

# Methodological Challenges in Long-term Trials of Bipolar Depression

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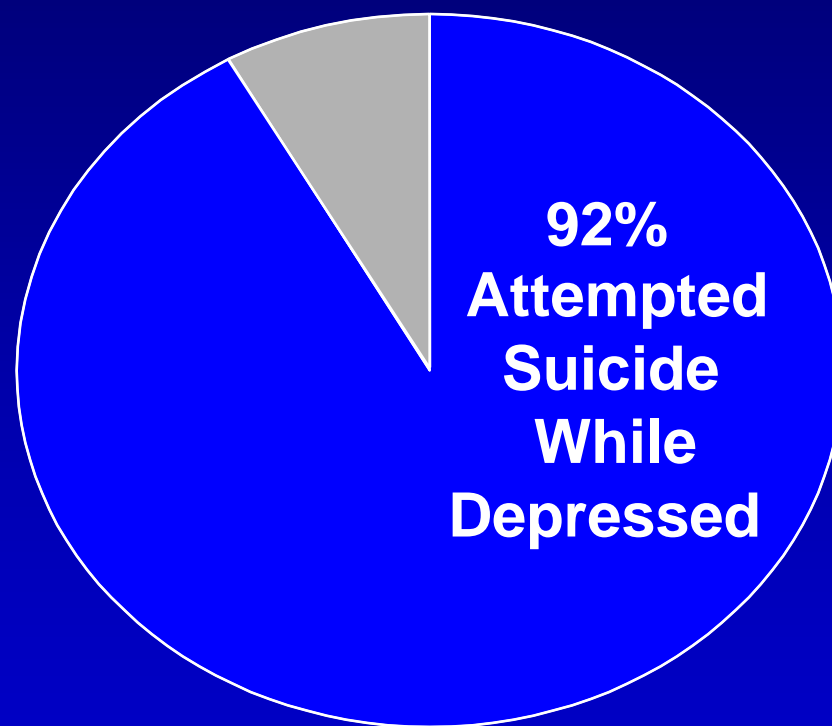
# Depression as the Predominant Mood State in Bipolar I vs. II Disorder

	Bipolar I	Bipolar II	P
<b>N</b>	<b>135</b>	<b>71</b>	
<b>% of time ill</b>			
<b>Any depression</b>	<b>31</b>	<b>52</b>	<b>.001</b>
<b>Any mania / hypomania</b>	<b>10</b>	<b>1.4</b>	<b>.001</b>
<b>Ratio D/M</b>	<b>3</b>	<b>37</b>	
<b>Episode duration (weeks)</b>	<b>31</b>	<b>127</b>	<b>.001</b>

Judd LL, et al. *Arch Gen Psychiatry*. 2002 and 2003.

# Impact of Depressive Symptoms on Suicidality

- Of 2,839 patients studied
- 50% reported at least 1 previous suicide attempt
- 92% had at least 1 attempt while depressed
- 27% had at least 1 attempt while manic



Kupfer D et al. 2002

# High Response Heterogeneity

- Little is known about response characteristics of bipolar depression, so clinicians' employ trial and error methodology assisted by algorithms and clinical judgment.
- The 'what' and 'when' and for 'whom' usually goes unanswered?
  - Sequencing of treatments is never studied.

Murphy SA et al: Neuropsychopharm. 2006.

# Peculiarities Associated with the Depressed Phase of Bipolar Disorder

- Response heterogeneity associated with bipolar depression appears greater than that associated with mania.
  - In mania, what gets patients well, keeps them well.
  - In depression, what gets patients well doesn't necessarily keep them well.
- As a result, 'sequential decision-making' is more important to the treatment of bipolar depression.

# Methodological Unmet Needs

- Standard maintenance designs assess safety, efficacy in a restricted population, and tolerability.
- The increased response heterogeneity associated with bipolar depression demands methodological innovation, including:
  - The construction of effective treatment sequences
  - The assessment of response characteristics around individual patients.

# Basic Unanswered Questions in Long-term Treatment

- Should a switch to a different treatment be made, with the risk of losing the benefit of the initial treatment?
- Should a second treatment be added with the risk of increasing side effect burden?
- Or should 'Watchful Waiting' be employed in the hopes of continued gradual improvement?

APA 2002 Guidelines.

# Adaptive Study Designs

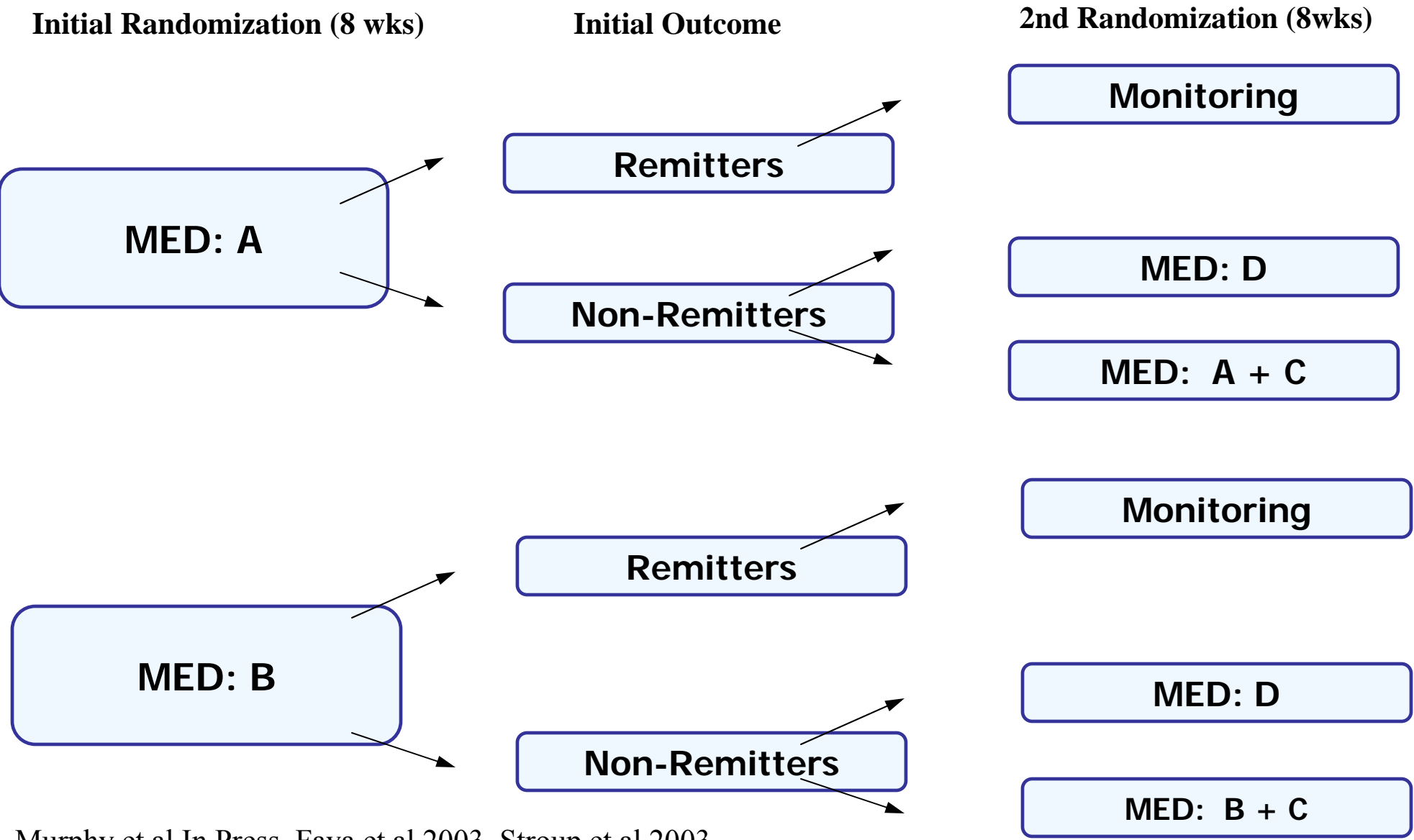
- Treatment algorithms become ‘adaptive study designs’ when sequential randomizations are used.
  - When should a treatment be used?
  - When should an inadequate treatment be changed?
  - What should the intensity or type of maintenance treatment be changed?

# Features of Sequential, Multiple Assignment, Randomized (SMART)

- Multiple randomizations are used
- Randomization occurs at each critical decision point.
- Not designed to be confirmatory
- May not involve a control condition

Lavori & Dawson 2003. Dawson & Lavori 2004, Murphy 2005. Stone et al 1995, Tummarello et al 1997, Stroup et al 2003, Fava et al 2003, Rush et al 2004, Rabinowitz et al 2005.

# Sequential Multiple Assignment Randomized Trial



Murphy et al In Press. Fava et al 2003, Stroup et al 2003.

# Longitudinal Primary Outcome Measures - Relapse Rates vs. Illness/Wellness -

- Relapse rates (Tohen et al 2006, Keck et al 2006)
- % Time ill (Denicoff et al 1977)
- Time well (Denicoff et al 1997)

# Percent of Time ill in Bipolar Disorder

Randomized, Cross-Over Treatment Periods of 1 Year

	% Time Depressed	% Time Manic
Retrospective	32 ± 25	25 ± 20
Lithium	31 ± 25	9 ± 7
Carbamazepine	26 ± 23	19 ± 19
Lithium + Carbamazepine	29 ± 27	8 ± 11

Denicoff KD, et al. *J Clin Psychiatry* 1997.

# Two Maintenance Studies with Index Episodes of Depression

<u>Study</u>	<u>Prien Study</u>	<u>Ltg</u>
Design	Li vs. Imi vs. Pbo	Ltg vs. Li vs. Pbo
N	18 vs. 13 vs. 13	221 vs. 121 vs. 121
Duration (yrs)	2	1.5
Sites	18	71
Recent hospitalization	required	not required
Primary Outcome	% relapse rates	time to treatment
Lithium levels	.5-1.4	.8-1.1

Prien et al 1973 and 1974. Calabrese et al 2003.

# Time to Intervention as Primary Outcome

- Possible more sensitive
- Needs validation by obtaining symptoms-severity and/or syndromal data at endpoint.
- More ethical since relapse or hospitalization is not required.
- Study endpoint and intervention is earlier, mimicking clinical practice patterns.

**Bowden et al 2003, Calabrese et al 2003.**

# Return of Subsyndromal Symptoms as Primary Outcome

- Subsyndromal symptoms are important because they predict risk of relapse and morbidity.
- Frye and colleagues used the following to operationalize subsyndromal symptoms:
  - Symptom free (HAM-D 0-7, MRS 0-7)
  - Sub-syndromal (HAM-D 8-14, MRS 8-13)
  - Syndromal (HAM-D  $\geq 15$ , MRS  $\geq 14$ )

Keller et al 1992. MacQueen et al 2003. Frye M et al submitted.

# **Subsyndromal Symptoms as an Outcome in the Lamotrigine Maintenance Studies**

- **Subsyndromal symptoms were common during maintenance treatment.**
- **Subsyndromal symptoms predicted relapse into an episode of the 'same polarity'.**
- **Treatments that delayed the onset of intervention did the same for the onset of subsyndromal symptoms and the time from onset of subsyndromal symptoms to subsequent full relapse.**

**Frye M, Yatham L, Calabrese J, Bowden et al: submitted.**

# **Relapse Versus Recurrence in Long-term Bipolar Maintenance Studies**

# Polarity of the Index Episode Predicted the Polarity of Mood Episodes on Placebo

-Robustly in Those Presenting Depressed,  
Less so in the Recently Manic

	<u>Depression %</u>	<u>Mania %</u>
<b><u>Index Mania</u></b>		
Prien 1973 (n = 104)	26	68
Bowden 2000 (n = 94)	16	22
Bowden 2003 (n = 70)	30	40
Tohen 2006 (n = 136)	48	41
Keck 2006 (n = 83)	11	12
<b><u>Index Depression</u></b>		
Prien 1973 & 74 (n = 13)	62	38
Calabrese 2003 (n = 119)	39	16

Calabrese et al 2005. n=randomized to PBO. % = proportion relapsing on placebo.

# Delaying Depressive Episodes in the Recently Manic

## - A Paradigm Shift -

- Depression robustly begets depression. Mania begets mania, but less so; depression bleeds over into the recently manic patient.
- Targeting depressive episodes in the recently manic patient represents a paradigm shift.
- Lamotrigine appeared more useful in delaying recurrence into depression in recently manic patients.

# Lithium Relapse and Recurrence Prevention -Mood Episode Relapse Rates in Recently Depressed-

	n	<u>1 - 4 mos</u>	n	<u>5 - 24 mos</u>
Lithium	18	4 (22%)	17	3 (18%)
Imipramine	13	6 (46%)	9	6 (67%)
Placebo	13	7 (54%)	9	6 (67%)

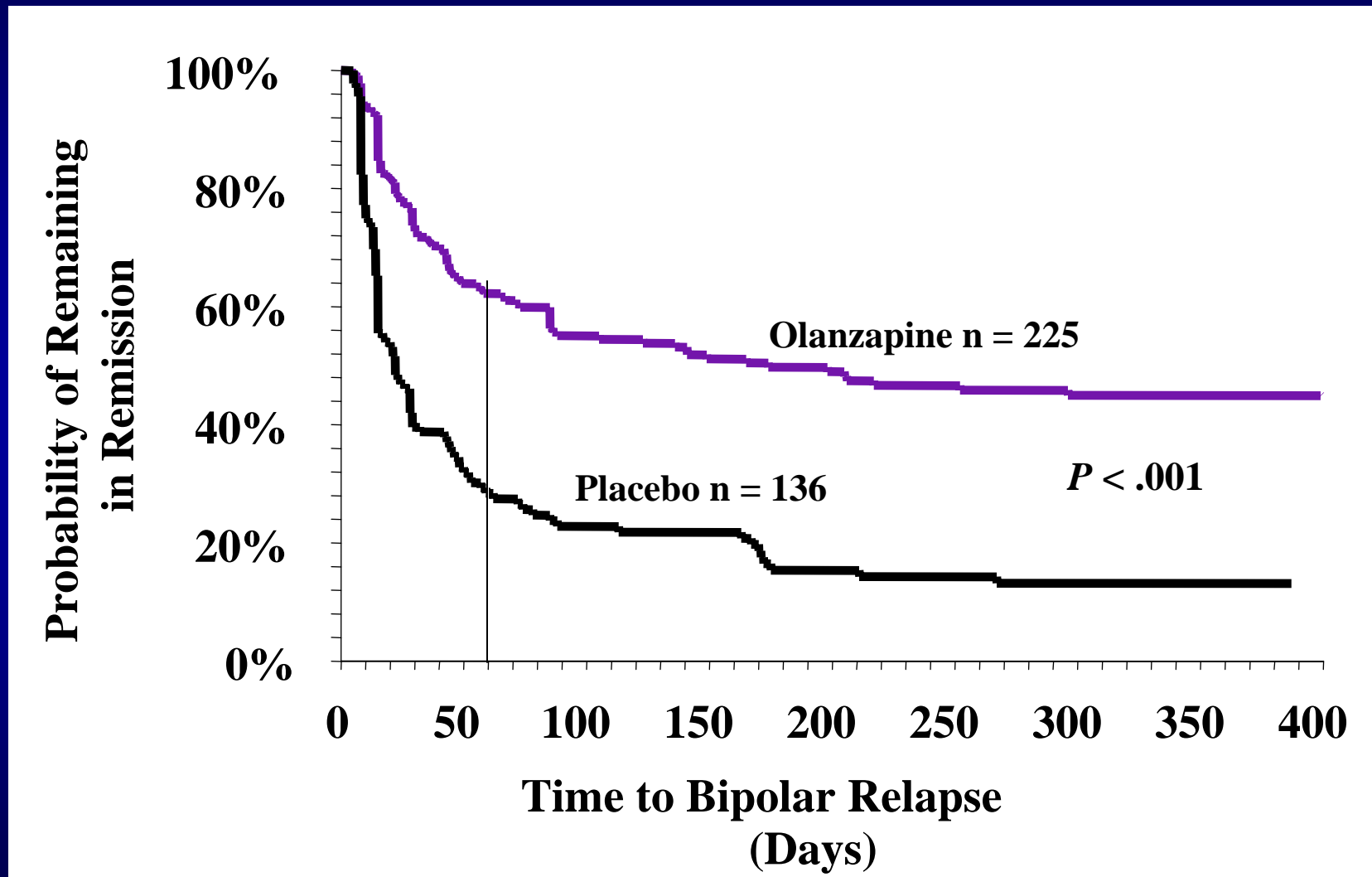
**“By removing all early mood events, a crude proxy for true prophylaxis was ascertained.”**

Prien et al. AGP 1973;29:420-5.

# OLA vs. PBO in Relapse and Recurrence Prevention

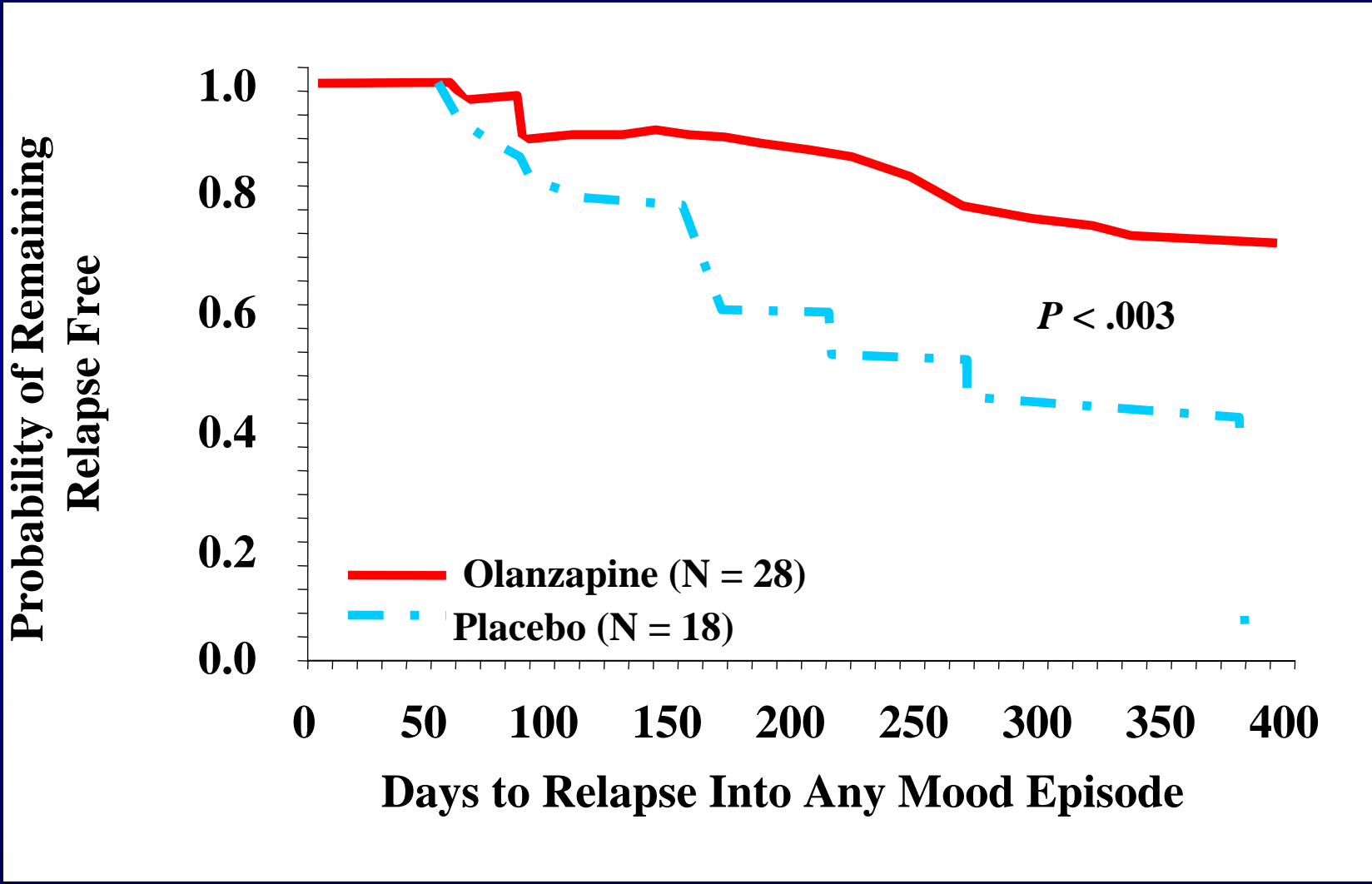
- 75% of patients assigned to placebo relapsed within 2 months after abrupt withdrawal of OLA, accounting for most of the overall drug/placebo difference.
- This is consistent with a substantial contribution of a withdrawal effect during the *continuation* phase of treatment.

# Time to Relapse Into Mania or Depression With Olanzapine Versus Placebo



Tohen M, et al. AJP. 2006;163:247-256. Response = 2 weeks Hosp or YMRS  $\geq 15$  and/or HAM-D  $\geq 15$ .

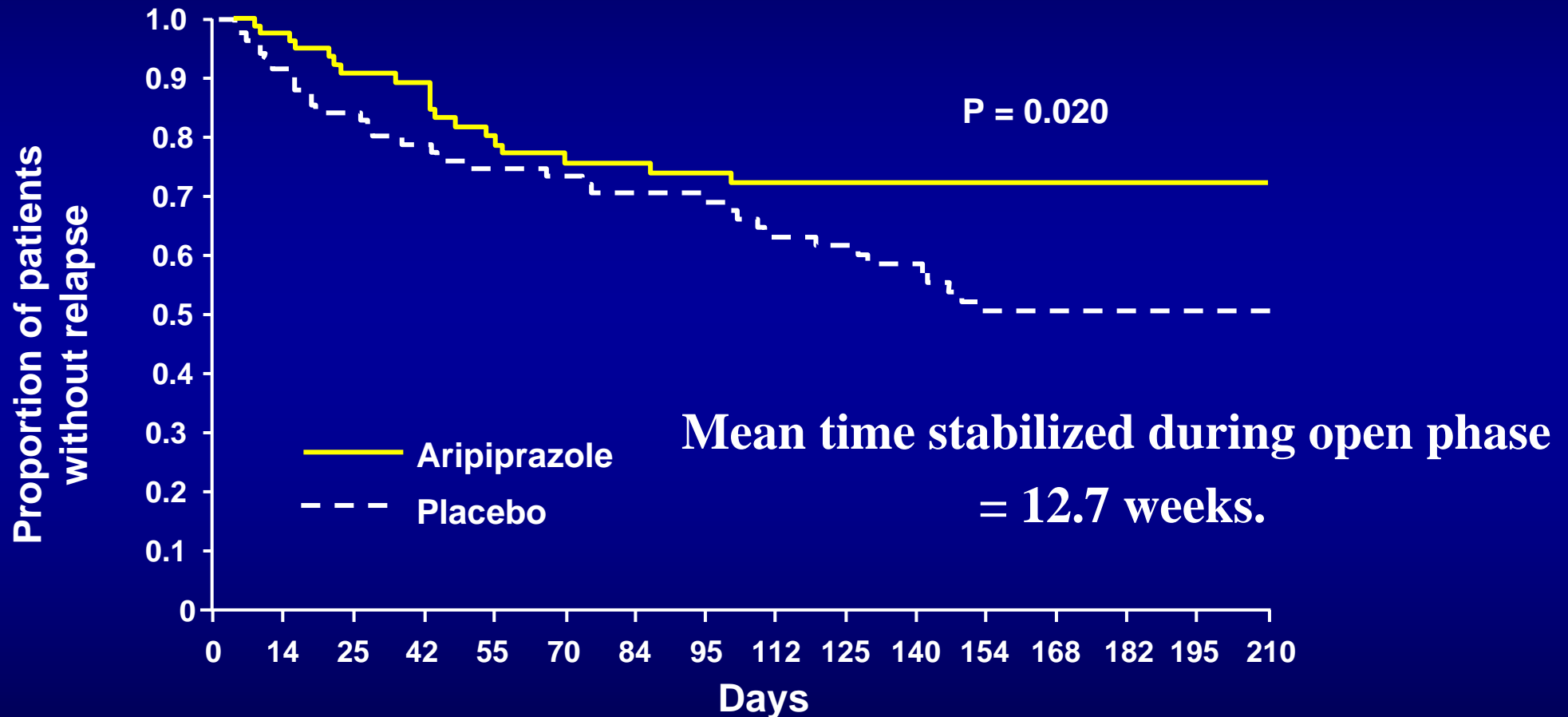
# Time to Symptomatic Relapse For the 46 Patients Still in Remission 2 Months After Randomization



Tohen M, et al. *Am J Psychiatry*. 2006;163:247-256. Hospitalization or YMRS  $\geq 15$  and/or HAM-D  $\geq 15$ .

# Aripiprazole vs. Placebo in Recently Manic

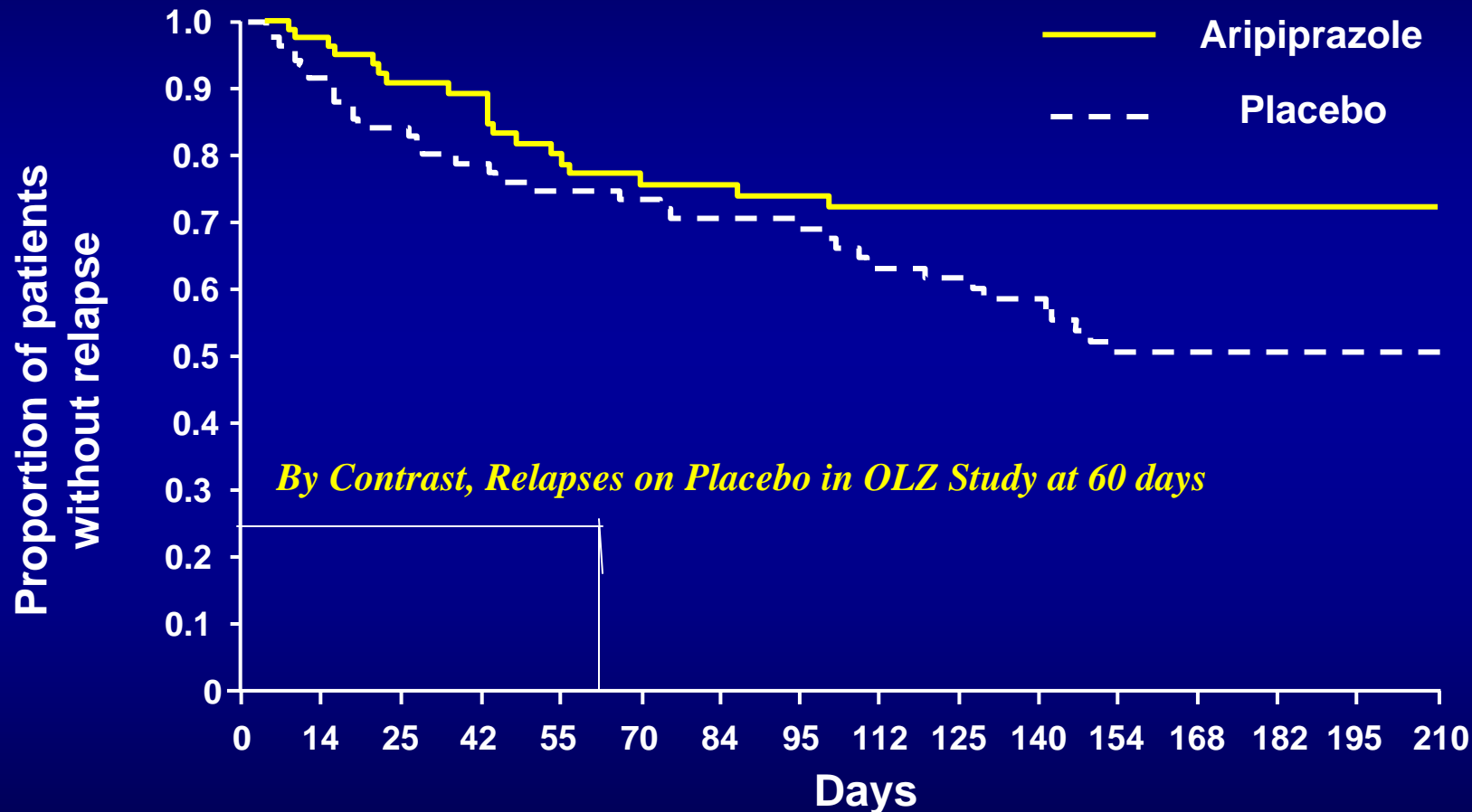
- Increasing Time Well Shifts the Hazard -



Keck et al 2006. Primary Outcome – time to relapse. Patients 48% less likely to relapse on aripiprazole.

# Aripiprazole vs. Placebo in Recently Manic

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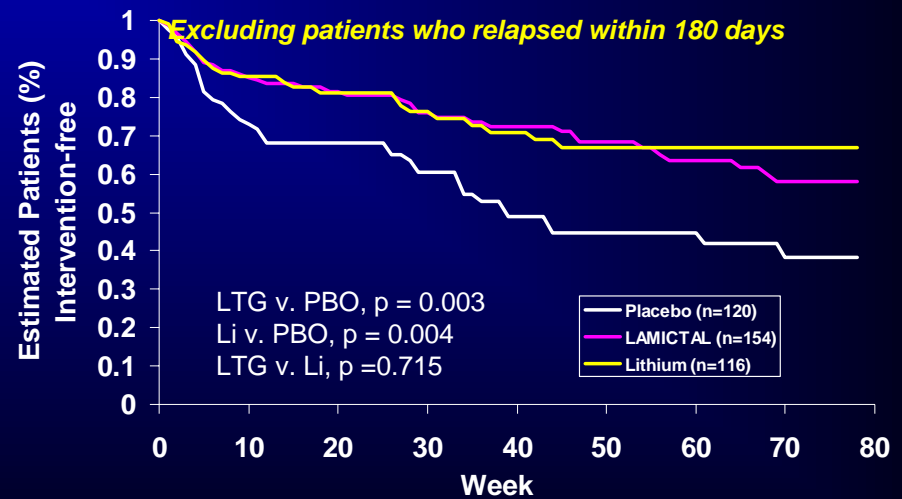
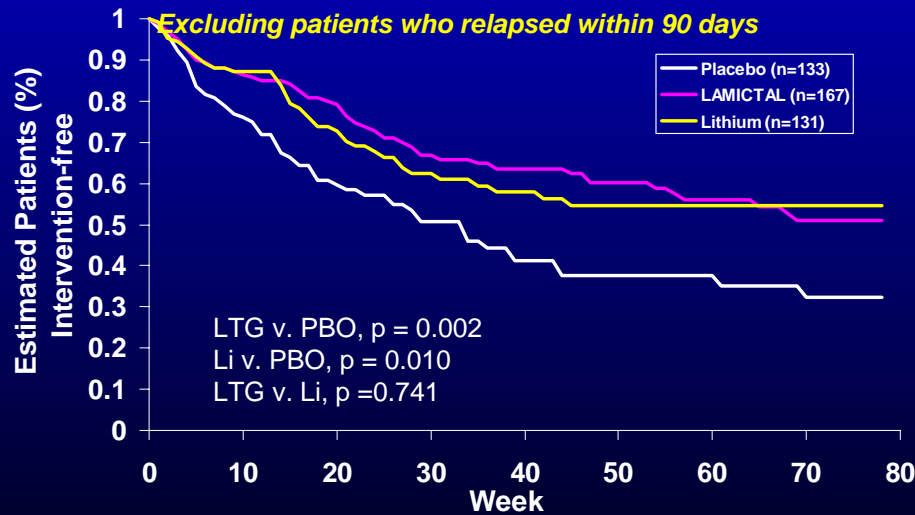
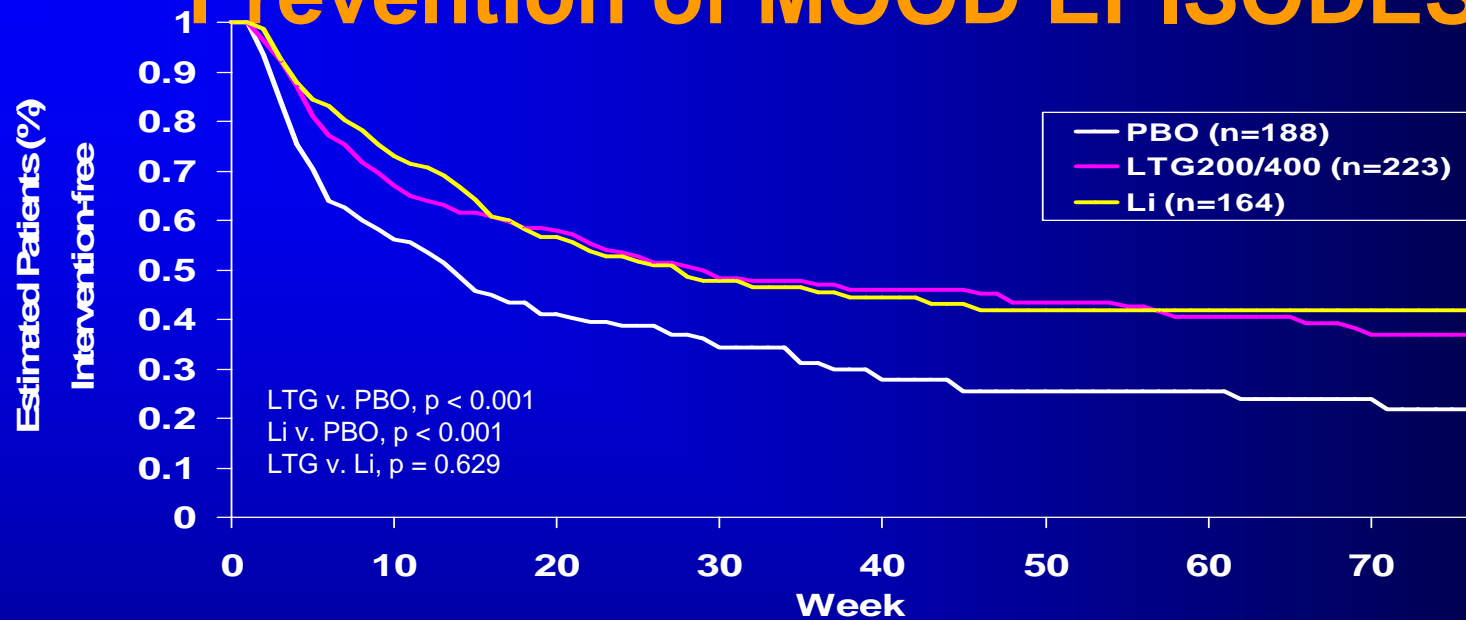
Keck et al 2006. Primary Outcome – time to relapse. Patients 48% less likely to relapse on aripiprazole.

# Post Hoc Analysis on 'Recurrence' as a Measure of True Prophylaxis

- The effect of LTG on recurrence was assessed by excluding data from patients who relapsed into the polarity of their index mood episode within 90 days or 180 days of randomization.
- Relapse is the return of symptoms during the first 8 weeks and hypothesized to imply a continuation of the index episode.
- Recurrence is the return of symptoms after 8 weeks and implies the development of a new episode.

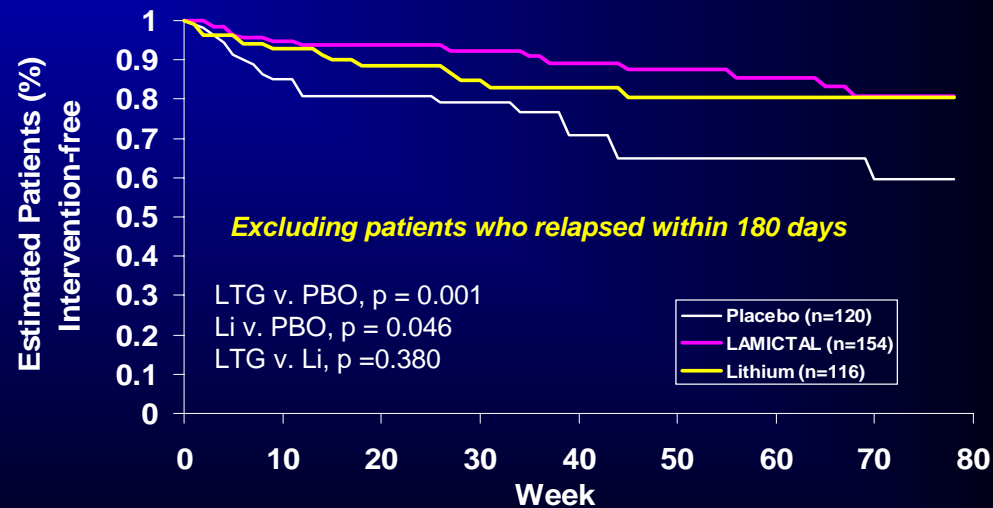
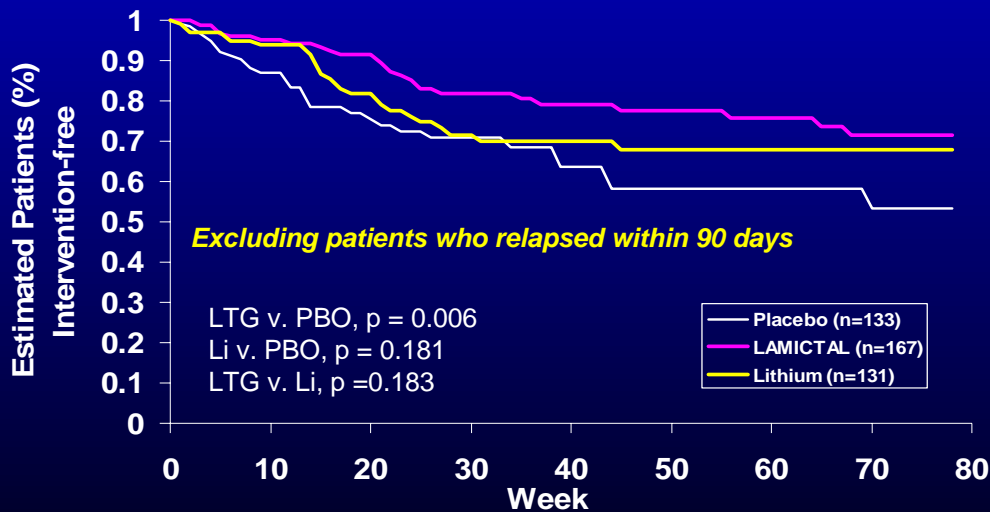
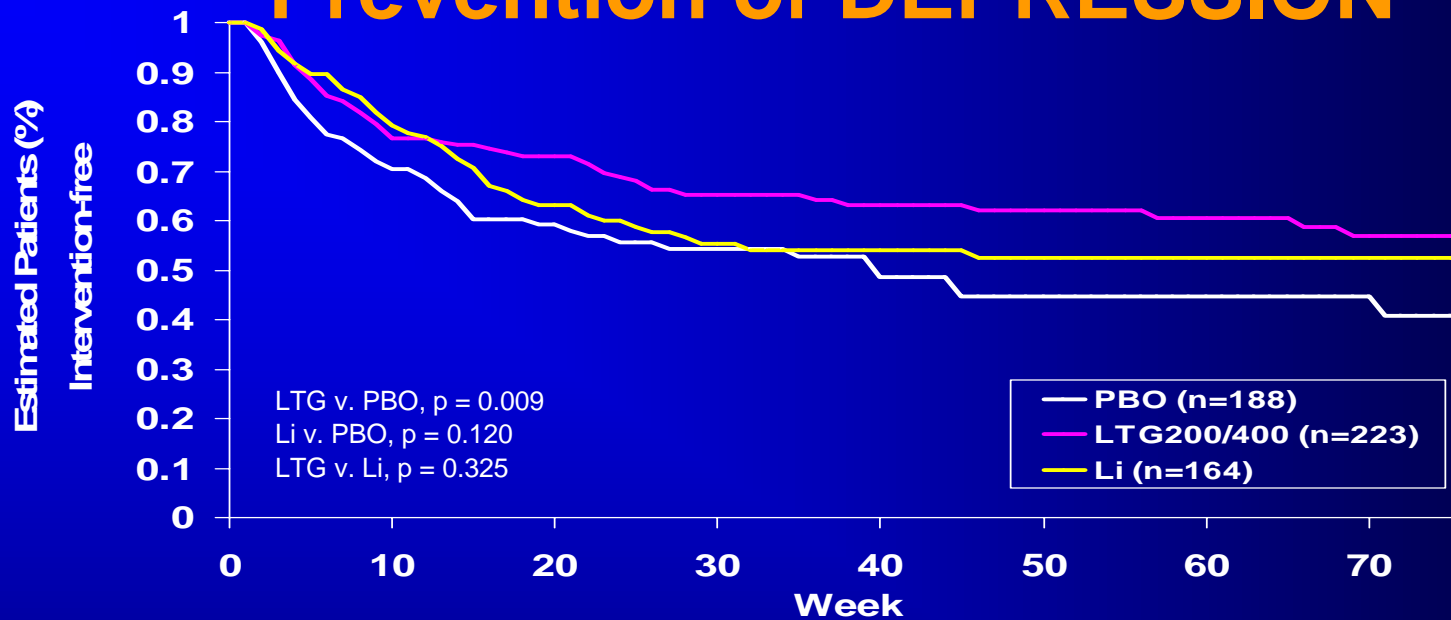
Calabrese, Goldberg, Ketter et al. Biol. Psychiatry. 2006. Frank et al 1991 and DSM.

# LAMICTAL Relapse and Recurrence Prevention of MOOD EPISODES



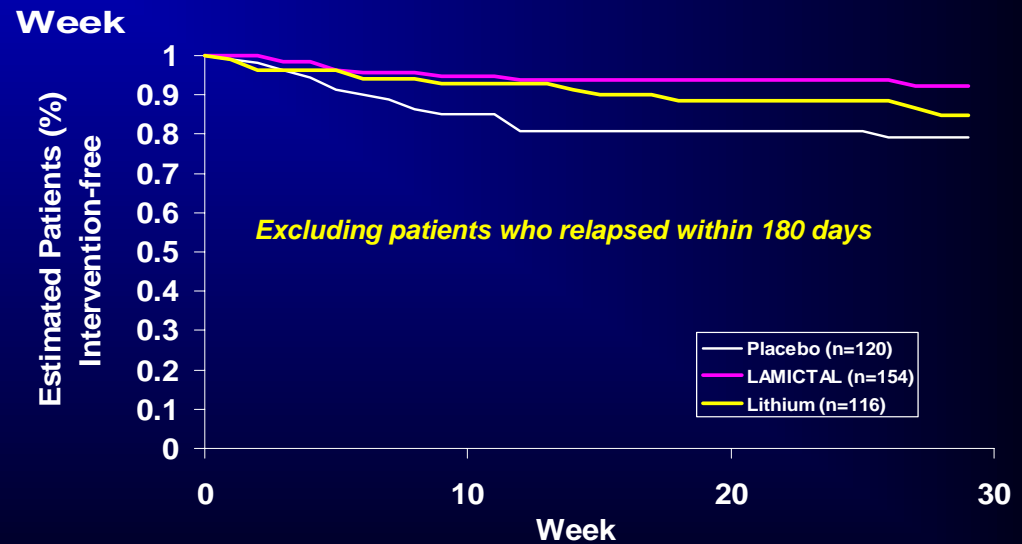
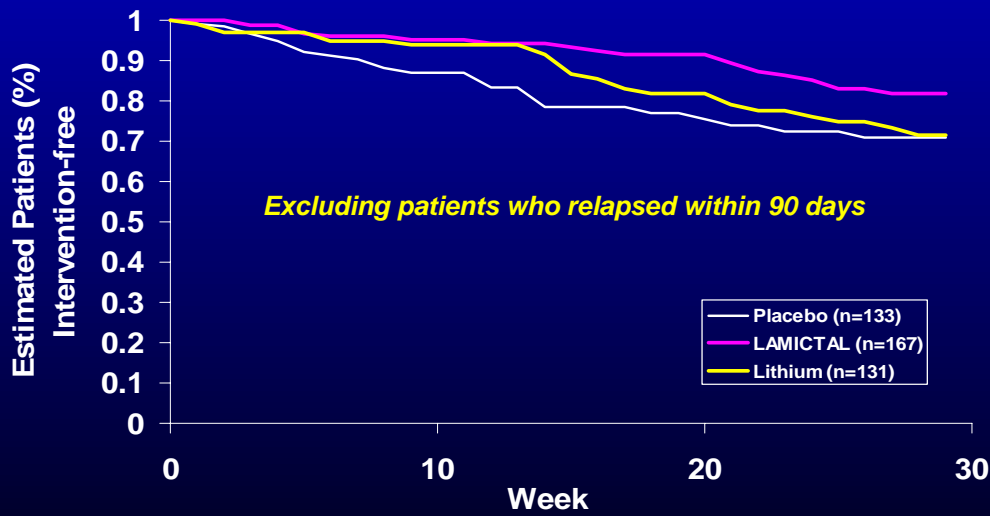
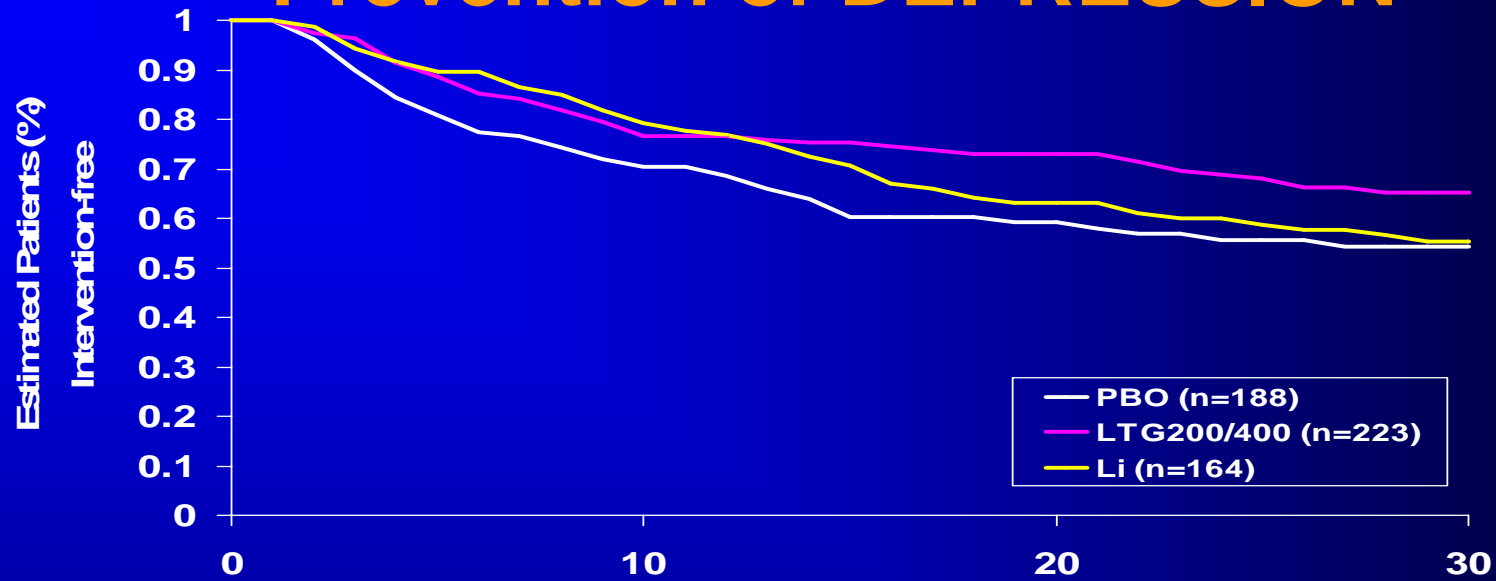
Calabrese et al 2006. Goodwin et al 2004, Bowden et al 2003. Calabrese et al 2003.

# LAMICTAL Relapse and Recurrence Prevention of DEPRESSION



Calabrese et al 2006. Goodwin et al 2004. Bowden et al 2003. Calabrese et al 2003.

# LAMICTAL Relapse and Recurrence Prevention of DEPRESSION



Adapted from Calabrese et al. Biol. Psychiatry 2006.

# PBO Relapse and Recurrence Prevention -Distribution of TIME Events by Polarity-

