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

Revised November 2009

Part 1: Overview and Treatment of Acute Mania

Revised November 2009

Teaching Points

1. The concept of bipolar disorder extends beyond DSM-IV.
2. Over time, most bipolar patients require combination therapy.
3. Treatment guidelines and algorithms abound.
4. There are at least 11 FDA-approved drugs for treating acute mania. There is no clear “winner”.

Outline

I. DSM-IV Bipolar Disorders Classification
II. The Bipolar Spectrum Concept
III. General Treatment Principles
    A. Improving Adherence
    B. Role of Psychotherapies
    C. Choosing Medications
    D. Combination Therapies
IV. Guidelines and Algorithms
V. Pharmacotherapy of Acute Manic and Mixed Episodes
    A. FDA-Approved Drugs
    B. Supportive Data for Efficacy
    C. Texas Implication of Medication Algorithm (TIMA)

Pre-Lecture Exam Question 1

1. All of the following are FDA-approved for treating acute mania except:
   a. Carbamazepine
   b. Chlorpromazine
   c. Clonazepam
   d. Divalproex
   e. Aripiprazole

Question 2

2. A patient with a history of hypomanic episodes and major depressive episodes would receive which DSM-IV diagnosis?
   a. Cyclothymic disorder
   b. Bipolar NOS
   c. Bipolar I
   d. Bipolar II
   e. Bipolar III

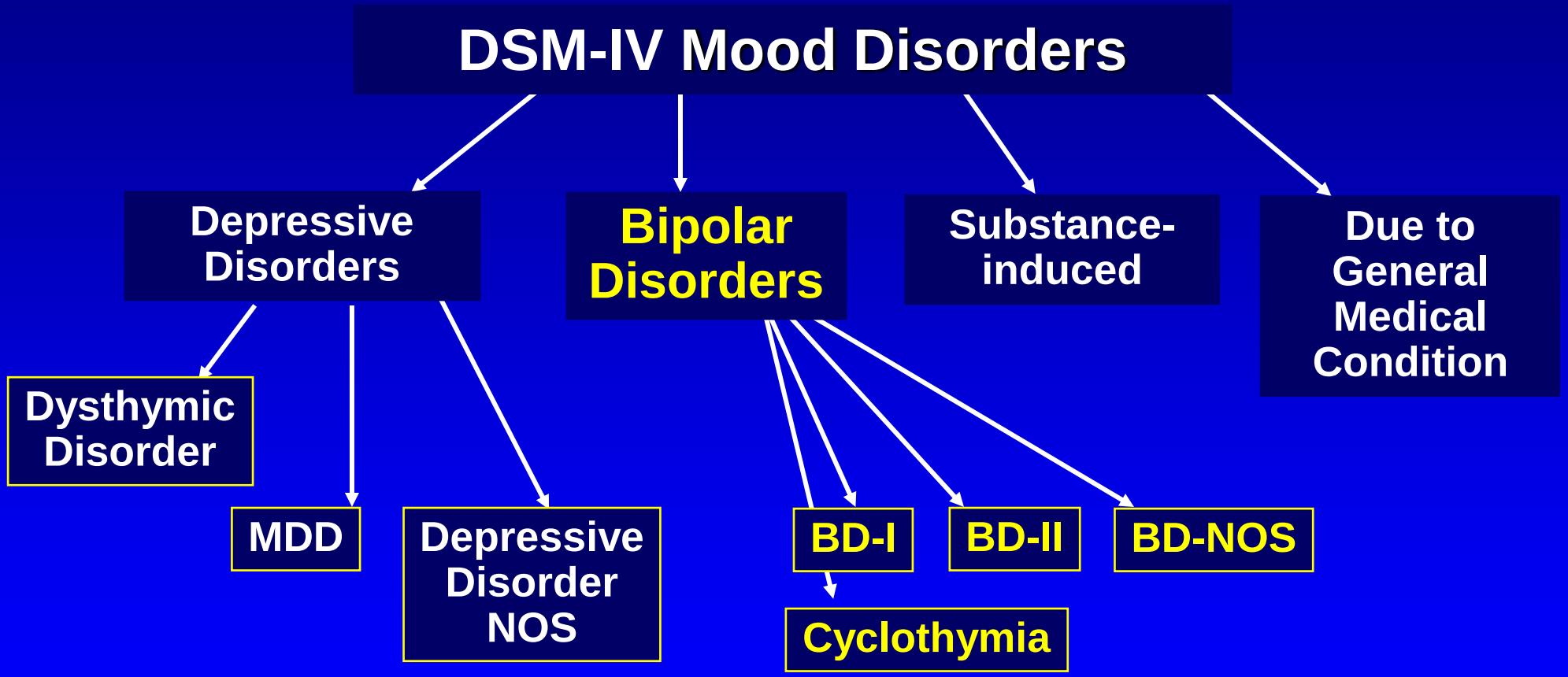
Question 3

3. **Which of the following drugs has a recommended starting dose for acute mania of 25 mg/kg/day?**
   a. **Divalproex ER**
   b. **Carbamazepine ER**
   c. **Risperidone**
   d. **Divalproex**
   e. **Quetiapine**

Question 4

4. **Why is olanzapine not listed in Stage IA of the TIMA algorithm for acute mania monotherapy?**
   a. **Issues about efficacy**
   b. **Safety and tolerability concerns**
   c. **Cost**
   d. **Complexity of use**

Mood Disorders: DSM-IV Classification



APA (1994), Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, D.C.: APA

Bipolar Disorders: DSM-IV

- Bipolar I disorder
  - Hypomanic, manic, mixed, depressed, unspecified
- Bipolar II disorder
- Cyclothymic disorder
- Bipolar disorder NOS (not otherwise specified)

Bipolar Lifetime Prevalence Rates

Diagnosis	No. of Studies	Range of Rates (%)
BD-I	19	0.0-2.4
BD-II	10	0.3-2.0
Cyclothymia	5	0.5-2.8
Bipolar spectrum disorders	10	2.6-7.8

BP-I: 0.8-1.6%, BP-II: 0.5-5.5%

Tohen M, Angst J (2002), In: Textbook in Psychiatric Epidemiology, Tsuang MT, Tohen M, eds. New York: Wiley-Liss, pp427-444

Mixed Bipolar Episode (DSM-IV)

- Criteria for **both** a major depressive episode and a manic episode
- For at least 1 week

Bipolar Spectrum Disorders

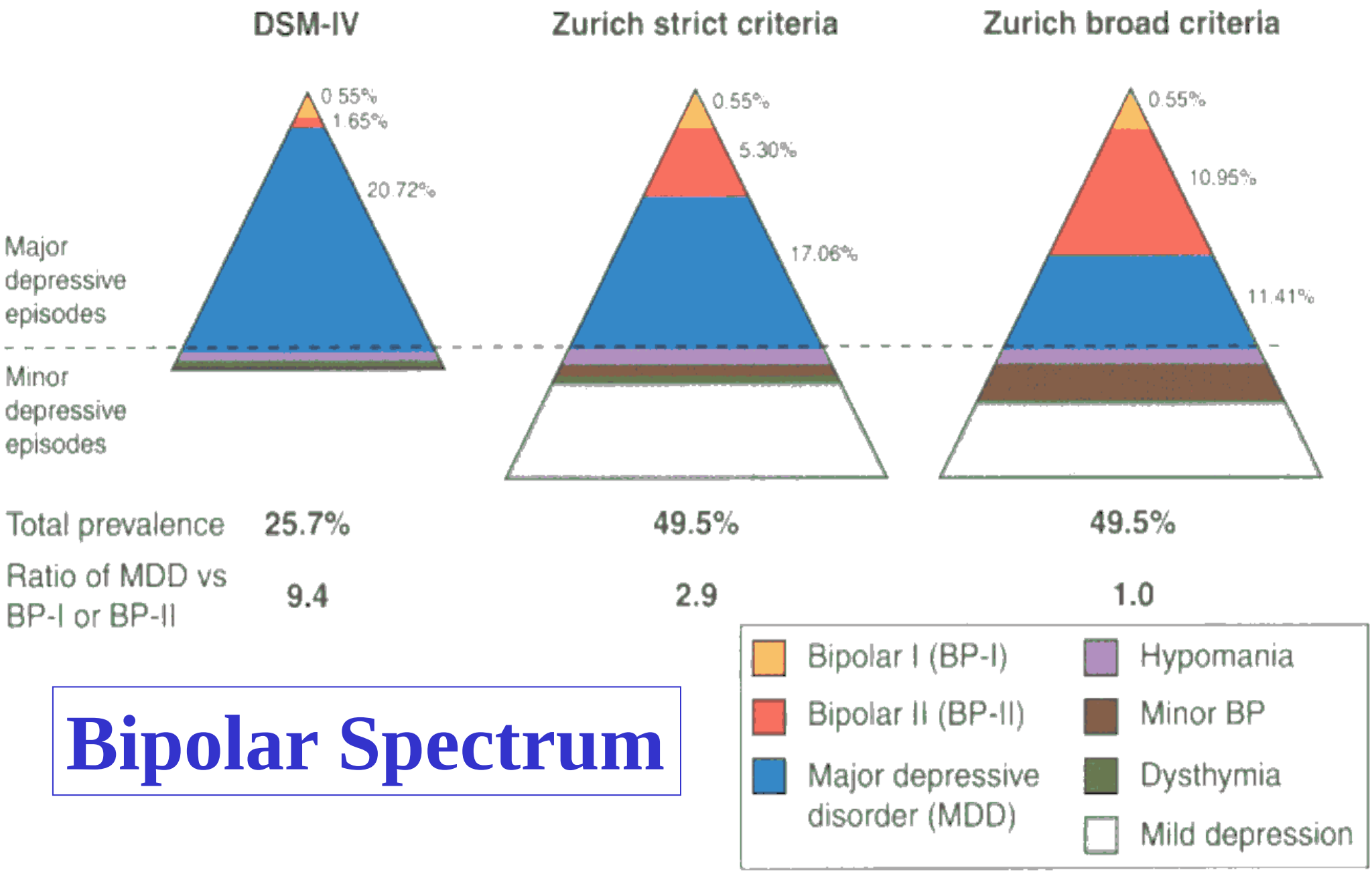
- Bipolar I disorder: history of mania*
- Bipolar II disorder: history of hypomania and major depressive episodes*
- Cyclothymia*
- Hyperthymic temperament
- Secondary mania (to other illnesses or drugs)
- Antidepressant-induced mania and hypomania

*DSM-IV categories; American Psychiatric Association (1994), Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, D.C.: American Psychiatric Publishing, Inc.

Hyperthymic Temperament*

- Extroverted and people-seeking
- High energy level
- Extremely sociable to the point of intrusive
- Overconfident, boastful and grandiose
- Stimulus seeking
- Short sleeper (less than 6 hours per night)

*Habitual long-term functioning of the individual;
Akiskal HS (1996), J Clin Psychopharmacol 16(2 suppl 1):4S-14S



Bipolar Spectrum

Angst and Cassano. Bipolar Disord 2005;7(Suppl 4):4-12

Zurich Study Hypomania Criteria

Strict

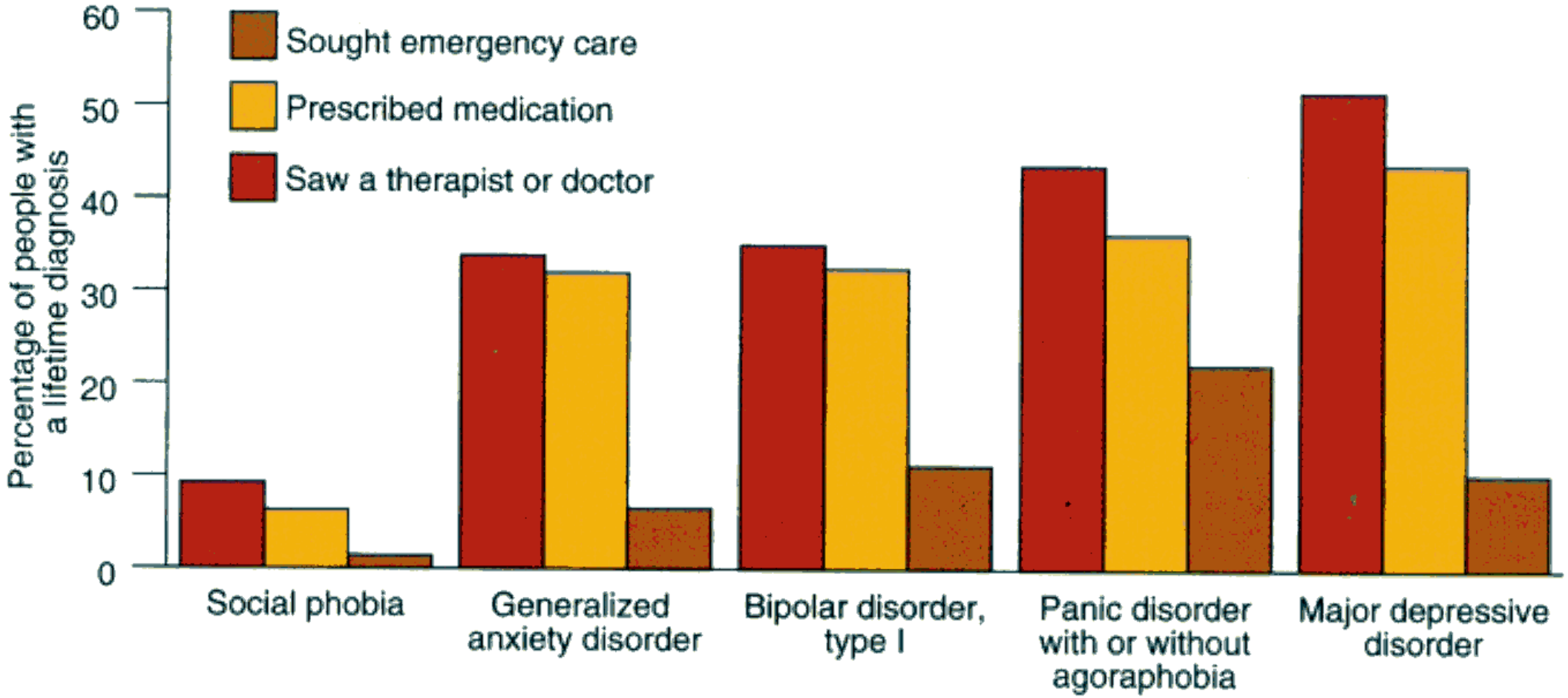
- 3 or more DSM-IV criteria
- Minimum duration 1 day
- Consequences

Loose

- 2 or more DSM-IV criteria
- No minimum duration
- No consequences

Angst and Cassano. Bipolar Disorders 2005;7(suppl):4-12

Treatment Seeking: NESARC* Study

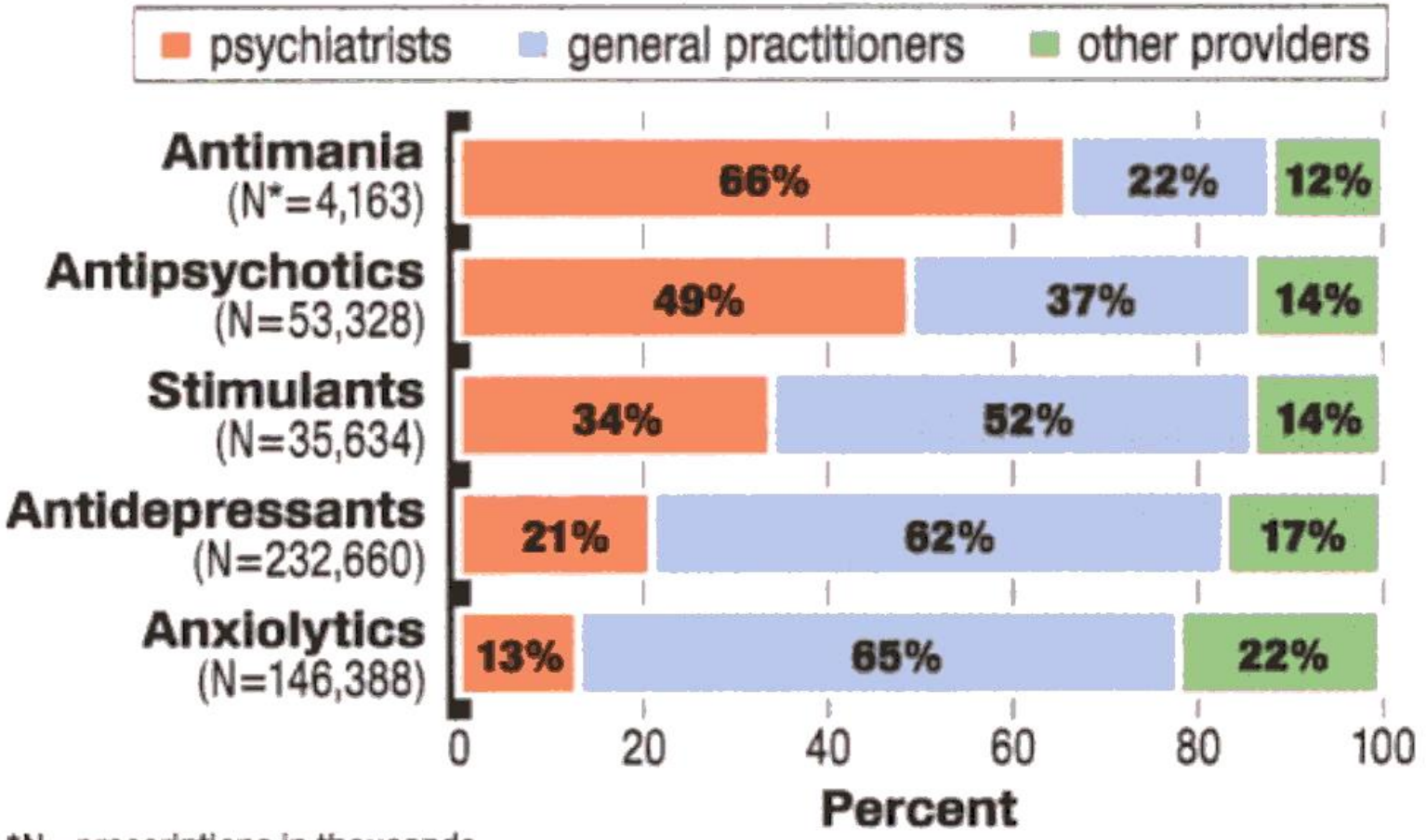


*NESARC: National Epidemiologic Survey on Alcohol and Related Conditions

Giacobbe et al. Psychiatric Serv 2008;59(10):1099

General Practitioners Prescribe Most Psychotropics

Of the 472 million prescriptions for psychotropic medications written between August 2006 and July 2007, 59% were written by general practitioners, 23% by psychiatrists, and 19% by other physicians and nonphysician providers. Below is a breakdown by class.



*N=prescriptions in thousands

Source: *Psychiatric Services*, September 2009

General Treatment Principles

- Psychosocial interventions
- Pharmacologic interventions
- Promote education
- Enhance compliance

Improving Treatment Adherence

- Therapeutic alliance
- Education
- Availability and support
- Psychotherapy
- Medication -- minimize side effects, complexity, cost

Bipolar Psychotherapies

- Family Focused
- Interpersonal and Social Rhythm
- Cognitive-Behavioral
- Life Goals Program

Choice of Medication(s)

- Phase of illness
- Prior response and tolerability
- Medical and psychiatric comorbidities
- Side effects
- Drug interactions
- Patient preferences

Polypharmacy is Not a Bad Word

- Monotherapy is the exception
- Combination therapy is effective
- Increased risk of side effects and drug interactions

Algorithms and Guidelines

- Synthesize current evidence
- Add expert consensus
- Balance with safety and tolerability
- Not written in stone

Bipolar Guidelines Abound

- **APA Practice Guidelines** **2002**
  Am J Psychiatry 2002;159(suppl):1-50 (April)
- **Br Assoc Psychopharmacol** **2003**
  J Psychopharmacol 2003;17:149-173
- **Expert Consensus Guidelines** **2004**
  Postgrad Med Special Report 2004 (Dec)
- **WFSBP Guidelines** **2004**
  World J Biol Psychiatry 2002, 2003, 2004
- **CANMAT Guidelines** **2005***
  Bipolar Disorders 2005;7(suppl 3):5-69
- **TIMA Algorithms** **2005**
  J Clin Psychiatyy 2005;66:870-886 (July)

***Updated: Yatham et al. Bipolar Disorders 2006;8:721-739; Yatham et al. Bipolar Disorders 2009;11:225-255**

“All guidelines have similar objectives, but they often reach different conclusions.”

Vieta et al., Bipolar Disord 2005;7(Suppl 3):73-76

Acute Manic and Mixed Episodes

Opium

"… it calms and sooths the Disorders and Perturbations of the animal Spirits; which, when lulled and charmed by this soporiferous Drug cease their Tumults, and settle into a State of Tranquility"

Sir Richard Blackmore, 1725

Acute Mania: FDA-Approved

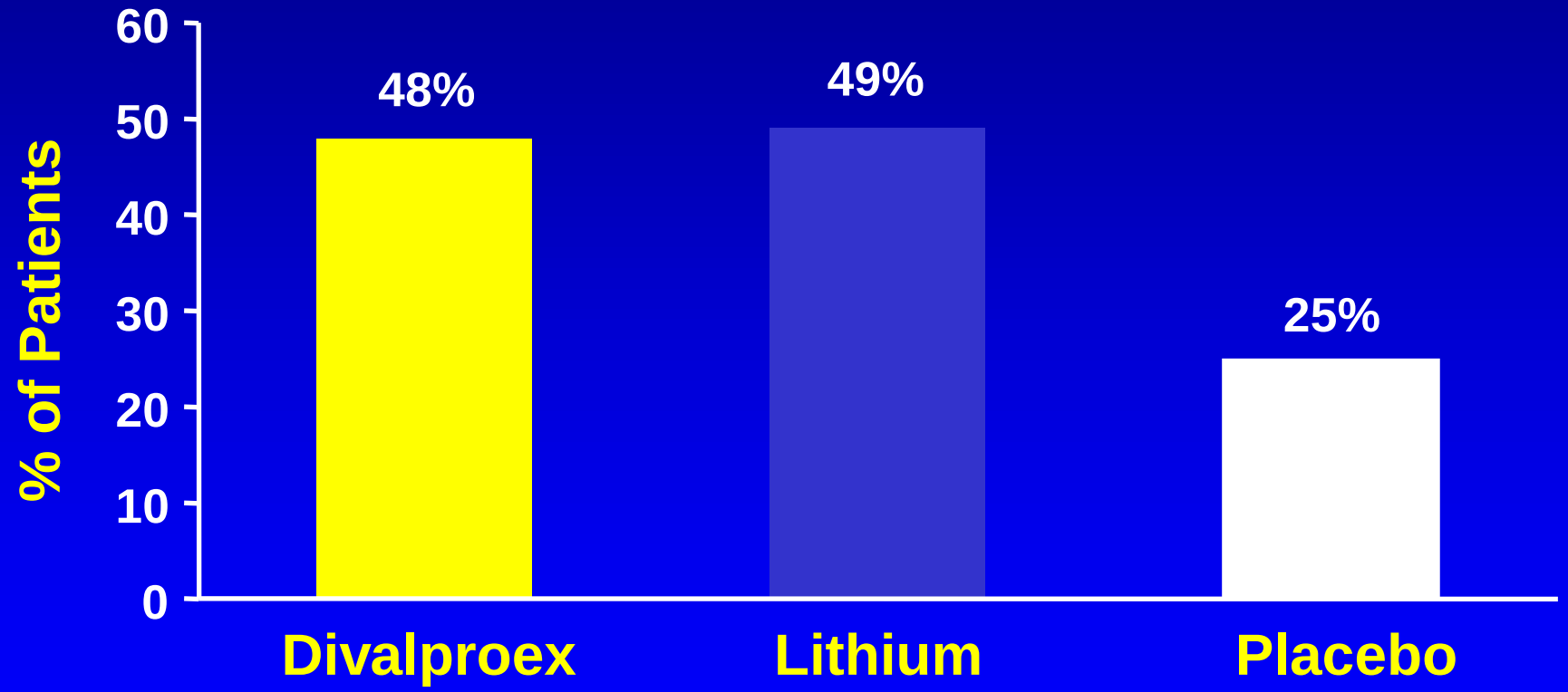
- 1970 Lithium
- 1973 Chlorpromazine
- 1995 Divalproex

- 2000 Olanzapine
- 2003 Risperidone*
- 2004 Quetiapine*
- 2004 Ziprasidone
- 2004 Aripiprazole*
- 2004 Carbamazepine ER
- 2005 Divalproex ER
- 2009 Asenapine

*Also pediatric (10-17) mania (RIS 2007, ARI 2008, QTP 2009)

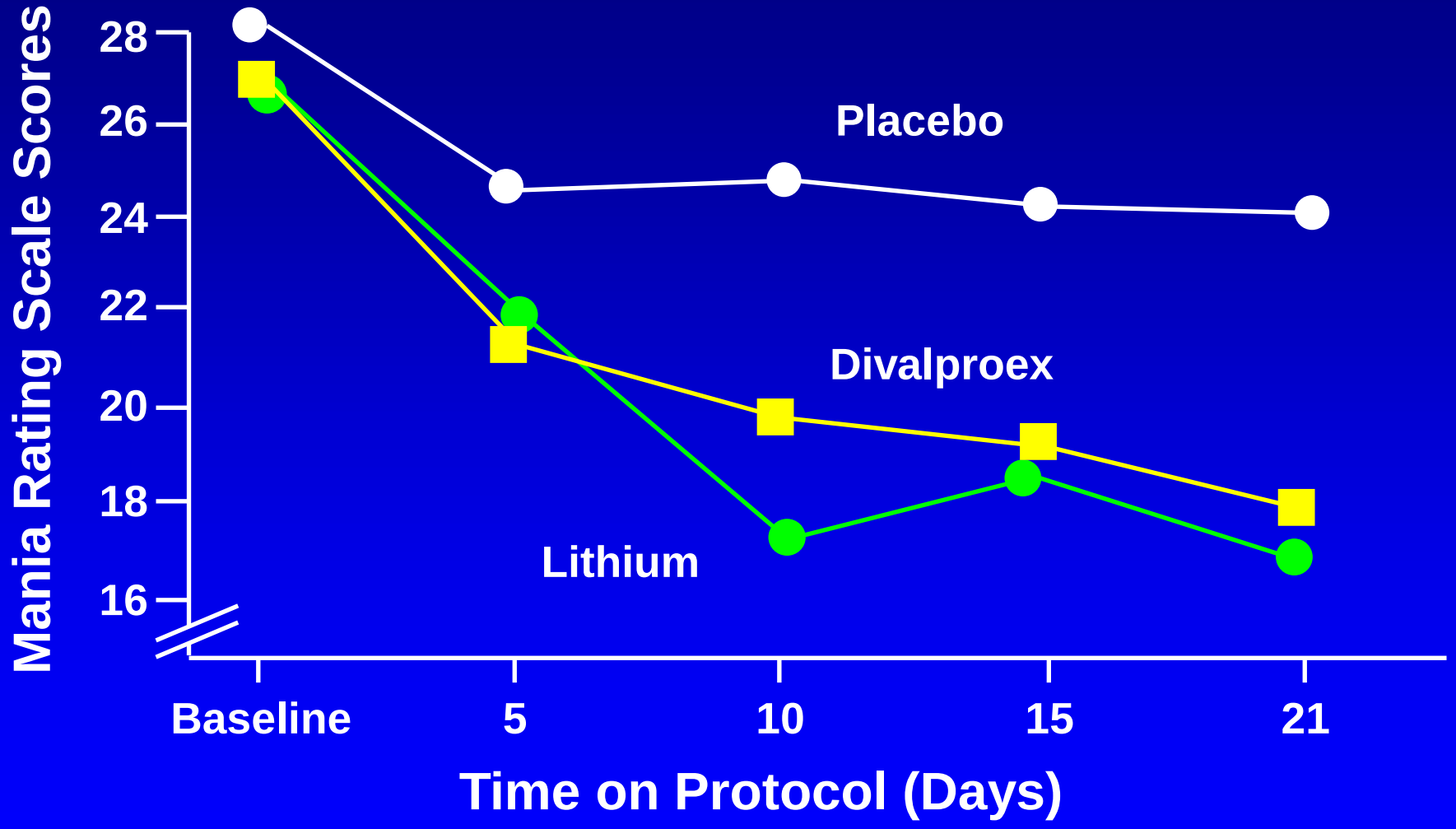
Acute Mania: Divalproex vs Lithium

(≥50% ↓ in Mania Subscale)



Bowden et al. JAMA. 1994;271:918-924

Divalproex vs. Lithium for Mania



Bowden et al. JAMA. 1994;271:918-924

Note: Y-axis does not begin at zero

Divalproex ER for Bipolar Disorder

- FDA-approved 12/05 for acute manic and mixed episodes
- Bioequivalent to divalproex at ER dose 8 to 20% higher
- Start 25 mg/kg/day (once daily)
- 250 mg and 500 mg tablets
- Target: 85-125 mcg/mL

Package insert 12/05

Divalproex ER for Acute Mania (Manic and Mixed Episodes)

3-week, placebo-controlled, n=364

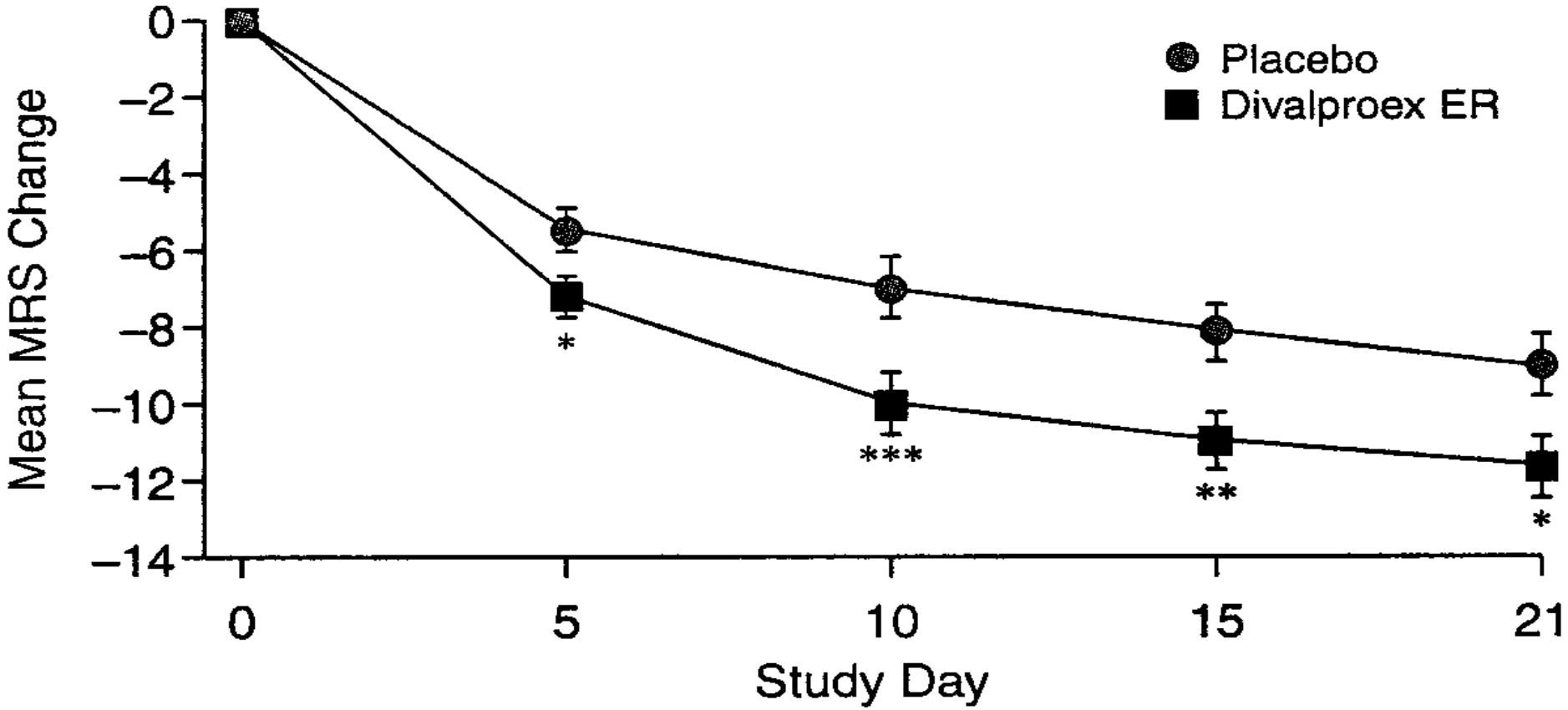
- **Primary outcome: MRS change from baseline**
  ER> Placebo at all points

- **Response (≥ 50% MRS improvement)**
  ER 48%
  Placebo 34% **(P=0.012)**

- **Remission (MRS ≤12)**
  ER 48%
  Placebo 35% **(P=0.015)**

Bowden et al., J Clin Psychiatry 2006;67:1501-1510

Divalproex ER for Acute Mania



Bowden et al.: J Clin Psychiatry 2006;67:1501-1510 (Oct)

Divalproex ER for Bipolar Mania/Mixed in Children and Adolescent Outpatients

- 4-week, double-blind, 6-month open follow-up, ages 10-17, n=150
- Mean endpoint VPA concentration 80 mcg/mL
- No significant differences from placebo on primary (YMRS change) or secondary outcome measures

Wagner et al. J Am Acad Child Adolesc. Psychiatry 2009;48:519-532

Neuroleptics* plus Valproate or Placebo for Acute Mania

- European Valproate Mania Study Group (10 sites, 3 weeks, n=136)
- VPA (20 mg/kg) > placebo
  - faster and better response (58% vs 30%)
  - lower neuroleptic dose
  - well tolerated
- What about VPA alone?

*Haloperidol or perazine

Müller-Oerlinghausen et al: J Clin Psychopharmacol 20:195-203, Apr 2000

Atypical Antipsychotic + Mood Stabilizer (Lithium or Divalproex) for Acute Mania

- Effective vs. placebo (FDA-approved)
  - Aripiprazole
  - Olanzapine
  - Quetiapine
  - Risperidone
- Probably effective (pending studies)
  - Others

Tohen M, Chengappa KN, Suppes T, et al. Arch Gen Psychiatry. 2002(Jan);59(1):62-69; Sachs GS, Grossman F, Ghaemi SN, et al. Am J Psychiatry. 2002(July);159(7):1146-1154; Mullen JA et al. APA, May 2003

Quetiapine vs. Placebo as Add-on to Lithium or Divalproex in Acute Mania (6-week, double-blind, n=211)

- **Dose:** Day 21 mean 423 mg/day
- **Primary efficacy measure:** YMRS change day 21
- **Day 21:** Quetiapine = placebo
- **Day 42:** Quetiapine = placebo

Yatham et al. Int Clin Psychopharmacology 2007;22:212-220

Aripiprazole vs. Placebo as Add-on to Lithium or Divalproex in Acute Mania (6-week, double-blind, n=384)

- **Dose: Week 6 mean- 19 mg/day**
- **Primary efficacy measure: YMRS (l.o.c.f.)**
- **ARI > PBO by week 1 and all subsequent endpoints**
- **Response: ARI > PBO weeks 5 and 6 (l.o.c.f.)**
- **Remission: ARI > PBO weeks 1, 3-6 (l.o.c.f.)**

Vieta et al. Am J Psychiatry 2008;165:1316-1325

Ziprasidone vs. Placebo as Adjunct to Lithium in Acute Mania (3-week, double-blind, n=205)

- **Dose:** 80 to 160 mg/day
- **Day 4:** Ziprasidone > placebo
- **Day 14:** Ziprasidone = placebo

Weisler et al., APA NR 358, May 2004

All Antipsychotic Drugs Are Antimanic

Name one that isn't!

Olanzapine

Divalproex vs. Olanzapine: Acute Mania

	Tohen et al., 2002	Zajecka et al., 2002
Start	OLZ 15 mg DVPX 750 mg	OLZ 10 mg DVPX 20mg/kg/day
MRS	OLZ -13.4 DVPX -10.4 (p=.028)	OLZ -17.2 DVPX -14.8 (n.s.)
↑ Weight	OLZ > DVPX	OLZ > DVPX

(Note differences in study design)

Tohen et al. Am J Psychiatry 2002;159:1011-1017
Zajecka et al. J Clin Psychiatry 2002;63:1148-1155

Olanzapine for Acute Mania
(pooled analysis – 2 studies)

	OLZ	PBO
• **Response (≥ 50% ↓ YMRS)**	**55%**	**29.5%**
• **Euthymia (YMRS ≤ 12)**	**50%**	**27%**
• **Remission (YMRS ≤ 7, etc.)**	**18%**	**7%**

Chengappa et al. Bipolar Disord 5:1-5, 2003

Olanzapine vs. Lithium for Acute Mania in China (4-week, double-blind, n=140)

- **OLZ > Li: ↓ YMRS (p=0.013), response (87% vs. 73.2) (p=0.035), but not remission (82.6% vs. 70.4%) (p=0.073)**
- **OLZ > Li: weight gain ≥ 7% (16.2% vs. 2.9%)**

Niufan et al. J Affective Disorders 2008;105:101-108

Olanzapine vs Risperidone for Manic or Mixed Episodes (3-week, double-blind, n=329)

- Similar improvements in mania (YMRS, response, remission)
- OLZ: better depression improvement (HAM-D but not MADRS) and study completion, but more weight gain and ↑LFTs
- RIS: more ↑prolactin, sexual dysfunction

Perlis et al., J Clin Psychiatry 2006;67:1747-1753 (November)

Olanzapine + Carbamazepine vs. Carbamazepine Alone for Acute Mania

6-week, double-blind, n=118

- No significant difference on any efficacy measure
- OLZ+CBZ: more weight gain, increased ALT and triglycerides

Tohen et al. ACNP, poster 59, Dec 2006

Olanzapine for Acute Manic or Mixed Episodes in Adolescents
(3 week, double-blind)

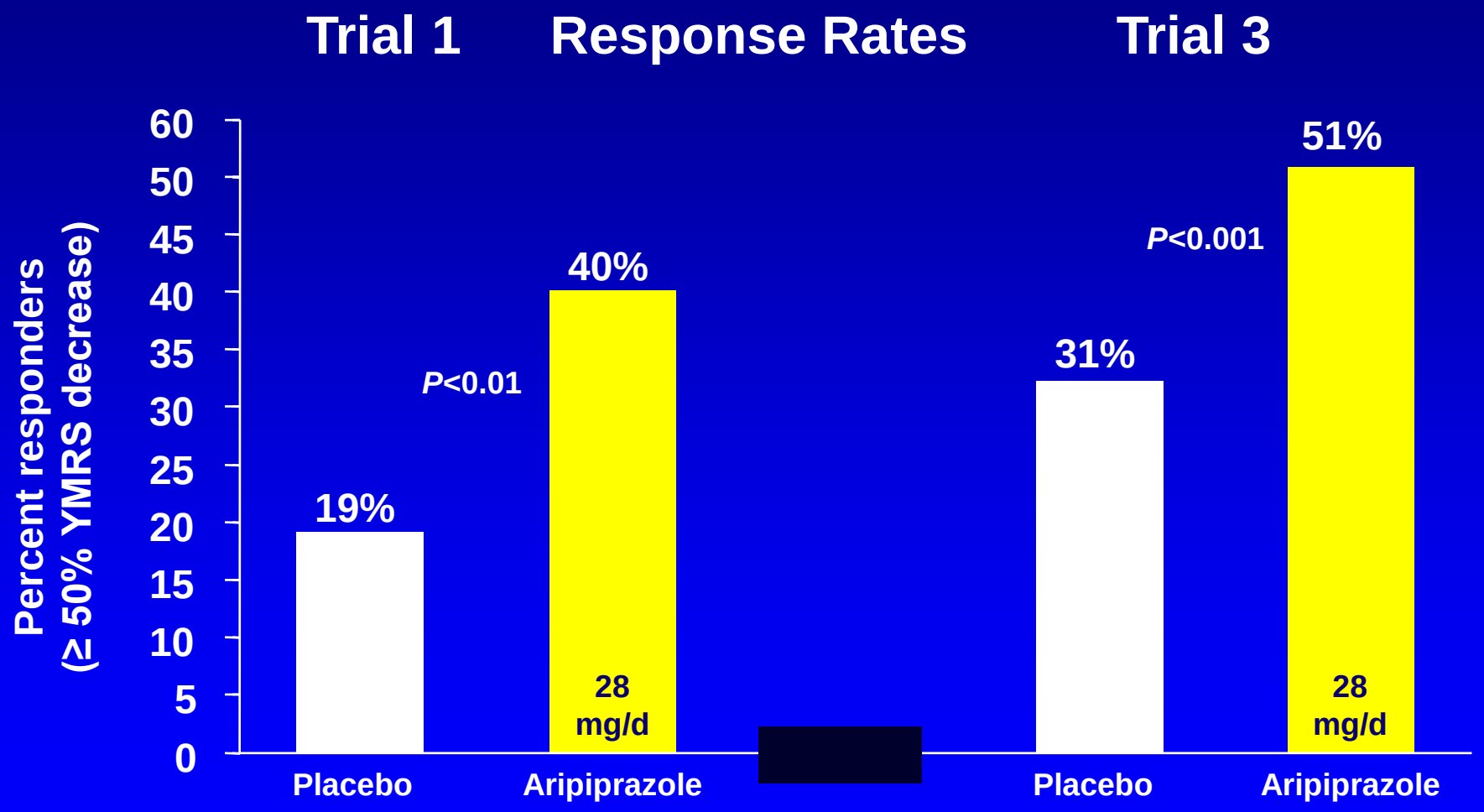
	OLZ (n=107)	PBO (n=54)
Response	48.6%	22.2%
Remission	35.2%	11.1%
Weight Gain ≥7%	41.9%	1.9%
High Prolactin-female	25.7%	0%
High prolactin-male	62.5%	5%

Tohen et al. Am J Psychiatry 2007;164:1547-1556

Aripiprazole

Aripiprazole in Acute Mania

(3-week, double-blind, start 30 mg)



Keck et al. *AJP 160:1651-1658, Sep 2003.*

Data on file, Bristol-Myers Squibb Company and Otsuka Pharmaceutical Co., Ltd.

Aripiprazole vs. Lithium and Placebo for Acute Bipolar Mania (3-week, db, n=480)

- ARI 15-30 mg, mean 23.2 mg; Li_2CO_3 900-1500 mg, mean 0.76 mEq/L)
- ↓ YMRS: ARI = Li2 > PBO (week 3 l.o.c.f.). Same for response and remission
- Additional 9 weeks double-blind (placebo patients got aripiprazole): Aripiprazole=Lithium

• Keck et al. J Affctive Disorders 2009;112:36-49

Aripiprazole for Pediatric Bipolar Mania

- On Feb 29, 2008: FDA-approved for bipolar I manic and mixed episodes , ages 10-17
- Based on one 4-week, placebo-controlled trial, n=296
- Start 2 mg/day, titrate to target of 10 mg or 30 mg/day

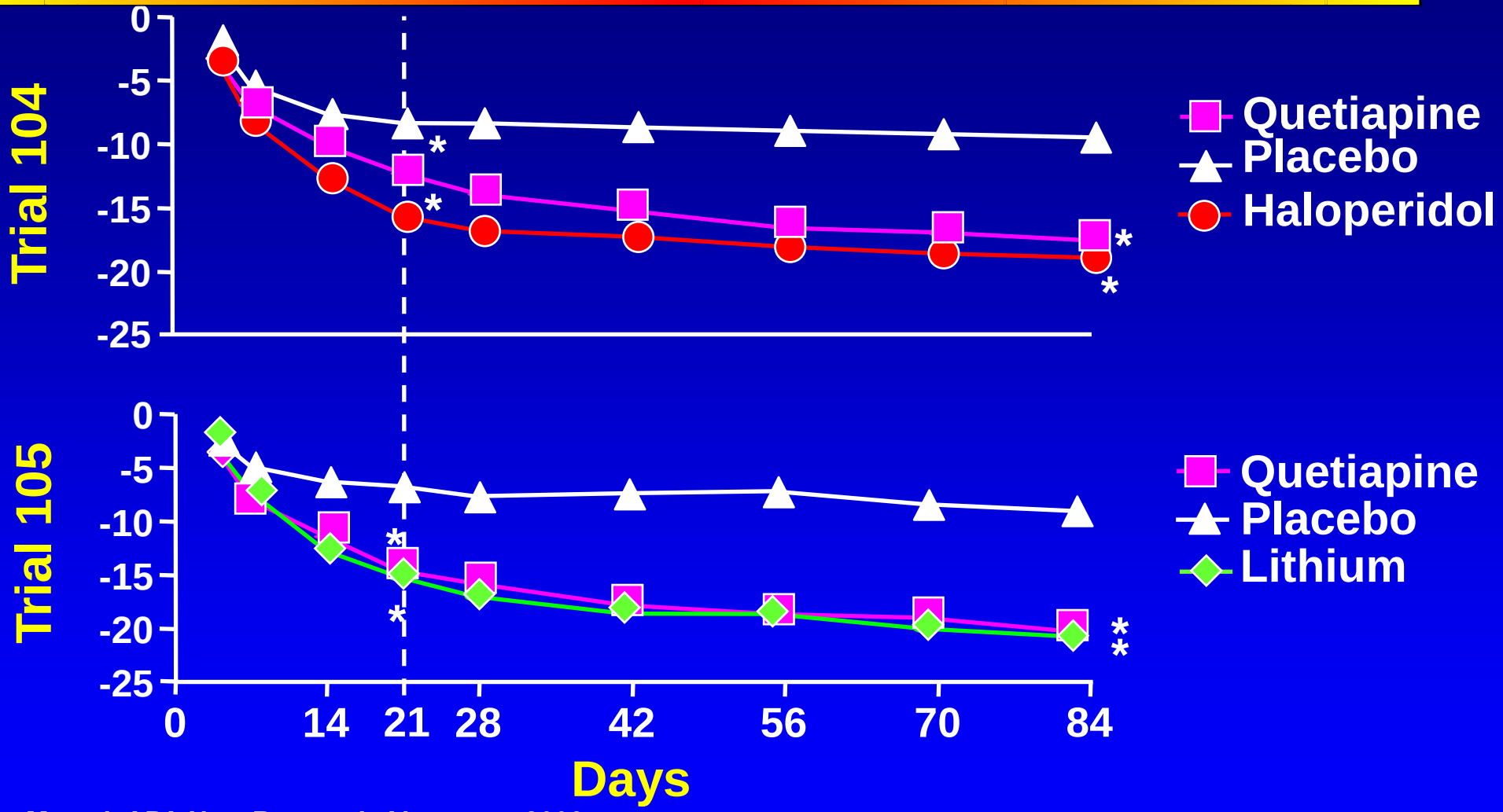
Aripiprazole for Pediatric Bipolar Mania Comorbid with ADHD

- 6-week, double-blind, n =43, monotherapy
- Mean final dose: 13.6 mg
- ↓ YMRS: ARI 27.22, PBO 19.52 (p=0.02)
- Response (≥ 50% ↓ YMRS):
  ARI 88.9%, PBO 52% (p=0.02)
- Remission (YMRS ≤ 12)
  ARI 72%, PBO 32% (p=0.01)
- No effect on ADHD symptoms

Tramontina et al. J Clin Psychiatry 2009;70:756-764

Quetiapine

Quetiapine for Acute Mania



Jones M et al. APA New Research Abstracts, 2003

Trial 105-McIntyre et al., Eur Neuropsychopharmacol 15:573-585, 2005

Trial 105-Bowden et al., J Clin Psychiatry 66:111-121, 2005

Quetiapine vs. Divalproex in Adolescent Mania (4-week, double-blind, n=50)

- QTP: 400-600 mg/day (mean 412 mg)
  DVPX: mean serum level 101 mcg/ml
- YMRS change (primary outcome)

QTP	23	(n.s.)
DVPX	19	

- Response (CGI-I-mania 1 or 2)

QTP	72%	(p=0.02)
DVPX	40%	

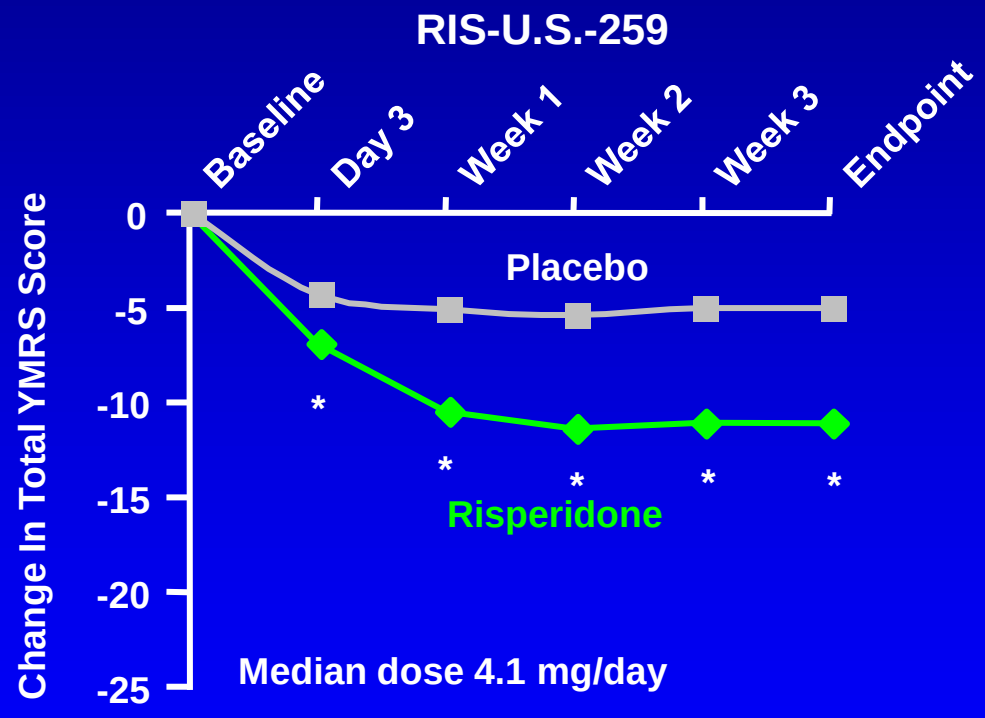
- Remission: QTP 60%, DVPX 28% (p=0.02)

DelBello et al. J Am Acad Child Adolesc Psychiatry 2006;45:305-313 (March)

Risperidone

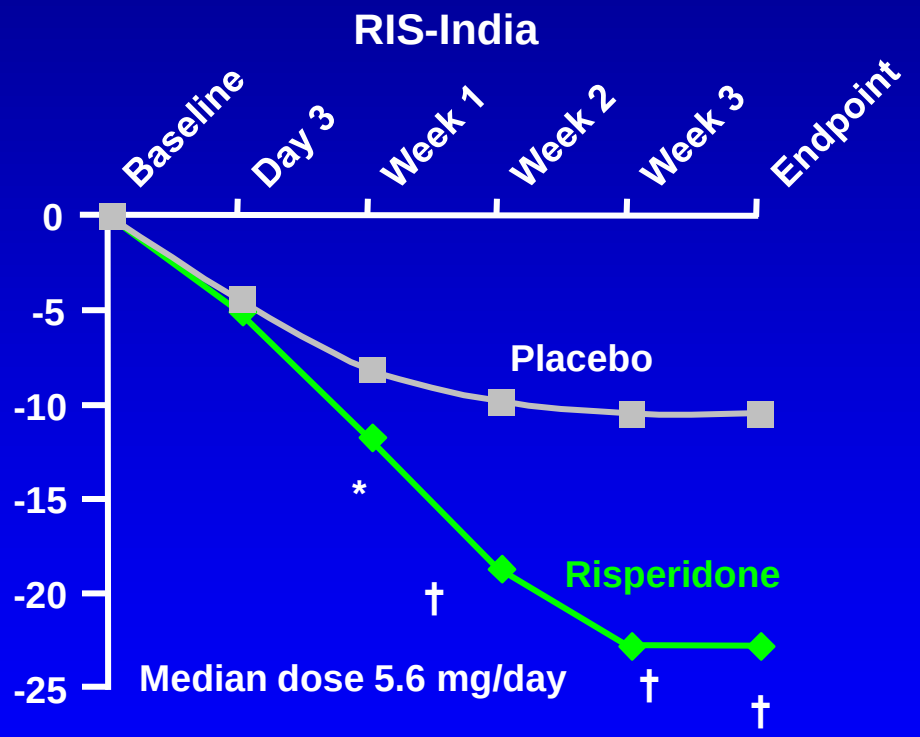
Risperidone in Acute Bipolar Mania

Change From Baseline in Total YMRS (Primary Efficacy Variable)



LOCF analysis. *P<.001 risperidone vs placebo.

Hirschfeld RM et al. *Am J Psychiatry* 2004;161:1057-1065 (excluded mixed)



LOCF analysis. *P<.01; †P<.001 risperidone vs placebo.

Khanna S et al. Br J Psychiatry 2005;187:229-234 (Sept) (included mixed)

Risperidone for Pediatric Bipolar Mania

- **Aug 20, 2007: FDA-approved for bipolar I manic and mixed episodes , ages 10-17**
- **Based on one 3-week, placebo-controlled trial**
- **Doses above 2.5 mg/day-no trend towards greater efficacy**

Package insert, revised 8/07

Risperidone for Pediatric Bipolar Mania (3-week, double-blind, ages 10-17, n=169)

- RIS 0.5-2.5 mg (n=50), RIS 3-6 mg (n=61), PBO (n=58)
- Primary efficacy ↓ YMRS (l.o.c.f.):

  RIS 0.5-2.5 mg = RIS 3-6 mg > PBO
- Response (↓ YMRS ≥ 50%)

RIS 0.5-2.5 mg	59.2%
RIS 3-6 mg	63.3%
PBO	26.3%

Haas et al. Bipolar Disorders 2009;11:687-700

Risperidone for Pediatric Bipolar Mania (3-week, double-blind, ages 10-17, n=169)

- **Adverse event dropouts:**

RIS 0.5-2.5 mg	6%
RIS 3-6 mg	16%
PBO	7%

- **Weight gain ≥ 7%**

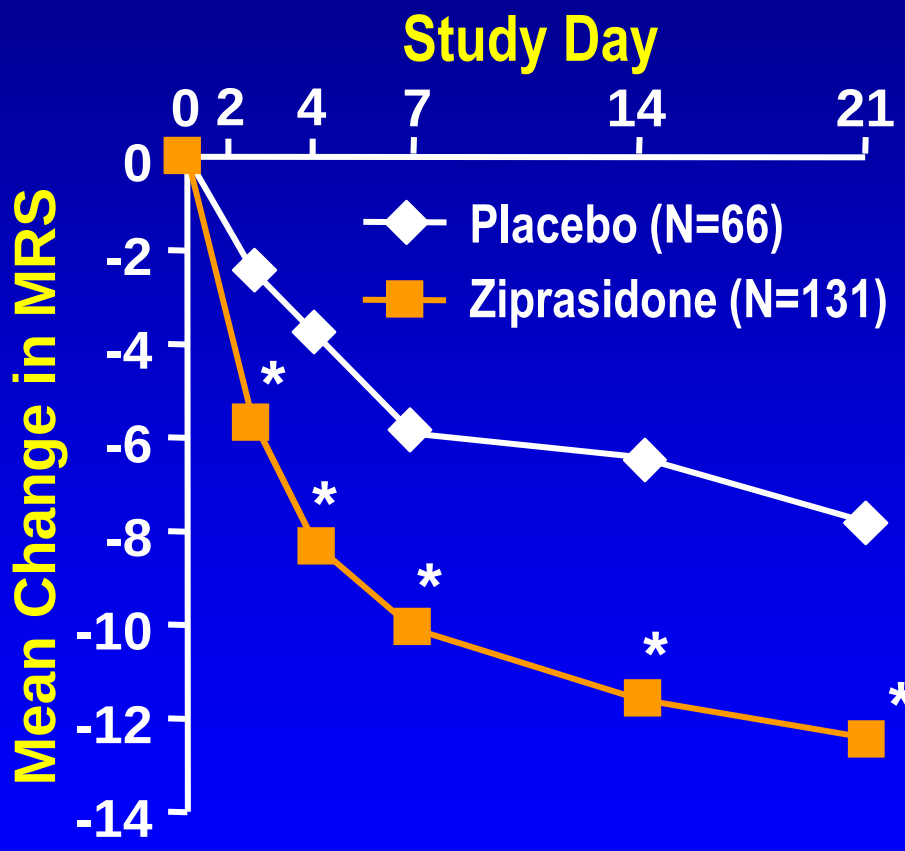
RIS 0.5-2.5 mg	14.3%
RIS 3-6 mg	10%
PBO	5.3%

Haas et al. Bipolar Disorders 2009;11:687-700

Ziprasidone

Ziprasidone: Efficacy in Acute Mania

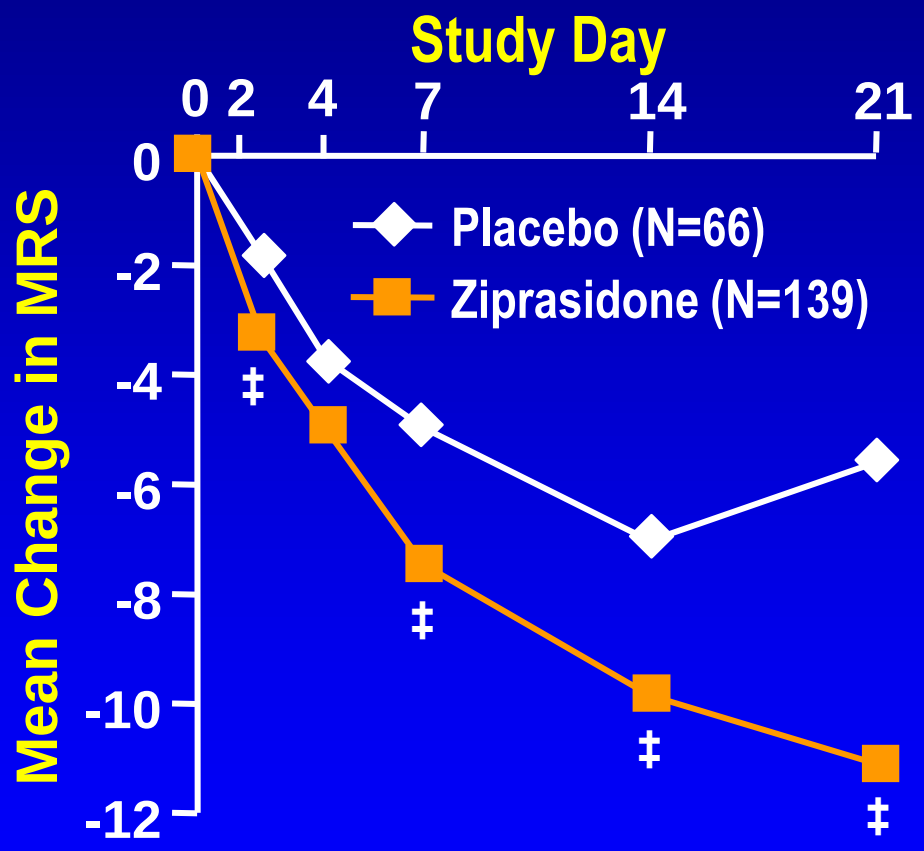
Mean Change From Baseline (LOCF)



*p<0.01;

Keck et al., Am J Psychiatry 2003;160:741-748

Mean Change From Baseline† (LOCF)

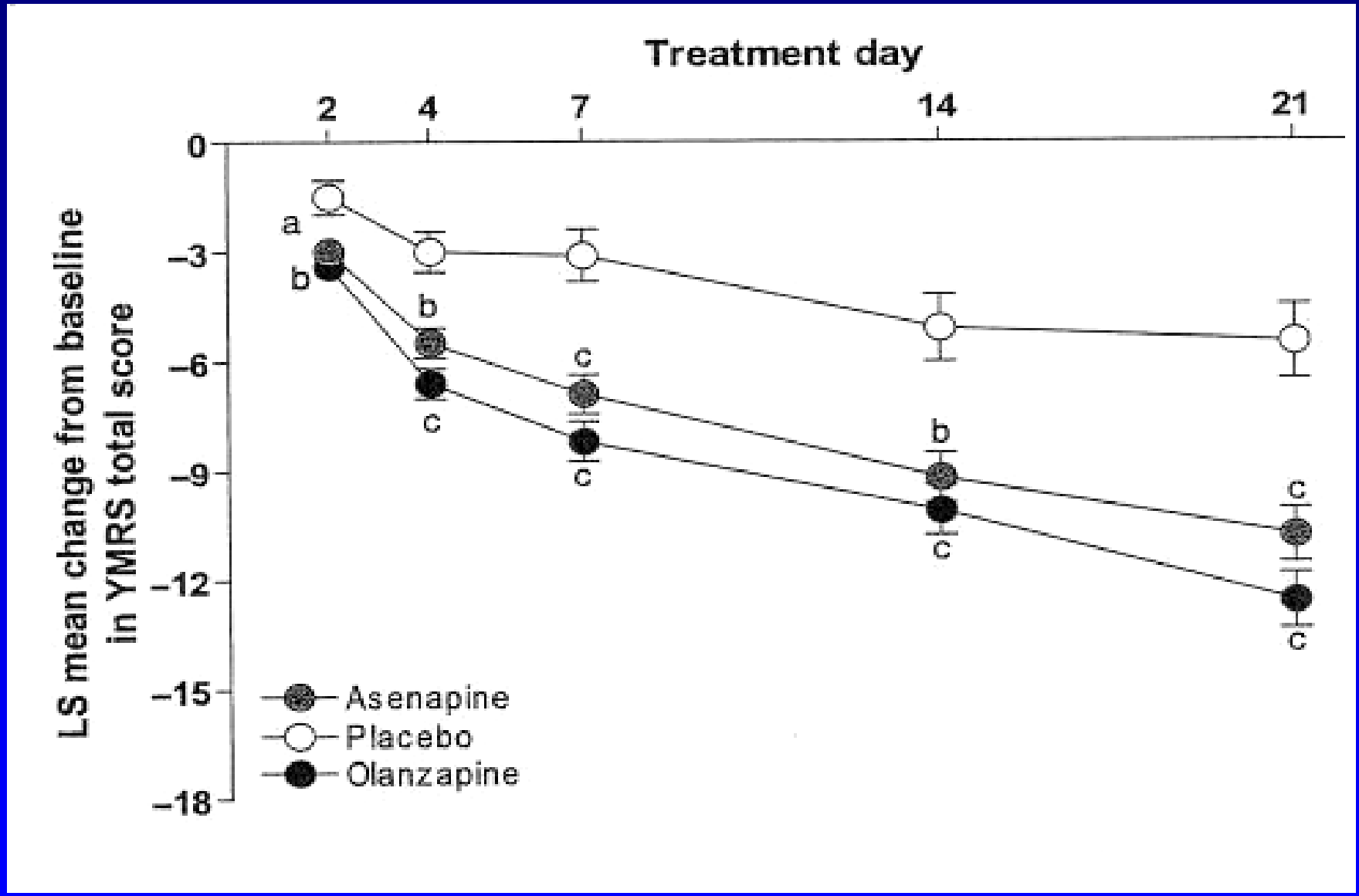


†ziprasidone = 26.19; placebo = 26.49; ‡p<0.05;

Potkin et al.,J Clin Psychopharmacol 2005;25:301-310

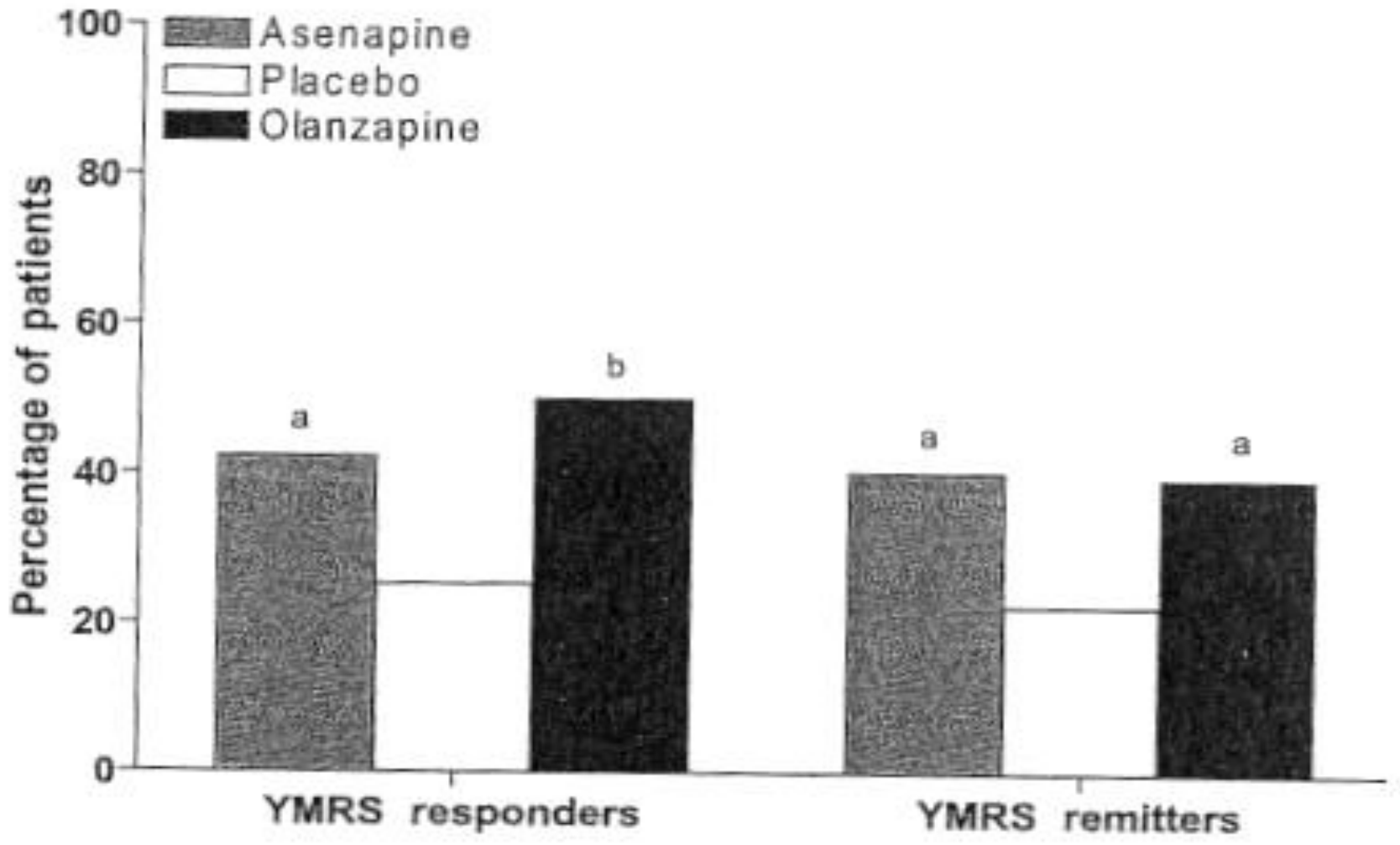
Asenapine

Asenapine for Acute Mania



McIntyre et al. Bipolar disorders. 2009; 11:673-686

Asenapine for Acute Mania



McIntyre et al. Bipolar disorders. 2009; 11:673-686

Texas Implementation of Medication Algorithms (TIMA)-Bipolar I Update Acute Mania: Monotherapy Stage IA

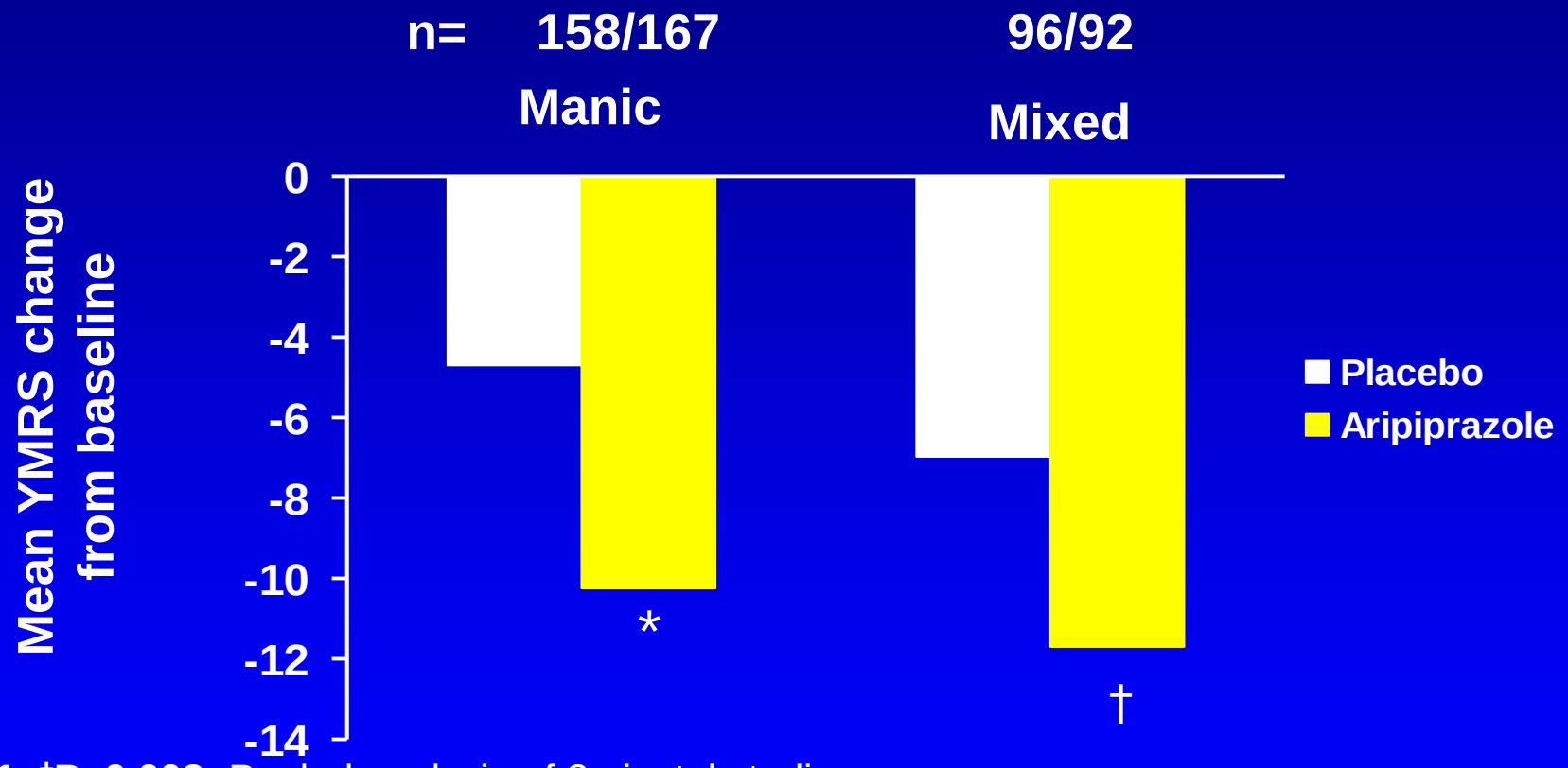
- **Euphoric: lithium, divalproex, aripiprazole, quetiapine, risperidone, ziprasidone**
- **Mixed: divalproex, aripiprazole, risperidone, ziprasidone (not lithium or quetiapine)**

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

Why Not Lithium or Quetiapine for Mixed Episodes?

- **Lithium-May be less effective for mixed**
- **Quetiapine: Mixed excluded from pivotal trials, so not FDA-approved**
- **Divalproex ER, but not divalproex: FDA-approved for mixed**

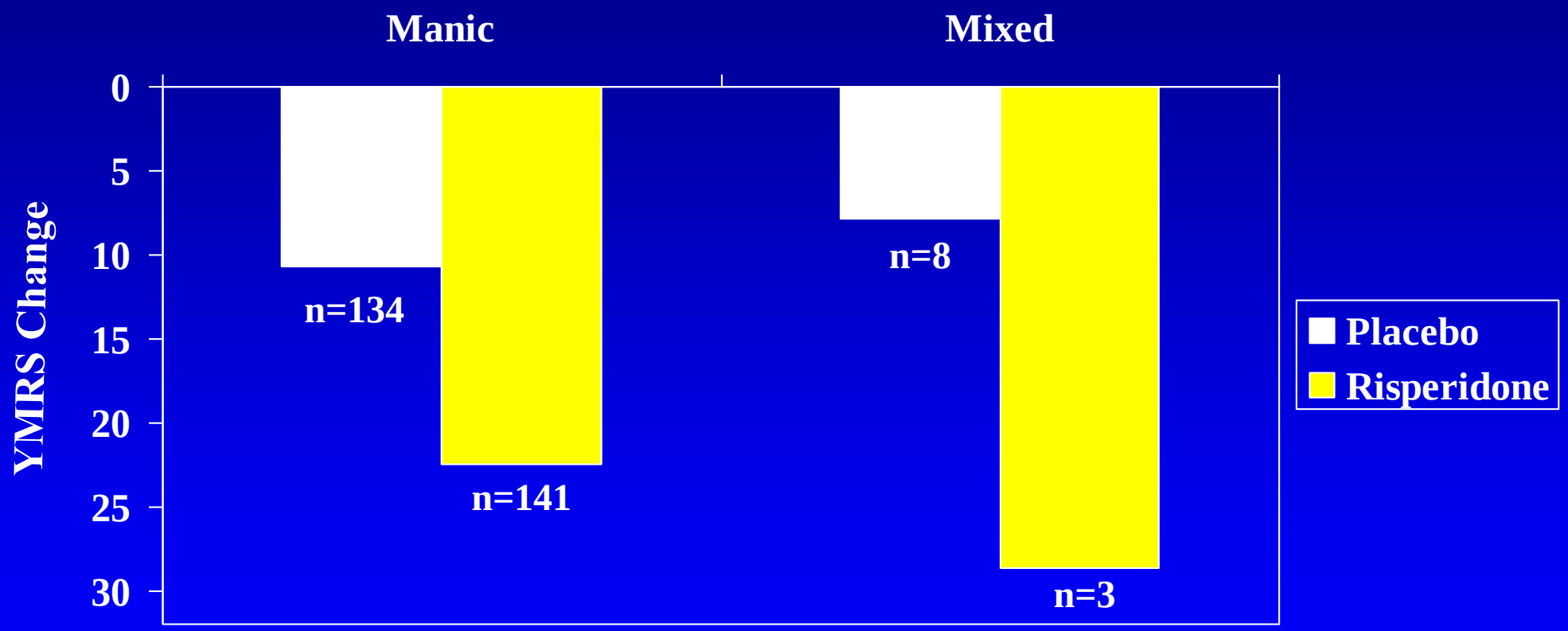
Aripiprazole in Acute Manic and Mixed Episodes



***P*≤0.001, †P=0.002**; Pooled analysis of 2 pivotal studies.

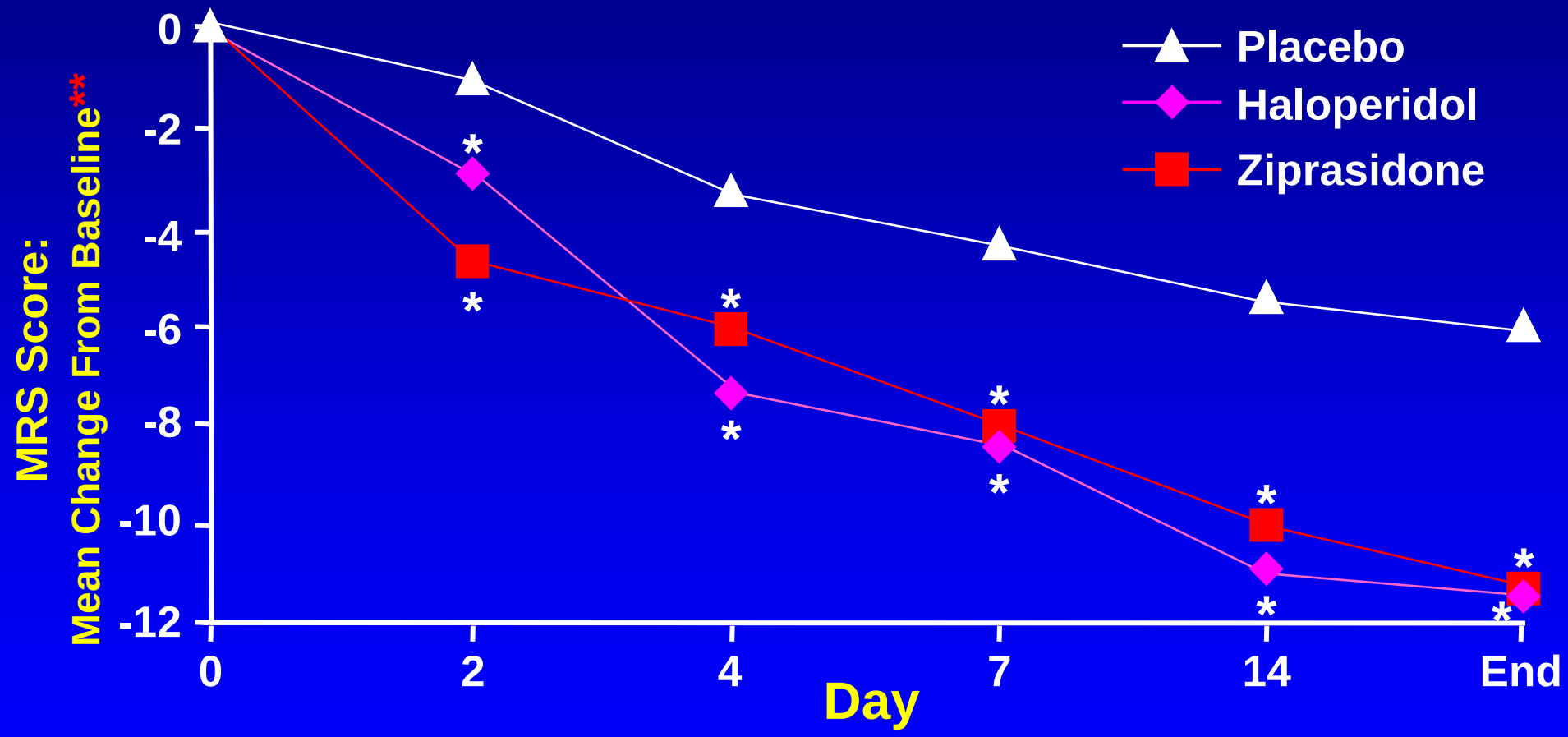
Keck et al. *Am J Psychiatry*. 2003;160:1651.
Sachs et al. J Pharmacology 2006;20:536-546
Data on file, Otsuka America Pharmaceutical, Inc.

Risperidone in Mania
Manic vs. Mixed Episodes



Khanna et al., Br J Psychiatry 2005;187:229-234

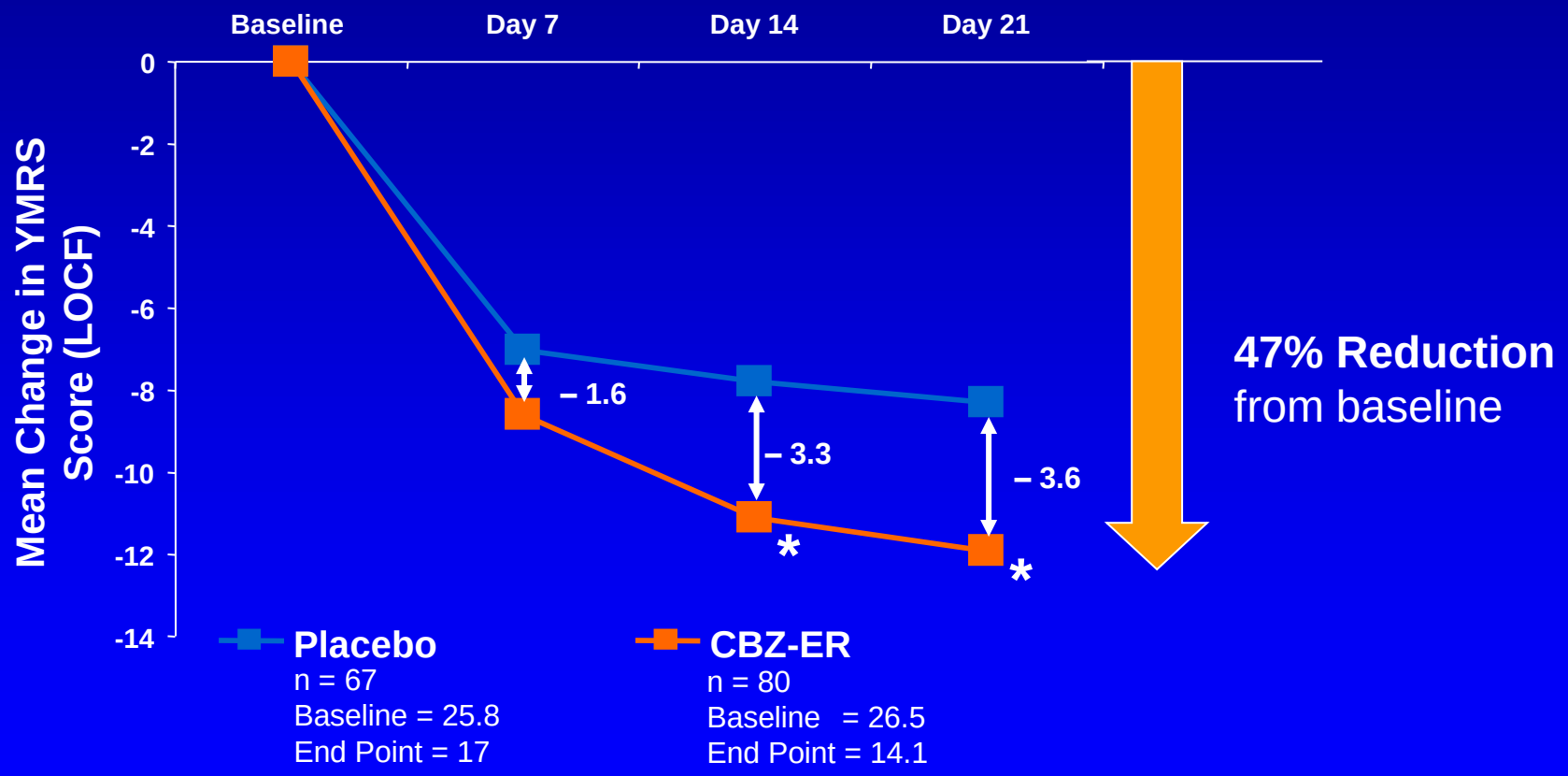
Ziprasidone in Dysphoric Mania: Mania Rating Scale Score



**The placebo line represents pooled placebo data; *P* values for haloperidol were calculated in comparison to placebo data only from 1 of 3 pooled studies; *p<0.001; Zajecka J et al. (2005), Presented at the 158th Annual Meeting of the APA. Atlanta, Georgia; May 2005

Carbamazepine ER Reduces Manic Symptoms of Mixed Episodes

Pooled Analysis of YMRS Change (Mixed Episodes)[1]



**P*<.01 compared to placebo following analysis of covariance with baseline score as covariate.

1. Weisler RH, et al. 17th Annual US Psychiatric & Mental Health Congress; November 18-21, 2004; San Diego, Calif. (Abstract 24).

Acute Mania: Monotherapy TIMA Stage IB

- Euphoric and mixed
  - Olanzapine, carbamazepine ER
- Both FDA-approved, why not Stage 1A?
  - Complexity of use and/or safety/tolerability

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

Consensus Development Conference (Weight Gain, Diabetes, Dyslipidemia)

- **Clozapine, olanzapine**
  --Increased risk
- **Quetiapine, risperidone**
  --Some risk
- **Aripiprazole, ziprasidone**
  --Little or no risk

- **Diabetes Care 2004;27:596-601; J Clin Psychiatry 2004;65:267-272; Obesity Research 2004;12:362-368**

Carbamazepine-Drug Interactions

An Incomplete Listing

- **CBZ decreases levels of:**
  - **Clonazepam, clozapine, olanzapine, haloperidol, alprazolam, bupropion, oral contraceptives**
- **CBZ levels increased by:**
  - **Cimetidine, macrolides, fluoxetine, valproate, isoniazid, verapamil, ketoconazole**

Acute Mania: 2-Drug Combos

TIMA Stage 2

- Lithium, valproate, atypical antipsychotics
- But **not** aripiprazole, clozapine, 2 atypical antipsychotics
- Why not aripiprazole?
  - No combination trials yet (subsequently completed)
- Why not start at Stage 2?
  - Many clinicians do

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

Acute Mania: TIMA

- **Stage 3: less established 2-drug combinations**
- **Stage 4: ECT, clozapine, 3+ drug combinations, etc.**

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

Clozapine for Bipolar Disorder

- The ace in the hole
- Open label reports of benefit for mania, maintenance, and possibly depression
- No double-blind studies

Alphs and Campbell. Psychiatric Annals 32:722-729, Dec. 2002

Tamoxifen for Acute Mania
3-week, double-blind, placebo-controlled, n=16

- Relatively selective protein kinase C inhibitor
- Dose: Start 20 mg/day, range 20 to 140 mg/day
- Tamoxifen > placebo on ↓ YMRS from day 5 on.
- Response: Tamoxifen 63%
  Placebo 13%

Zarate et al., Bipolar Disorders 2007;9:561-570

Tamoxifen for Acute Mania

3-week, double-blind, placebo-controlled, n=66

- Relatively selective protein kinase C inhibitor and selective estrogen receptor modulator
- Dose: Start 40 mg/day, max 80 mg/day
- Tamoxifen > placebo on ↓ YMRS, response (44% vs. 5%), remission (28% vs. 0%)*

Response ≥ 50% ↓YMRS; Remission YMRS ≤12

*No patient achieved response or remission prior to day 21

Yildiz et al. Arch Gen Psychiatry 2008;65:255-263

Post-Lecture Exam Question 1

1. All of the following are FDA-approved for treating acute mania except:
   a. Carbamazepine
   b. Chlorpromazine
   c. Clonazepam
   d. Divalproex
   e. Aripiprazole

Question 2

2. A patient with a history of hypomanic episodes and major depressive episodes would receive which DSM-IV diagnosis?
   a. Cyclothymic disorder
   b. Bipolar NOS
   c. Bipolar I
   d. Bipolar II
   e. Bipolar III

Question 3

3. Which of the following drugs has a recommended starting dose for acute mania of 25 mg/kg/day?
   a. Divalproex ER
   b. Carbamazepine ER
   c. Risperidone
   d. Divalproex
   e. Quetiapine

Question 4

4. **Why is olanzapine not listed in Stage IA of the TIMA algorithm for acute mania monotherapy?**
   a. **Issues about efficacy**
   b. **Safety and tolerability**
   c. **Cost**
   d. **Complexity of use**

Answers to Pre & Post Lecture Exams

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