Newcastle University

Psychobiology Research Group

Guidelines for the Pharmacological Management of Bipolar Disorder

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Declaration of Interests

- I have received:
  - Speaker fees from:
    - Astra Zeneca, BMS, Eli Lilly, GSK, Janssen-Cilag, Lundbeck, Organon, Pfiser, Wyeth
  - Consultancy fees from:
    - Astra Zeneca, BMS, Eli Lilly, Janssen-Cilag, Lundbeck, Wyeth
  - Independent investigator led research support from:
    - Astra Zeneca, Eli Lilly and Wyeth

BAP Guidelines for the Management of Bipolar Disorder

G.M. Goodwin "Evidenced based guidelines for treating bipolar disorder: recommendations from the BAP." J Psychopharmacology 17(2) 2003 149-173

National Institute for Clinical Excellence

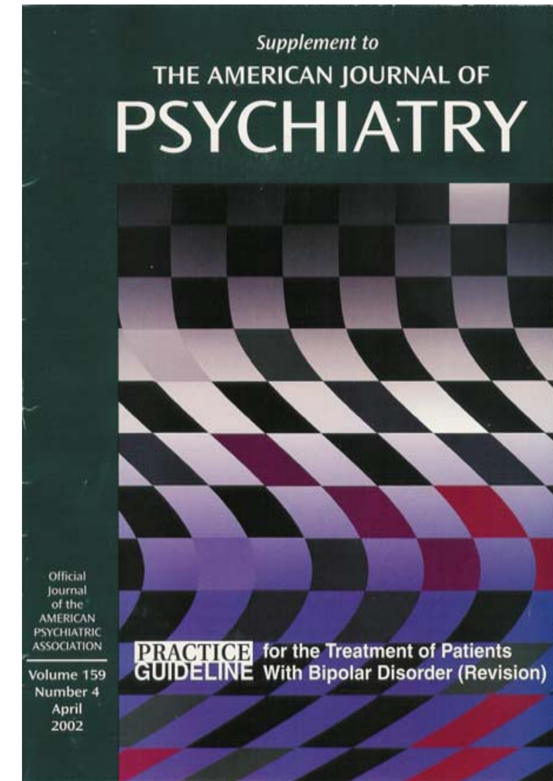
NICE Clinical Guideline

July 2006

Bipolar Disorder: The management of bipolar disorder in adults, children and adolescents, in primary and secondary care

Practice Guidelines for the Treatment of Patients with Bipolar Disorder

Hirschfeld et al., Am. J. Psychiatry 2002



TEXAS
Department of State Health Services

The Texas Implementation of Medication Algorithms (TIMA): Update to the algorithms for treatment of bipolar I disorder

Suppes et al. 2005 J. Clin. Psychiatry 66:870-886

THE JOURNAL OF
CLINICAL PSYCHIATRY
VOLUME 66 AUGUST 2005 NUMBER 8

CME PRETEST 963 CME POSTTEST 1082

ORIGINAL ARTICLES

964 Antidepressant Exposure May Protect Against Decrement in Frontal Gray Matter Volumes in Geriatric Depression.
Helen Lavretsky, Donna J. Roybal, Martina Ballmaier, Arthur W. Toga, and Anand Kumar

968 Clinical Utility of Magnetic Resonance Imaging Radiographs for Suspected Organic Syndromes in Adult Psychiatry.
Stephen M. Erhart, Alexander S. Young, Stephen R. Marder, and Jim Mintz

974 Remission Rates Following Antidepressant Therapy With Bupropion or Selective Serotonin Reuptake Inhibitors: A Meta-Analysis of Original Data From 7 Randomized Controlled Trials.
Michael E. Thase, Barbara R. Haight, Nathalie Richard, Carol B. Rockett, Melinda Mitton, Jack G. Modell, Susan VanMeter, April E. Harriett, and Yonghua Wang

982 Association Between Pain and Depression Among Older Adults in Europe: Results From the Aged in Home Care (AdHOC) Project: A Cross-Sectional Study.
Graziano Onder, Francesco Landi, Giovanni Gambassi, Rosa Liperoti, Manuel Soldato, Chiara Catananti, Harriet Finne-Soveri, Cornelius Katona, Iain Carpenter, and Roberto Bernabei

989 Improved Sleep Continuity and Increased Slow Wave Sleep and REM Latency During Ziprasidone Treatment: A Randomized, Controlled, Crossover Trial of 12 Healthy Male Subjects.
Stefan Cohrs, Andreas Meier, Anne-Catharina Neumann, Wolfgang Jordan, Eckart Rüther, and Andrea Rodenbeck

997 A Trial of Compliance Therapy in Outpatients With Schizophrenia or Schizoaffective Disorder.
Matthew J. Byerly, Robert Fisher, Thomas Carmody, and A. John Rush

1002 Clinical and Demographic Features of Atypical Depression in Outpatients With Major Depressive Disorder: Preliminary Findings From STAR*D. [CME]
*Jon S. Novick, Jonathan W. Stewart, Stephen R. Wisniewski, Ian A. Cook, Radaela Manev, Andrew A. Nierenberg, Jerrold F. Rosenbaum, Kathy Shores-Wilson, G. K. Balasubramani, Melanie M. Biggs, Sid Zisook, and A. John Rush, for the STAR*D Investigators*

1012 Topiramate Add-On in Treatment-Resistant Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled, Crossover Trial.
Jari Tiihonen, Pirjo Halonen, Kristian Wahlbeck, Eila Repo-Tiihonen, Soile Hyvärinen, Markku Eronen, Hannu Putkonen, Pirjo Takala, Olli-Pekka Mehtonen, Martin Puck, Jorma Oksanen, Pasi Koskelainen, Grigori Joffe, Juhani Aer, Tero Hallikainen, Olli-Pekka Ryynänen, and Erkki Tupala

1016 Symptomatic Remission in Patients With Bipolar Mania: Results From a Double-Blind, Placebo-Controlled Trial of Risperidone Monotherapy.
Srihari Gopal, David C. Steffens, Michelle L. Kramer, and Maren K. Olsen

1021 Response and Relapse in Patients With Schizophrenia Treated With Olanzapine, Risperidone, Quetiapine, or Haloperidol: 12-Month Follow-Up of the Intercontinental Schizophrenia Outpatient Health Outcomes (IC-SOHO) Study.
Martin Dossenbach, Cesar Arango-Dávila, Herman Silva Ibarra, Eric Landa, Jaime Aguilar, Osvaldo Caro, Joanna Leadbetter, and Sheila Assunção

1031 Posttraumatic Stress Disorder Among Israeli Ex-Prisoners of War 18 and 30 Years After Release. [CME]
Zahava Solomon and Rachel Dekel

1038 An Open Study of Triiodothyronine Augmentation of Selective Serotonin Reuptake Inhibitors in Treatment-Resistant Major Depressive Disorder.
Dan V. Iosifescu, Andrew A. Nierenberg, David Mischoulon, Roy H. Perlis, George I. Papakostas, Julie L. Ryan, Jonathan E. Alpert, and Maurizio Fava

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Guidance

- Common aspects of care for all people with bipolar disorder
- Assessment, recognition and diagnosis
- Treatment setting and pathways to care
- Physical care
- Treatment and management of bipolar disorder
- Long-term management
- Treatment and management of women of child-bearing potential
- Assessment, diagnosis and treatment of children and adolescents

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Common aspects of care

- Information and informed consent
  - Provide good information re disorder
  - Collaborative working
  - Information about self-help groups
- Psychological principles
  - Therapeutic relationship
  - Identify early warning signs
  - Advice re life style
- Appropriate language and written material
- Support for families
- Advanced statements
- Comorbid personality disorder
- Drugs and alcohol

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Treatment setting and pathways to care

NHS
National Institute for Clinical Excellence

- Long-term illness needing long-term care
- Integrated primary / secondary care programmes
- Primary care registers and telephone support
- CMHTs for:
  - Problems engaging with services, poor adherence
  - Frequent relapses, poor symptom control, poor functioning, comorbid anxiety
  - Substance misuse
  - Significant risk
- EIP, CAT, AO, IP, day hospitals, rehab. should all be available
- Trusts providing specialist mental health care should ensure that clinicians have access to specialist advice

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Physical care

- At presentation
  - Smoking and alcohol history
  - Renal function, LFTs, TFTs, FBC, Glucose, lipids
  - BP, height and weight
  - Consider ECG, CXR, drug screening, EEG, CT, MRI
- Annual review
- Management of weight gain
  - Diet, exercise, diet clinic, dietician
  - Sibutramine and topiramate NOT recommended

Physical care

- Antipsychotics
  - At initiation: wt, ht, gluc, lipids, (ECG and prolactin)
  - Monitoring: wt every 3/12 for 1 yr, gluc and lipids at 3/12 (olanz at 1/12), prolactin if indicated
  - Be aware of NMS and DKA
- Lithium
  - Not for primary care
  - Warn re probs of stopping
  - Renal, TFT, ht and wt (ECG, FBC)
  - Levels 0.6 – 0.8 (or 0.8 – 1.0 if poor response)
  - Warn re NSAIDs

Physical care

- Valproate
  - At initiation and 6/12: Ht, wt, FBC, LFTs
  - Not for women under 18 or of child baring potential
  - Levels if ineffective, poor adherence or toxicity
- Lamotrigine
  - Slow titration (N.B. S-JS)
  - Beware interaction with OCP
- Carbamazepine
  - Only on specialist advice
  - At initiation: FBC, LFTs, ht and wt (repeat at 6/12 with U&Es)
  - Levels every 6 months
  - Beware interaction with OCP

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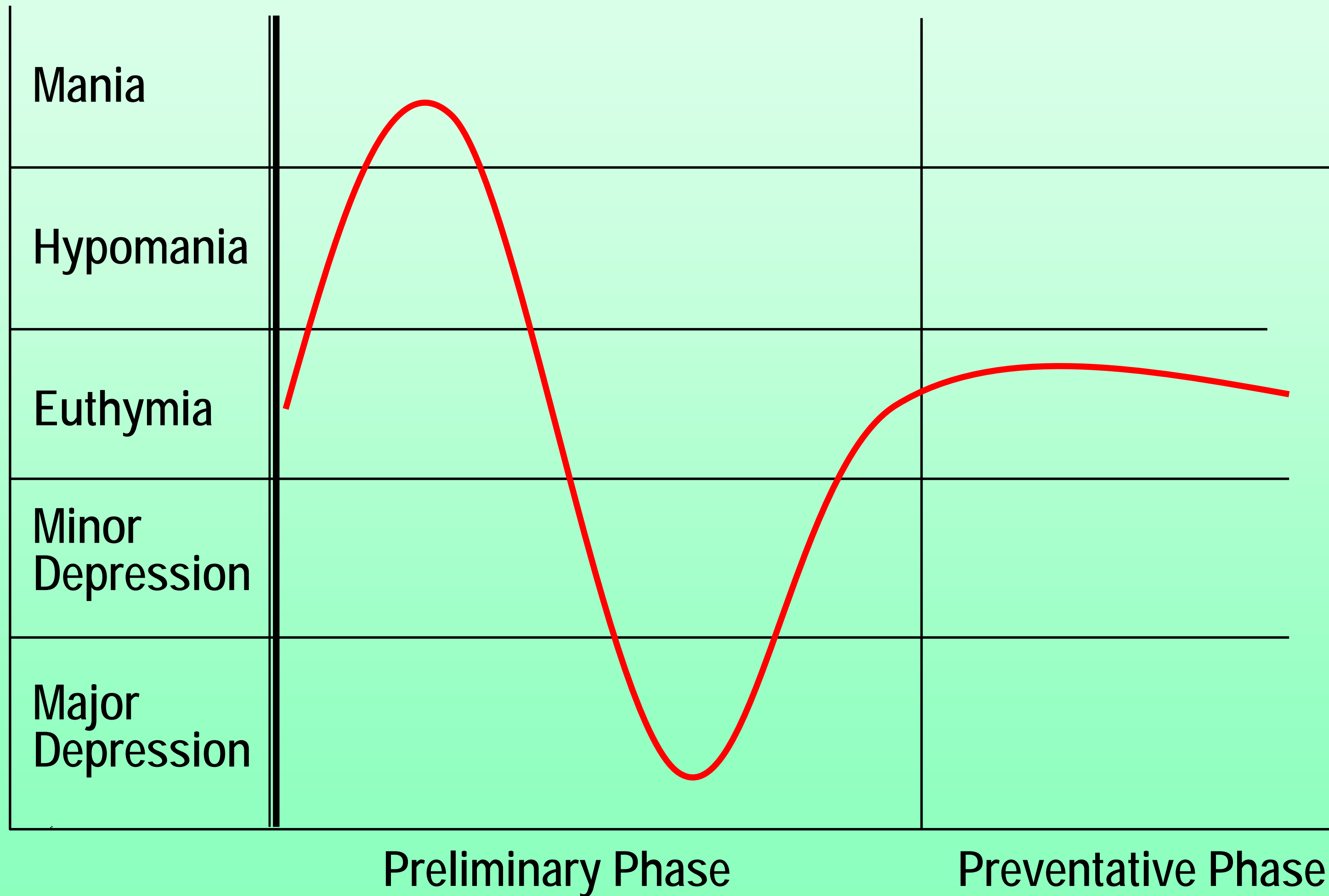
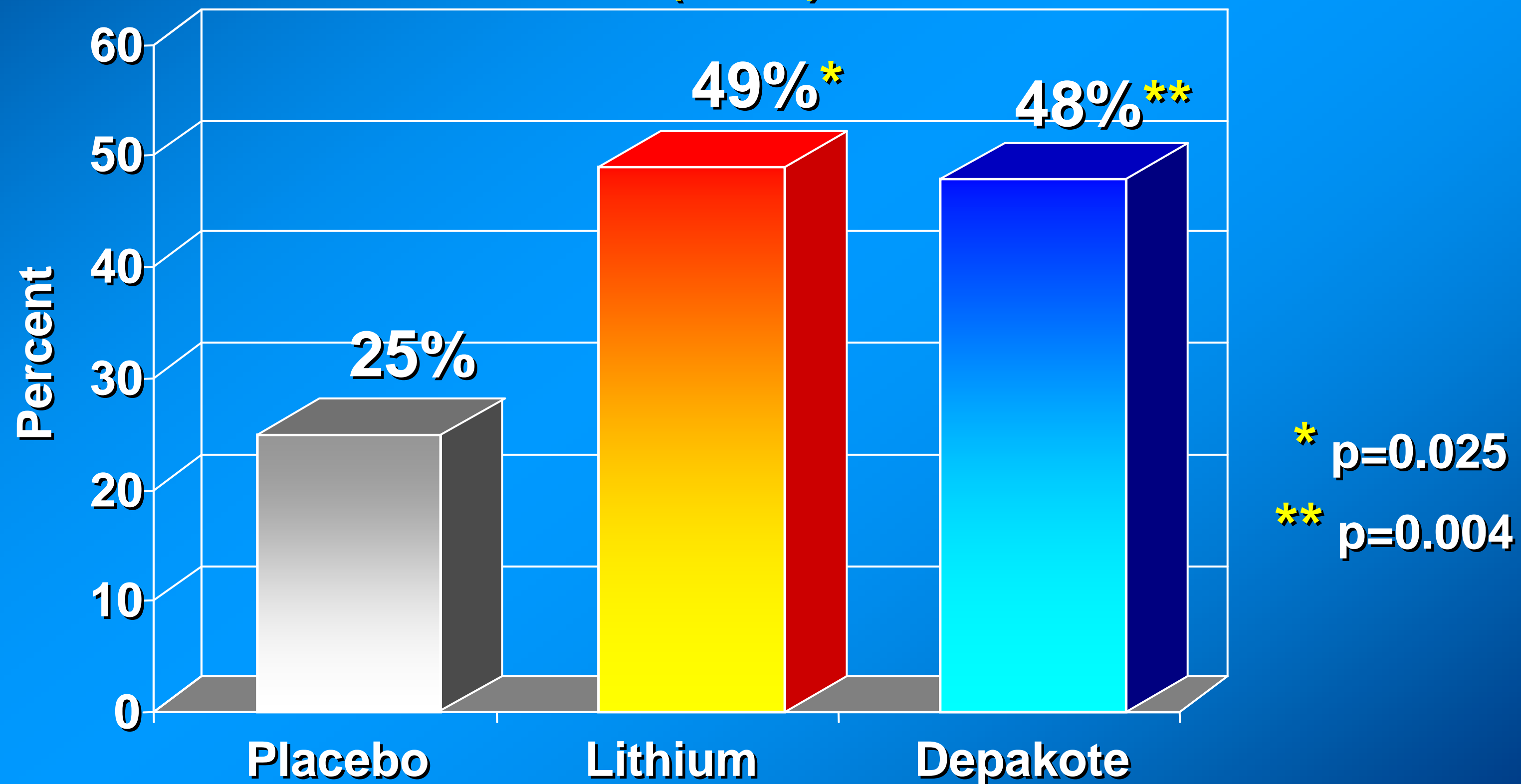
The course of Bipolar Disorder

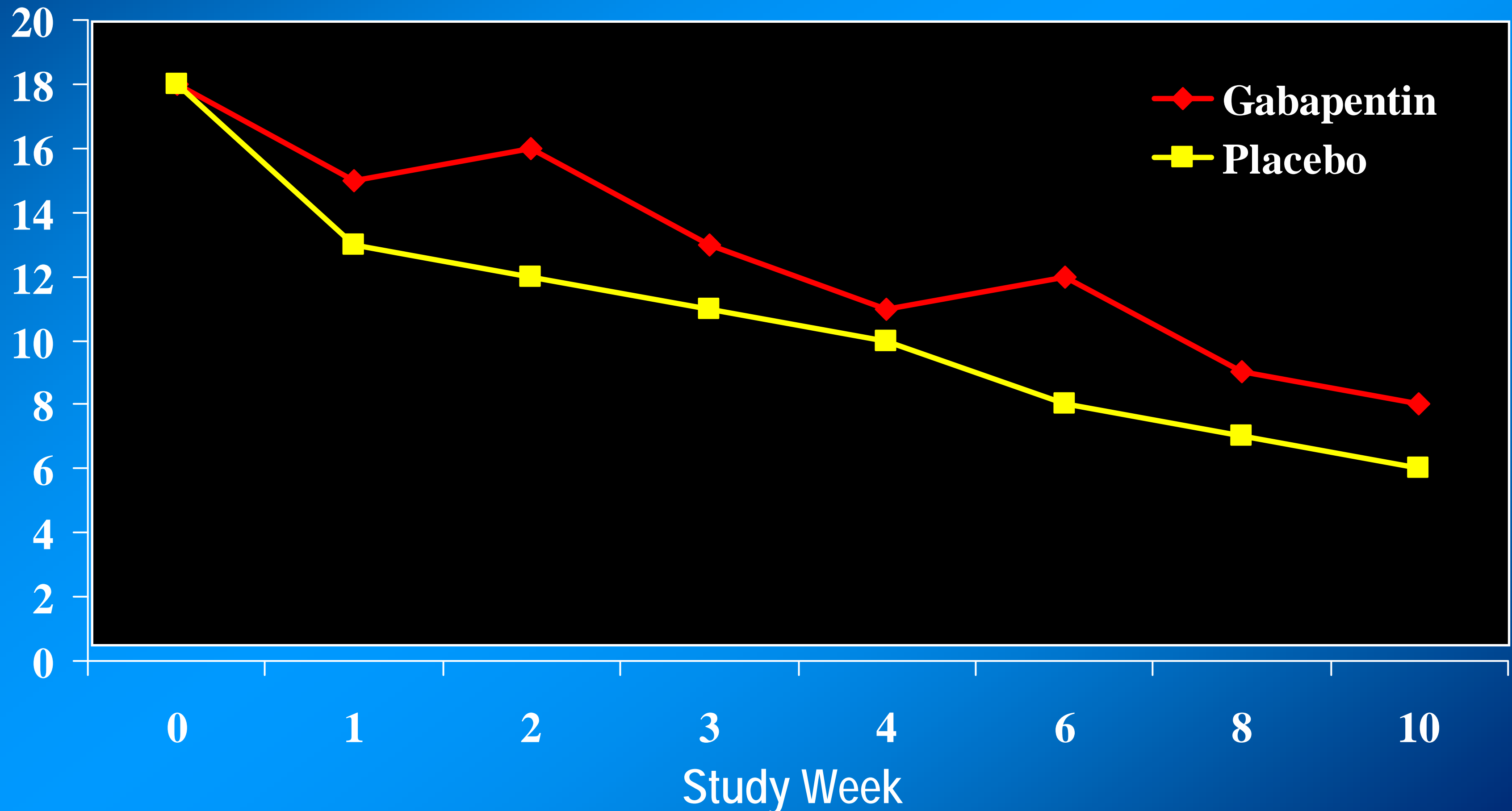


Valproate and Lithium in acute mania
Bowden et al 1994



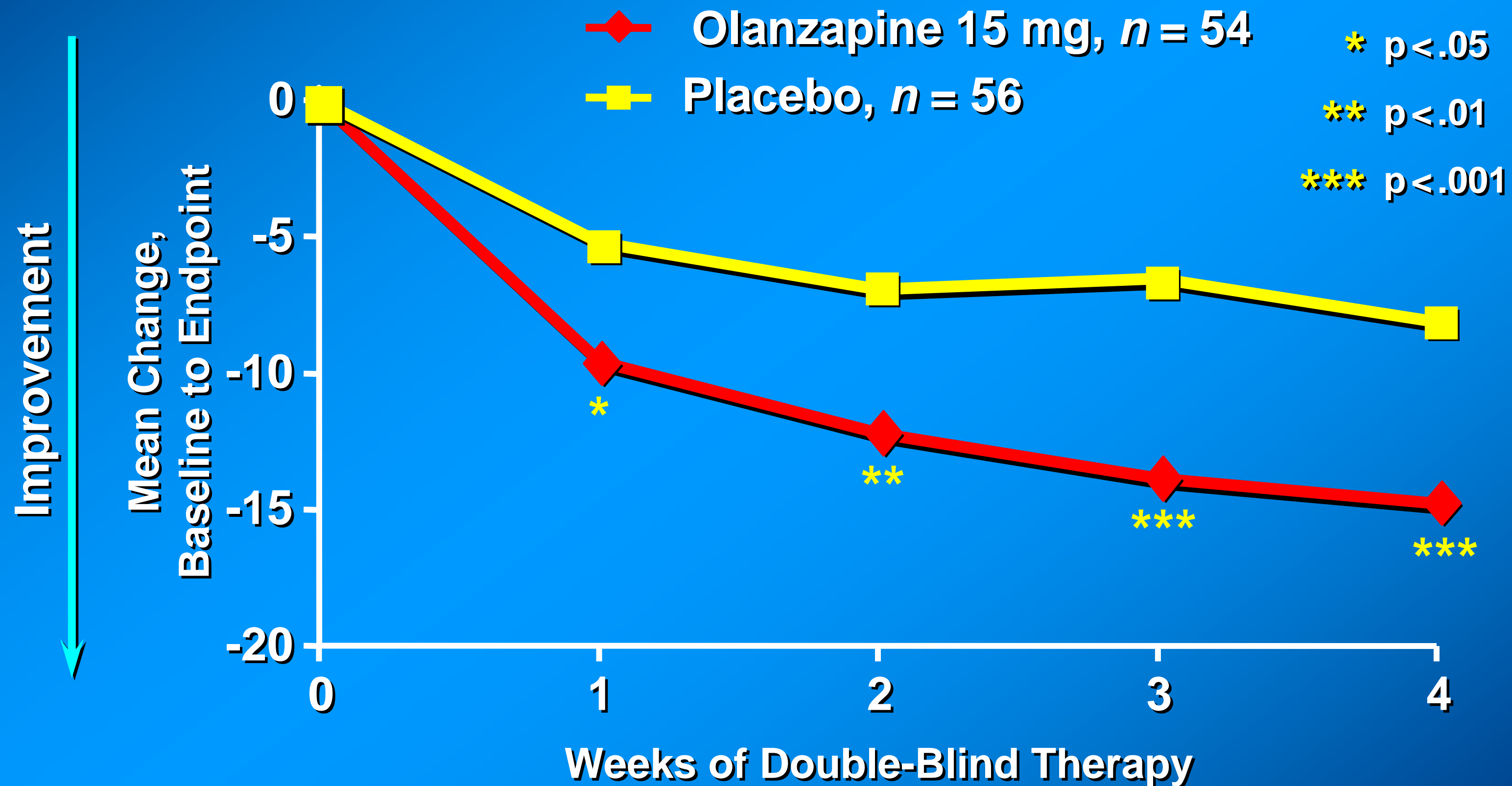
N.B. Efficacy of Depakote independent to prior responsiveness to Lithium

Gabapentin vs Placebo



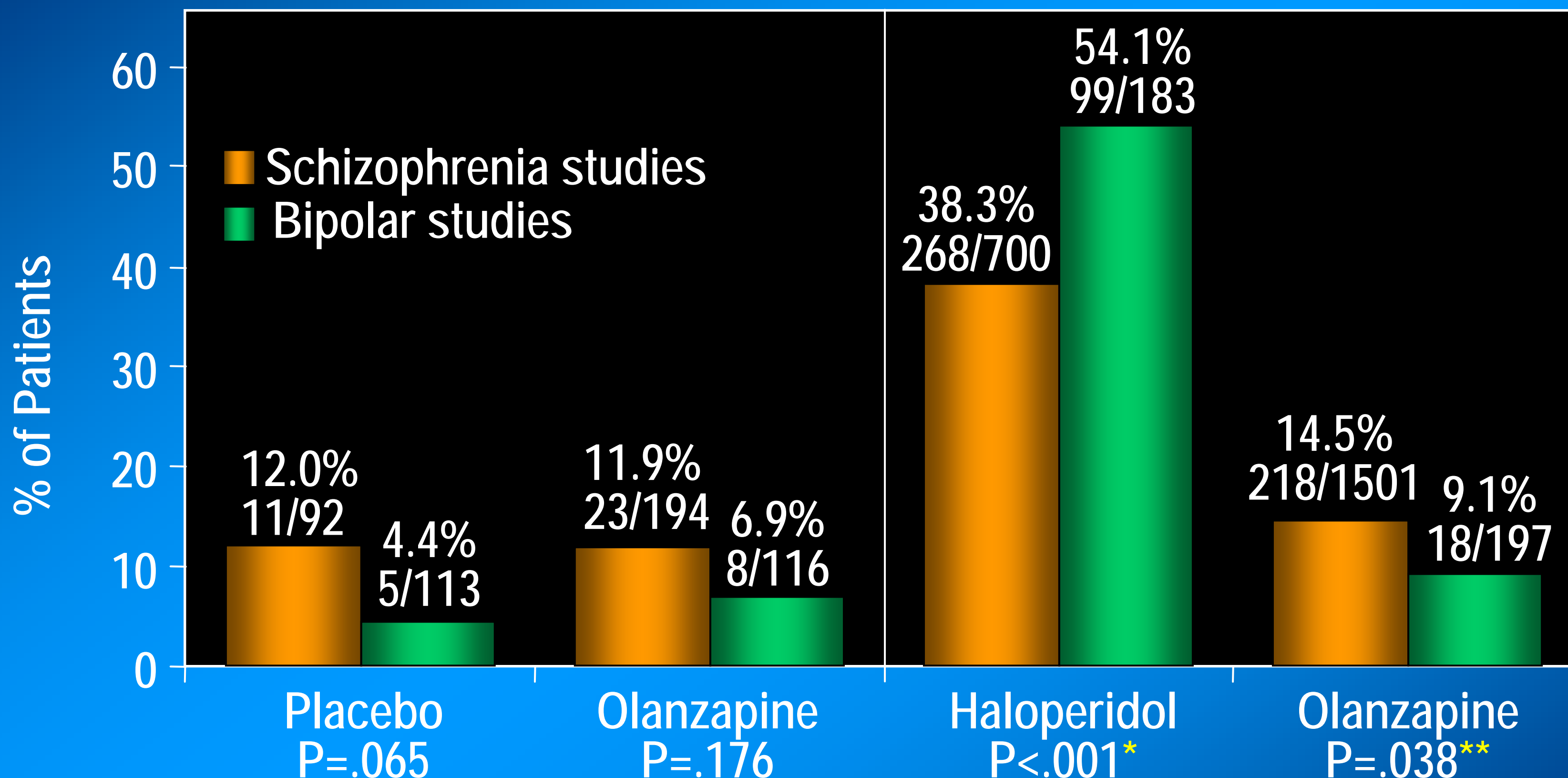
Pande AC, et al. *J Clin Psychopharmacol.* 1999;19(4):341-348.

Olanzapine: Mania, acute treatment



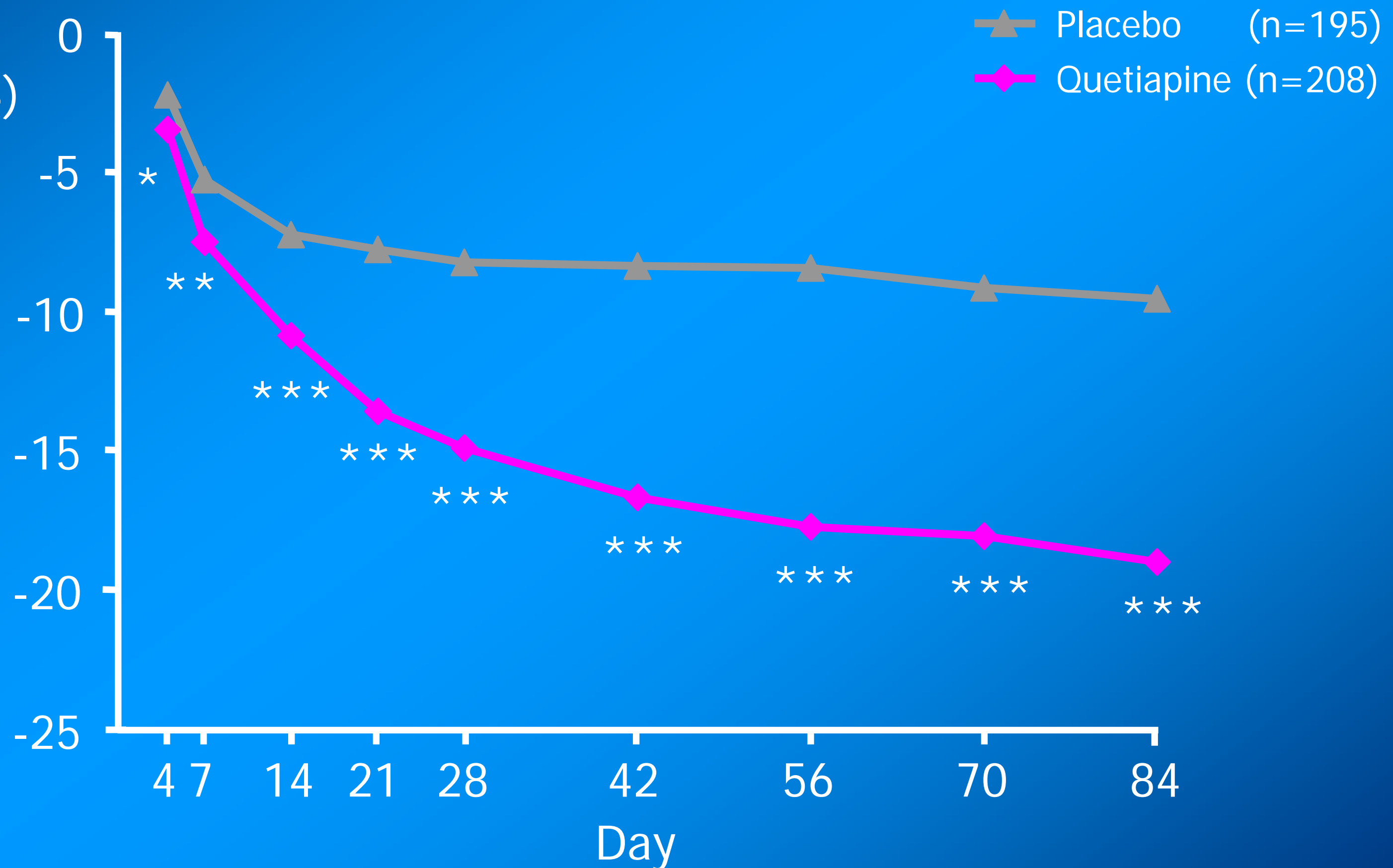
Compared to placebo, olanzapine patients had a statistically significantly greater LOCF mean improvement at week 1 which was maintained throughout the study

Treatment-Emergent Parkinsonism†: Categorical Analysis of Simpson-Angus Scale



*Haloperidol was associated with significantly higher rates of EPS in the bipolar group.
**Olanzapine was associated with significantly lower rates of EPS in the bipolar group.
†Defined as a score on the Simpson-Angus Scale of ≤3 at baseline >3 anytime thereafter.

Quetiapine: Mania, acute treatment

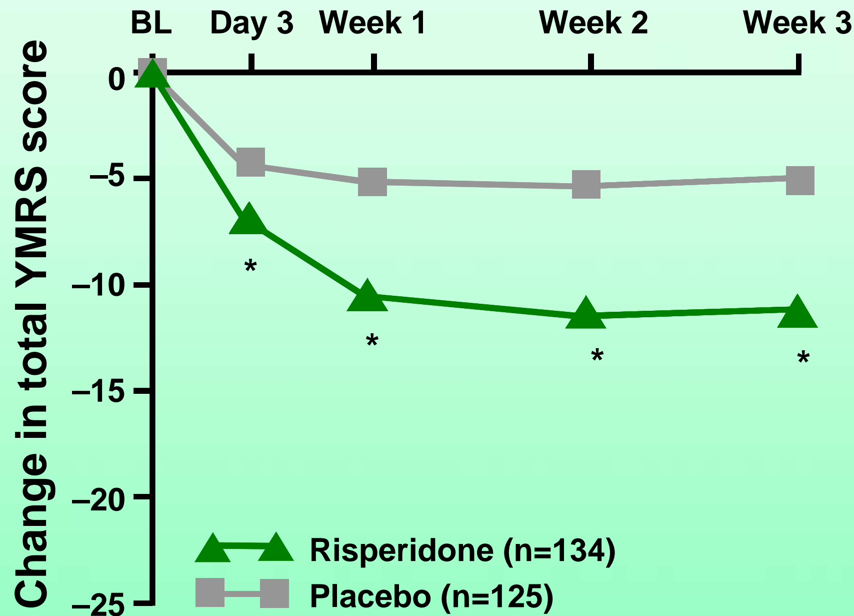


Study 104 + 105

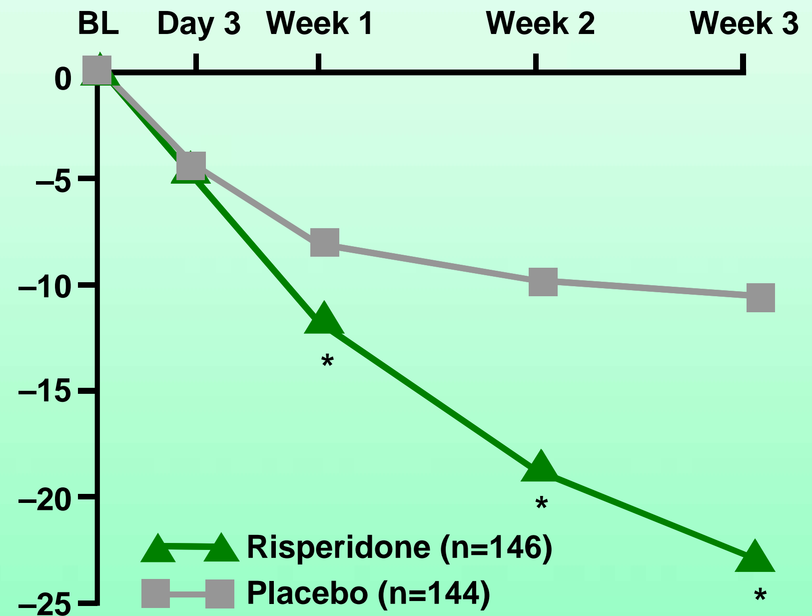
***p<0.05; **p<0.01; ***p<0.001**

Brecher & Huizar 2003; Paulsson & Huizar 2003; Jones & Huizar 2003

Risperidone studies in the acute treatment of mania



Median dose 4mg/day
BL: Risperidone = 29.1; placebo = 29.2

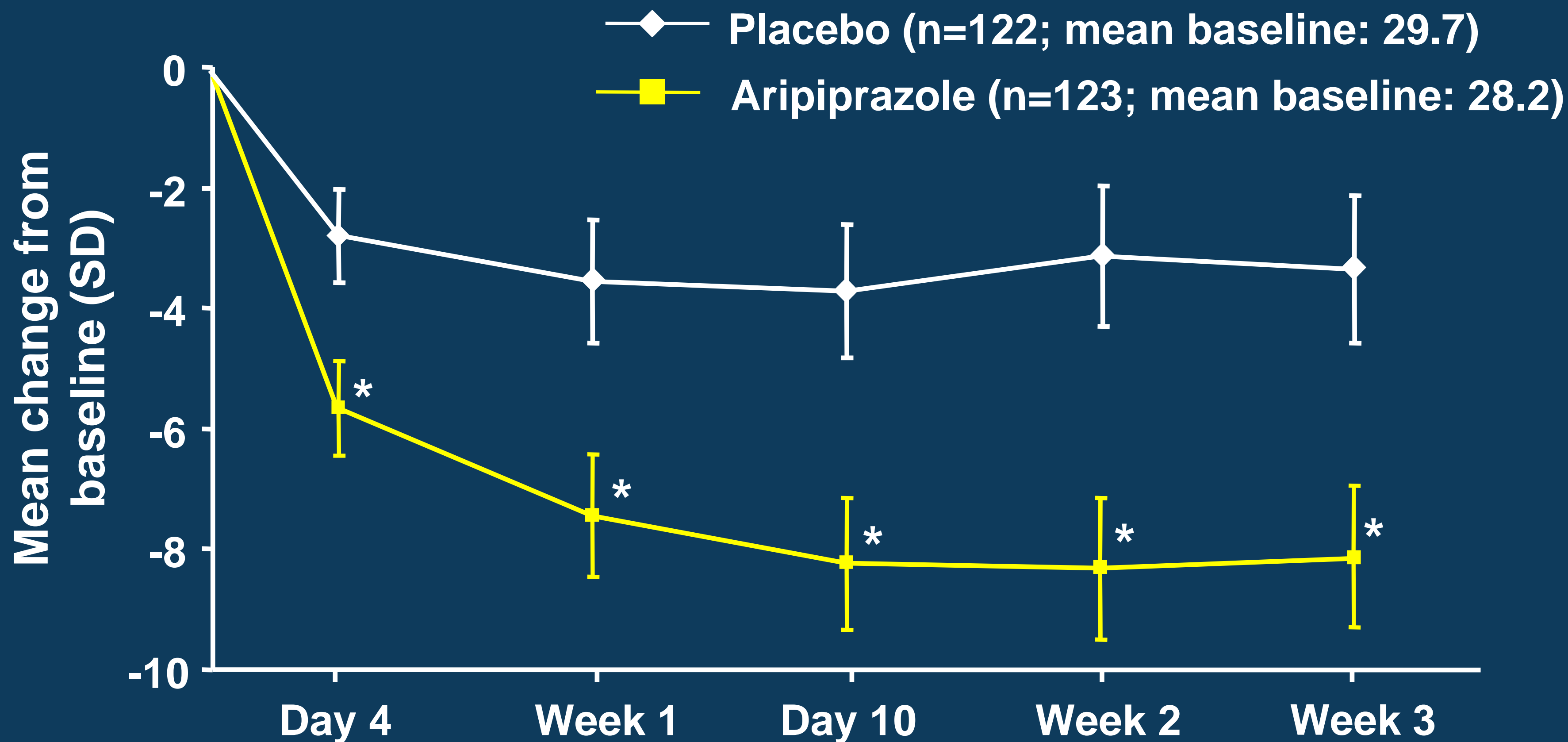


Median dose 6mg/day
BL: Risperidone = 37.4; placebo = 37.0

LOCF analysis; *P<0.001 risperidone vs placebo; Hirschfeld RM, et al. Am J Psychiatry 2004;161:1057–65

LOCF analysis; *P<0.01 risperidone vs placebo; Khanna et al. Brit J Psychiatry 2005;187, 229-34

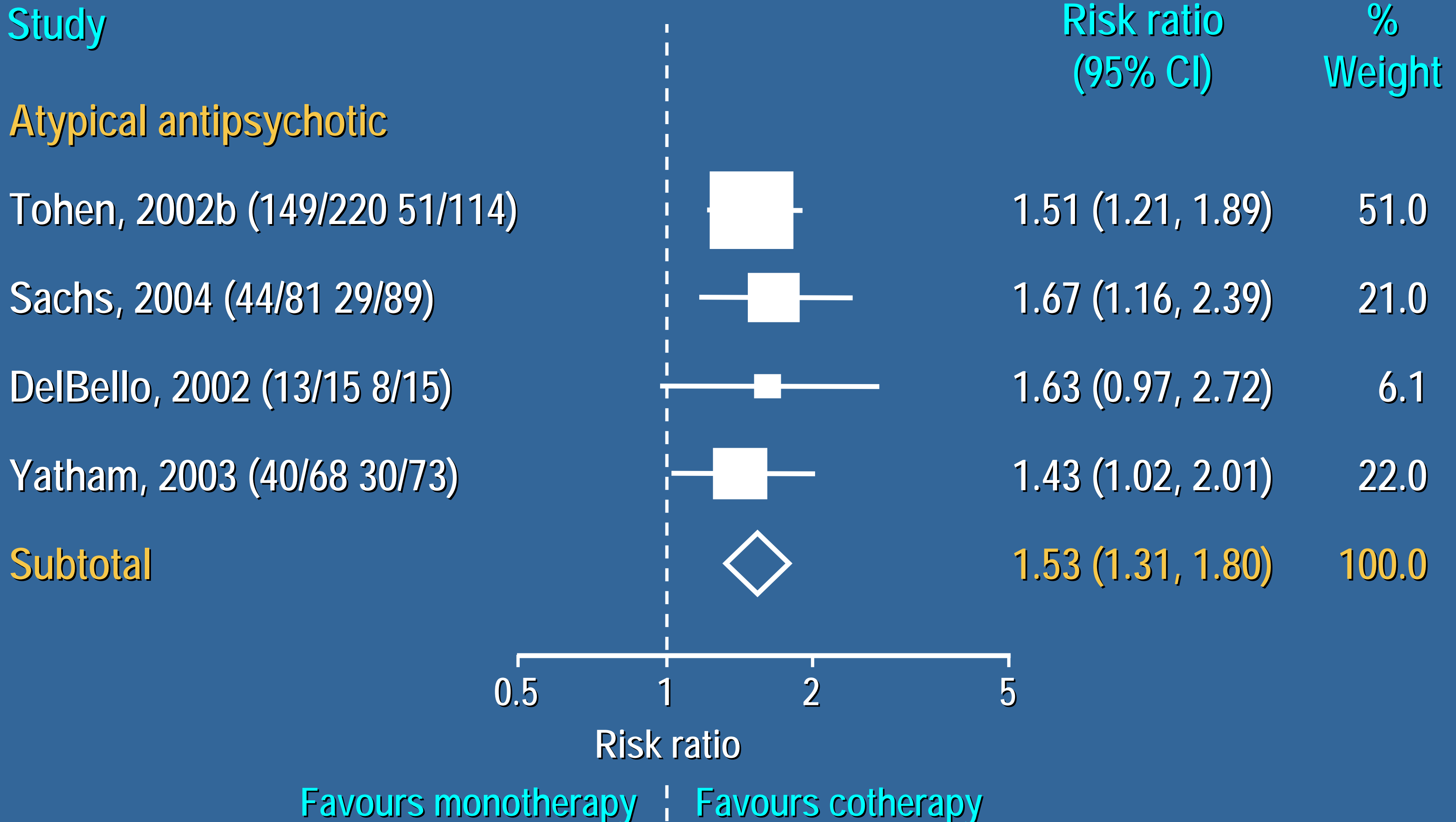
Aripiprazole in Acute Mania: Mean Change From Baseline in YMRS



*$P<0.01$ vs placebo, LOCF analysis.

Keck et al.; *Am J Psych*, in press

Cotherapy vs monotherapy in mania



Acute Mania:
Those not on anti-manic treatment

- Atypical antipsychotic (olanzapine, risperidone, quetiapine) for those with severe mania
  - If ineffective consider adding Li or valproate
- Valproate or Li if previous good response and compliance
  - Avoid valproate in women of child baring potential
  - Li only if less severe
- Don’t use carbamazepine routinely and avoid gabapentine, lamotrigine and topiramte

Acute Mania:
Those on anti-manic treatment

- Optimise treatment
  - Li level 0.8-1.0
  - Valproate to max. licensed dose (depending on SEs)
  - Don’t generally increase carbamazepine
- Add olanzapine, risperidone or quetiapine

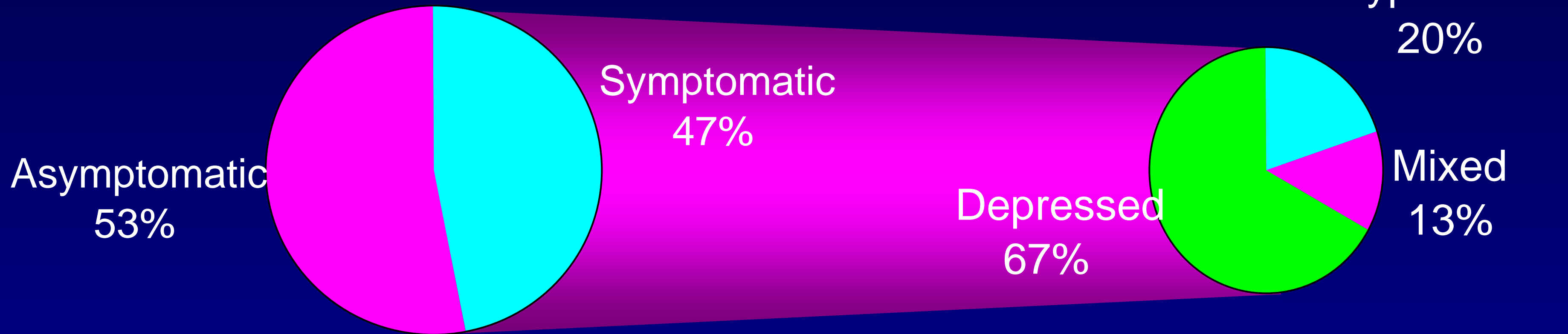
Guideline Evolution: Acute mania

- Place of antipsychotics has changed:
  - Only in combination (APA)
  - Alternative to Li or valproate (BAP, TIMA)
    - NB olanzapine “1B” in TIMA
  - Main first line option (NICE)
- Valproate has had extra cautions added by NICE
- Carbamazepine has been downgraded
  - level “1B” (TIMA)
  - Only on specialist recommendation (NICE)
- Second line fairly consistent
  - Li or valproate + atypical

Depression is THE Problem

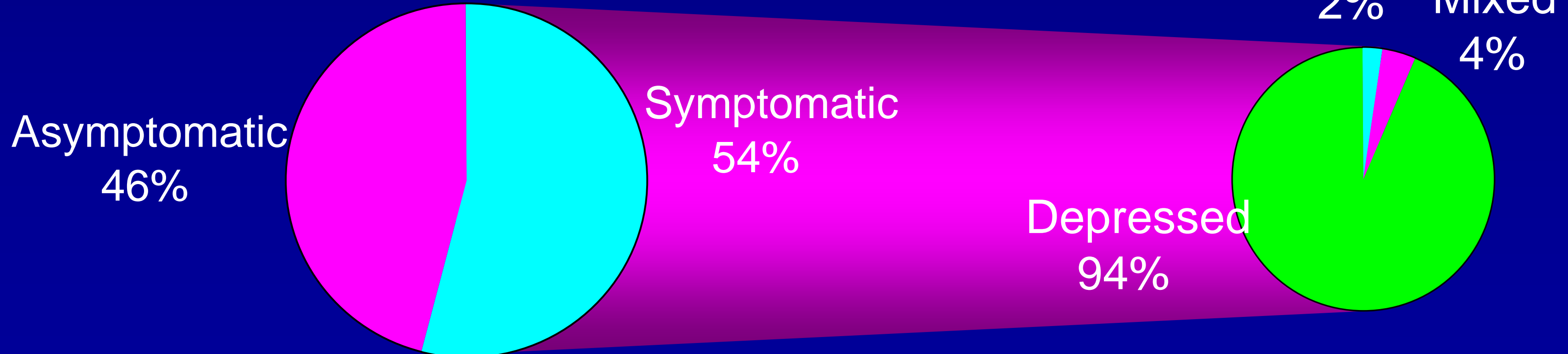
Bipolar I

(Judd et al. *Archives of General Psychiatry* 59:530-537, 2002)



Bipolar II

(Judd LL et al. *Archives of General Psychiatry* 60:261-269, 2003)

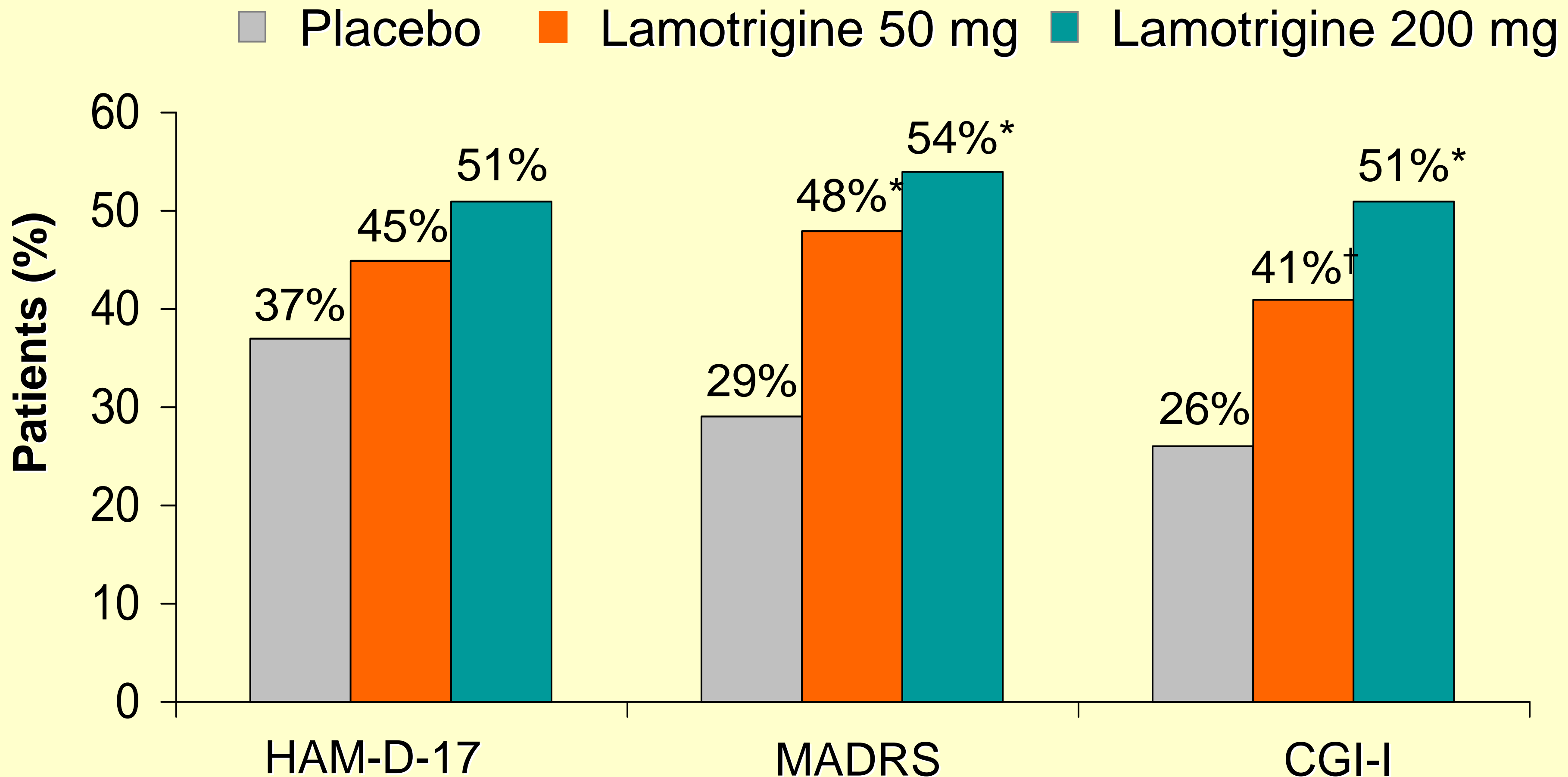


Antidepressants and bipolar disorder

Antidepressant vs Placebo (5 trials)	**Response** OR 1.86 (1.49-2.3); NNT 4.2; superiority achieved
	Switching into Mania/Hypomania OR 1.00 (.47-2.13); Rates 3.8% vs 4.7%
TCA vs other Antidepressants	**Response** OR 0.8 (.76-1.06); equivocal inferiority
	Switching into Mania/Hypomania OR 2.92 (1.28-6.71); Rates 10% vs 3.2%

Gijsman et al Am J Psychiatry 2004

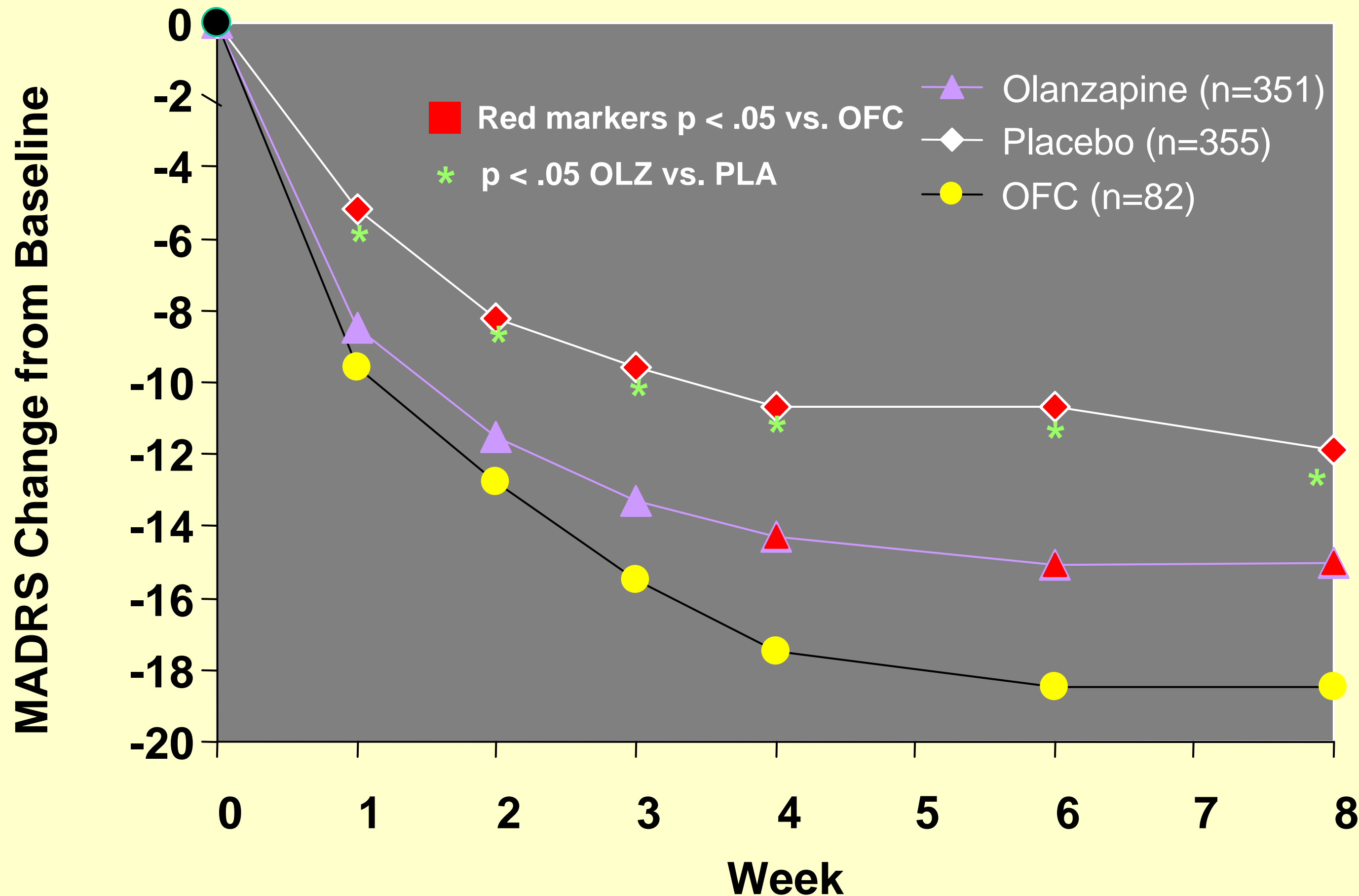
Lamotrigine vs Placebo in Bipolar Depression: Acute Treatment



* *P*<0.05 vs placebo. † *P*<0.1 vs placebo.

Calabrese et al. *J Clin Psychiatry*. 1999;60:79-88.

Olanzapine + fluoxetine in bipolar depression



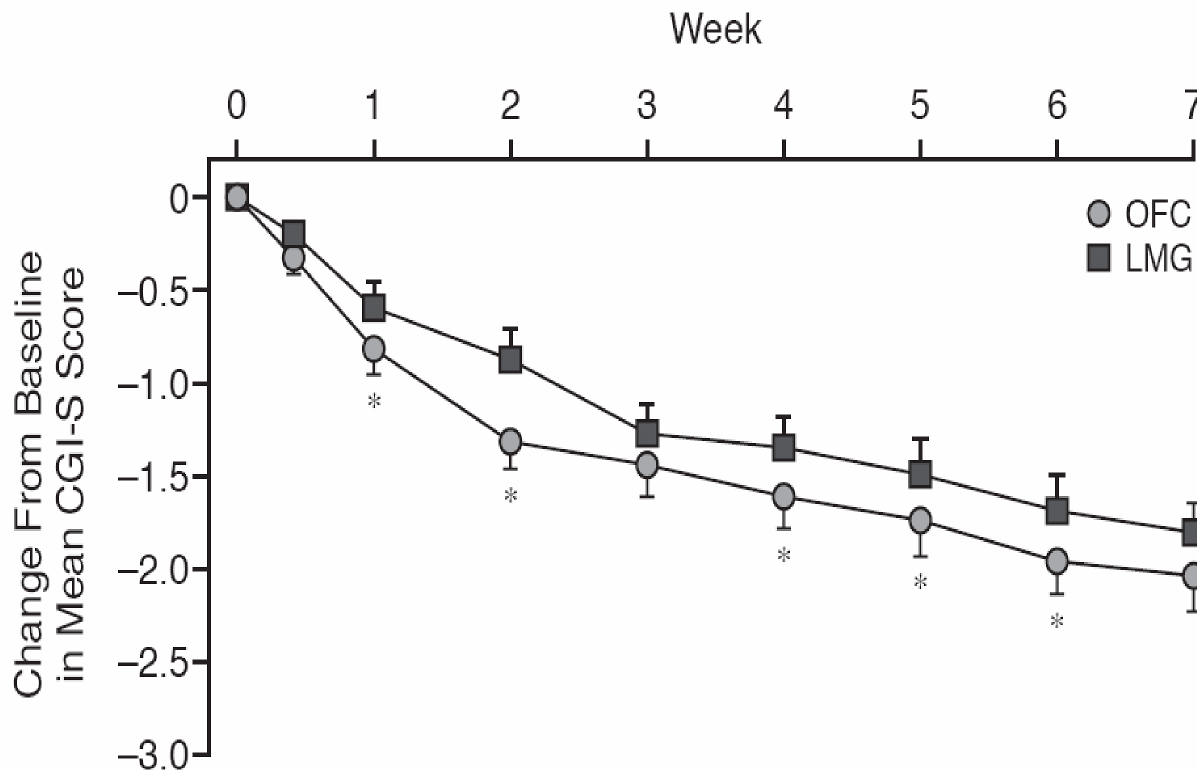
***MMRM = Mixed-Model Repeated Measures**

F1D-MC-HGGY

Tohen M et al. *Arch Gen Psychiatry* 60:1079-1088, 2003

OFC vs lamotrigine in BPI Depression

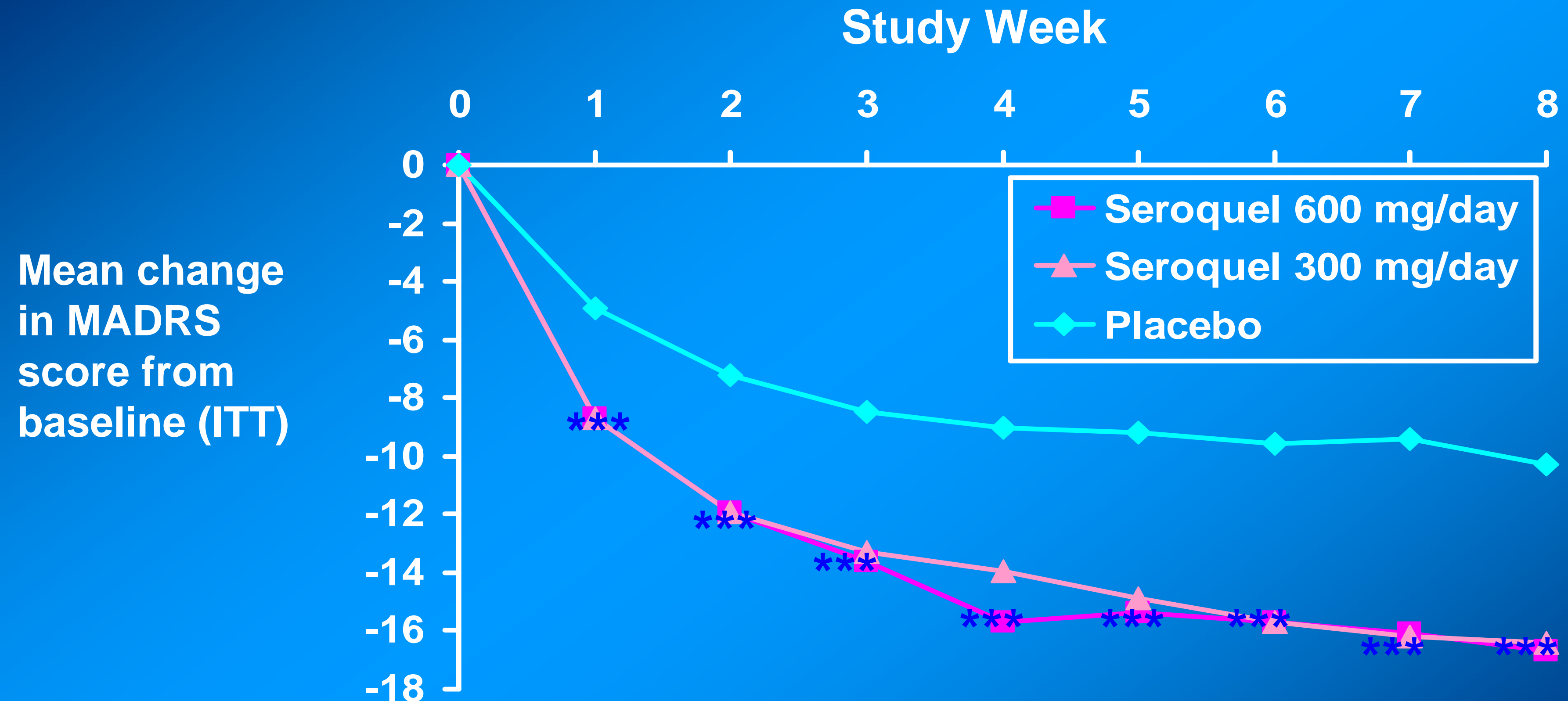
Brown et al. 2006 J Clin Psychiatry 67;1025-33



Note:

- Small difference in effect
- OFC associated with more AEs, weight gain and metabolic changes than lamotrigine
- N= 205 each arm

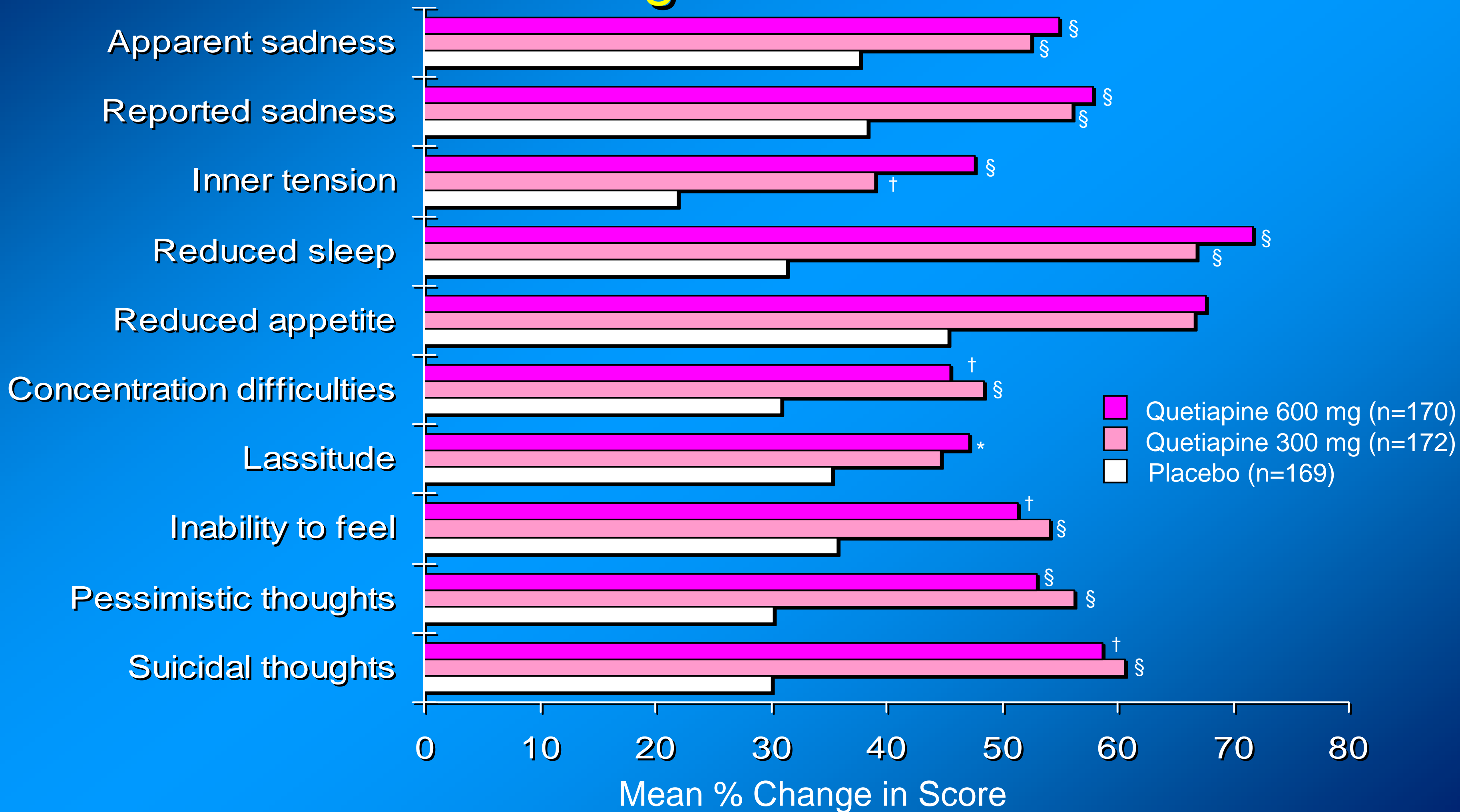
Quetiapine monotherapy in bipolar depression



***p<0.001 vs placebo for both active arms at all time points
Mean baseline scores: BP I 30.5; BP II 30.2

Calabrese J et al. 2005 Am J Psychiatry 162;1351-60.

MADRS Items: Change From Baseline



*$p<0.05$ †$p<0.01$ §$p<0.001$ vs placebo

ITT, LOCF

Acute Depression

- First line: SSRI plus antimanic agent
- If on antimanic: SSRI or quetiapine (if not on antipsychotic)
- If recent unstable mood: avoid antidepressants – increase antimanic and consider lamotrigine
  - NB avoid lamotrigine as a single first line agent in bipolar I but consider this in bipolar II
- If doesn't respond to SSRI switch to mirtazepine or venlafaxine or add quetiapine or olanzapine if not on an antipsychotic
- Taper antidepressants after symptoms reduced for 8 weeks

Guideline Evolution: Acute Depression

- Much less consensus:
  - Don’t use antidepressant monotherapy esp. in bipolar I
- Change in views over lamotrigine
  - Consider if antidepressants lead to problems (BAP)
  - First line (APA and TIMA)
  - Not first line or single agent in BPI (NICE)
- Increasing role for antipsychotics
  - Consider, esp if psychotic (BAP)
  - Quetiapine and OFC second line (TIMA)
  - Quetiapine possible alternative to SSRI (NICE)

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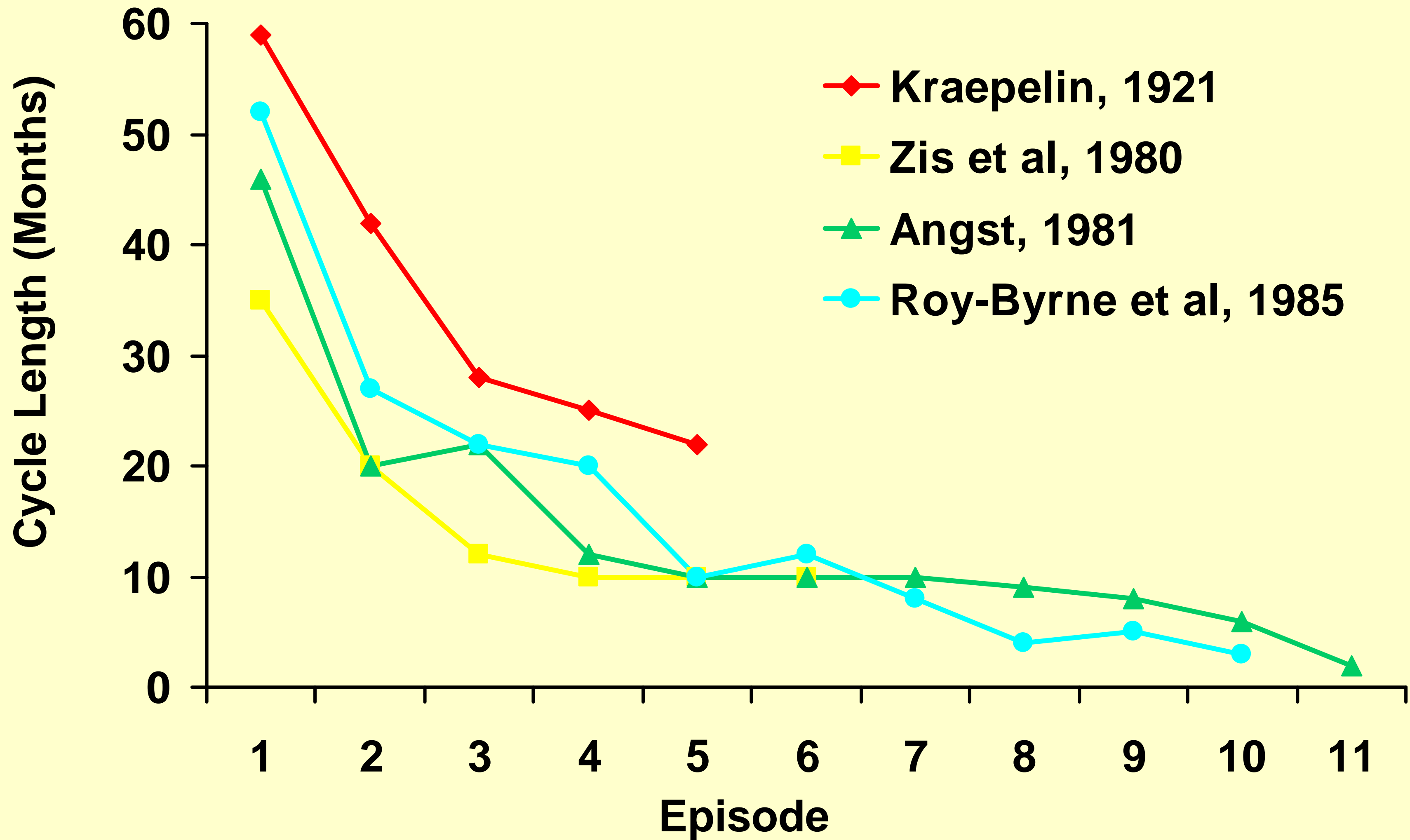
Relationship between cycle length and number of episodes



Mood Disorders: Risk of relapse

Bipolar Disorder, constant risk of relapse over 40yrs; 0.4episodes/year

Fig. 1 Bipolar disorder vs. unipolar disorder (vertical bars indicate 95 % confidence intervals)

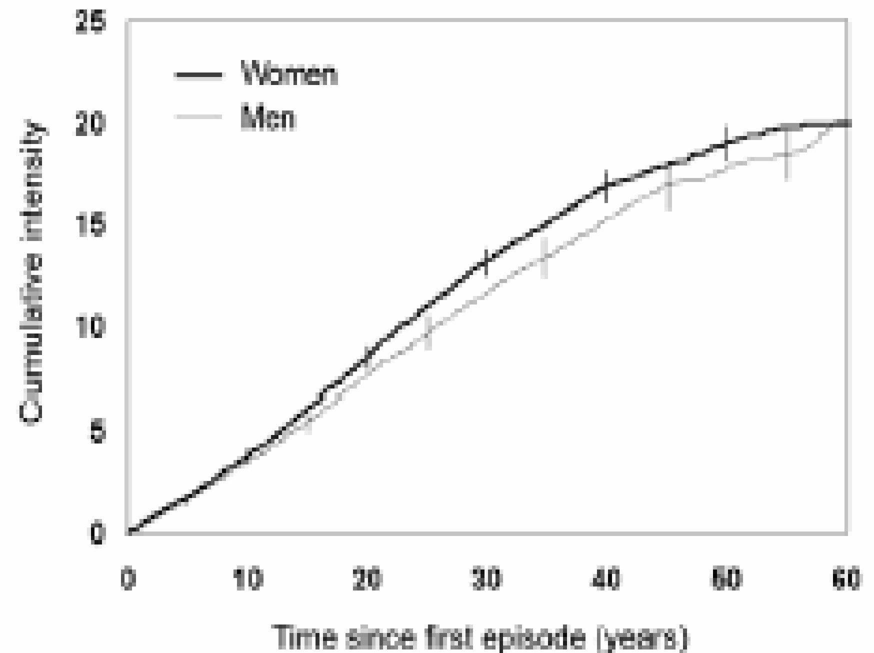


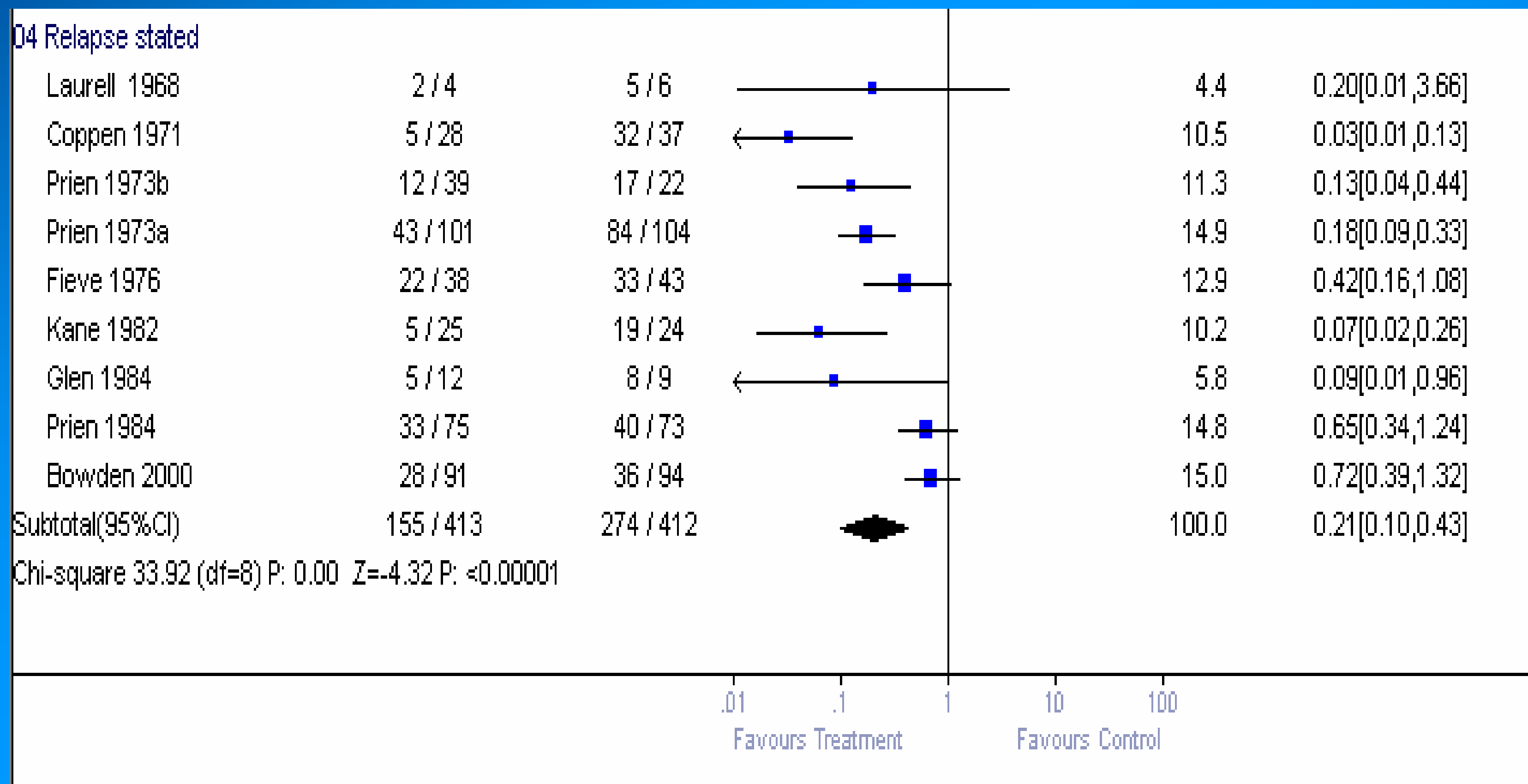
Fig. 3 Bipolar disorders divided into men and women (vertical bars indicate 95 % confidence intervals)

Angst et al. Eur Arch Psychiatry Clin Neurosci. 2003

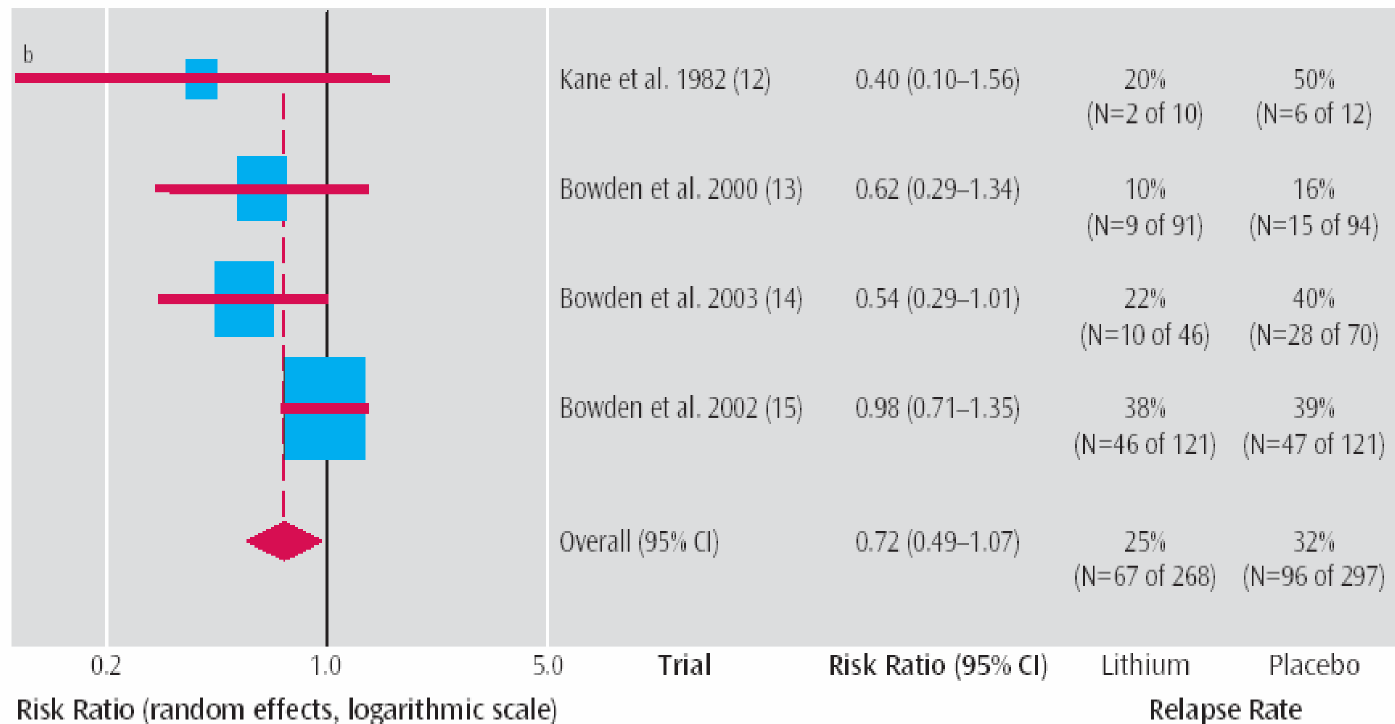
Long-term Treatment: When?

- Single manic episode with significant risk/consequences
- 2+ episodes in bipolar I
- In bipolar II if:
  - Significant risk
  - Frequent episodes
  - Significant functional impairment

Lithium v placebo, maintenance in bipolar disorder



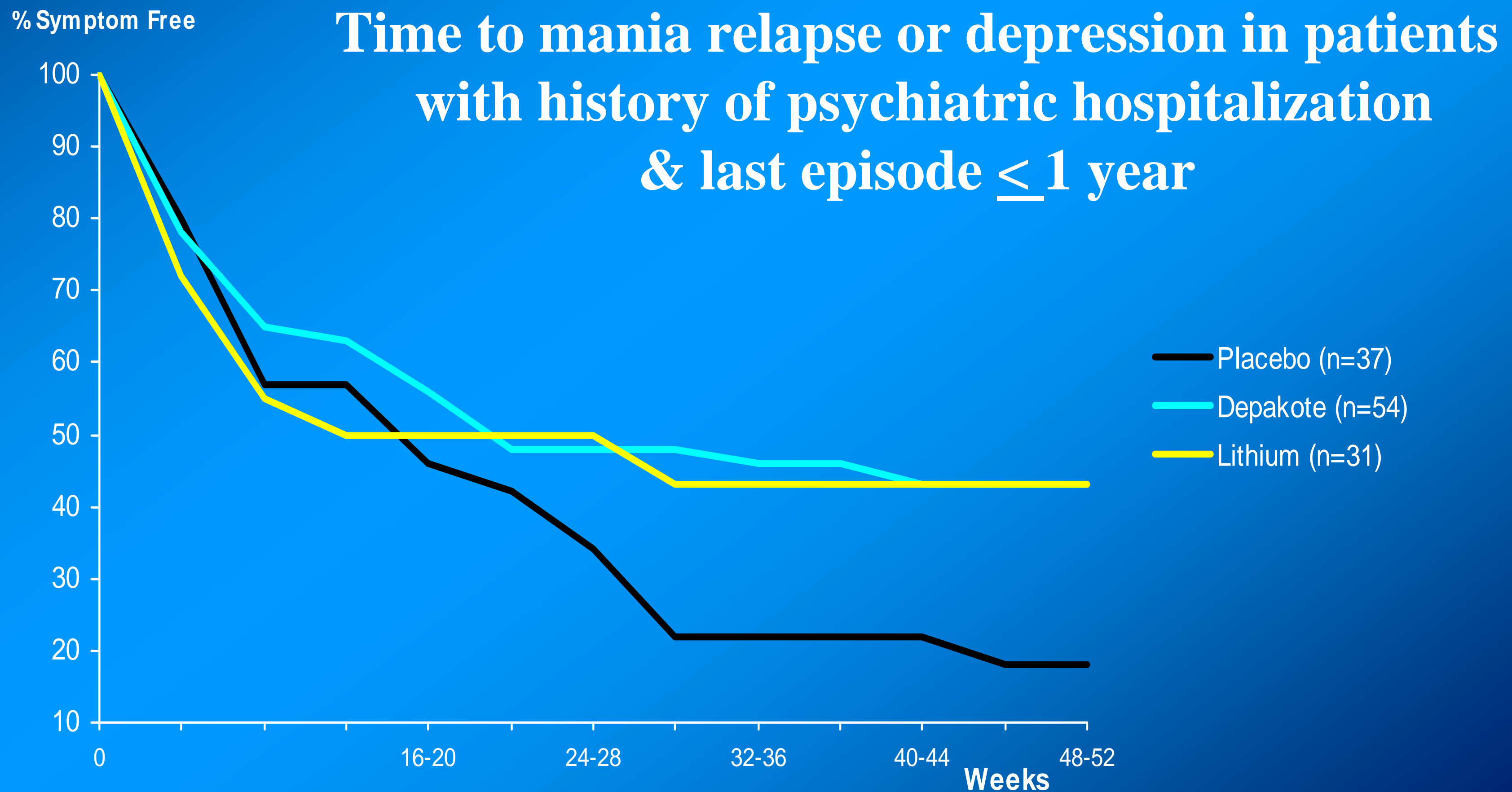
Lithium *Not* Clearly Superior to Placebo in Preventing Depression



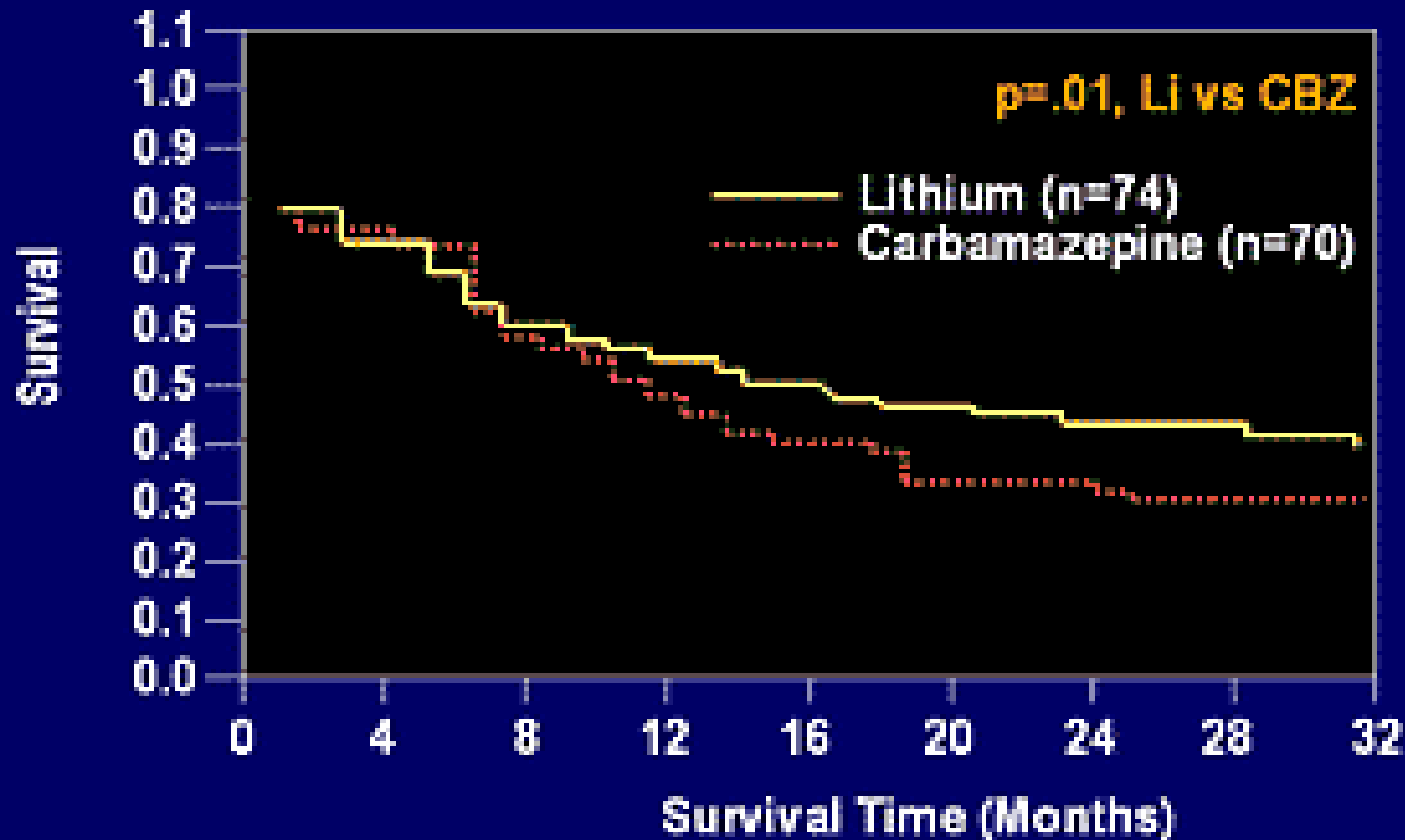
Random effects *p* = 0.10

Geddes J et al. *Am J Psychiatry* 161:217-222, 2004

Efficacy of depakote in prophylaxis of bipolar disorder



Long Term Treatments – Carbamazepine



Greil et al J Affect Disord 1997

Lamotrigine protection against depressive episodes: Combined analysis

39% increase in the percent of patients who remained intervention-free for depression at 18 months compared with placebo

Lamotrigine 100-400 mg (n=233)
Placebo (n=188)

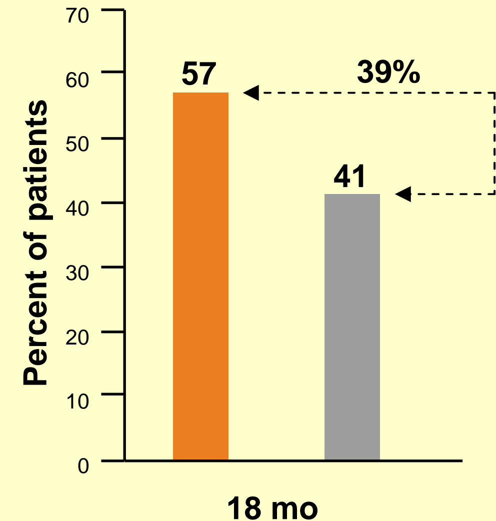
Estimated % of pts intervention-free*

100
90
80
70
60
50
40
30
20
10
0

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

Month

LTG vs PBO, *P*=0.009



* Some patients considered intervention-free for depressive episodes could have had intervention for manic episodes.

Goodwin et al. 2004 J. Clin. Psychiatry

Lamotrigine protection against manic episodes: Combined analysis

22% increase in the percent of patients who remained intervention-free for mania at 18 months compared with placebo

Lamotrigine 100-400 mg (n=223)
Placebo (n=188)

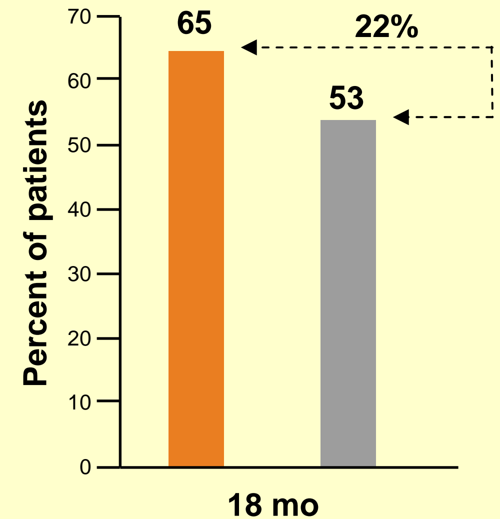
Estimated % of pts intervention-free*

100
90
80
70
60
50
40
30
20
10
0

LTG vs PBO, *P*=0.034

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

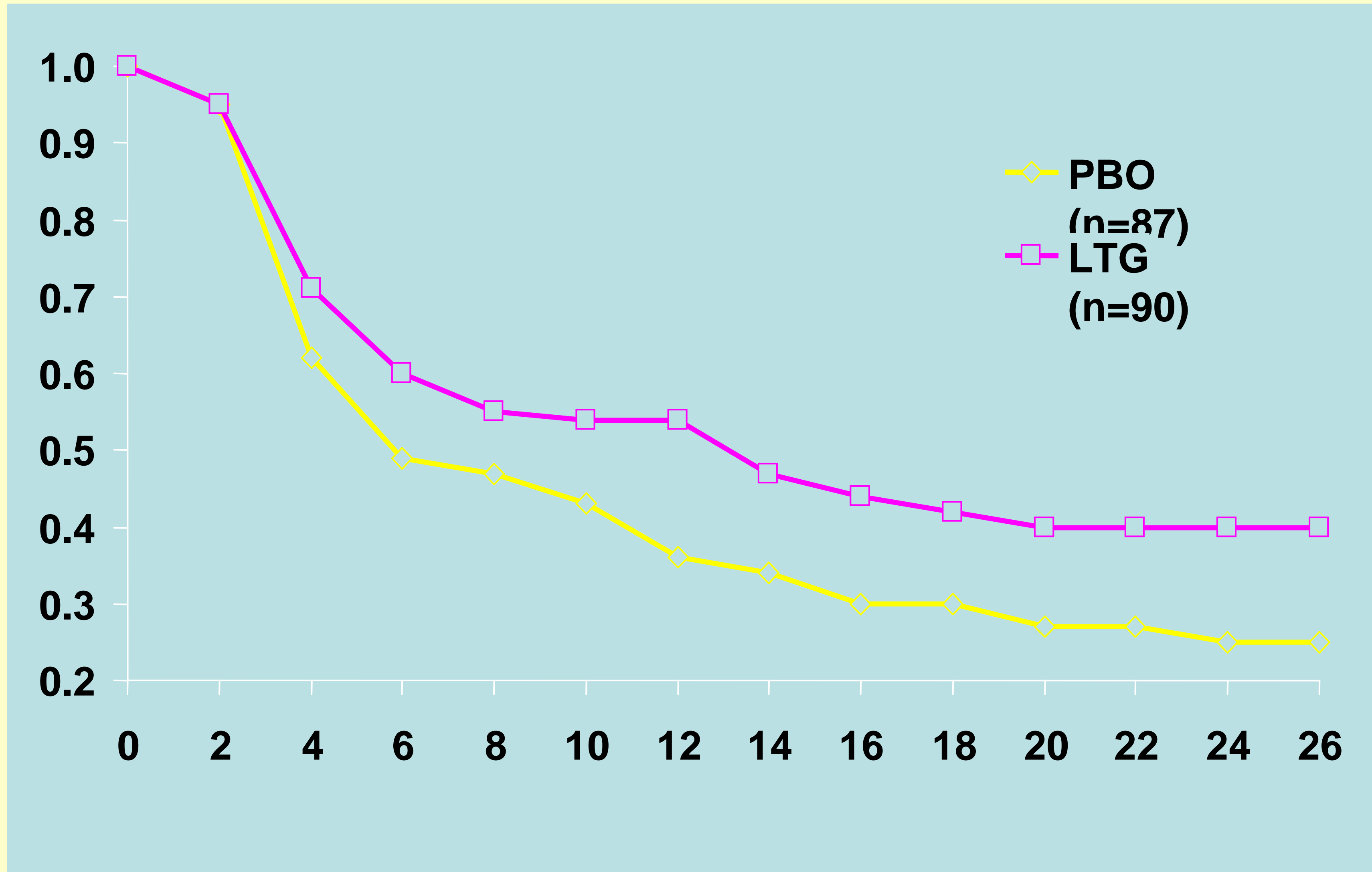
Month



* Some patients considered intervention-free for manic episodes could have had intervention for depressive episodes.

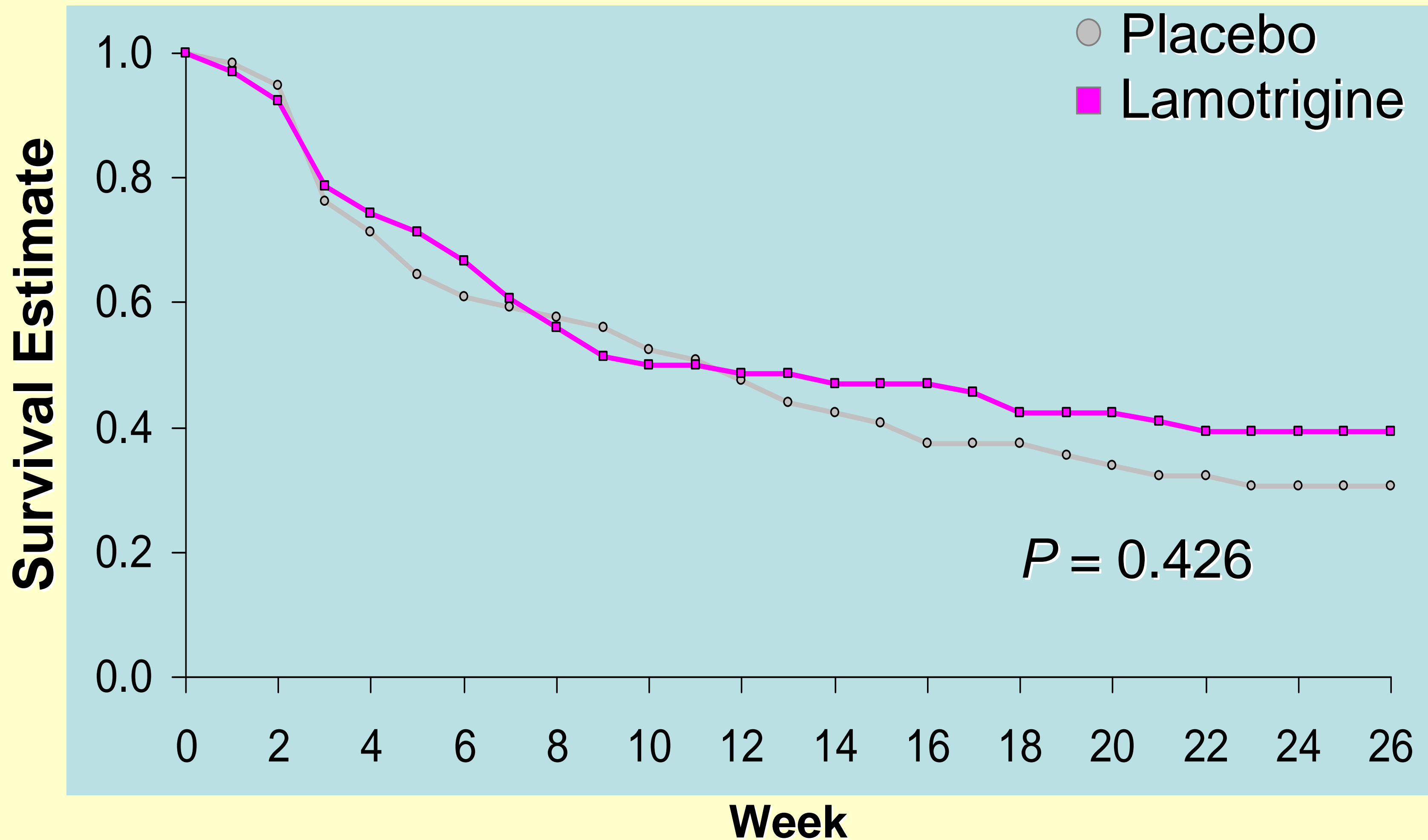
Goodwin et al. 2004 J. Clin. Psychiatry

Lamotrigine long term treatment in rapid cycling BP disorder



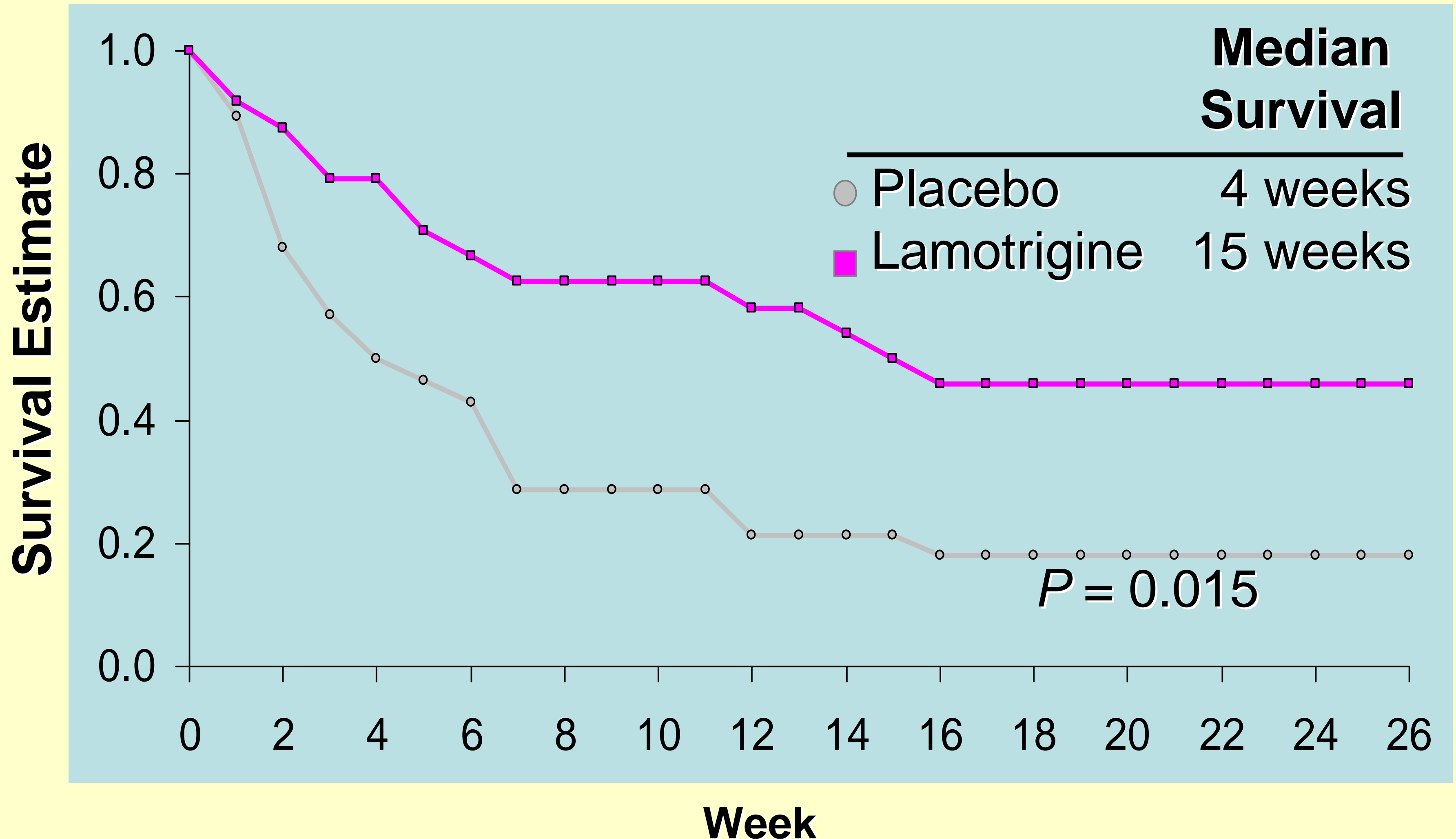
Calabrese JR, et al. *J Clin Psychiatry.* 2000;61(11):841-850.

Lamotrigine vs. Placebo Overall Survival BPI (n = 125)



Calabrese et al. *J Clin Psychiatry*. 2000;61:841-50.

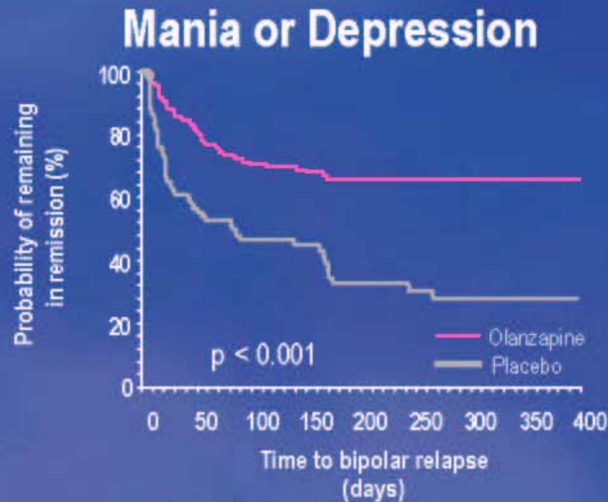
Lamotrigine vs. Placebo Overall Survival BP II (n = 52)

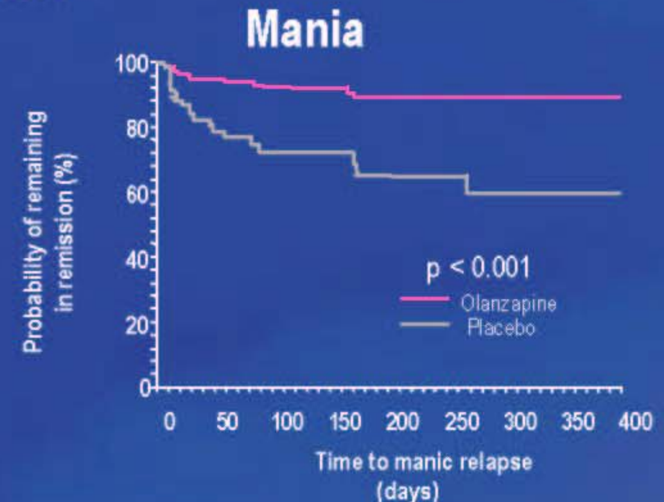


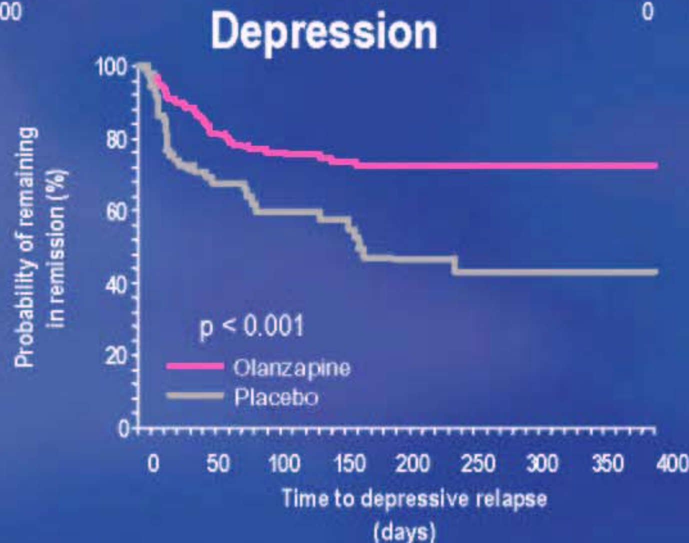
Calabrese et al. *J Clin Psychiatry*. 2000;61:841-50.

Olanzapine continuation in bipolar disorder

Syndrome Criteria

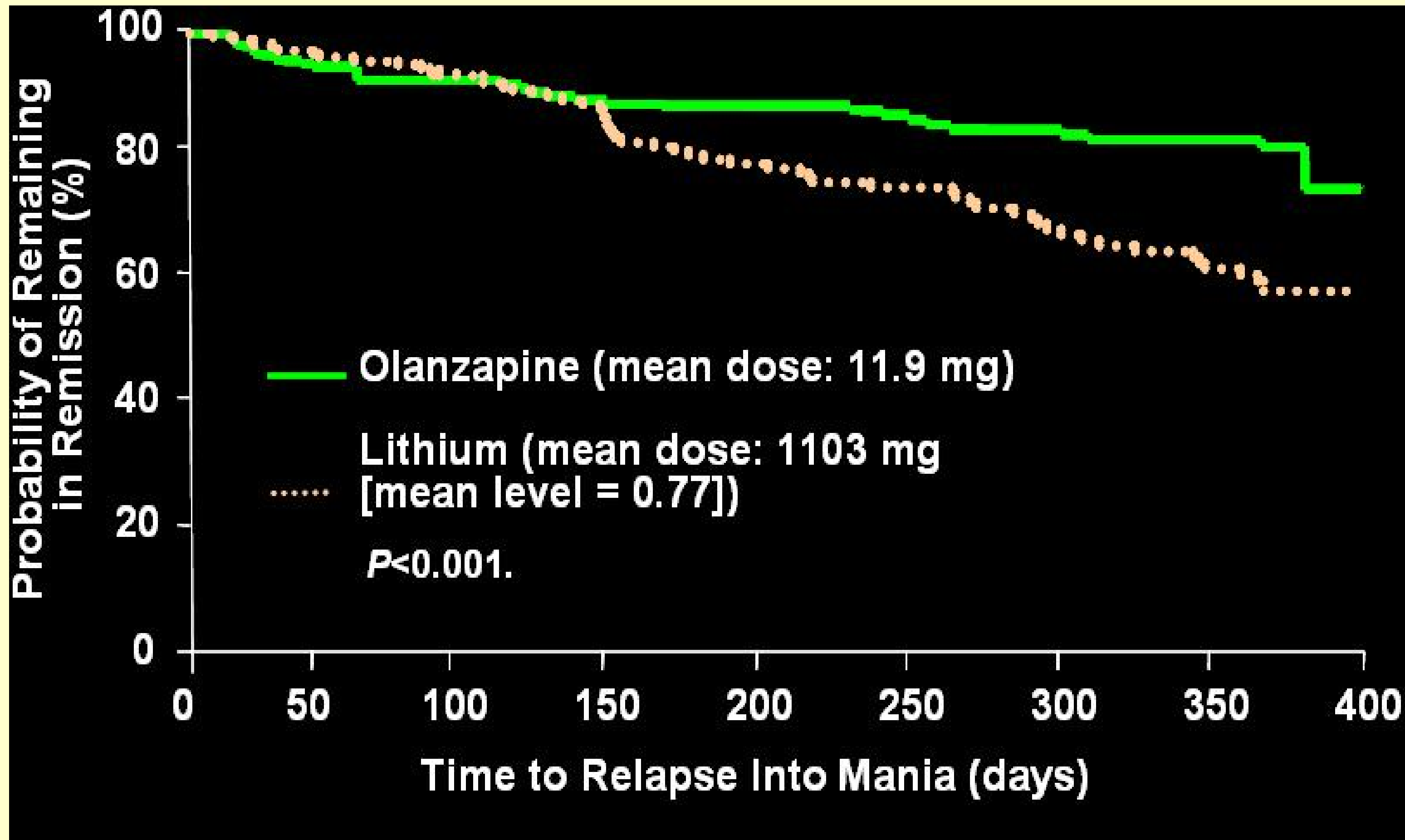






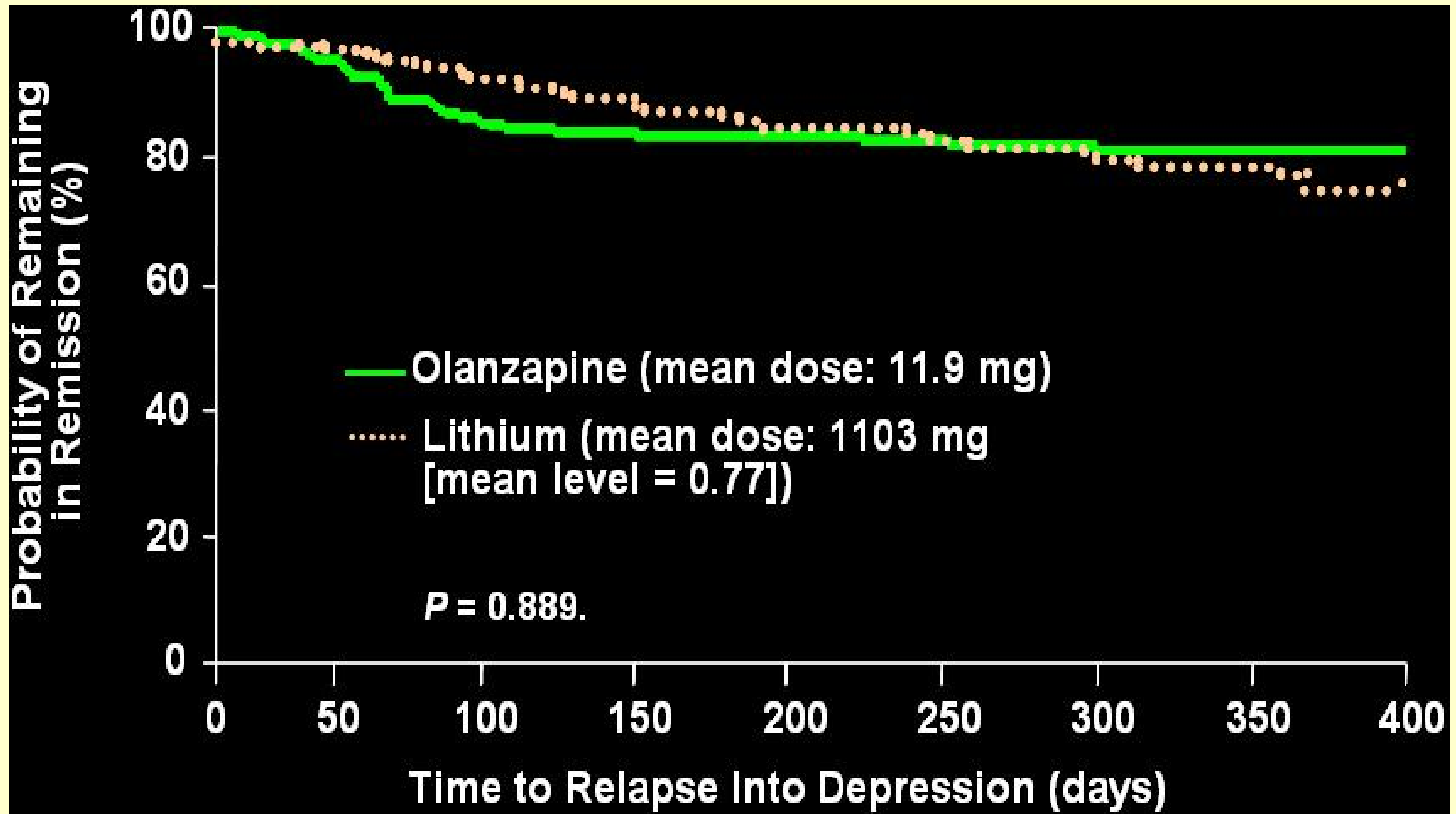
Tohen M et al. 2006 Am J Psychiatry 163;247-56.

Long Term Treatments – Olanzapine vs lithium for mania



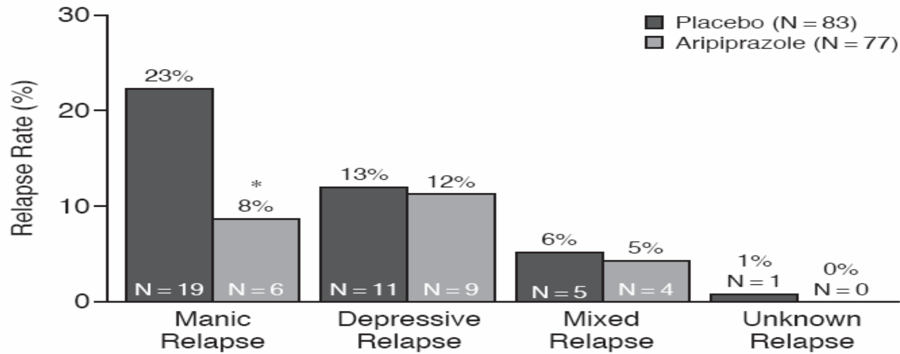
Tohenl et al Am J Psychiatry 2003

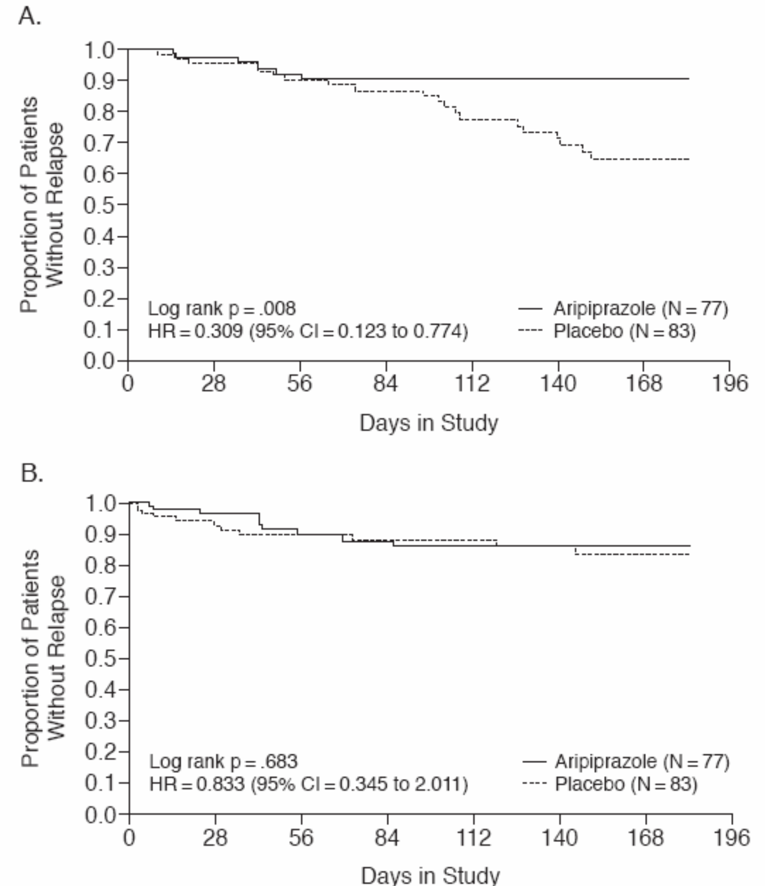
Long Term Treatments – Olanzapine vs lithium for depression



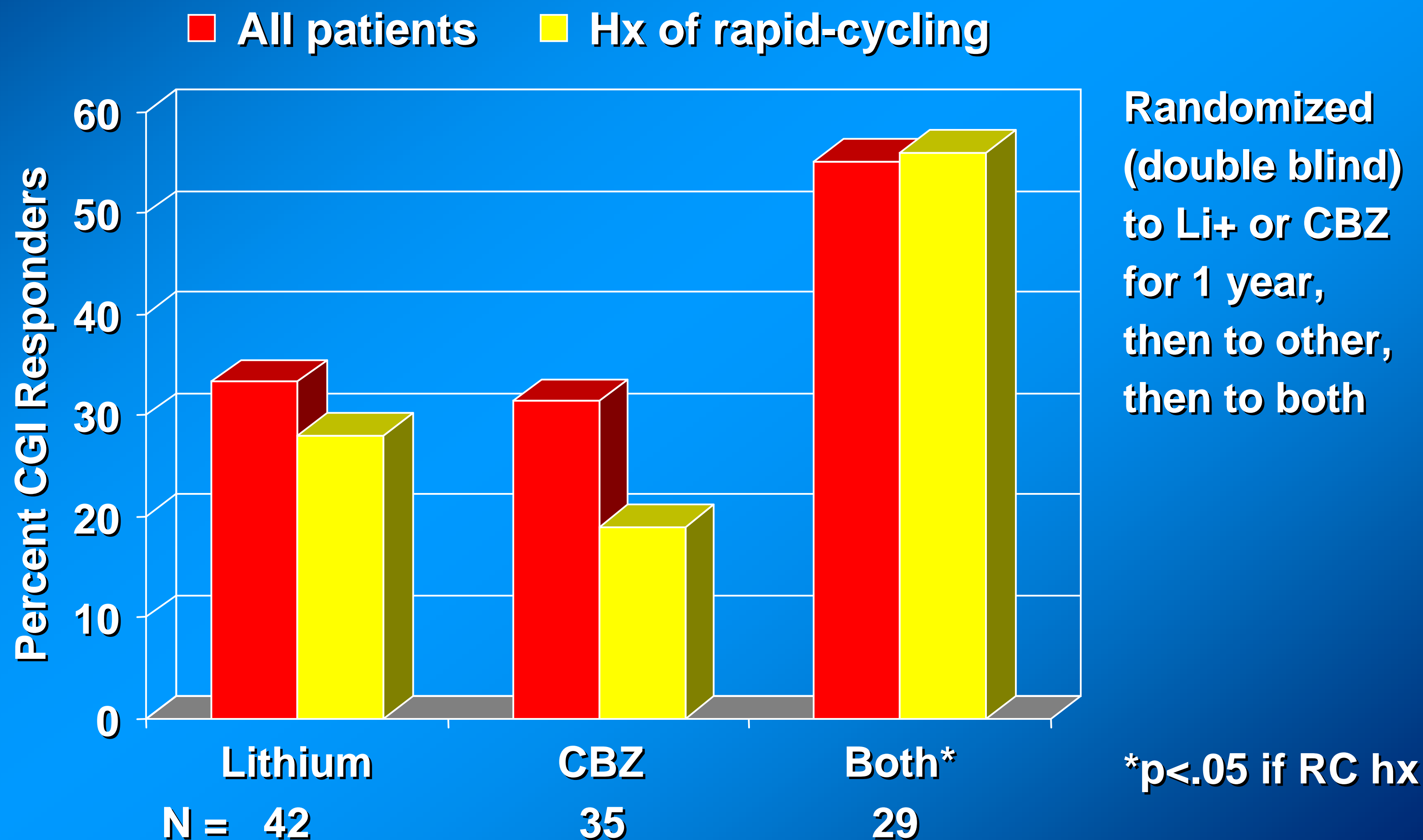
Tohenl et al Am J Psychiatry 2003

26 week trial of aripiprazole in recently manic BPI patients (Keck et al. 2006)





Lithium and/or Carbamazepine Maintenance Response



Randomized (double blind) to Li+ or CBZ for 1 year, then to other, then to both

*p<.05 if RC hx

Long-term Treatment: What?

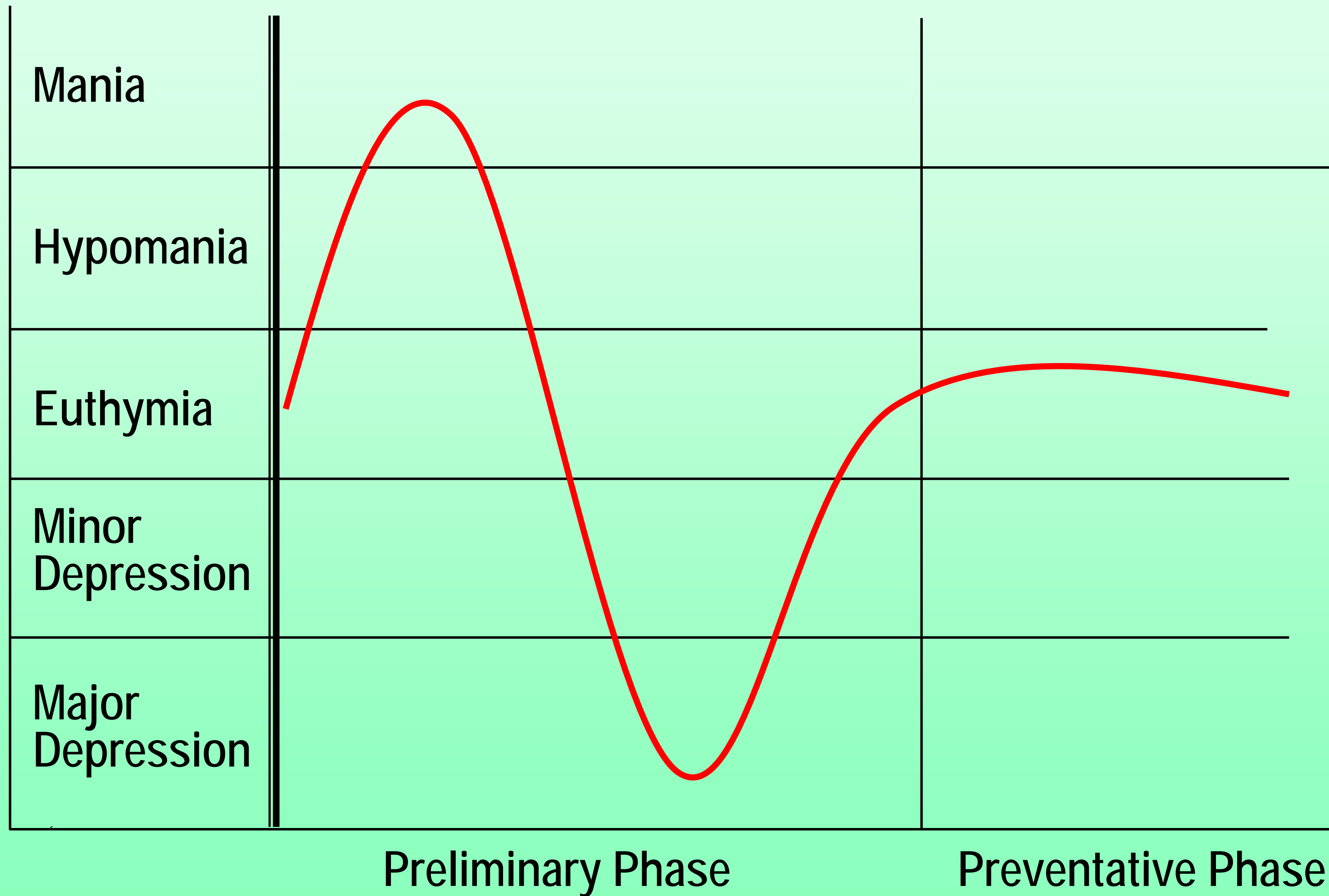
NHS
National Institute for Clinical Excellence

- First line: lithium, olanzapine or valproate
- If fails monotherapy over 6 months
  - Li + valp, Li + olanz, Valp + olanz
- If combination fails
  - Consider lamotrigine (esp. BPII), carbamazepine, referral to tertiary centre
- NOT antidepressants routinely (unless no mania X 5 yrs)
- Normally treat for at least 5 years

Guideline Evolution: Long term treatment

- Variations in guidelines due to poor evidence base
- Change in role of antipsychotics
  - Withdraw antipsychotics used in acute episode (APA)
  - Olanzapine as alternative to Li (BAP)
  - Atypical first line (NICE)
- Lithium down graded
  - First line (APA, BAP, TIMA – after mania)
  - Second line (NICE)
- Valproate down graded
  - First line (APA, TIMA – after mania)
  - Consider after Li (BAP)
  - Concern in women (NICE)
- Carbamazepine down graded
  - First line (APA)
  - Poor alternative to Li (BAP)
  - Third or fourth line (TIMA)
  - On specialist advice (NICE)
- Increased caution recommended re use of antidepressants
- NICE emphasise the need for physical health monitoring

The course of Bipolar Disorder



The course of Bipolar Disorder

Mania

Hypomania

Euthymia

Minor Depression

Major Depression

Preliminary Phase

Preventative Phase

Frank E, et al. *Biol Psychiatry.* 2000;48(6):593-604.

“The study of MEDICINE is prosecuted under two relations, namely as a *Science* and as an *Art*”

The Science and Practice of Medicine
W. Aitken
1872

RC PSYCH
ROYAL COLLEGE OF PSYCHIATRISTS

Annual Residential Meeting of the Faculty of General and Community Psychiatry

The Science and Practice of Psychiatry
Twin themes: Vulnerability and Service Delivery

Hilton Hotel and Sage Gateshead
Newcastle Gateshead
18-19th October 2007

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