

Bipolar Disorders: Therapeutic Options

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Revised October 2011¹

Part 1: Overview and Treatment of Acute Mania

Revised October 2011

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**

Pre-Lecture Exam

Question 1

1. All of the following are FDA-approved for treating acute mania except:
 - a. Carbamazepine
 - b. Chlorpromazine
 - c. Clozapine
 - 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

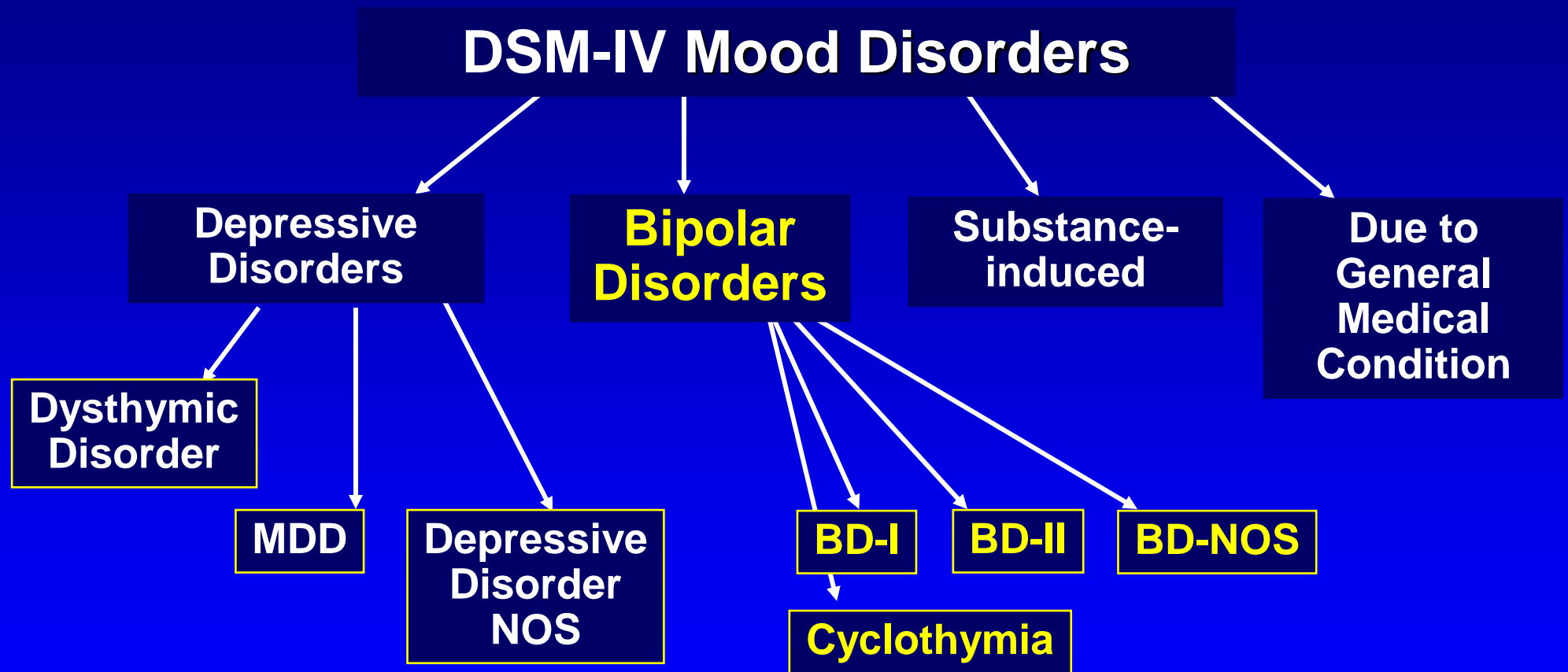
Question 3

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. The first antipsychotic FDA-approved for the treatment of acute mania was which of the following?**
- a. Olanzapine**
 - b. Chlorpromazine**
 - c. Haloperidol**
 - d. Aripiprazole**
 - e. Risperdone**

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)**

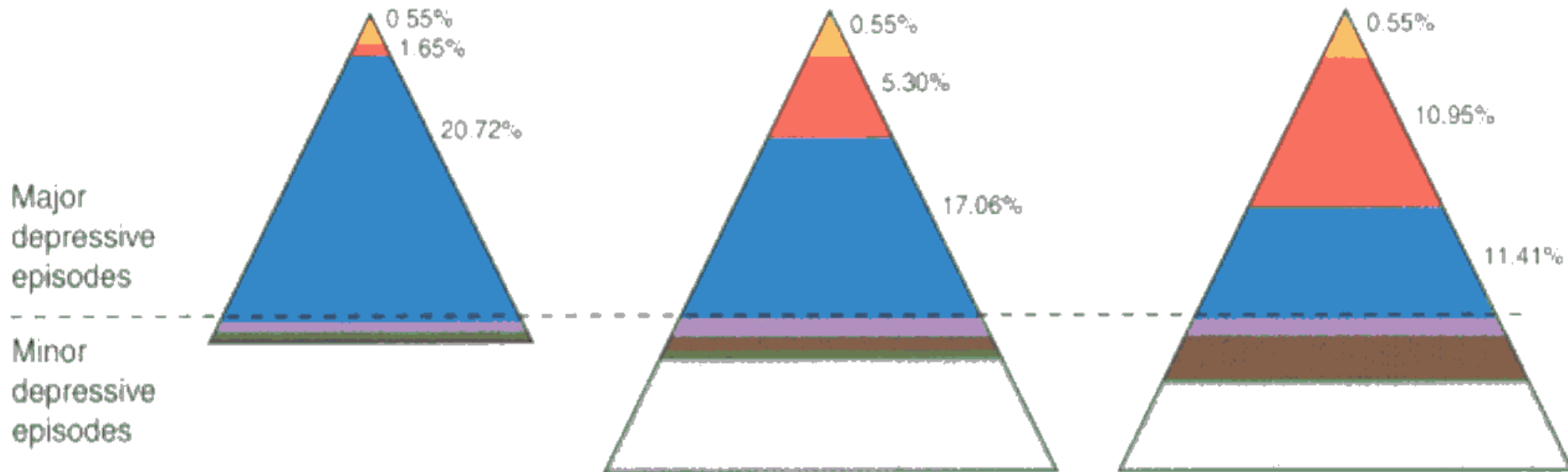
***Habitual long-term functioning of the individual;**

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

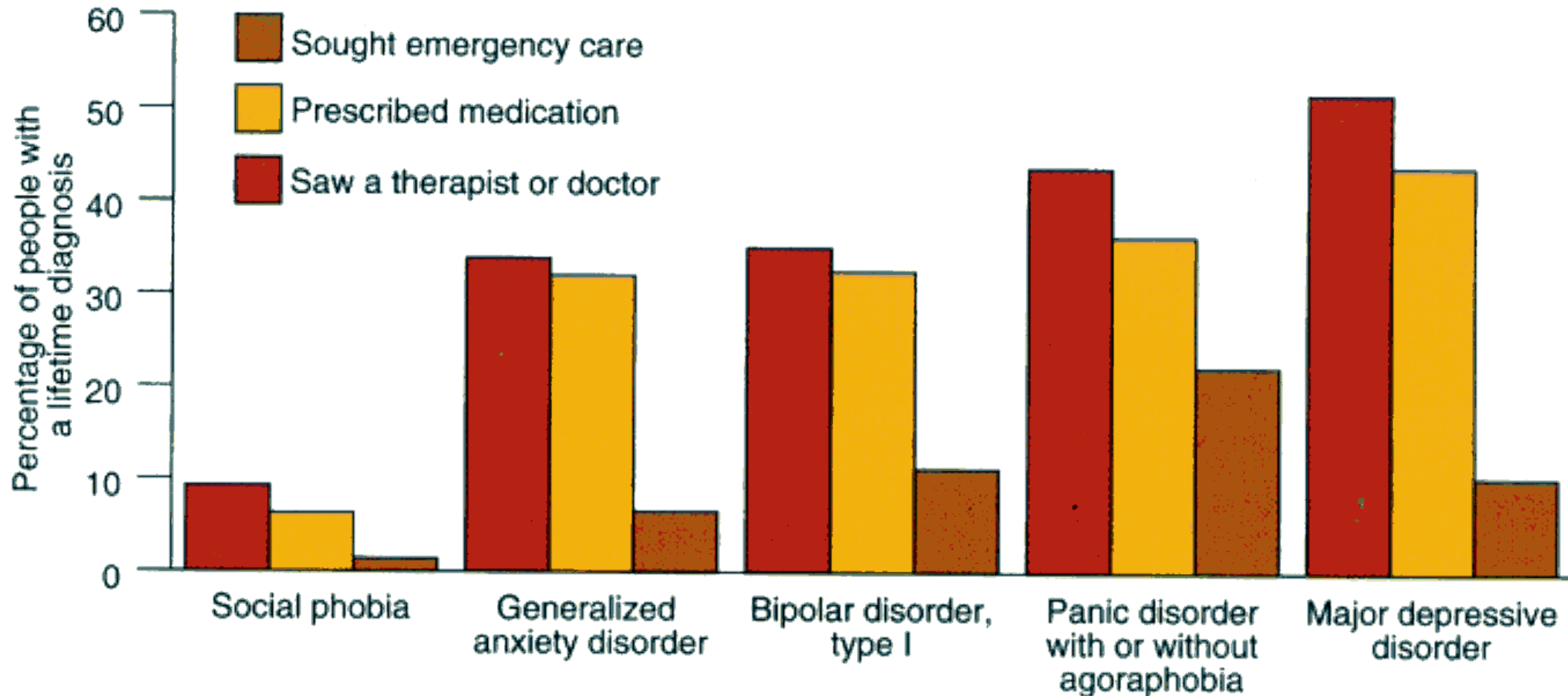
2 or more DSM-IV criteria

No minimum duration

No consequences

“Widespread acceptance of increasingly broad definitions risk weakening or trivializing the core concept of bipolar.”

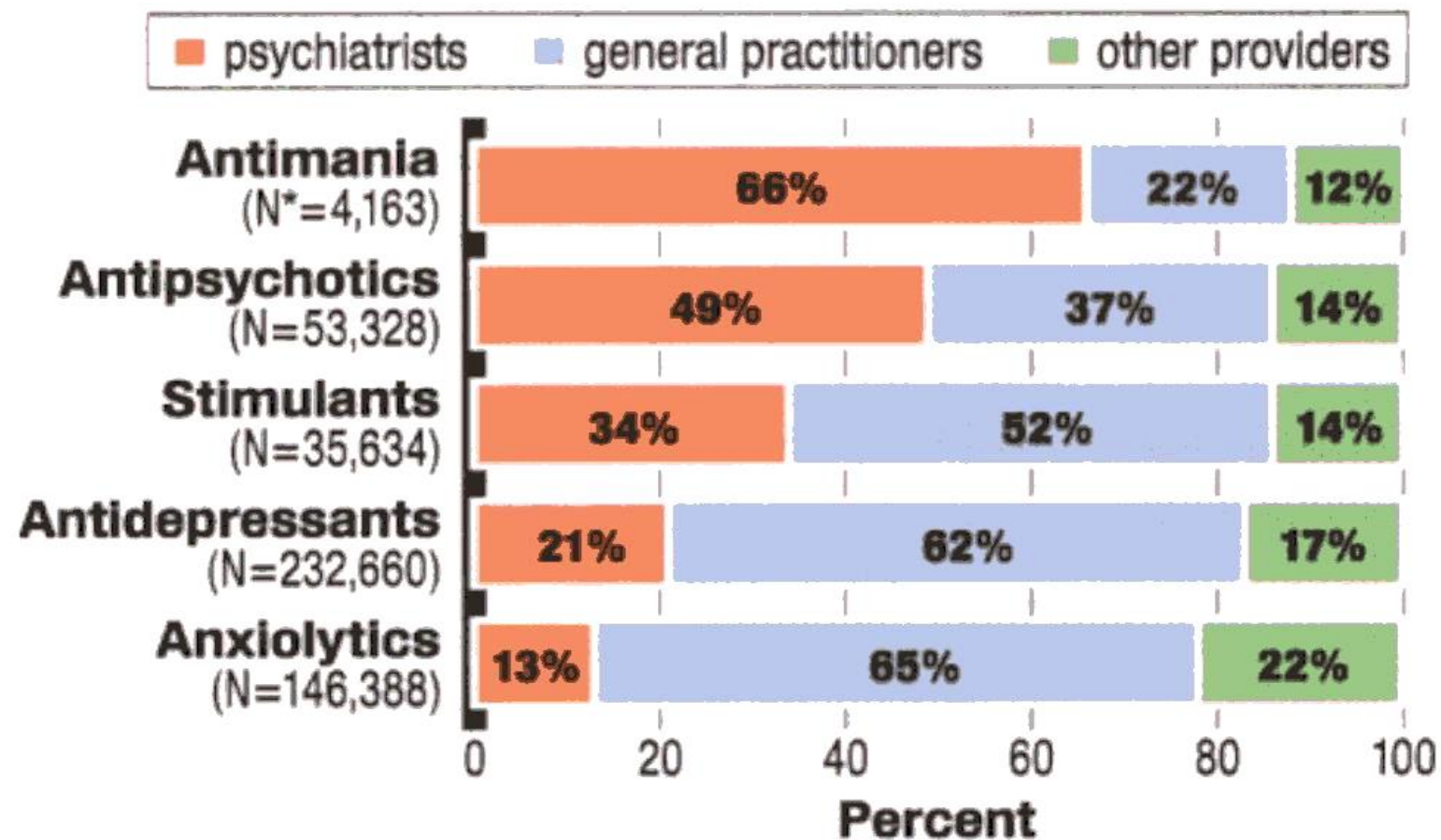
Treatment Seeking: NESARC* Study



*NESARC: National Epidemiologic Survey on Alcohol and Related Conditions

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**
- **Increased cost**

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
- **Br Assoc Psychopharmacol** 2003, 2009
- **Expert Consensus Guidelines** 2004
- **WFSBP Guidelines** 2004, 2009, 2010
- **CANMAT Guidelines** 2005, 2006, 2009
- **TIMA Algorithms** 2005

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

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

**Guidelines must stay up-to-date
(but often do not)**

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
- 2009 Asenapine

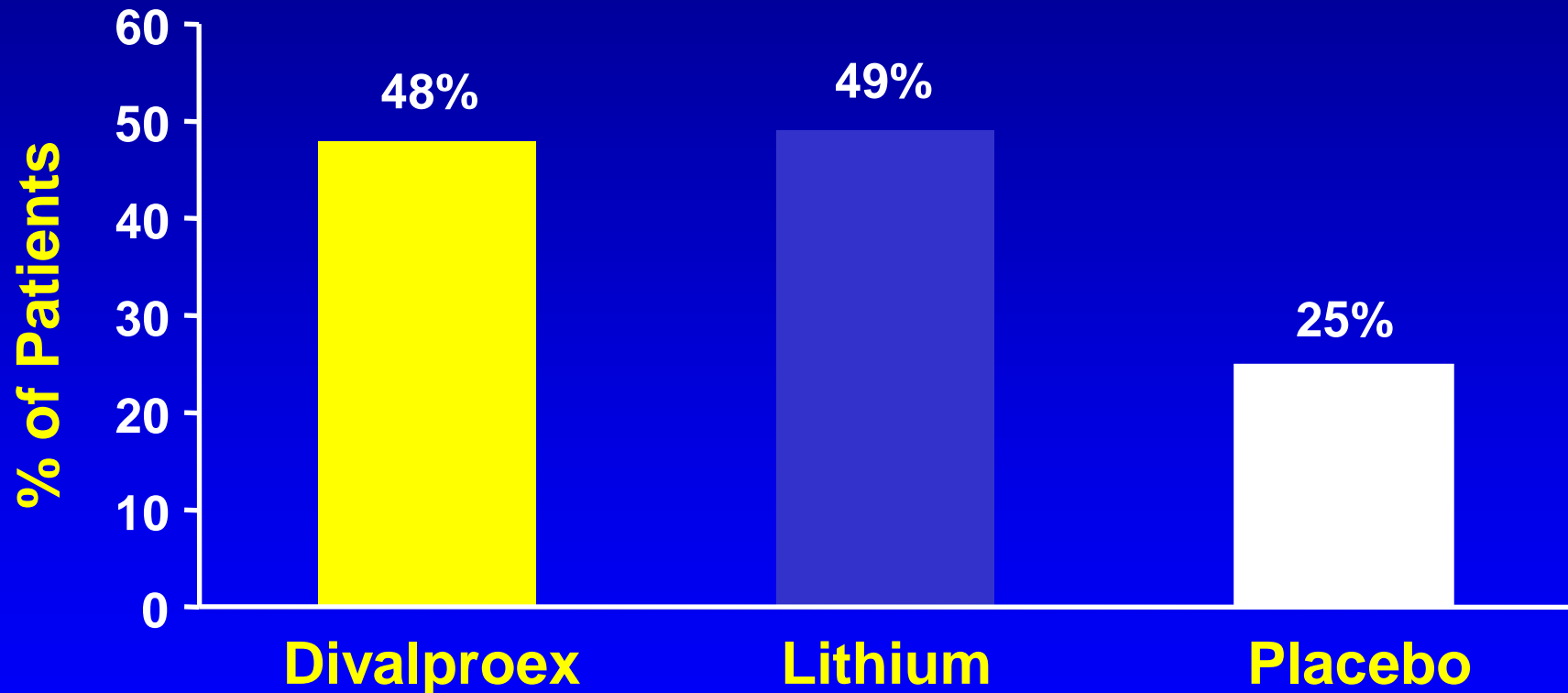
*Also pediatric (10-17) mania (RIS 2007, ARI 2008, QTP 2009)

**Also adolescent (13-17) mania (OLZ 2009)

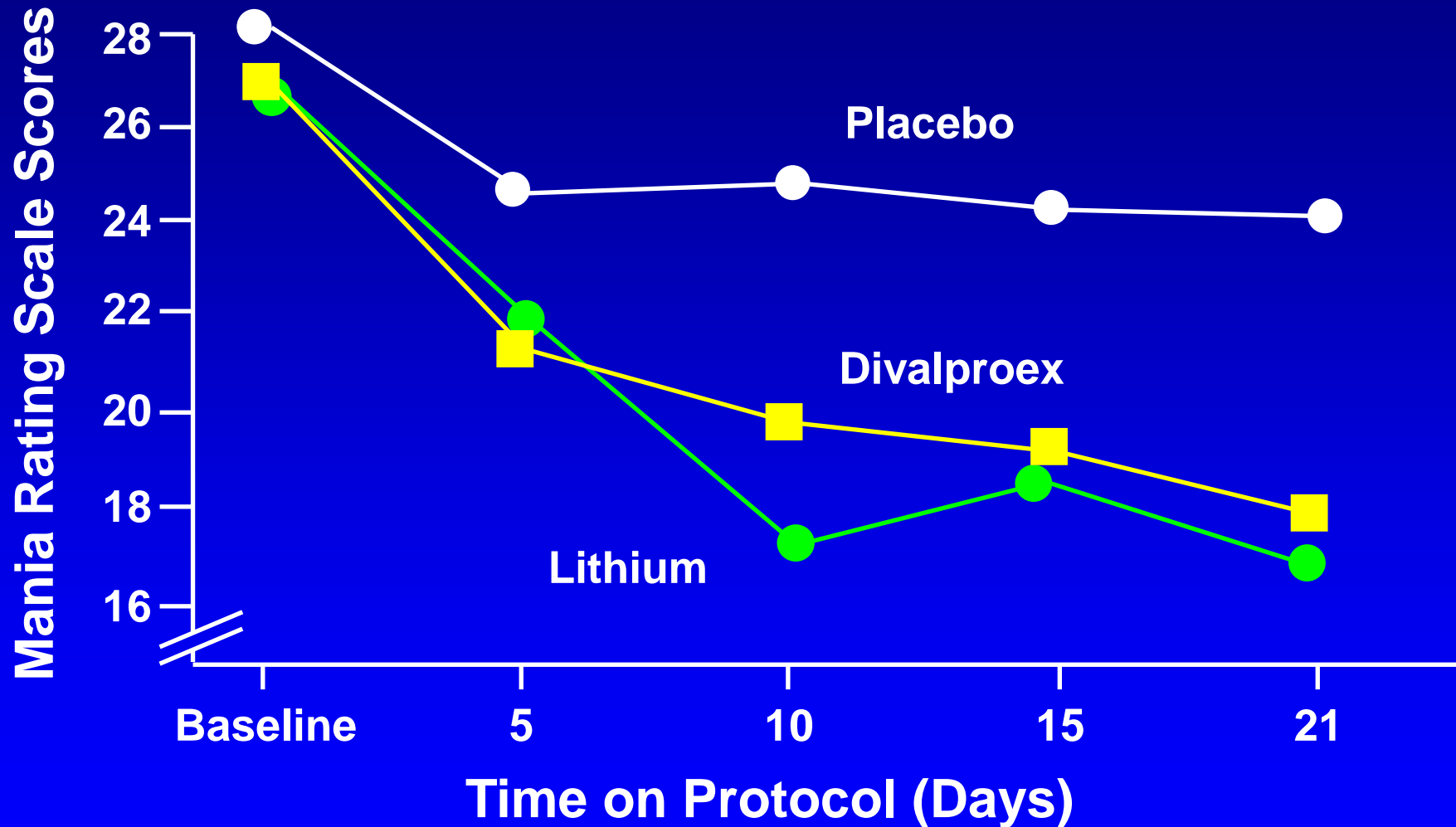
***Also pediatric (12-17)

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 Acute Mania (Manic and Mixed Episodes)

3-week, placebo-controlled, n=364

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

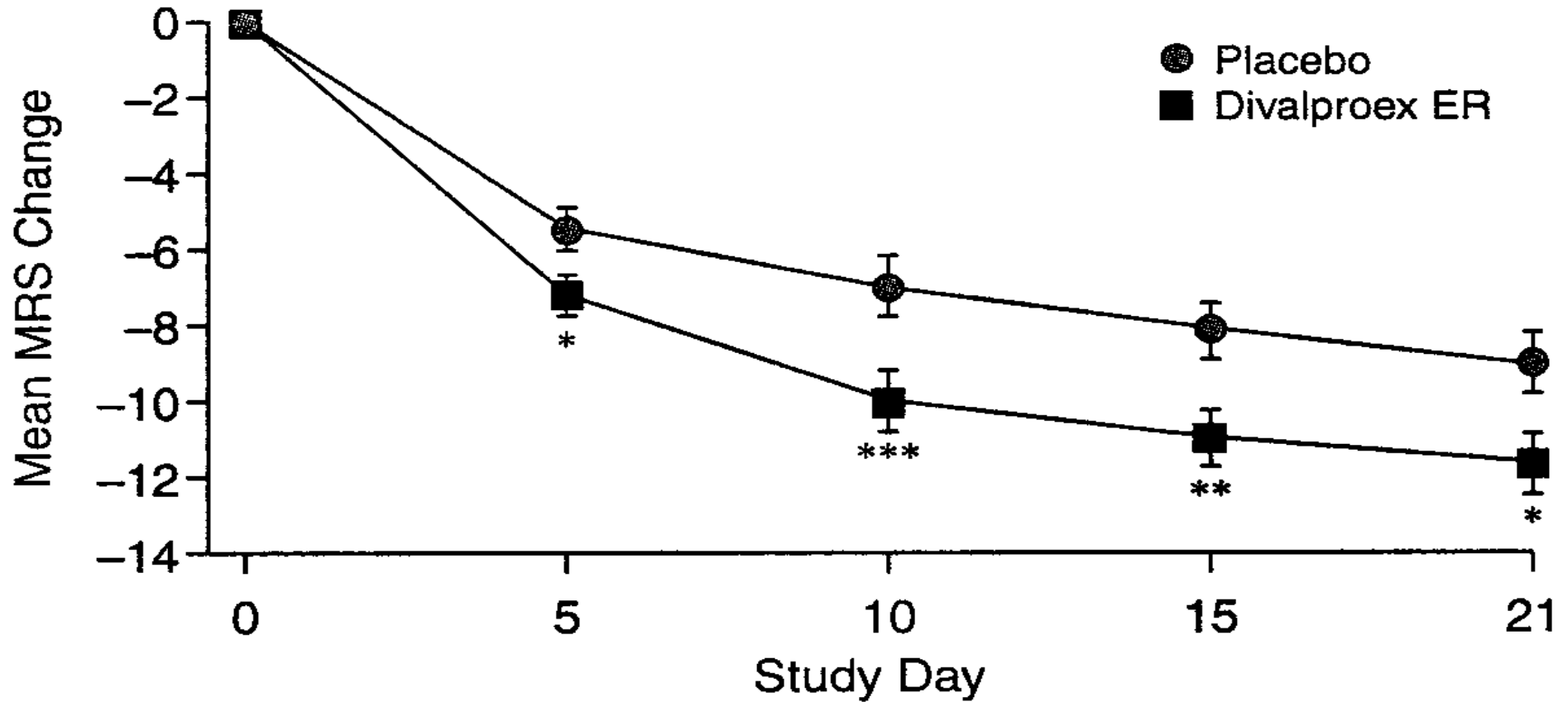
- **Response ($\geq 50\%$ MRS improvement)**

ER	48%	(P=0.012)
Placebo	34%	

- **Remission (MRS ≤ 12)**

ER	48%	(P=0.015)
Placebo	35%	

Divalproex ER for Acute Mania



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**

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**

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**
- **How would this have compared to 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**

All Antipsychotic Drugs Are Antimanic

Name one that isn't!

Olanzapine

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%

Divalproex vs. Olanzapine: Acute Mania

	<u>Tohen et al., 2002</u>	<u>Zajacka 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	OLZ -17.2 DVPX -14.8
↑ Weight	OLZ > DVPX (p=.028)	OLZ > DVPX (n.s.)

(Note differences in study design)

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 $\geq 7\%$ (16.2% vs. 2.9%)**

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**

Olanzapine + Divalproex vs. Divalproex Alone for Acute Bipolar Mixed Episodes

6-week, double-blind, n=202

- Inadequate response to DVPX alone for ≥ 14 days (blood level 75-125 mcg/ml)**
- OLZ: start 15 mg/day (flexible dosing 5-20 mg)**
- OLZ > PBO on HAM-D by day 14, on YMRS by day 7**

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 Adolescent Bipolar Mania

- **In December 2009: FDA-approved for bipolar I manic and mixed episodes , ages 13-17**
- **Based on one 3-week, placebo-controlled trial, n=161**
- **Flexible dose 2.5 to 20 mg/day, mean 8.9 mg/day**

Olanzapine for Acute Manic or Mixed Episodes in Adolescents (Ages 13-17) (3 week, double-blind)

	<u>OLZ (n=107)</u>	<u>PBO (n=54)</u>
Response	48.6%	22.2%
Remission	35.2%	11.1%
Weight Gain $\geq 7\%$	41.9%	1.9%
High Prolactin-female	25.7%	0%
High prolactin-male	62.5%	5%

Olanzapine for Acute Manic or Mixed Episodes in Adolescents (Ages 13-17)

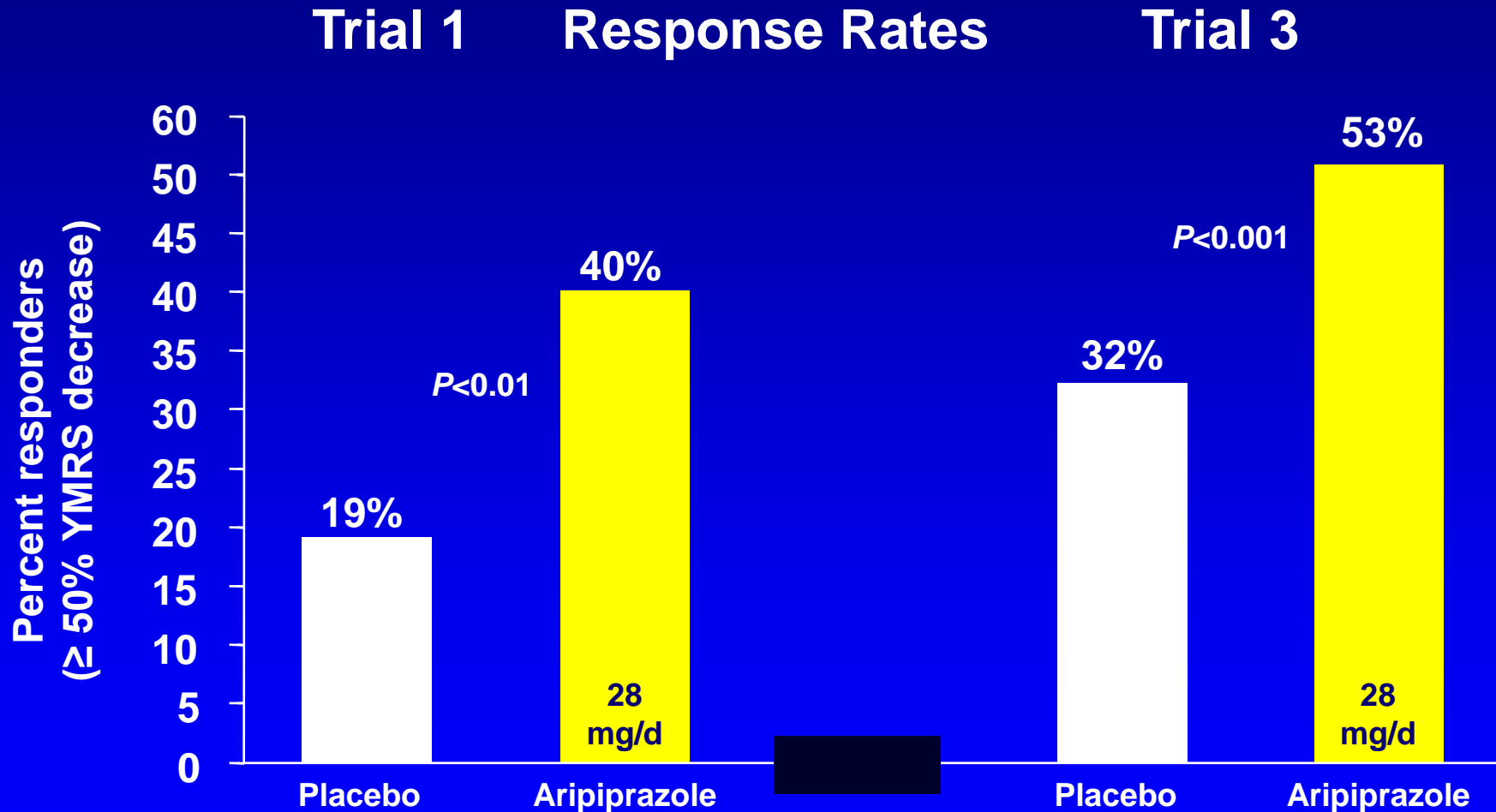
(3 week, double-blind)

- **Recommended starting dose 2.5-5 mg, target 10 mg (lower than in adults)**
- **Compared to adult trials, adolescents more likely to**
 - Gain weight**
 - Be sedated**
 - Increase lipids**
 - Increase prolactin**
 - Increase ALT**

Aripiprazole

Aripiprazole in Acute Mania

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



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

- **ARI 15-30 mg, mean 23.2 mg; Li₂CO₃ 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 Affective Disorders 2009;112:36-49**

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.)**

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 I Manic or Mixed Episode (ages 10-17)

- 4-week, double-blind, placebo-controlled, n=296.
- Start 2 mg/day, titrate to either 10 or 30 mg/day

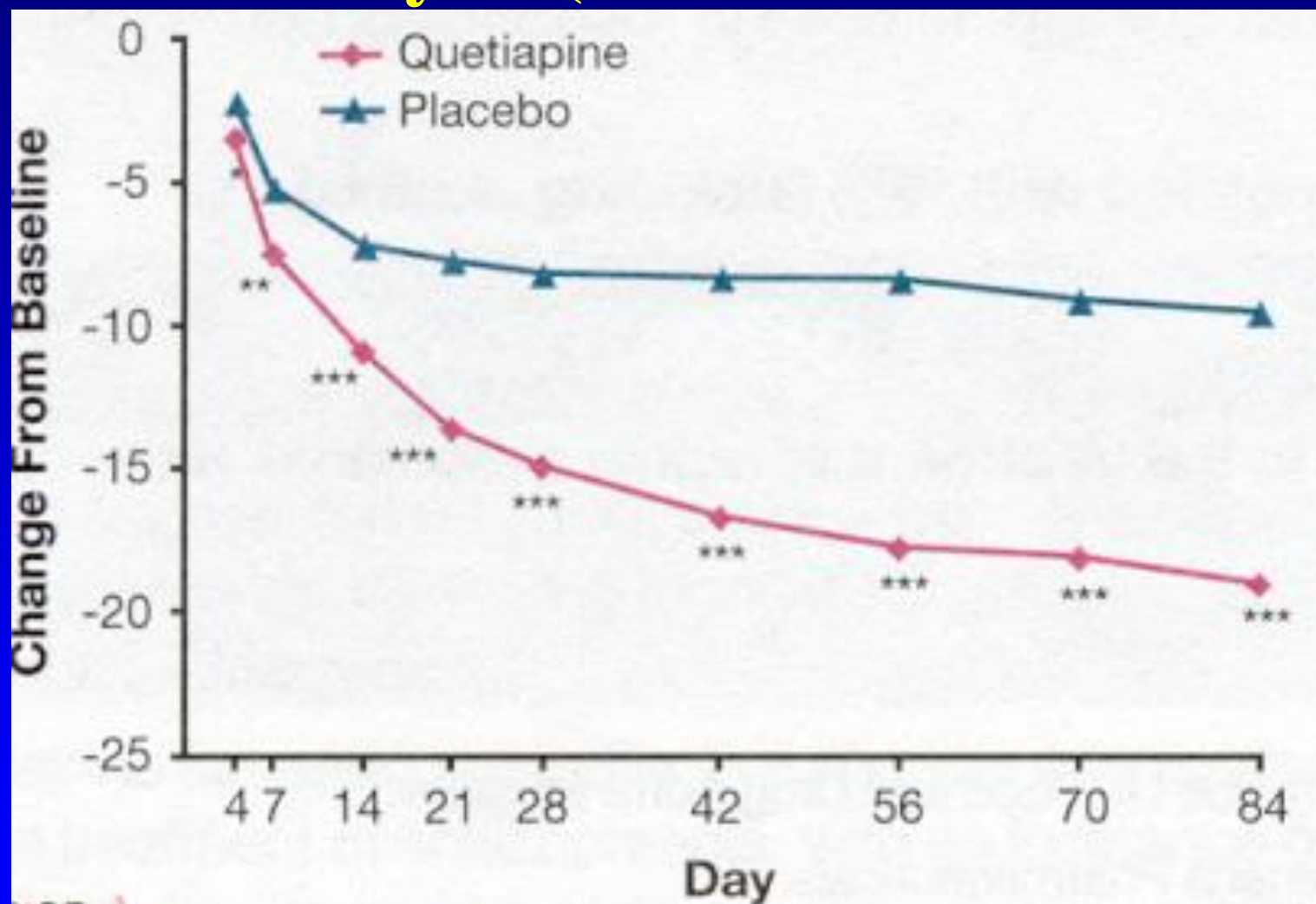
	<u>10 mg</u>	<u>30 mg</u>	<u>PBO</u>
• Response (LOCF):	44.8%	63.6%	26.1%
Remission	25.0%	47.5%	5.4%
A.E. drops	4.1%	7.1%	1.0%

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 ($\geq 50\%$ ↓ YMRS):
ARI 88.9%, PBO 52% (p=0.02)**
- **Remission (YMRS ≤ 12)
ARI 72%, PBO 32% (p=0.01)**
- **No effect on ADHD symptoms**

Quetiapine

Quetiapine vs. Placebo for Acute Mania (N=403) Pooled Analysis (2 double-blind studies)

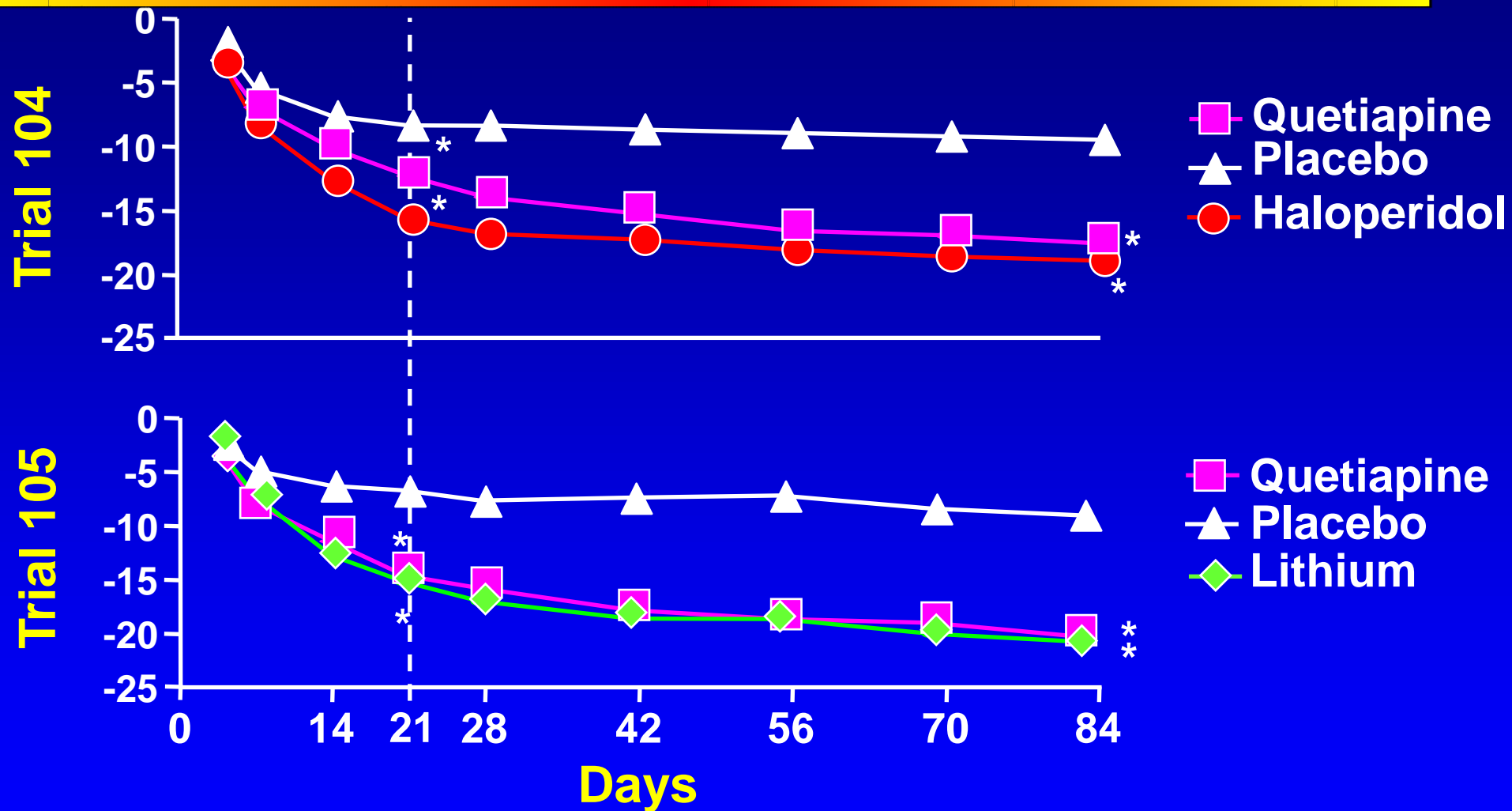


Jones et al., APA 5/03

Mean dose final week—597 mg

Full article: Vieta et al. *Curr Med Res Opin.* 2005;21:923-934

Quetiapine for Acute Mania



Jones M et al. APA New Research Abstracts, 2003

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

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

Quetiapine vs. Placebo as Add-on to Lithium or Divalproex in Acute Mania

3 positive studies

	<u>Response</u>		<u>Remission</u>	
	QTP	PBO	QTP	PBO
1.	55.7%	41.6%	48.7%	33.0%
2.	54.3%	32.6%	45.7%	25.8%
3.	72.1%	57.3%	48.7%	33.0%

1. Yatham et al. J Clin Psychopharmacol 2004;24:599-606
2. Sachs et al. Bipolar Disorders 2004;6:213-223
3. Sussman et al. J Affective Disorders 2007;100:s55-s63

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**

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)**

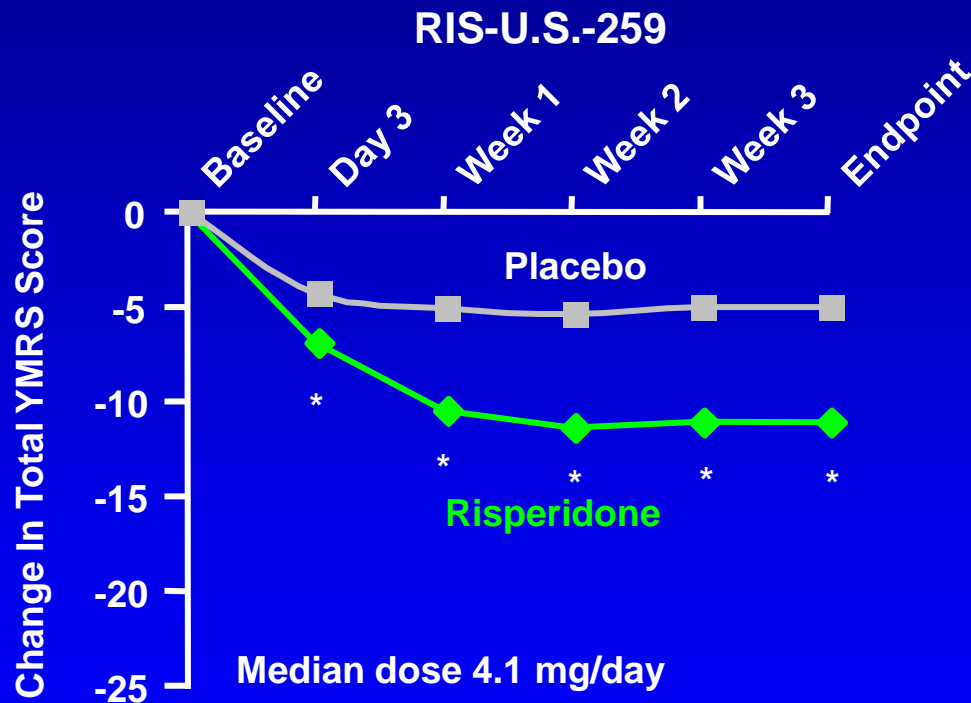
QTP	23	(n.s.)
DVPX	19	
- **Response (CGI-I-mania 1 or 2)**

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

Risperidone

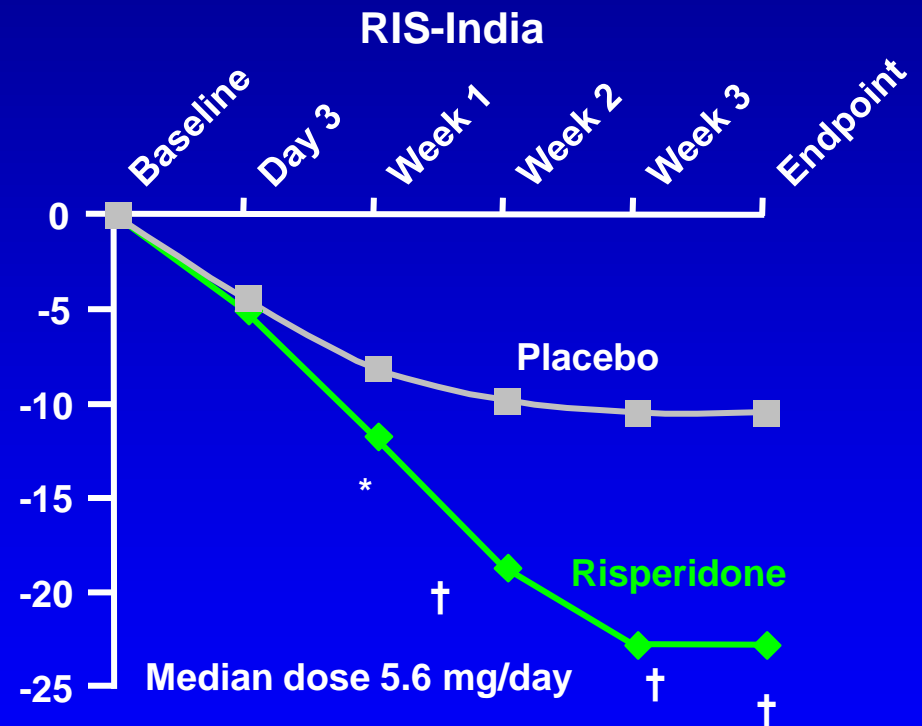
Risperidone in Acute Bipolar Mania

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**

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%

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

- Adverse event dropouts:

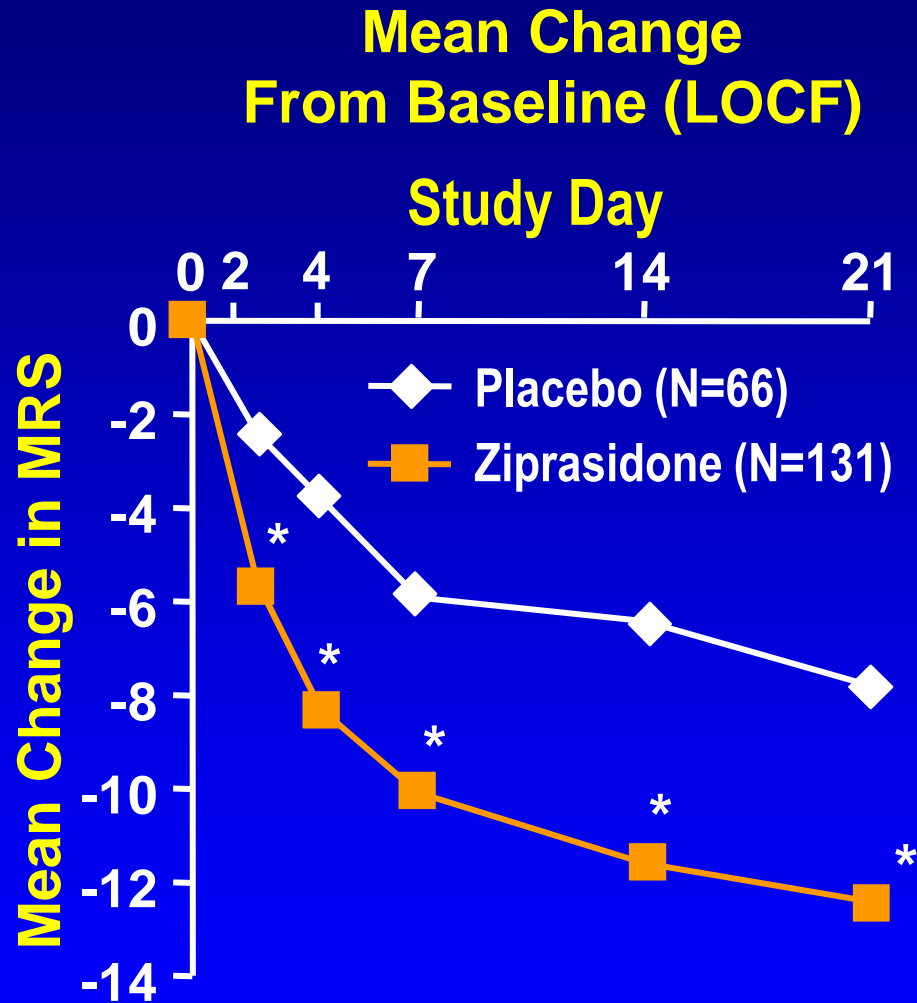
RIS 0.5-2.5 mg	6.0%
RIS 3-6 mg	16.0%
PBO	7.0%

- Weight gain $\geq 7\%$

RIS 0.5-2.5 mg	14.3%
RIS 3-6 mg	10.0%
PBO	5.3%

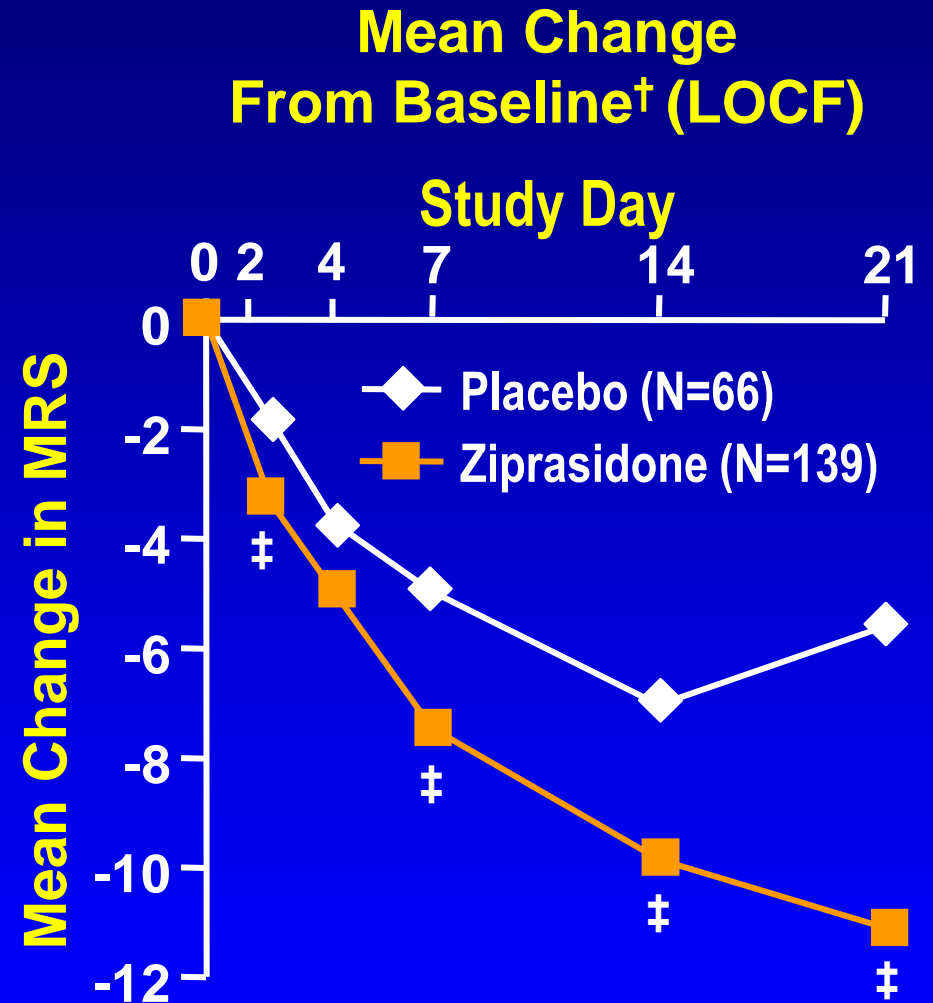
Ziprasidone

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;

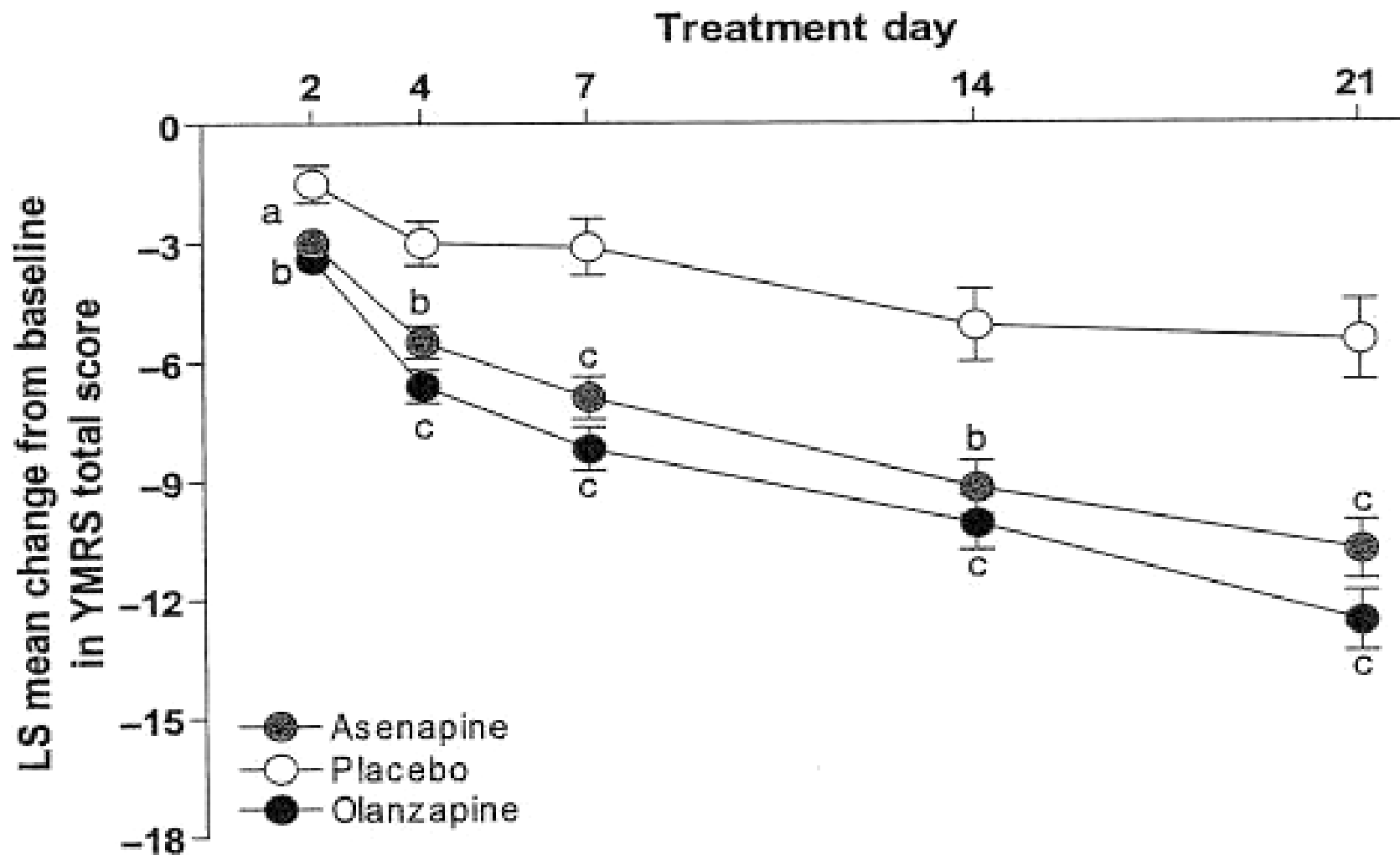
Potkin et al., J Clin Psychopharmacol 2005;25:301-310

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

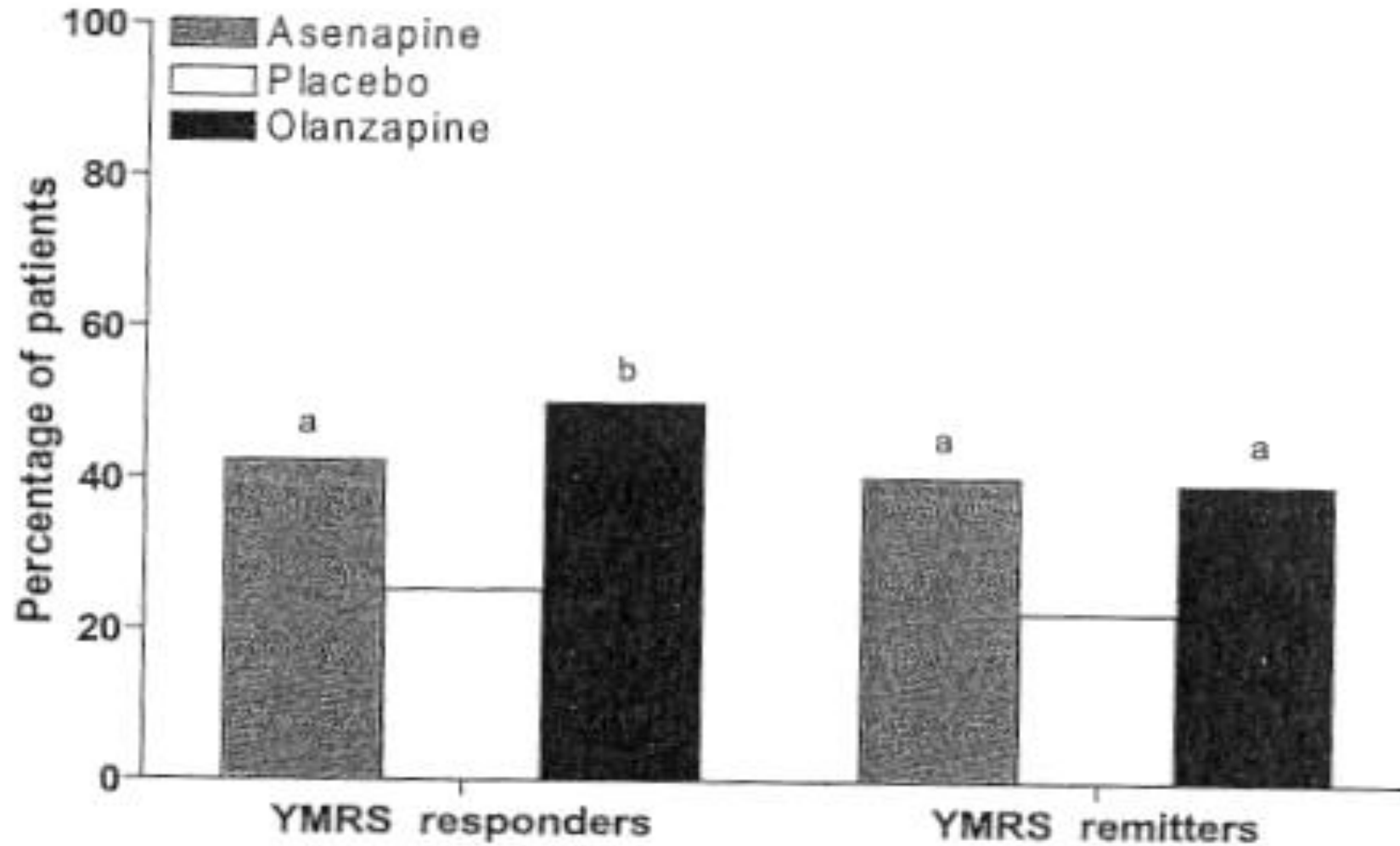
- **Dose: 80 to 160 mg/day**
- **Day 4: Ziprasidone > placebo**
- **Day 14: Ziprasidone = placebo**

Asenapine

Asenapine for Acute Mania



Asenapine for Acute Mania



Asenapine for Acute Mania

3-week, db, PBO and OLZ controlled*

- **YMRS ↓: Asenapine > PBO (p<0.007)**
OLZ > PBO (p<0.001)
- **YMRS response: Asenapine = PBO**
OLZ > PBO
- **YMRS remission: Asenapine = PBO**
OLZ > PBO

***Studied not powered to compare asenapine and olanzapine**

Paliperidone ER

Paliperidone ER vs. Placebo and Quetiapine for Manic and Mixed Episodes (3-week acute, 9-week maintenance, n=493)

- Dose: ER 3-12 mg, mean 9 mg; QTP mean 600 mg
- Primary efficacy: YMRS change (LOCF) at week 3
ER=QTP>PBO
- Response (\downarrow YMRS \geq 50%): **ER=QTP>PBO**
- Remission (YMRS \leq 12) : **ER=QTP>PBO**
- At 12 weeks: **ER=QTP**

Paliperidone ER (3, 6, 12 mg) vs. Placebo for Acute Manic and Mixed Episodes (3-week, double-blind, n=469)

- Primary efficacy measure: YMRS change (LOCF)
12 mg/day > 6 mg=3mg=placebo (p=0.005),
but at US sites all doses=placebo
- Response (\downarrow YMRS \geq 50%) and remission (YMRS \leq 12)
No dose more effective than placebo

Adjunctive Paliperidone ER (3-12 mg/day vs. Placebo) for Acute Manic and Mixed Episodes (6-week, double-blind, n=300)

- **No more effective than monotherapy with Li or VPA (Primary efficacy measure: YMRS change LOCF)**
- **Response (\downarrow YMRS \geq 50%) and remission (YMRS \leq 12)
No more effective than placebo**

Clozapine for Bipolar Disorder

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

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%

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 $\geq 50\%$ ↓YMRS; Remission YMRS ≤ 12

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

***No patient achieved response or remission prior to day 21**

Post-Lecture Exam

Question 1

1. All of the following are FDA-approved for treating acute mania except:
 - a. Carbamazepine
 - b. Chlorpromazine
 - c. Clozapine
 - 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. The first antipsychotic FDA-approved for the treatment of acute mania was which of the following?**
- a. Olanzapine**
 - b. Chlorpromazine**
 - c. Haloperidol**
 - d. Aripiprazole**
 - e. Risperdone**

Answers to Pre & Post Lecture Exams

1. c

2. d

3. a

4. b