Mood stabilization: Clinical needs and study designs for long-term trials in bipolar disorders

Eduard Vieta

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Disclosure: Eduard Vieta, MD, PhD

Company	Consultant	Grants/ Research Support	Speakers Bureau
AstraZeneca	X	X	X
Bial	X	X	
Bristol-Myers Squibb	X	X	X
Eli Lilly and Company	X	X	X
GlaxoSmithKline	X	X	X
Janssen-Cilag	X	X	X
Lundbeck	X		X
Novartis	X	X	X
Organon	X		
Pfizer Inc	X	X	X
Sanofi-Aventis	X	X	X
Servier	X	X	
UCB Pharmaceuticals	X		

Methodological flaws of long-term trials in bipolar disorders

- External validity
- Extrapolation of data from other conditions
- Outcomes
- Trial design

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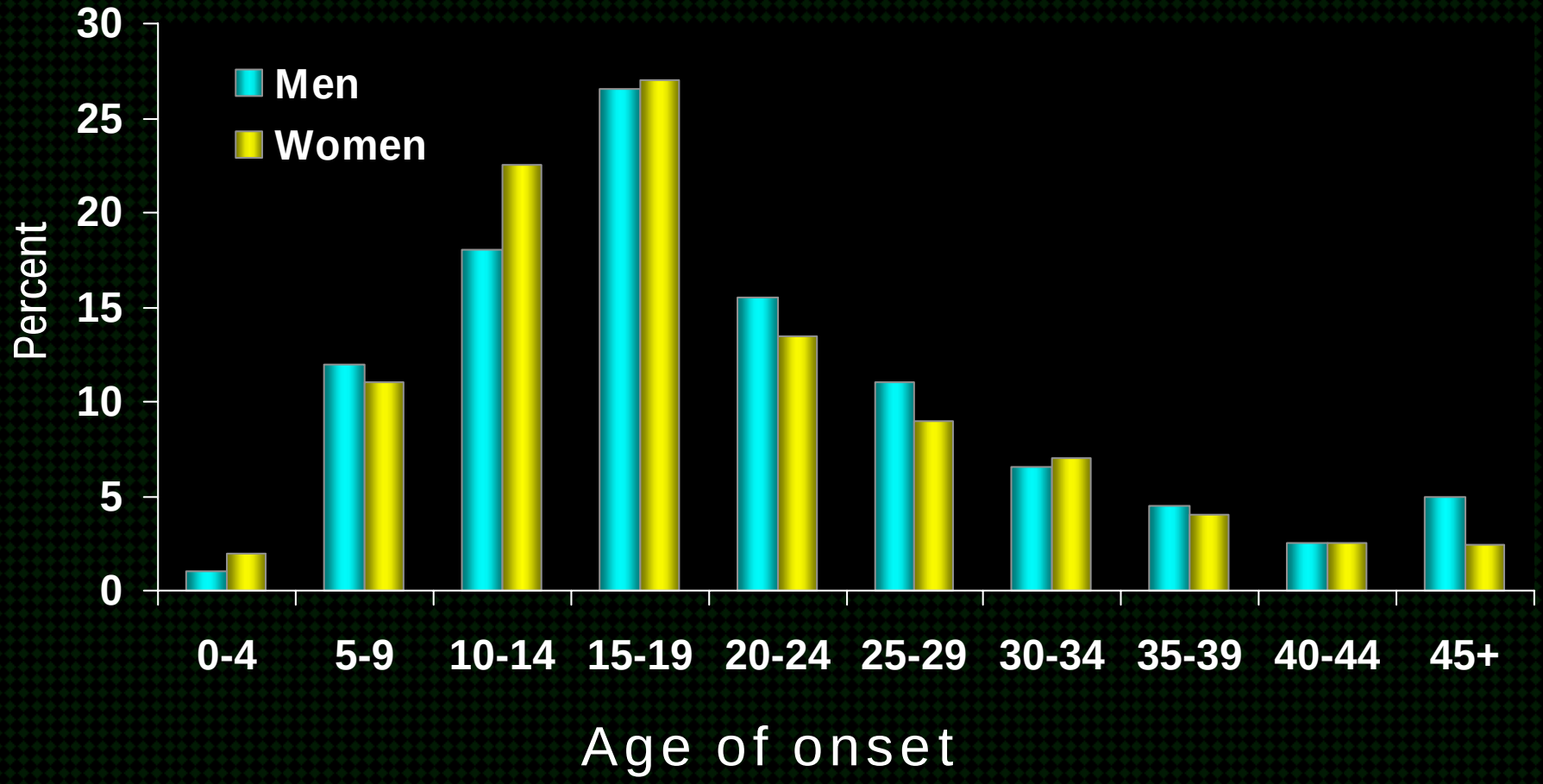
Methodological flaws of long-term trials in bipolar disorders

- External validity
  - Age
  - Comorbidity
  - Polypharmacy
  - Subtypes
    - Bipolar II
    - Rapid cyclers
  - Severity
  - Suicidality
  - Adherence

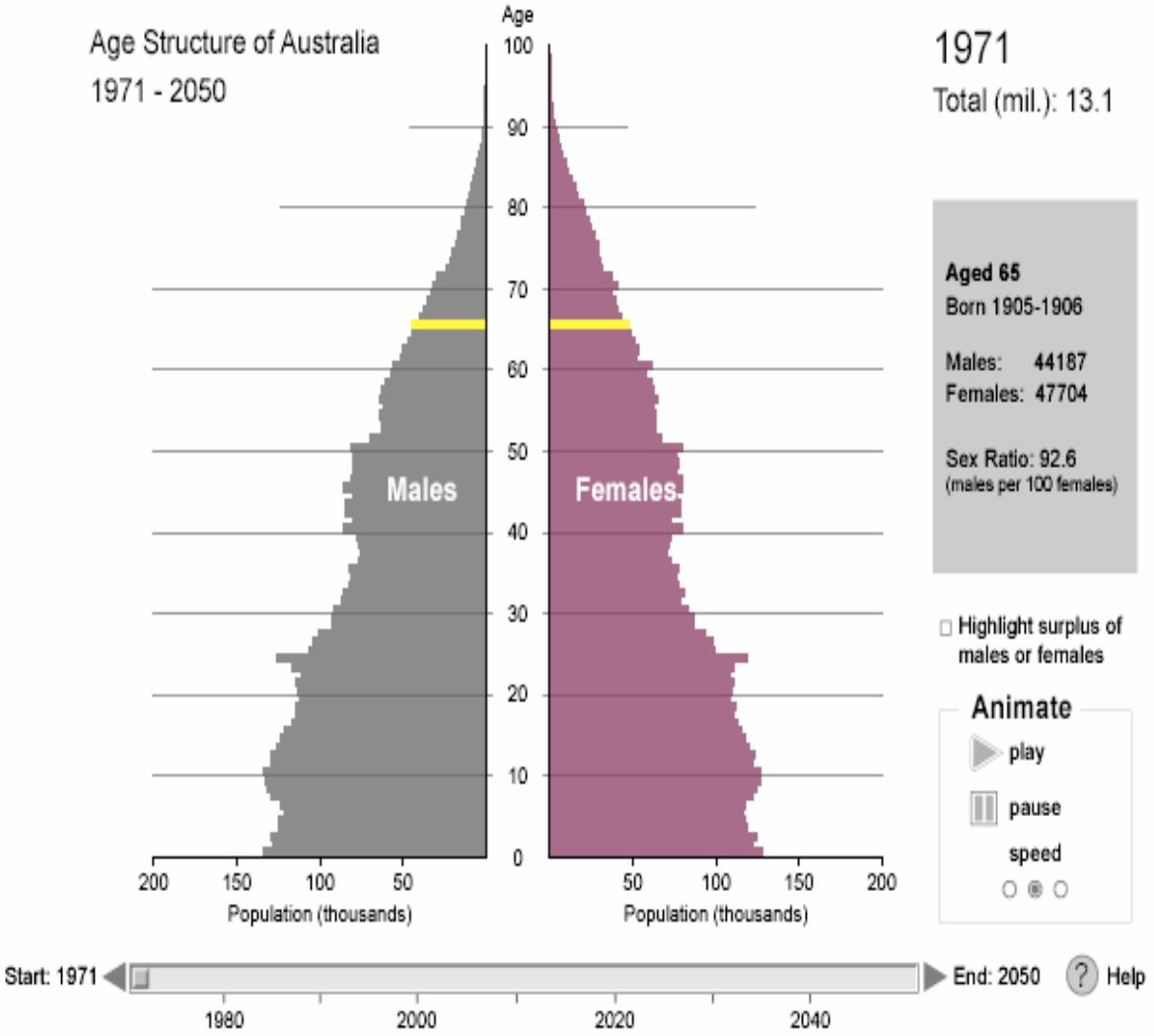
Adolescence Onset is common in Bipolar Disorder



Australian Bureau of Statistics

Australian Bureau of Statistics

An agency of the Australian Government



Australian Bureau of Statistics

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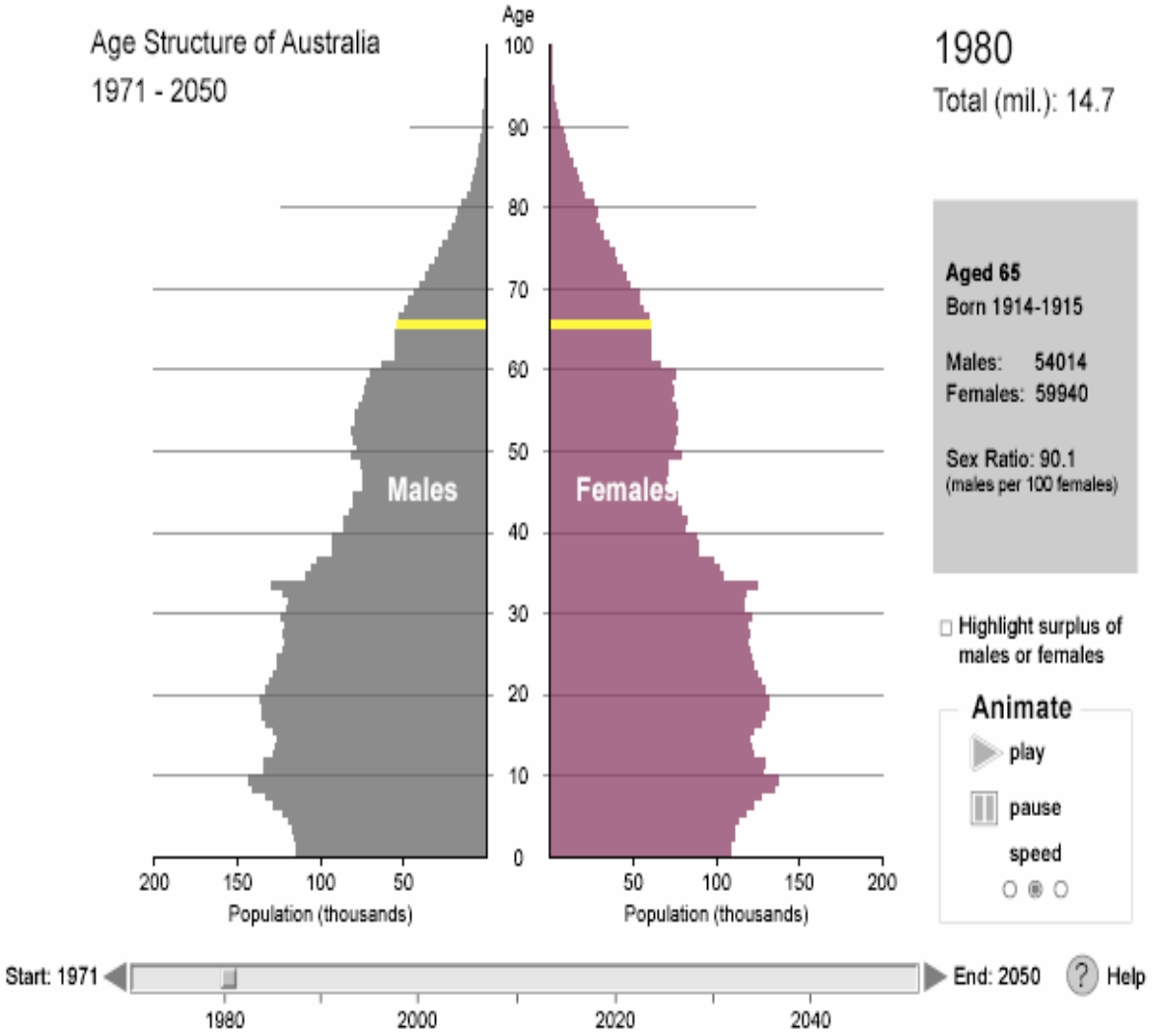

Australian Bureau of Statistics

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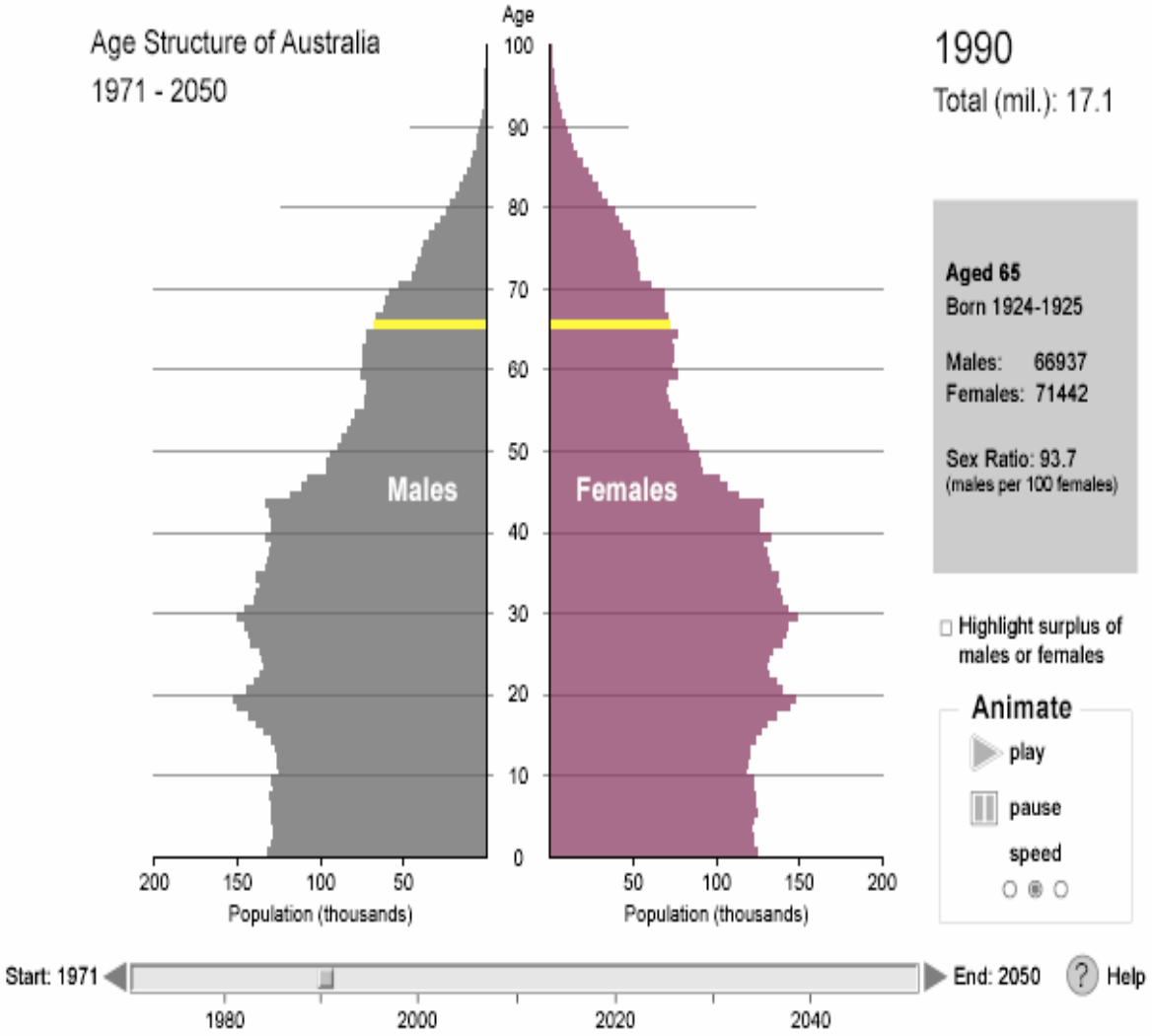
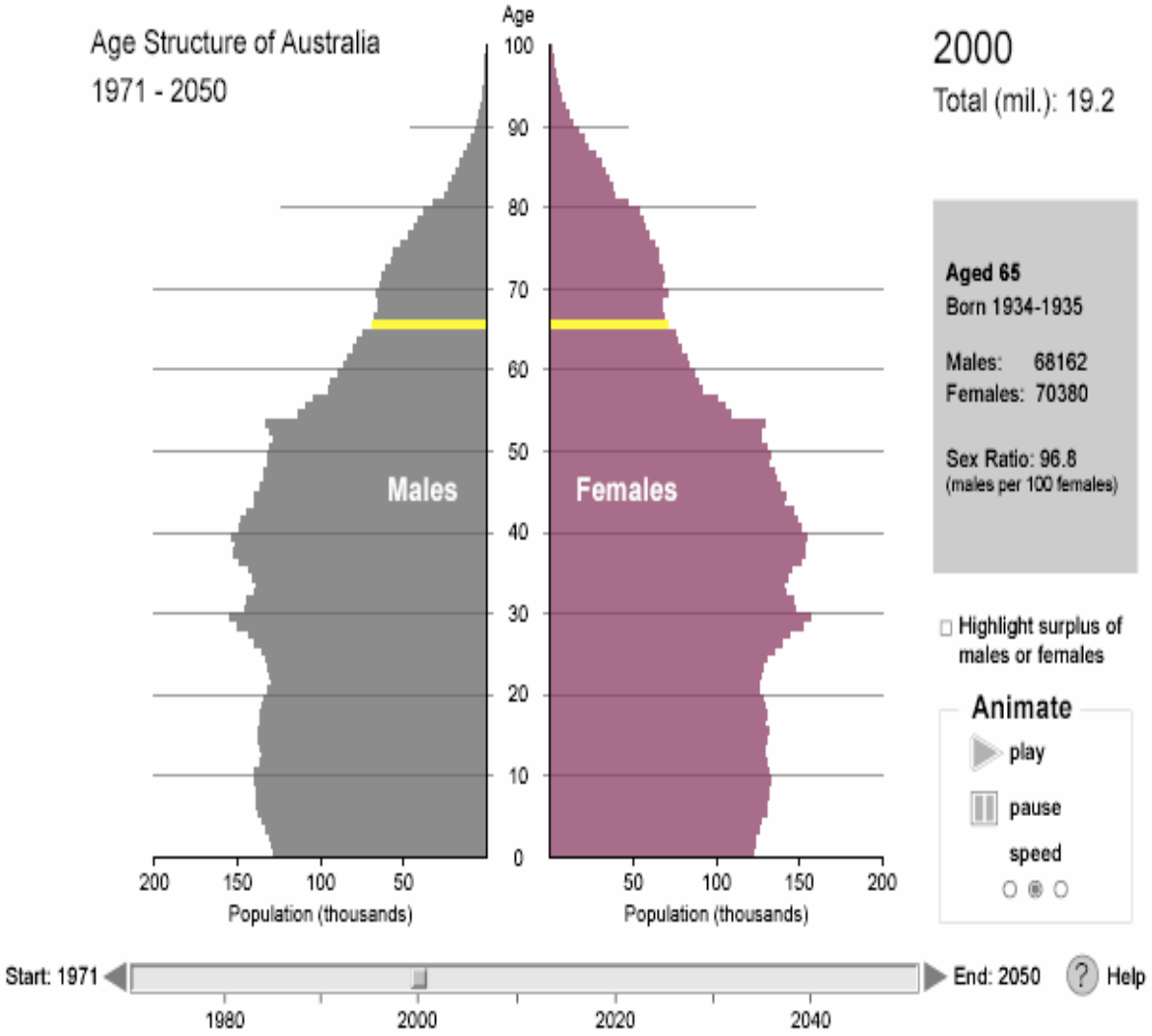


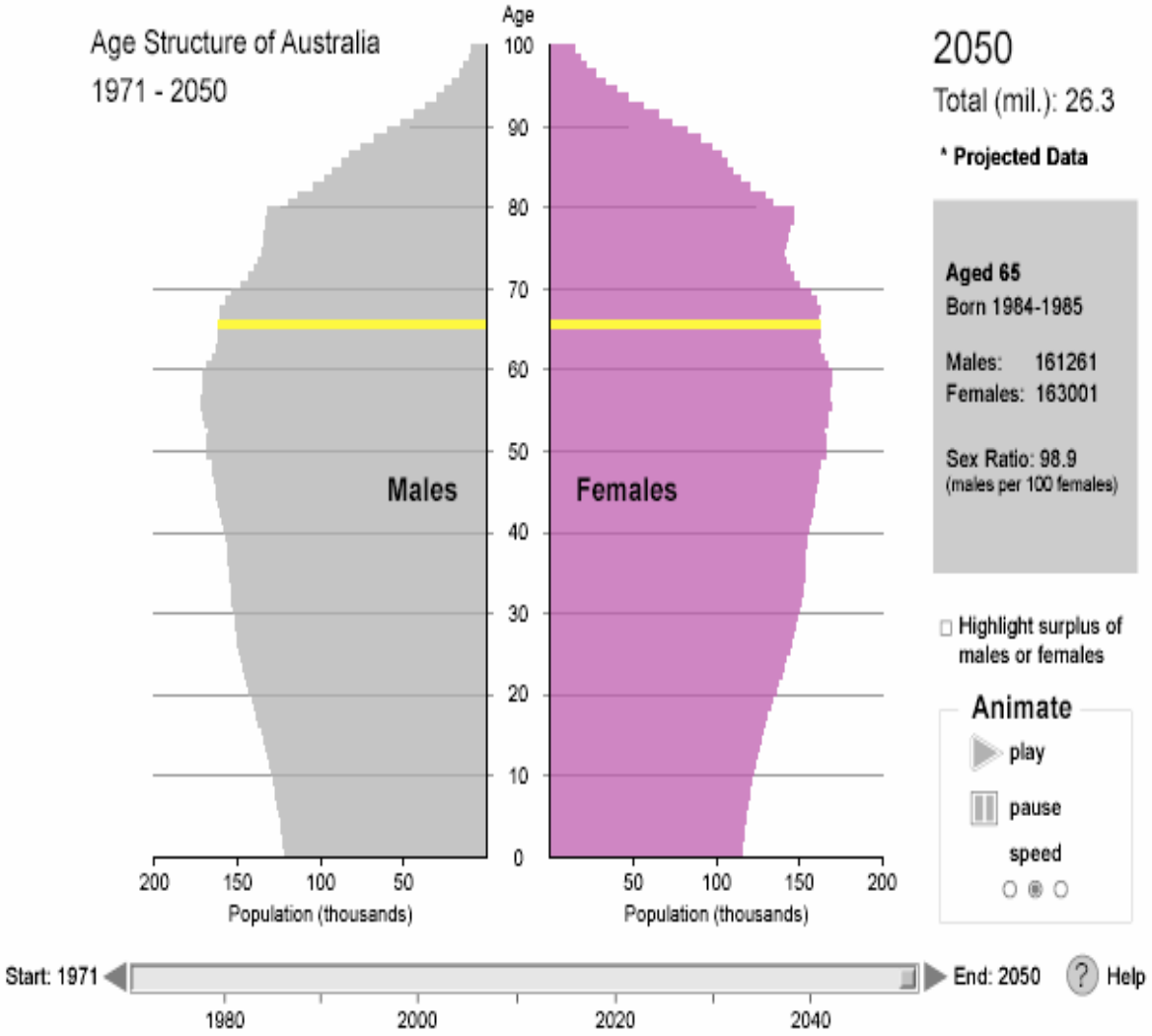

Age Structure of Australia
1971 - 2050
Age
100
90
80
70
60
50
40
30
20
10
0
Males
Females
200
150
100
50
Population (thousands)
50
100
150
200
Population (thousands)
2000
Total (mil.): 19.2
Aged 65
Born 1934-1935
Males: 68162
Females: 70380
Sex Ratio: 96.8
(males per 100 females)
Highlight surplus of males or females
Animate
play
pause
speed
Start: 1971
End: 2050
Help
1980
2000
2020
2040


Age Structure of Australia
1971 - 2050
Age
100
90
80
70
60
50
40
30
20
10
0
Males
Females
200
150
100
50
Population (thousands)
50
100
150
200
Population (thousands)
2010
Total (mil.): 21.3
* Projected Data
Aged 65
Born 1944-1945
Males: 103626
Females: 103321
Sex Ratio: 100.3
(males per 100 females)
Highlight surplus of males or females
Animate
play
pause
speed
Start: 1971
End: 2050
Help
1980
2000
2020
2040

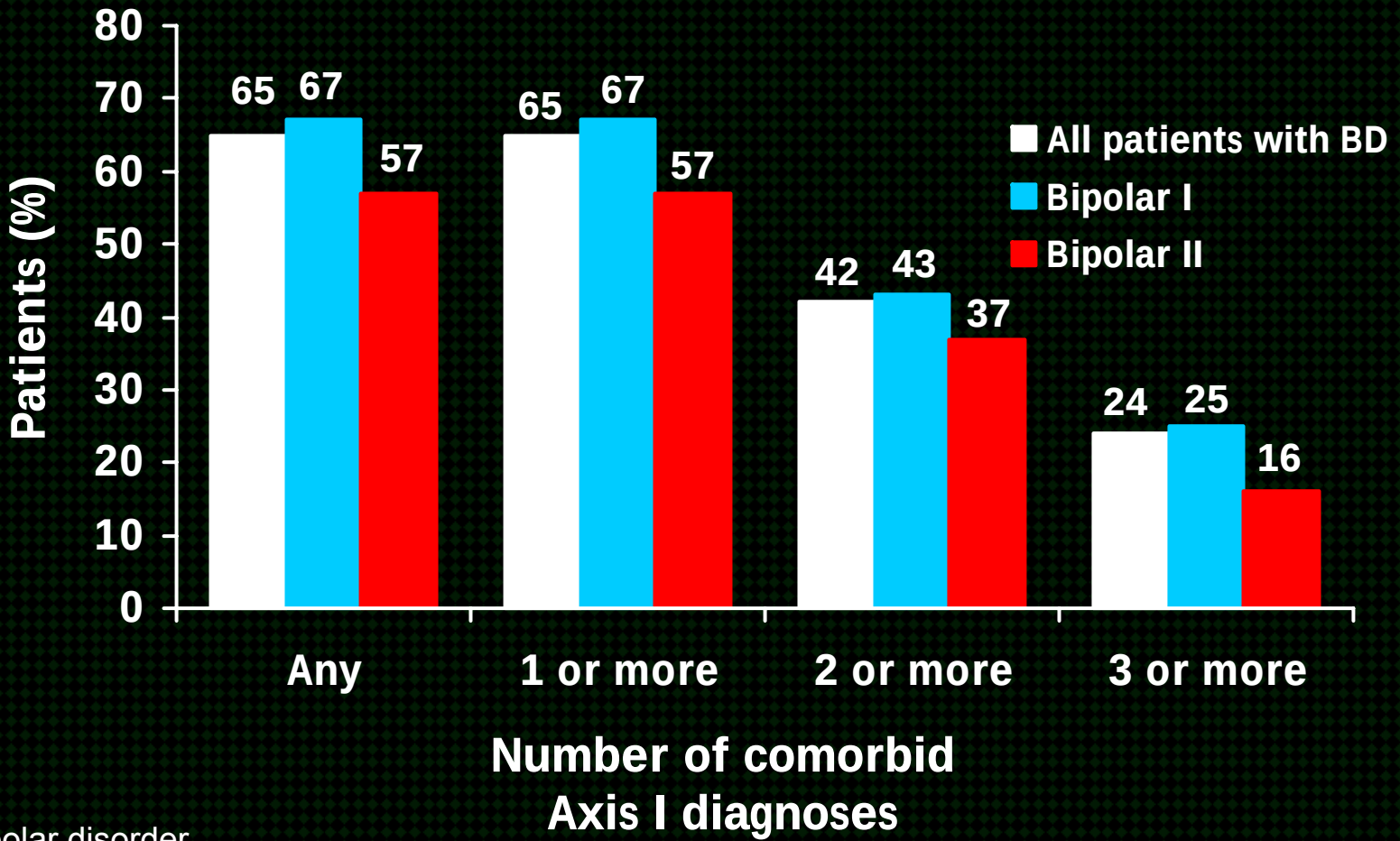

Age Structure of Australia
1971 - 2050
Age
100
90
80
70
60
50
40
30
20
10
0
Males
Females
200
150
100
50
Population (thousands)
50
100
150
200
Population (thousands)
2020
Total (mil.): 23.2
* Projected Data
Aged 65
Born 1954-1955
Males: 130627
Females: 137011
Sex Ratio: 95.3
(males per 100 females)
Highlight surplus of males or females
Animate
play
pause
speed
Start: 1971
End: 2050
Help
1980
2000
2020
2040


Age Structure of Australia
1971 - 2050
Age
100
90
80
70
60
50
40
30
20
10
0
Males
Females
200
150
100
50
Population (thousands)
50
100
150
200
Population (thousands)
2030
Total (mil.): 24.8
* Projected Data
Aged 65
Born 1964-1965
Males: 144827
Females: 149668
Sex Ratio: 96.8
(males per 100 females)
Highlight surplus of males or females
Animate
play
pause
speed
Start: 1971
End: 2050
Help
1980
2000
2020
2040


Age Structure of Australia
1971 - 2050
Age
100
90
80
70
60
50
40
30
20
10
0
Males
Females
200
150
100
50
Population (thousands)
50
100
150
200
Population (thousands)
2040
Total (mil.): 25.8
* Projected Data
Aged 65
Born 1974-1975
Males: 147773
Females: 151127
Sex Ratio: 97.8
(males per 100 females)
Highlight surplus of males or females
Animate
play
pause
speed
Start: 1971
End: 2050
Help
1980
2000
2020
2040


Age Structure of Australia
1971 - 2050
Age
100
90
80
70
60
50
40
30
20
10
0
Males
Females
200
150
100
50
Population (thousands)
50
100
150
200
Population (thousands)
2050
Total (mil.): 26.3
* Projected Data
Aged 65
Born 1984-1985
Males: 161261
Females: 163001
Sex Ratio: 98.9
(males per 100 females)
Highlight surplus of males or females
Animate
play
pause
speed
Start: 1971
End: 2050
Help
1980
2000
2020
2040

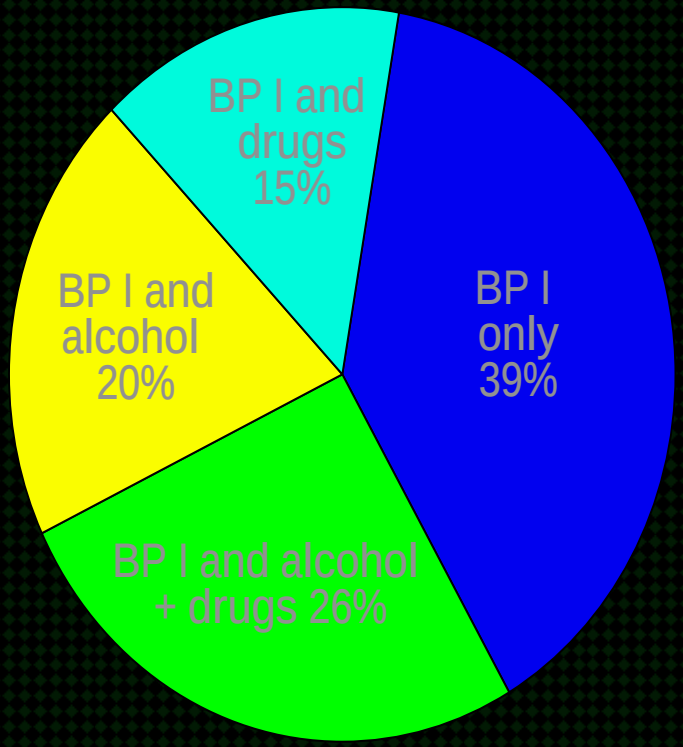
Lifetime Comorbid Axis I Diagnoses in Patients With Bipolar Disorder



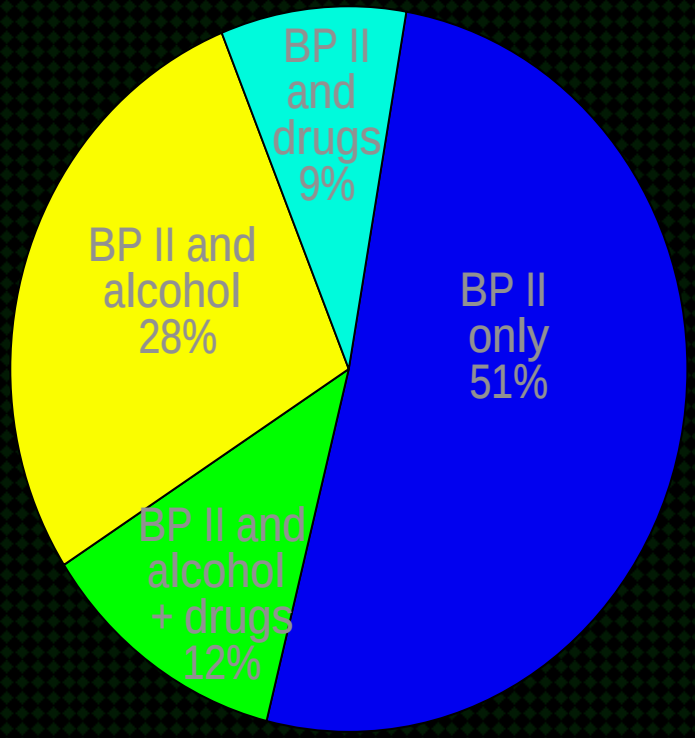
BD=bipolar disorder.

McElroy SL et al. *Am J Psychiatry*. 2001;158:420-426.

Substance Abuse and Bipolar Disorder



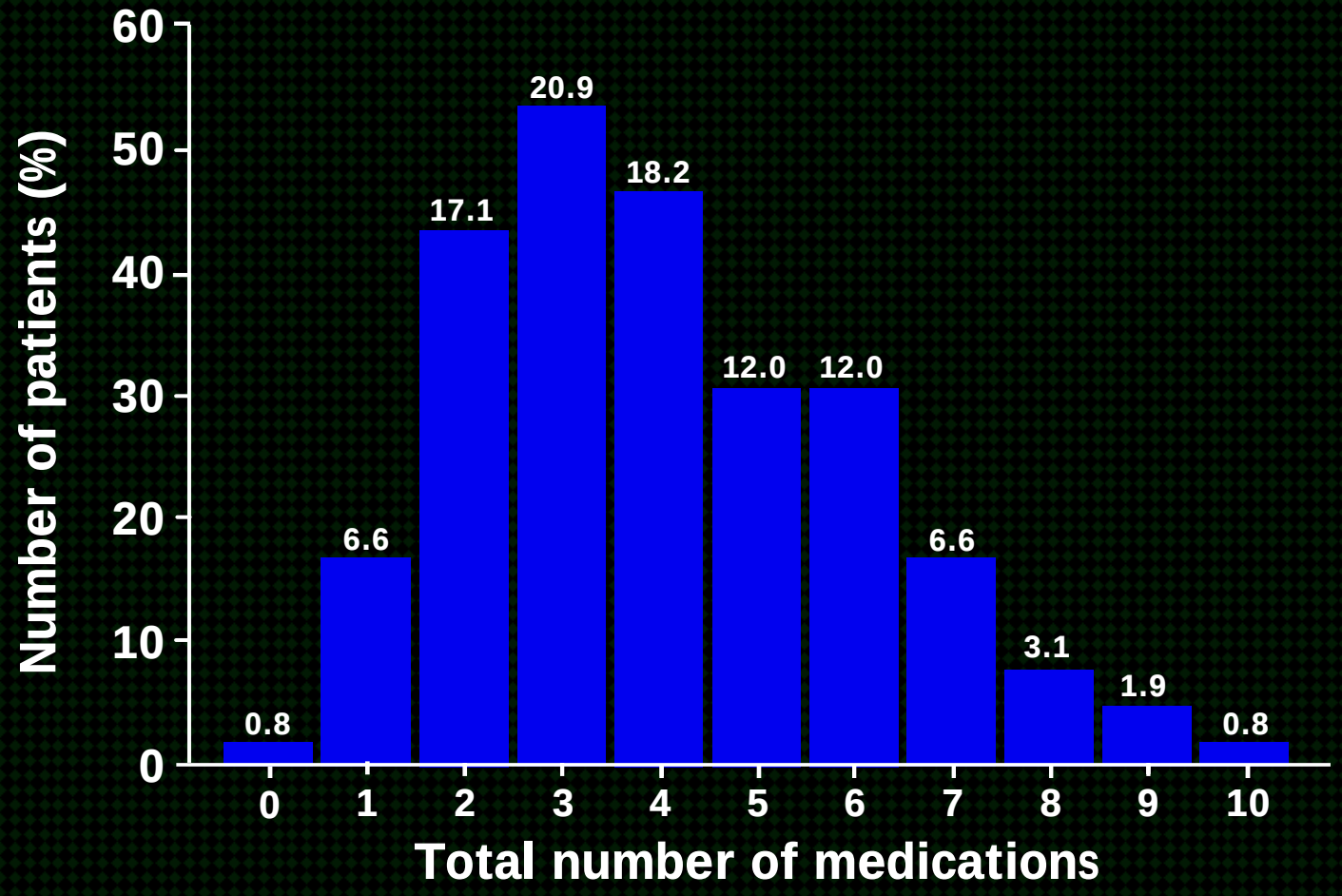
Bipolar I with SA



Bipolar II with SA

Weissman et al, 1991.

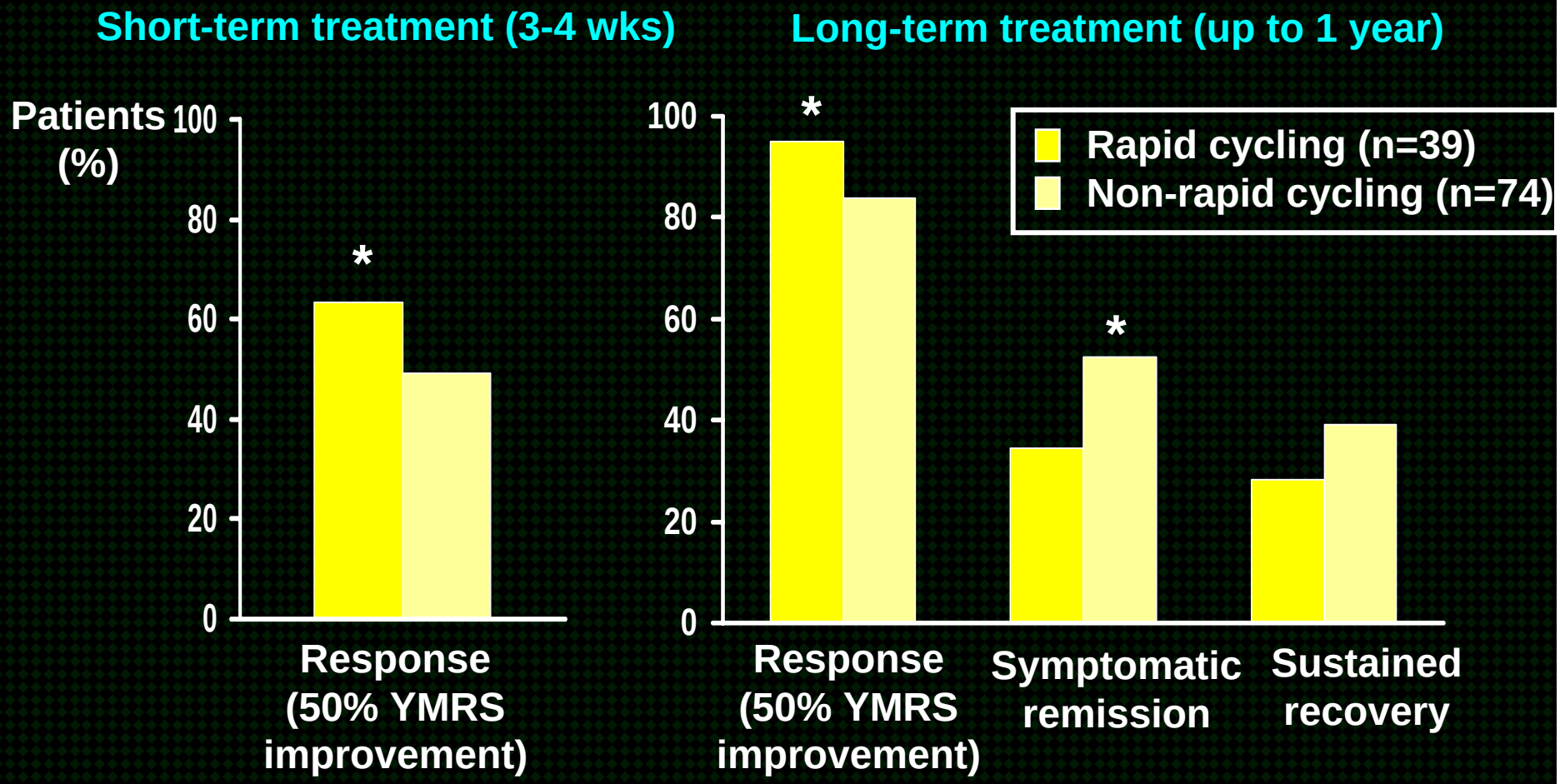
Polypharmacy Therapy in Bipolar Disorder



N=258.

Post RM et al. *J Clin Psychiatry*. 2003;64:680-690.

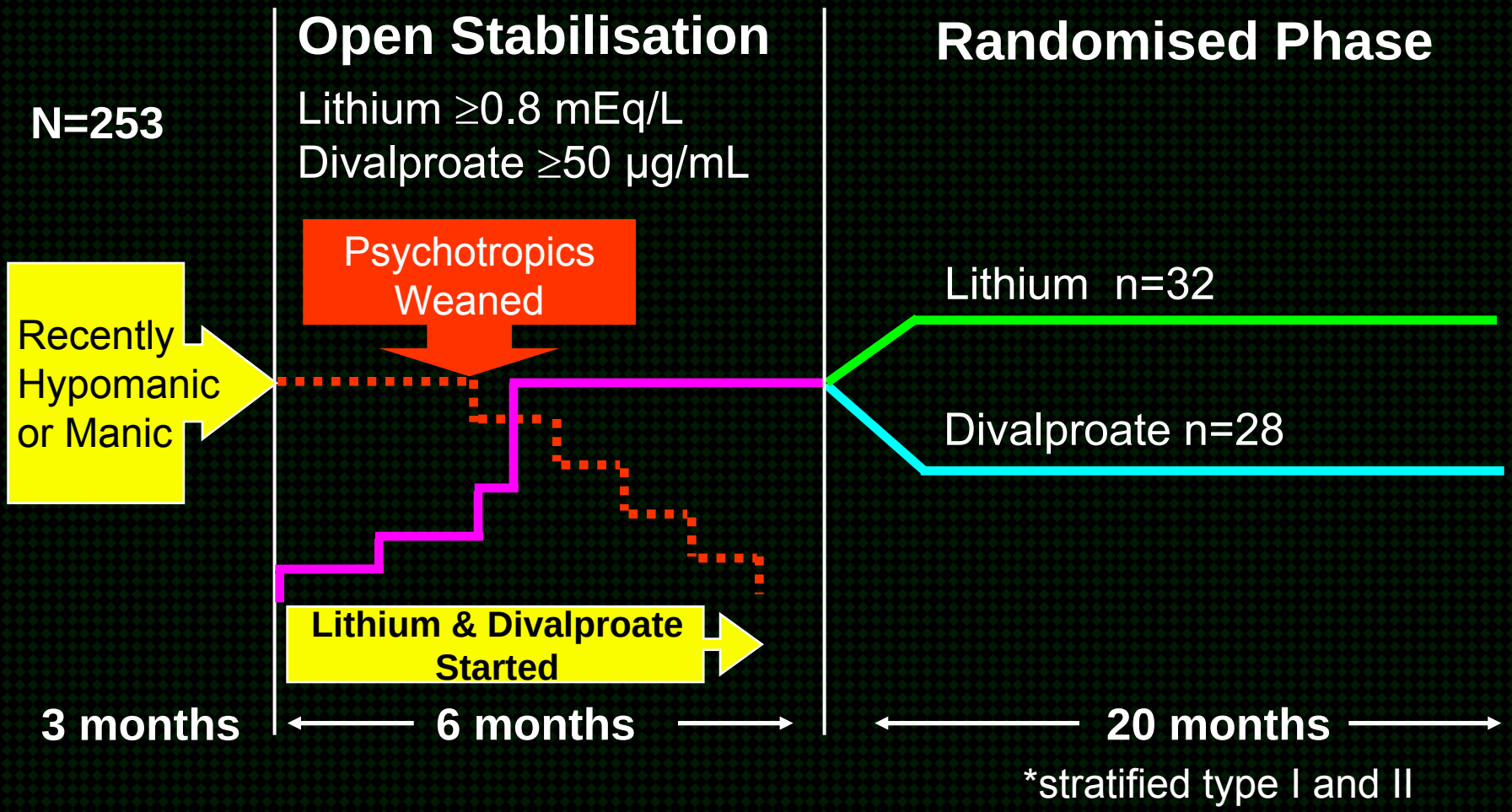
Differential outcome in rapid cycling vs non-rapid cycling



*p≤0.05

Vieta et al, J Clin Psychiatry 2004

Lithium vs. divalproate in rapid cycling bipolar disorder

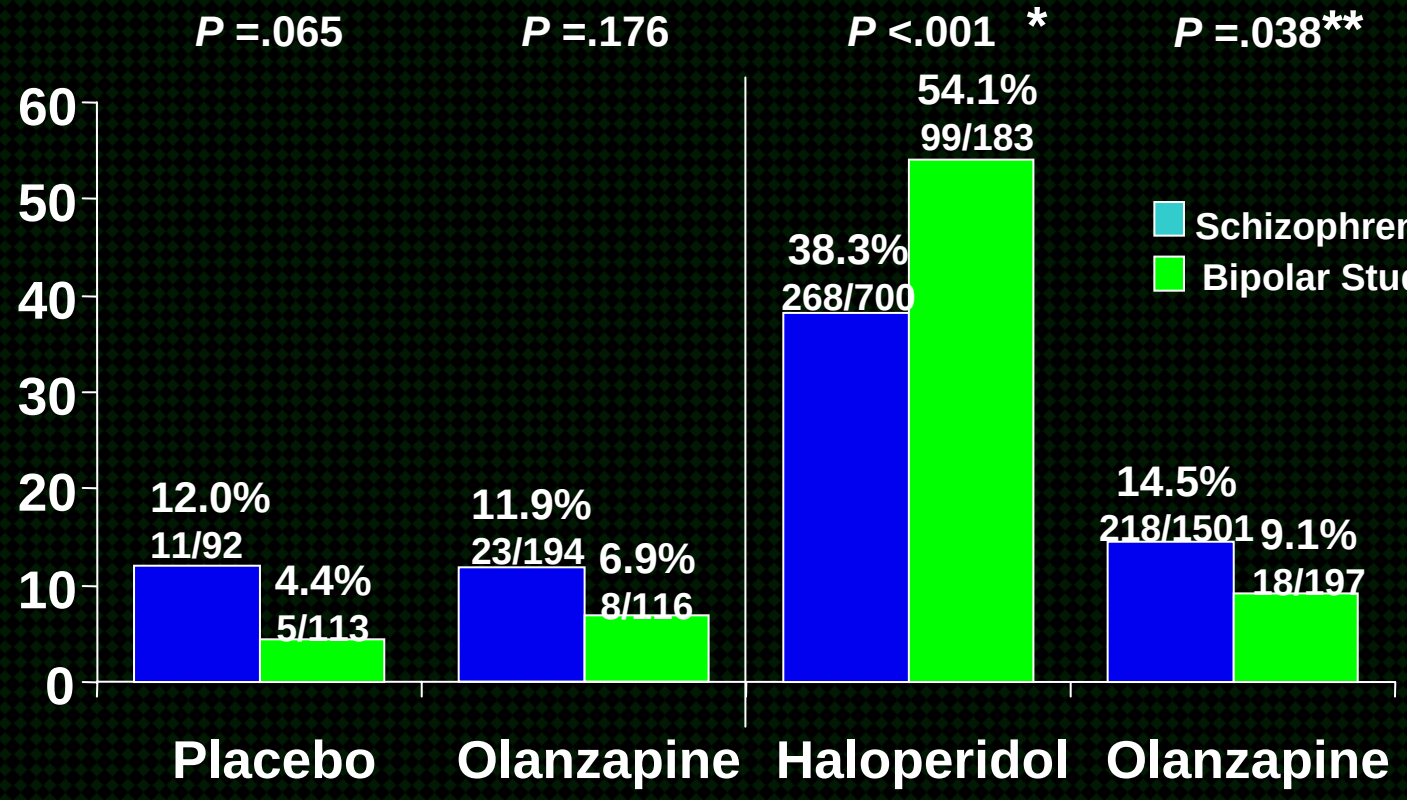


Calabrese et al. *Am J Psychiatry*. 2005.

Methodological flaws of long-term trials in bipolar disorders

- External validity
- Extrapolation of data from other conditions
- Outcomes
- Trial design

Treatment-emergent Parkinsonism (SAS†) in Bipolar Disorder



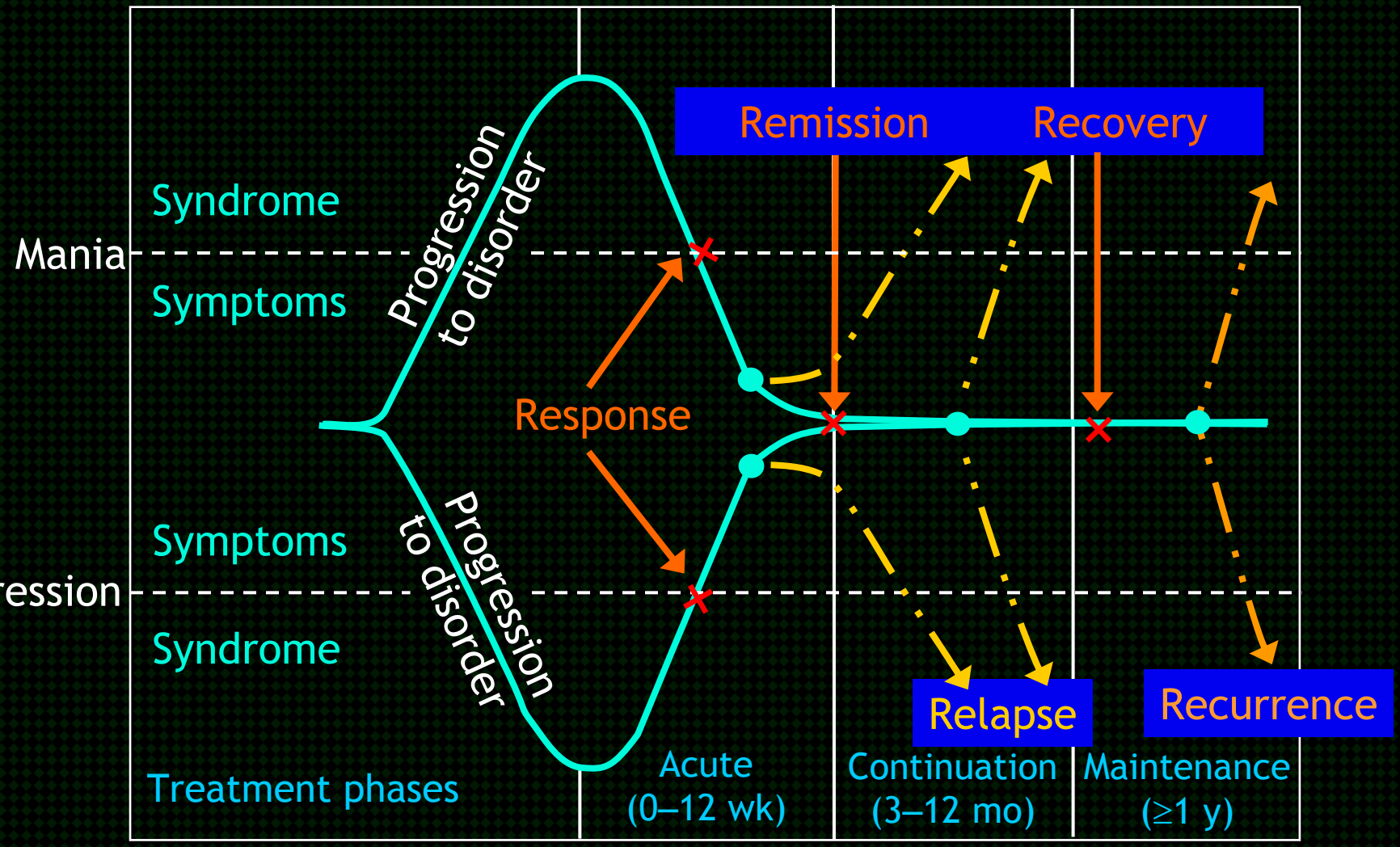
† Defined as a score on the Simpson-Angus scale of ≤ 3 at baseline > 3 anytime thereafter

Cavazzoni PA, et al. *J Clin Psychiatry.* 2006;67:107-113.

Methodological flaws of long-term trials in bipolar disorders

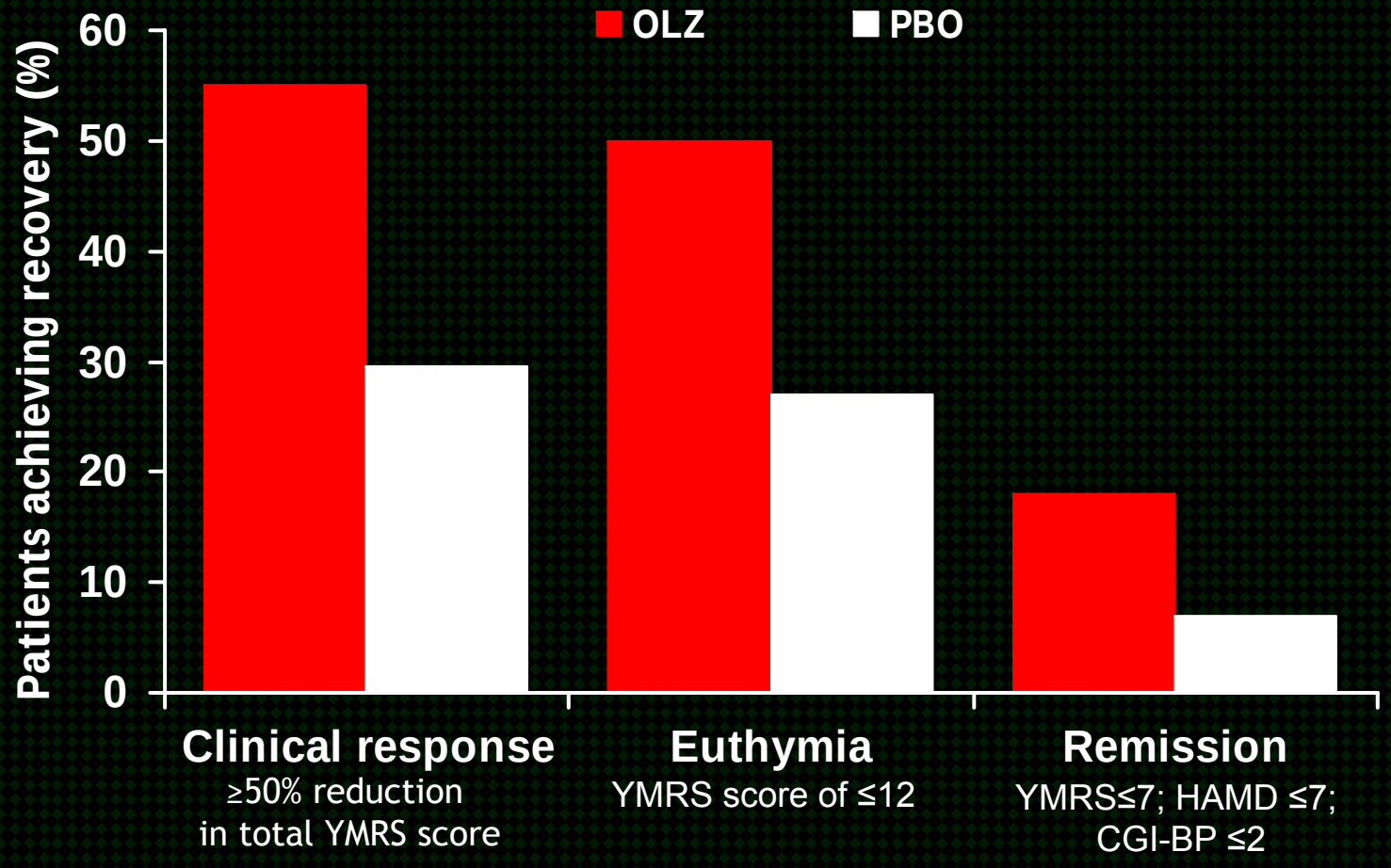
- External validity
- Extrapolation of data from other conditions
- **Outcomes**
- Trial design

Outcomes in Bipolar Disorder



Adapted from Kupfer DJ. *J Clin Psychiatry.* 1991;52(suppl 5):28-34.

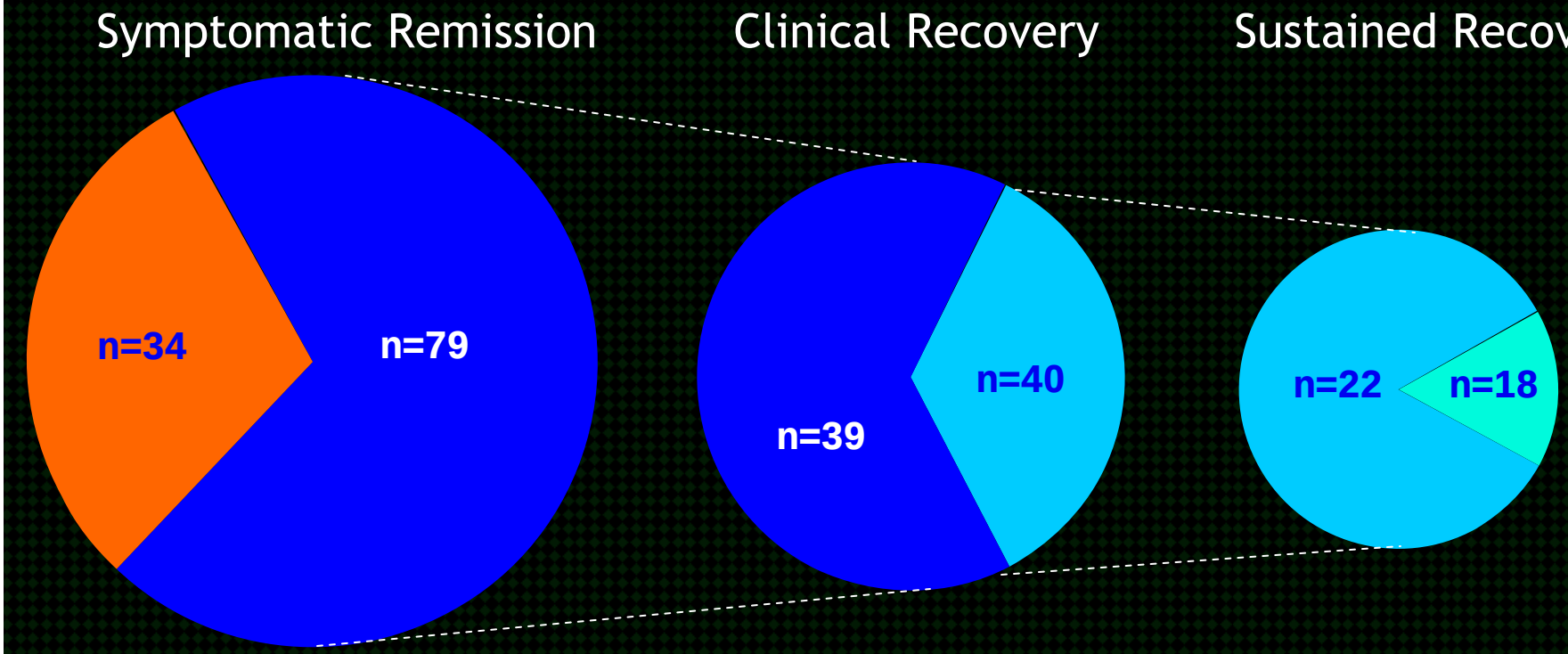
Are We Measuring Remission?



Pooled data from two 3-week acute mania trials using olanzapine vs placebo. N=246.

Chengappa KNR et al. *Bipolar Disord*. 2003;5:1-5.

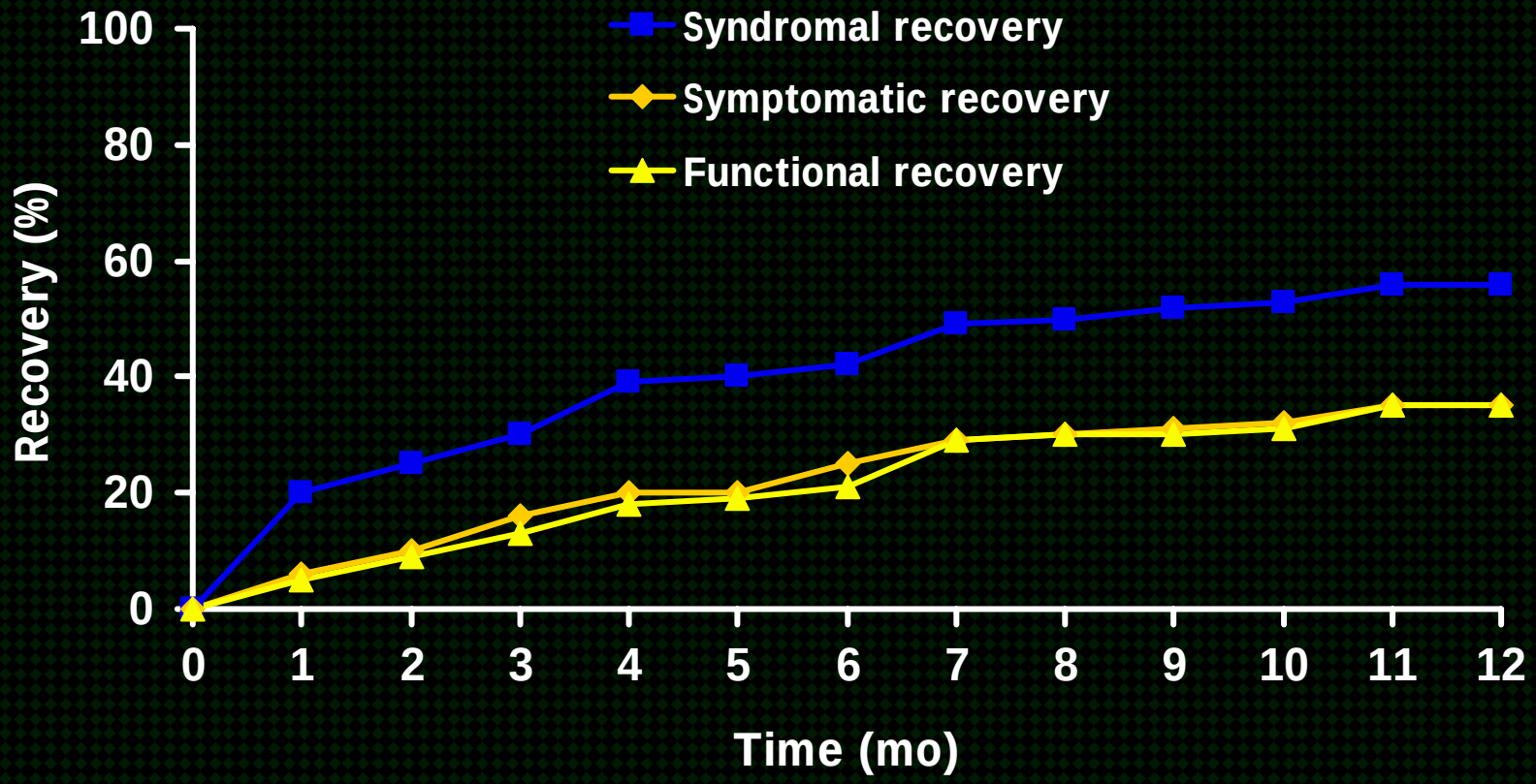
Are We Measuring Remission? Recovery



Open-label continuation study of olanzapine treatment of acute mania.
N=113 patients followed for up to 1 year (mean duration 27.9 ± 20.1 weeks).

Chengappa KNR et al. *Bipolar Disord*. 2005;7:68-76.

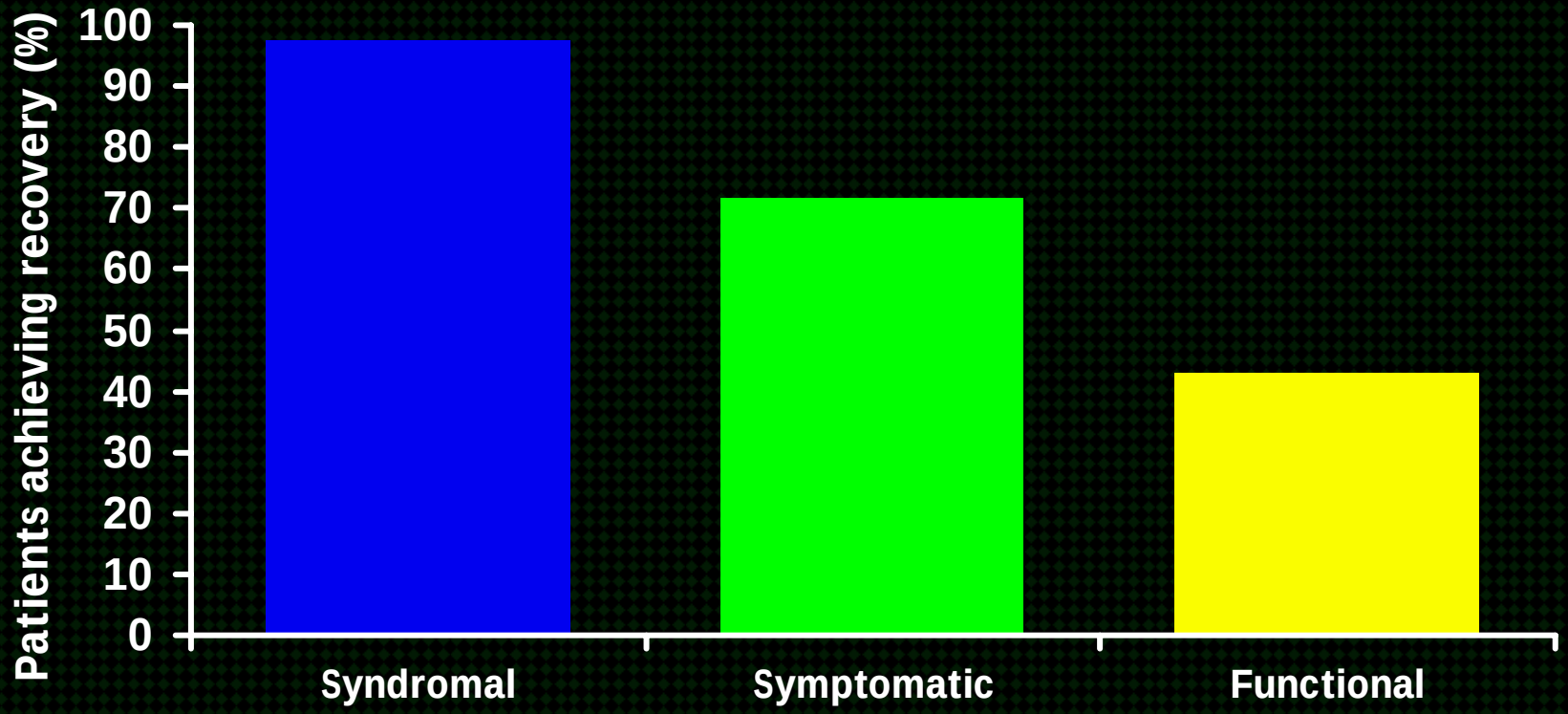
Are We Measuring Remission? Recovery



N=109 patients admitted for first psychiatric hospitalization of affective psychosis.
Evaluated every 2 months for a year.

Strakowski SM et al. *Arch Gen Psychiatry*. 1998;55:49-55.

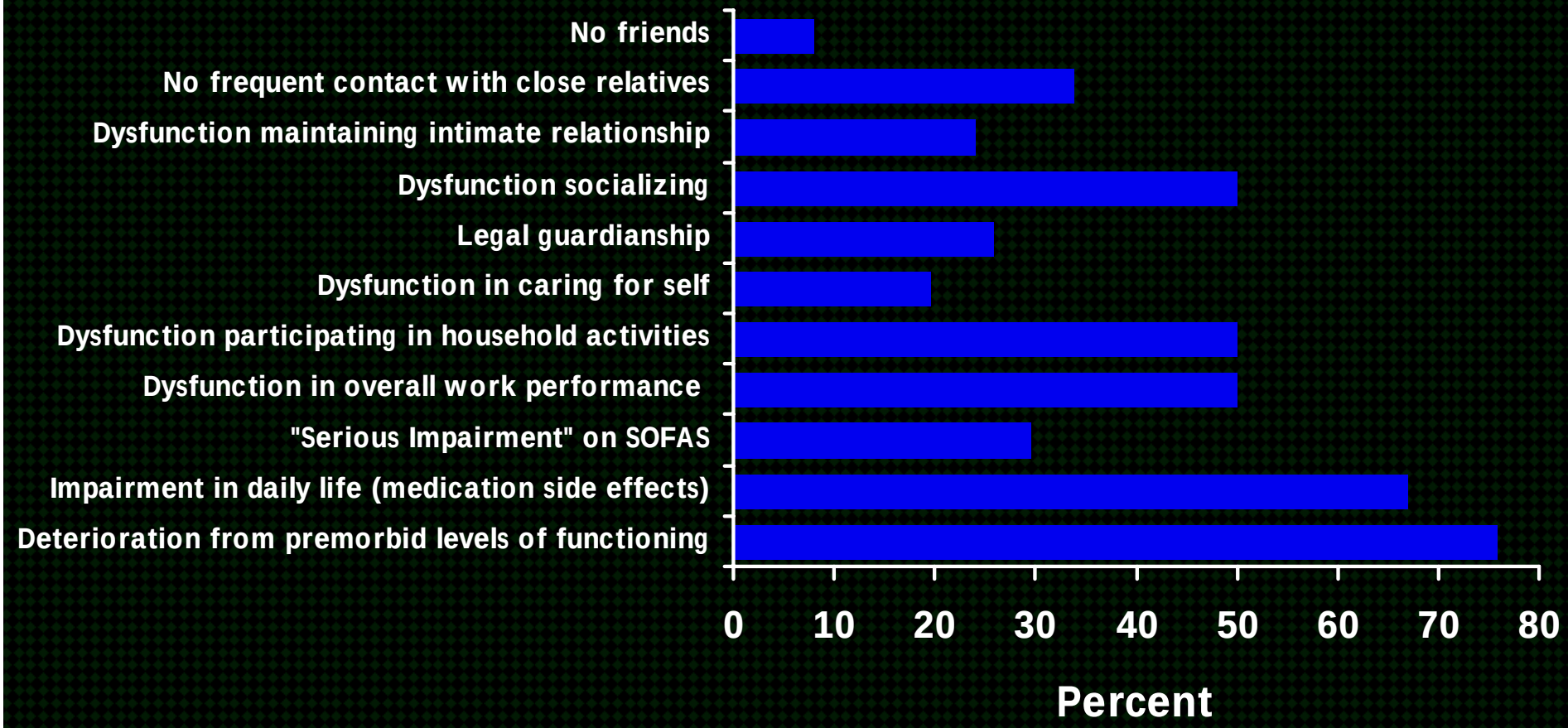
Are We Measuring Remission? Functioning



Prospective 2-year follow-up of 173 bipolar patients after their first lifetime hospitalization.

Tohen M et al. *Am J Psychiatry*. 2003;160:2099-2107.

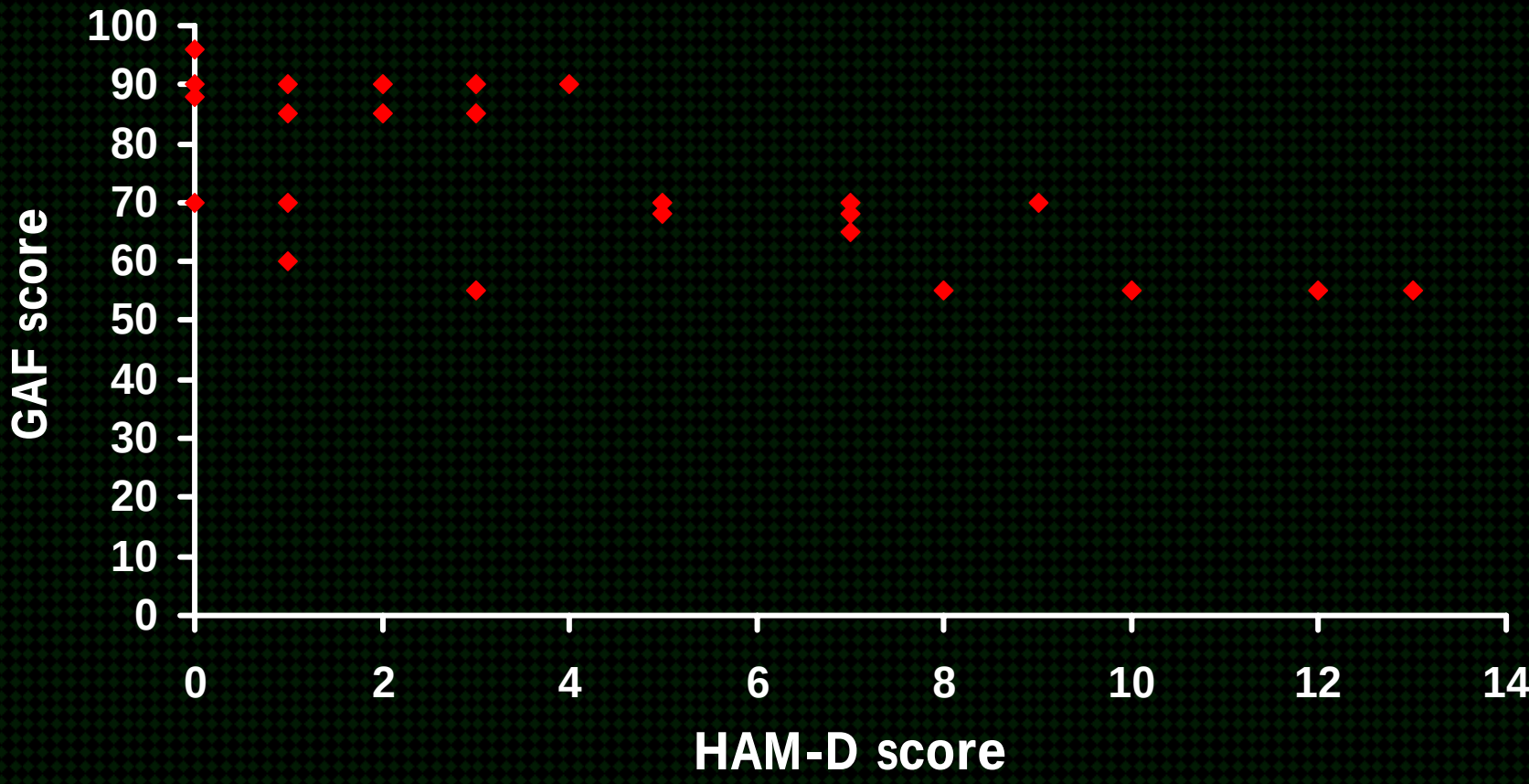
Are We Measuring Remission? Functioning



Australian National Study of Low Prevalence (Psychotic) Disorders.
1-month census of contacts with mental health services and private psychiatric and general practices.
N=112 bipolar subjects.
SOFAS=Social and Occupational Functioning Assessment Score.

Morgan V et al. *Bipolar Disord*. 2005;7:326-337.

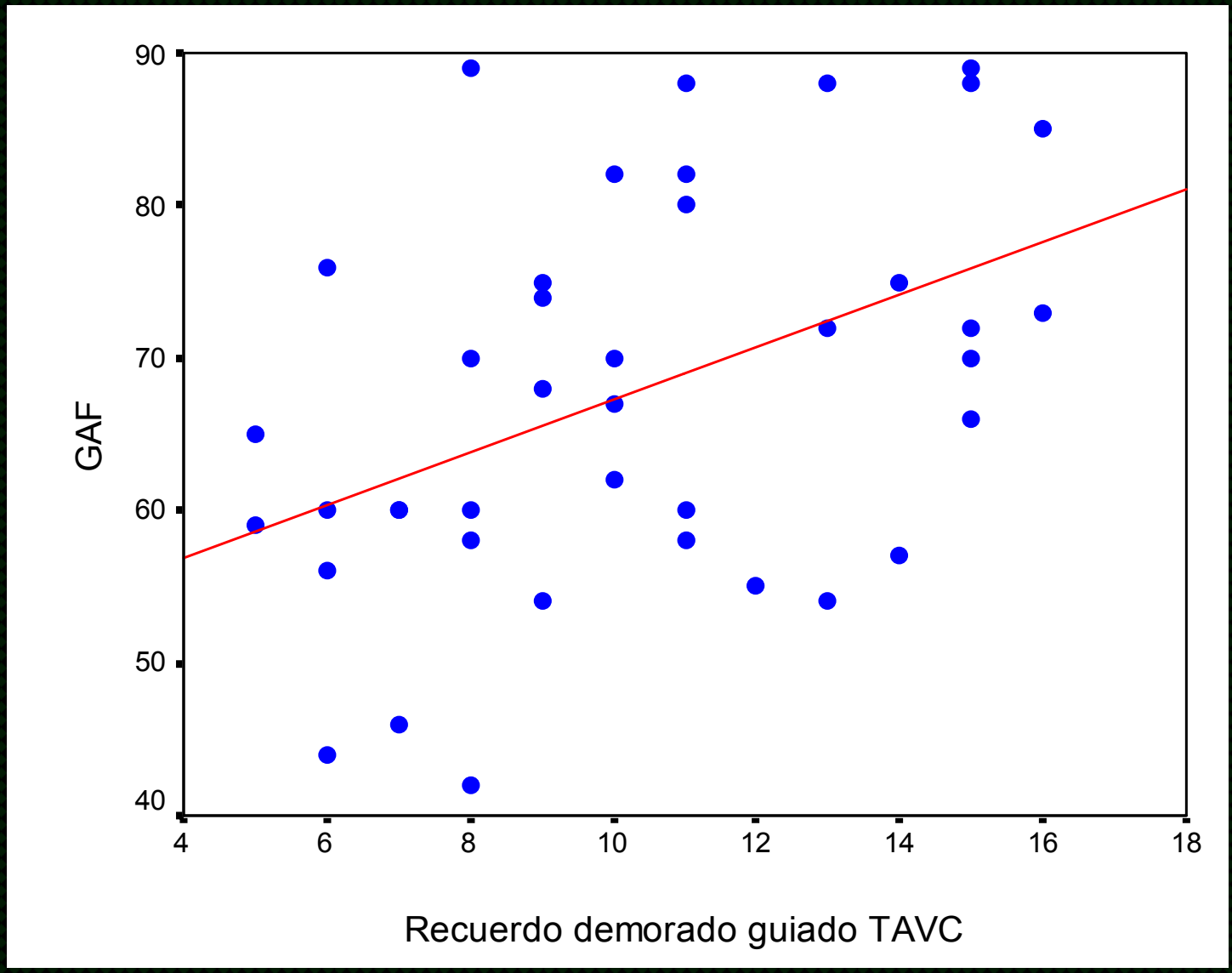
Impact of Subsyndromal Symptoms on Functioning



N=25 bipolar patients euthymic for 3 months.
P=.001 for correlation.

Altshuler LL et al. *J Clin Psychiatry*. 2002;63:807-811.

Verbal memory and functional outcome



Martinez-Aran et al, *Am J Psychiatry*, 2004;161:262-270.

Methodological flaws of long-term trials in bipolar disorders

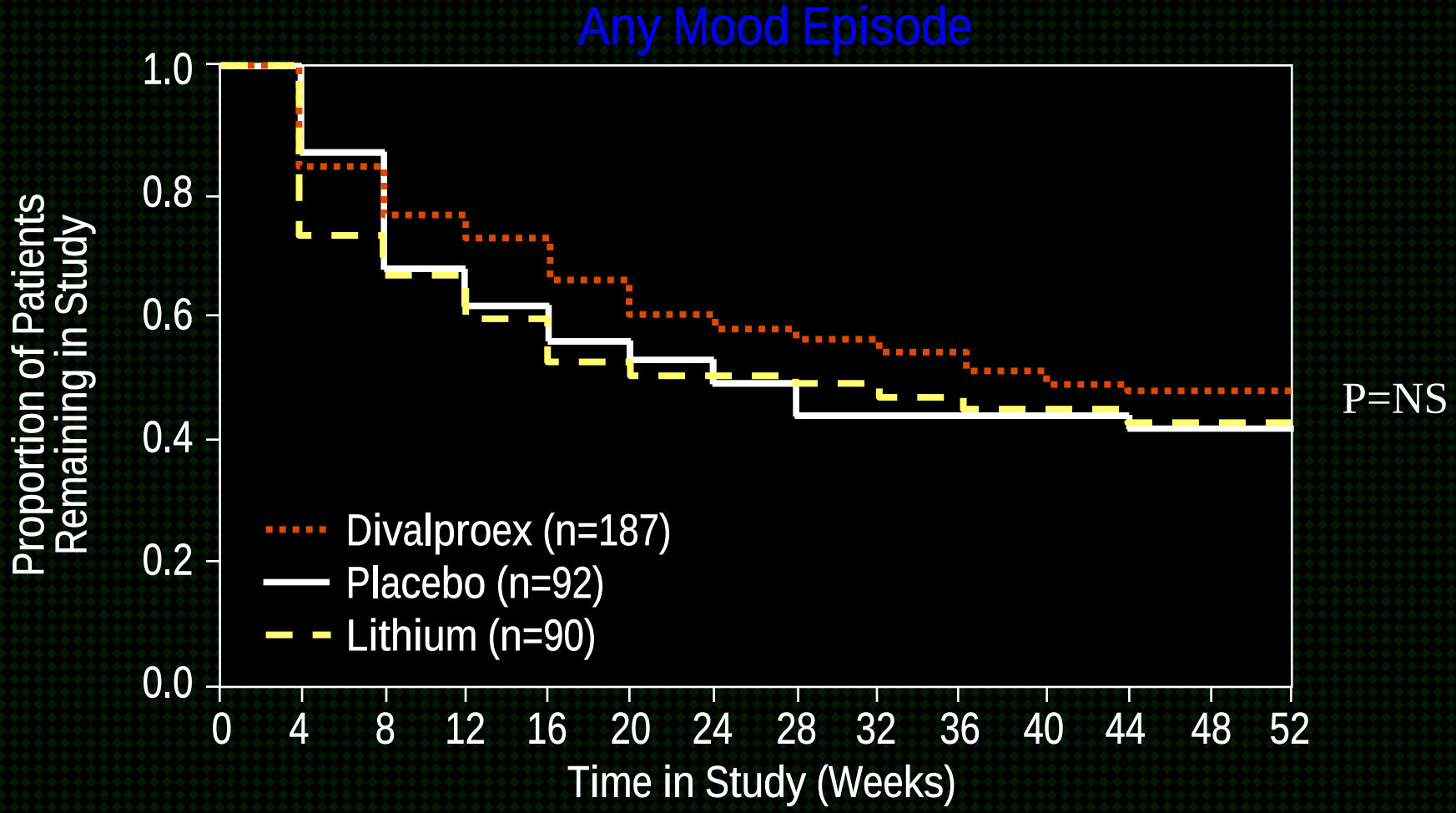
- External validity
- Extrapolation of data from other conditions
- Outcomes
- **Trial design**

Methodological biases of clinical trials in bipolar disorders

- Enriched designs
- Small comparators' samples
- Large samples of experimental drug
- Inadequate dose of the comparator
- Availability of concomitant medication
- Underpowered non-inferiority designs
- Inclusion of patients who are resistant to the comparator
- Taylored outcome measures

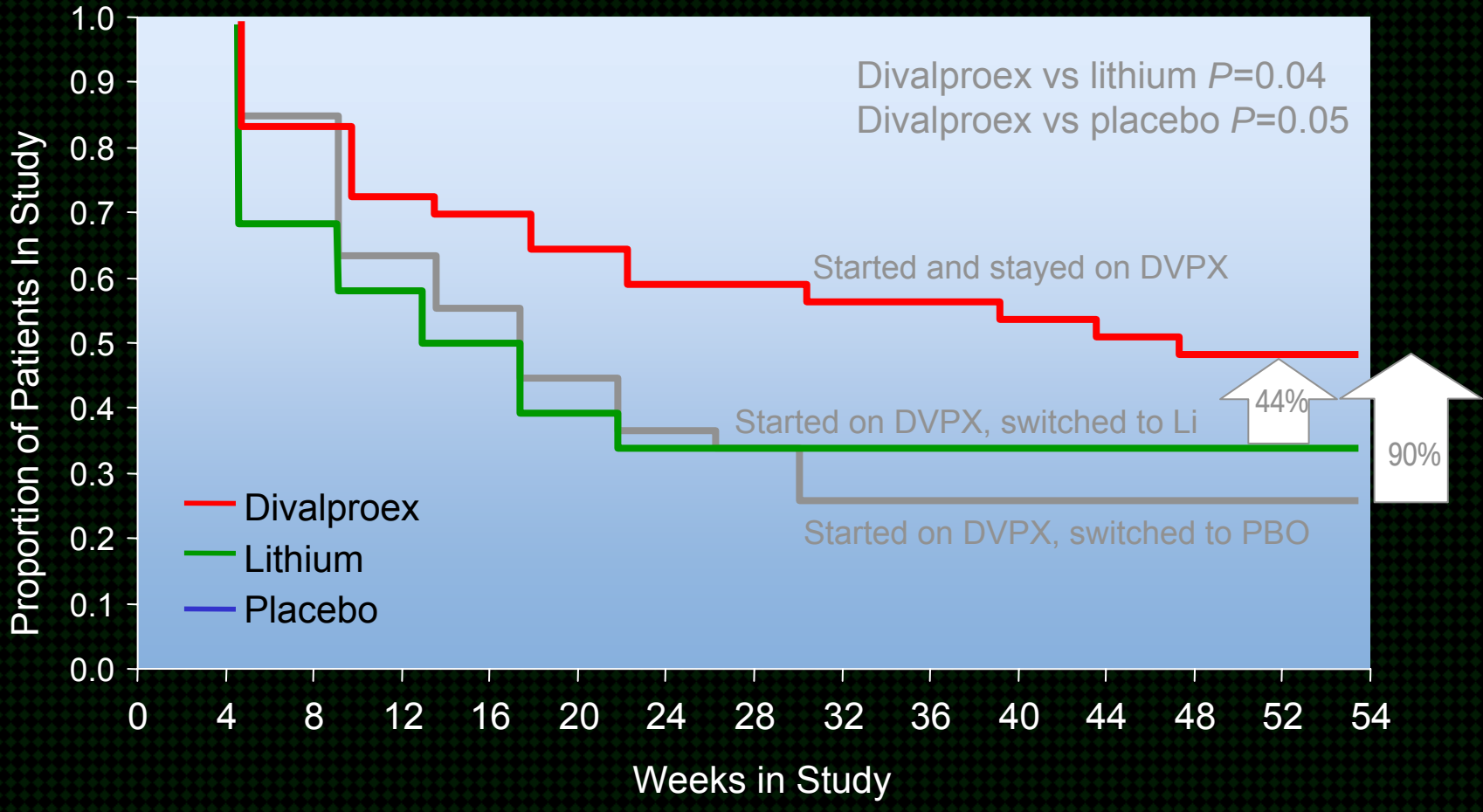
Vieta, in preparation

Divalproex vs Lithium vs Placebo: Time to Any Mood Episode



Bowden CL, et al. *Arch Gen Psychiatry.* 2000;57(5):481-489.

Time to Any Mood Episode for Patients Who Used Divalproex During the Open Phase

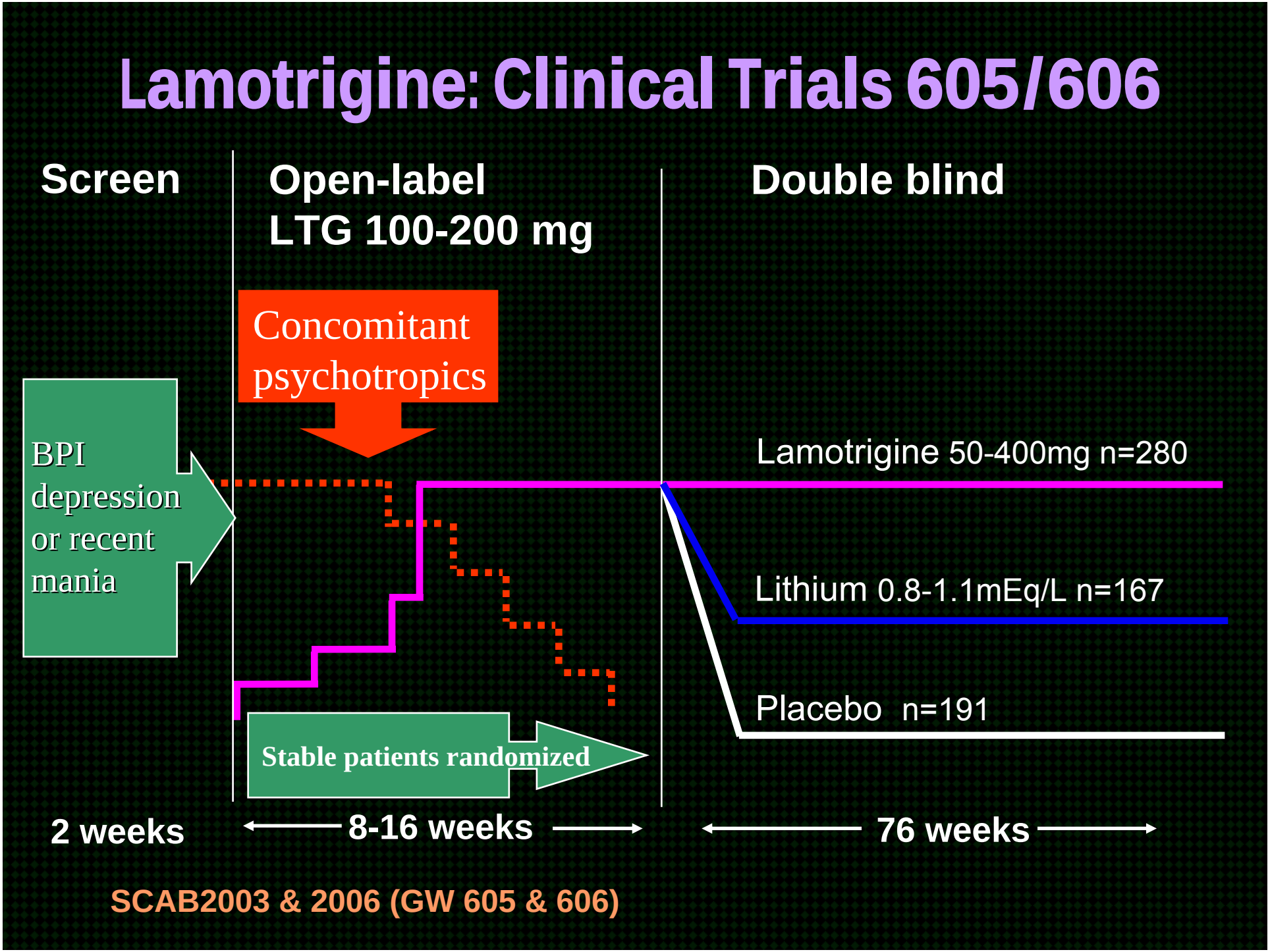


Additional Analyses, Bowden, et. al.
McElroy, et al. Poster presented at IPS, 2003.

Slide 35

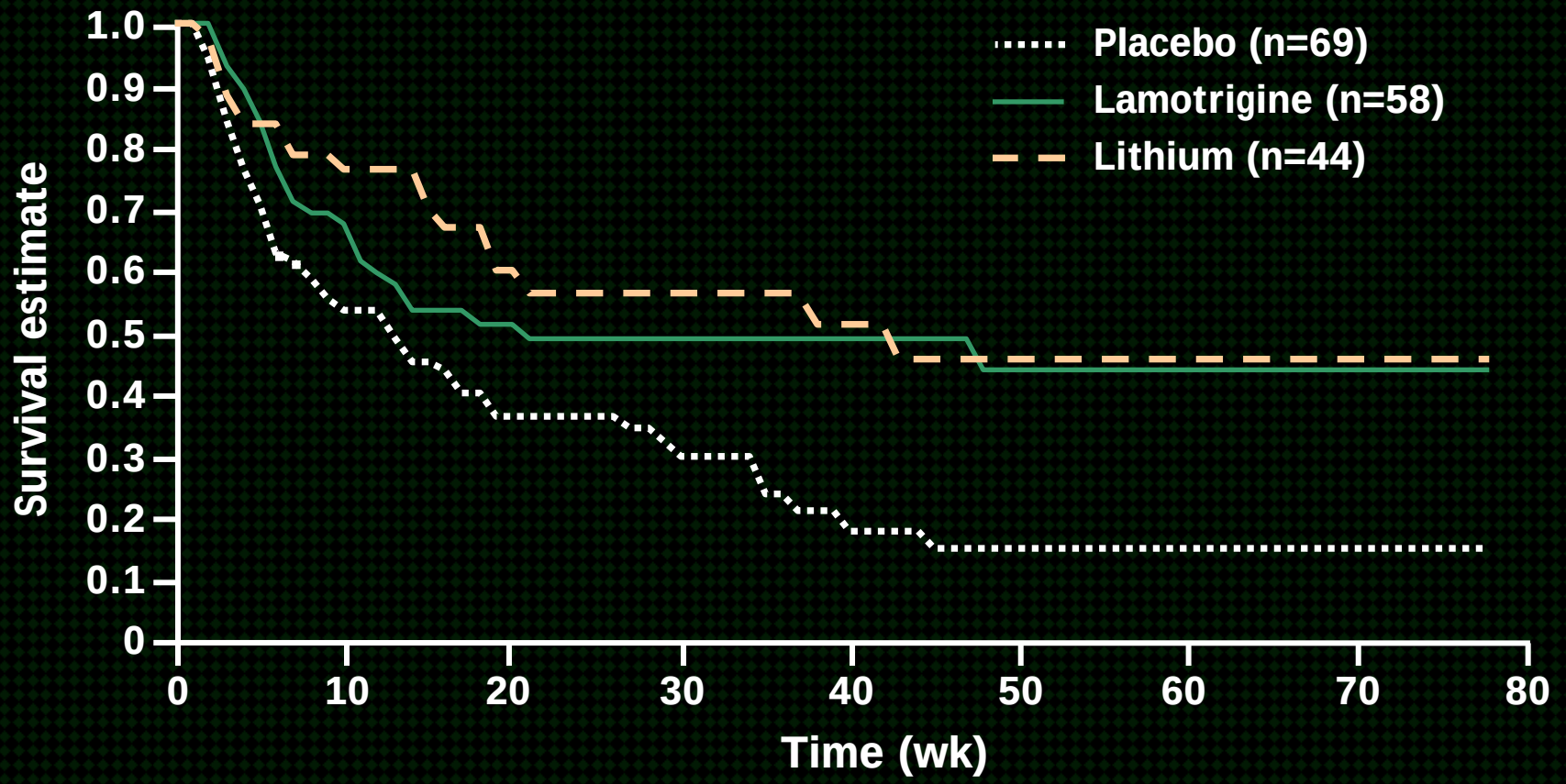
MSOffice2 Not sure Dr. El-Mallakh has signed off on this slide. Will ask during slide review
, 1/10/2006

Lamotrigine: Clinical Trials 605/606



SCAB2003 & 2006 (GW 605 & 606)

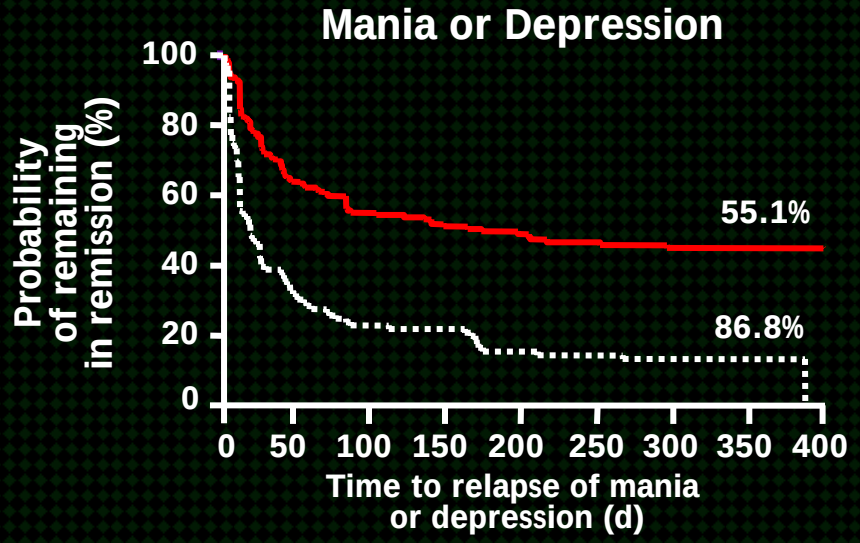
Lamotrigine and Lithium Maintenance Treatment for Bipolar I Disorder in Recently Manic or Hypomanic Patients

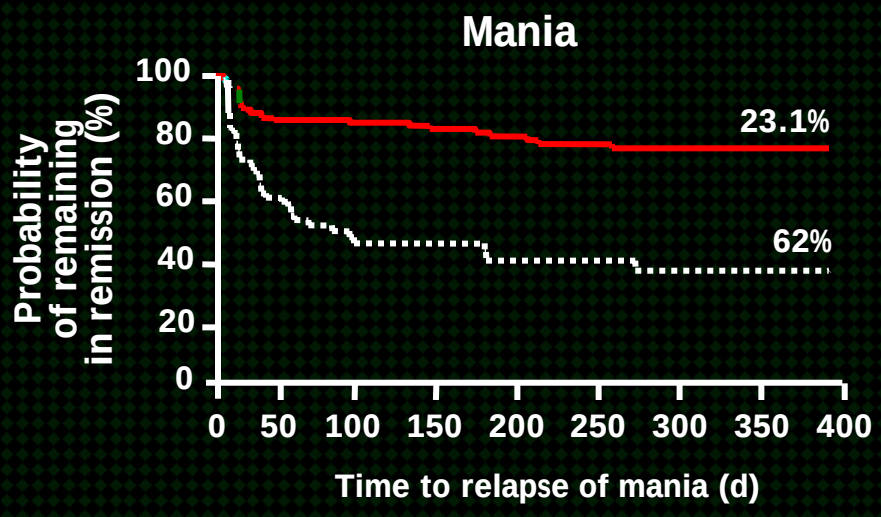


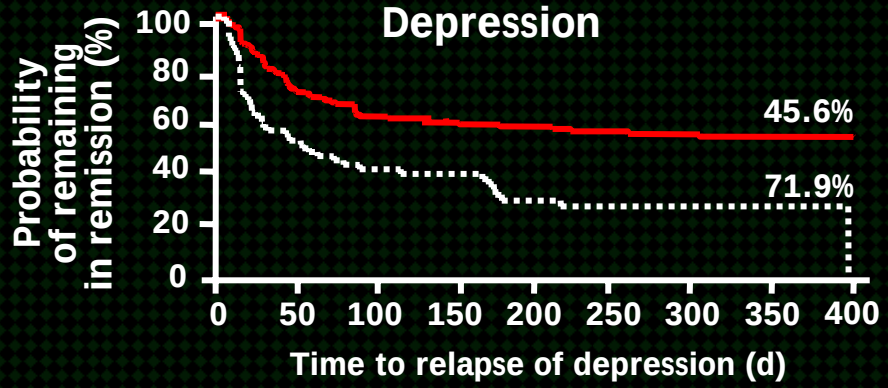
P=.02, lamotrigine vs placebo; *P*=.003, lithium vs placebo; *P*=.46, lamotrigine vs lithium.

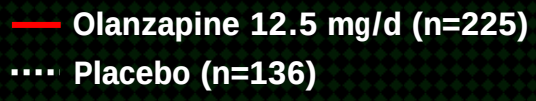
Adapted with permission: Bowden CL et al. *Arch Gen Psychiatry*. 2003;60:392-400.

52-week Olanzapine vs Placebo Maintenance: Time to Relapse Based on Hospitalization and/or Symptomatic Rating Scale Criteria*







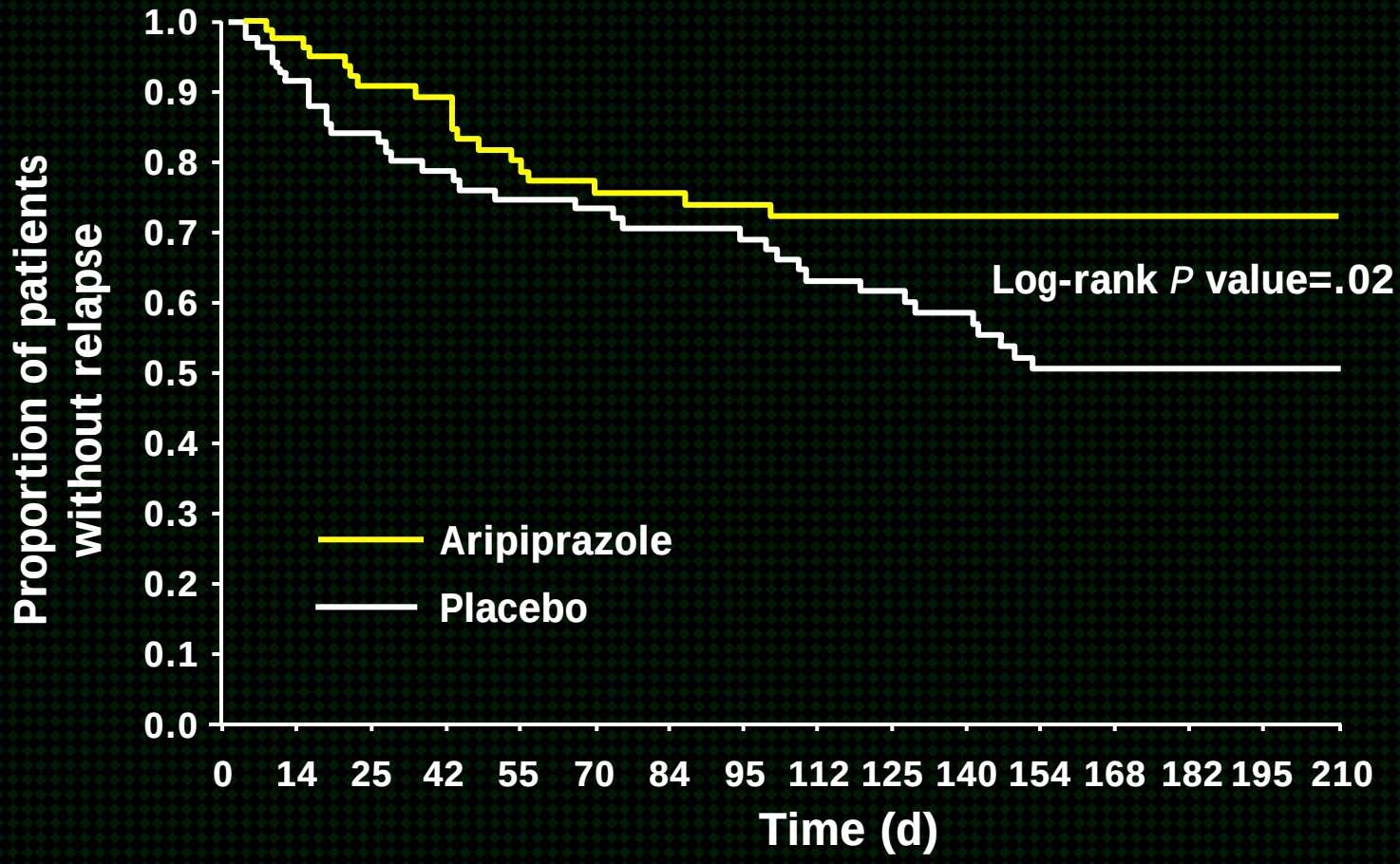


P<.001.

*YMRS or HAM-D-21 total scores ≥15.

Tohen M et al. Presented at: 156th Annual Meeting of the American Psychiatric Association; May 17-22, 2003; San Francisco, CA. Abstract NR197.

Aripiprazole Compared to Placebo After Manic/Mixed Episodes



Relative risk of relapse on aripiprazole=.52 (0.30–0.91).

Keck PE et al. *J Clin Psychiatry.* 2006;67:626-637.

Conclusions

- **Current long-term trials for bipolar disorders have important limitations**
  - Poor external validity
  - Extrapolation of data from other conditions
  - Questionable outcomes
  - Trial design flaws
- **Potential solutions include:**
  - Inclusion of more representative patients
  - Bipolar disorder as a primary indication
  - Definition of meaningful outcomes
  - Development of alternative trial designs

The Stanley
Medical Research
Institute

First Announcement

The Fifth European Stanley Conference on Bipolar Disorder

5-7 October 2006
Barcelona, Catalonia, Spain

Auditorium Sant Joan de Déu
Esplugues de Llobregat (Barcelona)

The number of participants is strictly limited

Professor Eduard Vieta
Chairman
Dr. Francesc Colom
Organizing Committee

It is our great pleasure to welcome you to our beautiful city and to the Fifth European Stanley Conference on Bipolar Disorder. The present conference will focus on newer studies on several promising therapies for bipolar disorders, including drugs, psychological and psychosocial approaches and non-pharmacological biological strategies. We do not want to hold simply another nice conference on bipolar disorders in a pleasant city. Moreover, we think this will be a unique opportunity to gather round a group of experts and freely discuss the recent therapeutic advances in this illness. We personally would like to encourage each and every attendee to participate actively in every session with their questions and comments and to have a very ambitious attitude during all the conference. This is why we hope we will have lots of new research posters presenting non-published and, probably, challenging studies. All together we may find new answers to this very old problem named bipolar disorder.

For more information or to register, please contact:

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