Bipolar Disorders: Therapeutic Options

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Part 2: Treatment of Acute Bipolar Depression

Teaching Points

1. Treatment algorithms and guidelines rely on both data and expert opinion.
2. Olanzapine/fluoxetine combination is the only FDA-approved product for acute bipolar depression (as of early May 2006).
3. Quetiapine data are quite promising.
4. 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 of early May 2006, which is the only FDA-approved treatment for acute bipolar I depression?
   a. Olanzapine/fluoxetine combination
   b. Lamotrigine
   c. Quetiapine
   d. Bupropion
   e. Duloxetine

Question 3

3. Which of the following was found to be more effective than placebo in two placebo-controlled studies of bipolar I and II depression?
   a. Lamotrigine
   b. Olanzapine
   c. Imipramine
   d. Quetiapine
   e. Aripiprazole

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

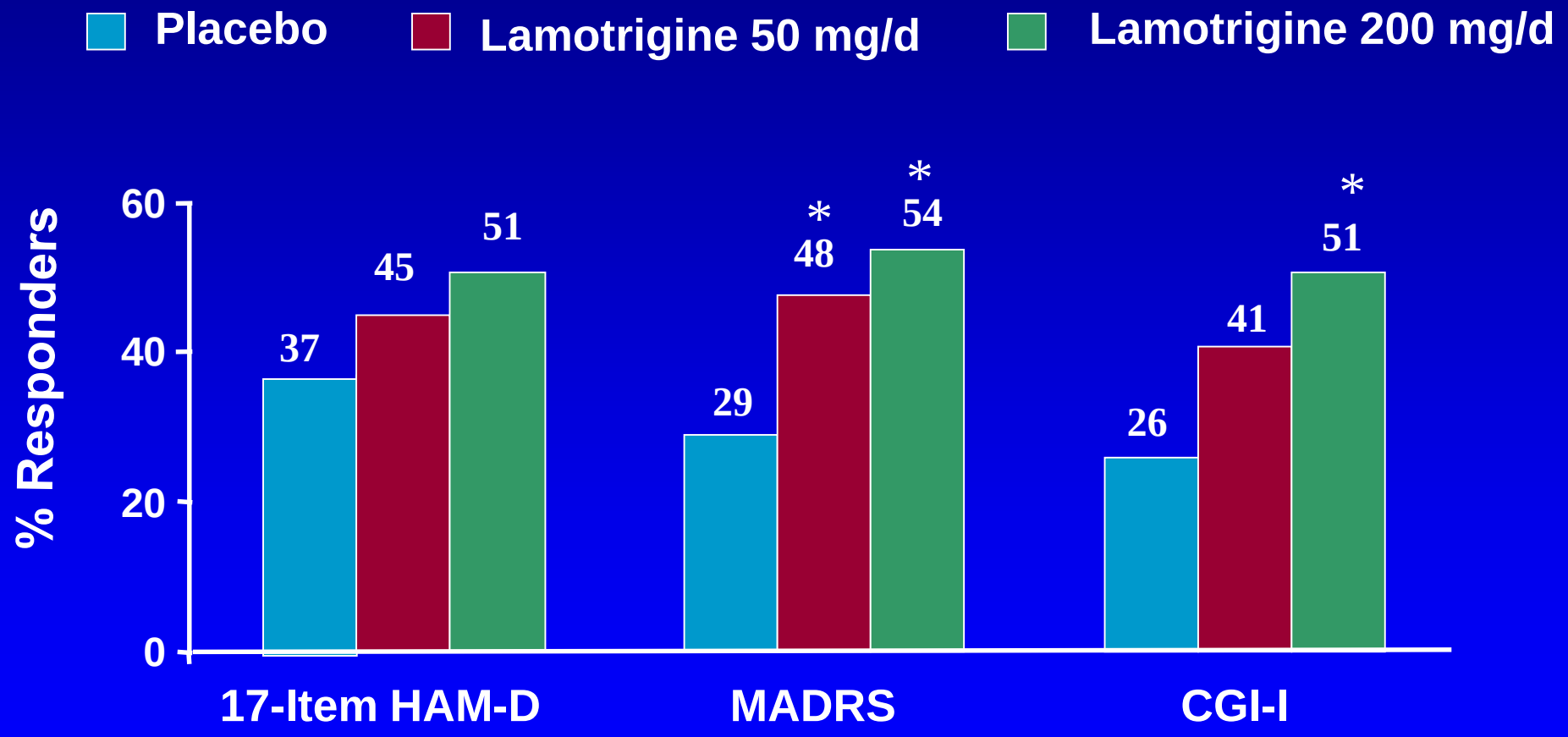
Suppes T et al. (2005), J Clin Psychiatry 66(7):870-886

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 Monotherapy in Bipolar I Depression

	50 mg/day		200 mg/day	
	Observed	LOCF	Observed	LOCF
HAM-D_{17}	S	NS	S	NS
HAM-D_{31}	NS	NS	NS	NS
MADRS	S	NS	S	S
CGI-S	S	NS	S	S
CGI-I	S	NS	S	S

Jefferson JW, CNS Spectr 2005;10(3:224-232 (from Calabrese et al J Clin Psychiatry 2/99)

Lamotrigine for Bipolar I Depression
(multicenter, placebo-controlled)

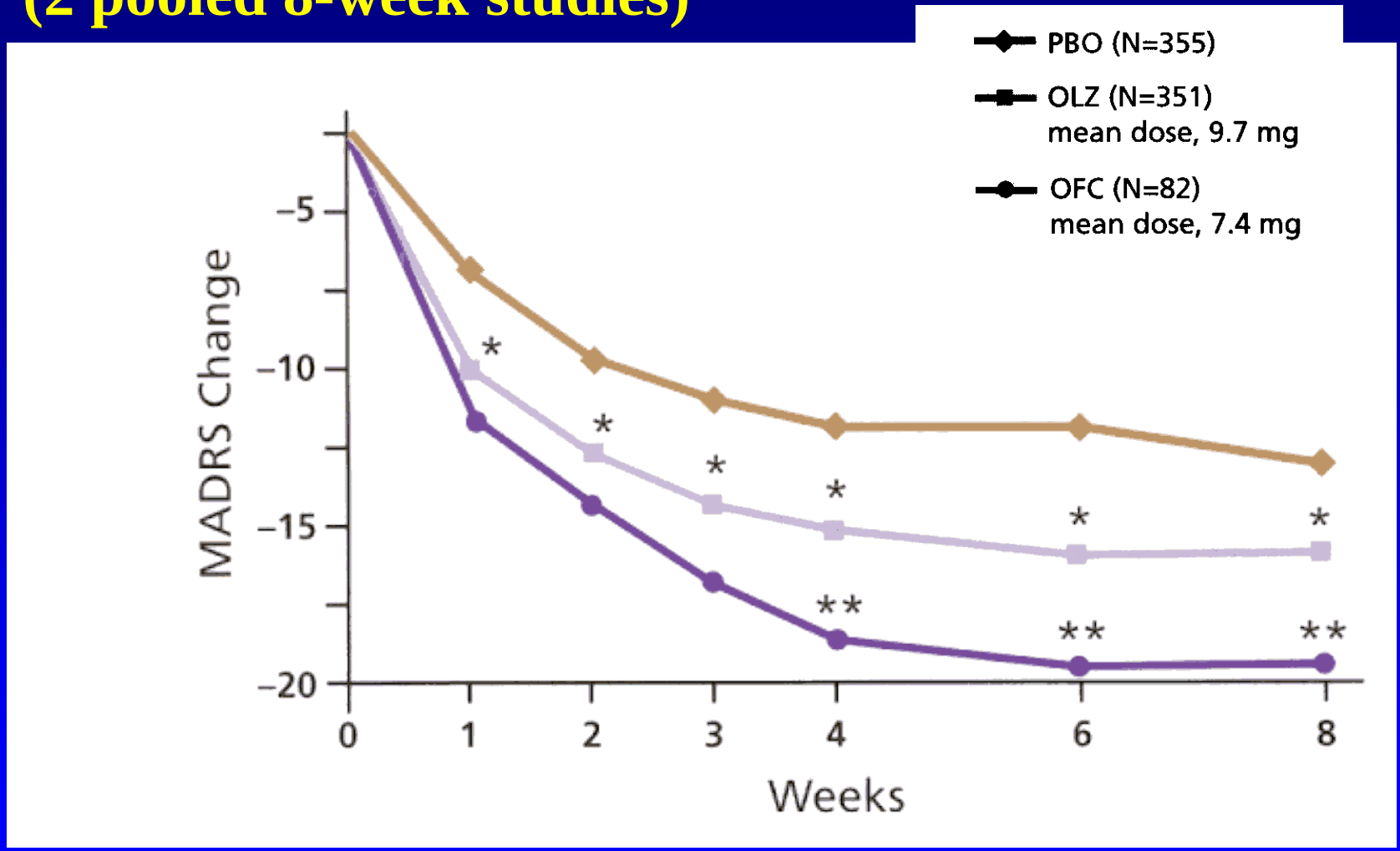
- GW 602 (n=195), GW 603 (n=206), GW 40910 (n=257)
- Lamotrigine did not separate from placebo on the primary endpoint

Hirschfeld et al., NCDEU poster , 6/05

Bipolar Depression: FDA Approved

- **Olanzapine/fluoxetine -- 2003 combination**

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

OFC: The Only FDA-Approved Treatment for Acute BP I Depression

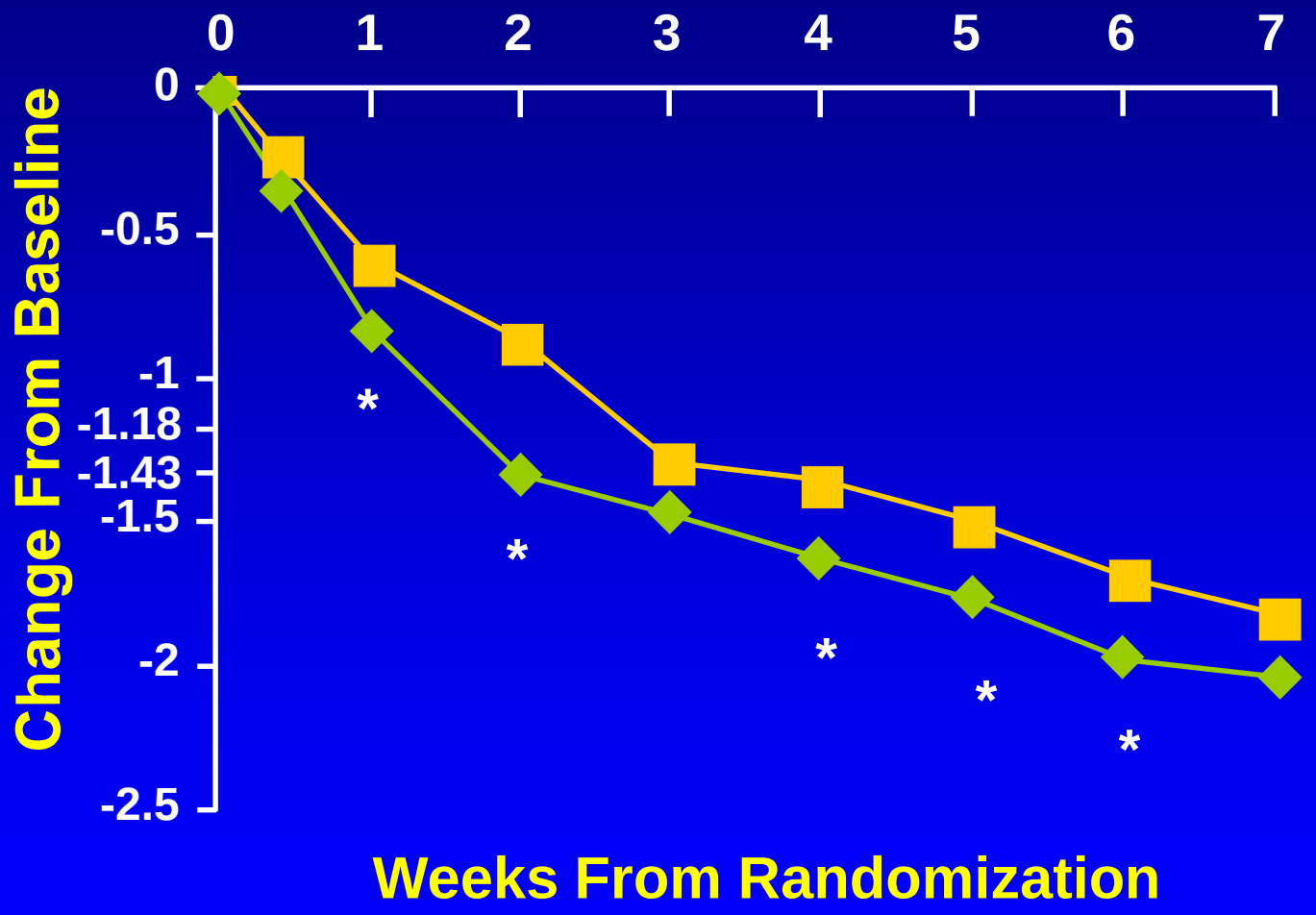
- Why only TIMA Stage 2? (long-term tolerability)
- How does it compare to LTG?

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



CGI-Severity
N=410

Overall: LS means across 7 weeks
OFC -1.43
Lamotrigine -1.18
p=0.002

OFC (n=205)
Lamotrigine (n=205)

MMRM = mixed model repeated measures analysis of variance; *p<0.05 at individual time point;
Brown EB et al. (2005), NR376. Presented at the 158th Annual Meeting of the APA. Atlanta; May 24

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%

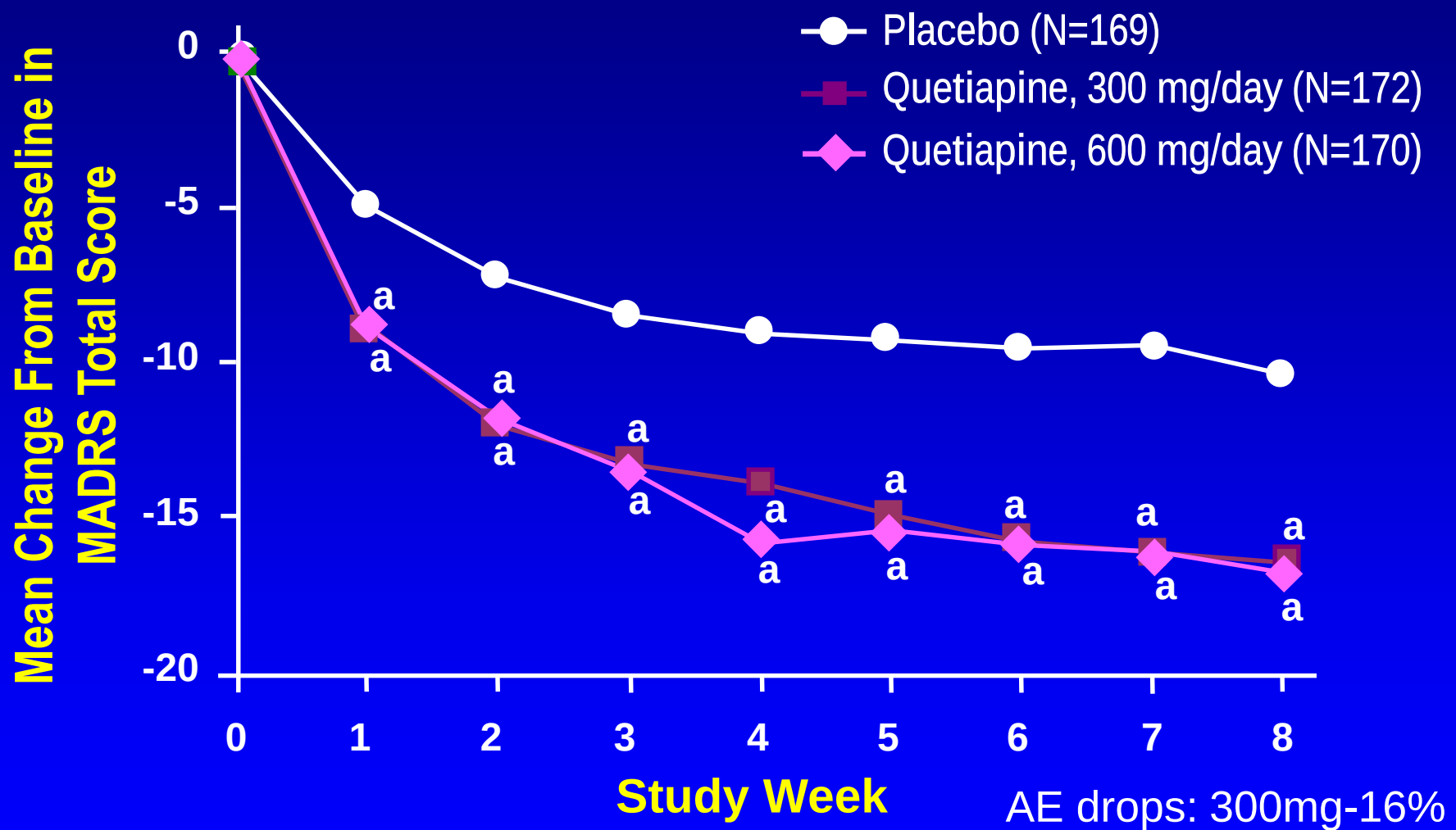
Brown et al., APA NR 376, May 2005

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**

Calabrese et al., Am J Psychiatry 2005;162:1351-1360 (July); APA NR756, May 2004

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 Adverse Event Dropouts

Quetiapine 600 mg	26.1%
Quetiapine 300 mg	16.0%
Placebo	8.8%

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

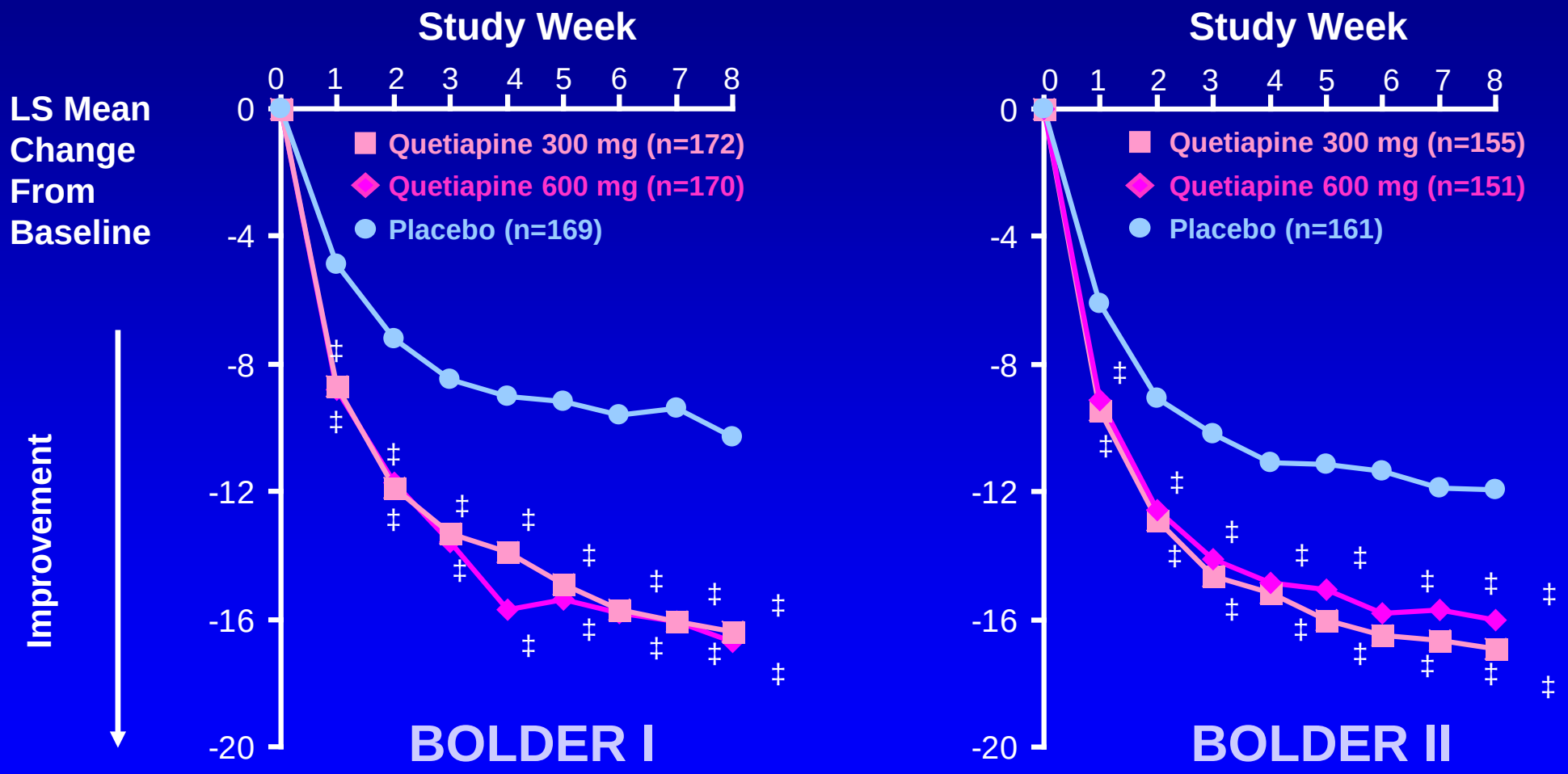
Bipolar Depression: Quetiapine vs Placebo Weight Change (8 weeks)

	QTP 600 mg	QTP 300 mg	Placebo
Mean change (kg)	1.6	1.0	0.2
>7% increase in weight (%)	9.0	8.5	1.7

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

Quetiapine for Bipolar I and II Depression

MADRS Total Score



‡p<0.001 vs placebo

ITT, LOCF

Calabrese et al 2005;
In-house data, AstraZeneca Pharmaceutical, LP. December 2005

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

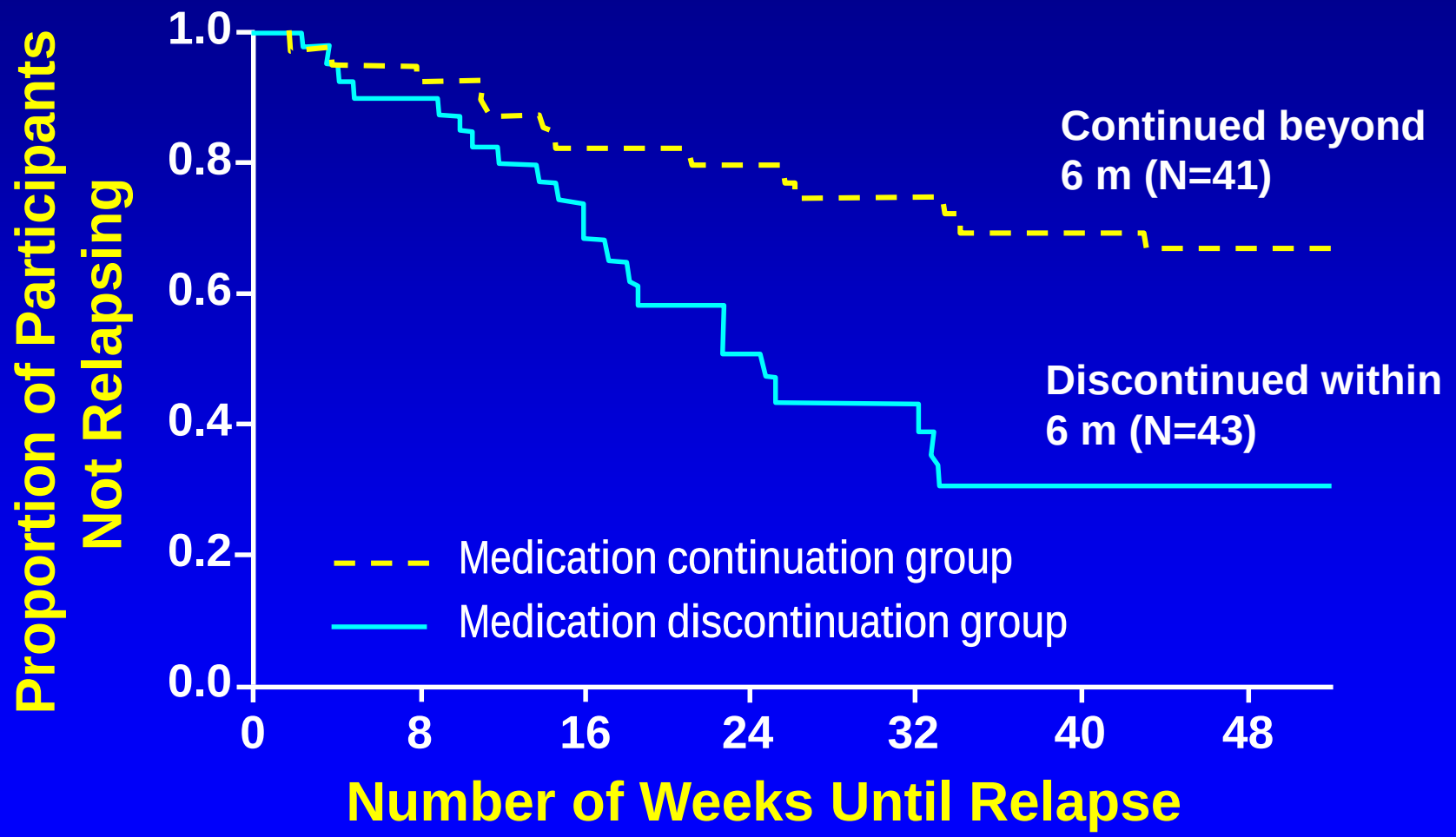
Suppes T et al. (2005), J Clin Psychiatry 66(7):870-886

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

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"

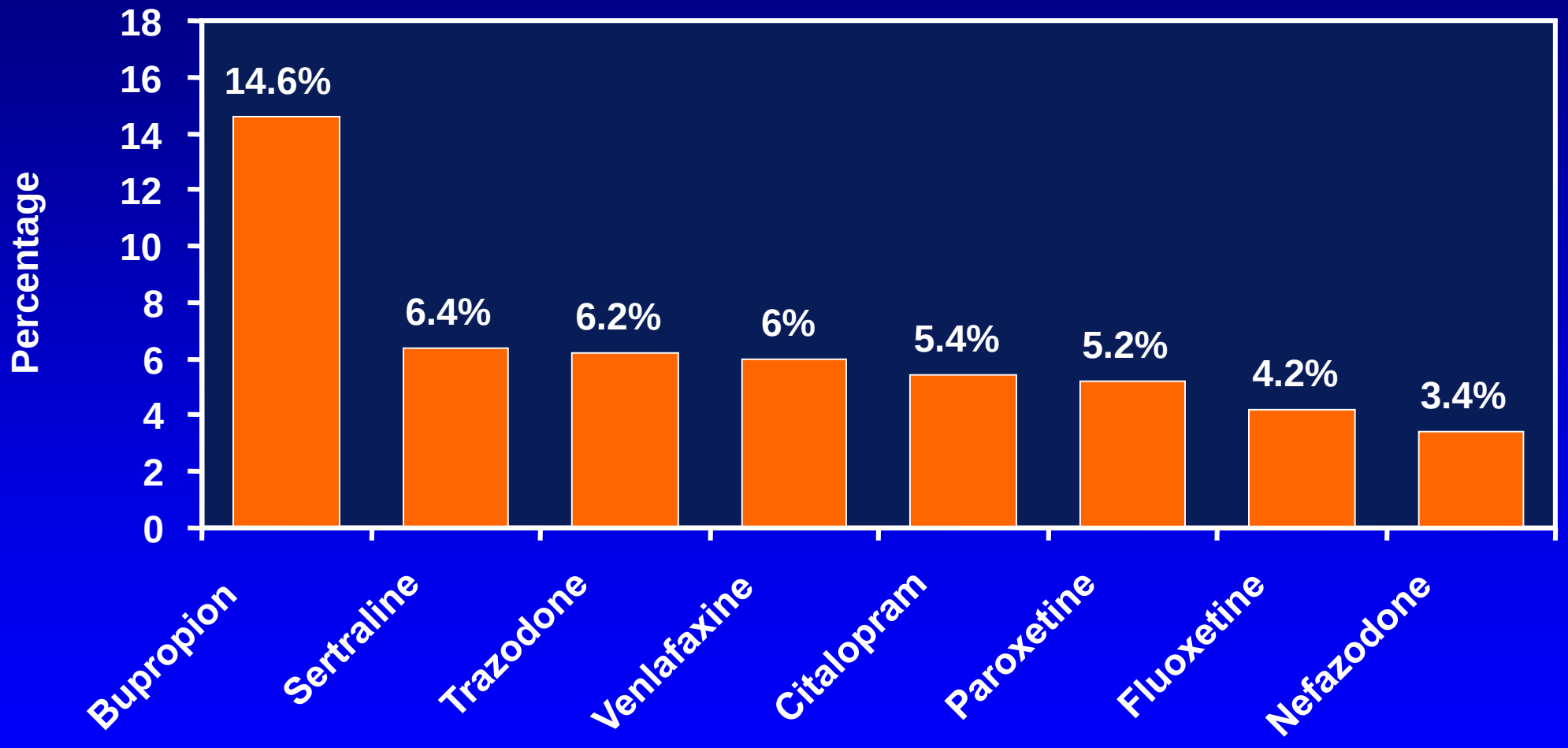
Gijsman et al., Am J Psychiatry 161:1537-1547, Sep 2004

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

STEP 500: *Antidepressants*



Ghaemi SN et al. Presented at: 5th International Conference on Bipolar Disorder; June 2003; Pittsburgh, Pa.

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

Post-Lecture Exam
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   b. **Sertraline**
   c. **Venlafaxine**

Answers to Pre & Post Lecture Exams

1. D
2. A
3. D
4. C