

Summary of Critical Factors in Long Term Bipolar Studies

- **Imprecise, heterogenous diagnoses**
- **Simple phenotypes and endophenotypes**
- **Focus on behavioral domains in play, not total scores**
- **Durable outcomes, not point in time**
- **Adapt survival methods to bipolar realities**
- **Recognize the unique contributions of placebo groups**

Imprecision Consequent to “or” Criterion Sets in DSM-IV

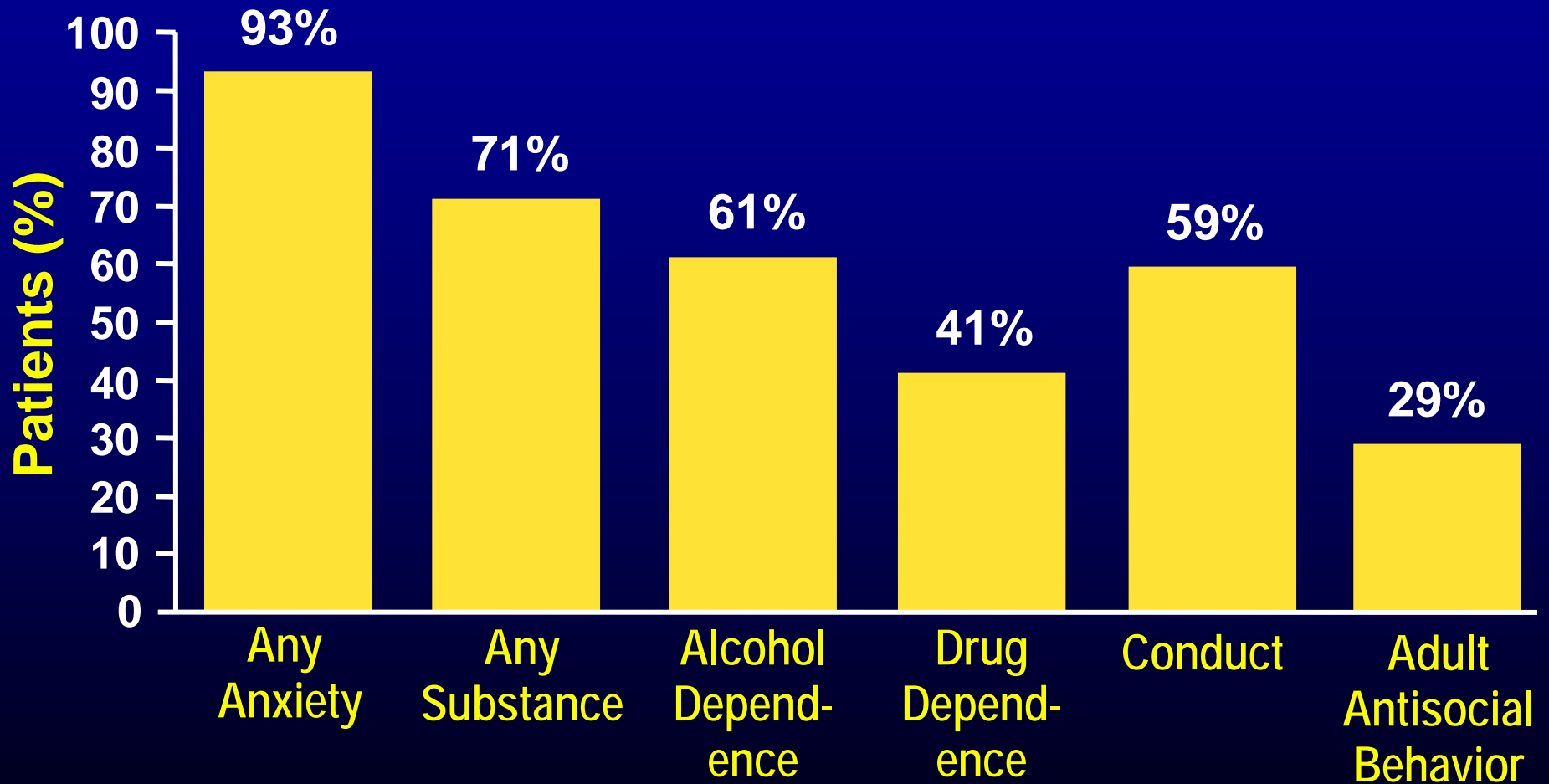
- **Mania example: expansive mood, more talkative, distractible, increased goal directed activity**
- **Expansive mood, grandiosity, decreased need for sleep, racing thoughts**
- **70 possible combinations for mania using the minimal number of symptoms, more if more symptoms included.**

DSM-IV Depressive Episode

- **At least 2 weeks** during which there is either depressed mood **or** the loss of interest or pleasure in nearly all activities
- **At least 5 of the following:**
 - Depressed mood most of the day, nearly every day
 - Markedly diminished interest **or** pleasure in all (or almost all) activities
 - Significant weight loss when not dieting **or** weight gain
 - Insomnia **or** hypersomnia nearly every day
 - Psychomotor agitation **or** retardation
 - Fatigue **or** loss of energy
 - Feelings of worthlessness **or** excessive guilt
 - Diminished ability to think **or** concentrate
 - Recurrent thoughts of death or suicidal ideation, **or** suicide attempt
- **Consequent to the many “ors”, over 1700 symptom sets can meet criteria for mixed mania**

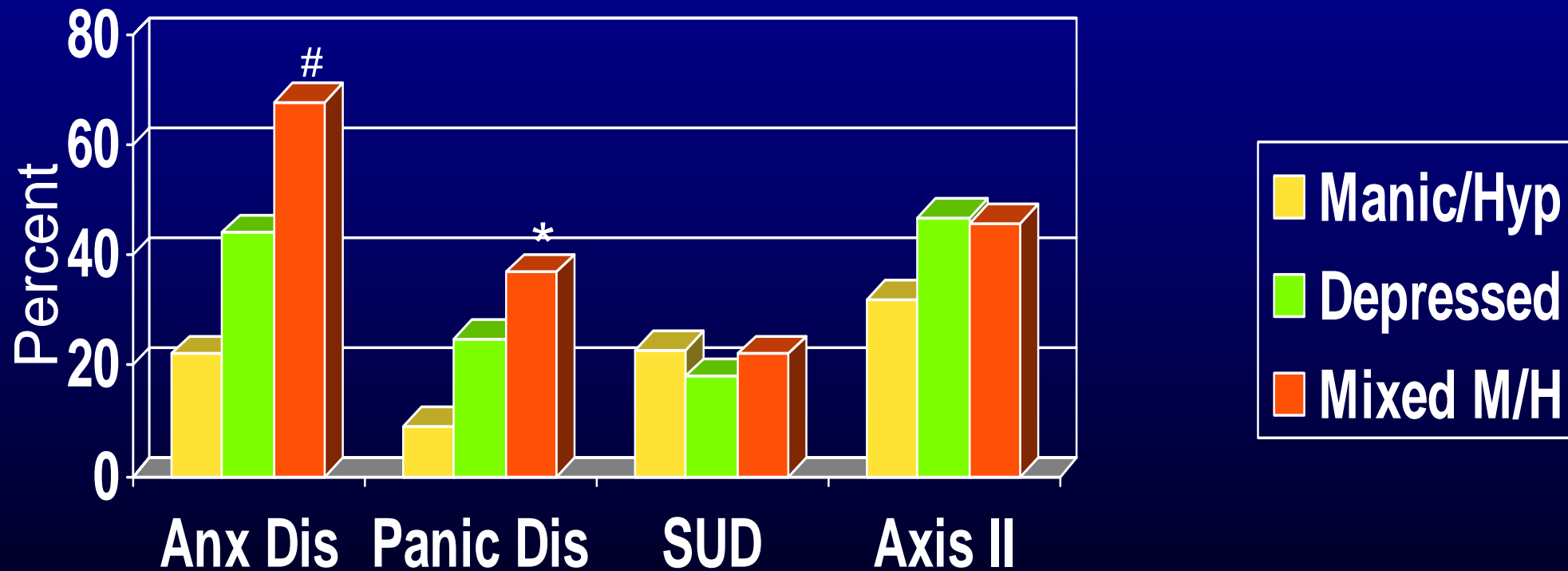


Bipolar I Disorder* Is Highly Comorbid With Other Psychiatric Disorders



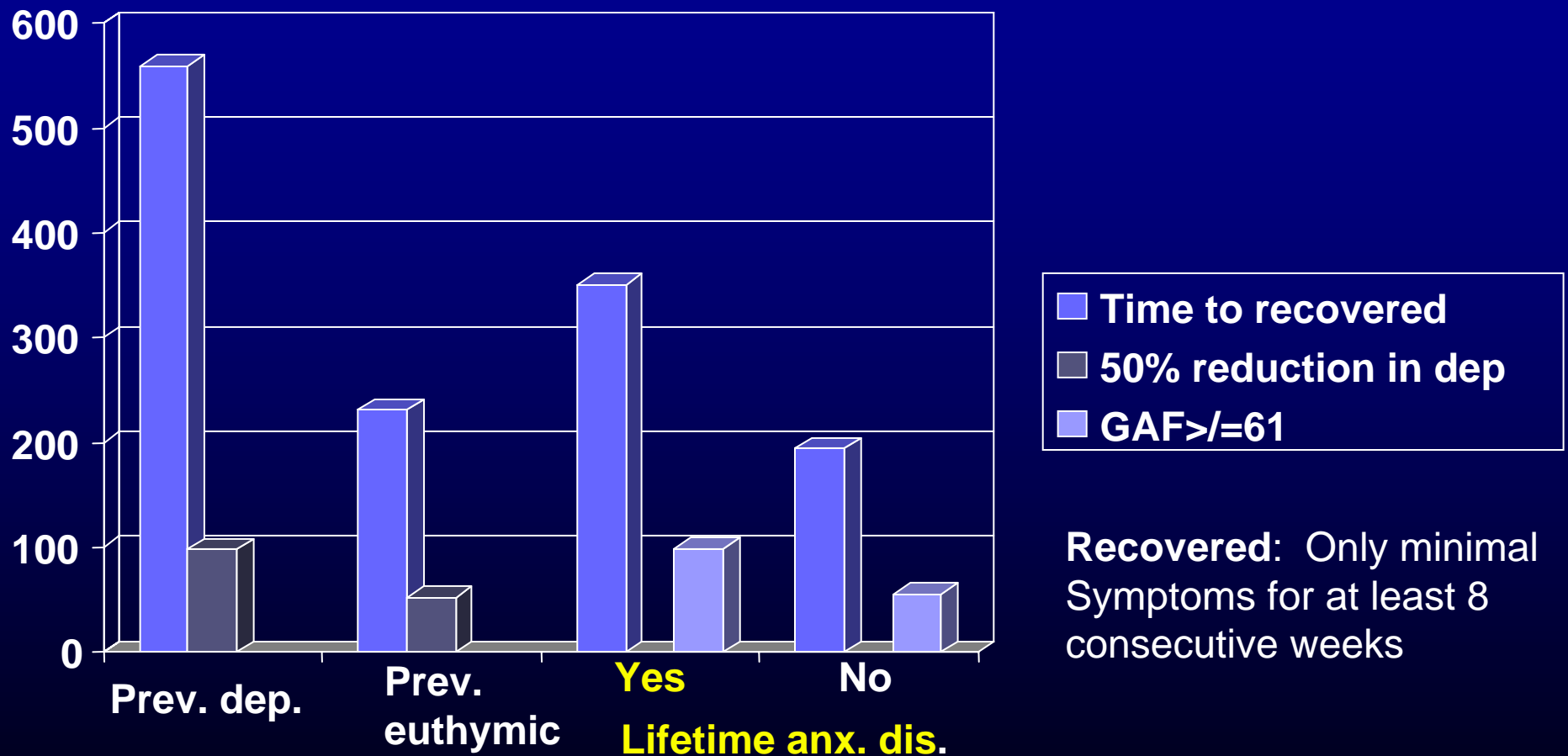
*Euphoric-grandiose subtype; Kessler RC et al. 1997, Psychol Med 27:1079-1089

Anxiety Disorders Comorbidity Specific to Mixed Mania, Unlike Other Bipolar Comorbidities



#: $p < .001$, *: $p = .01$, Anx dis=any axis I anxiety disorder, SUD= any substance use disorder, Axis II=any axis II disorder. Sample: M/H=106, Dep.=44, Mixed=41

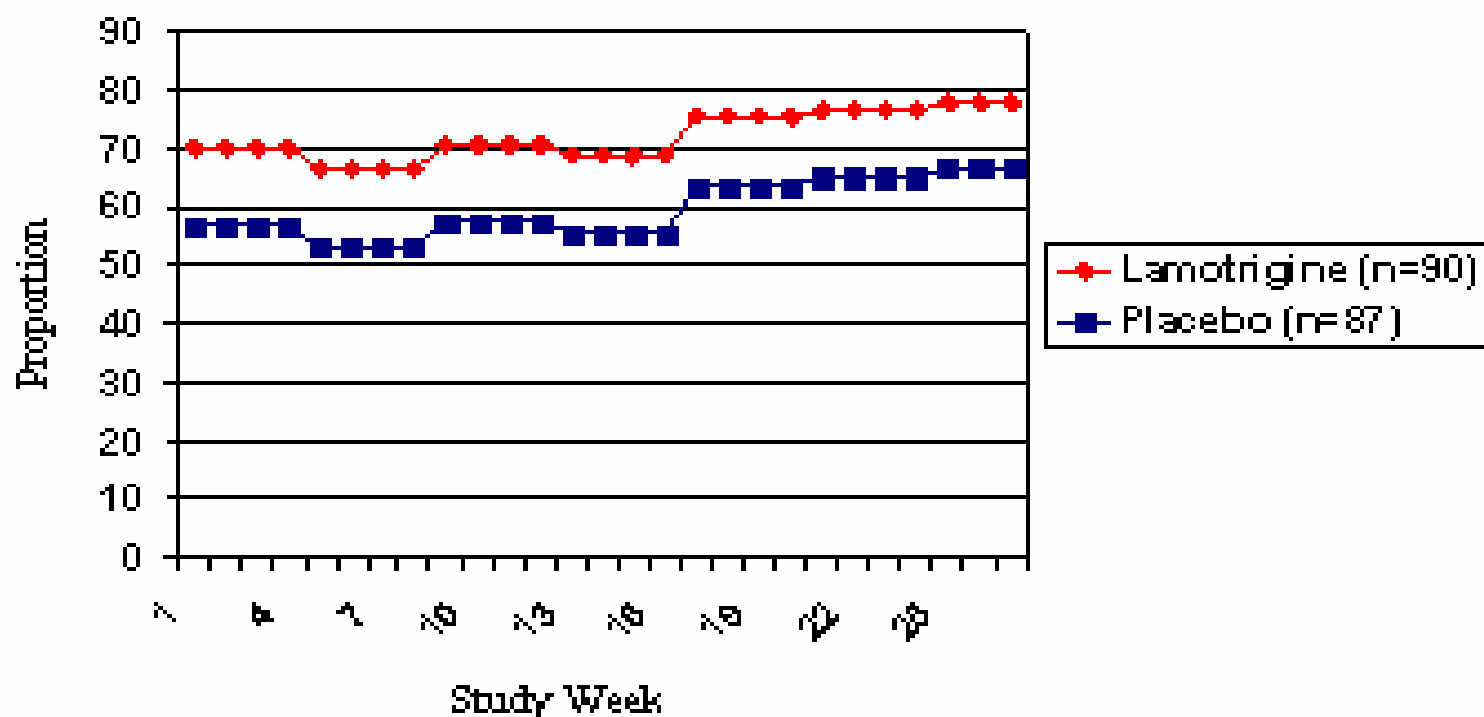
Times to Different Criteria for Improvement in Relationship to Predictors of Outcomes in Bipolar Depression in STEP



Bowden et al, submitted, 2006

Rates of Euthymia based on Patient Daily Reports in 6 Month Study of Rapid Cycling Bipolar Disorder

OBSERVED PROPORTION OF SUBJECTS ACHIEVING EUTHYMIA AT EACH WEEK



Predictors of Poor Outcomes in BP I and II Depressed Patients in STEP

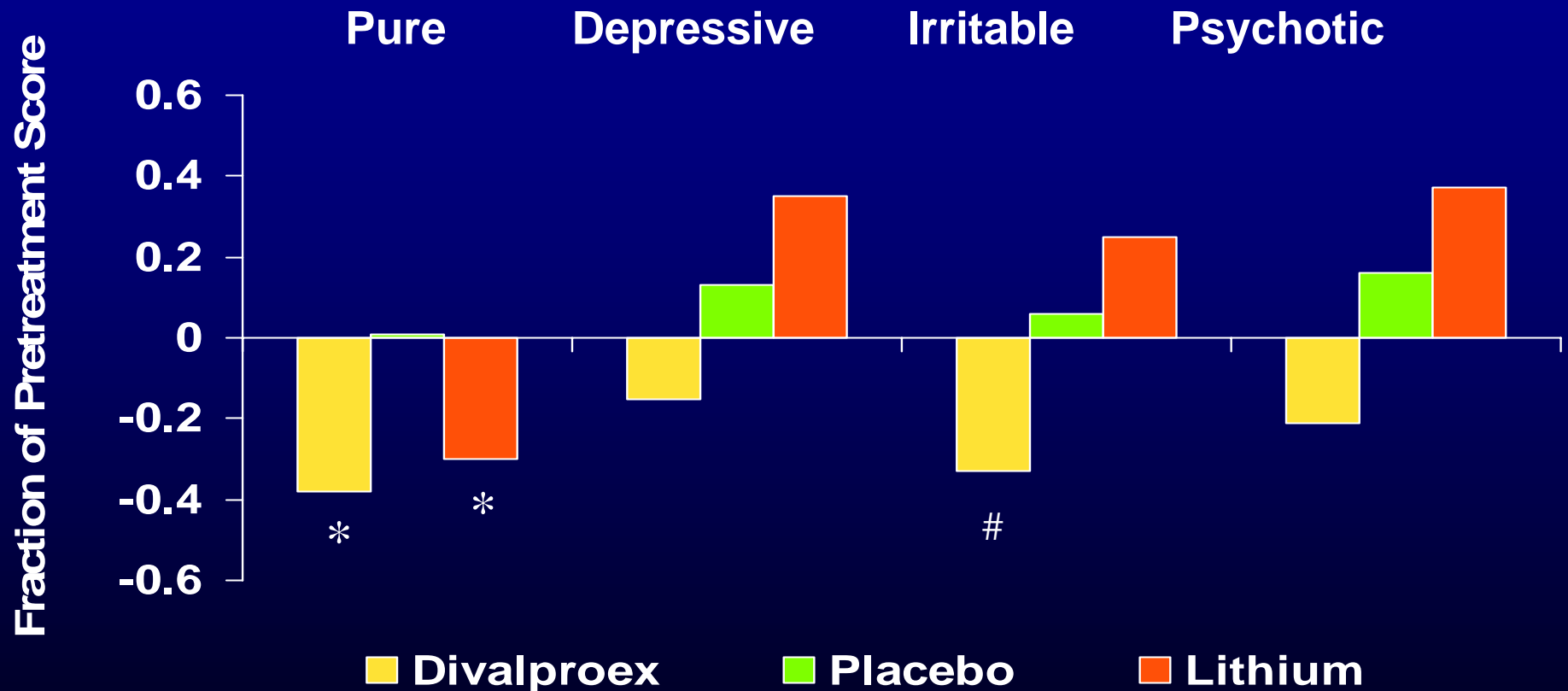
- Polarity of preceding episode, Depressed, mixed
- Lifetime anxiety disorder
- Greater duration of longest remission
- Lifetime ADHD
- More lifetime phases depression
- Higher baseline MADRS
- Higher total PDQ score
- Higher asocial temperament
- Higher impulsivity/lability temp.
- Higher anxious/depressive temperament
- Lower income
- Older age

Endophenotypes

- Synonymous with dimensions, components
- **Reveal latent variables underlying a scale or phenotype**
- Complementary to syndromal classifications
- Behavioral, physiological, genetic, brain structure or function based, treatment outcome based, or combinations thereof
- **Informed by exploratory factor analyses**

Floyd and Widaman, *Psychological Assessment* 7:286, 1995

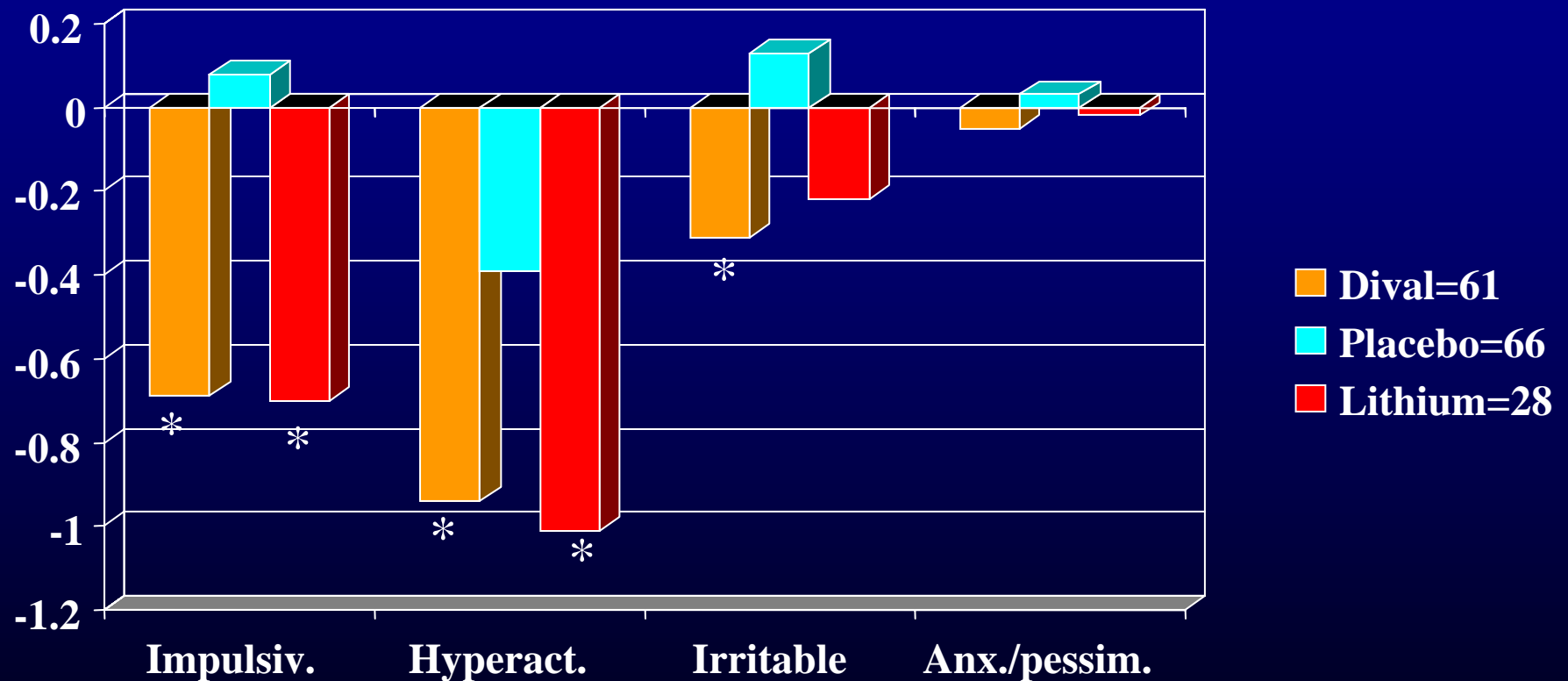
Differences in Response for Divalproex or Lithium for Manic Subtypes



*D>PBO,0.001; L>PBO,0.006; #D>PBO,0.04;D>L,0.004; Treatment X subtype, $P=0.02$

Swann AC, et al. *Neuropsychopharmacology*. 2002;26:530-536.

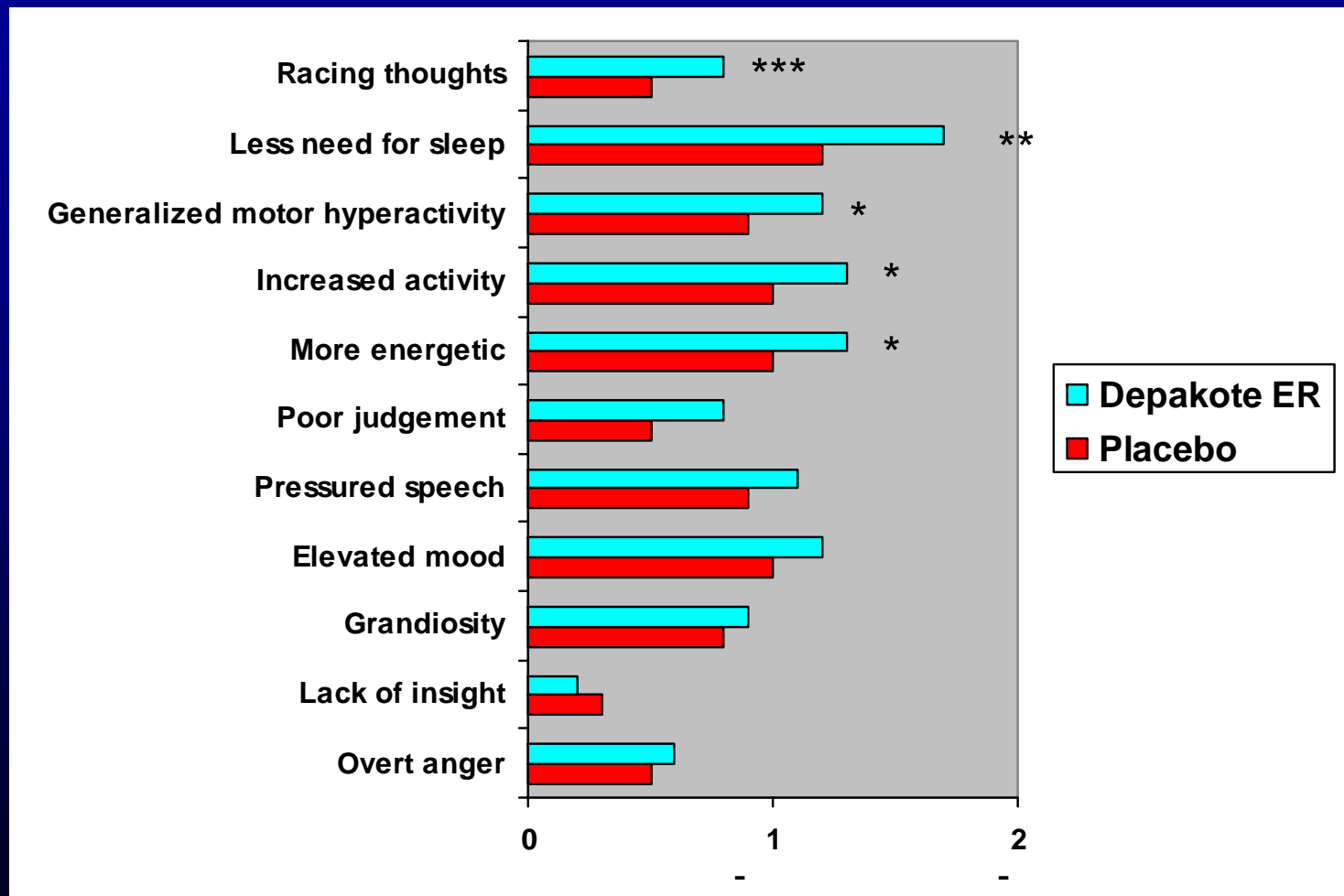
Treatment Effects on Behavioral Components in Mania



P<.05 vs placebo, Newman-Keuls test

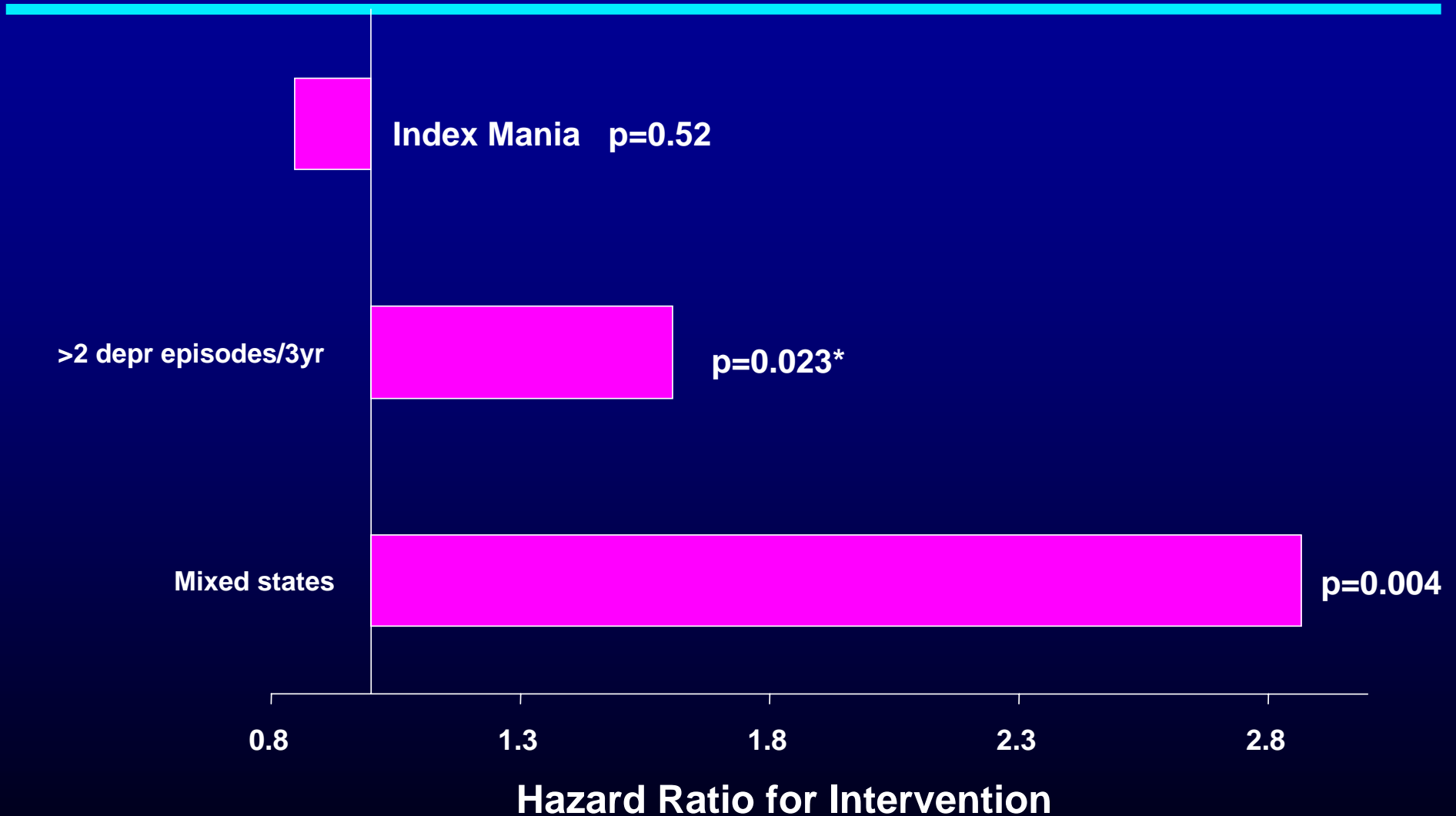
Swann et al, Neuropsychopharmacology, 2002

Change in MRS Items in 21 Day Study of Divalproex ER in Mania



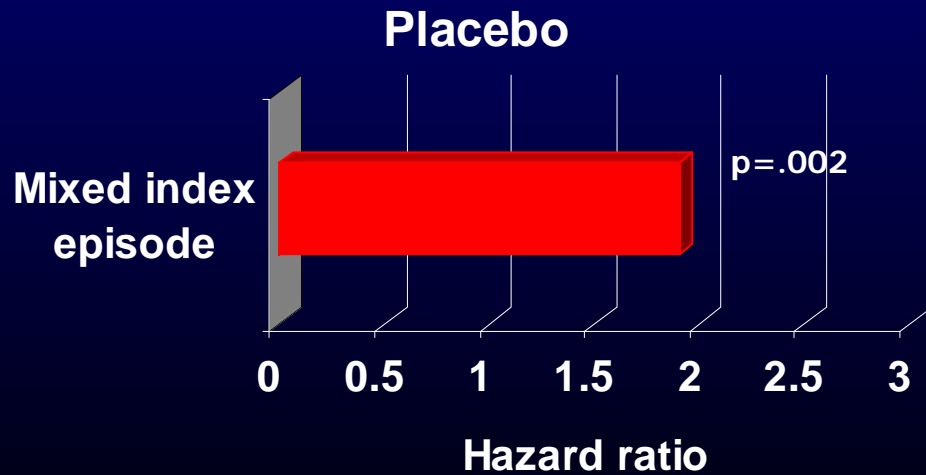
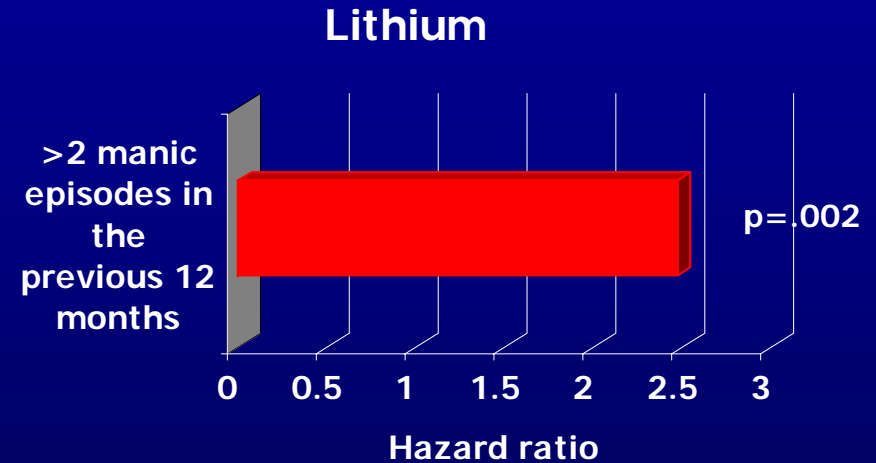
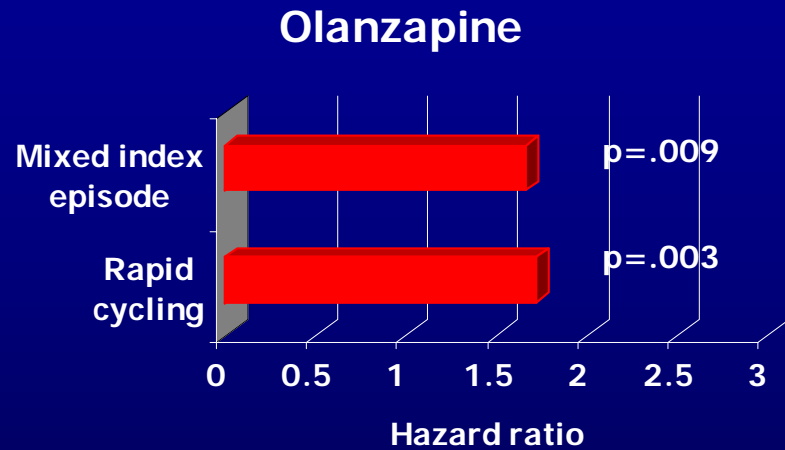
* $p \leq 0.050$ ** $p \leq 0.010$ *** $p \leq 0.001$
Bowden et al, submitted, 2006

Predictors of Relapse for Lamotrigine



Bowden et al. American Psychiatric Association. San Francisco, May 2003

Predictors of Relapse in Olanzapine, Lithium, Placebo Studies



Factor Analysis of Response to Lamotrigine in Bipolar Depression

- Lamotrigine more effective than placebo for 'depressive cognitions' and 'psychomotor retardation'
- 'Depressive cognitions' comprise mood, guilt, suicidal thoughts, helplessness, hopelessness, worthlessness items
- 'Psychomotor retardation' comprises retardation, retardation-psychic, retardation-motoric items

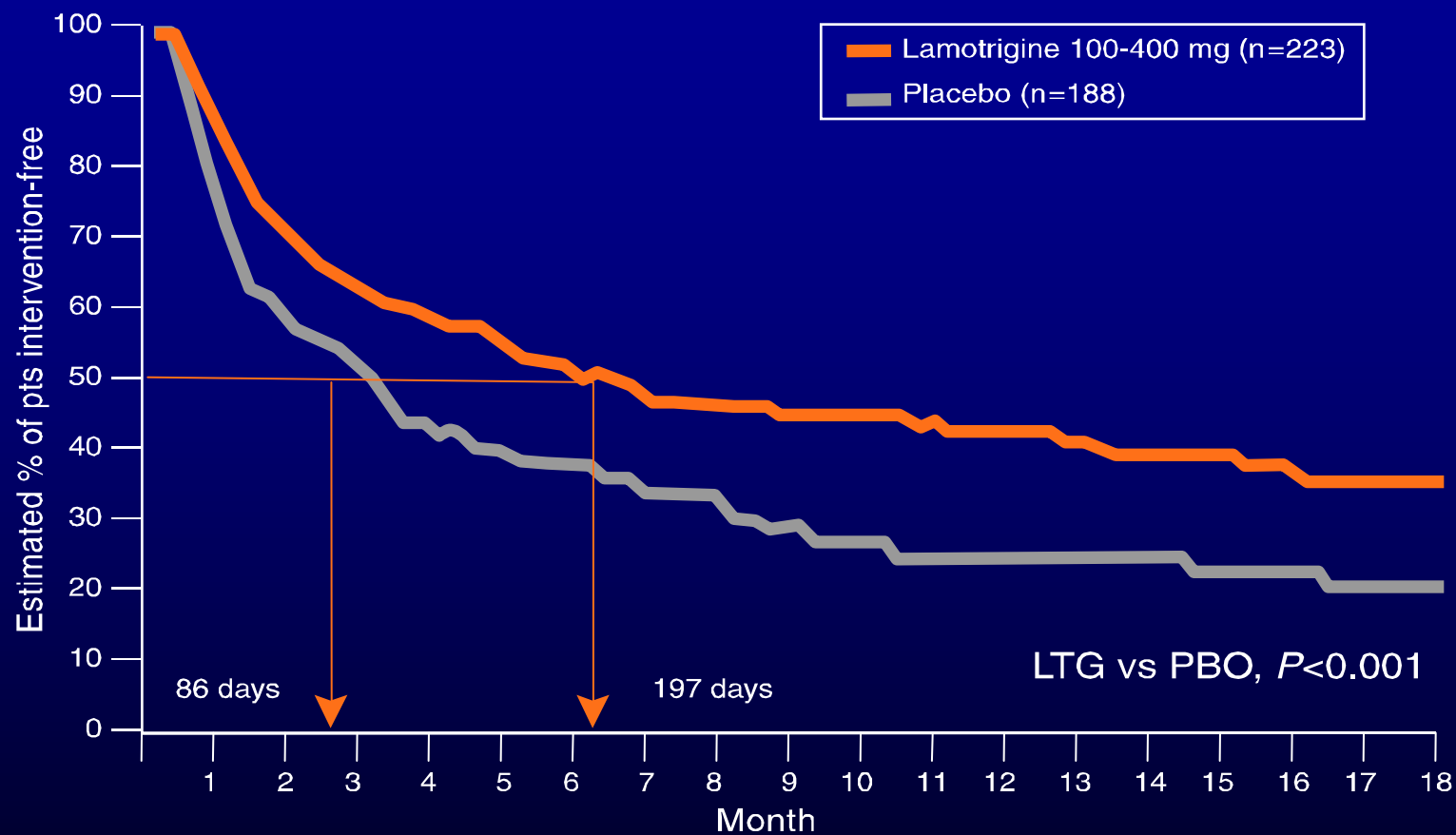
Association Between Clinically Detectable Increase in Mania Symptoms and Subsequent Relapse

YMRS Items	Olanzapine (n=15)		Lithium (n=17)	
	Odds ratio*	p value	Odds ratio	p value
Increased Motor Activity / Energy	14.13	<.001	2.95	.102
Irritability	7.24	.002	2.52	.166
Elevated Mood	4.31	.016	2.79	.115
Disheveled Appearance	9.23	.021	3.84	.179
Insight	5.28	.064	5.91	.066
Sexual Interest	4.26	.071	4.07	.08
Sleep	2.98	.119	3.41	.101
Language Thought Disorder	2.66	.249	1.7	.583
Speech – Rate/Amount	2.11	.271	3.77	.042
Disruptive-Aggressive Behavior	2.11	.499	6.94	.022
Content	NA	NA	NA	NA
At least one symptom increased	6.09	.002	3.86	.007

* Odds ratios computed using repeated measures logistic regression (GEE).

Houston J, Lipkovich I, Ahmed S, et al, 2004

An Example of a Kaplan-Meier Survival Analysis of Time to Intervention* for Mood Episodes†

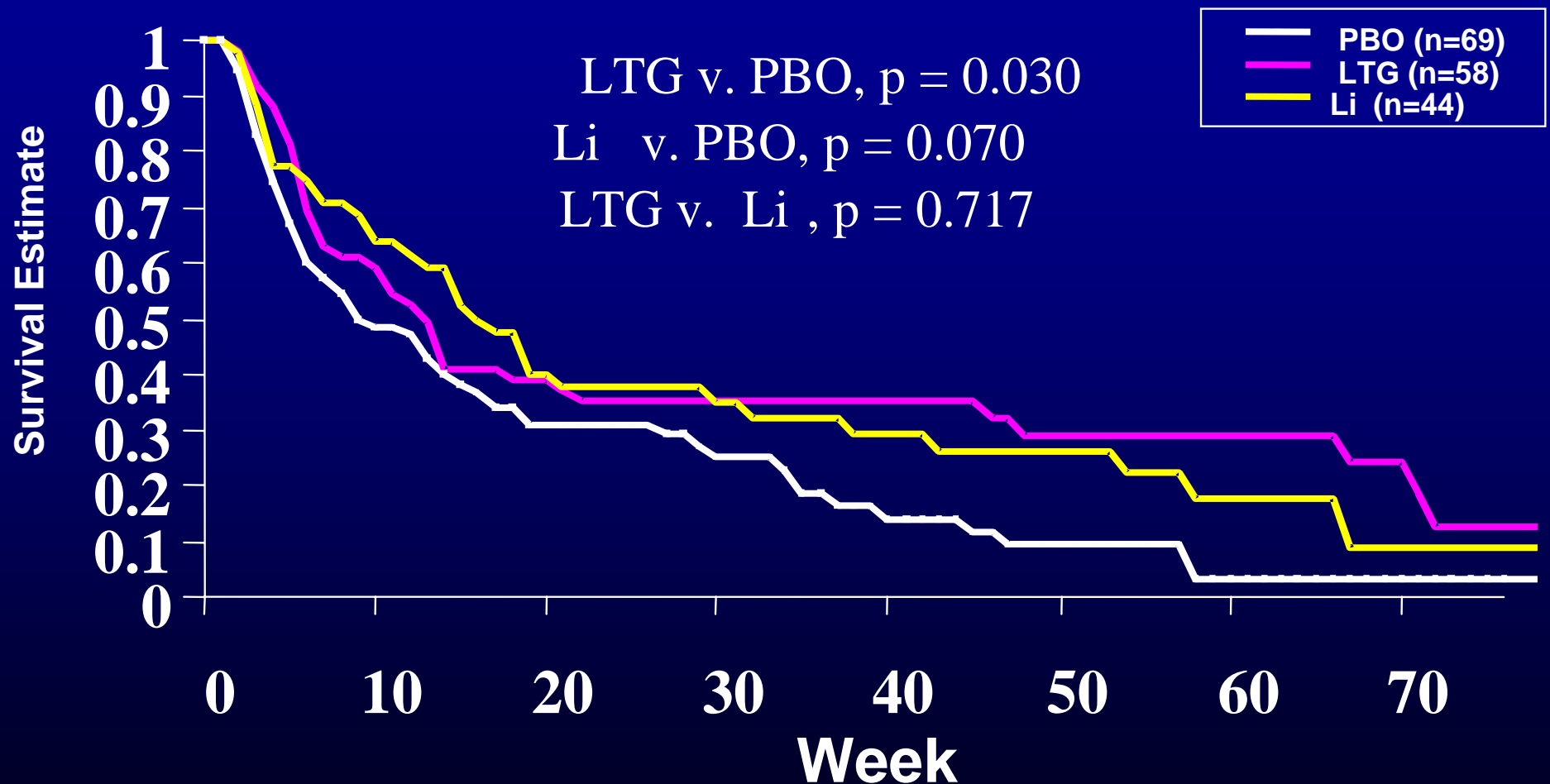


* Intervention is defined as the addition of pharmacotherapy or ECT for a mood episode or one that was emerging.

† Prospectively defined combined analysis.

Goodwin et al. *J Clin Psychiatry*. 2004;65:432-441.

Time to Recurrence, Added Medication, or Early Termination for Any Reason



Bowden CL, et al. *Arch Gen Psych*. 2003

Adaptation of Survival Analysis to Specifics of Bipolar Disorders

- **Quality-of-life adjusted survival analysis approaches. Survival time weighted by an index of quality life or functional status for each compartment of survival over time**
- **Techniques that allow for informative censoring**
- **Techniques that allow for multiple events**
- **MMRM procedures as alternative, providing area under curve and estimates of missing data.**

Effects of Placebo on Adverse Outcomes

- **No increase in morbidity or mortality with placebo compared to 5 marketed drugs. Khan Arch Gen Psychiat 2001**
- **Rates of suicide attempts, completed suicides were lowest among placebo assigned patients**
- **Predictors of poor outcomes often clearer, though similar, with placebo than active drug treatment arm.**
- **Placebo prevents interpretation of illness symptoms as adverse effects of an active treatment.**

Leber Biol Psychiat 47:699-706

Discussion
