Challenges to design of treatment trials for bipolar depression: An international perspective

Eduard Vieta

Professor of Psychiatry

University of Barcelona

Director of the Bipolar Disorder Unit

Hospital Clínic, Barcelona, Spain

Centro de Investigación Biomédica En Red de Salud Mental

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Challenges

- Diagnostic flaws
- Phenotypic Heterogeneity
- Limited Generalizability
- Trial Duration
- Fixed/Flexible dose
- Choice of comparator (placebo, active, both?)
- Limited interest from patent owners if drug can apply for broader label (major depression)
- Bipolar II disorder
- Mixed states
- Issues related to children and adolescents

Vieta, ISCTM 2009

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ECNP consensus meeting. Bipolar depression. Nice, March 2007

Guy M. Goodwin[a,*], Ian Anderson[b], Celso Arango[c], Charles L. Bowden[d], Chantal Henry[e,f], Philip B. Mitchell[g,h], Willem A. Nolen[i], Eduard Vieta[j], Hans-Ulrich Wittchen[k]

[a] *University Department of Psychiatry, Warneford Hospital, Oxford OX3 7JX, UK*
[b] *Neuroscience and Psychiatry Unit, The University of Manchester, Room G809, Stopford Building, Oxford Road, Manchester, M13 7PT England*
[c] *Unidad de Adolescentes, Hospital General Universitario Gregorio Marañón, CIBER-SAM, Madrid, Spain*
[d] *Department of Psychiatry, University of Texas Health Science Center, San Antonio, TX 78229-3900, USA*
[e] *INSERM, U 841, IMRB, Department of Genetics, Psychiatry Genetics, Creteil, F-94000, France*
[f] *University Paris 12, Faculty of Medicine, IFR10, Creteil, Paris, France*
[g] *School of Psychiatry, University of New South Wales, Sydney, NSW, Australia*
[h] *Black Dog Institute, Sydney, NSW, Australia*
[i] *Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands*
[j] *Bipolar Disorders Program, Institute of Clinical Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, CIBER-SAM, Barcelona, Spain*
[k] *Institute of Clinical Psychology, Center of Clinical Epidemiology and Longitudinal Studies, Technische Universitaet, Dresden, Germany*

ECNP Consensus

- Depression in bipolar disorder: This is where most of the burden is
- Diagnosis: DSM-IV. Undistinguishable from unipolar major depression
- Children: Conservative definition
- Generalizability: Allow comorbidities (especially anxiety disorders) and rapid cycling
- Severity: Entry cut-off: 20 (HAM-D), best assay sensitivity for 24

Goodwin et al, Eur Neuropsychopharmacol 2008

ECNP Consensus

- Rating scales: Atypical symptoms not well captured with MADRS/HAM-D-17 (HAM-D-24?)
- Trial design: 3-arm (experimental drug, placebo, active comparator) preferred
- Monotherapy preferred, adjunctive design advisable after positive results with monotherapy
- Duration: 6-8 weeks primary outcome, plus 6 more weeks for safety assessment (switch)
- Long-term trials: discontinuation design (time to intervention)

Goodwin et al, Eur Neuropsychopharmacol 2008

Key factors for study success

- Compound
- Good selection of study sites
- Trained raters
- Fixed-dose design
- Severity

Vieta, ISCTM 2009

Reasons for placebo response in Bipolar Depression

- Patients less severe
- Close and careful follow-up
- Collaborating pacients (consent)
- Subjective measurements of efficacy
- Spontaneous remission (regression to the mean)
- Diagnostic uncertainity/heterogeneity
- Rescue medication
- “Background noise” (poor rating/number of sites)

Vieta, Bipolar Disord 2002; Vieta & Carne, Psychother Psychosom, 2005


You may be suffering from Bipolar Disorder and you're not alone.
Do you have a decreased need for sleep or have mood swings?
Have you engaged in risky activities, or spent money that got you into trouble?
Ever feel so hyper people comment that you don't seem like yourself?
Do you have thoughts race through your mind that you can't slow down?
A research study of an investigational drug for Bipolar Disorder is now accepting volunteers to participate in this study at no cost to you.
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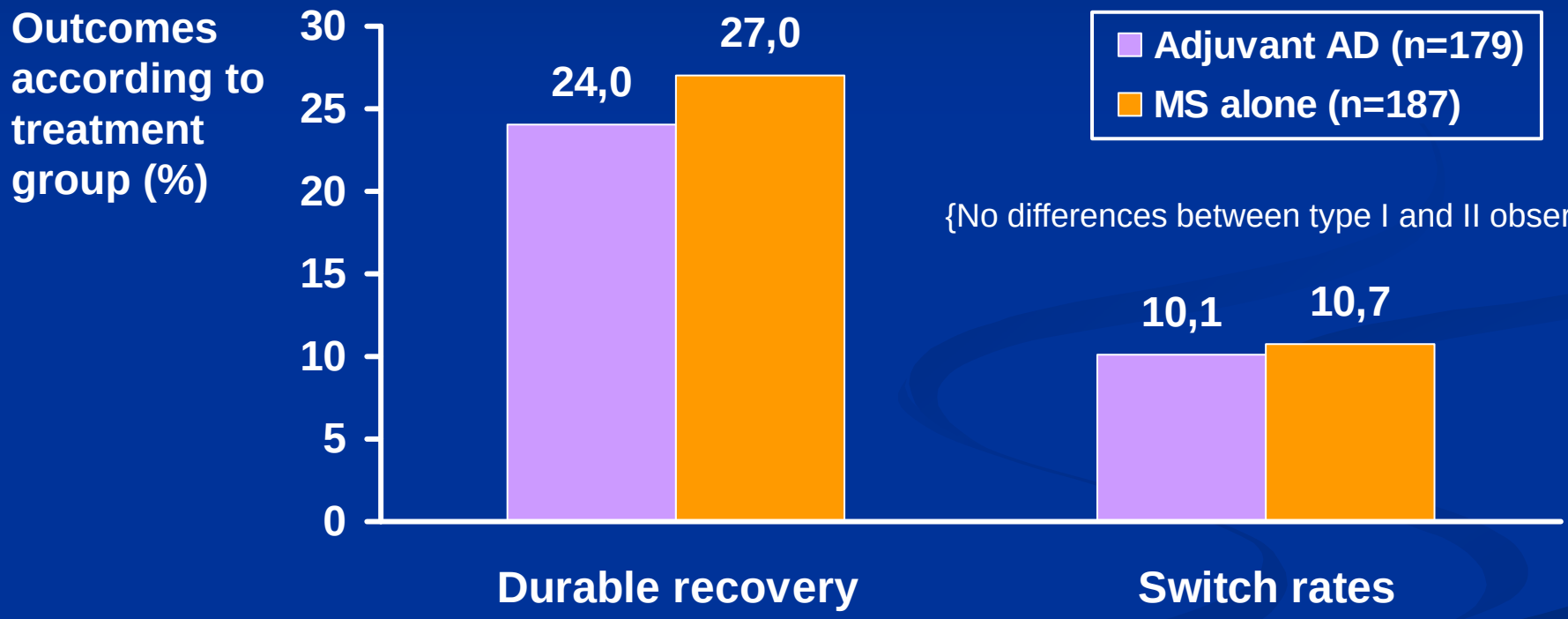
The failure of antidepressants in bipolar I or II depression

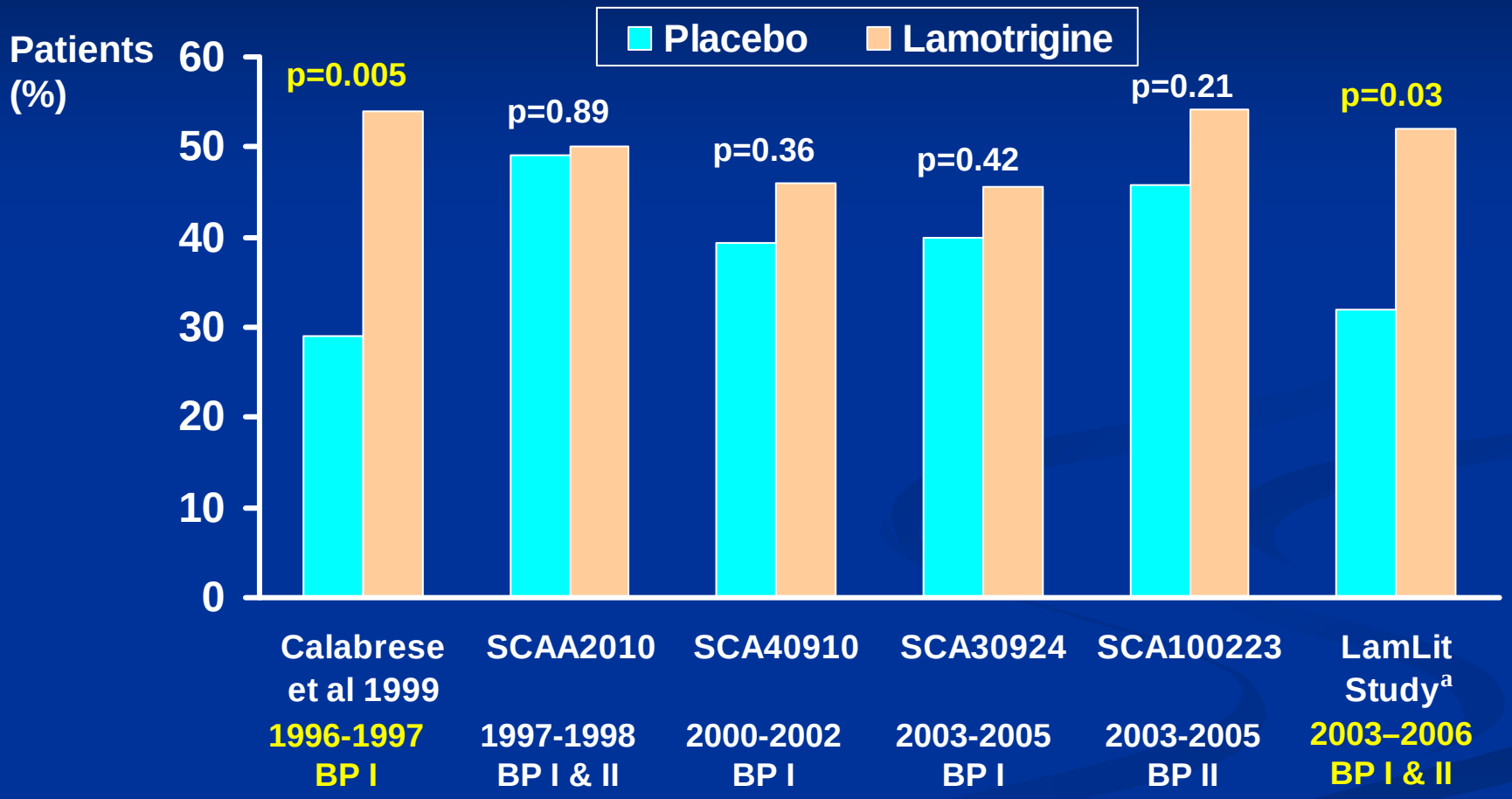
Primary effectiveness outcome



Durable recovery = 8 wks euthymia (no more than 2 depressive or 2 manic symptoms)
Switch = DSM criteria for hypomania or mania or required treatment
MS = lithium, carbamazepine, valproate or any approved atypical; AD = bupropion or paroxetine

Sachs G, Nierenberg A, Calabrese J, et al. **NEJM** 2007 Apr 26;356(17):1711-22.

Selection of sites and rater training: MADRS response rates across six lamotrigine multicentre acute bipolar depression studies



MADRS response = 50% improvement over baseline

Pooled Relative Risk of Response: 1.22 CI 1.06-1.41. p=0.005. Geddes et al 2007

Calabrese et al 1999; Calabrese et al 2008;
[a]Van der Loos et al, 2009

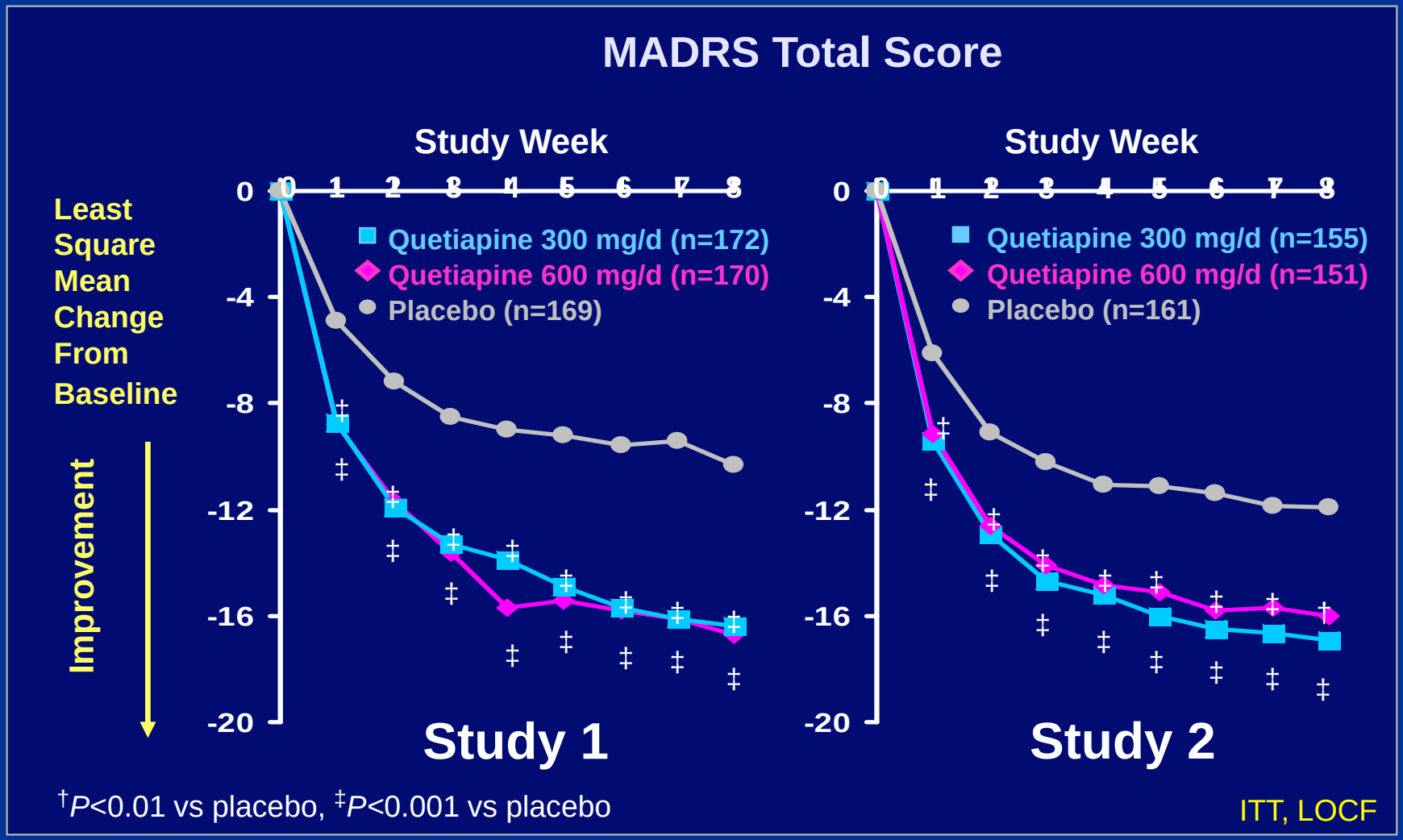
Breaking paradigms: Atypical antipsychotics in acute bipolar depression

	Olanzapine	Quetiapine	Aripiprazole
Comparator	Placebo, OFC	Placebo	Placebo
Dose (mg/day)	5-20 (25 & 50 Flu)	300 & 600	5-30mg
Time (weeks)	8	8	8
Patients	BP I in & outpatients incl. rapid cycling	BP I and II outpatients incl. rapid cycling	BP I outpatients incl. rapid cycling
Endpoints	MADRS, CGI, HAM-A	MADRS, HAM-D, HAM-A, CGI, PSQI, Q-LES-Q	MADRS, CGI-BP

OFC, olanzapine plus fluoxetine
Flu, fluoxetine

Tohen et al 2003; Calabrese et al 2005
Thase et al 2006; Thase et al 2008

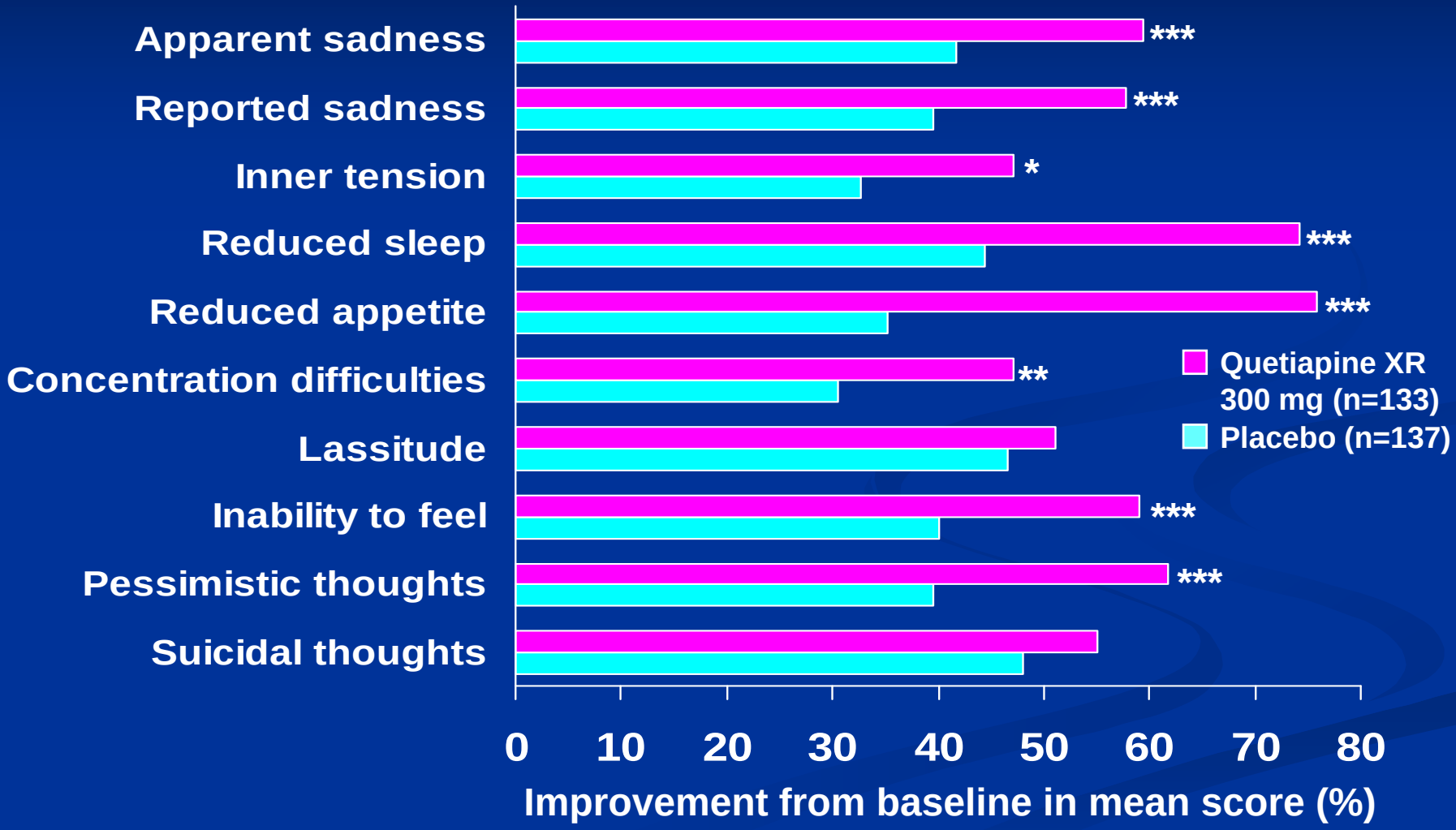
Trial design: Fixed dose studies



Calabrese J, et al. *Am J Psychiatry*. 2005;162:1351-1360.

Thase ME, et al. *J Clin Psychopharm*. 2006; 26:600-609.

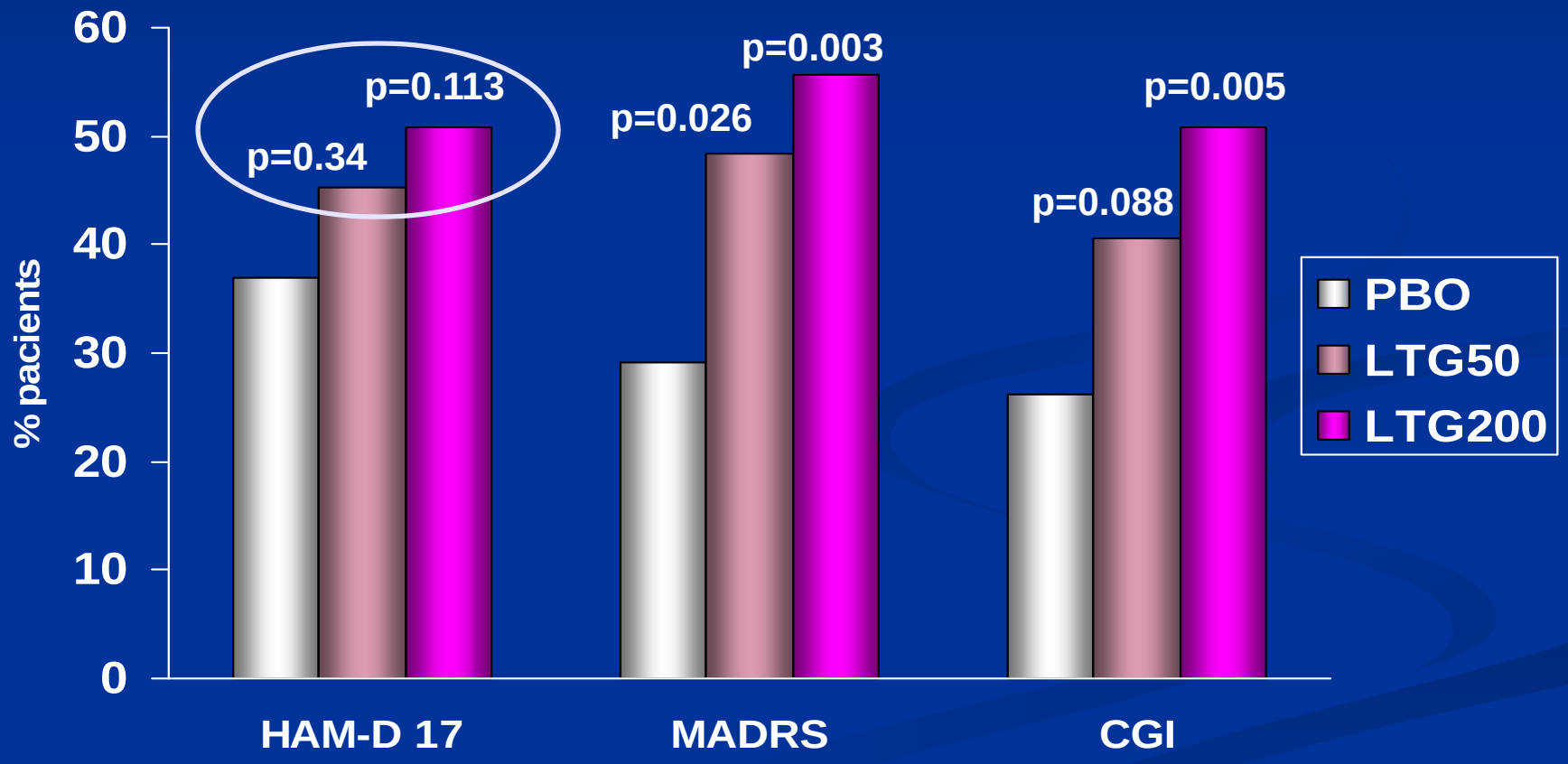
Internal validity: Impact on core items



*p<0.05; **p<0.01; ***p<0.001 vs placebo
MITT, LOCF

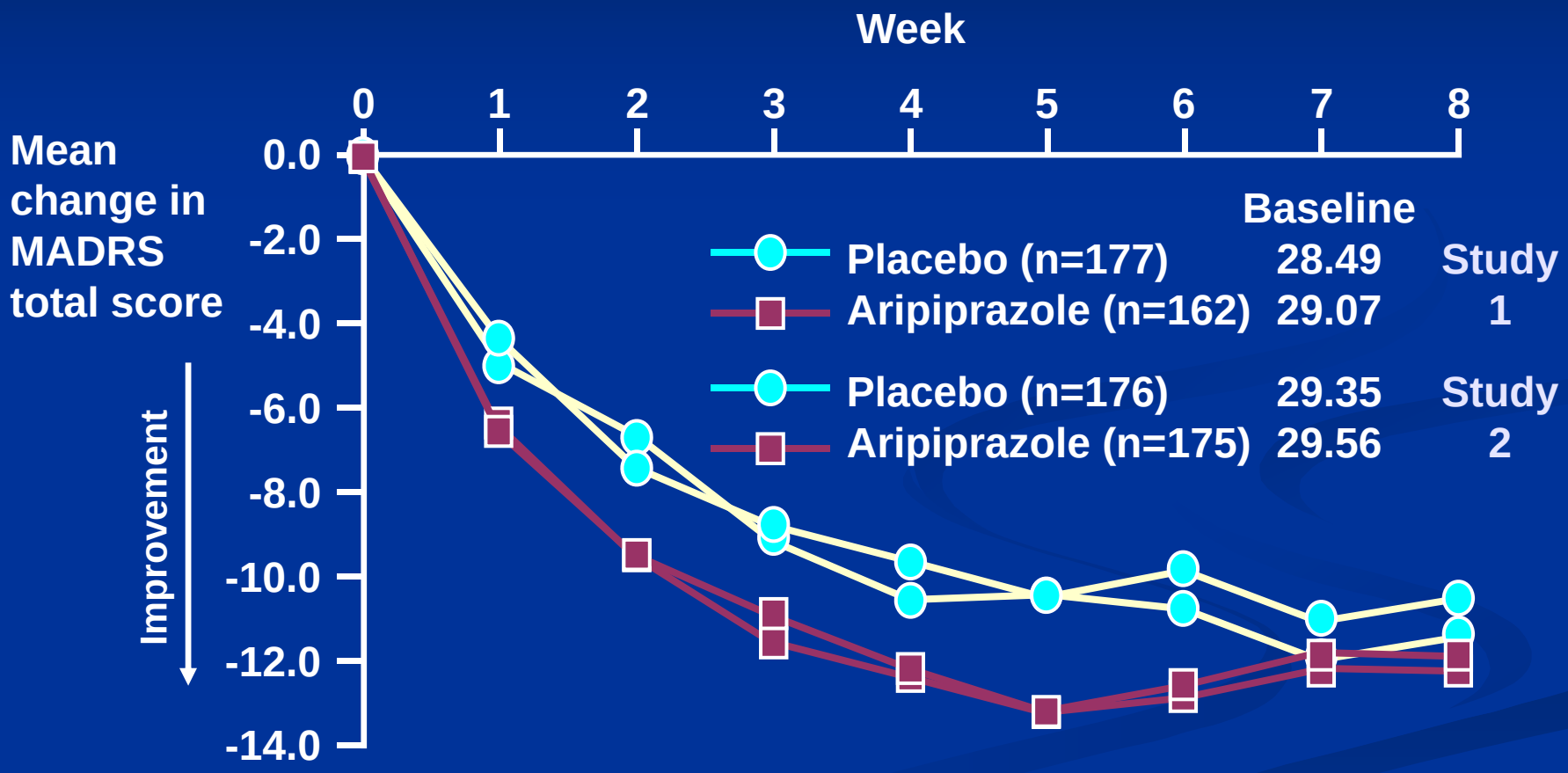
Suppes et al, 2008

Selection of the primary outcome: Rating scales



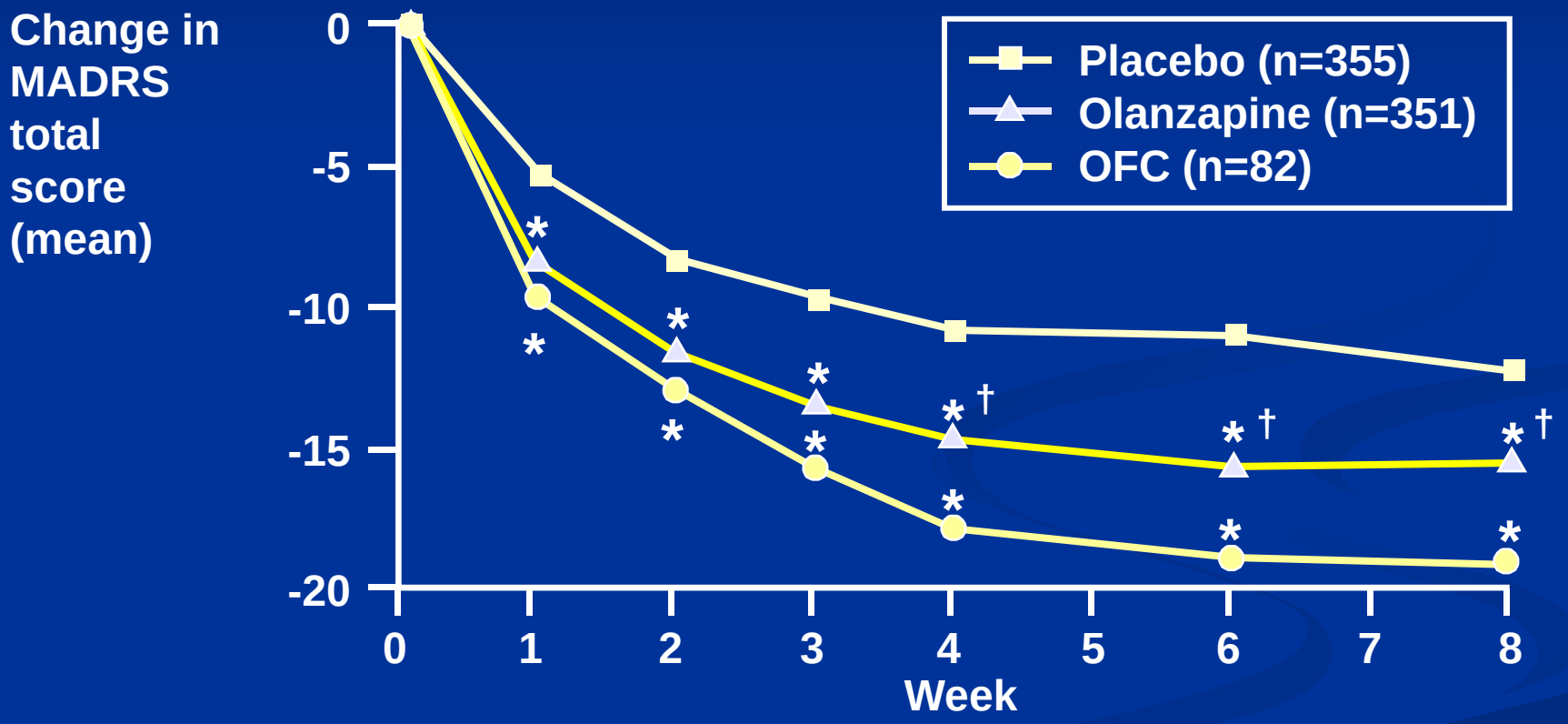
Study SCAB2001(602), Calabrese et al. 1999

Trial duration: positive at week 6, negative at week 8



Thase et al 2008

Positive data for antidepressants?: MADRS total score over 8 weeks for olanzapine, OFC or placebo

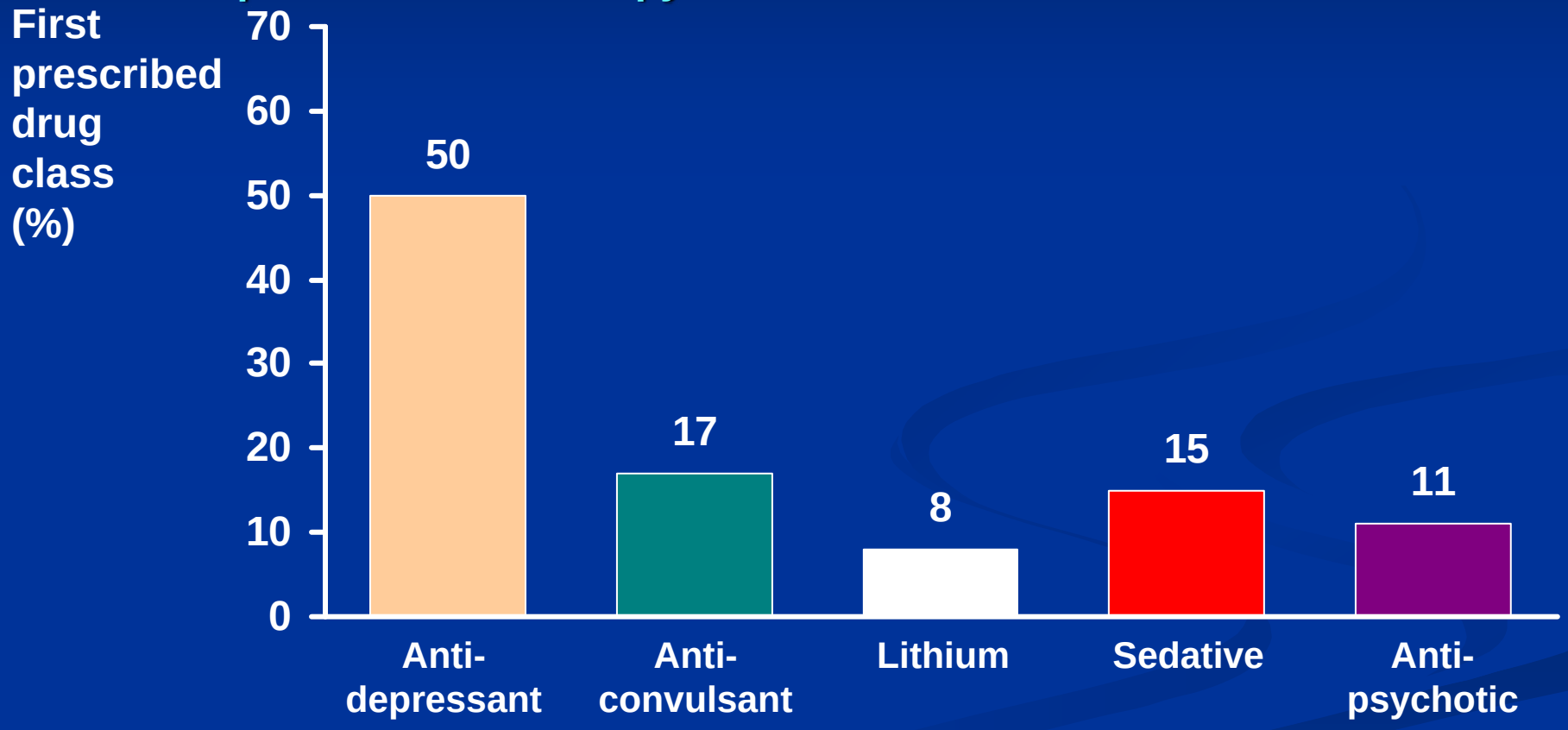


*p<0.001 vs placebo for olanzapine and OFC
†p<0.02 OFC vs olanzapine
OFC, olanzapine plus fluoxetine

Tohen et al 2003

The gap between scientific evidence and prescription habits: Initial treatment of bipolar disorders in the US

Antidepressant monotherapy twice as common as mood stabilisers



n=7,760 (63% of 12,237 received monotherapy); based on Commercial and Medicare claims. Mood stabilisers: lithium, valproate, carbamazapine, gabapentin, lamotrigine, oxcarbazepine, topiramate and zotepine

Baldessarini et al 2007

Conclusions

- Bipolar depression trials face many challenges
  - Phenotype
  - Incentives to sponsors
  - Trial design issues
  - Ethics and feasibility of placebo RCTs
  - Choice of comparator and trial duration
  - Signal detection
  - Special populations (children, elderly)
- Consensus is needed on all these issues
- The gap between evidence and practice has to be filled