Bipolar Disorders: Therapeutic Options

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Revised November 2009

Part 2: Treatment of Acute Bipolar Depression

Revised November 2009

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 November 2009, 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

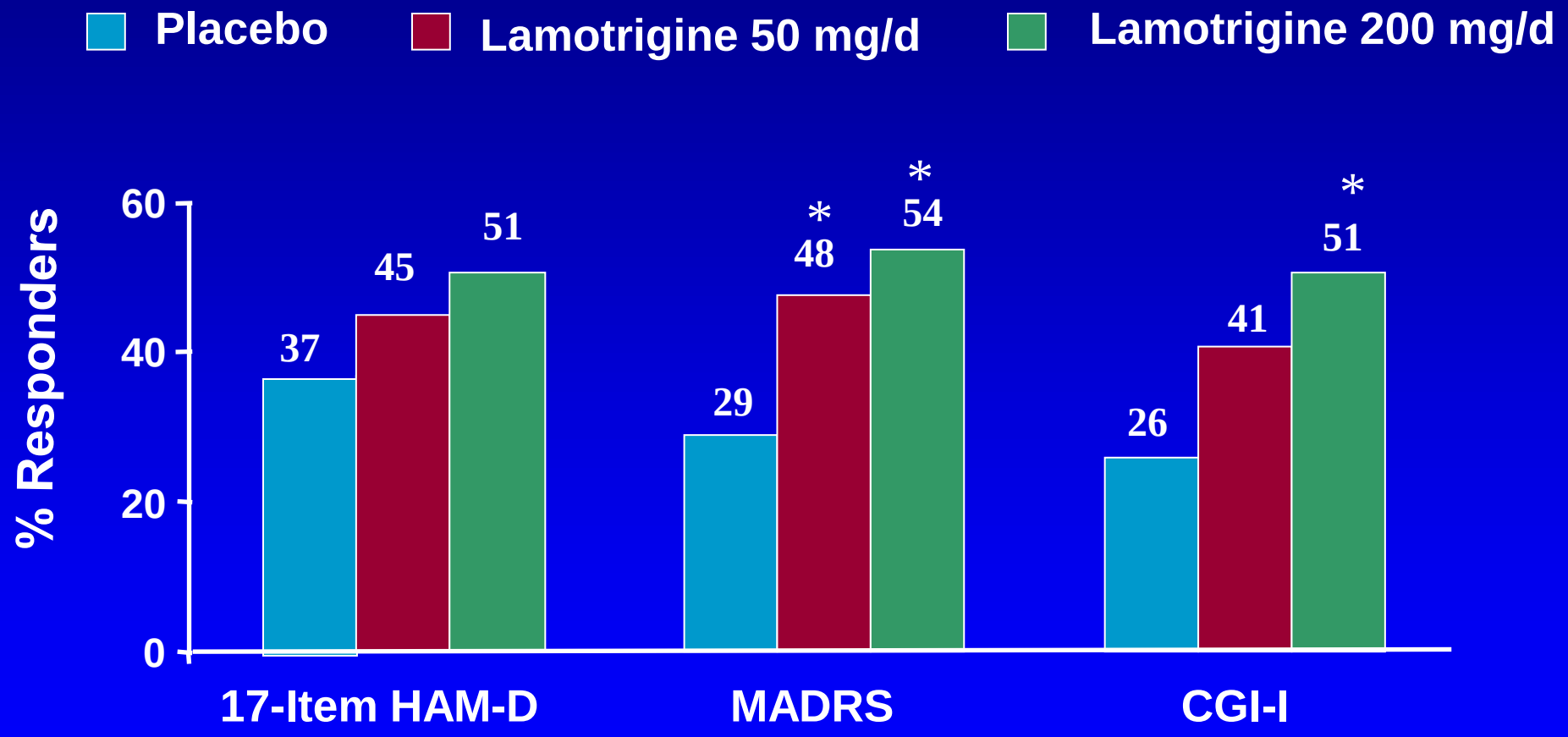
Lamotrigine

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 endpoint of any of the 5 studies
- But a meta-analysis found "consistent evidence of a mild to modest, but clinically worthwhile benefit for lamotrigine that is unlikely to be due to chance."*
- Benefit greater in more severely depressed**

*Geddes et al., NCDEU Annual Meeting poster I-64, June 2007
**Geddes et al. Br J Psychiatry 2009;194:4-9
Calabrese et al. Bipolar Disorders 2008;10:323-333

Lamotrigine for Bipolar Depression (meta-analysis and meta-regression of individual patient data from 5 randomized trials)

- 3 trials- bipolar I only, 1 trial- bipolar II only, 1 trial- bipolar I and II
- Response: NNT on HAM-D 11, on MADRS 13 (both significant)
- Response significant only with baseline HAM-D >24
- Remission: HAM-D not significant, MADRS significant (NNTs not provided)

Geddes et al. Br J Psychiatry 2009;194:4-9

Lamotrigine Add-On to Lithium for Bipolar Depression (8-week, double-blind, placebo-controlled, n=124)

- **Dose: maximum 200 mg/day**
- **LTG > PBO on MADRS change, MADRS response (51/6% vs. 31.7%)**
- **No remission data**
- **Well tolerated**

Van der Loos et al. Poster at APA Annual Meeting, May 2007

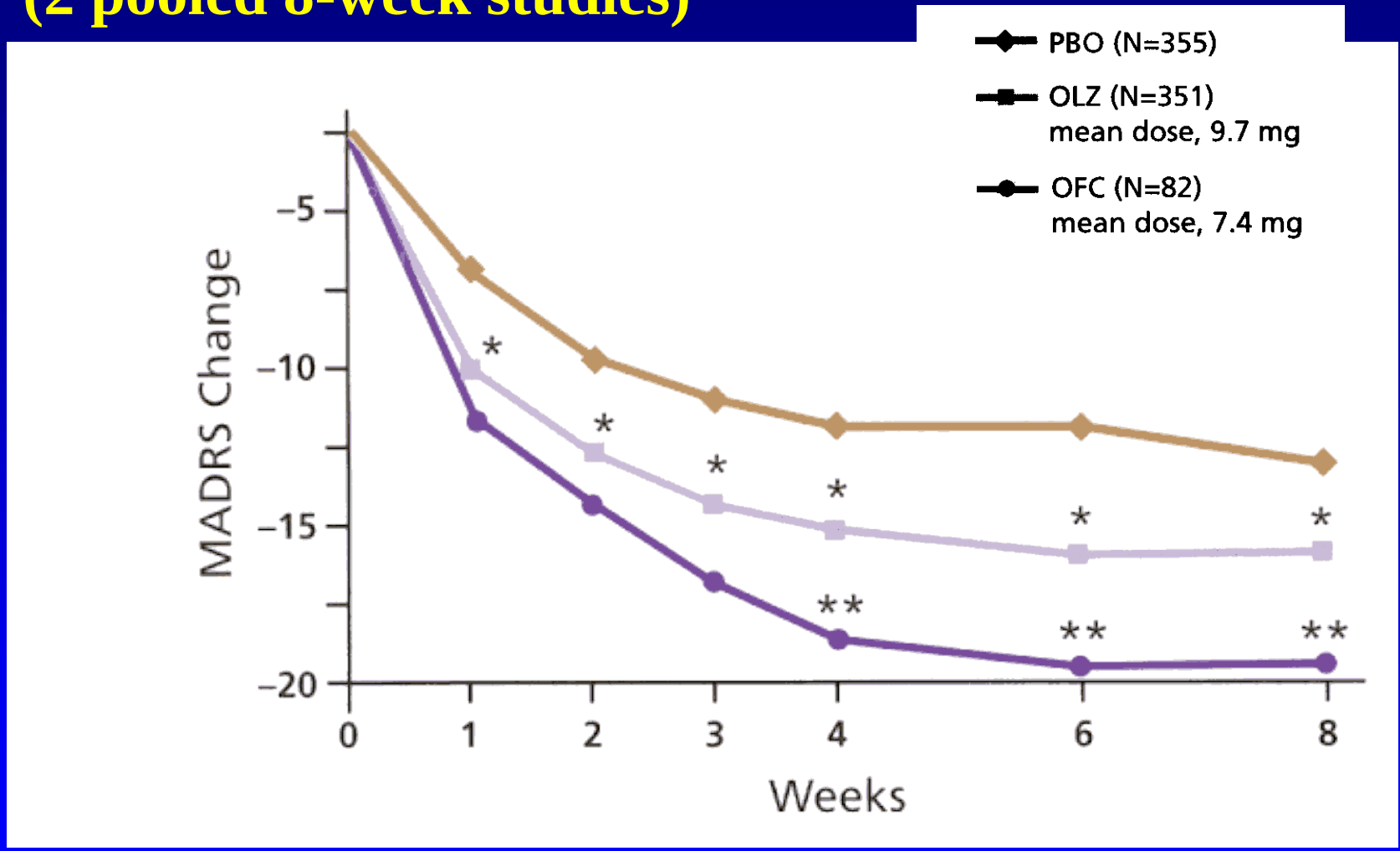
Bipolar Depression: FDA Approval

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

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

Olanzapine/Fluoxetine

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

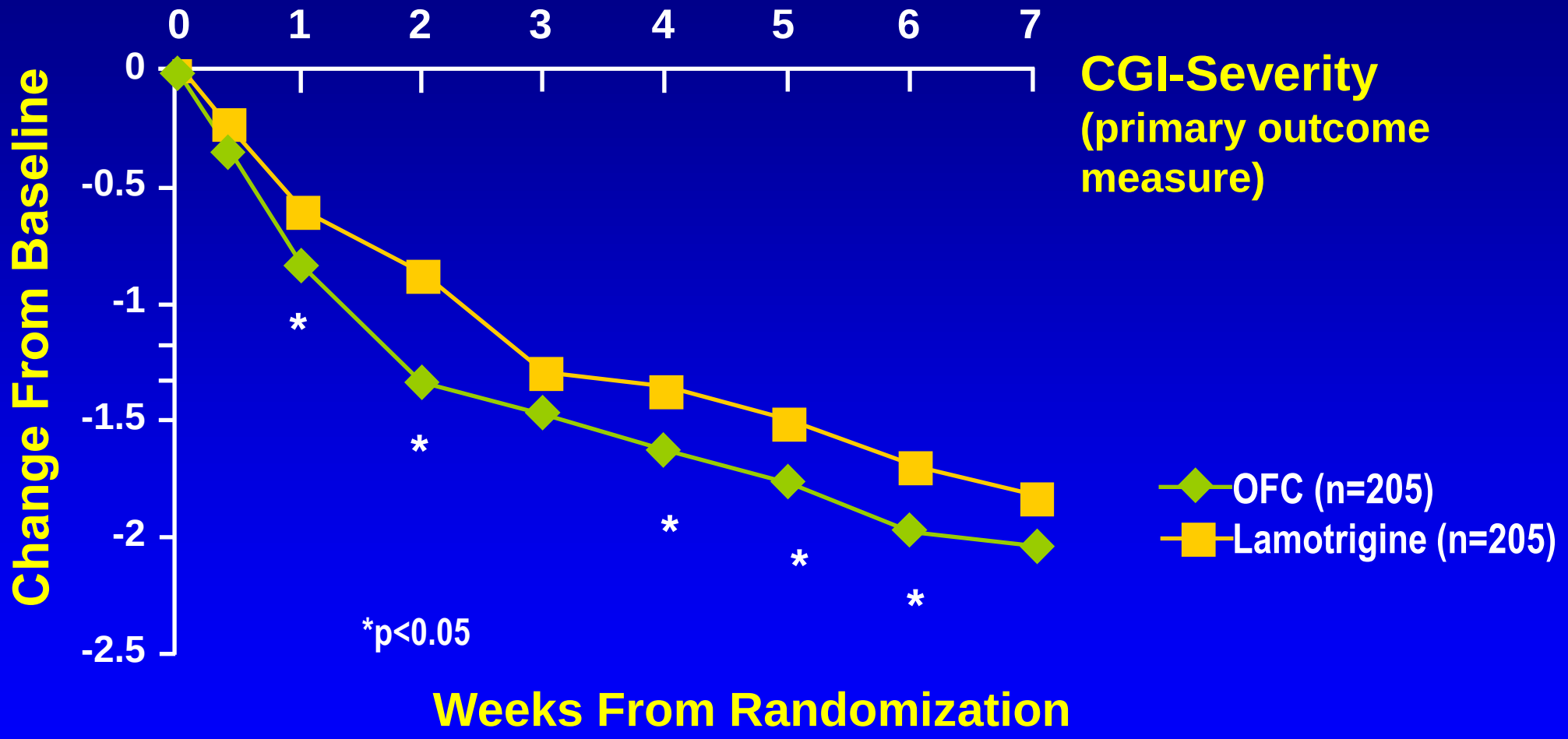
- Why only TIMA Stage 2? (long-term tolerability)
- How does it compare to LTG?

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

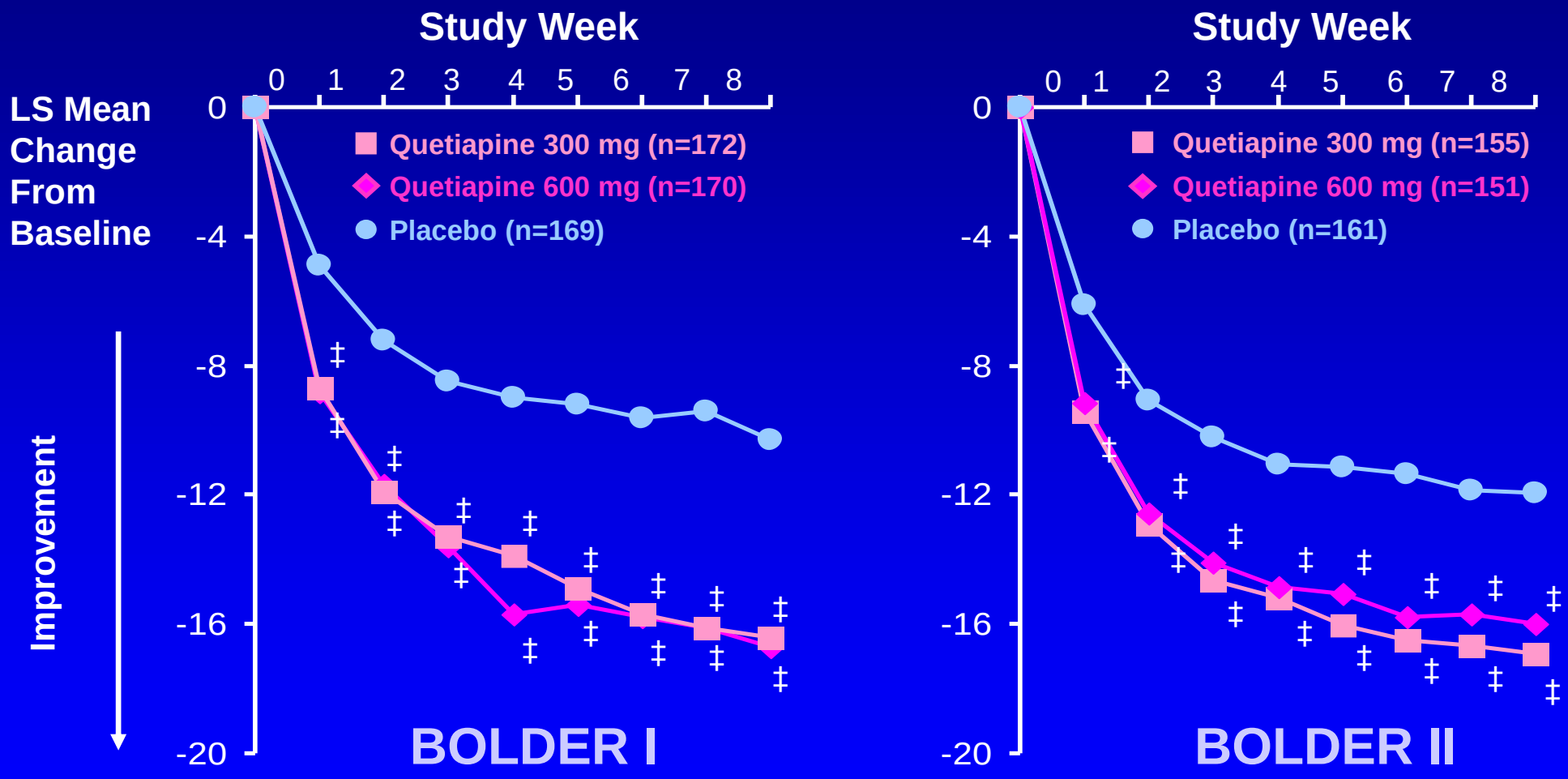
OFC vs. LTG for Bipolar I Depression (25-week analysis)

- Results favored OFC (Clinical significance?)
- Primary efficacy measure: CGI-S (MMRM)
  OFC > LTG at weeks 1,2,4,5,6, and 17 ($p<0.05$)
- No sig. difference in response, remission, relapse
- AEs favored LTG: weight, lipids, prolactin, HgA1c, somnolence, dry mouth, tremor, edema
- Weight ≥ 7%: OLZ: 33.8%, LTG: 2.1%

Brown et al. Int J Neuropsychopharmacol 2009;12:773-782

Quetiapine

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

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 (BOLDER I)

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 vs Lithium and Placebo for Bipolar I/II Depression (EMBOLDEN I) (8-week, double-blind,, n=794)

- ↓ MADRS: QTP 300 mg = QTP 600 mg
  > Lithium (0.6-1.2 meq/l) = placebo
- Remission at week 8 (MADRS ≤ 12)

QTP 300 mg	69.8%	(p<0.01)
QTP 600 mg	70.3%	(p<0.01)
Lithium	62.5%	(n.s.)
Placebo	55.0%	

Young et al. Poster. Internat Soc Bipolar Disorders, India, Jan 2008

Quetiapine vs Paroxetine and Placebo Monotherapy for Bipolar I/II Depression (EMBOLDEN II)
(8-week, double-blind,, n=740)

- ↓ MADRS: QTP 300 mg = QTP 600 m > Paroxetine = PBO
- Remission at week 8 (MADRS ≤ 12)

QTP 600 mg	68.5%	(p<0.05)
QTP 300 mg	64.6%	(n.s.)
Paroxetine	56.8%	(n.s.)
Placebo	55.4%	

McElroy et al. Poster. Internat Soc Bipolar Disorders, India, Jan 2008

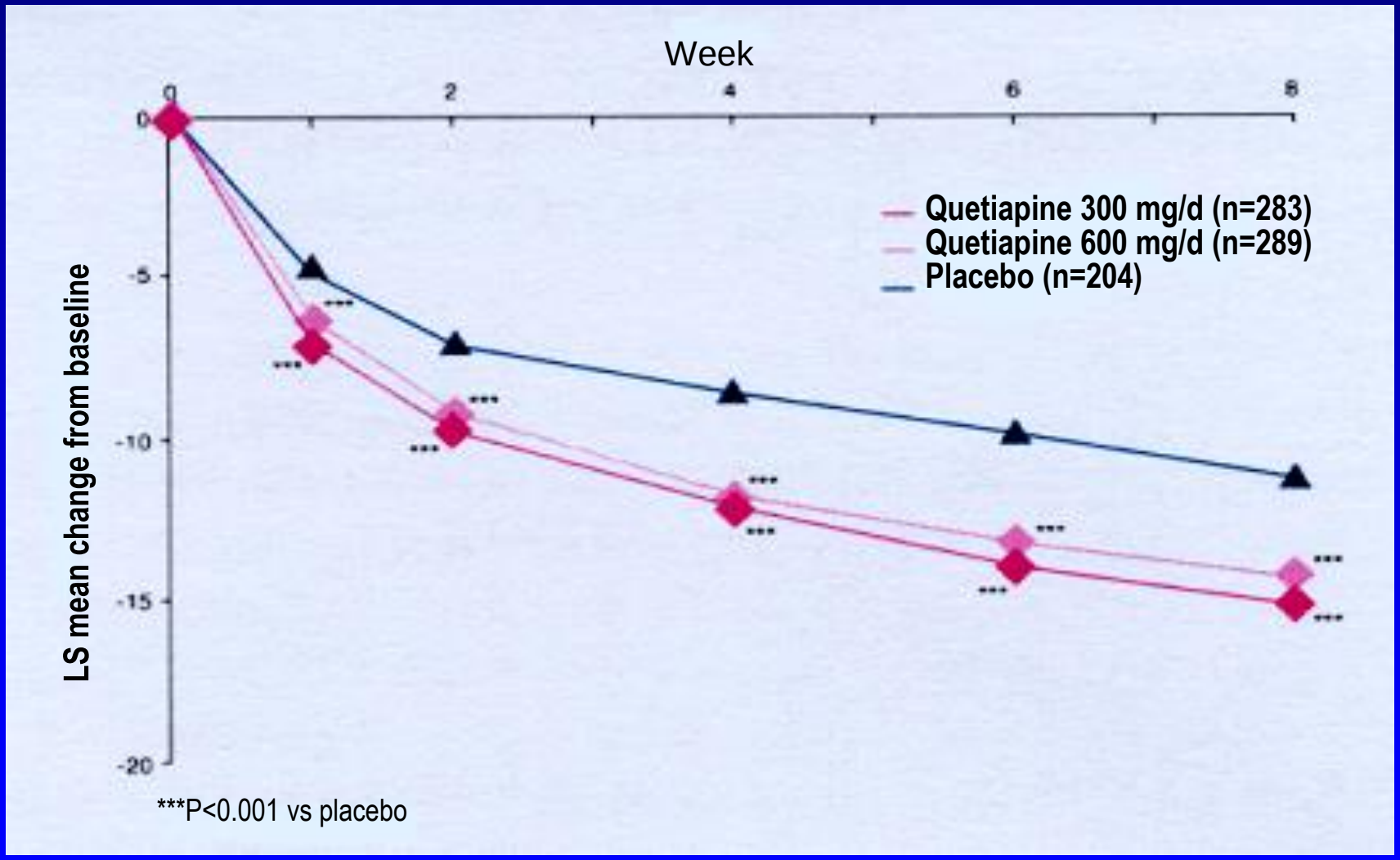
Quetiapine Monotherapy for Bipolar II Depression: Combined Data From 4 Double-Blind, 8-Week Studies

- ↓ MADRS: QTP 300 mg = QTP 600 mg > placebo beginning at week 1
- Remission at week 8 (MADRS ≤ 12)

QTP 300 mg	65.0%	(p<0.01)	NNT 5
QTP 600 mg	61.9%	(p<0.01)	NNT 6
Placebo	46.1%		

Young et al. APA NR4-116, 162 Annual Meeting, San Francisco, 5/16-21, 2009

Quetiapine Monotherapy for Bipolar II Depression: Combined Data From 4 Double-Blind, 8-Week Studies



Young et al. APA NR4-116, 162 Annual Meeting, San Francisco, 5/16-21, 2009

Quetiapine Monotherapy for Acute Bipolar I Depression in Adolescents

- 8-week, double-blind, placebo-controlled, n=32
- Dose: 300-600 mg/day
- No significant difference in primary (↓ CDRS-R) or secondary efficacy measures

DelBello et al. Bipolar Disorders 2009;11:483-493

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

Aripiprazole Monotherapy 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

Thase et al., J Clin Psychopharmacology 2008;28:13-20

Divalproex

Divalproex for Acute Bipolar Depression

- 4 small double-blind studies
- **Positive results**: Ghaemi et al. J Clin Psychiatry 2007;68:1840-1844 (n=18); Davis et al. J Affect Dis 2005;85:259-266 (n=25); Muzina et al. NCDEU poster, May 2008 (n=54)
- **Negative results**: Sachs et al. ACNP poster, December 2001 (n=45)

Antidepressants

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

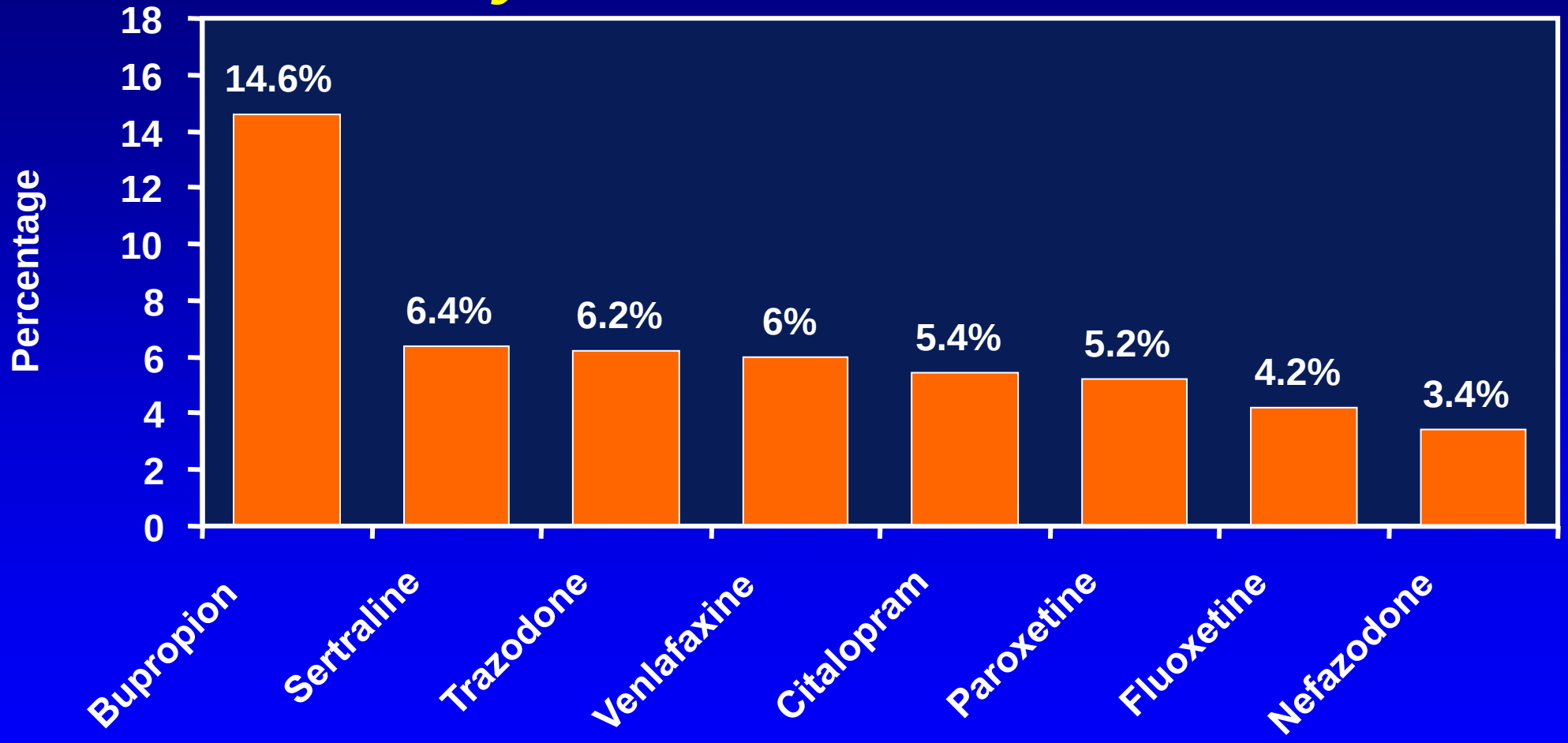
Suppes T et al. (2005), J Clin Psychiatry 66(7):870-886

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

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



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

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

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

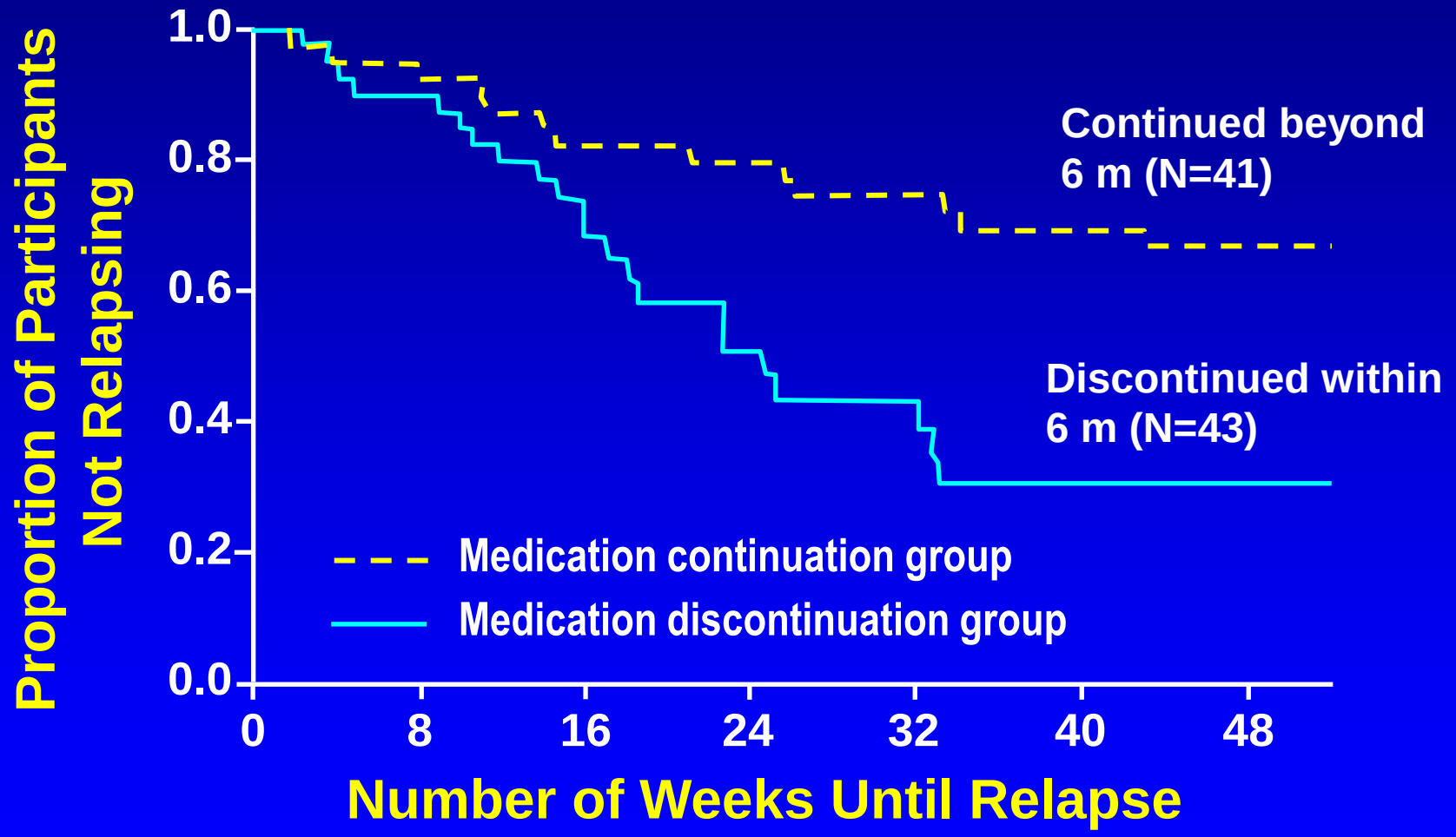
- Bupropion, paroxetine or placebo
- Primary outcome: 8 consecutive euthymic weeks
- Results: NO DIFFERENCE

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

Antidepressants in Bipolar Depression An Updated Review (18 RCTs, n=2515)

- Antidepressants exert some efficacy in some populations
- Increased switch rate associated with substance abuse, many previous episodes, depression with manic/hypomanic features

Salvi et al., J Clin Psychiatry 2008;69:1307-1318 (August)

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

Quetiapine vs Paroxetine and Placebo Monotherapy for Bipolar I/II Depression (EMBOLDEN II)

(8-week, double-blind, n=740)

- **Mania/hypomania**

QTP 600 mg	4.1%
QTP 300 mg	2.1%
Paroxetine	10.7%
Placebo	8.9%

McElroy et al. Poster. Internat Soc Bipolar Disorders, India, Jan 2008

Adjunctive Paroxetine vs. Venlafaxine for Bipolar Depression (6-week, single-blind, n=60)

- No significant difference on HAM-D change, response or remission rates

- Mania/hypomania switch rates:

Paroxetine	3%	(1/30)
Venlafaxine	13%	(4/30)

Vieta et al. J Clin Psychiatry 2002;63:508-512

Do Antidepressants Cause Rapid Cycling?

Do Antidepressants Cause Rapid Cycling?

Maybe

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

Is antidepressant monotherapy safe and effective for bipolar II depression?

Is antidepressant monotherapy safe and effective for bipolar II depression?

Maybe

Amsterdam and Brunswick. Bipolar Disorders 2003;5:388-395
Agosti and Stewart. Int Clin Psychopharmacol 2007;22:309-311

Venlafaxine vs. Lithium Monotherapy for Bipolar II Depression (12-week, open-label, n=83)

- **VEN: mean daily dose 185.6mg**
  Lithium: mean serum level 0.64 meq/l
- **VEN > Lithium ↓HAM-D$_{28}$**
  Response 60.4% vs. 20%
  Remission 44.2% vs. 7.5%
- **Young Mania Rating Scale: No significant increase**

Amsterdam and Shults. J Clin Psychopharmacol 2008;28:171-181

Odds and Ends

Adjunctive Modafinil for Bipolar I or II Depression (6-week, double-blind, n=85)

- Dose: 100 mg x 1-w, then 100 mg bid (mean 174 mg/day)
- Reponse (↓ IDS ≥50%): MOD 43.9% PBO 22.7% (P=0.038)
- Remission (IDS<12): MOD 39% PBO 18% (P=0.033)

Frye et al. Am J Psychiatry 2007;164:1242-1249

Adjunctive Pramipexole for Bipolar Depression (6-week, double-blind)

- Study 1: n=22, dose- start 0.125 mg bid, max 5 mg, mean 1.7 mg/day
  Response Pram 67%, PBO 20%
- Study 2: n=21 (BPII), dose- start 0.125 mg tid max 4.5 mg, mean 1.7 mg/day
  Response Pram 60% PBO 9%

1 Goldberg et al Am J Psychiatry 2004;161:564-566
2 Zarate et al Biol Psychiatry 2004;56:54-60

Omega-3 Fatty Acid Augmentation For Bipolar Depression

- Two double-blind, placebo-controlled studies
- "Adjunctive ethyl-EPA is an effective and well-tolerated intervention in bipolar depression."[1]
- "Overall, there were no significant differences on any outcome measure between the EPA and placebo groups."[2]

1 Frangou et al. Br J Psychiatry 2006;188:46-50
2 Keck et al Biol Psychiatry 2006;60:1020-1022

Adjunctive Riluzole for Bipolar Depression (8-week, open-label, n=14)

- Approved for ALS
- Anti-glutamergic, sodium channel blocker
- 50-200 mg/day added to lithium:
  -significant on MADRS at weeks 5-8
- 57% completion
- AE dropouts 14%
- No manic switches

Zarate et al. Biol Psychiatry 2005;57:430-432

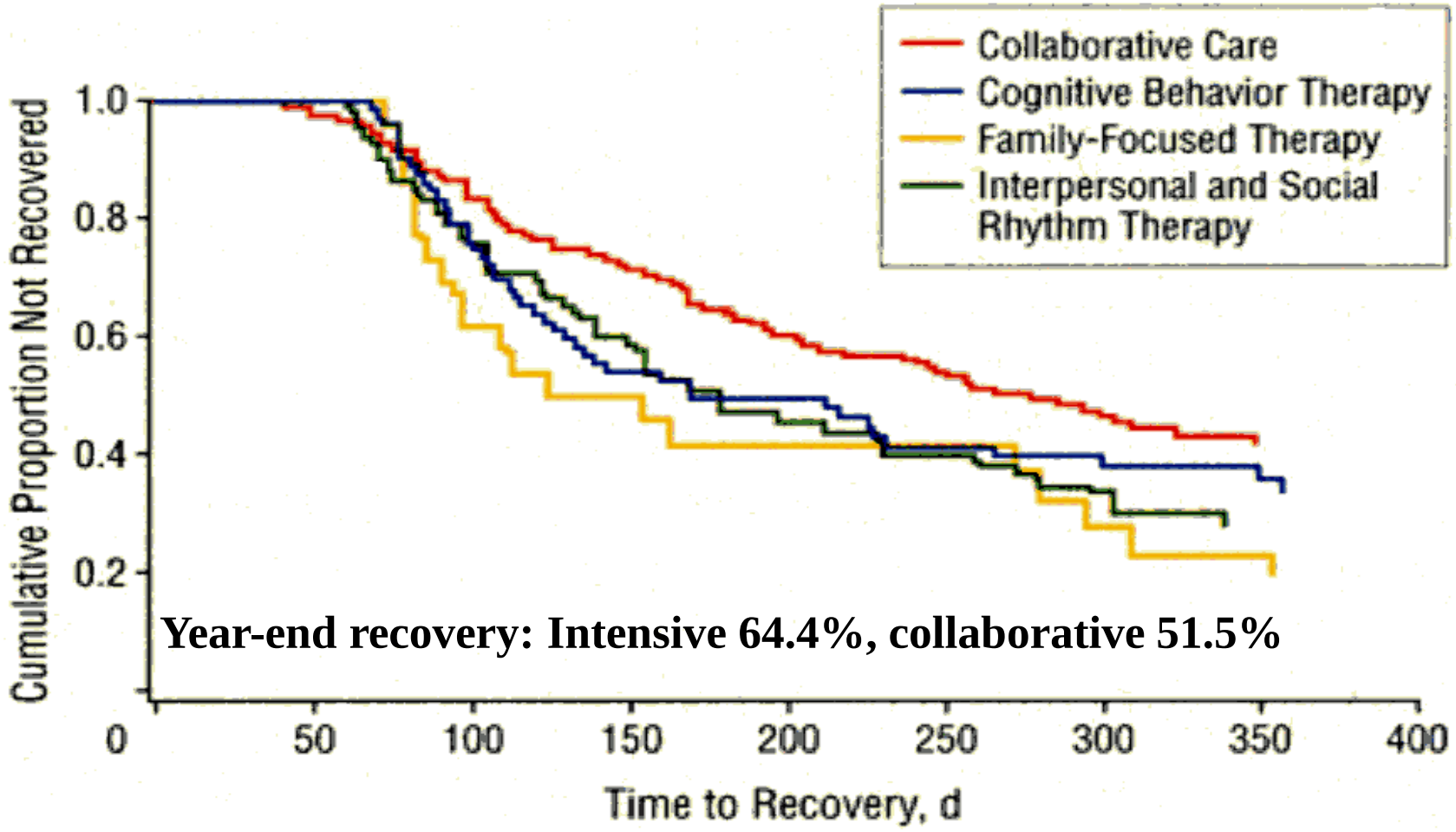
Adjunctive N-Acetyl Cysteine (NAC) for Subthreshold Bipolar Depressive Symptoms
(24-week, db, PBO-controlled, n=75)

- Glutathione: antioxidant substrate
- NAC: glutathione precursor (2 gm/day)
- MADRS: Significant ↓ at week 20 and after
- Time to mood episode: Not significant
- Cheap, safe, OTC, but how effective?

Berk et al. Biol Psychiatry 2008;64:468-475

STEP-BD: Adjunctive Psychosocial Treatments for Bipolar Depression

Higher recovery rates and shorter time to recovery



Miklowitz et al. Arch Gen Psychiatry 2007;64:419-427

Conclusions

- **Bipolar depression: common, under-diagnosed, misdiagnosed**
- **Treatment: two FDA-approved treatments**
- **Treatment: data vs. expert opinion**
- **Treatment: role of antidepressants?**
- **Treatment: need for more research**

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 November 2009, 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