Bipolar Disorders: Therapeutic Options

James W. Jefferson, M.D.

Clinical Professor of Psychiatry
University of Wisconsin School
Of Medicine and Public Health
Distinguished Senior Scientist
Madison Institute of Medicine

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Part 2: Treatment of Acute Bipolar Depression

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Teaching Points

1. Treatment algorithms and guidelines rely on both data and expert opinion.
2. Olanzapine/fluoxetine combination and quetiapine are the only FDA-approved products for acute bipolar depression (as of August 2007)
3. The role that antidepressants should play or not play in bipolar depression continues to be debated.

Outline

I. TIMA Stages of Treatment for Acute Bipolar Depression
   - A. Lamotrigine – Pros and Cons of Stage I
   - B. Olanzapine/Fluoxetine Combination – Pros and Cons of Stage II
   - C. Quetiapine – Pros and Cons of Stage II
   - D. Antidepressants at Stage IV – Why?

II. Antidepressants: Advantages and Disadvantages for Bipolar Depression

Pre-Lecture Exam
Question 1

1. **Which medication is recommended for use in Stage I of TIMA for acute bipolar I depression?**
   a. **Quetiapine**
   b. **Olanzapine/fluoxetine combination**
   c. **Bupropion**
   d. **Lamotrigine**
   e. **Lithium**

Question 2

2. As August 2007, which of the following is FDA-approved treatment for acute bipolar I and II depression?
   a. Lithium
   b. Lamotrigine
   c. Quetiapine
   d. Bupropion
   e. Duloxetine

Question 3

3. Which of the following was the most commonly used antidepressant in the STEP 500 survey?
   a. Bupropion
   b. Citalopram
   c. Venlafaxine
   d. Sertraline
   e. Paroxetine

Question 4

4. **Which antidepressant appears to have the highest switch rate when used to treat bipolar depression?**
   a. **Bupropion**
   b. **Sertraline**
   c. **Venlafaxine**

Bipolar Depression

Acute Bipolar I Depression: Texas Implementation of Medication Algorithms (TIMA)

- Optimize current mood stabilizer
- Antimanic agent if history of severe and/or recent mania
- Stage 1 – LTG alone or with antimanic

Suppes et al., J Clin Psychiatry 2005;66:870-886 (July)

Acute Bipolar I Depression: TIMA

- Stage 1: lamotrigine
- Stage 2: quetiapine or olanzapine-fluoxetine combination (OFC)*
- Stage 3: lithium, lamotrigine, quetiapine or olanzapine-fluoxetine combination
- Stage 4: ECT, SSRI, bupropion or venlafaxine
- Stage 5: MAOI, TCA, DA agonist, etc.

*OFC is FDA-approved

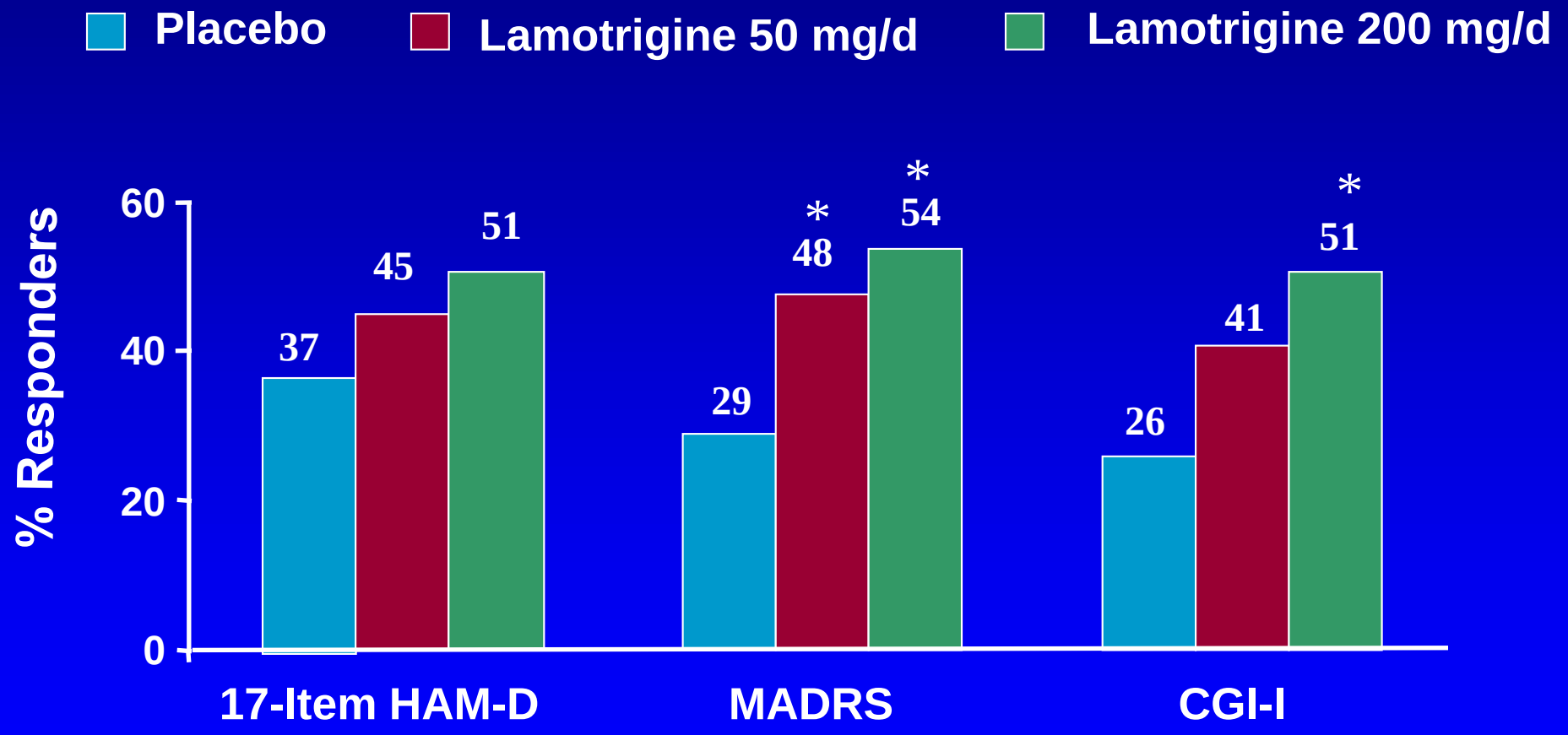
Suppes T et al. (2005), J Clin Psychiatry 66(7):870-886

Why Lamotrigine in Stage 1?

- **Based on 2 open-label add-on and 2 placebo-controlled monotherapy trials (n=195) (n=25)**
- **"A relatively greater weight of expert consensus"**

TIMA: Texas Implementation of Medication Algorithms
Suppes et al., J Clin Psychiatry 2005;66:870-886 (July)

Lamotrigine Monotherapy for Bipolar I Depression (7 weeks, n=192)



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

*p<0.05

Lamotrigine for Bipolar Depression
Change Score LOCF (P-values)

	SCAB2001	SCAA2010	SCA40910	SCA30924	SCA100223
MADRS	0.008	0.86	**0.52**	**0.54**	**0.33**
HAMD-17	**0.084**	**0.71**	0.49	0.63	0.13
HAMD-31	0.13	0.47	0.42	0.43	0.19
HAMD-1	0.002	0.73	0.25	0.50	0.58
Bech	0.005	0.47	0.12	0.63	0.045
CGI-S	0.031	0.69	0.40	0.78	0.46
CGI-I	0.006	0.69	0.98	0.66	0.11
	LTG > PBO p<0.05		LTG > PBO	LTG ≤ PBO	

Data on file with GSK, presented with permission

(Primary endpoints underlined)

Lamotrigine for Bipolar Depression
(5 multicenter, placebo-controlled studies)

- **Lamotrigine did not separate from placebo on the primary endpoints**
- **Yet a meta-analysis of the data found "consistent evidence of a mild to modest, but clinically worthwhile benefit for lamotrigine that is unlikely to be due to chance."***

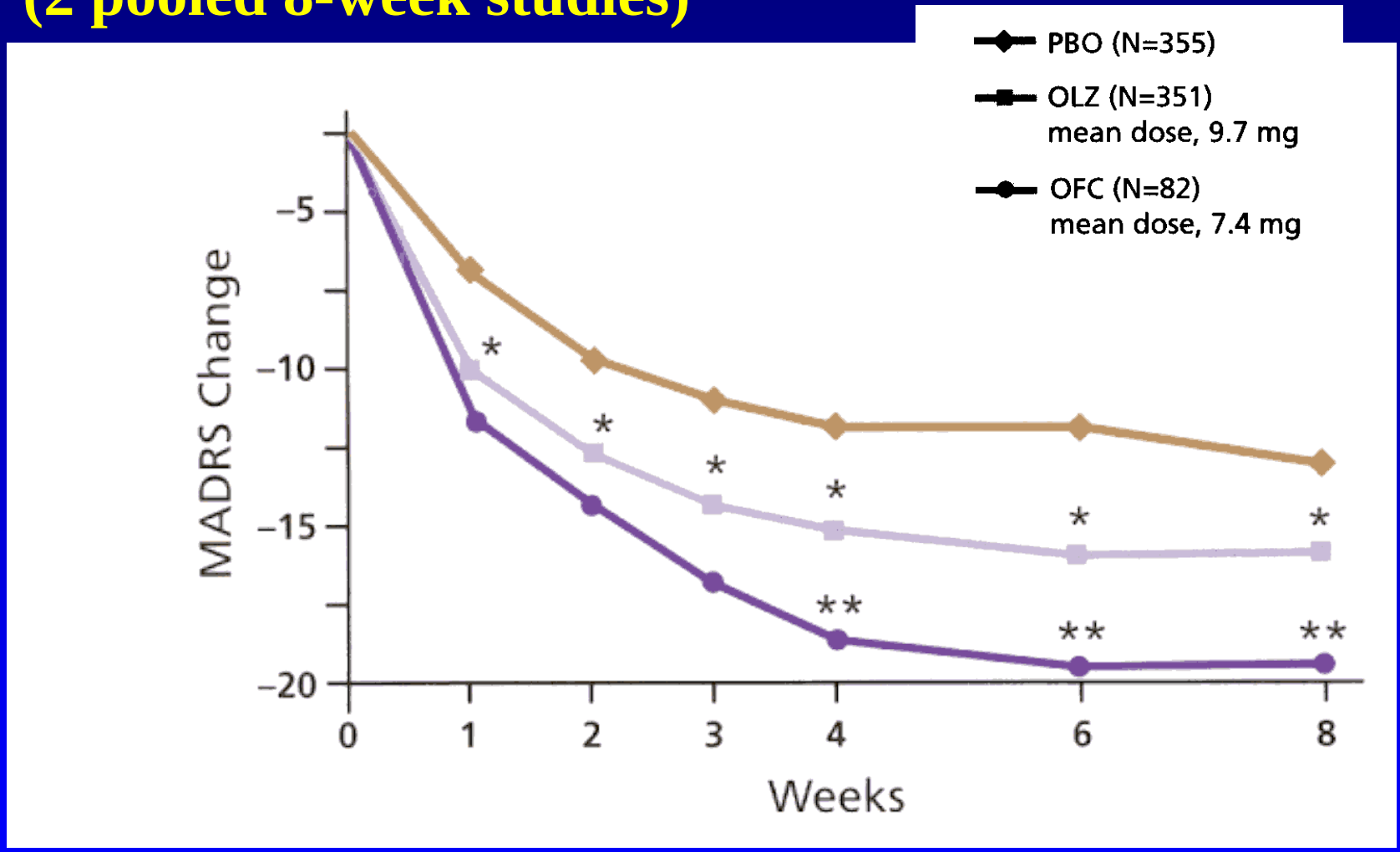
***Geddes et al., NCDEU Annual Meeting poster I-64, June 2007**

Bipolar Depression: FDA Approval

- **Olanzapine/fluoxetine combination 2003 for bipolar I depression**

- **Quetiapine 2006 for bipolar I and II depression**

Olanzapine/OFC for Bipolar I Depression
(2 pooled 8-week studies)



MMRM=Mixed Modal Repeated Measures,
OFC=Olanzapine-Fluoxetine Combination

Tohen et al. APA 5/02 Full article AGP 60:1079-1088, Nov 2003

Olanzapine/Fluoxetine Combination : FDA-Approved for Acute BP I Depression

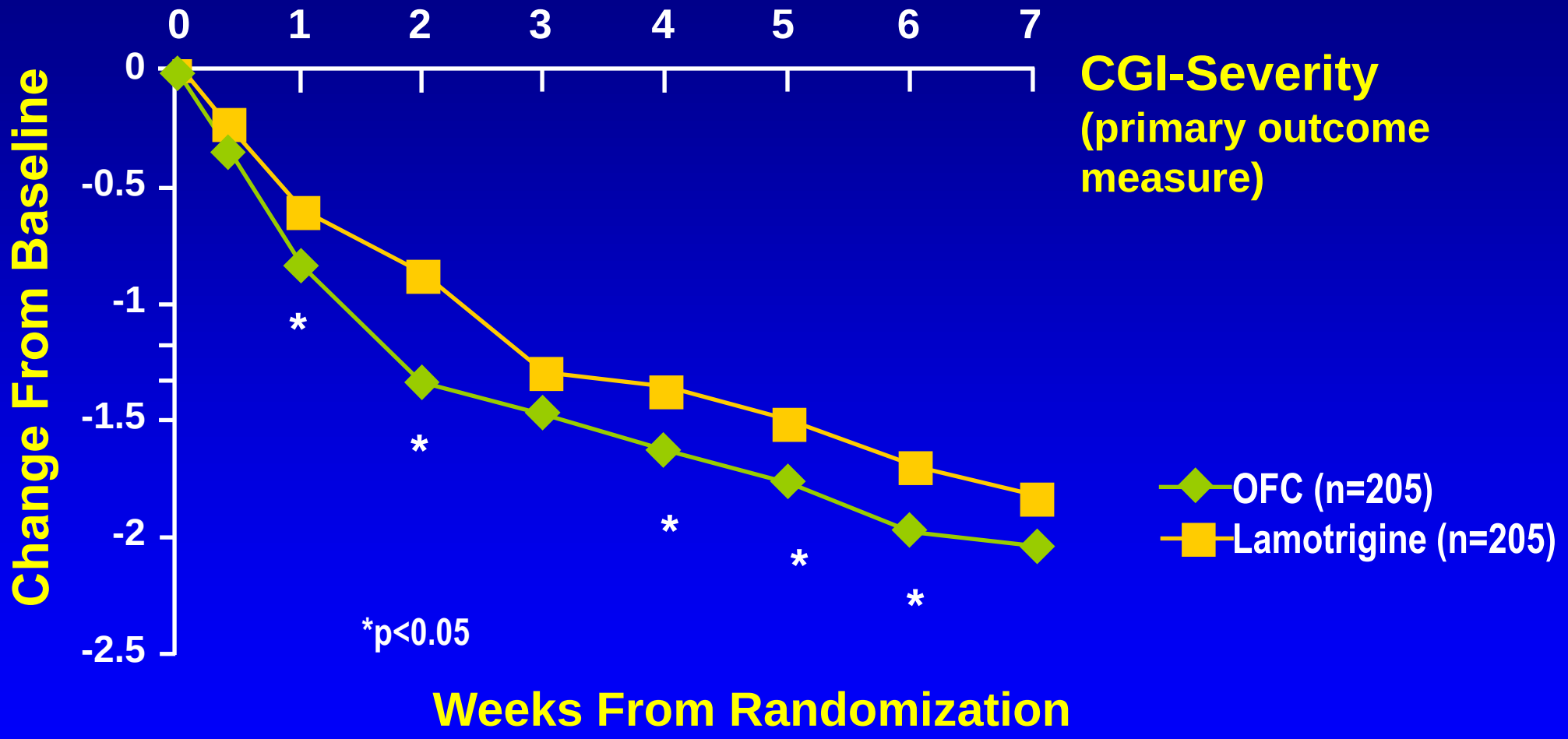
- Why only TIMA Stage 2? (long-term tolerability)
- How does it compare to LTG?

Bipolar I Depression: Weight Change Over 8 Weeks

	Kg	≥7%
• Placebo	- 0.5	0.3%
• Olanzapine	+2.6	18.7%
• OFC	+2.8	19.5%

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

OFC vs. Lamotrigine in Bipolar I Depression (N=410)



MMRM = mixed model repeated measures analysis of variance

Brown et al. J Clin Psychiatry 2006;67:1025-1033

OFC vs. LTG for Bipolar I Depression (7-week, double-blind, n=410)

- Results favored OFC (Clinical significance?)
- AEs favored LTG: weight, lipids, prolactin, somnolence, dry mouth, tremor
- Weight ≥ 7% OLZ: 23%, LTG: 0%
- Serious AEs (wide variety): OLZ 1.0%, LTG 5.4%

Brown et al., APA NR 376, May 2005
Brown et al. J Clin Psychiatry 2006;67:1025-1033

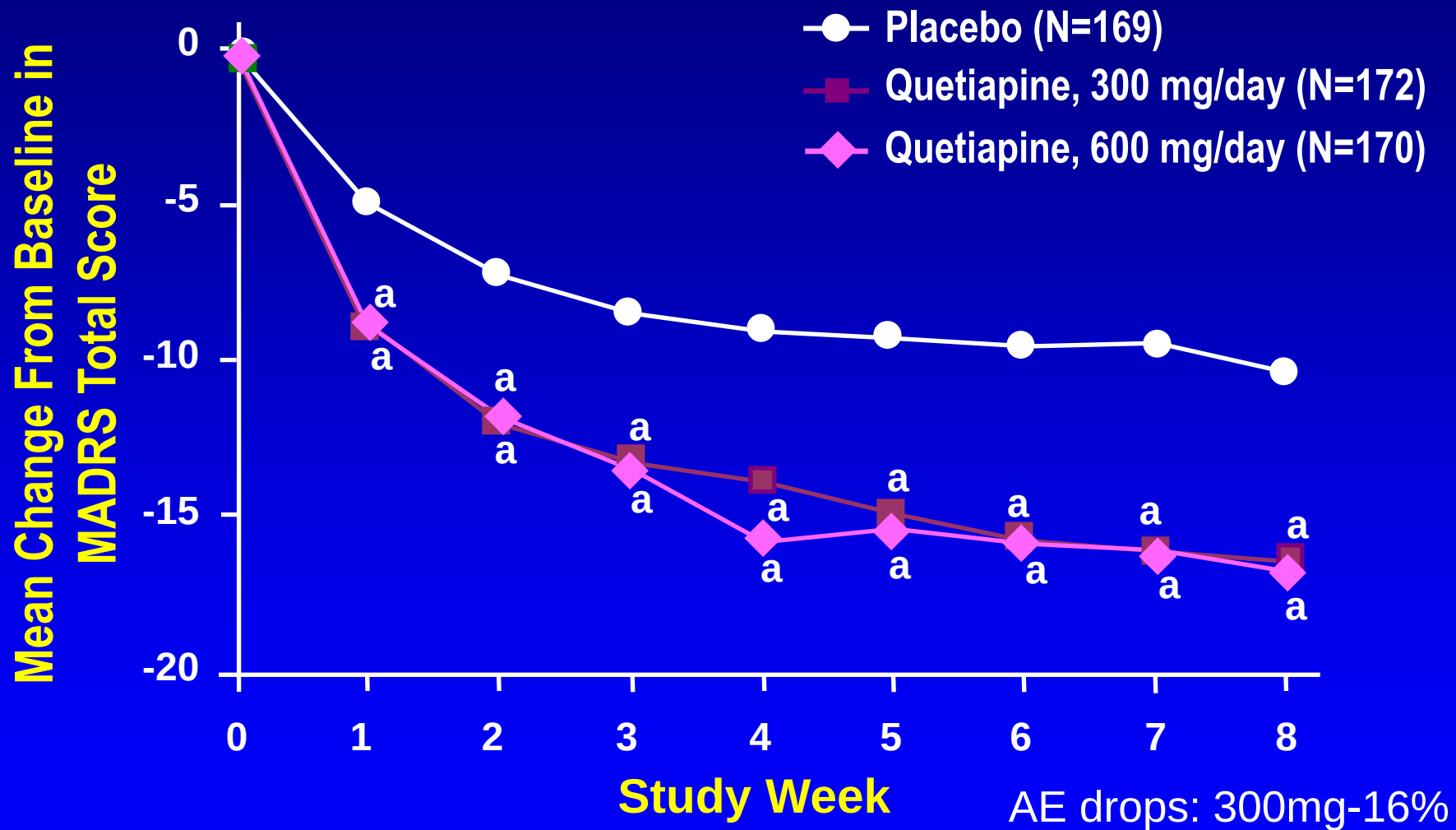
Quetiapine for Bipolar I and II Depression (8-week, double-blind, n=539)

- **Dose: 300 or 600 mg/day**
- **Both doses > placebo from week 1 through week 8 on MADRS**
- **Remission (MADRS ≤ 12)**

300 mg	**52.9%**	
600 mg	**52.9%**	**(P< 0.001)**
Placebo	**28.4%**	

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

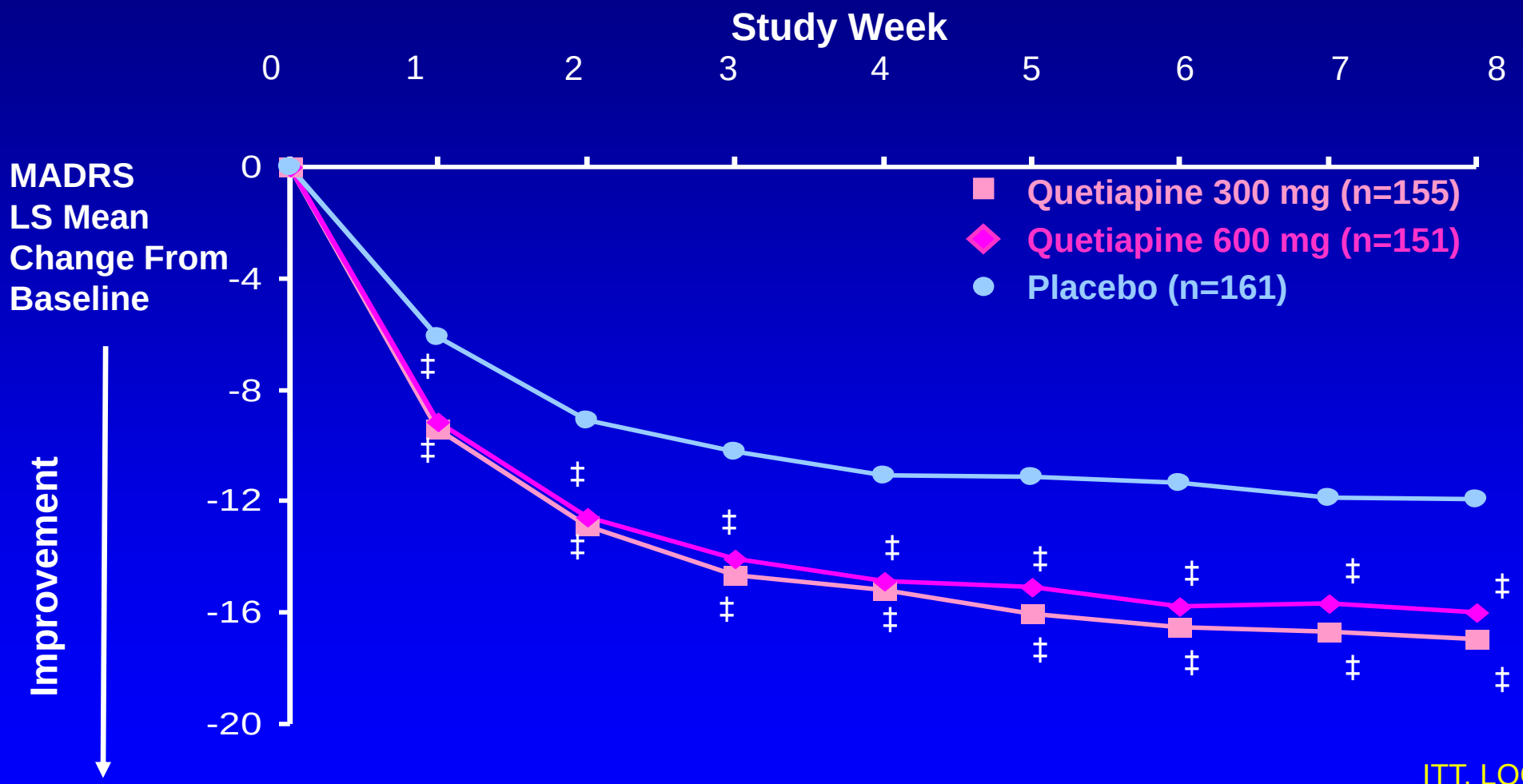
Quetiapine for Bipolar I and II Depression



AE drops: 300mg-16%
600mg-26%

Calabrese JR et al. (2005), Am J Psychiatry 162(7):1351-1360

Quetiapine for Bipolar I and II Depression
BOLDER II



ITT, LOCF

‡p<0.001 vs placebo

Thase et al., J Clin Psychopharmacol 2006;26:600-609

Quetiapine for Bipolar I and II Depression Adverse Event Dropouts

	BOLDER I*	BOLDER II**
Quetiapine 600 mg	26.1%	11.2%
Quetiapine 300 mg	16.0%	8.1%
Placebo	8.8%	1.2%

*Calabrese et al., Am J Psychiatry 2005;162:1351-1360
**Thase et al., J Clin Psychopharmacol 2006;26:600-609

Quetiapine for Bipolar I and II Depression
Weight Gain ≥ 7%

	BOLDER I*	BOLDER II**
Quetiapine 600 mg	9.0%	8.6%
Quetiapine 300 mg	8.5%	3.9%
Placebo	1.7%	2.8%

*Calabrese et al., Am J Psychiatry 2005;162:1351-1360
**Thase et al., J Clin Psychopharmacol 2006;26:600-609

Quetiapine: FDA-Approved for Bipolar I and II Depression

- **Why only TIMA Stage 2?**
- **TIMA published 2005, Quetiapine approved 2006**
- **CANMAT update 2006: Quetiapine elevated to Level 1***

*CANMAT=Canadian Network for Mood and Anxiety Treatments

Yatham et al., Bipolar Disorders 2006;8:721-739

Aripiprazole for Acute Bipolar I Depression

- Two identical 8-week, double-blind, placebo-controlled studies (total n=749)
- Flexible dose: start 10 mg (range 5-30 mg)
- Primary endpoint: MADRS (LOCF)
  No significant difference in either study

Marcus et al., APA Annual Meeting New Research 311, May 2007

Antidepressants for Acute Bipolar Depression: TIMA Stage 4

- Antidepressant + antimanic
- Preferred: SSRI, bupropion, venlafaxine
  - Venlafaxine may have higher switch rate
- Why only Stage 4 for antidepressants?
- Monotherapy in select BD-II
  - Limited data

Suppes T et al. (2005), J Clin Psychiatry 66(7):870-886

Antidepressants in Bipolar Disorder

- Disadvantages[1]
  - Poor response
  - Manic switches
  - Cycle acceleration
  - Late response loss
- Advantages[2]
  - An exceptional subgroup

[1]Ghaemi SN et al. (2004), Am J Psychiatry 161(1):163-165; [2]Altshuler L et al. (2003), Am J Psychiatry 160(7):1252-1262

Adjunctive Antidepressant for Bipolar I or II Depression (STEP-BD)

(26-Week, double-blind, N=366)

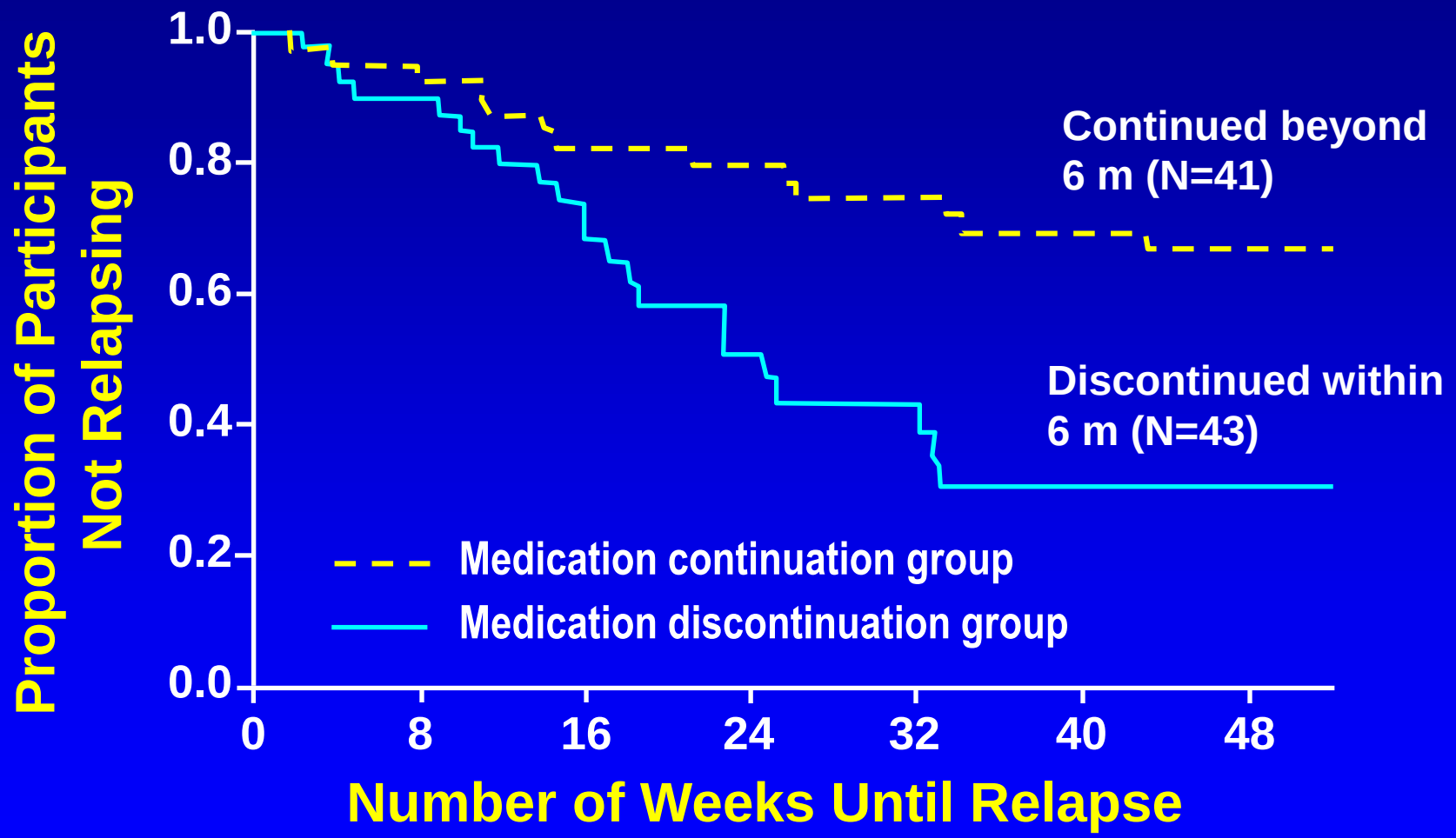
- Bupropion, paroxetine or placebo
- Primary outcome: 8 consecutive euthymic weeks
- Results:

Mood stabilizer + antidepressant	23.5%
Mood stabilizer + placebo	27.3%

- Affective switch: no difference

Sachs et al., N Eng J Med 2007;356:1711-1722
Belmaker (editorial) N Eng J Med 2007;356:1771-1772

Antidepressants in Bipolar Disorder: Continue or Discontinue?



Altshuler L et al. (2003), Am J Psychiatry 160(7):1252-1262.

Similar findings: Joffe et al. Acta Psychiatr Scand 2005;112:105-109

Antidepressants for Bipolar Depression:
Systematic Review- 12 Randomized, Controlled Trials

- Effective short-term (longest was 10 weeks)
- Switching not common
- Prefer SSRIs, MAOIs over TCAs
- To prefer bupropion or paroxetine moves "beyond the evidence"

Gijsman et al., Am J Psychiatry 161:1537-1547, Sep 2004

Bipolar Depression – Adding Citalopram or Lamotrigine (12-week, double-blind, n=20)

- Equal efficacy, 1/10 mood switch in each group
- Doses: not provided
- Total response rates: week 6- 31.6%
  week 12- 52.6%

Schaffer et al., APA Annual Meeting, NR283, May 2006

Antidepressant Switch Rate in Bipolar II Disorder (NIMH-CDS)

- **Antidepressant 3.6% switch**
- **No antidepressant 3.5% switch**

Truman et al, NCDEU poster, 6/05
CDS=Collaborative Depression Study

Bipolar Depression Switch Rates
10-week, adjunctive, db (mostly), n=174

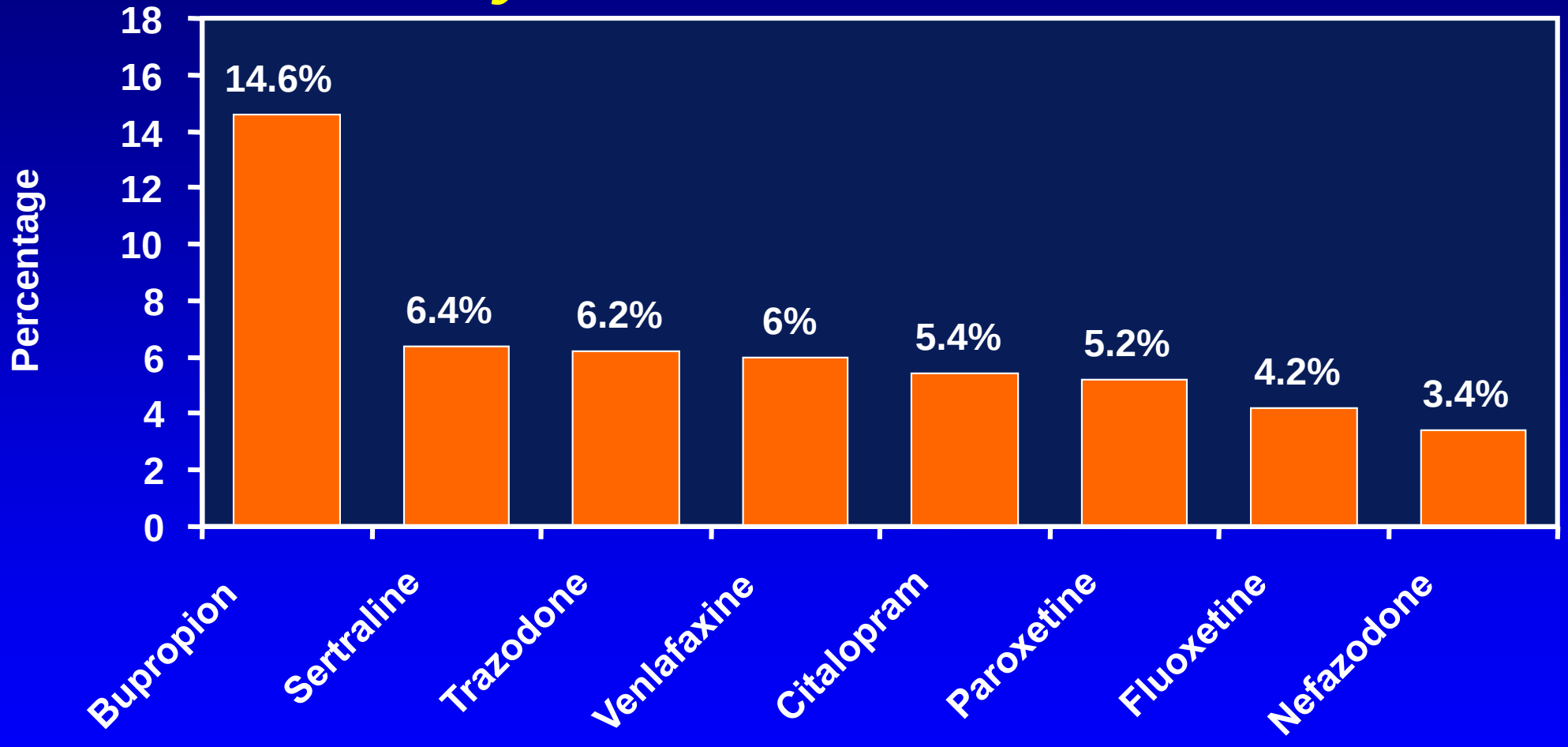
- Equal response and remission rates
- Switch rates

	CGI-BP-M	YMRS
Bupropion	10%	4%
Sertraline	9%	7%
Venlafaxine	29%	15%

- ↑ Venlafaxine risk in rapid cyclers

Post et al., Br J Psychiatry 2006;189:124-131

Antidepressant Use at STEP-BD Study Entry: First 500 Patients



Ghaemi SN et al. Psychiatric Services 2006;57:660-665

The Role of Antidepressants or the Lack Thereof in Bipolar Disorder Continues to Be Debated

But there is agreement that antidepressants should not be used as monotherapy for Bipolar I depression

Post-Lecture Exam
Question 1

1. Which medication is recommended for use in Stage I of TIMA for acute bipolar I depression?
   a. Quetiapine
   b. Olanzapine/fluoxetine combination
   c. Bupropion
   d. Lamotrigine
   e. Lithium

Question 2

2. As August 2007, which of the following is FDA-approved treatment for acute bipolar I and II depression?
   a. Lithium
   b. Lamotrigine
   c. Quetiapine
   d. Bupropion
   e. Duloxetine

Question 3

3. Which of the following was the most commonly used antidepressant in the STEP 500 survey?
   a. Bupropion
   b. Citalopram
   c. Venlafaxine
   d. Sertraline
   e. Paroxetine

Question 4

4. Which antidepressant appears to have the highest switch rate when used to treat bipolar depression?
   a. Bupropion
   b. Sertraline
   c. Venlafaxine

Answers to Pre & Post Lecture Exams

1. d
2. c
3. a
4. c