

*Myths and Realities: New
Treatments in Acute Mania*

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Disclosure Information

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Research Support: Bristol-Myers Squibb, Eli Lilly,
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Speaker Panel : AstraZeneca, Abbott Laboratories,
Bristol Myers, Eli Lily, Pfizer,
GlaxoSmithKline, Janssen

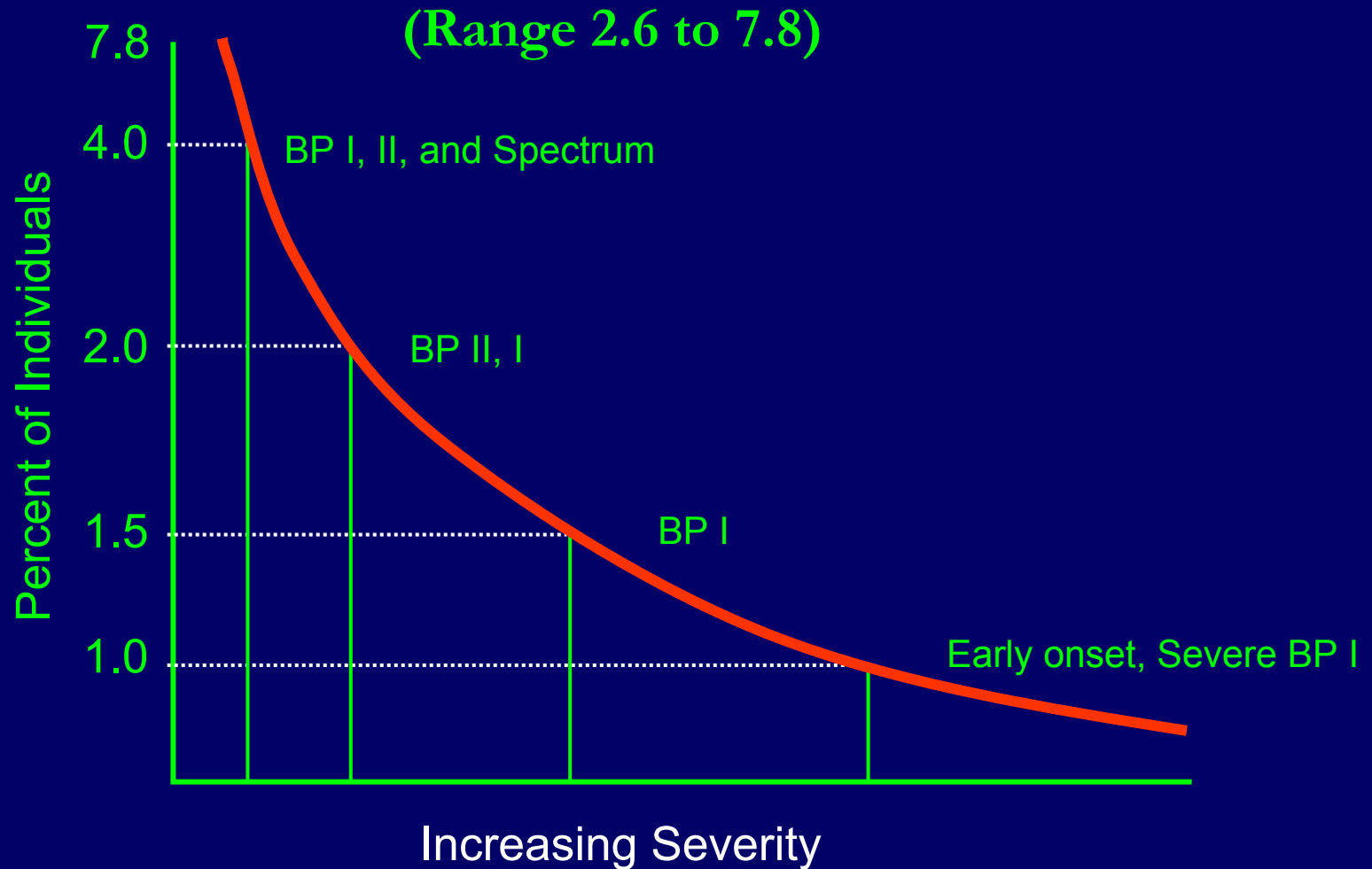
Clinical Advisor: Abbott Laboratories

Bipolar Disorder: Impact and Challenges

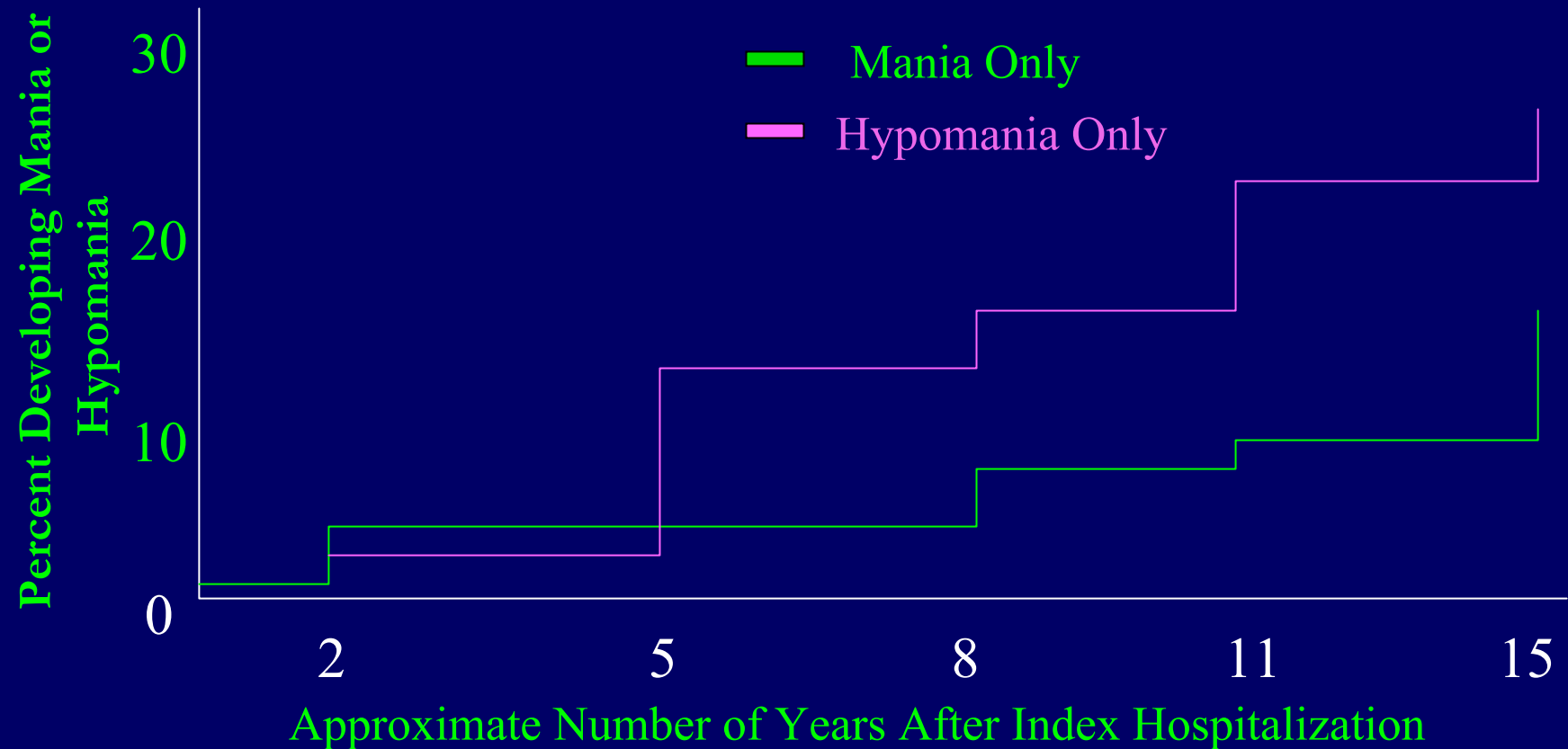
Epidemiology of Bipolar Disorder

- Estimated incidence = 2 million adults
- 60% with symptoms untreated for 6 months after onset
- 35% with disorder untreated for 10 years after onset
- 34% with disorder misdiagnosed at initial presentation
- 1/3 not optimally treated due to financial reasons

Prevalence Rates of Bipolar Spectrum Disorders



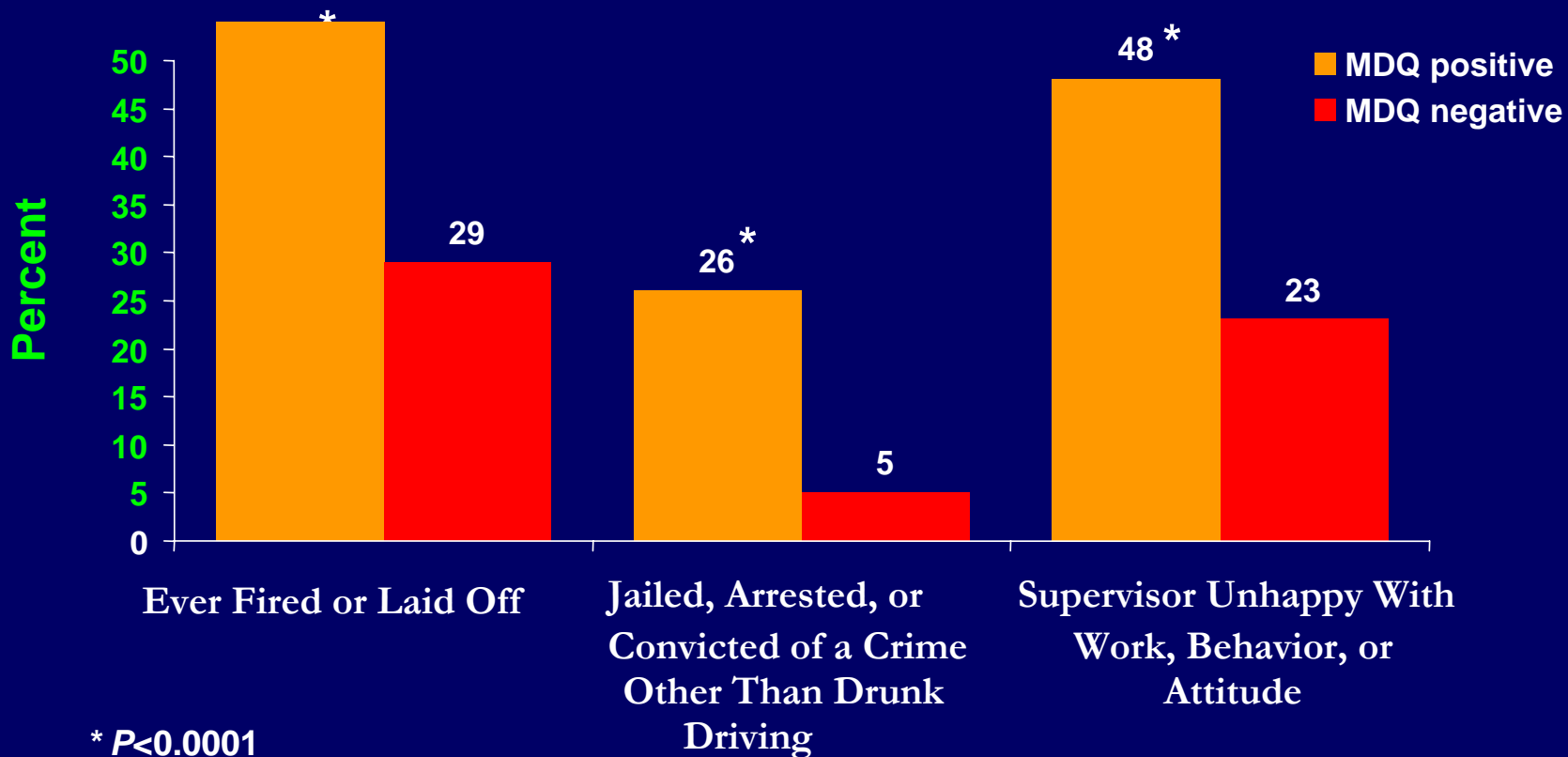
Risk for Bipolar Illness in Patients Initially Hospitalized for Unipolar Depression



Bipolar Disorder Morbidity and Financial Burden

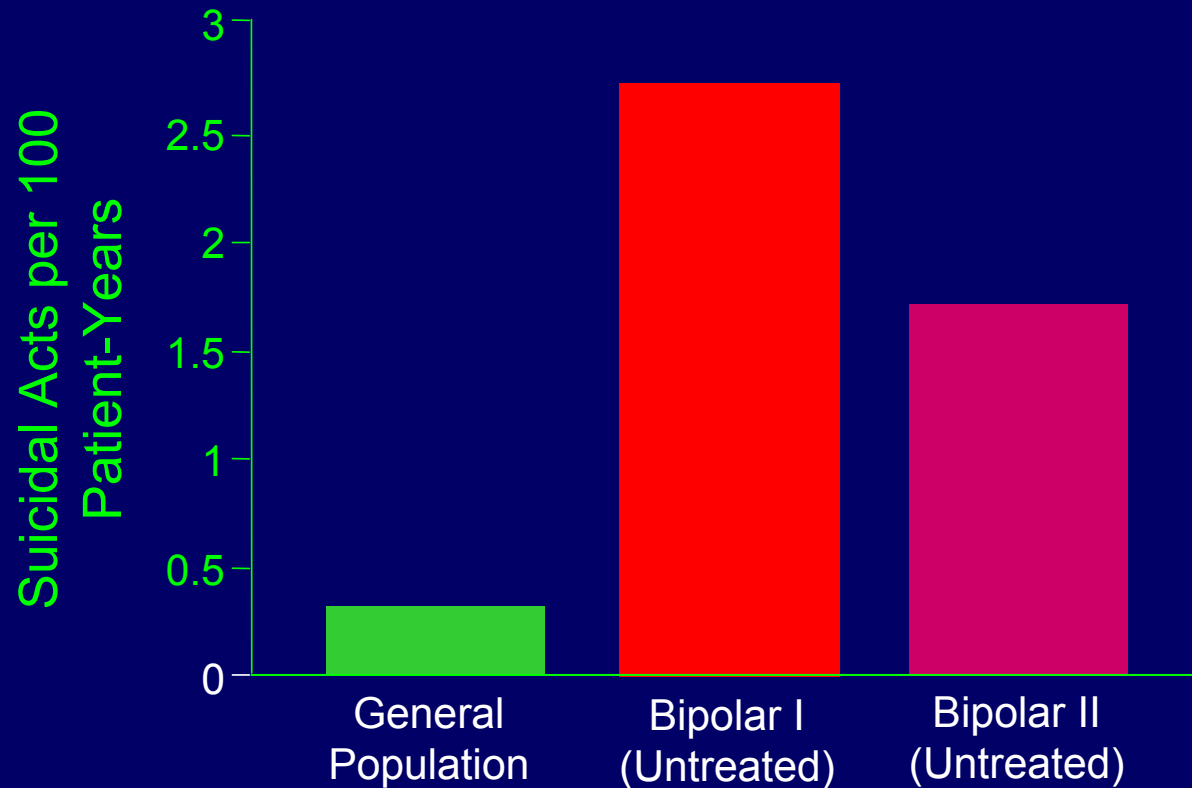
- Hospitalization
- Disability- 6th leading cause (WHO)
- Substance abuse/dependence (61%)
- Increased health care expenses
- Burden to family/caregivers
- Ruined or impoverished lives

Symptoms of Bipolar Disorder: Heavy Impact on Daily Life



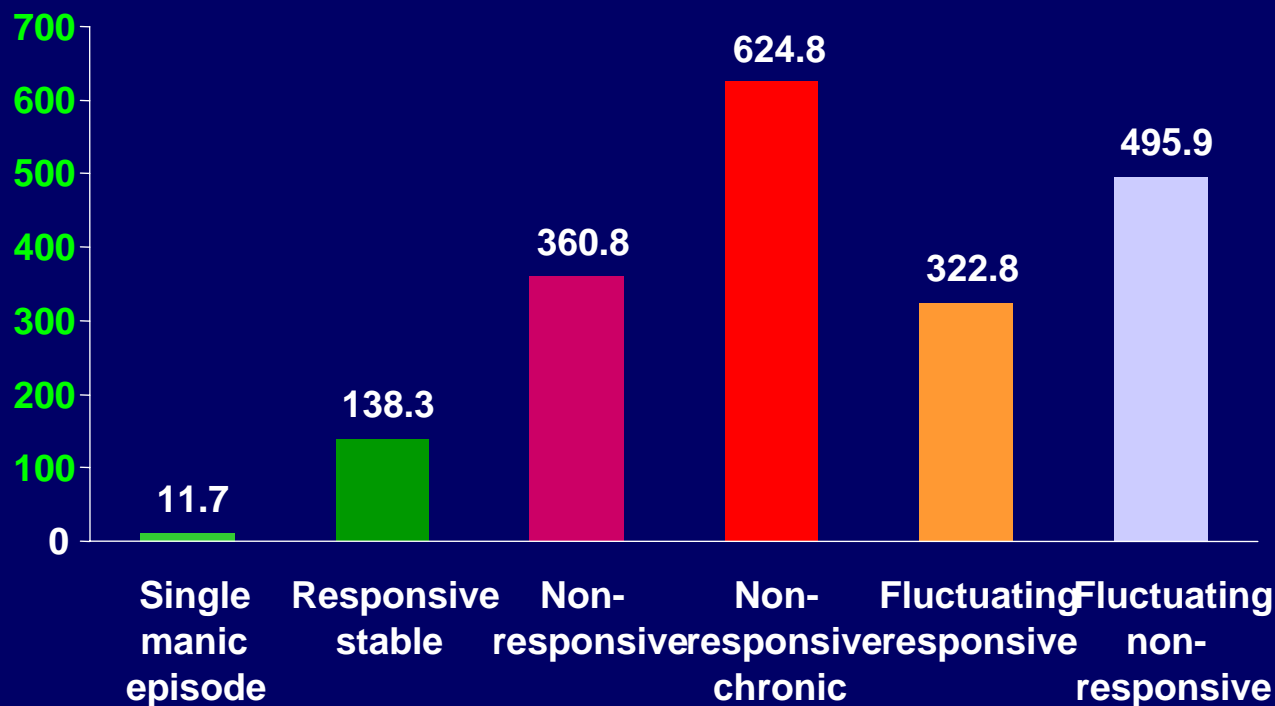
Suicide in Bipolar Disorder

Risk for suicidal acts is greatly increased among untreated bipolar patients.



Estimated Total Lifetime Cost per Case by Prognosis Group

Thousands of dollars,
1998



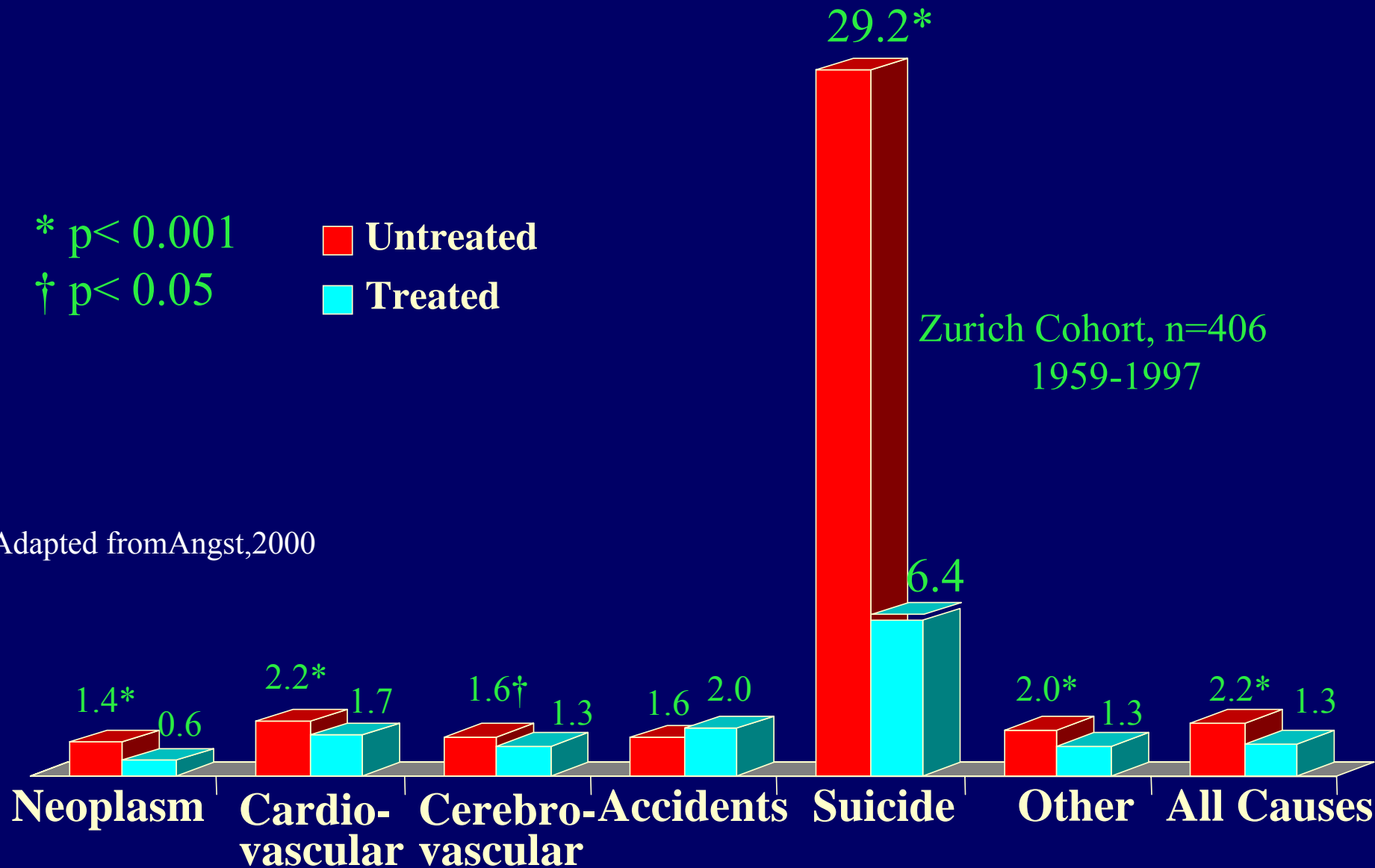
Bipolar Disorder: Untreated vs Treated Standardized Mortality Ratios

* $p < 0.001$
† $p < 0.05$

■ Untreated
■ Treated

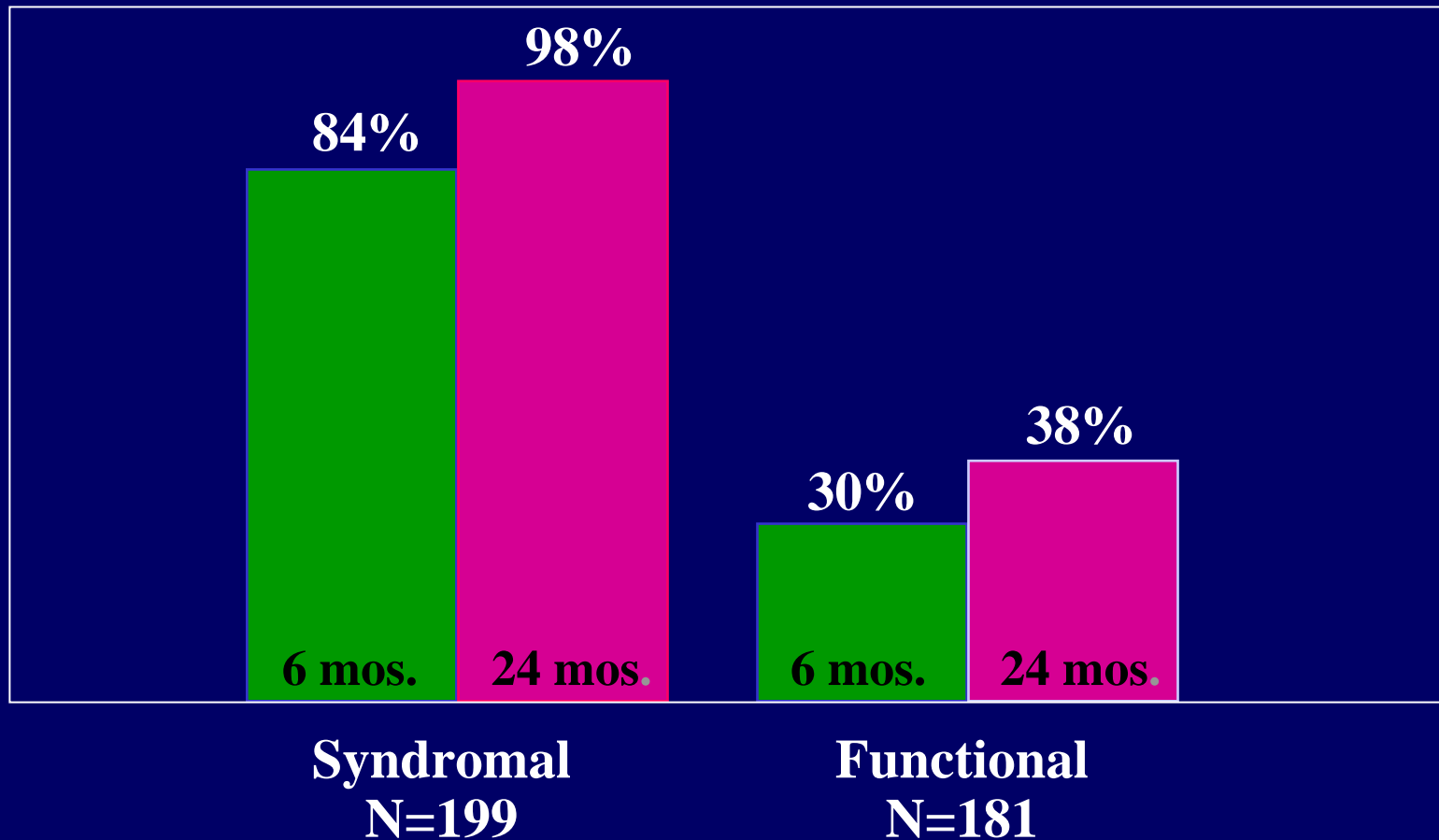
Zurich Cohort, n=406
1959-1997

Adapted from Angst, 2000



Remission of Psychotic-Affective Disorders

Syndromal vs. Functional Recovery



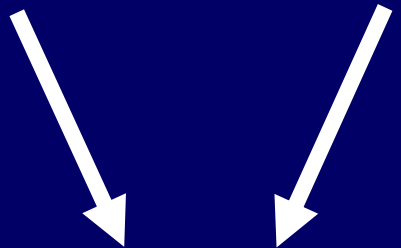
Symptom Domains of Bipolar Disorder

Manic Mood and Behavior

- Euphoria
- Grandiosity
- Pressured speech
- Impulsivity
- Excessive libido
- Recklessness
- Social intrusiveness
- Diminished need for sleep

Dysphoric or Negative Mood and Behavior

- Depression
- Anxiety
- Irritability
- Hostility
- Violence or suicide



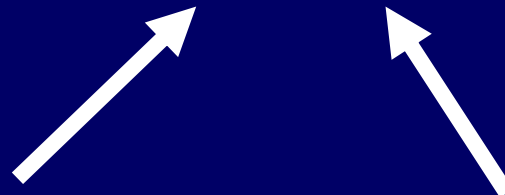
Bipolar Disorder

Psychotic Symptoms

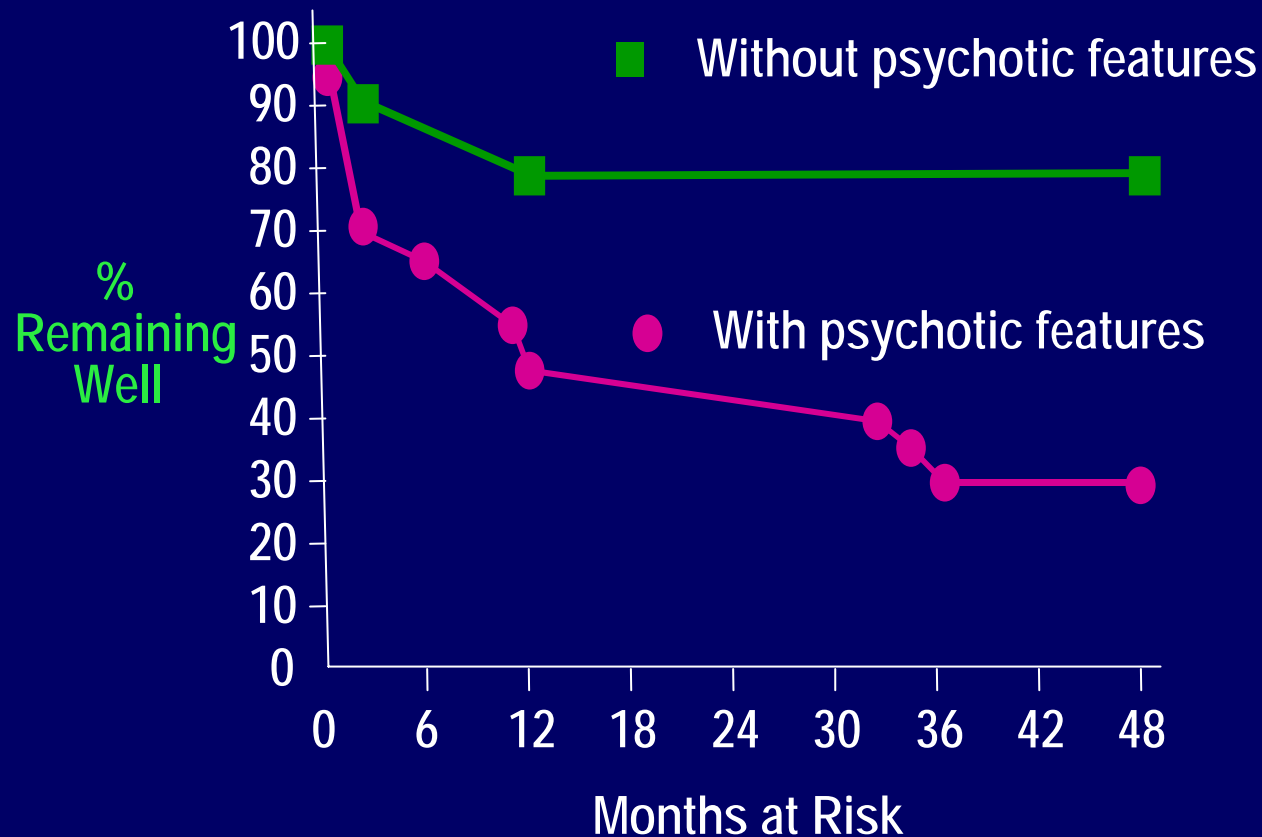
- Delusions
- Hallucinations
- Formal thought disorder

Cognitive Symptoms

- Racing thoughts
- Distractibility
- Disorganization
- Inattentiveness



Probability of Not Relapsing Into A Major Depressive or Manic Episode



Behavioral Dimensions of Bipolar Disorder

Impulsivity

Hyperactivity

Anxiety-depression

Motor retardation

Irritability

Delusions

Behavioral Dimensions of Schizophrenia

Irritability

Anxiety-depression

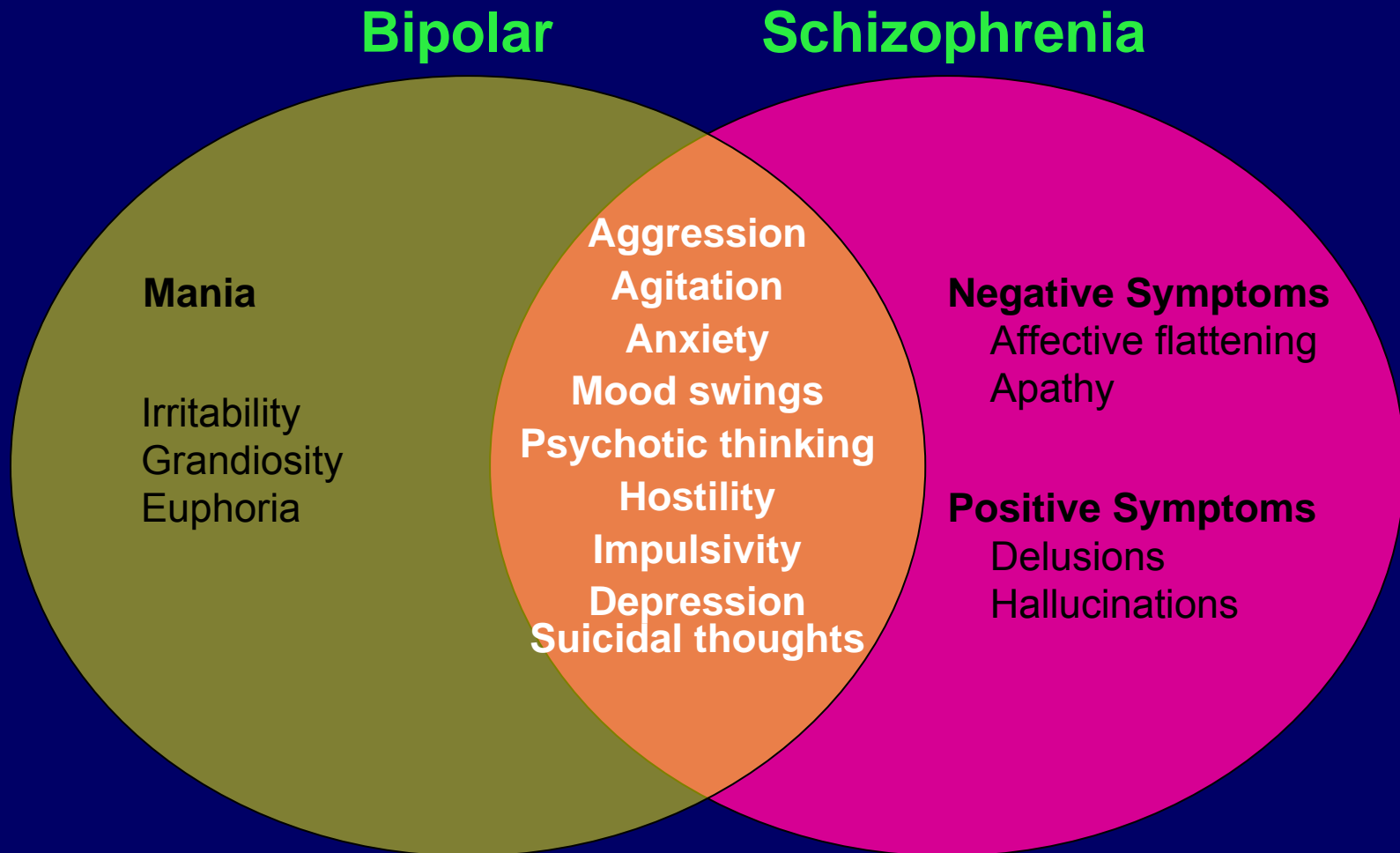
Delusions

Hostility

Deficit or Negative symptoms

Incoherent, illogical thought processes

Symptom Overlap Between Schizophrenia and Bipolar Disorder



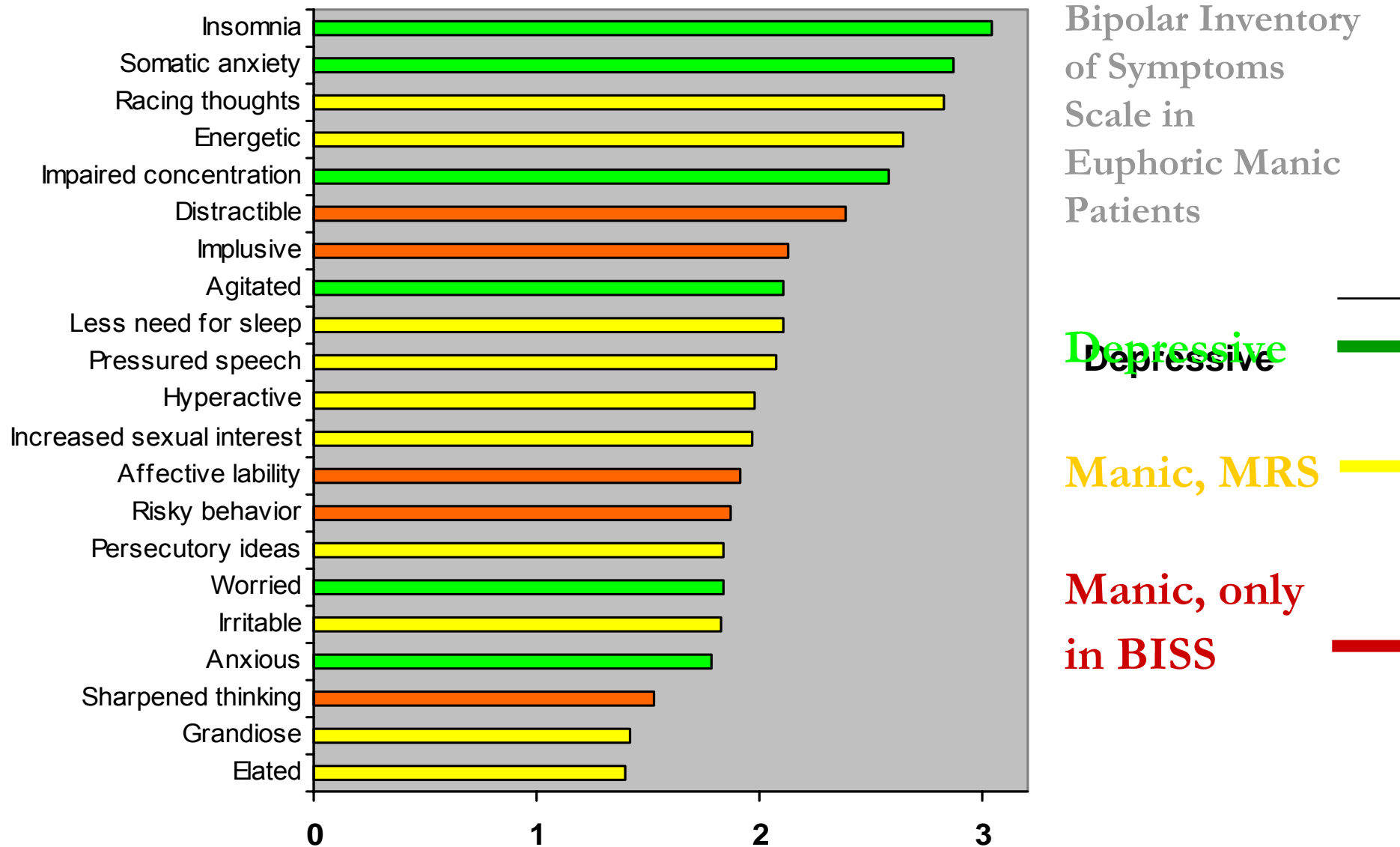
Functional Differences

- Higher proportion of bipolar patients with superior function antecedent to illness
- Higher proportion of bipolar patients with workplace success, currently married, upper socioeconomic status
- Advocacy organizations for bipolar disorder led by bipolar patients; those for schizophrenia led by unaffected parents

Treatment Differences

- Default categorical response set at 30% improvement for schizophrenia, 50% for bipolar disorder
- Approximately one third of bipolar patients are in non-syndromal, minimally symptomatic status in randomized, placebo controlled trials
- Dosage of D2 blocking drugs lower in bipolar disorder than schizophrenia, susceptibility to EPS, TD higher in bipolar

Relative Severity of Bipolar Symptoms in Euphoric Mania



Spectrum of Mania

Normal States

- Happiness
- Pleasure
- Joy

Hypomania

Heightened self-esteem
Increased creativity and work ability
Decreased need for sleep

Mania

Grandiosity
Flight of ideas
Symptoms interfere with social and occupational functions

Delirious or Psychotic Mania

Overly active
Hostile attitude
Destruction of property
Hallucinations
Delusions

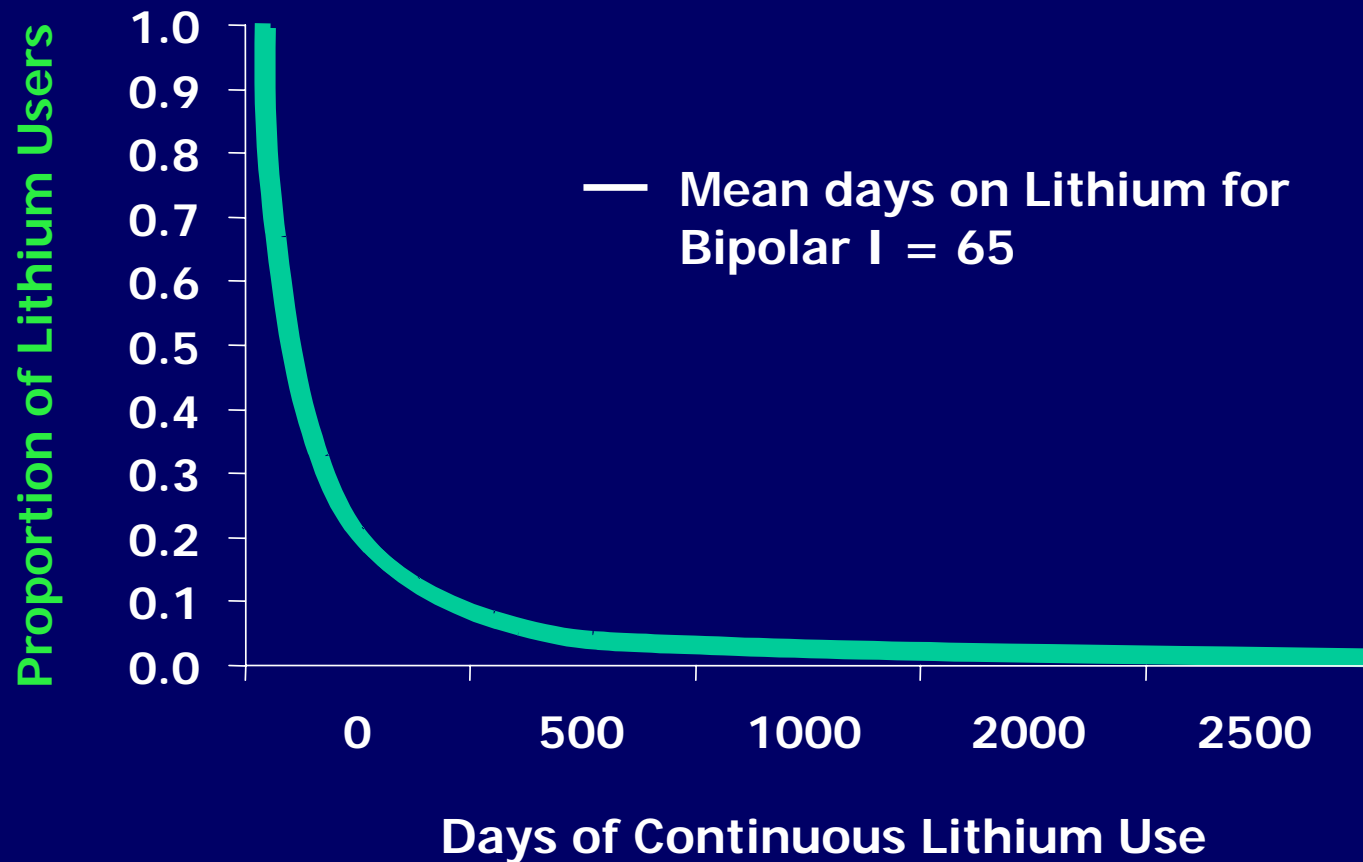
Myths in the Treatment of Acute Mania

- “Mood stabilizers” (lithium and valproate) are reliably effective in mania
- Antipsychotics exert their antimanic effect by causing sedation
- Antipsychotics are more effective in mania with psychotic symptoms
- Antipsychotics worsen depression
- Antipsychotics cause EPS

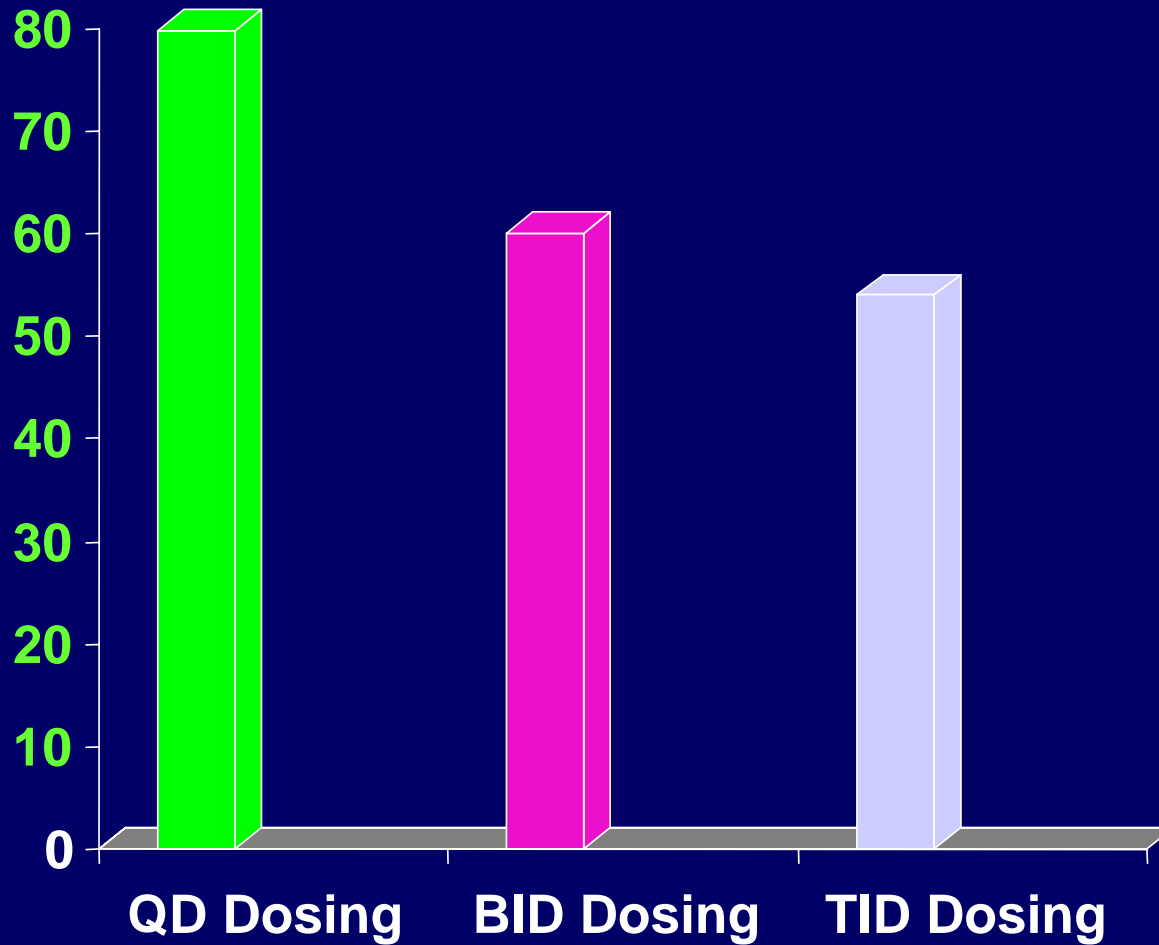
Effective but not Effective Enough

Treatment Criteria	Response %	Response
Lithium	49	50% reduction in SADS-M
Placebo	25	SAME
Divalproex	48	SAME

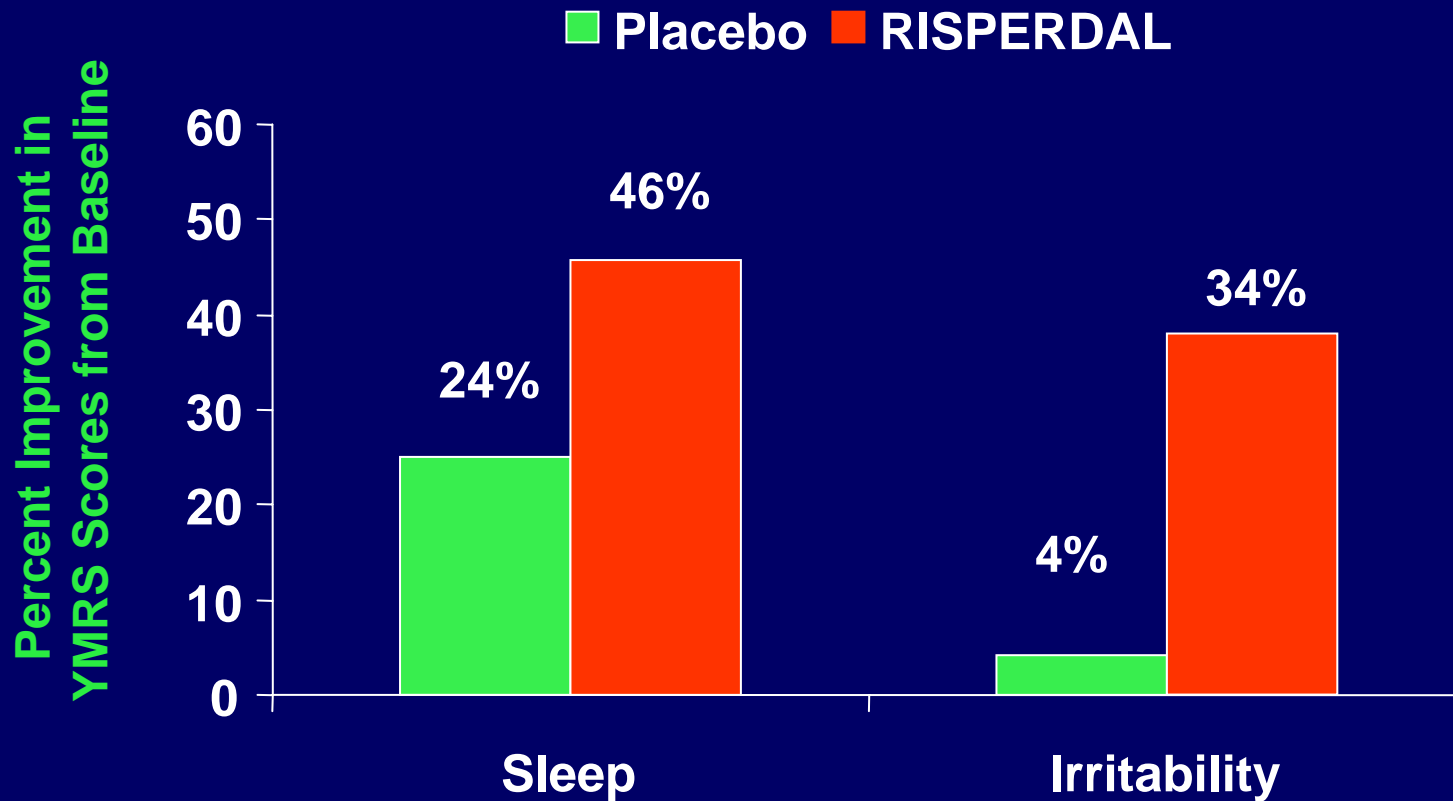
Time on Lithium Following Initial Prescription



Compliance Based on Dosage Regimen



Risperidone: Efficacy in Acute Mania



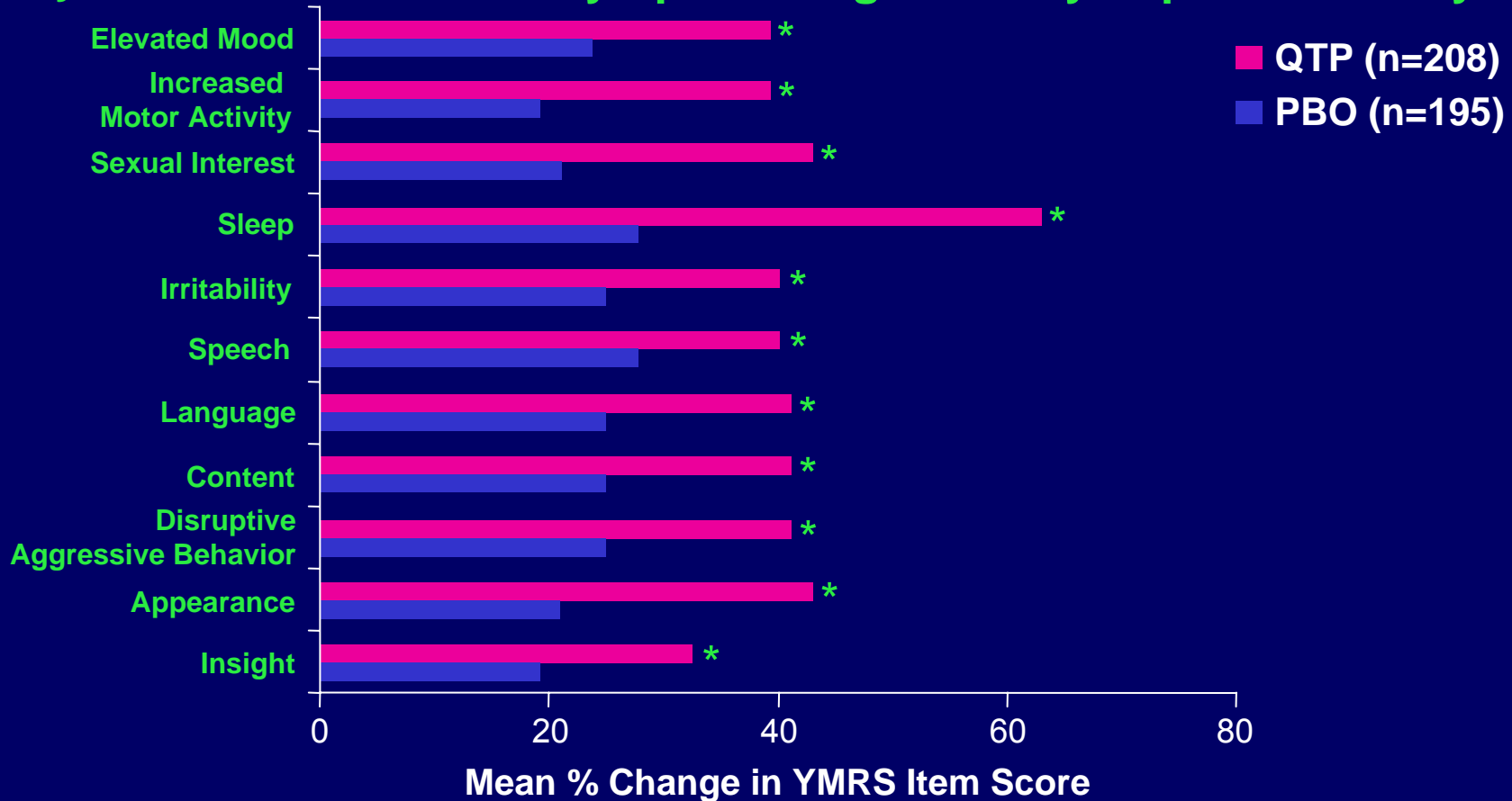
**LOCF analysis*

*All other items on YMRS (except appearance)
also achieved significant improvement*

Quetiapine: Effect on Different Symptoms

Study 1 + 2

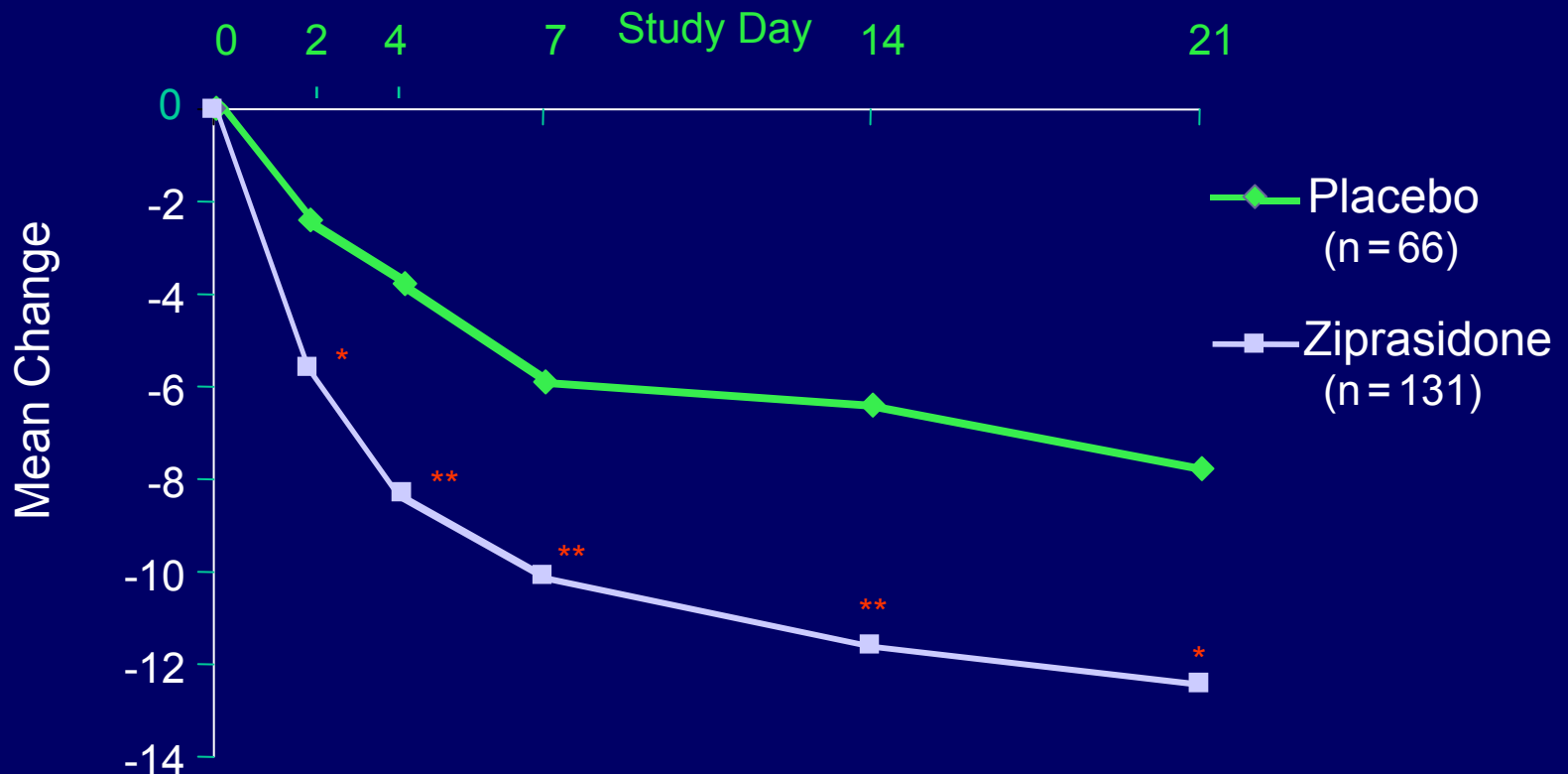
All manic symptoms significantly improved at Day 21



*P=0.007 vs PBO.

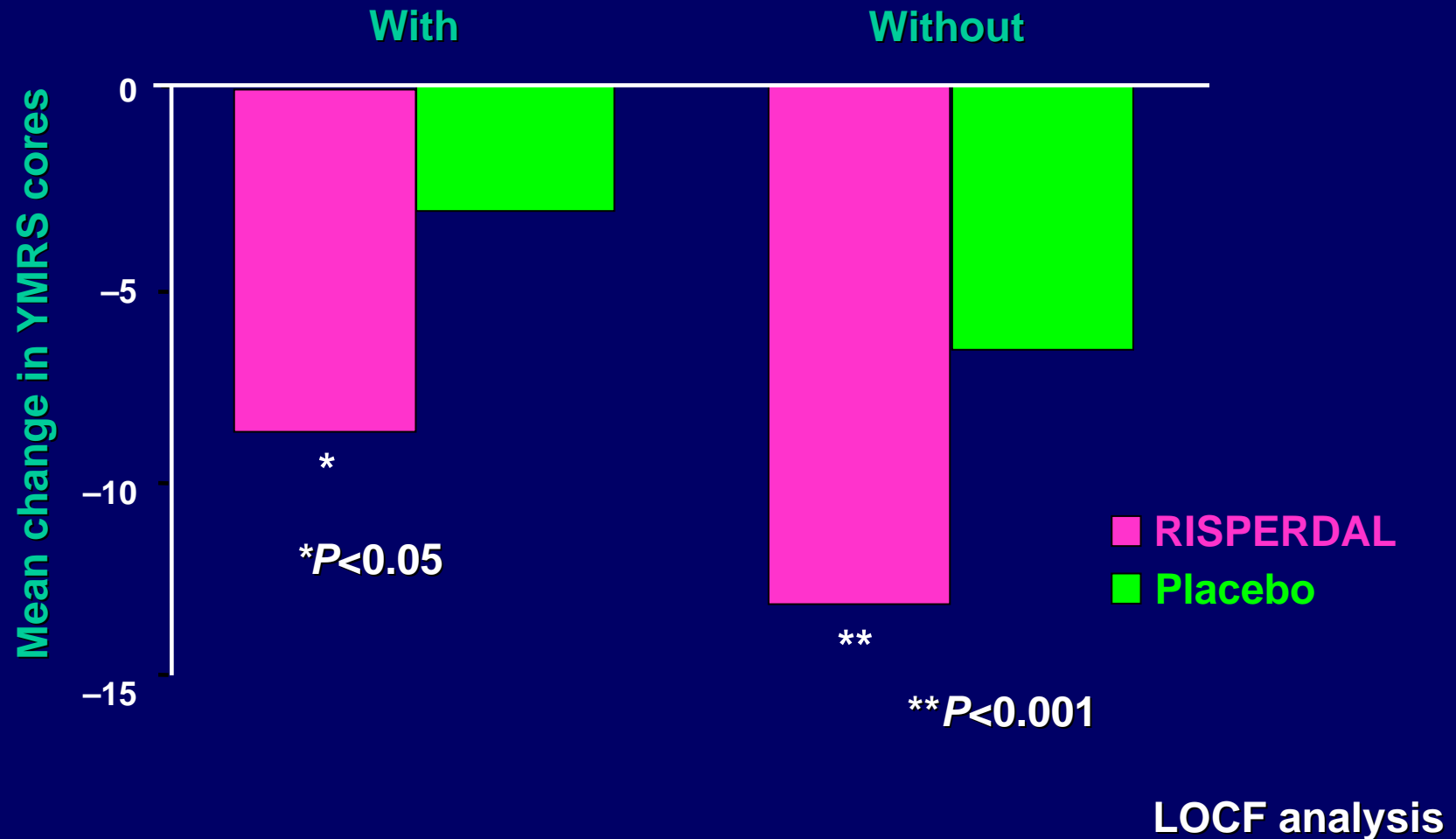
Mania Rating Scale

Mean Change From Baseline (LOCF)



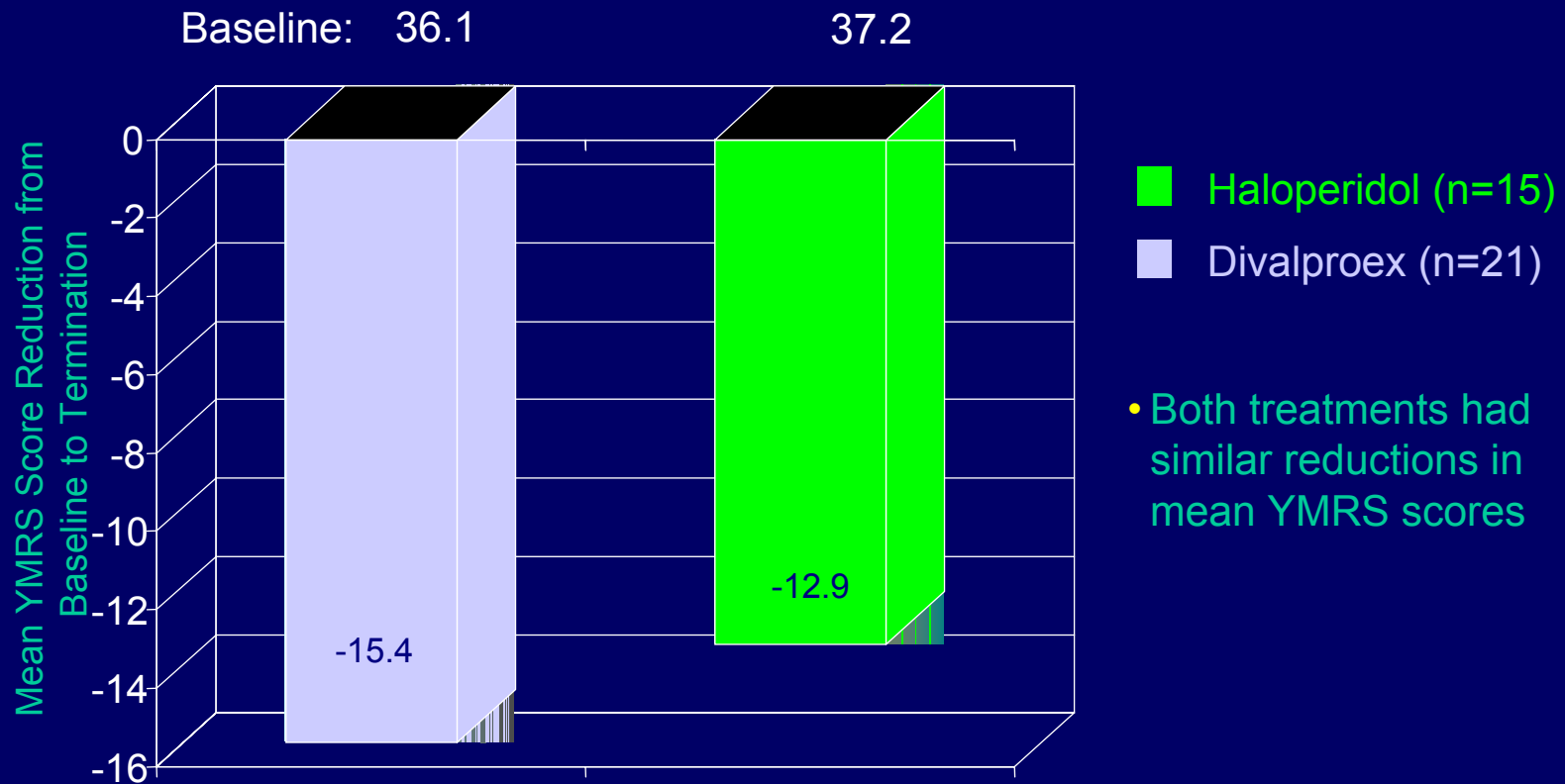
* $P < 0.01$, ** $P < 0.001$ versus placebo

Risperidone: Efficacy in Mania with and without Psychotic Symptoms



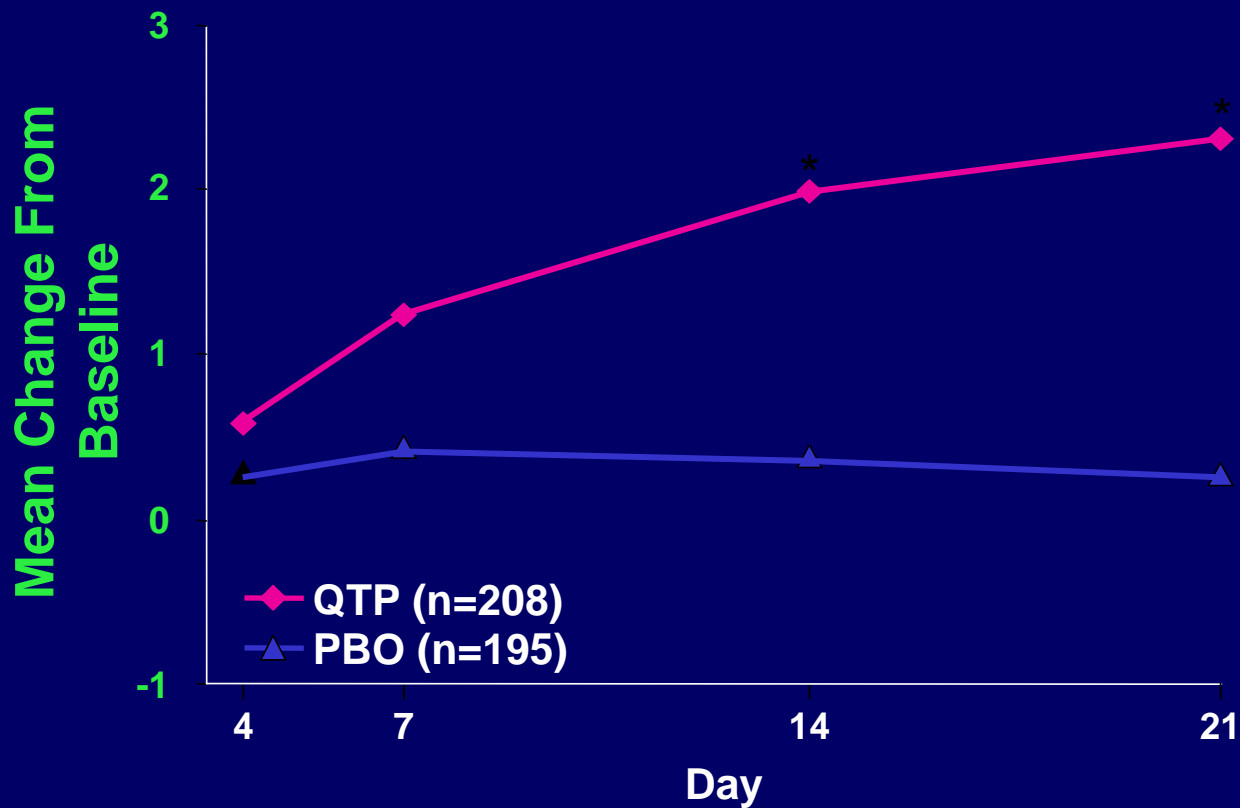
Treatment of Acute Psychotic Mania: Divalproex vs Haloperidol

All study participants met DSM-III-R criteria for bipolar disorder, manic or mixed phase and with **psychotic** features



Quetiapine: MADRS Total Score

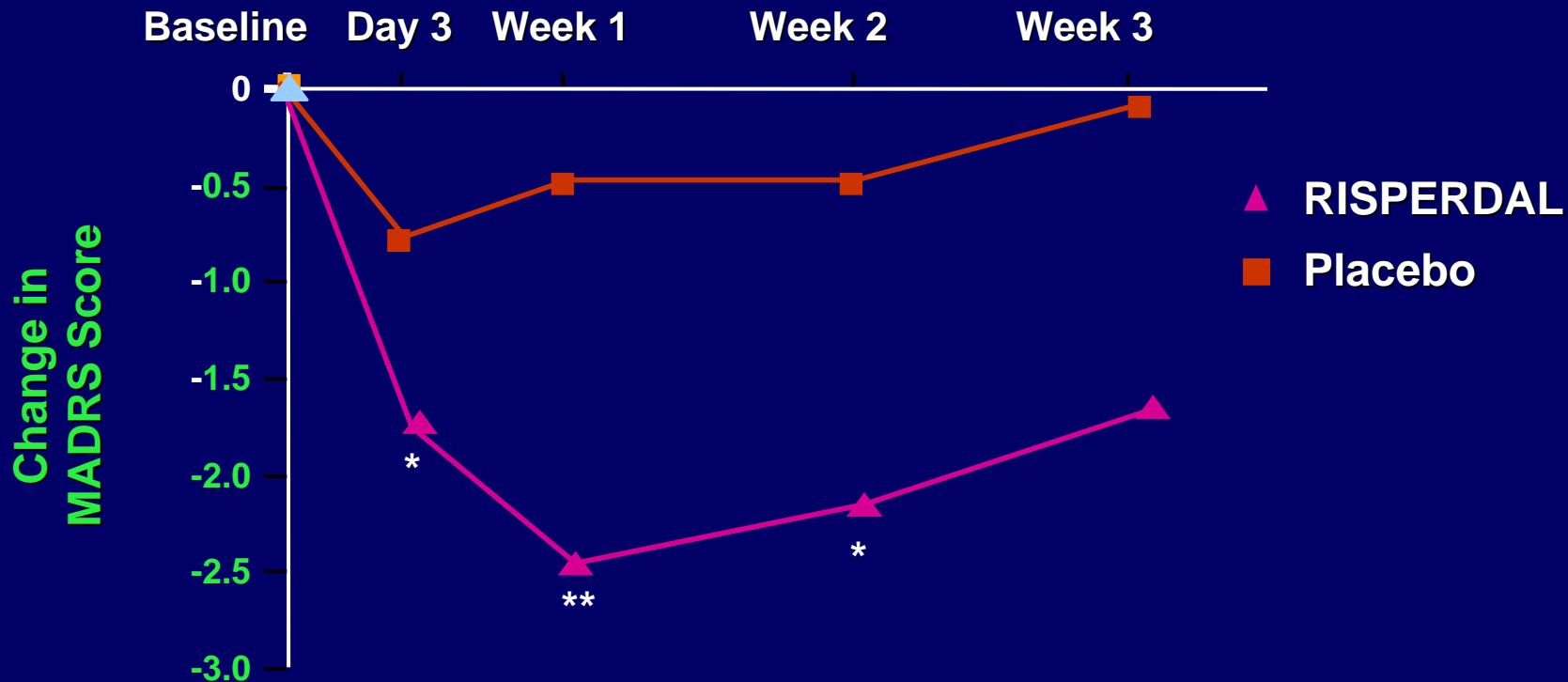
Study 1 + 2



MADRS=Montgomery-Asberg Depression Rating Scale; QTP=quetiapine; PBO=placebo.
Data on file, AstraZeneca Pharmaceuticals LP, Wilmington, DE

* $P < 0.01$ vs PBO.

Risperidone Monotherapy: Change in MADRS Scores over Time



Baseline MADRS: 9.2
End point MADRS RISPERDAL: 7.6

LOCF analysis; * $P < 0.05$; ** $P < 0.01$

Atypical Antipsychotic Mechanisms of Action in Mood Disorder

Drug	D ₂ Blocker	D ₂ Partial Agonist	5HT ₂ Blocker	5HT _{1a} Partial Agonist	NET Blocker
RIS	+++		++		
OLZ	++		++	+	
QTP	+		+		
ZIP	+++		+++	+	++
ARI		++	++	+	
CLOZ	+		+++	+	

Monotherapy Randomized Control Trials (RCTs) in Acute Mania

Monotherapy	Response Rate (%)
Lithium	49-70
Divalproex/valproate	48-80
Olanzapine	49-65
Risperidone	54-61
Quetiapine	54-72
Aripiprazole	40-50
Ziprasidone	50
Lamotrigine	44-52

Emrich HM, et al. *Adv Biochem Psychopharmacol*. 1981;26:287-296; Brennan MJW, et al. In: Emrich, Okuma, Muller, eds. *Excerpta Medica*. 1984:56-65; Pope HG Jr, et al. *Arch Gen Psychiatry*. 1991;48:62-68; Freeman TW, et al. *Am J Psychiatry*. 1992;149:108-111; Bowden CL, et al. *JAMA*. 1994;271:918-924; Bowden CL, et al. *Arch Gen Psychiatry*. 2000;57:481-489; Sachs et al, ACNP 2001. Peuskens J, et al. *Br J Psychiatry*. 1995;166:712-733; Marder SR, et al. *J Clin Psychiatry*. 1997;58:538-546; Tohen M, et al. *Am J Psychiatry*. 1999;156:702-709; Tohen M, et al. *Arch Gen Psychiatry*. 2000;57:841-849; Sanchez et al. 5th ICB, June, 2003; Ketter TA, et al. APA May 2003; Keck PE Jr, et al. *Am J Psychiatry*. 2003;160:1651-1658; Bowden CL, et al. *Arch Gen Psychiatry*. 2003;60:392-400; Calabrese JR, et al. *J Clin Psychiatry*. 1999;60:79-88; Jones MW, et al. 156th APA Congress, 2003; Mullen J, et al. *Clin Ther*. 2001;23:1839-1854; Copolov DL, et al. *Psychol Med*. 2000;30:95-105; McManus DQ, et al. *J Clin Psychiatry*. 1999;60:292-298; Arvanitis LA, et al. *Biol Psychiatry*. 1997;42:233-246; Solomon DA, et al. *Psychopharmacol Bull*. 1996;32:579-587; Hirschfeld RM, et

Monotherapy: Adverse Events

	RIS	OLZ	QTP	ARI	LTG	LI	DVPX
Dose-related EPS	++	+	0	+	0	0	0
Tardive dyskinesia	±	±	±	±	0	0	0
Prolactin elevation							
Erectile dysfunction	+++	+	±	0	0	0	0
Decreased libido							
Gynecomastia							
Somnolence	+	+++	++	0	+	0	0
Weight gain	+	+++	+	0	0	+	+
Diabetes	+	+++	+	0	0	0	0
Hyperlipidemia	+	+++	+	0	0	0	0

RIS=Risperidone, OLZ=Olanzapine, QTP=Quetiapine, ARI=Aripiprazole, LTG=Lamotrigine, Li=Lithium,

DVPX=Divalproex; + = mild, ++ = moderate, +++ = severe, ± = may occur, 0 = no occurrence

Adapted from Nasrallah HA et al, *Ann Clin Psychiatry* 2001;13:215-227; Halbreich UM et al, *Psychoneuroendocrinology* 2003;28:53-

Metabolic Effects: Comparison of Antipsychotics

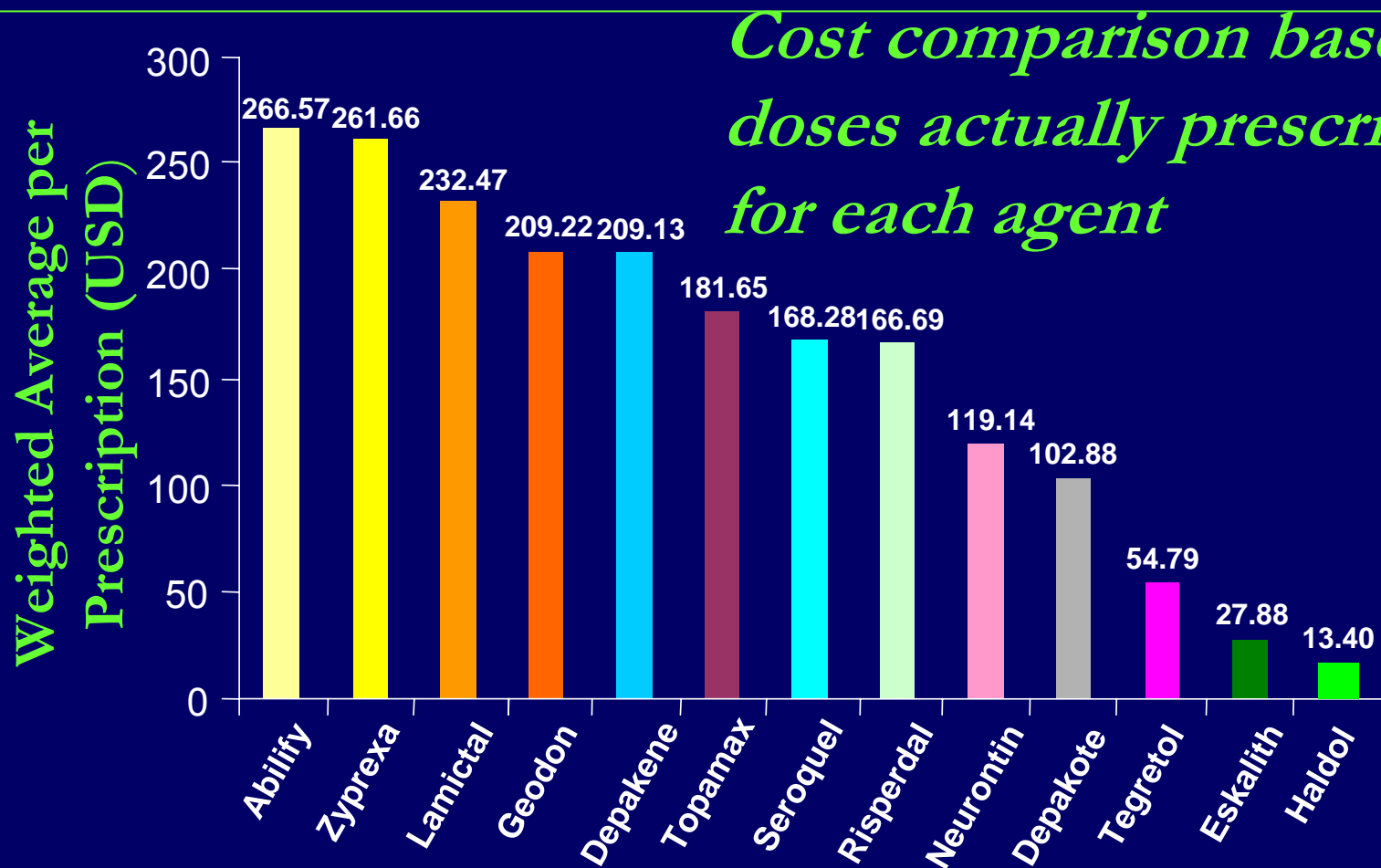
Medication	Weight Gain	Risk for Diabetes	Worsening Lipid Profile
Clozapine	+++	+	+
Risperidone	++	?	?
Olanzapine	+++	+	+
Quetiapine	++	?	?
Ziprasidone	+/-	—	—
Aripiprazole	+/-	—	—

*



**"I FEEL A LOT BETTER SINCE I RAN
OUT OF THESE PILLS YOU GAVE ME"**

Average Blended Prescription Price Based on WAC

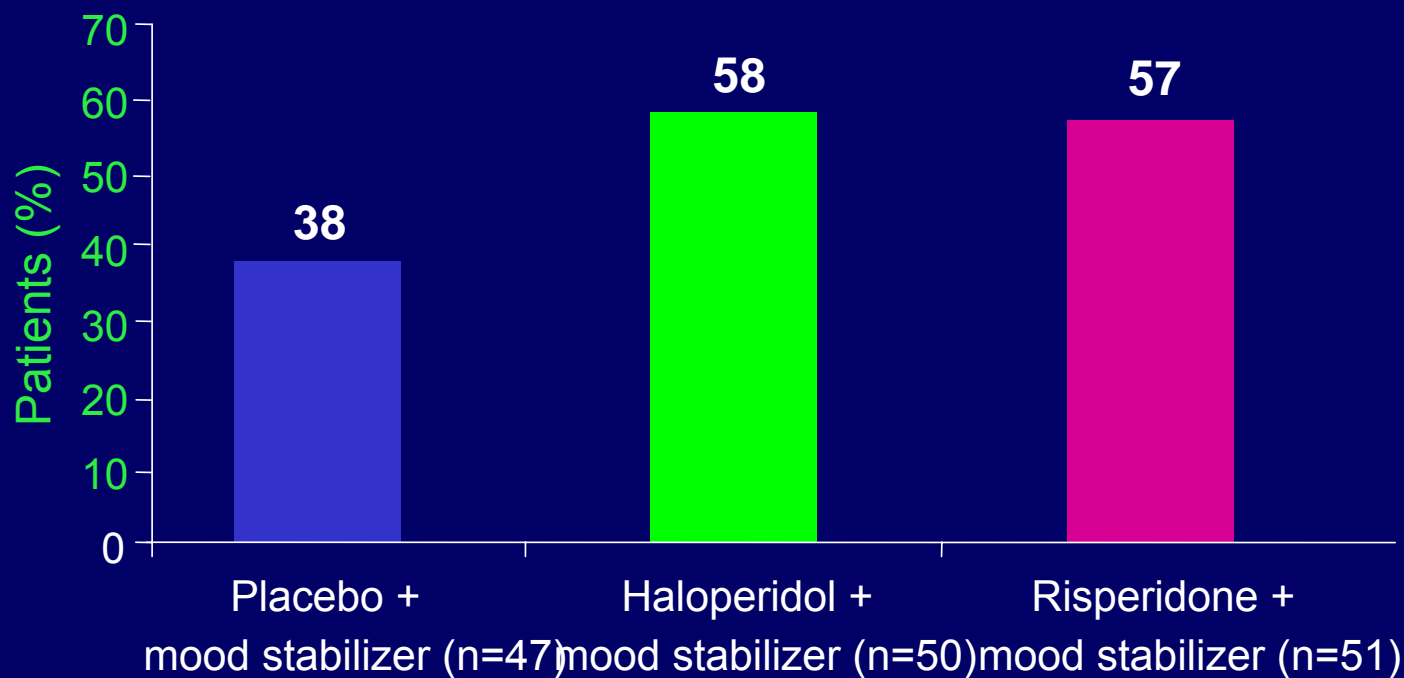


WAC = Wholesaler Acquisition Cost (price to pharmacy).

APA Guidelines: Treatment of Acute Mania

Manic (40-60%) ¹	Severe Divalproex + antipsychotic or lithium + antipsychotic
	Less Severe Divalproex or lithium or antipsychotic
Mixed Manic (40-60%) ¹	Severe Divalproex + antipsychotic or lithium + antipsychotic
	Less Severe Divalproex or lithium or antipsychotic
Rapid-Cycling Mania	Divalproex or lithium

Divalproex or Lithium + Risperidone, or Haloperidol in Acute Mania

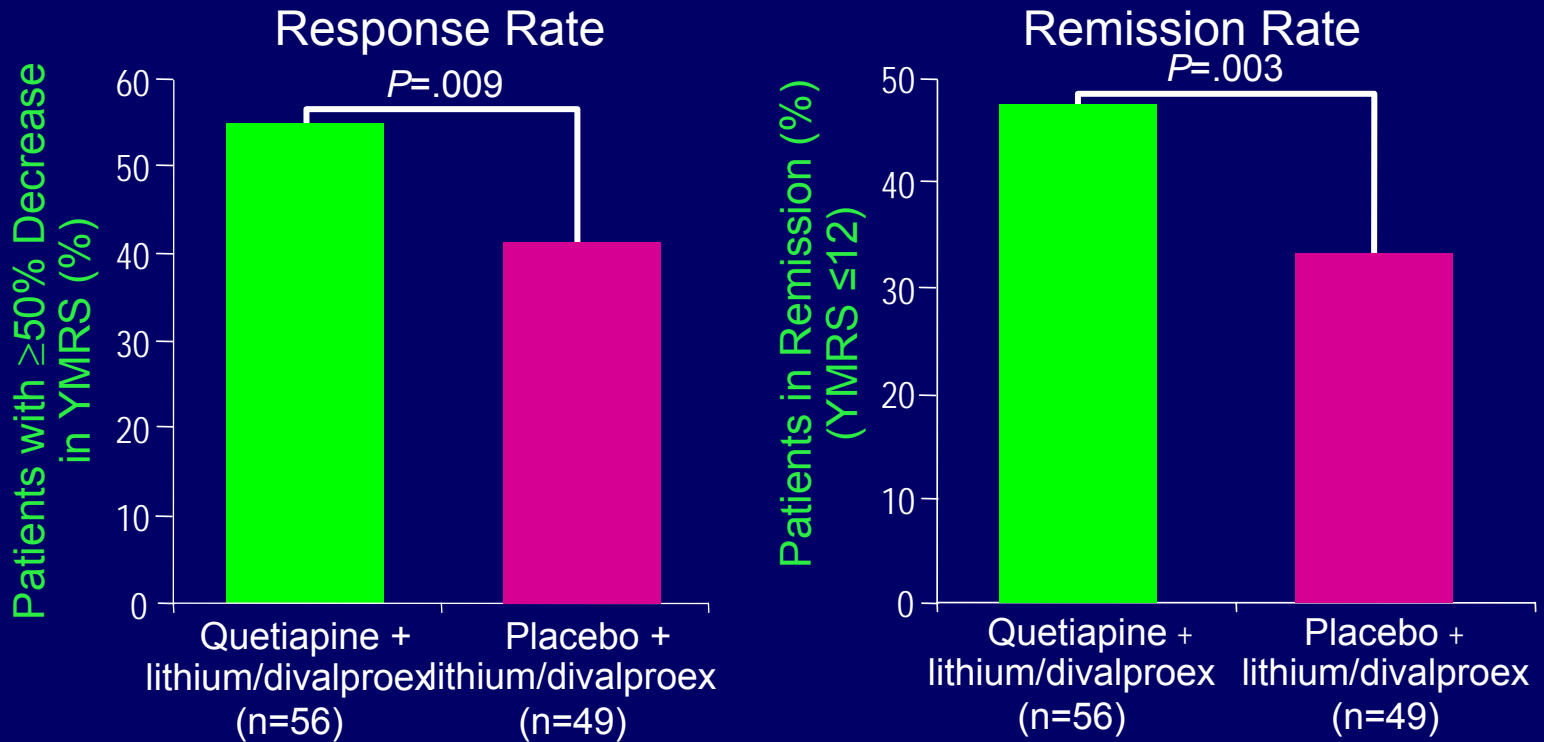


Median risperidone dose = 3.8 mg/d
Range of mean lithium levels = .7-.8 mEq/L
Range of mean divalproex levels = 65.4-77.3 mg/dL

*Response defined as $\geq 50\%$ decrease in YMRS from baseline.

YMRS = Young Mania Rating Scale

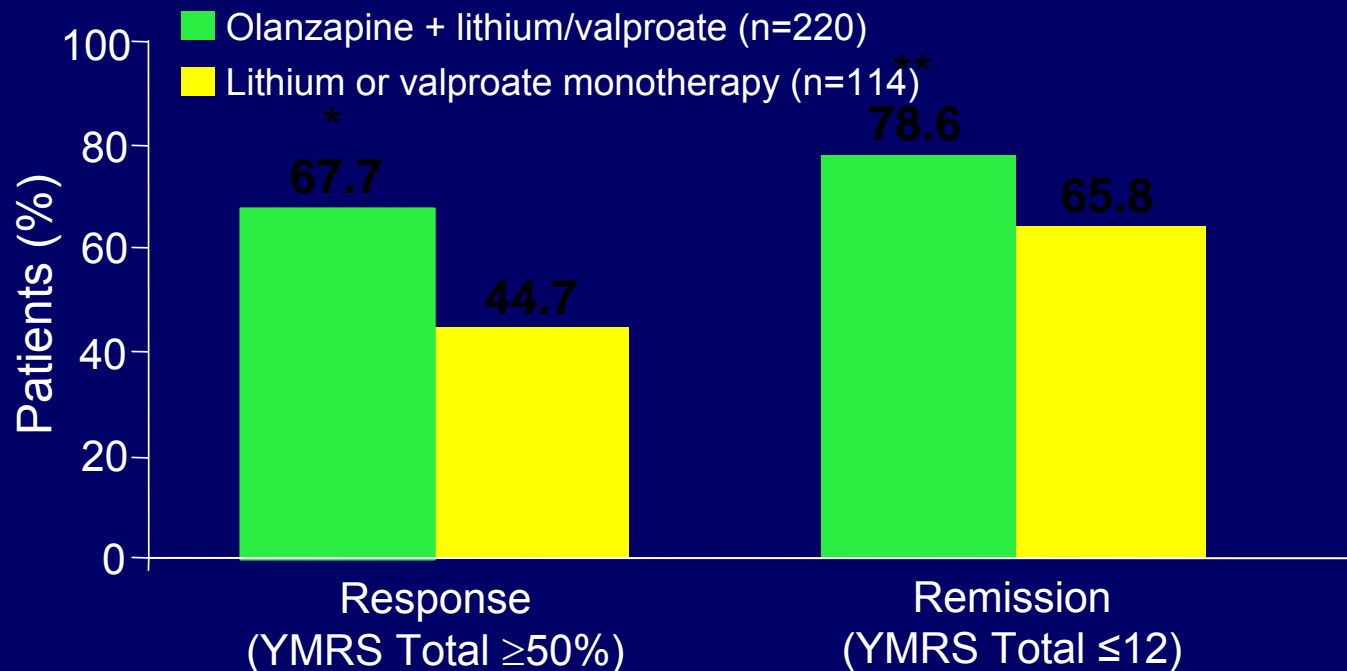
Adjunctive Quetiapine + Lithium or Divalproex in Acute Mania



Median quetiapine dose = 580 mg/d
Divalproex = 50-100 mg/mL
Target lithium trough level = .7-1.0 mEq/mL

YMRS = Young Mania Rating Scale

Co-therapy Olanzapine + Lithium or Valproate in Acute Mania



Median dose of olanzapine = 10.4 mg/d

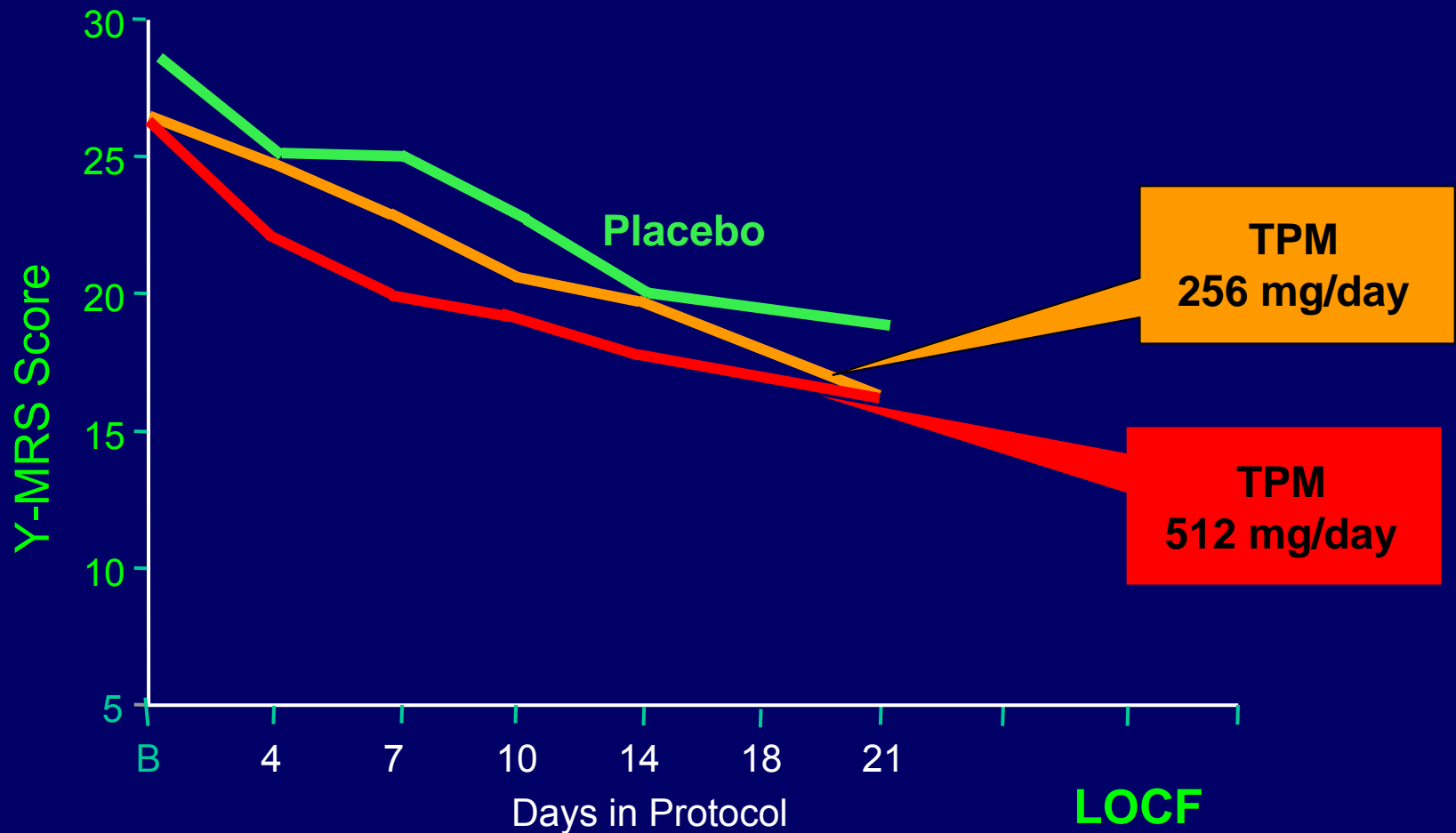
Mean lithium levels = .76 mEq/L

Mean valproate levels = 63.6 mg/dL

* $P=0.001$. ** $P=0.002$.

YMRS = Young Mania Rating Scale

Topiramate Versus Placebo in Acute Mania (N = 97)



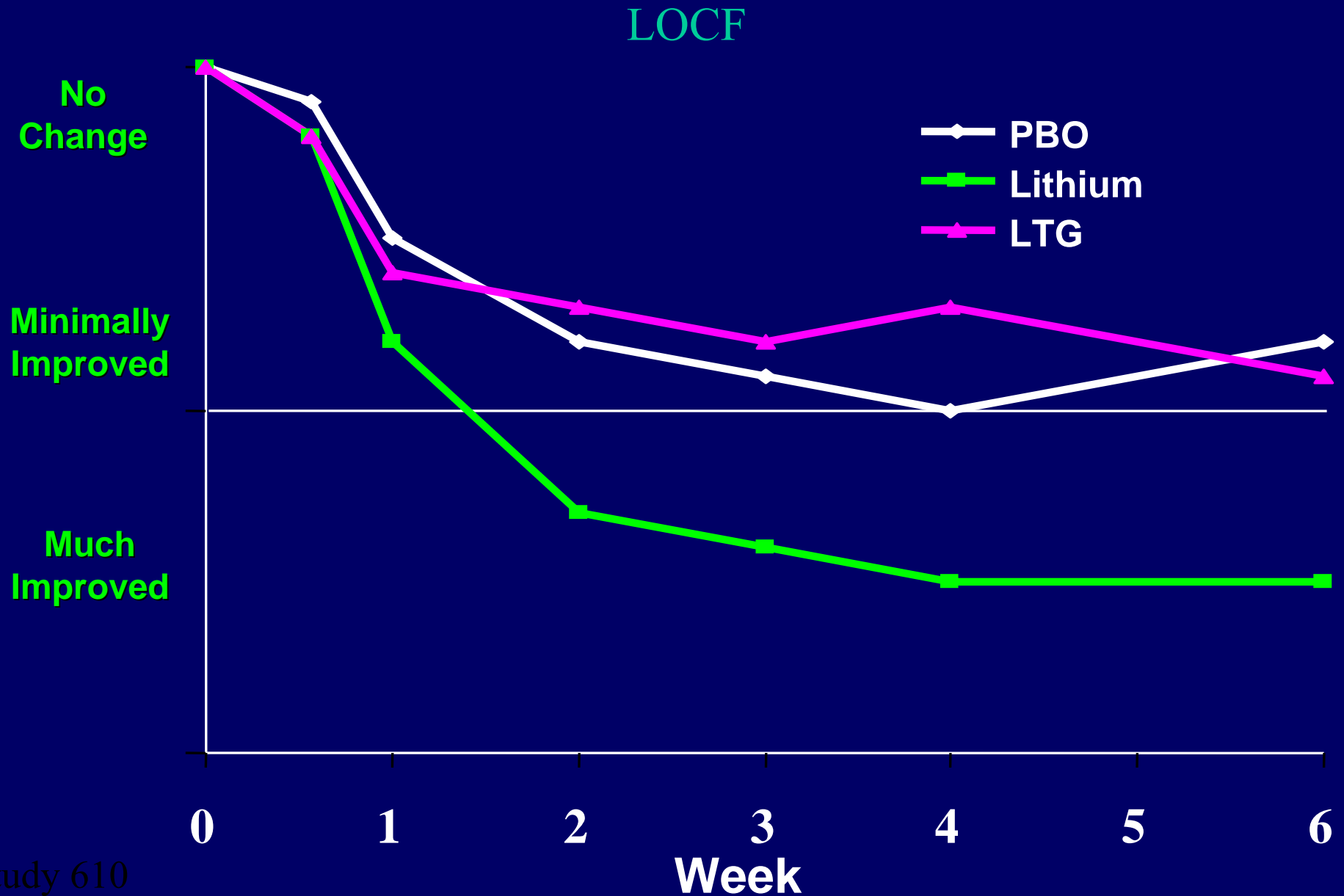
Gabapentin in Bipolar Mania

**12-week Double-blind Comparison of Lithium, Valproate,
or
Both Plus Gabapentin or Placebo in Acute Mania**

Y-MRS	Placebo	Gabapentin
Baseline	18.4	18.8
Endpoint (LOCF)	9.4	13.0
Change	-8.9*	-5.8

* $P < 0.05$

CGI - Improvement

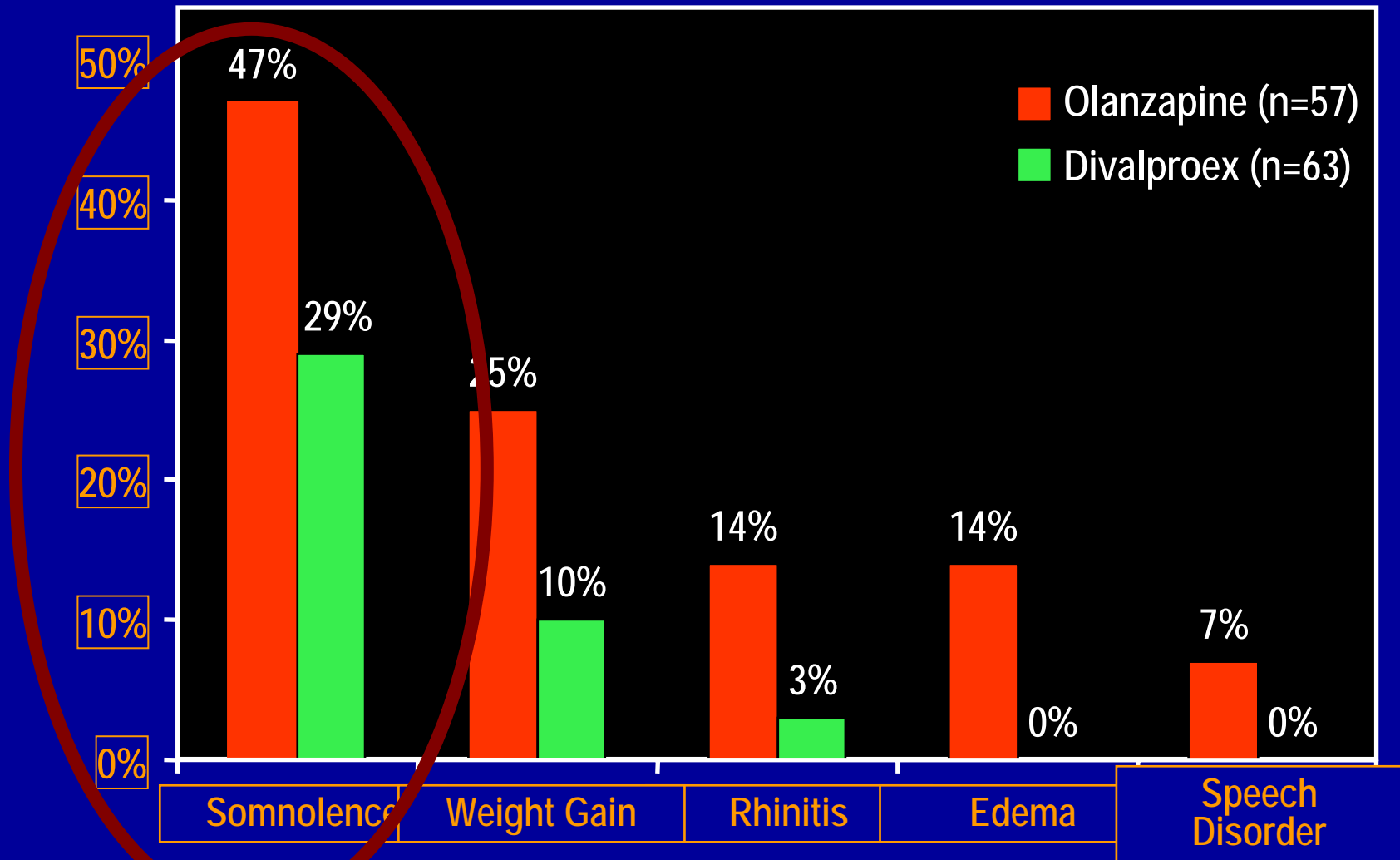


Conclusions

- Atypical antipsychotics are a safe and effective treatment option in acute mania- both as monotherapy and as adjuncts to lithium and valproate/divalproex
- Efficacy rates for treatments of acute mania are comparable
- However, not all antipsychotics are similar in their side effect profile
- Avoid use of Lamotrigine, Gabapentin and Topiramate in acute mania



Olanzapine vs Divalproex: Statistically Significant AEs (12-Week Study)



Clinical States in Bipolar Disorder

- Mania
- Hypomania
- Depression
- Mixed
- New syndromal roughening
- Subsyndromal continued symptomatic
- Recovering
- Recovered

Symptom Domains

- Mood Symptoms
- Psychotic Symptoms
- Cognitive Symptoms
- Activity and Behavior Symptoms

Frequency of Mood Symptoms in Mania

Symptom	%
Irritability	80
Depression	72
Euphoria	71
Lability of Mood	69
Expasiveness	60

Psychosis in Mania

- 47-75% of all patients will experience at least 1 psychotic symptom in their lifetime
- Delusions are 3 times more common than Hallucinations
- 20% of manic patients will have first-rank Schneiderian symptoms
- Early age of onset is associated with greater likelihood of psychotic symptoms

Cognitive Symptoms in Mania

Symptoms	%
Grandiosity	78
Racing Thoughts	71
Distractibility/Poor Conc	71
Confusion	25

Activity and Behavior Symptoms in Mania

Symptoms	%
Rapid/Pressured Speech	98
Hyperverborosity	89
Hyperactivity	87
Decreased Sleep	81
Hypersexual	57
Extravagant	55
Violent/Assaultive	49

Management of Acute Mania

- Establish a therapeutic alliance
- Provide a safe environment
- Ensure medical stability
- Ameliorate mood symptoms
- Ameliorate psychotic symptoms
- Do it rapidly
- Do it safely

Predictors of Response

Lithium

- Few previous episodes
- Absence of rapid cycling
- Absence of substance abuse
- Absence of depressive symptoms during mania
- Absence of comorbidity or psychosis

Potential Advantages of Atypical Antipsychotics in Bipolar Disorder

- Reduced risk of EPS*¹
- Reduced risk of prolactin elevation^{†1}
- Reduced risk of TD¹
- Improvement of depressive symptoms²

*May be dose-related; [†]Except risperidone; ¹Nemeroff CB. J Clin Psychiatry. 2000;61(supp 13):19-25 ²McElroy SL, Keck PE Jr. Biol Psychiatry. 2000(Sep 15);48(6):539-557

APA Guidelines for Acute Mania

- First line: monotherapy with lithium, valproate* or an “antipsychotic such as olanzapine”
- More severely ill patients should receive Li or VPA plus an antipsychotic
- Atypical antipsychotics are preferred over typical agents because of their “benign” side-effect profile
- ADs should be tapered or DC’d if possible

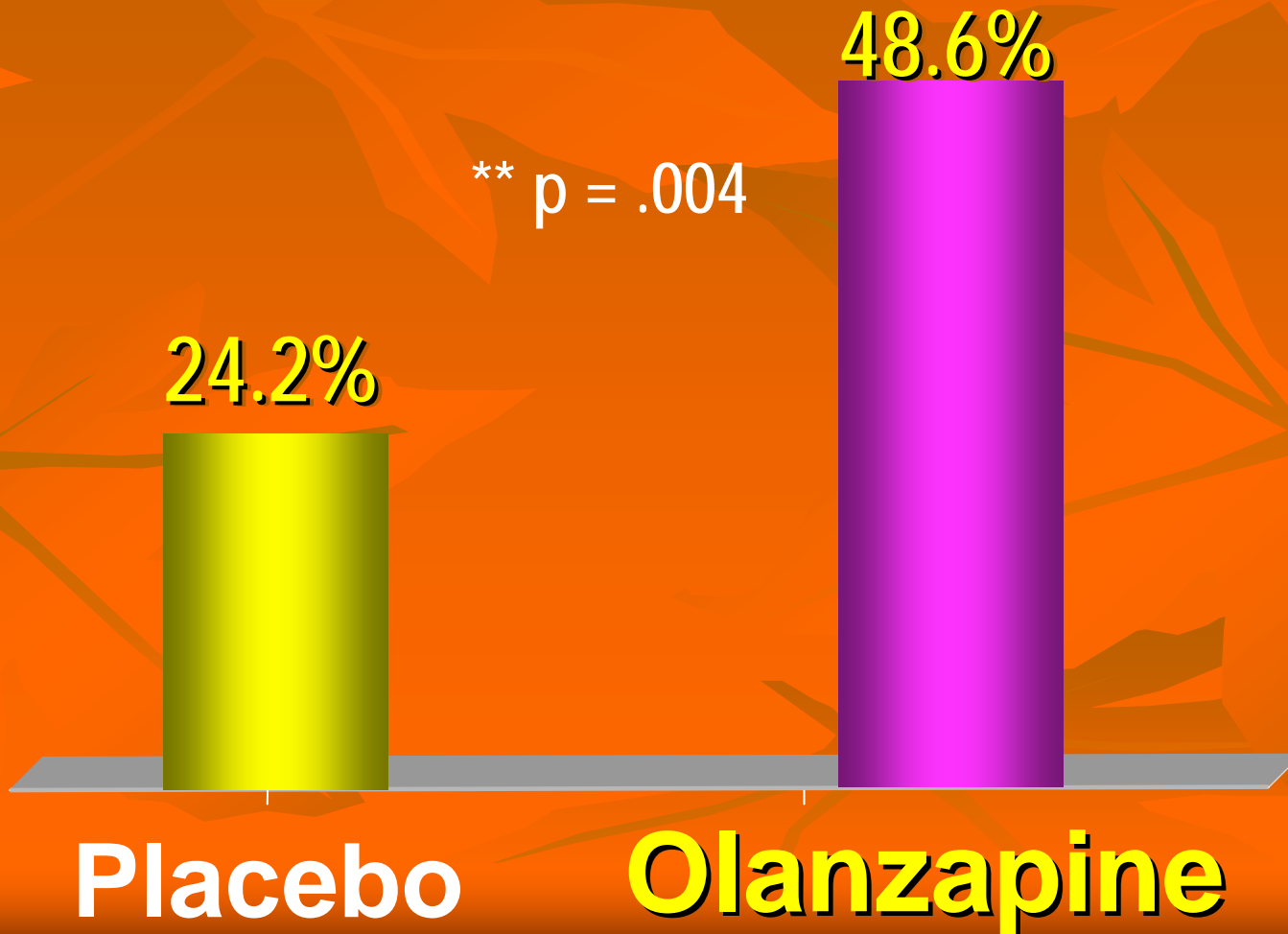
*Valproate (VPA) also refers to divalproex, which has FDA indication for treatment of BD
Hirschfeld RMA et al. Am J Psychiatry. 2002(April);159(4 suppl):1-50

Olanzapine vs Placebo: A Double Blind Study

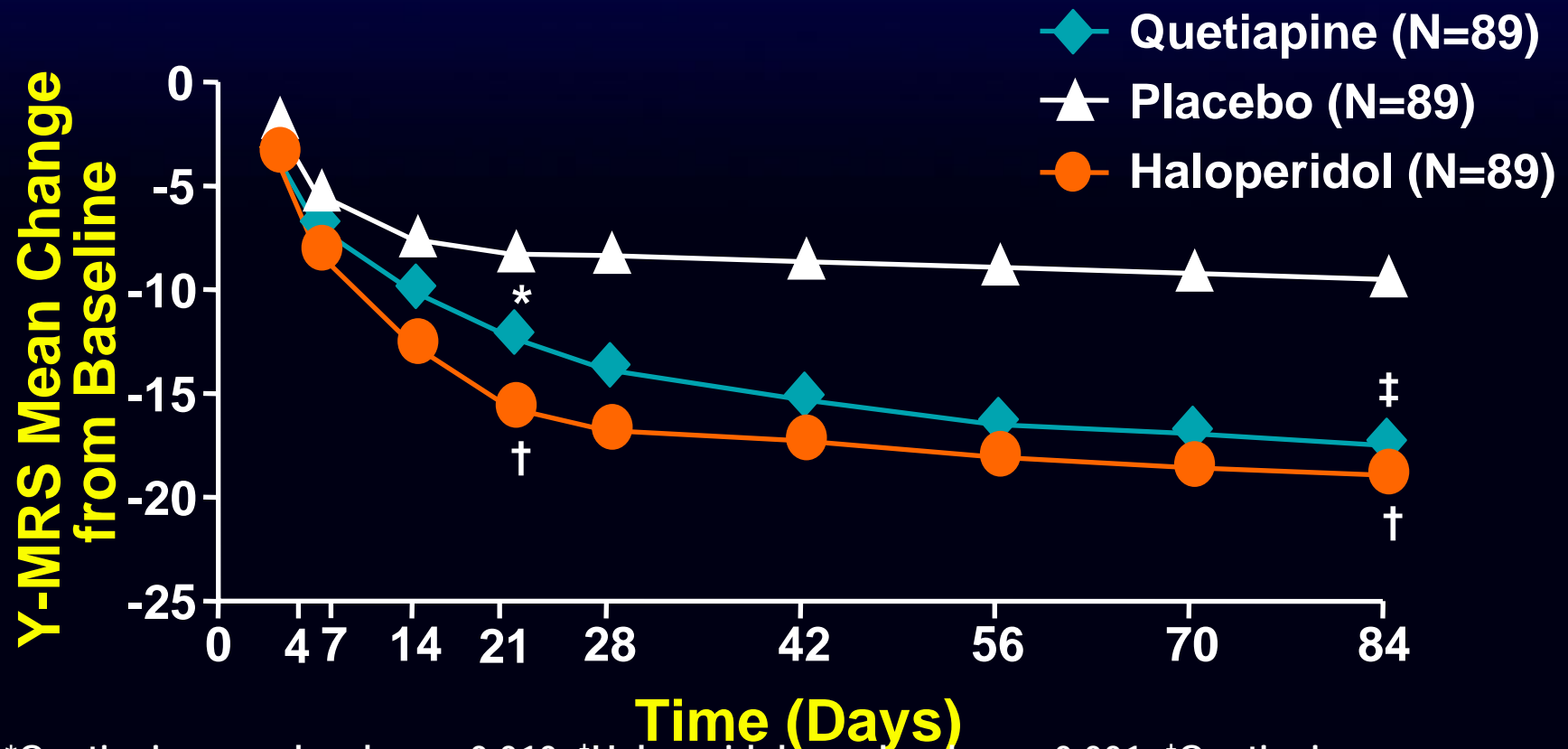
Tohen et al ACNP 1997

Response Rates*

* $\geq 50\%$ improvement on Y-MRS total from baseline

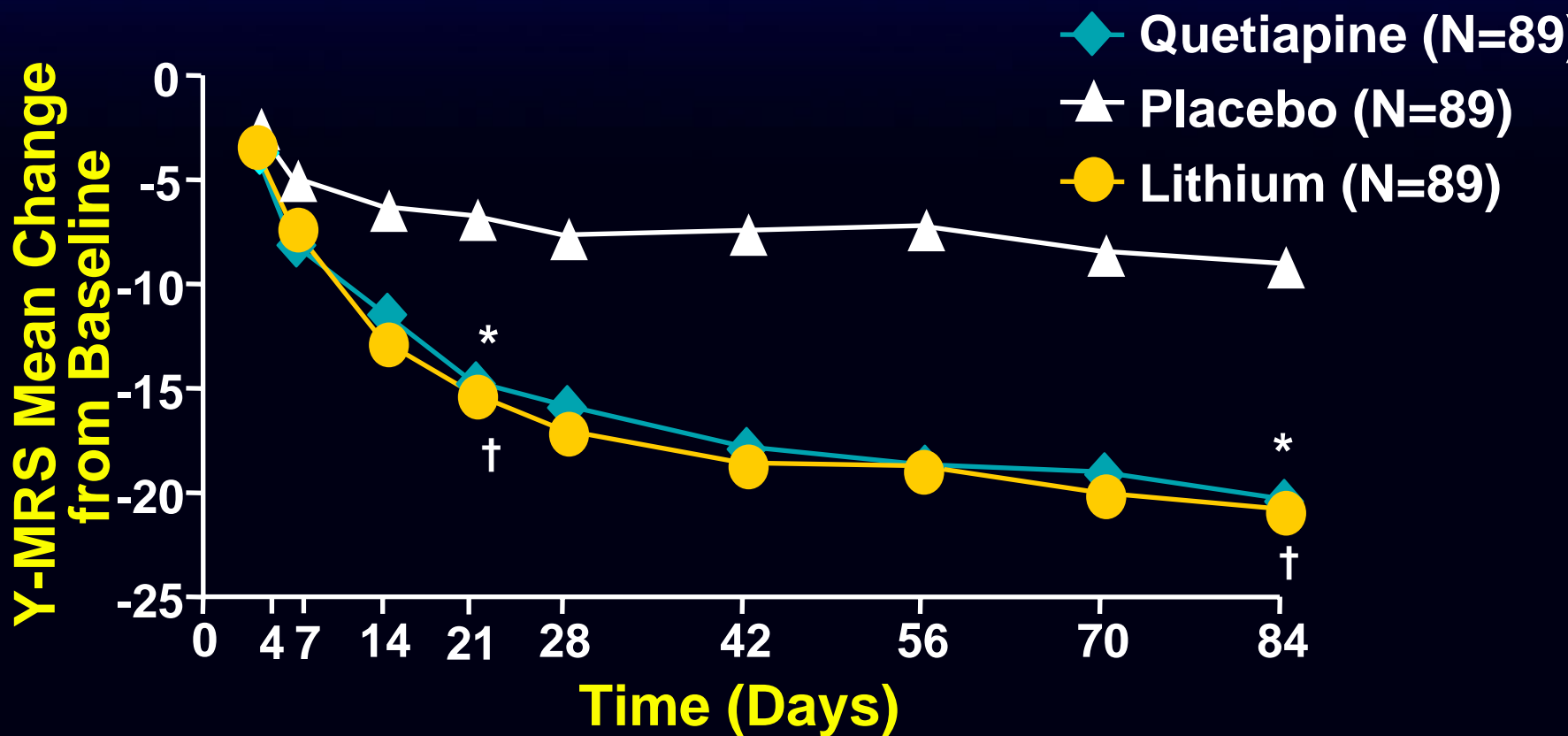


Quetiapine vs. Haloperidol vs. Placebo: Reduction in Y-MRS Score with Acute Mania



*Quetiapine vs. placebo, $p=0.010$, †Haloperidol vs. placebo, $p<0.001$; ‡Quetiapine vs. placebo, $p<0.001$; ITT, LOCF analysis; Results of a 12-week, multicenter, double-blind, randomized, parallel-group, placebo-controlled trial; Jones et al. APA 156th Annual Meeting. San Francisco; May 17-22, 2003

Quetiapine vs. Lithium vs. Placebo: Reduction in Y-MRS Score



*Quetiapine vs. placebo, $p < 0.001$; †Lithium vs. placebo, $p < 0.001$; ITT, LOCF analysis;
Results of a
12-week, multicenter, double-blind, randomized, parallel-group, placebo-controlled trial;
Jones et al. APA 156th Annual Meeting, San Francisco, May 17-22, 2003

Differences Between Bipolar and Unipolar Depression

BP depression associated with

- ▶ Earlier onset
- ▶ Greater number of episodes and time ill
- ▶ Improvement mainly in affective symptoms
- ▶ Family history of bipolar disorder
- ▶ Impulsivity, poor judgment
- ▶ Atypical symptoms

Bowden. *Psychiatr Serv.* 2001;52:51-55.

Maas, et al. *J. Psychiatr Res.* 1994;28:357-367.

Ghaemi, et al *J. Psychiatric Practice.* Sep 2001

Differences Between Bipolar and Unipolar Depression-Contd

BP depression associated with

- ▶ Psychotic symptoms
- ▶ Postpartum onset
- ▶ Recurrent episodes
- ▶ Poor response to antidepressants
- ▶ Affective switch with antidepressants

Management of Acute Mania

- Establish a therapeutic alliance
- Provide a safe environment
- Ensure medical stability
- Ameliorate mood symptoms
- Ameliorate psychotic symptoms
- Do it rapidly
- Do it safely