

Bipolar Disorders: Therapeutic Options

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Part 1: Overview and Treatment of Acute Mania

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 10 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. Clorpromazine
 - 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

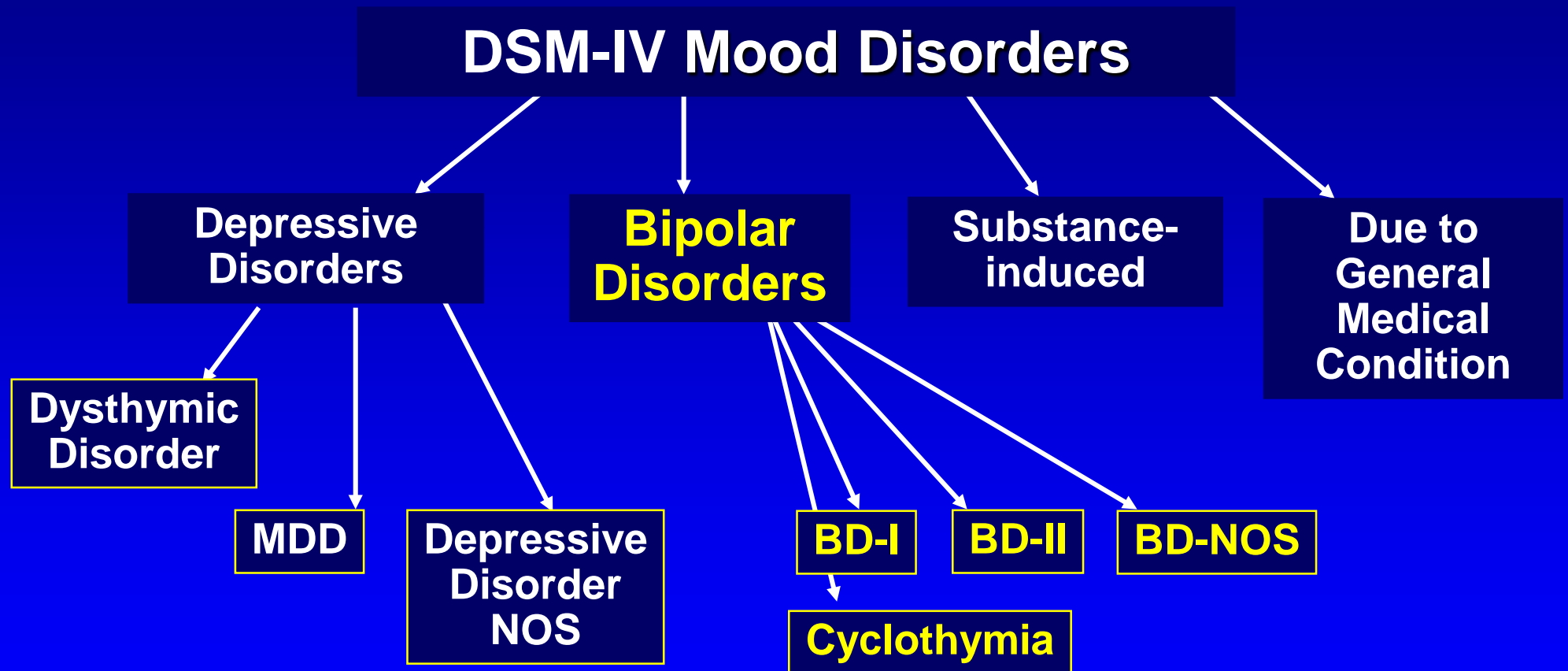
Question 3

- 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

Mood Disorders: DSM-IV Classification



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%

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)**

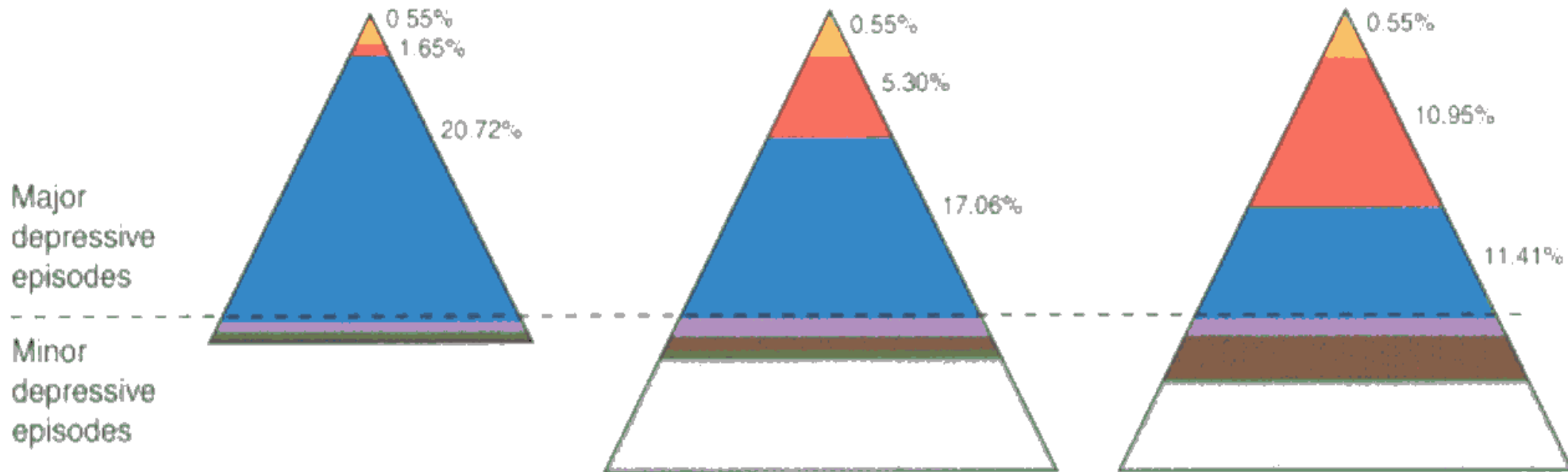
*Habitual long-term functioning of the individual;

Akiskal HS (1996), J Clin Psychopharmacol 16(2 suppl 1):4S-14S

DSM-IV

Zurich strict criteria

Zurich broad criteria



Total prevalence **25.7%**

49.5%

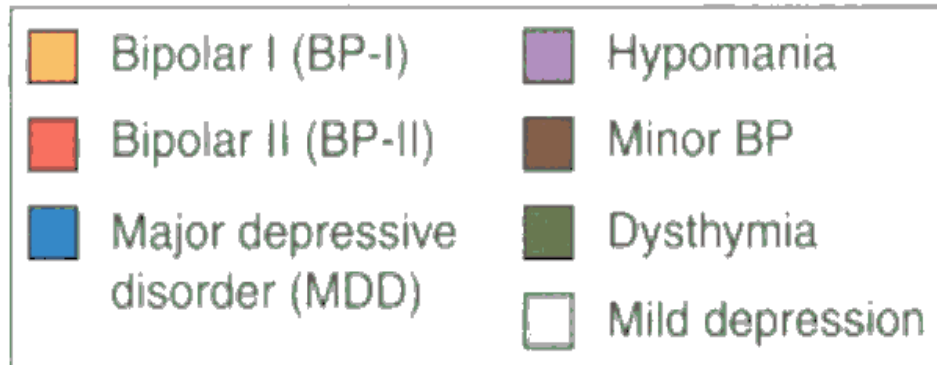
49.5%

Ratio of MDD vs BP-I or BP-II **9.4**

2.9

1.0

Bipolar Spectrum



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

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 Psychiatry 2005;66:870-886 (July)

“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 soothes 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”

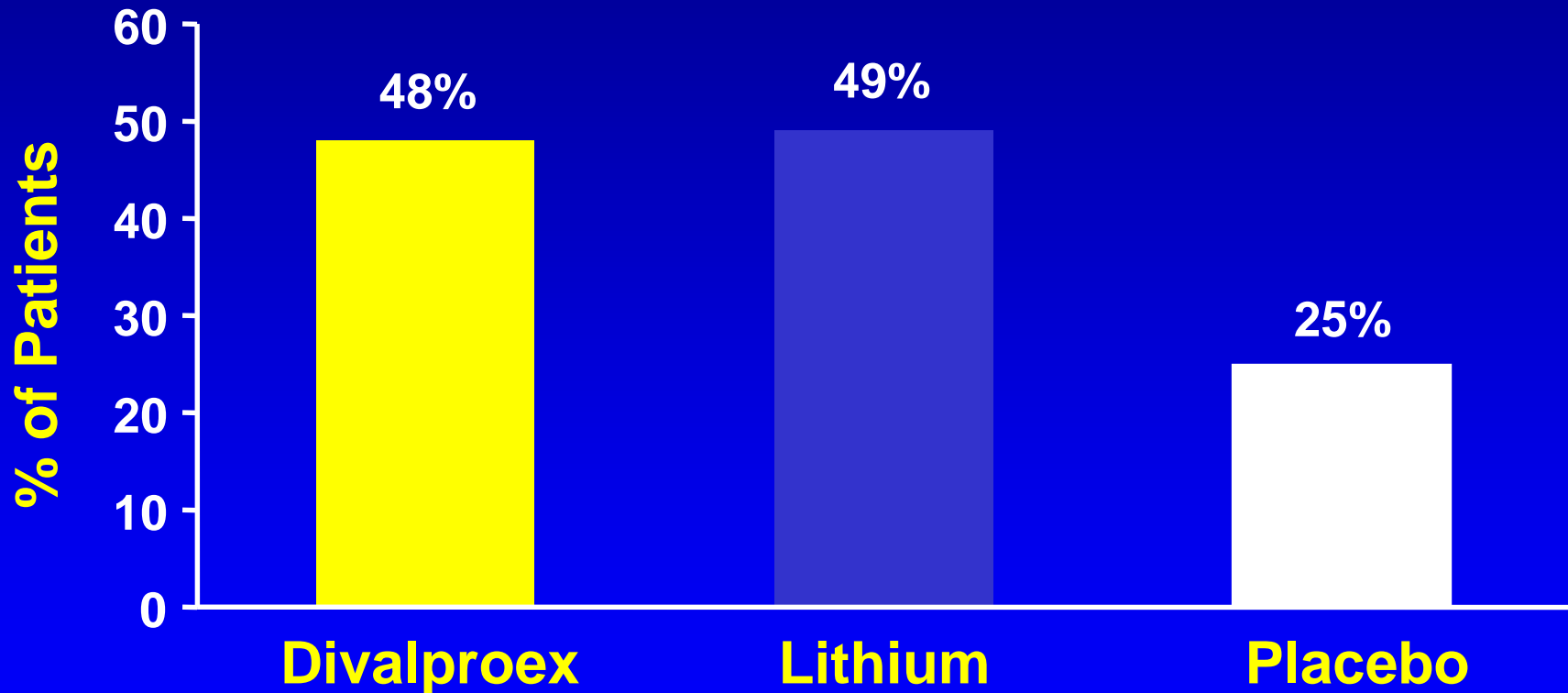
Sir Richard Blackmore, 1725

Acute Mania: FDA-Approved

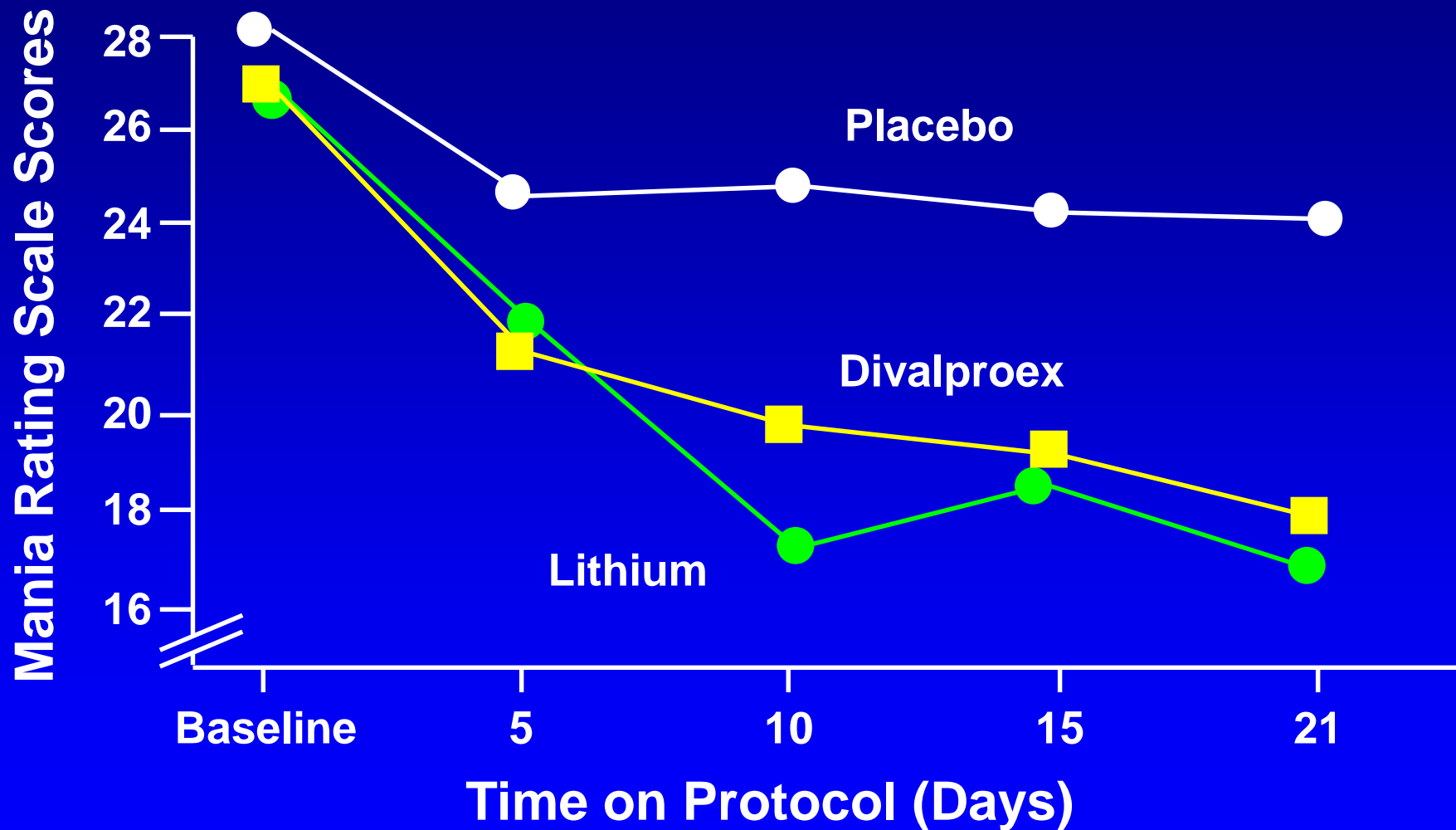
- **1970** **Lithium**
- **1973** **Chlorpromazine**
- **1995** **Divalproex**
- **2000** **Olanzapine**
- **2003** **Risperidone**
- **2004** **Quetiapine**
- **2004** **Ziprasidone**
- **2004** **Aripiprazole**
- **2004** **Carbamazepine ER**
- **2005** **Divalproex ER**

Acute Mania: Divalproex vs Lithium

($\geq 50\%$ ↓ in Mania Subscale)



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**

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**

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

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

All Antipsychotic Drugs Are Antimanic

Name one that isn't!

Divalproex vs. Olanzapine for Acute Mania

	<u>Tohen et al., 2002</u>	<u>Zajecka et al., 2002</u>
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

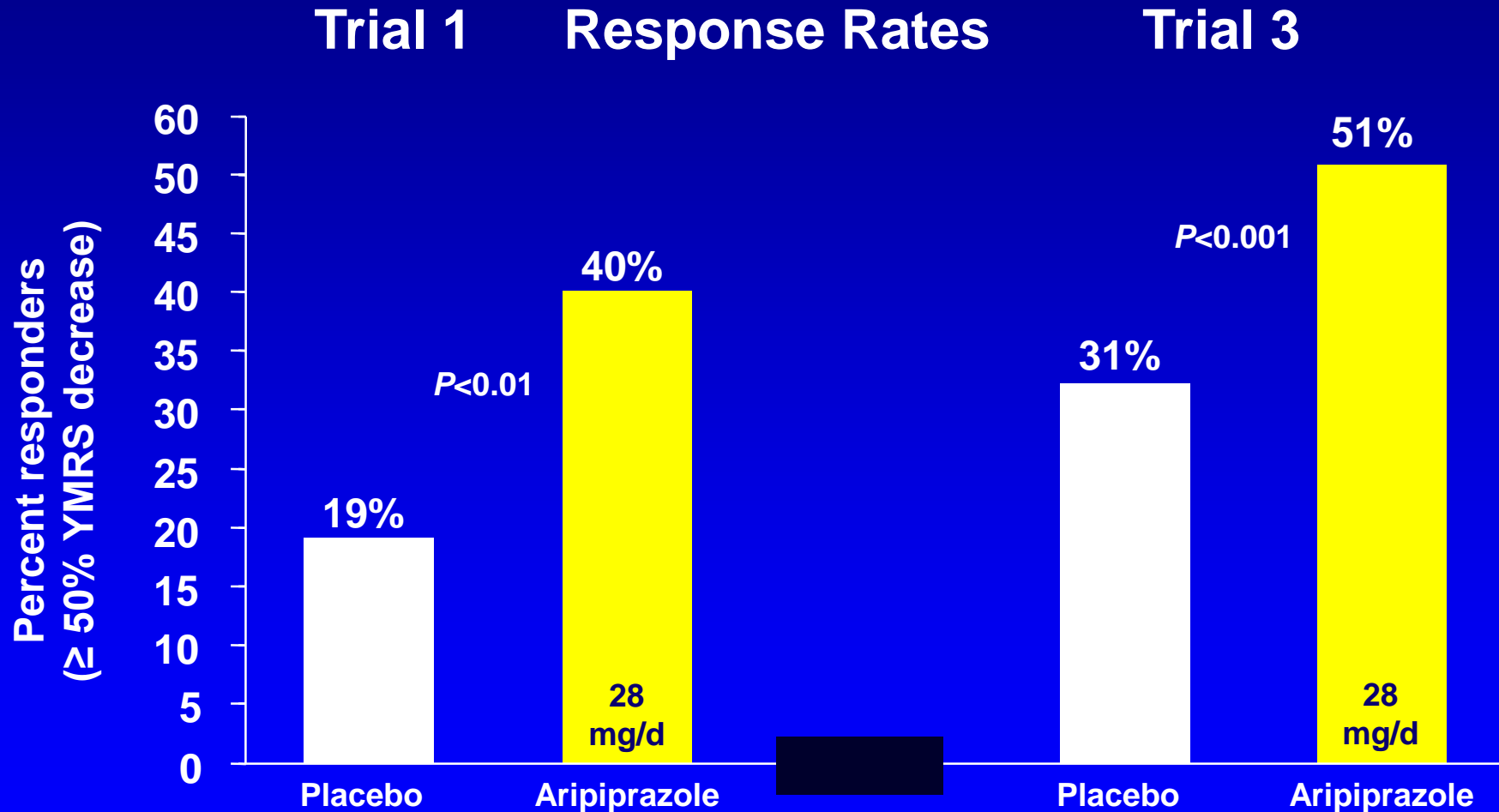
Olanzapine for Acute Mania

(pooled analysis – 2 studies)

	OLZ	PBO
• Response ($\geq 50\%$ \downarrow YMRS)	55%	29.5%
• Euthymia (YMRS ≤ 12)	50%	27%
• Remission (YMRS ≤ 7, etc.)	18%	7%

Aripiprazole in Acute Mania

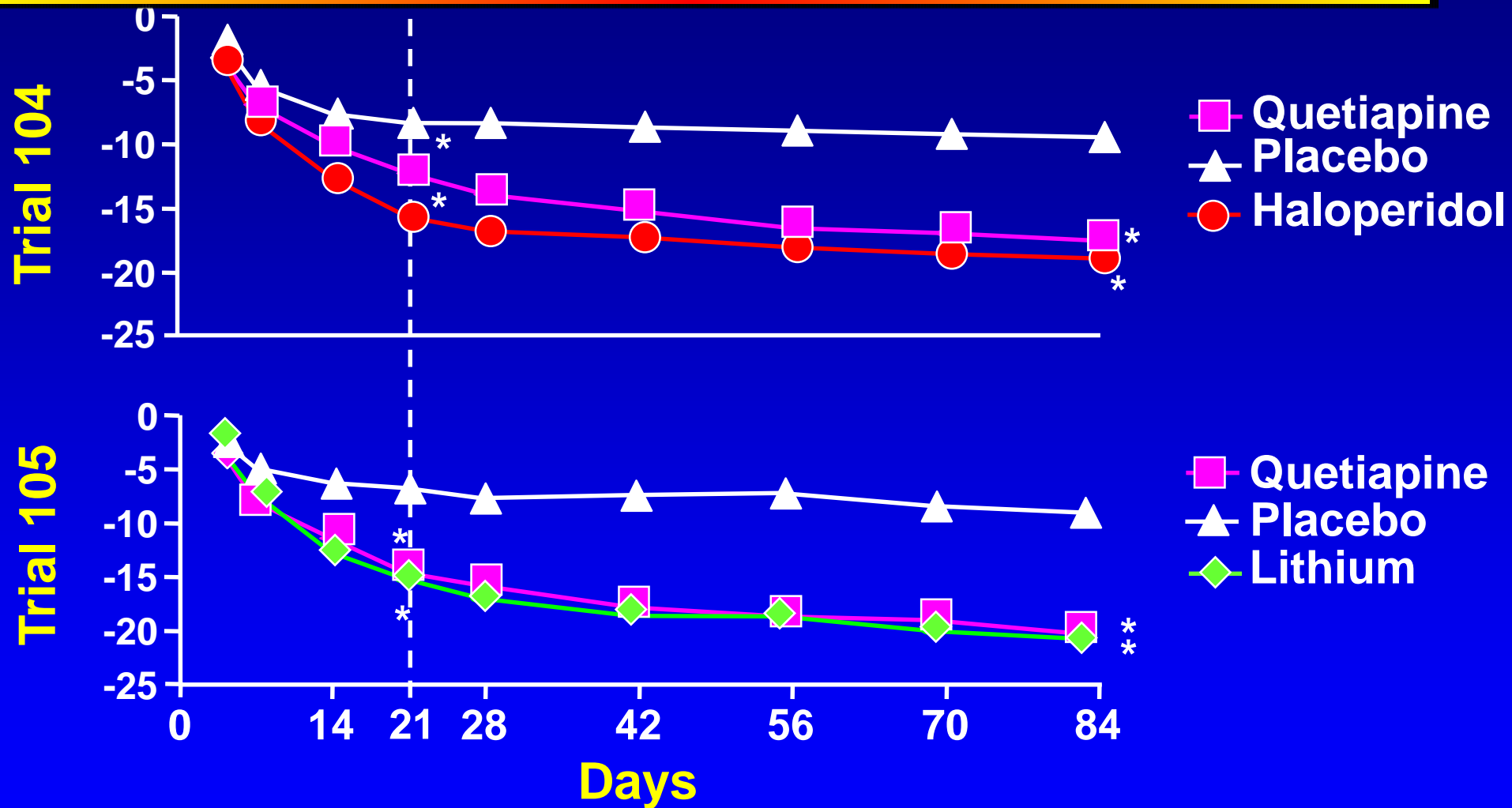
(3-week, double-blind, start 30 mg)



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

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

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)

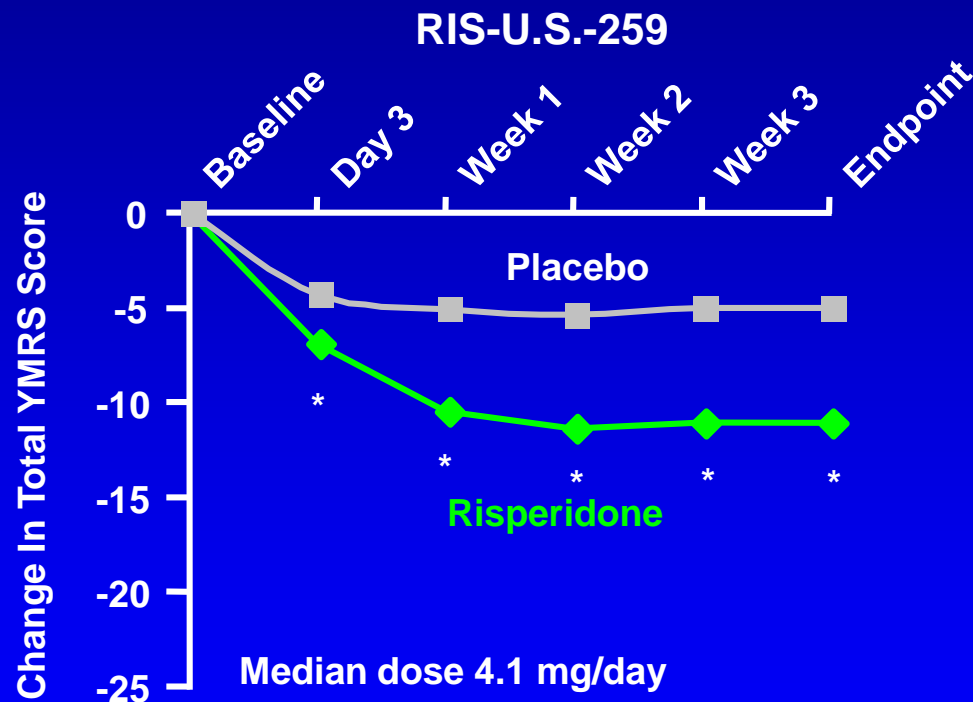
- **QTP: 400-600 mg/day (mean 412 mg)**
DVPX: mean serum level 101 mcg/ml
- **YMRS change (primary outcome)**

QTP	23	(n.s.)
DVPX	19	
- **Response (CGI-I-mania 1 or 2)**

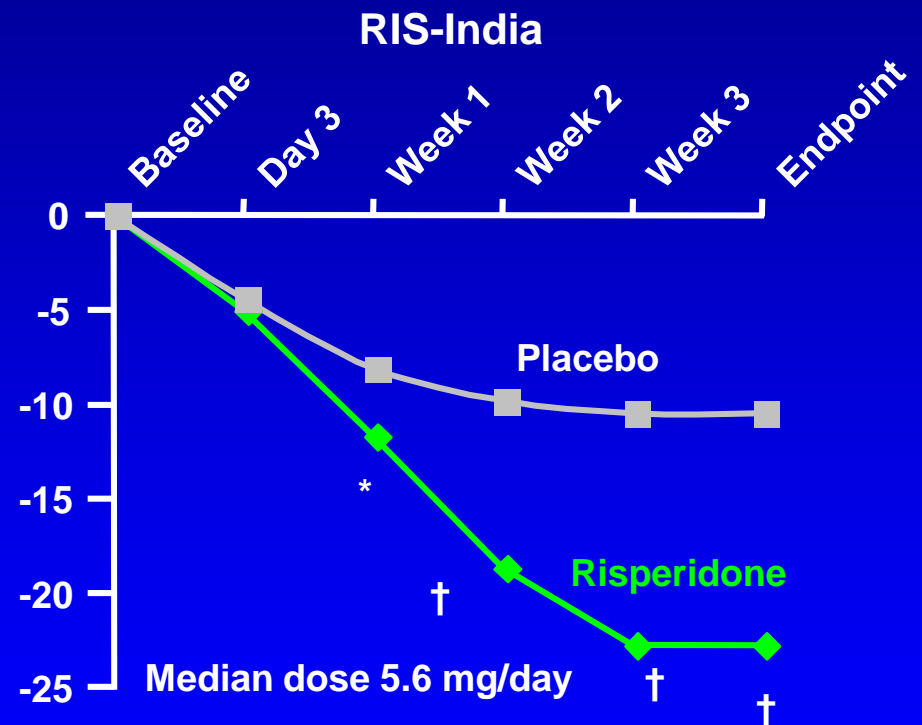
QTP	72%	(p=0.02)
DVPX	40%	
- **Remission: QTP 60%, DVPX 28% (p=0.02)**

Risperidone in Acute Bipolar Mania

Change From Baseline in Total YMRS (Primary Efficacy Variable)



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

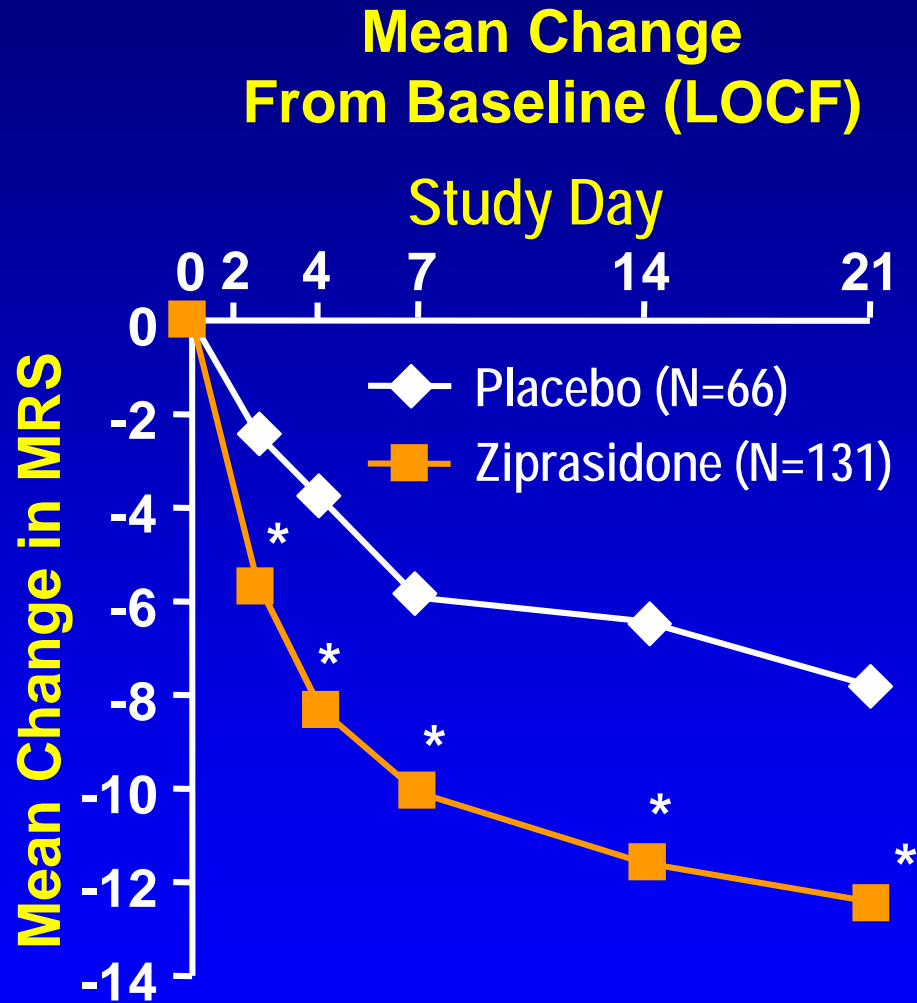


LOCF analysis. * $P < .01$; † $P < .001$ risperidone vs placebo.

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

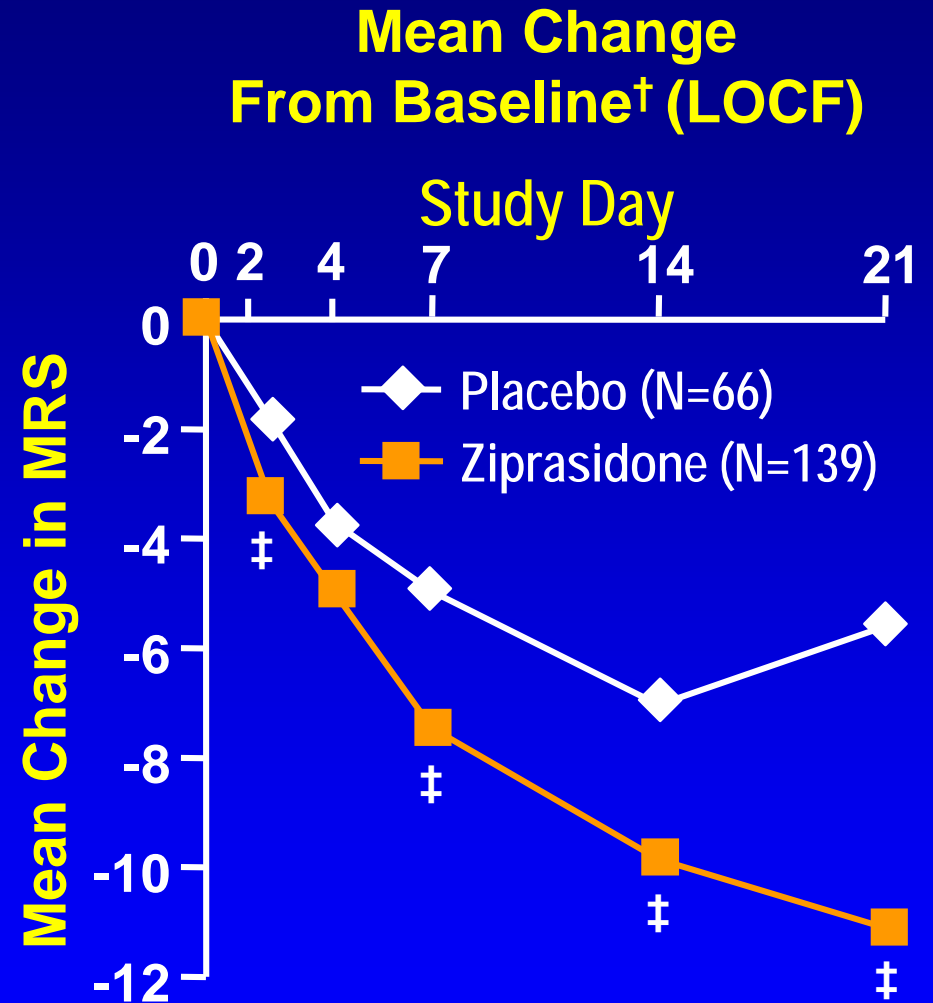
Khanna S et al. *Br J Psychiatry* 2005;187:229-234 (Sept)
(included mixed)

Ziprasidone: Efficacy in Acute Mania



*p<0.01;

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



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

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

Acute Mania: Monotherapy

TIMA Stage IA

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

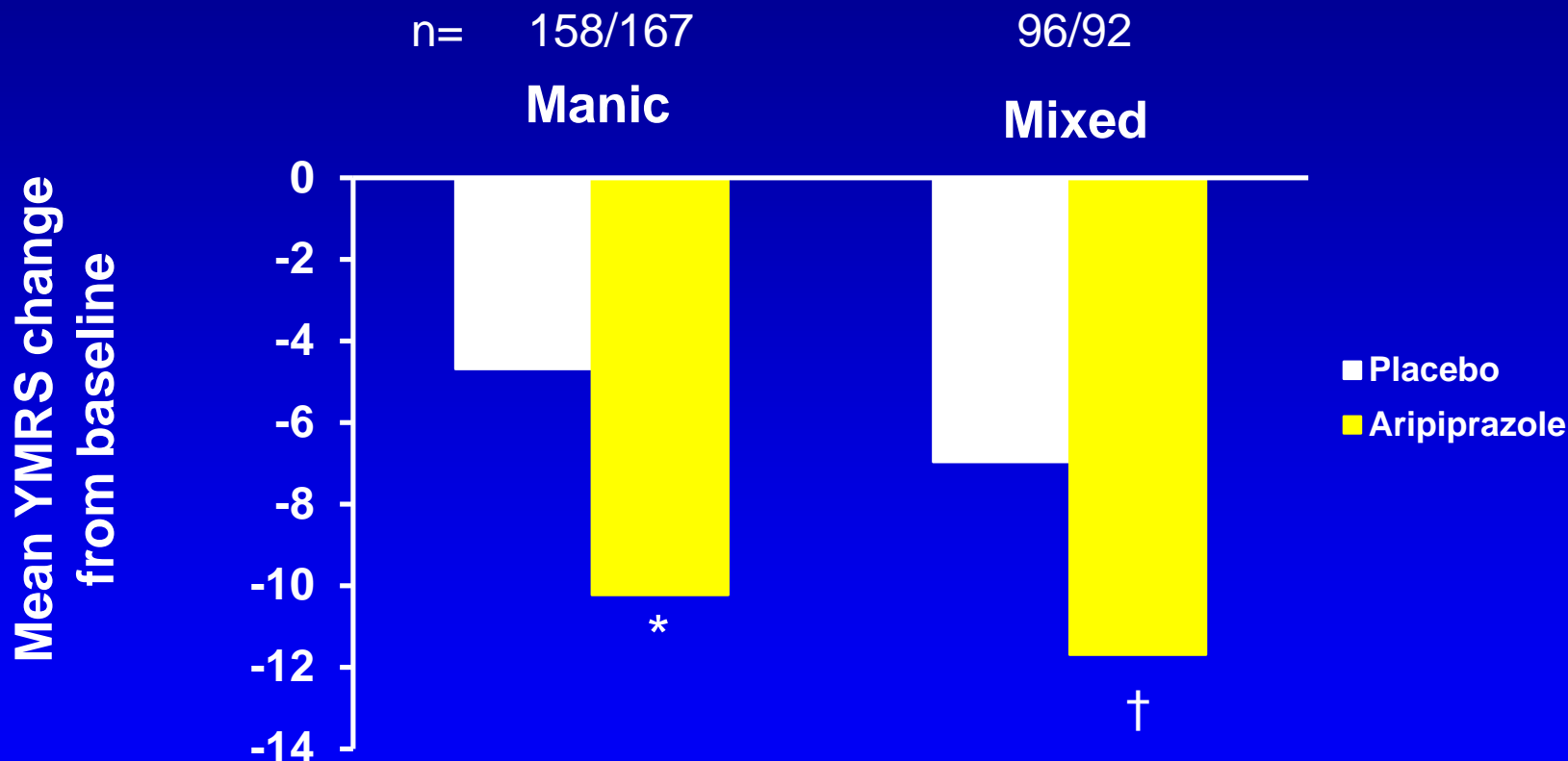
TIMA: Texas Implementation of Medication Algorithms

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 Mania

Manic and Mixed Episodes



* $P \leq 0.001$, † $P = 0.002$; Pooled analysis of 2 pivotal studies.

Keck et al. *Am J Psychiatry*. 2003;160:1651.

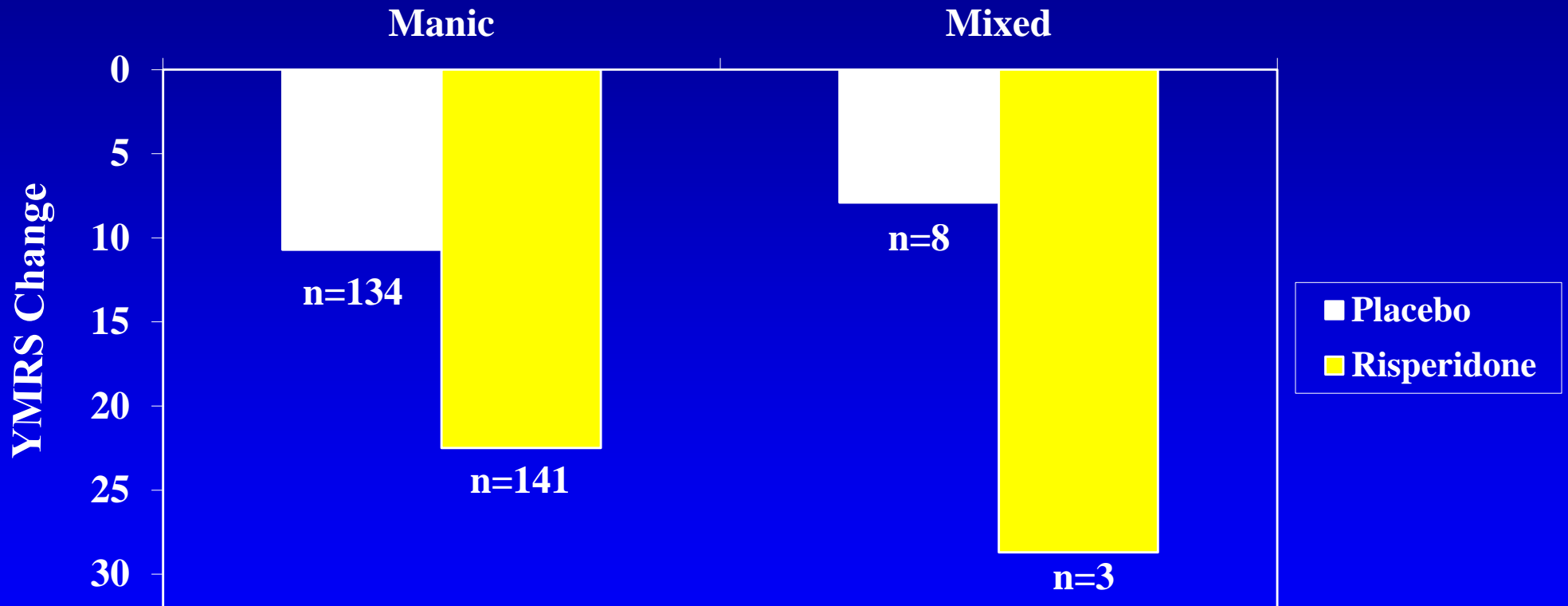
Sachs et al. IPS, 2003.

Data on file, Otsuka America Pharmaceutical, Inc.

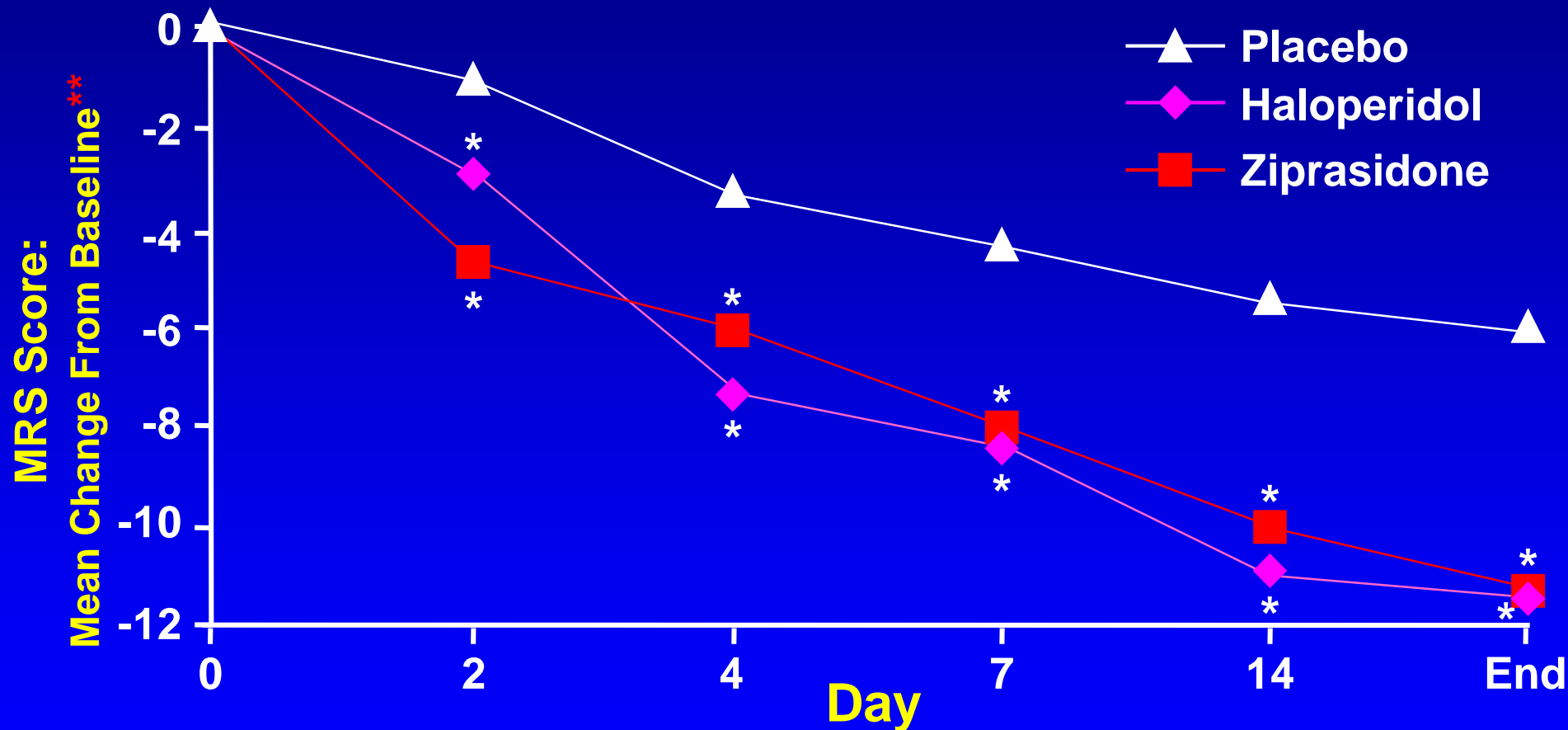
CONTAINS OFF-LABEL INFORMATION

Risperidone in Mania

Manic vs. Mixed Episodes



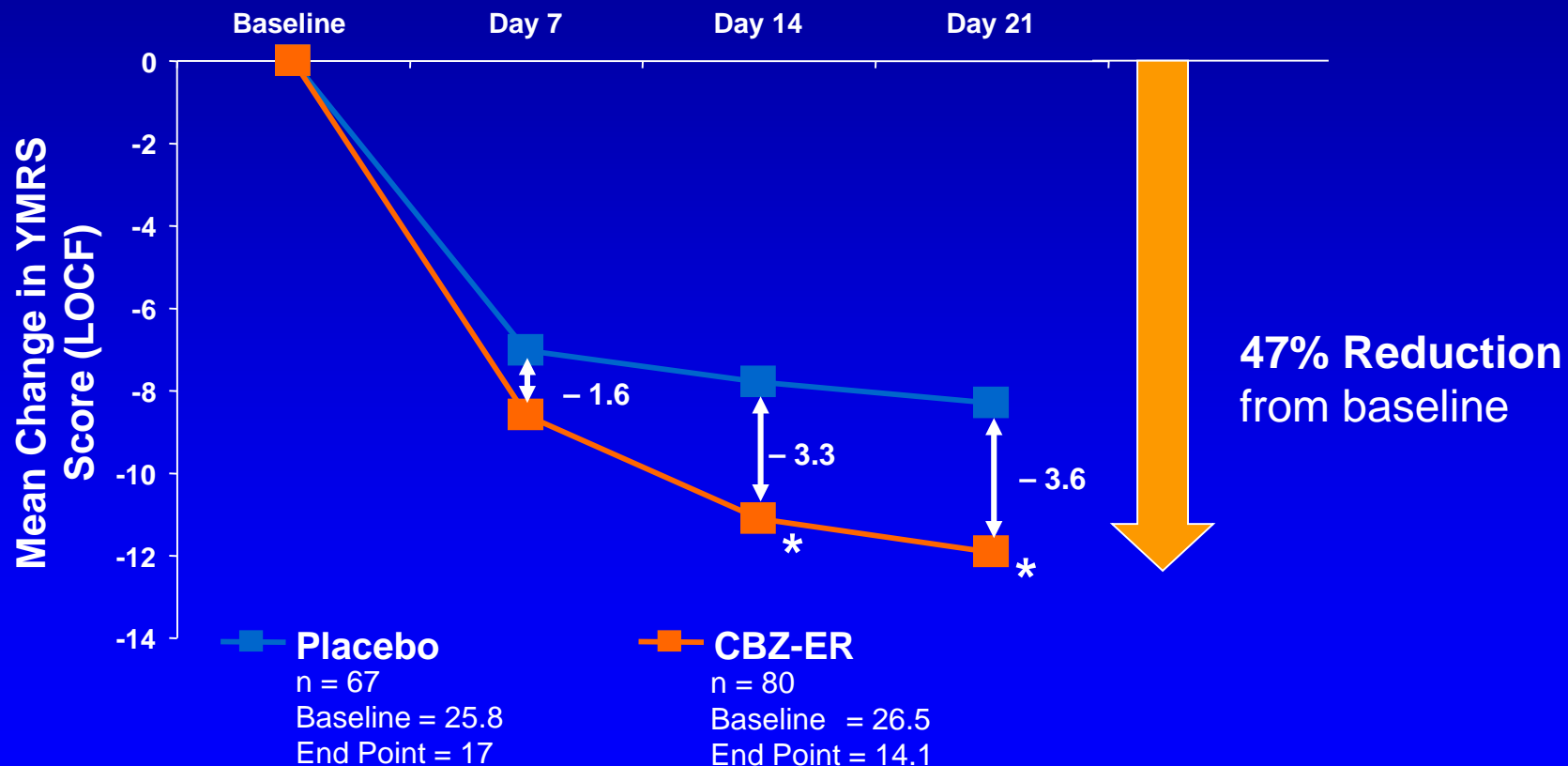
Ziprasidone in Dysphoric Mania: Mania Rating Scale Score



**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**

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**
- **Why not start at Stage 2?**
 - **Many clinicians do**

Acute Mania: TIMA

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

Clozapine for Bipolar Disorder

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

Post-Lecture Exam

Question 1

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 - 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?**
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 - 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