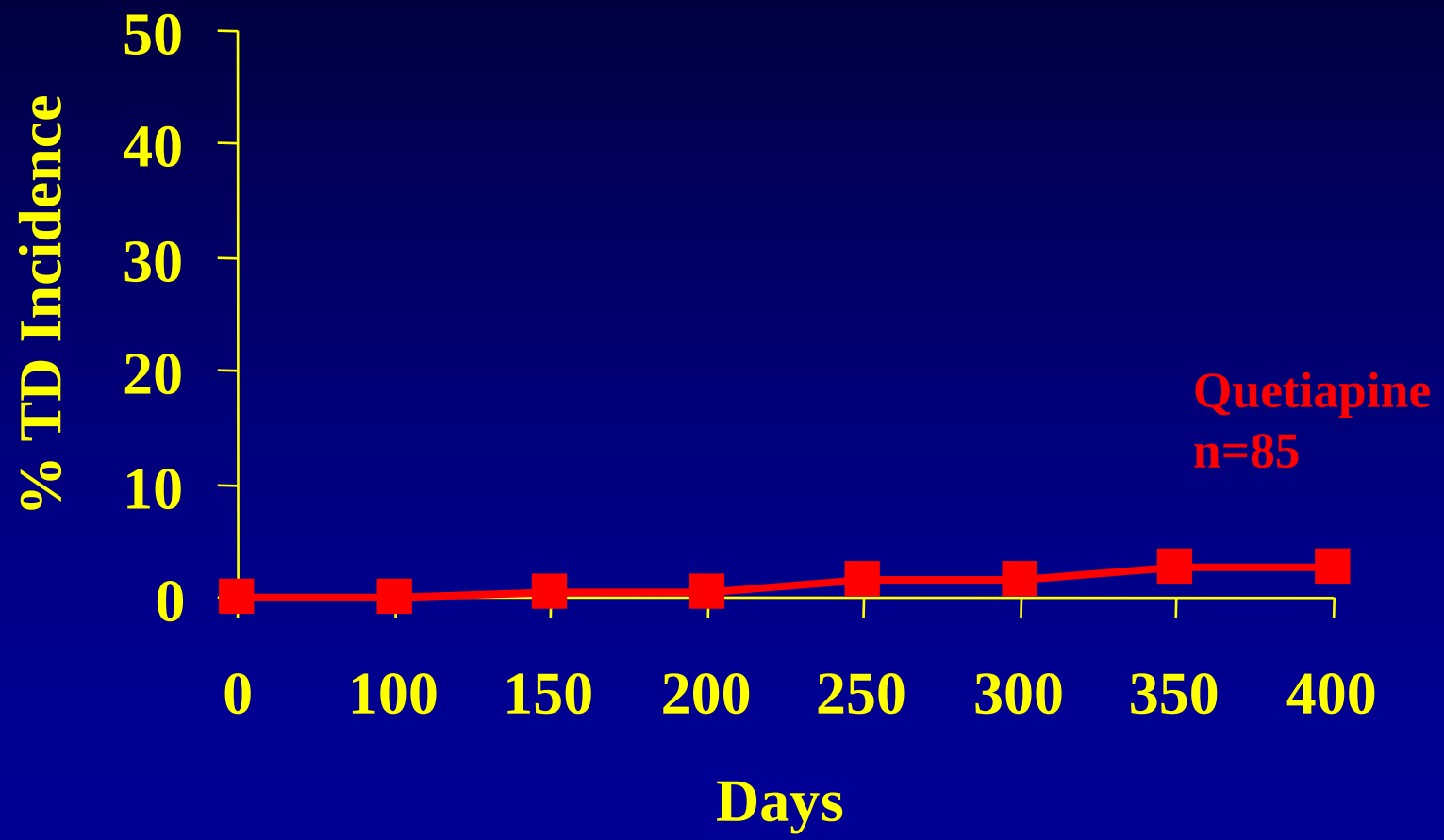
Kane JM, et al., J Clin Psychopharmacol 1988;8(4 Suppl):52S
Jeste D, et al., Am J Geriatric Psychiatry, 1999;7:70

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

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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

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CATIE

Clinical Antipsychotic Trials of Intervention Effectiveness

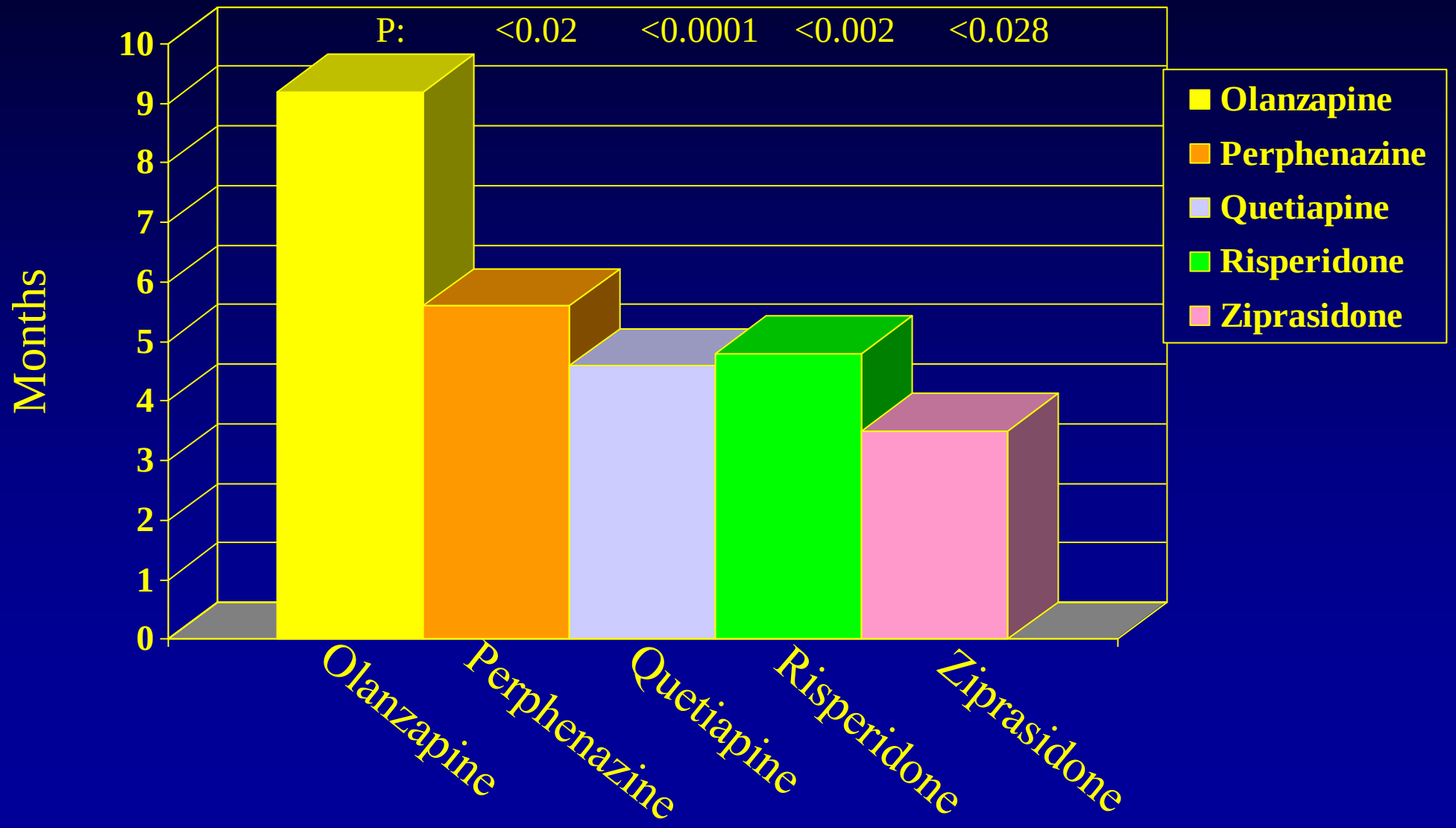
- 1493 outpatients with chronic schizophrenia
- Randomized, double-blind design
- NIMH sponsored
- 18 months
- Primary outcome was duration of treatment

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

*

CATIE

Duration of Treatment



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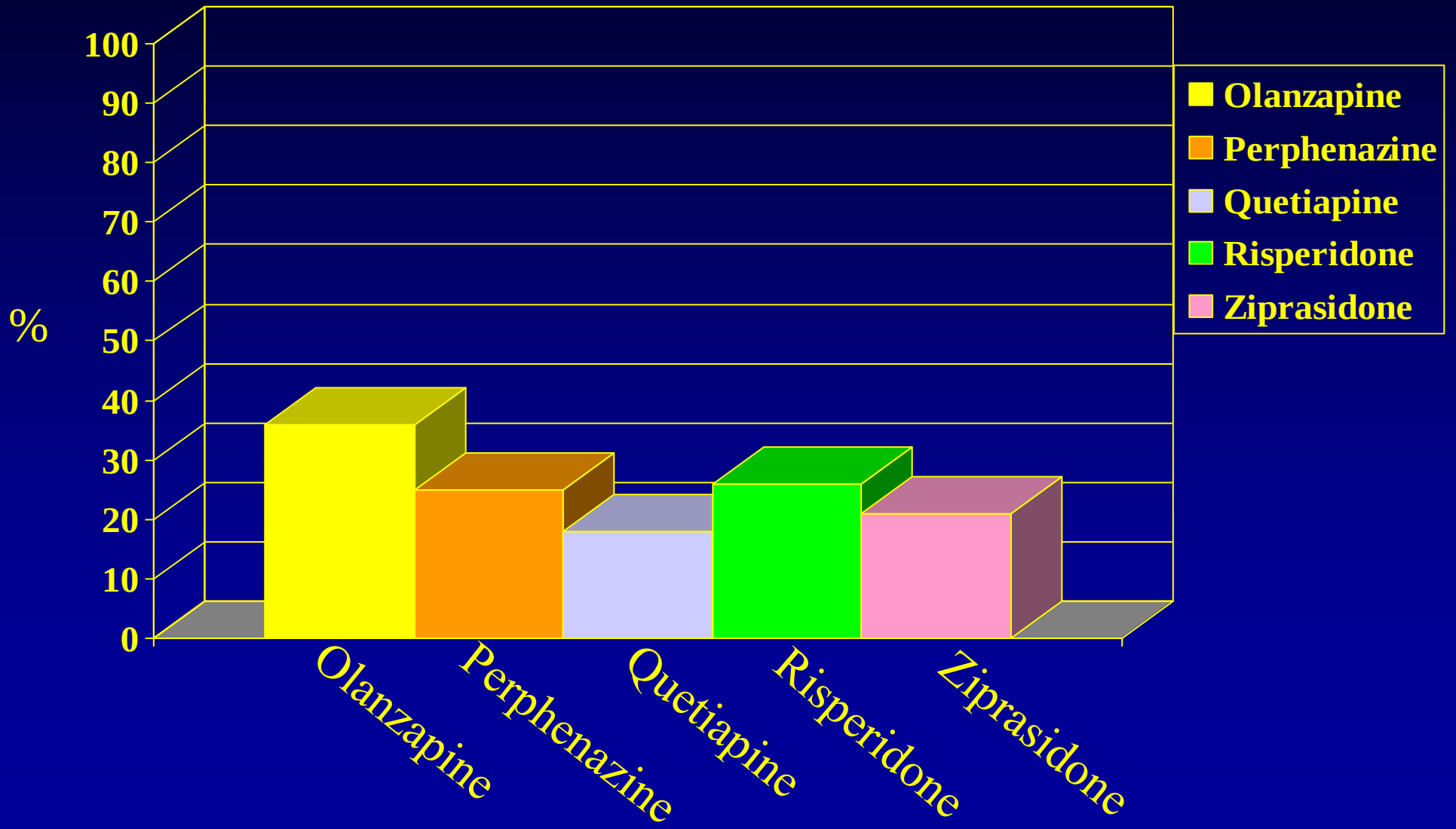
CATIE

Patients Completing 18 Months of Treatment



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CATIE

Critiques

- Power was not great enough to confirm equivalent efficacy among drugs
- Perphenazine patients were not randomly selected
- Correction for prior treatment reduced olanzapine advantage (lost statistical significance)
- Olanzapine dose was higher than other drugs

*

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

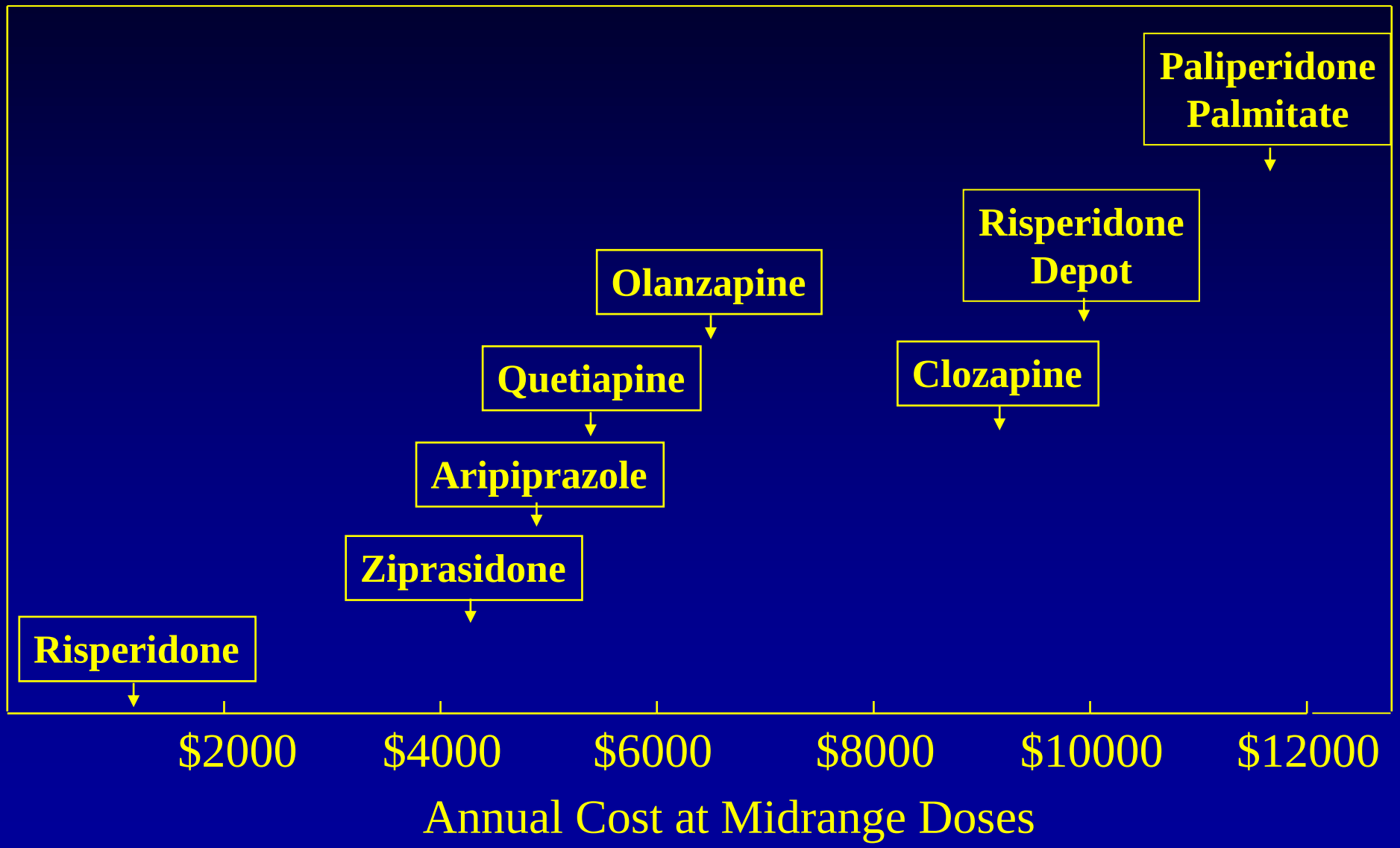
*

CATIE

Conclusions

- Patients may continue 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 but had more EPS

Relative Costs of Second Generation Antipsychotic Medications



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Treatment Selection with Antipsychotics

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

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

*

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 of the following second-generation antipsychotics 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 second-generation 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