The Use of Medications for Pediatric Bipolar Disorder

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Outline

- Use of mood stabilizers in pediatric bipolar disorder
- Use of atypical antipsychotics in pediatric bipolar disorder
- SSRI induced mania in children
- Treatment of bipolar depression in children
- Adverse effects of Mood stabilizers and Atypical antipsychotics in children

Question 1

Which of the following psychiatric disorders is most commonly comorbid with pediatric bipolar disorder:

- A) ADHD
- B) Conduct disorder
- C) Childhood schizophrenia
- D) Alcohol dependence
- E) Obsessive compulsive disorder

Question 2

The mood stabilizer that has been approved by FDA for treatment of bipolar disorder in adolescents is:

- A) Valproate
- B) Carbamazepine
- C) Lithium
- D) Oxcarbazepine
- E) Lamotrigine

Question 3

Which of the following is not a risk factor for SSRI induced manic episode in children?:

- A) Family history of bipolar disorder
- B) Psychomotor retardation
- C) Atypical depression
- D) Chronic, insidious onset
- E) Short allele of SERT gene

Bipolar Medication Classifications

Lithium

Anticonvulsants

- valproate (Depakote), carbamazepine (Tegretol), oxcarbazepine (Trileptal), lamotrigine (Lamictal)
- topiramate (Topamax), gabapentin (Neurontin)

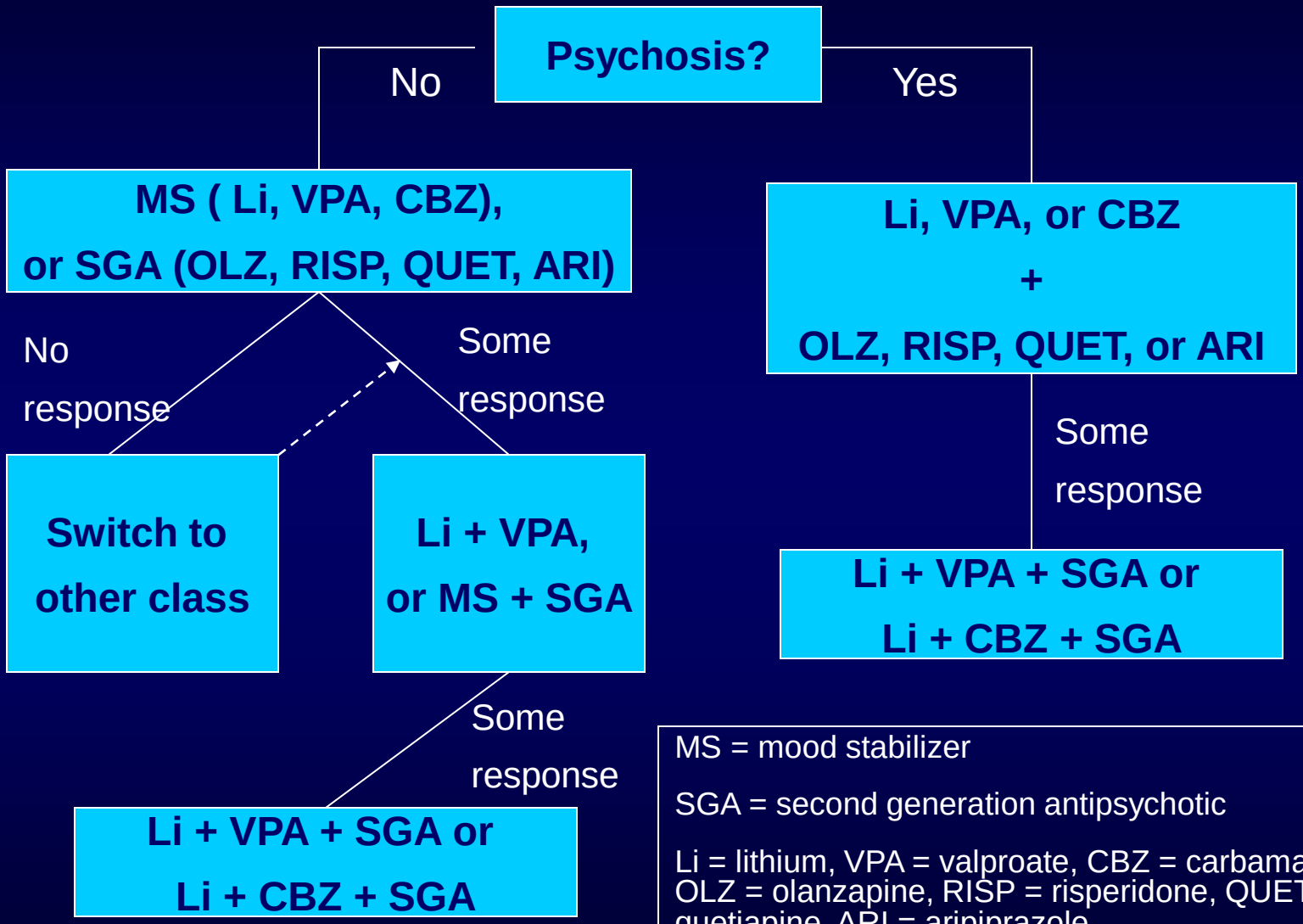
Antipsychotics

- “Typical”: haloperidol, perphenazine, molindone
- “Atypical”: olanzapine (Zyprexa), risperidone (Risperdal), paliperidone (Invega), quetiapine (Seroquel), ziprasidone (Geodon), aripiprazole (Abilify), clozapine (Clozaril), asenapine (Saphris)

Bipolar Medication Classifications

- Antidepressants
  - TCAs (amitriptyline, etc)
  - SSRIs (fluoxetine, sertraline, etc)
- ADHD treatments
  - Stimulants (methylphenidate, etc)
  - Atomoxetine
  - Modafinil
  - Alpha-2 agonists (clonidine, guanfacine)
- Anxiolytics
  - Benzodiazepines (clonazepam, lorazepam, etc)

Treatment of Acute Mania in Pediatric Bipolar Disorder



Adapted from Kowatch RA, et al. *J Am Acad Child Adolesc Psychiatry.* 2005;44(3):213-223.

Emerging Data in Pediatric Bipolar Disorder

	Case Report	Case Series	Open Prospective	RCT
Lithium	X	X	X	X
Valproate	X	X	X	X (Negative)
Carbamazepine		X	X	
Lamotrigine	X	X	X	
Topiramate		X		X (Negative)
Oxcarbazepine	X			X (Negative)
Gabapentin		X (Adjunct)		
Clozapine		X		
Olanzapine		X	X	X
Risperidone		X	X	X
Quetiapine			X	X
Ziprasidone	X			X
Aripiprazole		X		X

Lithium in Pediatric Bipolar Disorder

Year	First Author	Ages (years)	Disorder	Improved
1980	Hassanyeh	13 -15	Bipolar	6/7 (86%)
1981	McKnew	6 -12	Cyclothymia	2/2 (100%)
			Other	0/4 (0%)
1986	Hsu	14 -19	Bipolar	11/14 (79%)
1987	DeLong	3 - 20	Bipolar	39/59 (66%)
1988	Varanka	6 -12	Psychotic Mania	11/11 (100%)
1988	Strober	13 -17	Bipolar	34/50 (68%)
1998	Geller *	12 -18	Bipolar/MDD	6/13 (46%)
2000	Kowatch	6 -18	Bipolar I and II	5/13 (38%)
2003	Kafantaris	13-18	Bipolar I	63/100 (63%)
			TOTAL	177/273 (65%))

* RCT

Divalproex in Pediatric Bipolar Disorder

Year	First Author	Ages (years)	Disorder	# Improved
1994	West	12 -17	Bipolar	9/11 (82%)
1995	Papatheorodou	12 - 20	Bipolar	12/15 (80%)
2000	Kowatch	6 -18	Bipolar I and II	8/15 (53%)
2002	Wagner	7 -19	Bipolar I and II	22/36 (61%)
2005	Scheffer	6 – 17	Bipolar I and II	32/40 (80%)
2006	DelBello	12-18	Bipolar I	14/25 (56%)
2007	Wagner*	10-17	Bipolar I	18/74 (24%)
			TOTAL	115/216 (53%)

* RCT

Divalproex - ER in Pediatric Mania

- N = 150, 116 completers (66 in 6 month extension open label study)
- Mean age = 11.1 years (10-17 yrs)
- 4 week DBPC study
- Started at 15 mg/kg, titrated to 80-125 ug/mL (mean 1286 mg/day; final level = 79.9 ug/mL)
- Response considered as sig decrease in YMRS, 50% decrease in YMRS, or YMRS < 12
- Results: No difference between groups
  - DVPX ER = 24% response
  - Placebo = 23% response

Divalproex - ER in Pediatric Mania

- Adverse effects

	DVPX	PLACEBO
– Headache	16%	15%
– Vomiting	13%	8%
– Nausea	9%	1%

  - Significant decrease in WBC, platelets, AST/ALT, cholesterol
  - Significant increase in ammonia compared to controls

Available at: www.clinicalstudyresults.org/drugdetails/?company_id=1&sort=c.company_name&page=1&drug_id=1561. Accessed Aug. 20, 2007

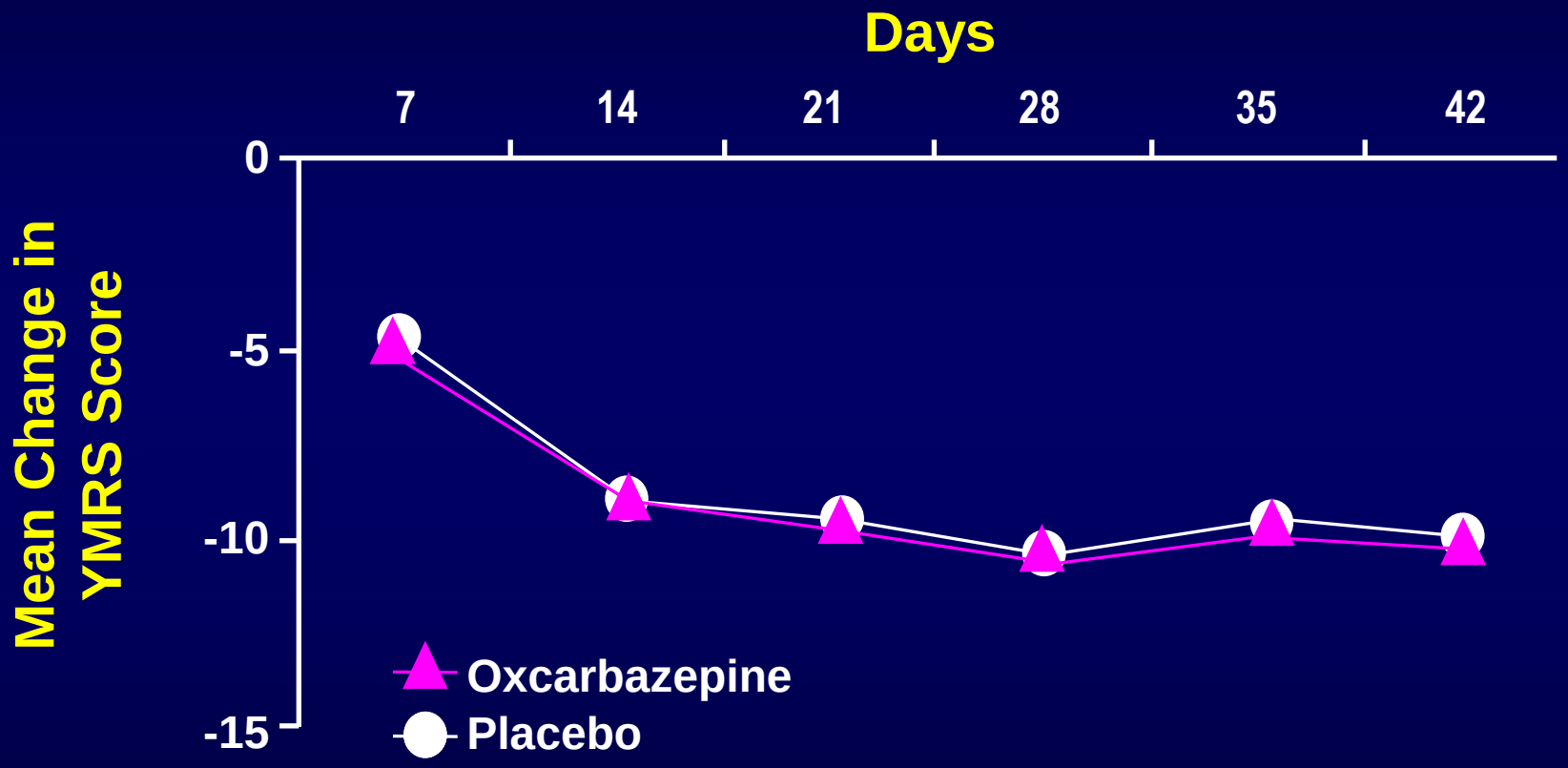
Oxcarbazepine in Pediatric BD

- N = 116, completers = 73
- Mean age = 11.1 years (7 - 18 yrs)
- 7 week DBPC study
- Mean dose = 1515 mg/day
  - Children = 1200 mg/day
  - Adolescents = 2040 mg/day
- Results: No difference between groups

Responders:	**OXC**	**PLACEBO**	***p***
– Children	41%	17%	.029
– Adolescents	43%	40%	.86

Wagner KD et al. (2006), Am J Psychiatry 163(7):1179-1186

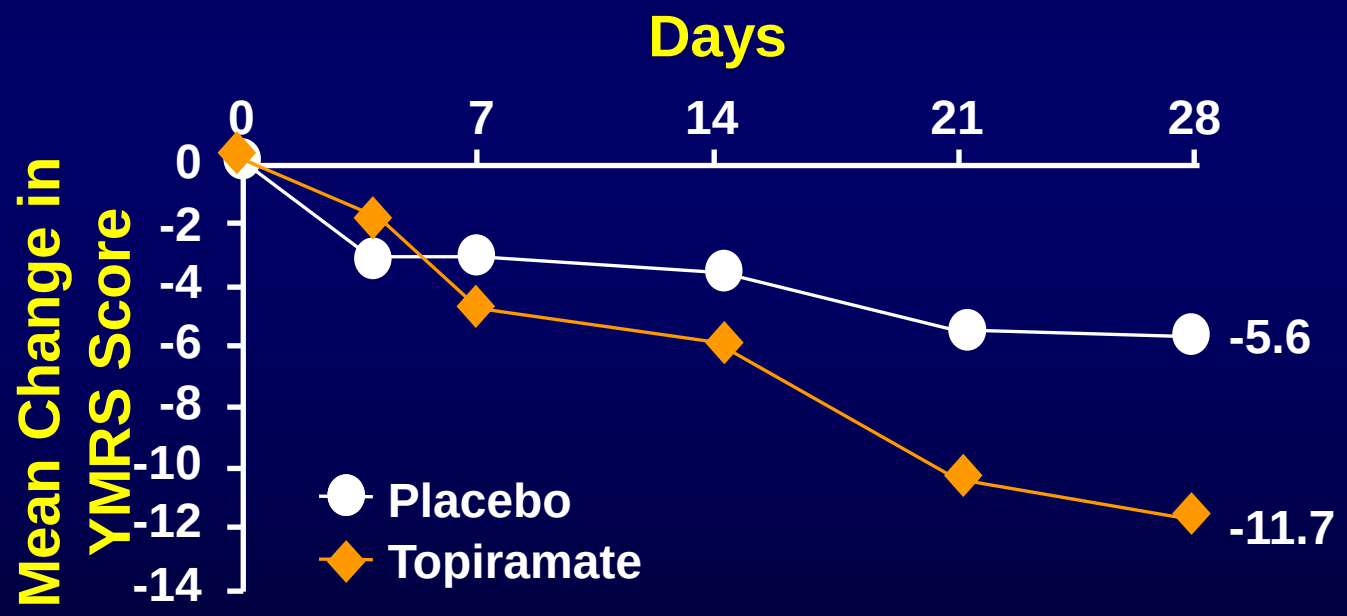
Oxcarbazepine in Pediatric BD



Wagner KD et al. (2006), Am J Psychiatry 163(7):1179-1186

Topiramate for Pediatric Bipolar I Disorder

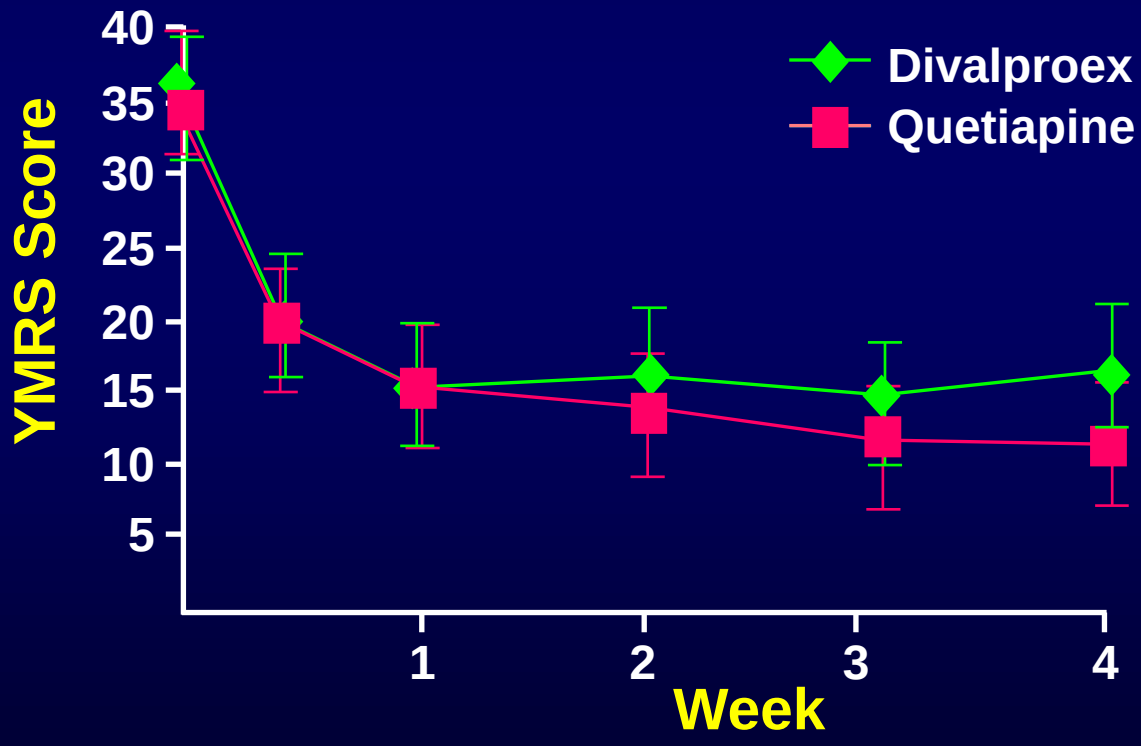
- 56 youths, ages 6-17, with bipolar I disorder, manic or mixed episodes
- Mean topiramate dose: 278 mg/day



DelBello MP et al. (2005), J Am Acad Child Adolesc Psychiatry 44(6):539-547

Quetiapine vs. Divalproex for Adolescent Mania

- 50 adolescent inpatients, with bipolar I disorder, manic or mixed episodes
- Quetiapine (400-600 mg/day) or divalproex (serum level 80-120 µg/mL) for 4 weeks



DelBello MP et al. (2006), J Am Acad Child Adolesc Psychiatry 45(3):305-313

Omega-3 Fatty Acids in Pediatric BD

- Open study: N=20, 6-17 yrs, YMRS > 15
- Omega-3 1290 mg-4300 mg combined EPA and DHA
- Statistically significant but modest 8.9+/-2.9 point reduction in the YMRS scores (baseline YMRS=28.9+/-10.1; endpoint YMRS=19.1+/-2.6, $p<0.001$).
- 35% responders

Wozniak J et al. (2007), Eur Neuropsychopharmacol 17:440-447

Omega-3 Fatty Acids in Pediatric BD

- 16 week, DBPC study using flax oil (ALA), monotherapy or adjunctive
- ALA = 550mg/1000mg flax oil; Placebo = olive oil
- N=40, 6-17 yrs, BD I or II
- Mean final dose 2965 mg/day
- No significant differences between groups
- 53% discontinued, mostly secondary to depression
- Few adverse events

Gracious, et al., 53rd Annual Meeting of the AACAP, San Diego, October 24-29, 2006

FDA Indications in Children Feb 2010

	Bipolar Disorder (10-17 yo)	Schizophrenia (13-17 yo)	Irritability in Autism
Clozapine			
Olanzapine	X (13-17 yo)	X	
Risperidone	X	X	X (5-16 yo)
Quetiapine	X	X	
Ziprasidone			
Aripiprazole	X	X	X (6-17 yo)
Paliperidone			
Asenapine			

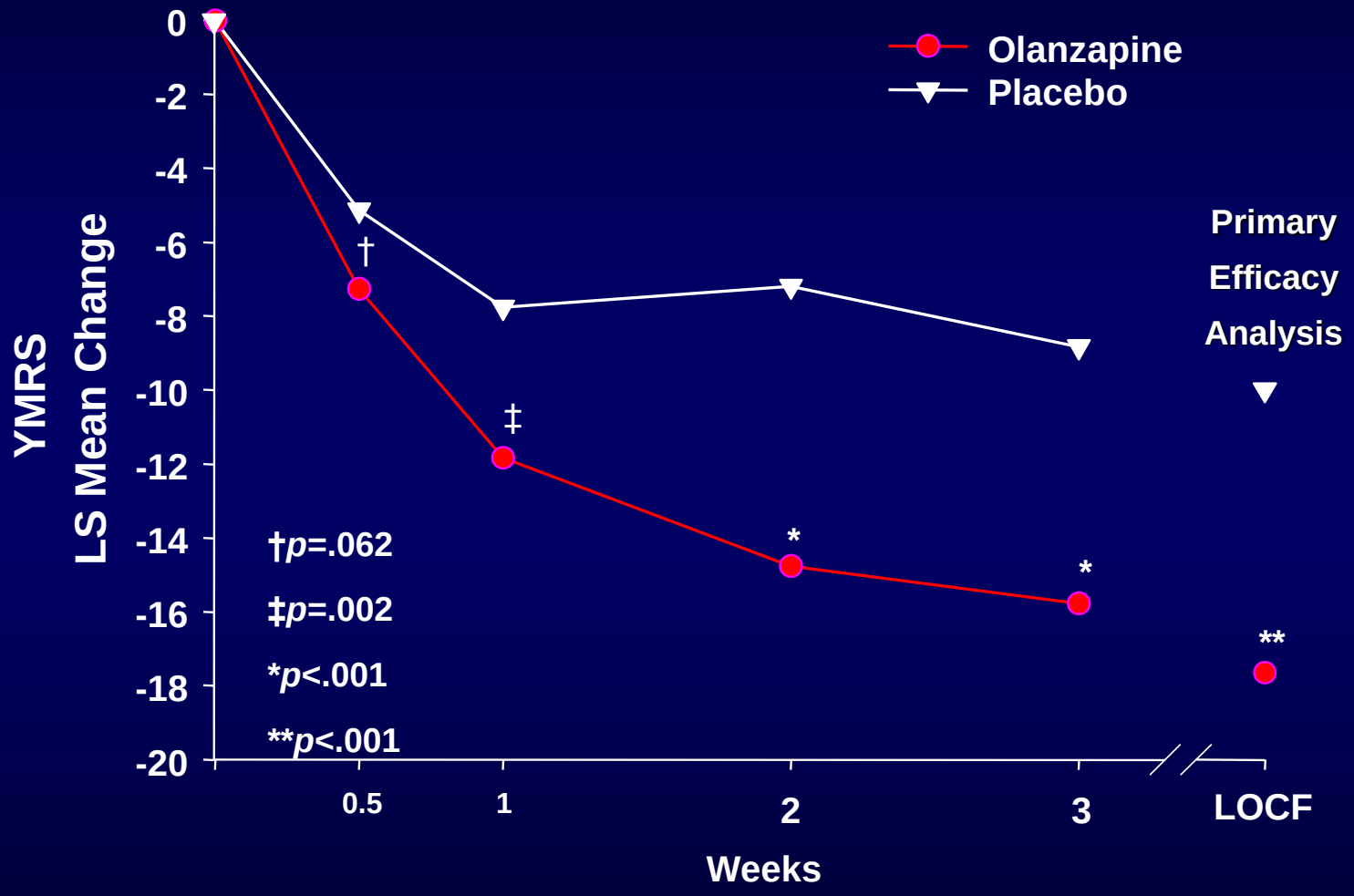
Olanzapine in Pediatric Bipolar Disorder

Methods

- N = 161, 10-17 y.o.
- Bipolar I disorder, mixed or manic, +/- psychosis
- YMRS ≥ 20
- 3 week double-blind placebo-controlled
- Start OLZ 2.5-5.0 mg/day, increase by same until 10-20 mg/day

Tohen M, et al. *Am J Psychiatry.* 2007;164:1547-56.

YMRS Change from Baseline: Olanzapine vs. Placebo



* † Mixed ANCOVA Model: Change = Baseline Therapy Country Visit Therapy*Visit.
**TYPE III sum of Squares from ANCOVA: Model= Baseline Country Therapy.

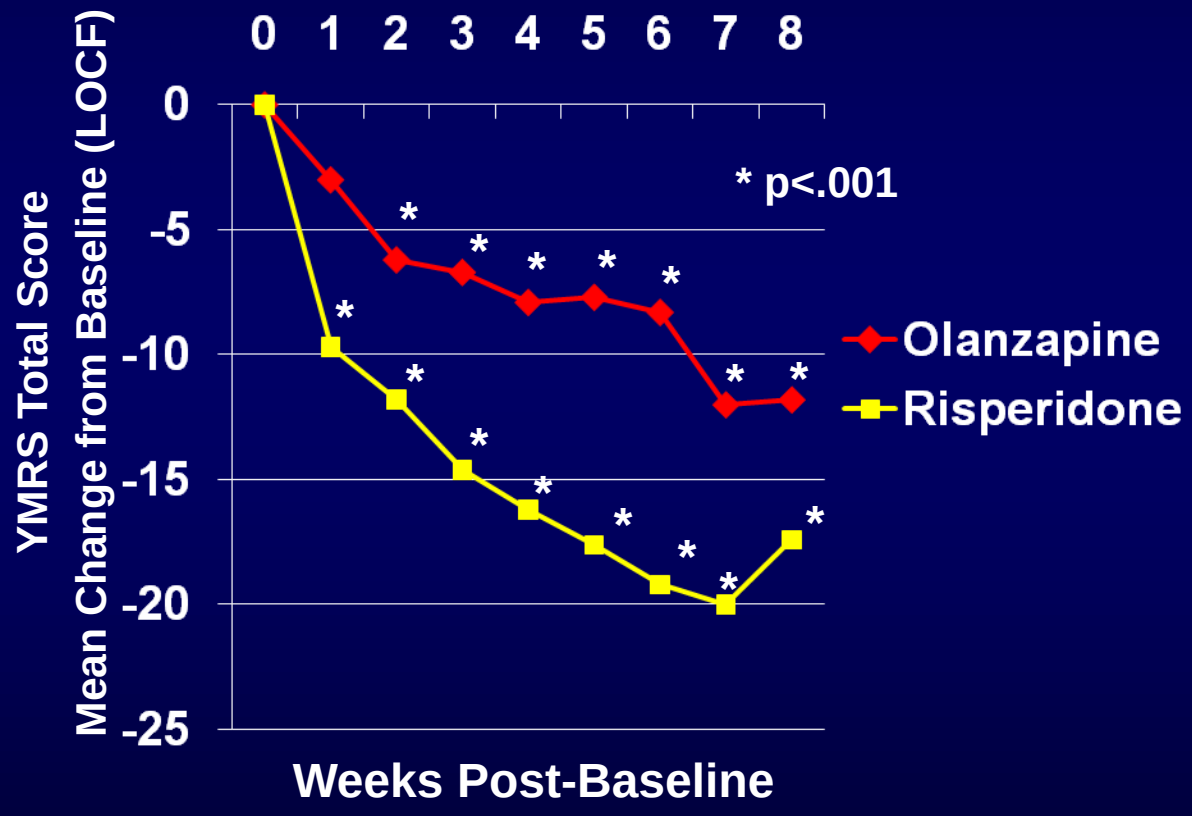
Tohen M, et al. *Am J Psychiatry.* 2007;164:1547-56.

Open Label Olanzapine Extension Study

- 146 subjects completing 3-week acute study
- Open label OLZ (2.5 mg - 20 mg) for up to 26 wks
- 63% response rate
  (50% reduction YMRS, CGI-BP Severity ≤ 3)
- Weight gain = 7.5 ± 6.8 kg
- ≥ 7% inc in weight = 69%
- Inc prolactin = 71%

Kryzhanovskaya L, et al. 47th Annual Meeting of the NCDEU. Boca Raton, FL: June 11-14, 2007.

Olanzapine and Risperidone in Preschool Bipolar Disorder



- N = 31
- Age 4-6 yrs, manic
- Open-label study
- RIS (n=16) up to 2 mg/day;
  OLZ up to 10 mg/day
- YMRS decreases:
  - RIS: 18.3
  - OLZ: 12.1
- Response rates similar (69% RIS vs. 53% OLZ)

Biederman J, et al. *Biol Psychiatry*. 2005;58:589-94.

Risperidone in Pediatric Bipolar Disorder

- N = 30, age 6-17 yrs, manic. Open-label study
- RIS mean dose 1.25 mg/day, 8 wks
- ADHD meds allowed
- Response: 30% dec in YMRS *or* CGI-I ≤ 2
- 70% responders (50% if using 50% criteria)
- Remission in 23% (YMRS < 10, CDRS < 29)
- YMRS: 28.0 → 13.5
- Weight gain = 2.2 kg
- Prolactin = 4-fold elevation

Biederman J, et al. *Biol Psychiatry*. 2005;58:589-94.

Risperidone in Pediatric Mania
Methods

- N = 166, 10-17 y.o.
- BD I, mixed or manic
- 3-week DBRCT
- Two doses of RIS (0.5 - 2.5 mg/day or 3.0 - 6.0 mg/day)

U.S. Food & Drug Administration. *FDA News.* August 22, 2007.
Available at: http://www.fda.gov/bbs/topics/NEWS/2007/NEW01686.html.

Risperidone in Pediatric Mania

	Placebo	0.5-2.5 mg/day	3.0-6.0 mg/day
Response rate	26%	59%	63%
YMRS change, mean (SD)	9 (11)	19 (10)	17 (10)
EPS	8%	5%	25%
Prolactin change, mean (SD)	Boys 0.6 (7) Girls 2 (7)	Boys 32 (23) Girls 50 (46)	Boys 50(23) Girls 68 (49)
Abnormal prolactin	0%	11%	25%
Weight change, mean kg (SD)	0.7 (1.9)	1.9 (1.7)	1.4 (2.4)

U.S. Food & Drug Administration. *FDA News.* August 22, 2007.
Available at: http://www.fda.gov/bbs/topics/NEWS/2007/NEW01686.html.

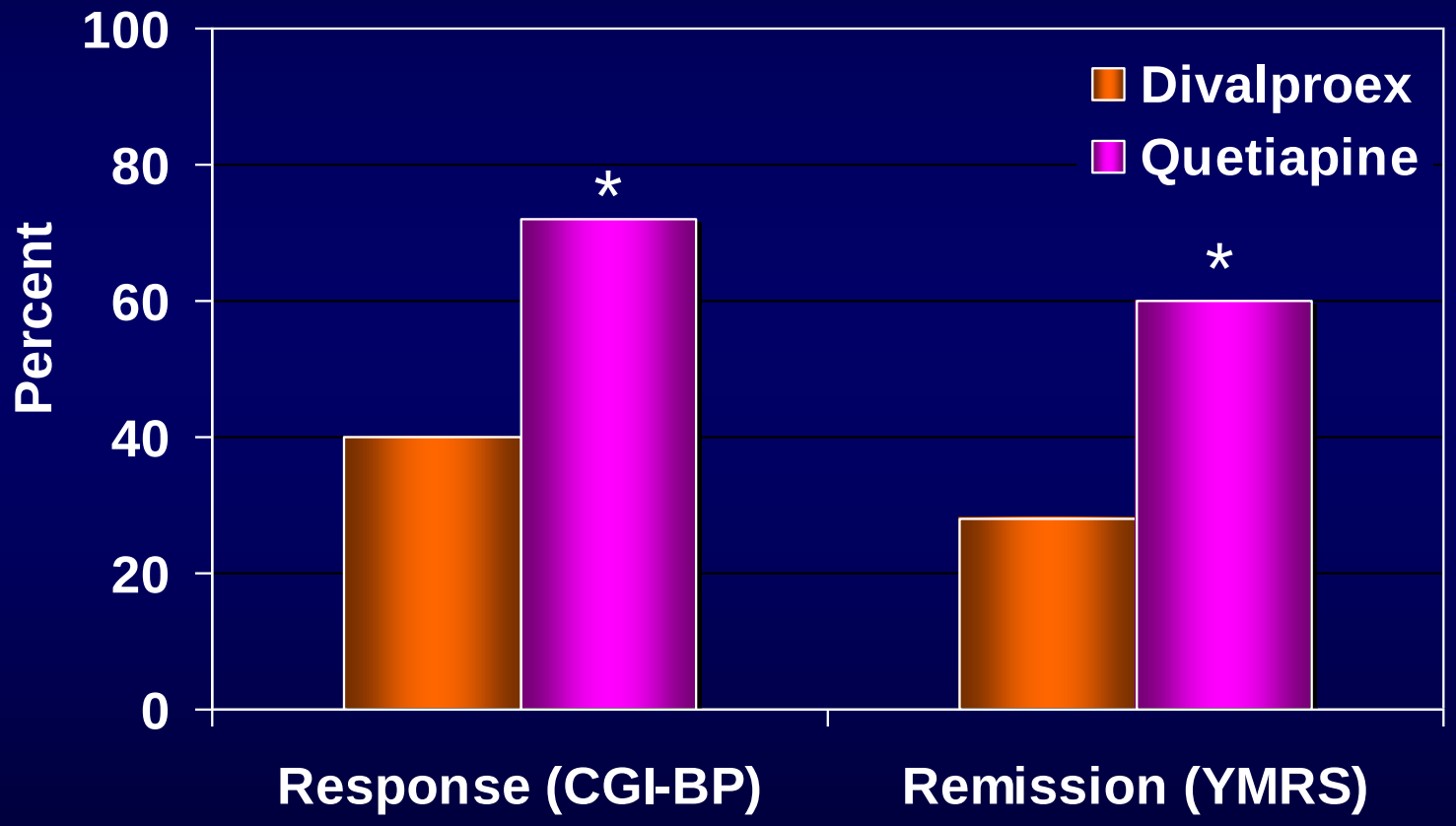
Quetiapine vs. Divalproex in Pediatric Mania

- 50 adolescent (15 ± 2 y.o.) inpatients
- Randomized:
  - DVPX: 80-120 ug/mL
  - QUET: 400-600 mg/d
- Similar side effect rates
  - Sedation: 60% (QUE) vs. 36% (DVP)
  - Dizziness: 36% vs. 36%
  - GI upset: 26% vs. 28%
- Similar weight increase
  - 4.4 ± 5.0 kg (QUE) vs. 3.6 ± 6.0 kg (DVP)

DelBello M, et al. *J Am Acad Child Adolesc Psychiatry.* 2006;45:305-13.

Quetiapine vs. Divalproex in Pediatric Mania Response Rates

Response: CGI-BP-Improvement = 1 or 2
Remission: YMRS ≤ 12



*p = .02

$\chi^2 = 4.7$, df=1, p=0.03

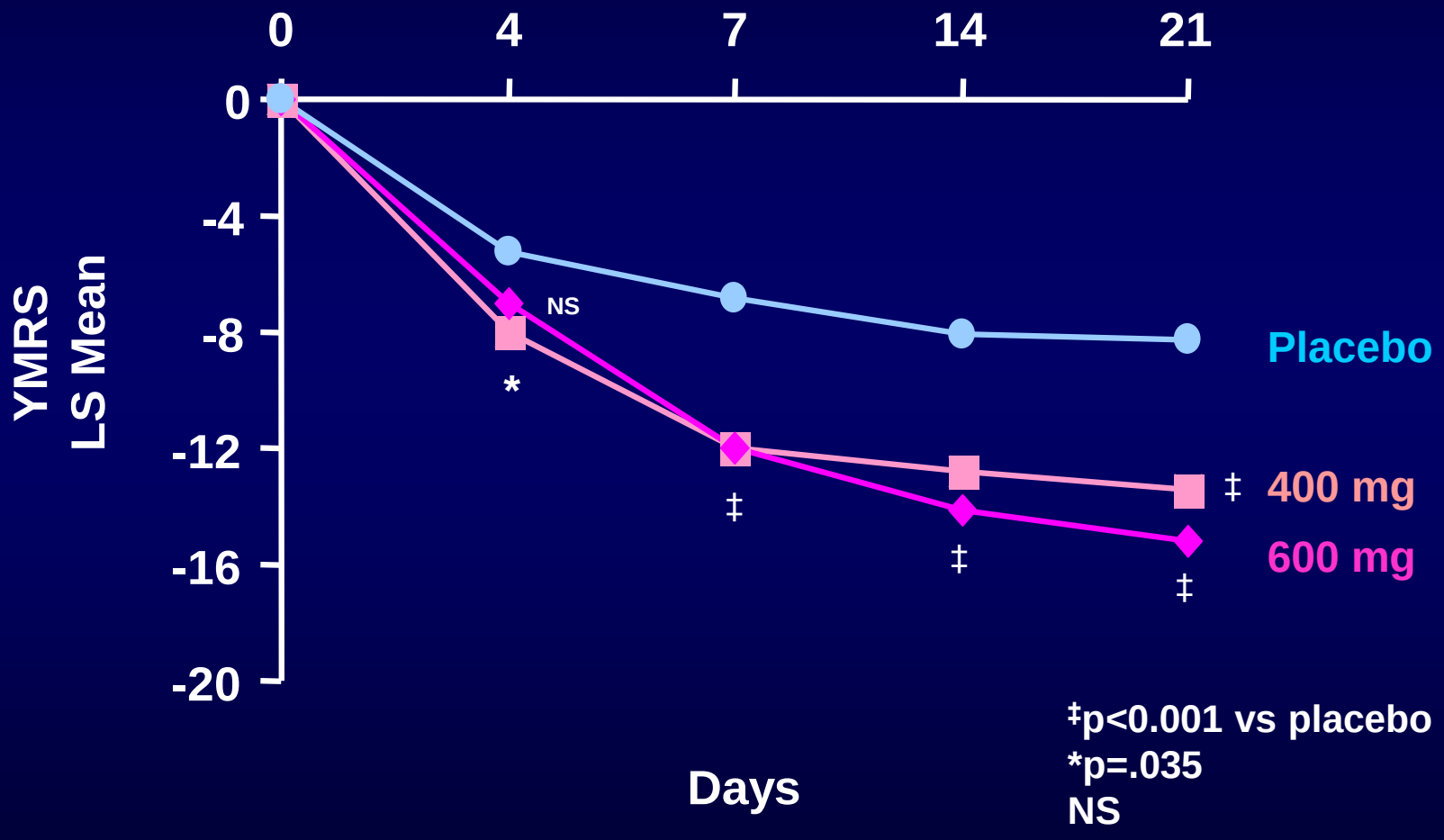
DelBello M, et al. *J Am Acad Child Adolesc Psychiatry.* 2006;45:305-13.

Quetiapine in Pediatric Mania
Methods

- N = 277, 10-17 y.o. (Mean = 13.2 y.o.)
- BD I, manic
- Baseline YMRS = 30
- 3-week DBRCT
- Two doses of QUE (400 or 600 mg/day)
- 15% with adjunctive stimulant continued for ADHD

DelBello MP, et al. AACAP Annual Meeting, October 25, 2007.

YMRS Change from Baseline: Quetiapine vs. Placebo



DelBello MP, et al. AACAP Annual Meeting, October 25, 2007.

Quetiapine Tolerability

Adverse Event (%)	Quetiapine 400 mg	Quetiapine 600 mg	Placebo
Somnolence	28.4	31.6	10
Sedation	23.2	25.5	4.4
Dizziness	18.9	17.3	2.2
Weight Gain	1.7 kg	1.7 kg	0.4 kg

- NNH (>7% weight gain) = 9 for quetiapine vs. 3 for olanzapine

DelBello MP, et al. AACAP Annual Meeting, October 25, 2007.

Ziprasidone in Pediatric Patients with Bipolar Disorder

	Manic/Mixed (N=46)	
	Low-dose 40 mg bid	High-dose 80 mg bid
BPRS-A baseline, mean (SD)	46 (10)	45 (10)
BPRS-A, mean change (SD)	-13 (11)	-15 (12)
YMRS baseline, mean (SD)	29 (5)	26 (7)
YMRS, mean change (SD)	-17 (8)	-13 (9)
QTc change, mean	1.3 msec	11.2 msec

Versavel M, et al. *Neuropsychopharmacology.* 2005;30(Suppl 1):122.

Aripiprazole for Pediatric Mania

- N=302
- 10-17 y.o., BD I, manic or mixed
- 4-week DBPCT
- Randomized 1:1:1 to placebo:10 mg:30 mg

Dosing Schedule	*Day*						
	1	*3*	*5*	*7*	*9*	*11*	*13*
Low Dose, mg/day	2	5	10	10	10	10	10
High Dose, mg/day	2	5	10	15	20	25	30

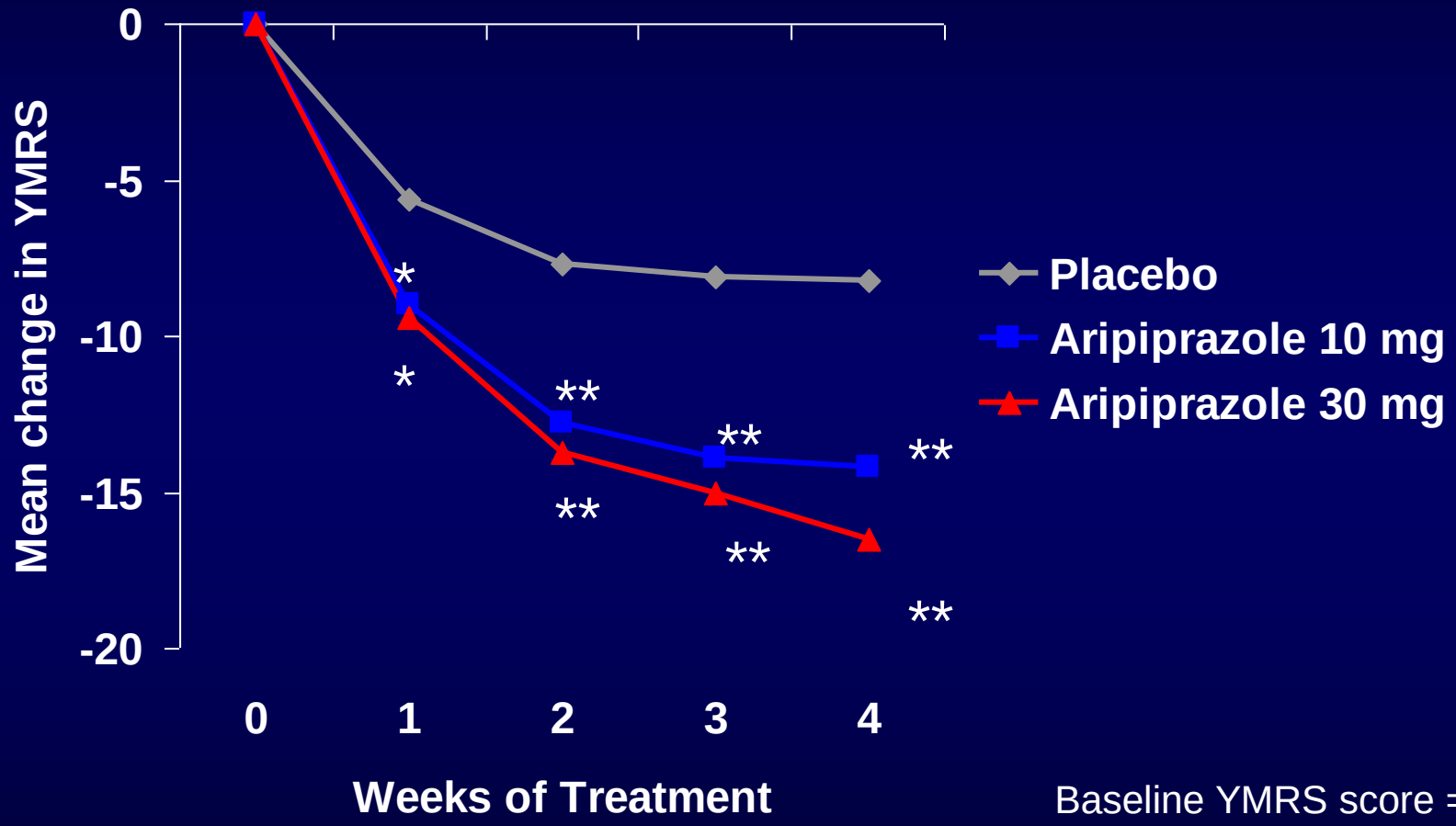
Findling et al, 2009

Aripiprazole for Pediatric Mania
Results

- Baseline YMRS = 30.1
- Decrease in YMRS:
  Placebo = 8.2,10 mg = 14.2, 30 mg = 16.5,
- 50% drop in YMRS:
  Placebo = 26%, Low dose = 45%, High dose = 64%
- Side effects: Akathisia (2%/9%/13%),
  weight gain (.5 kg/.6 kg/.9 kg - NS)
- 4.6%, 4%,12.3% with ≥ 7% gain in body weight

Findling et al, 2009

Primary Endpoint: Mean Change in YMRS Score (LOCF)

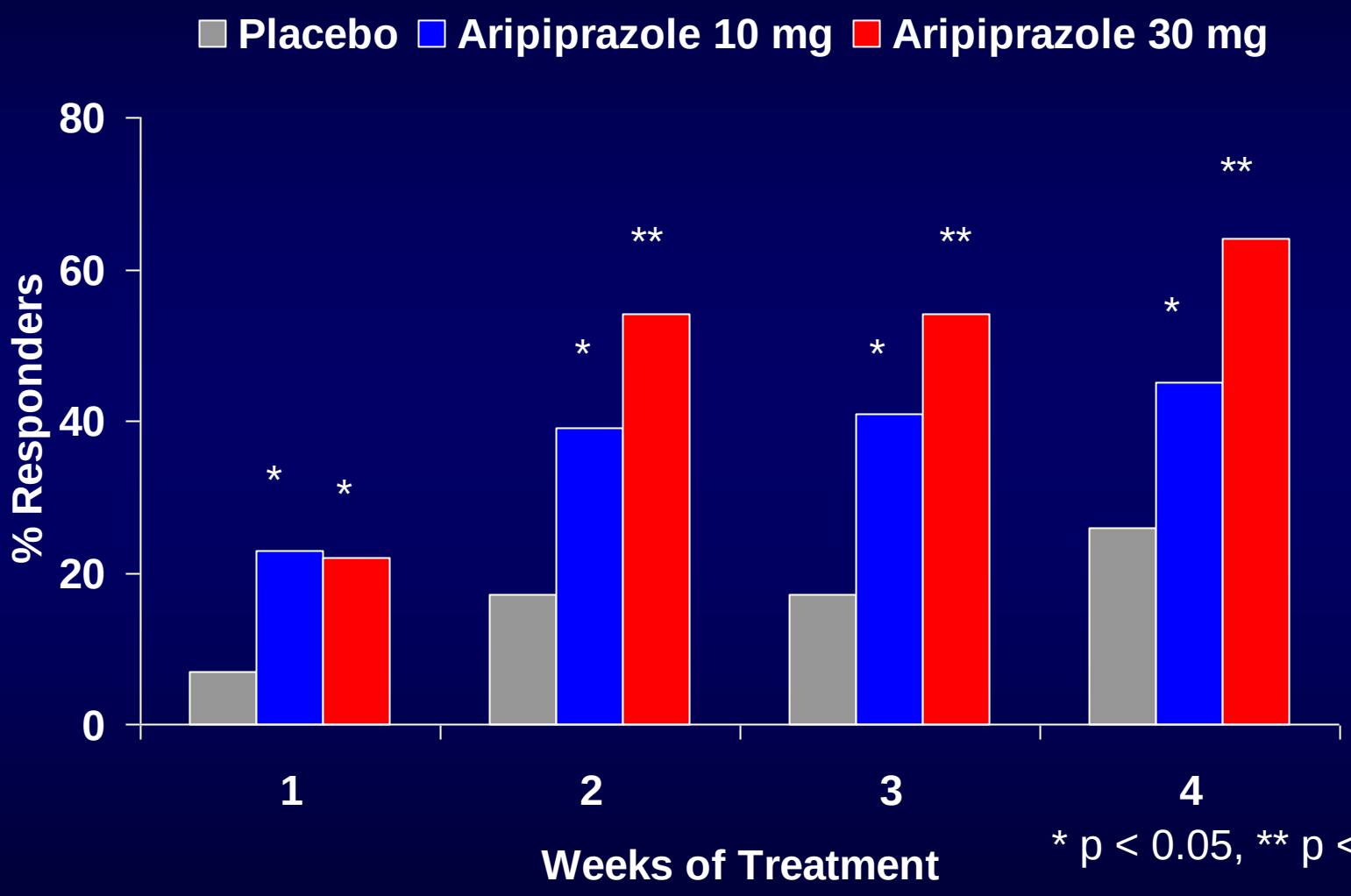


Baseline YMRS score = 30.1

*p < 0.05, **p < 0.0001

Findling et al, 2009

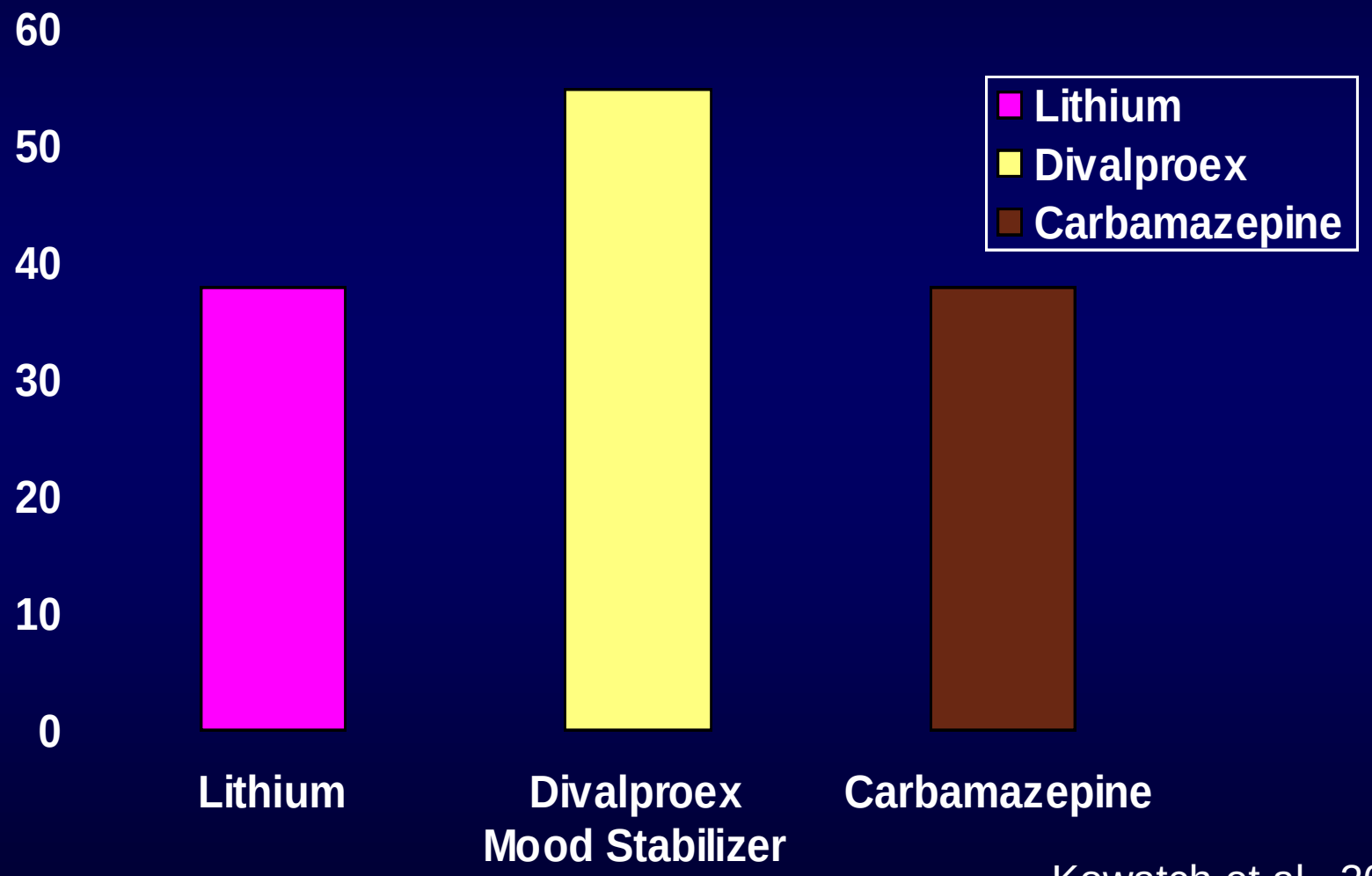
Response Rate (LOCF)



* p < 0.05, ** p < 0.0001

Findling et al, 2009

Response Rate of Mood Stabilizers in Pediatric BD



Kowatch et al., 2000

Stanley Continuation Phase Study

Kowatch et al 2002

- 42% responded to monotherapy
- 58% required combination treatment
  - Mood Stabilizer(s) + Stimulant (34%)
  - Mood Stabilizer(s) + Antipsychotic (11%)
  - Mood Stabilizer(s) + Antidepressant (6%)
- Addition of stimulant helpful for comorbid ADHD
  - 12/13 (92%) with positive response

Combination Therapies in Pediatric Bipolar Disorder

- Understudied, since monotherapy efficacies just recently established
- Usually needed in pediatric BD
- Can be used short- or long-term
- Basic guideline: use common sense
  - Maximize single agent dose if possible
  - Add additional agent to complete mood stabilization and/or treat comorbidity
  - Add different class of medication

Mood Stabilizer + Mood Stabilizer

Combination Divalproex and Lithium Treatment for Childhood Bipolar Disorder

- 139 child and adolescent outpatients, ages 5 to 17 years, with bipolar disorder I or II
- Lithium (mean 915 mg/day) and divalproex (mean 849 mg/day) treatment

Findling et al, 2003.

Combination Divalproex and Lithium Treatment for Childhood Bipolar Disorder

- Results
  - At week 8, significant improvement in all outcome measures (YMRS-R, CDRS-R, CGAS)
  - Sixty (43%) met remission criteria during trial
  - Seven (9%) failed to respond during trial to combination treatment

Findling et al, 2003.

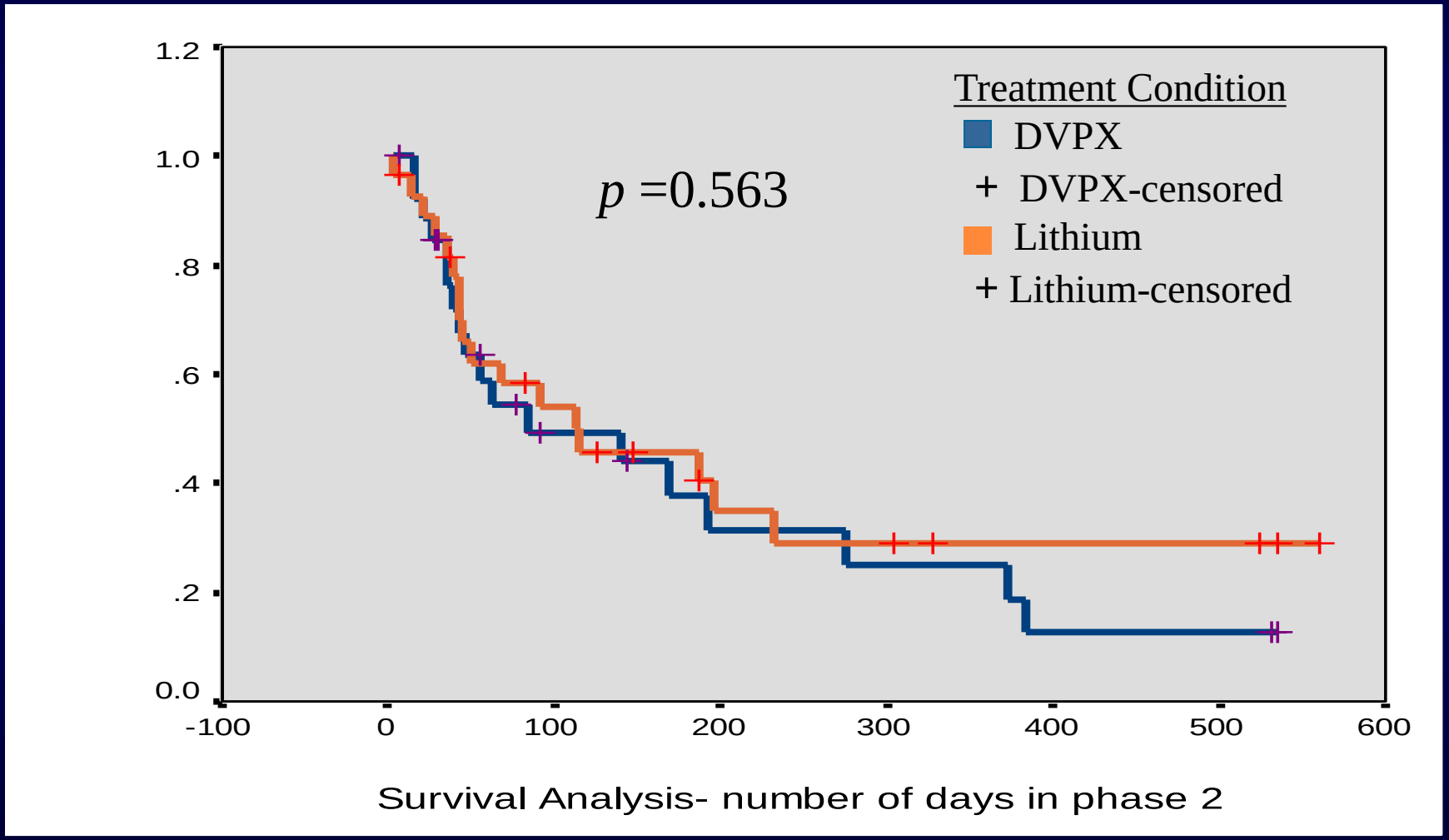
DVPX + Lithium

Findling et al 2005

Phase II

- 76 weeks
- VPA or Li only given
  - 8 week taper of other medication
  - Pharmacokinetically controlled
    - VPA levels 50-100 ug/mL
    - Li levels 0.6 - 1.2 mEq/L

DVPX vs Lithium in Juvenile Bipolar Disorder - Time to Relapse



Mood Stabilizer + Antipsychotic

Olanzapine in Prepubertal Bipolar Disorder

- 3 prepubertal boys with bipolar disorder
  - Already Rx divalproex, lithium
  - 1.25 - 5 mg QHS
- Acute mania - added olanzapine 2.5 mg QHS
- Resolution of symptoms within 5 days
- Normalization of sleep patterns
- Adverse effects = sedation, weight gain

Chang, KD et al. (2000): Mood stabilizer augmentation with olanzapine in acutely manic children. *J Child Adolesc Psychopharmacol* 10:45-9.

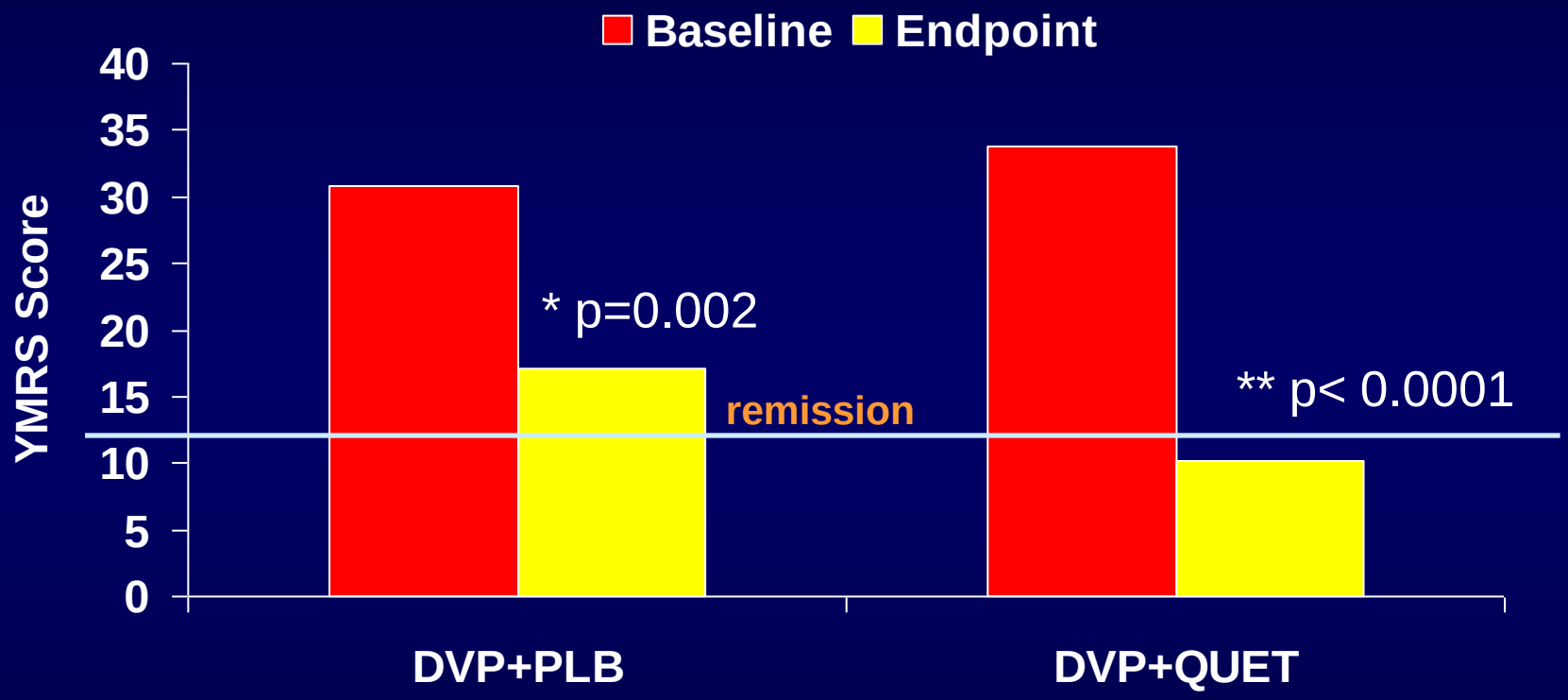
Quetiapine + Divalproex in Adolescent Mania

- 30 adolescents with BD I
- 6 wks double blind adjunctive study
- Begun on open divalproex, 20 mg/kg
- Randomized: quetiapine vs. placebo
- Mean quetiapine dose = 432 mg/d
- Mean valproate level = 102-104 ug/ml

Delbello, et al. *J Am Acad Child Adolesc Psychiatry*. 2002;41:1216-23.

Quetiapine for Adolescent Mania

Change Baseline to Endpoint in YMRS



***Significant group effect, t(28)=2.6, p<0.03

Delbello, et al. *J Am Acad Child Adolesc Psychiatry*. 2002;41:1216-23.

Mood Stabilizer + Stimulant

DVPX + Adderall

Scheffer et al, 2005.

Methods

- 40 children/adolescents with BP I or II
- Manic or mixed
- Marked comorbid ADHD Ages 6 - 17
- 8 week open DVPX
  - Goal is > 50% reduction in manic symptoms

DVPX + Adderall

Scheffer et al, 2005

Methods

- 2 week double-blind, placebo-controlled crossover design
- Open label follow up with DVPX and Adderall based upon patient/parent preference (24 week total)

Results: Divalproex Monotherapy

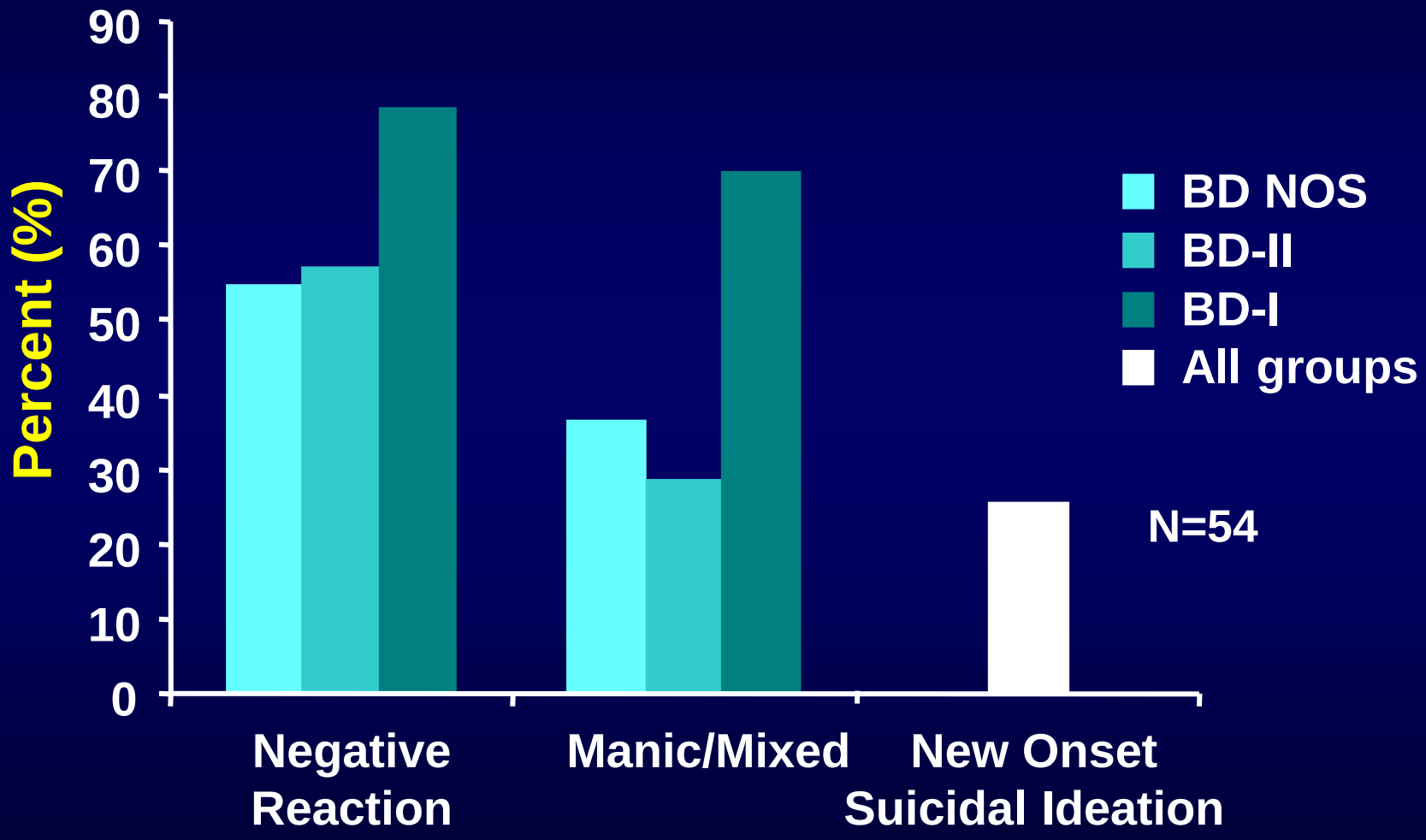
- Divalproex sodium monotherapy was safe and effective ($p<.0001$)
- 30 of 40 initial subjects were randomized.
- No subject withdrew due to side-effects.
- Most common side-effects were GI upset, hair loss (girls>boys), easy bruising (without decreased platelets).

Results: Adderall vs. Placebo

- Adderall was safe and effective ($p<.0001$) for the adjunctive treatment of ADHD symptoms after mania had been controlled.
- 1 of 30 subjects randomized experienced a worsening of mood symptoms while on Adderall.
  - Mood symptoms restabilized after discontinuation of Adderall.

Treatment of Bipolar Depression

Negative Reactions to Antidepressants in Bipolar Disorder in Children



Baumer et al. (2006), *Biol Psychiatry*

SSRI Induced Mania

- May be seen in as high as 50% of children with bipolar disorder
- Not to be confused with “behavioral disinhibition”
- May account for reports of increased suicidality in children rx with SSRIs
- Risk factors:
  - Bipolar family history
  - Psychomotor retardation
  - Atypical depression
  - Acute onset
  - Short (s) allele of SERT gene?

SERT = serotonin transporter.

Treatment of Bipolar Depression

- Chart review of 59 children and adolescents with bipolar disorder
- 42 youths had symptoms of depression at follow-up visits
- SSRIs compared to no medication:
  - 7 x more likely to improve depressive symptoms
  - But subsequent mania 3 x more likely to develop

Biederman, et al. 2000.

Lithium for Adolescent BP Depression

- Total N=30, BP I, depressed
- 42 day prospective open-label
- Clinical assessments
  - days 0, 7, 14, 28, 42 (endpoint)
- MRS scans
  - days 0, 7, 42 (endpoint)
- Outcome measures
  - Remitters: CDRS-R $\leq$ 28 and CGI-I $\leq$ 2
- Titrated to level of 1.0-1.2 mEq/L
  - Mean= 1.1 $\pm$ 0.2 mEq/L

Patel, et al. (2006) *JAACAP*.

Sample Characteristics: Lithium Study

VARIABLE	BP depressed N=27
Age, mean ± SD, years	15.6 (1.4)
Race, N (%), Caucasian	23 (81)
Sex, N (%), female	23 (81)
ADHD, N (%)	13 (48)
Psychosis, N (%)	6 (22)
Remitters, N (%)	12 (44)

Patel, et al. (2006) *JAACAP*.

CDRS Score vs Time

Patel, et al. (2006) *JAACAP*.

Lamotrigine in Adolescent Bipolar Depression

- 20 subjects enrolled
- 8-week open study
- MRS/fMRI conducted at Baseline and Week 8
- Lamotrigine begun at 12.5 – 25 mg/day and titrated by 12.5 – 25 mg every 1-2 weeks
- Target dose = 100 - 200 mg/day
- Mean final dose = 132 (+/- 31) mg/day
- Response by CGI-C (1 or 2), CDRS-R (50% dec)

Chang et al., *J Amer Acad Child Adolesc Psychiatry* (2006) 45:298-304

Cohort Characteristics

Age	15.8 yrs (12-17)
Gender	7M/13F
Dx	
Bipolar I	7 (35%)
Bipolar II	6 (30%)
Bipolar NOS	7 (35%)
Comorbidities	
ADHD/ODD	13 (65%)
GAD	9 (45%)
Psychosis	3 (15%)

Chang et al., *J Amer Acad Child Adolesc Psychiatry* (2006) 45:298-304

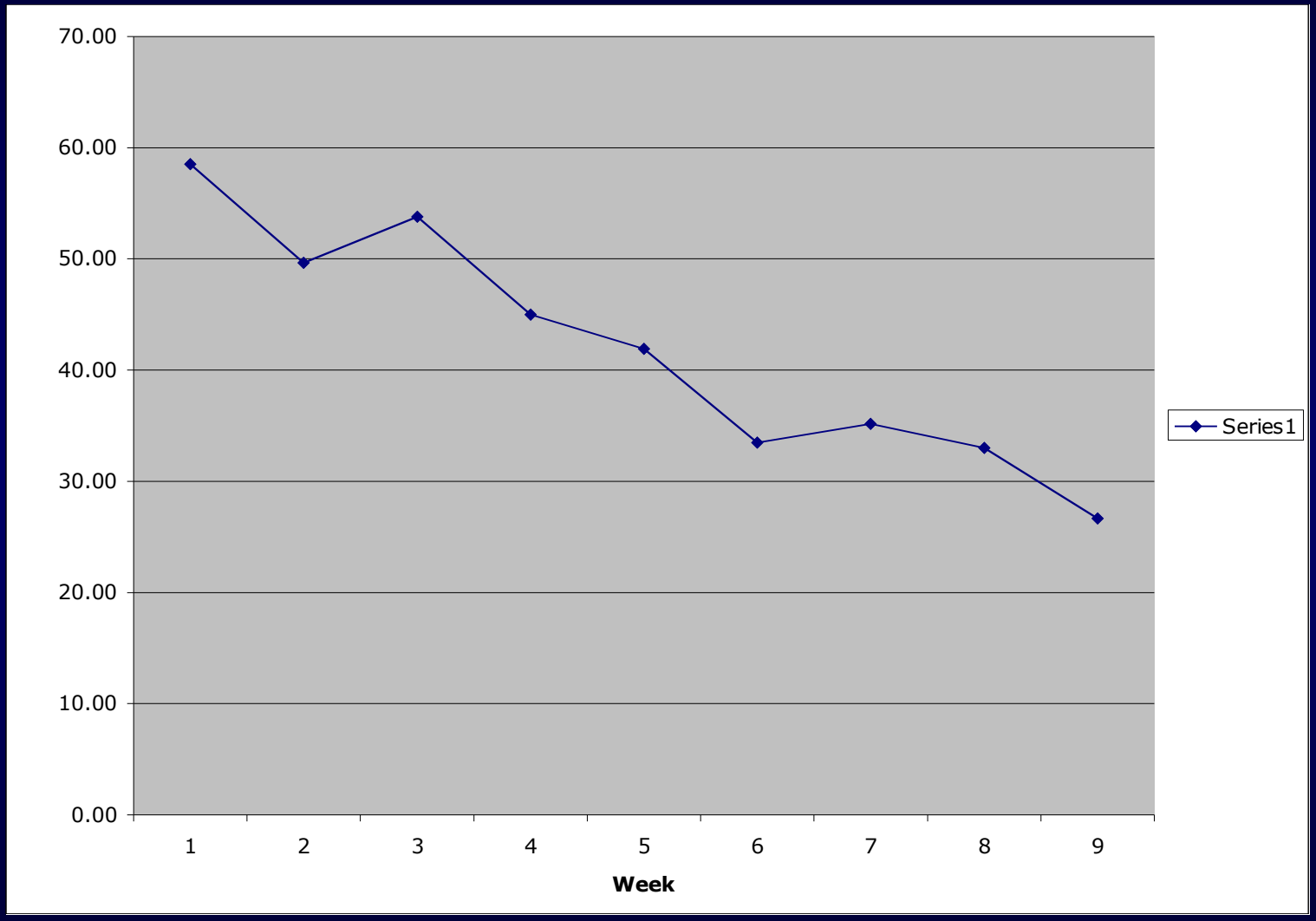
Results (Completed Subjects)

- One dropout, 19 completers
- 7 subjects with adjunct meds (2-DVPX, 1-ARI, 1-OLZ, 1-MPH, 1-ATX, 1- ALP, Li, 1-ATX, OROS-MPH, DVPX)

- Responders by CGI-C: 16/19 (84%)
- Responders by CDRS-R: 12/19 (63%)
- Remitters: 11/19 (58%)

Chang et al., *J Amer Acad Child Adolesc Psychiatry* (2006) 45:298-304

CDRS-R Score by Week



Chang et al., *J Amer Acad Child Adolesc Psychiatry* (2006) 45:298-304

Quetiapine vs. Placebo for Adolescent Bipolar Depression

- Design: DBPC, N=32, two-sites (UC & Stanford)
  - 8-weeks monotherapy (300-600mg/day, no changes after day 28)
  - BP I, current episode depressed
  - Inpatients or outpatients, ages 12-18 years
  - CDRS-R score $\geq$ 40, YMRS $\leq$ 12 (modified to 20)
  - March 2006-June 2007

DelBello, et al., *Bipolar Disord*, 2009

Outcome Measures

- Primary
  - Change in CDRS-R total scores from baseline to endpoint.
- Secondary
  - Change in HAM-A, YMRS, CGI-BP-S
- Response rate = $\geq$ 50% improvement CDRS-R from baseline and endpoint
- Remission rate = CDRS-R $\leq$ 28 & a Clinical Global Impression-Bipolar Disorder Version Improvement (CGI-BP-I) score for overall illness $\leq$ 2 at endpoint.

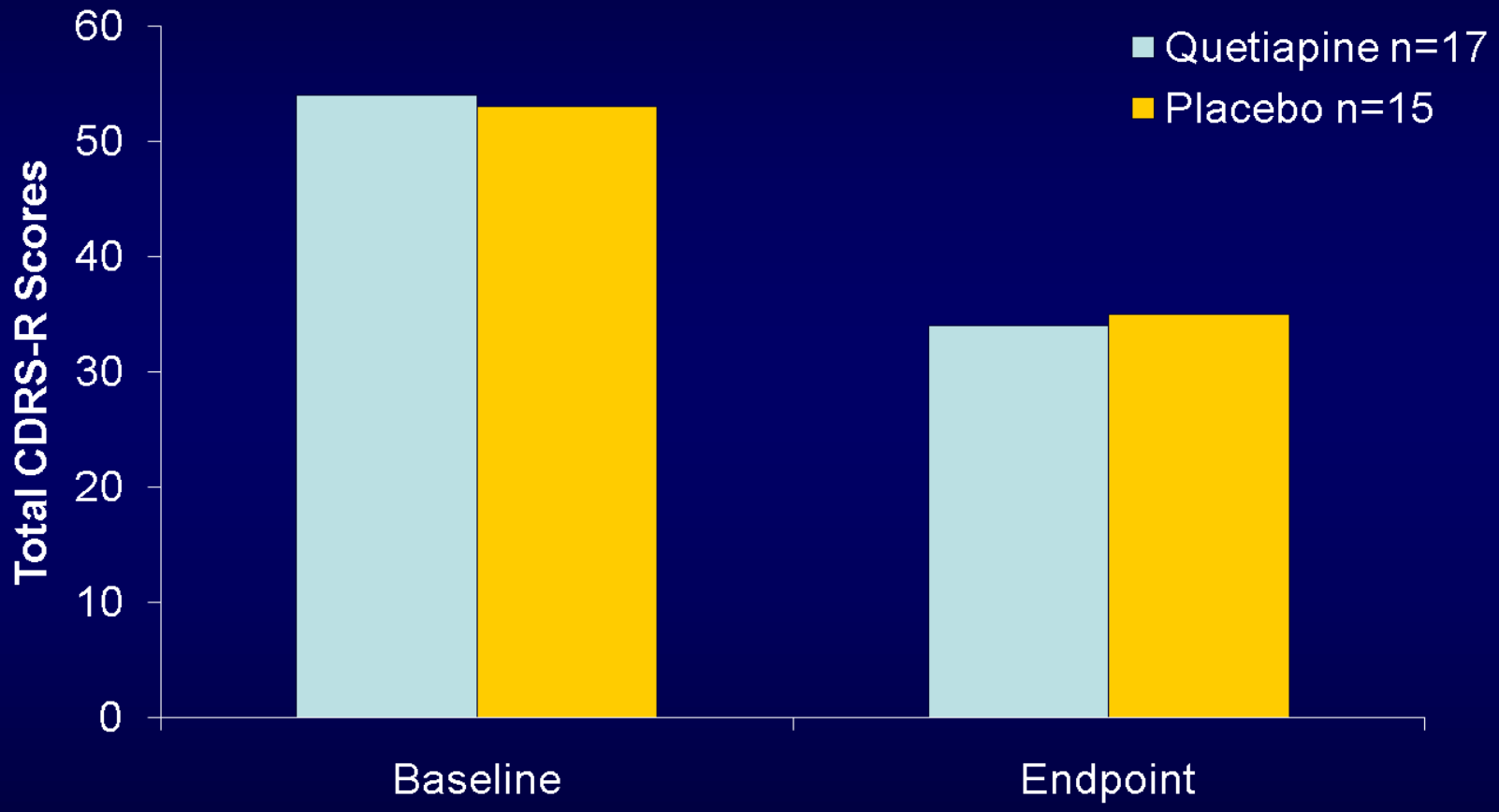
DelBello et al., *Bipolar Disord*, 2009

Demographic & Clinical Variables

Variable	Quetiapine (n = 17)	Placebo (n = 15)
Sex (female), n (%)	12 (71)	10 (67)
Age (years), mean (SD)	16 (2)	15 (2)
Race (white), n (%)	14 (82)	12 (80)
Length of current episode (weeks), mean (SD)	7 (2)	5 (4)
Age at onset of bipolar disorder (years), mean (SD)	12 (2)	11 (3)
Inpatient at enrollment, n (%)	7 (41)	8 (53)
Psychosis, n (%)	2 (12)	1 (7)
Attention-deficit hyperactivity disorder	2 (12)	2 (13)
Anxiety disorders	5 (29)	3 (20)
Disruptive behavior disorders	6 (35)	2 (13)

DelBello et al., *Bipolar Disord*, 2009

Change in CDRS-R from Baseline to Endpoint



Group difference, t=-0.14, df=30, p=0.89

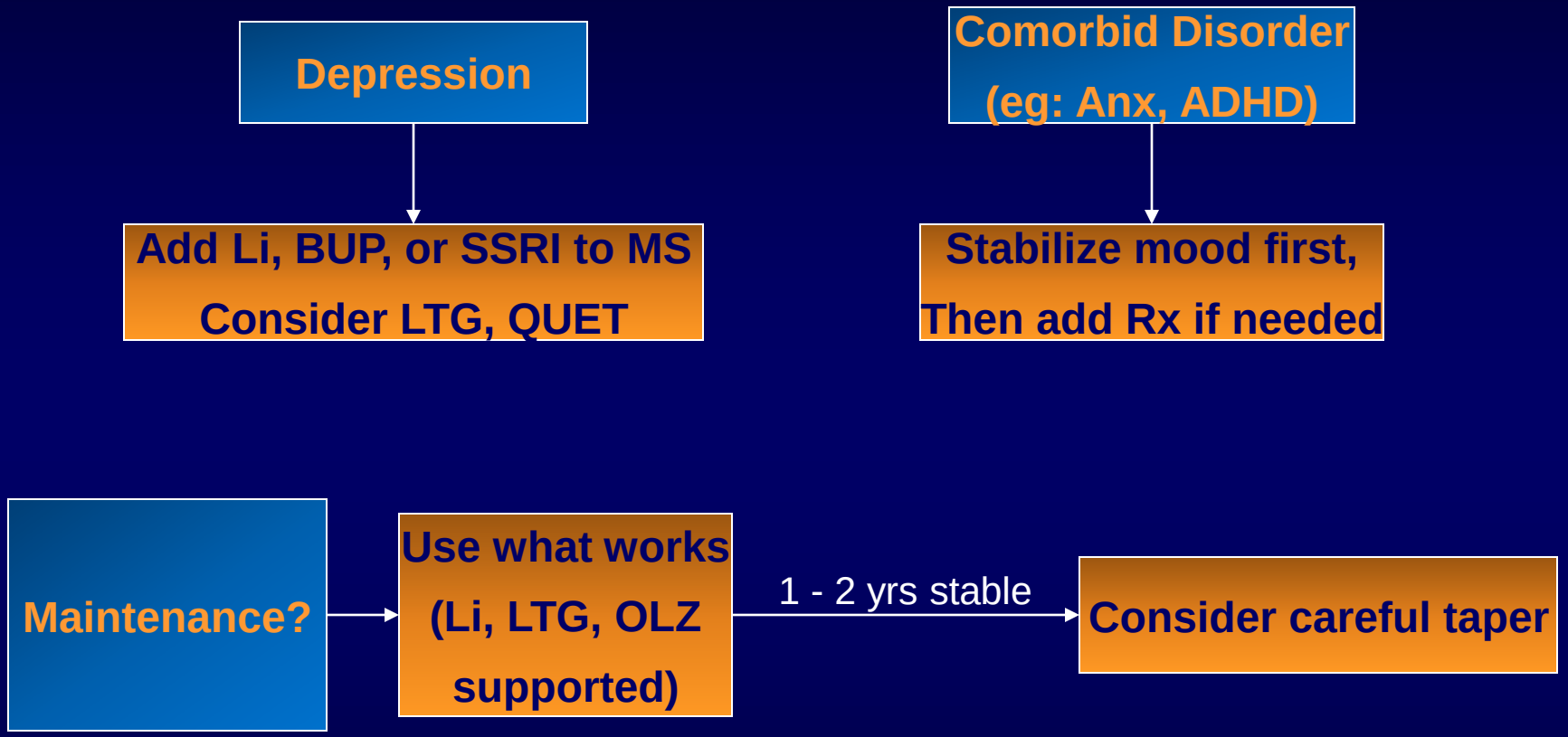
DelBello et al., *Bipolar Disord*, 2009

Secondary Outcome Measures: CDRS-R

- Response rates
  - Placebo = 67% (10/15)
  - Quetiapine = 71% (12/17), p=1.0
- Remission rates
  - Placebo = 40% (6/15)
  - Quetiapine = 35% (6/17), p=1.0.

DelBello et al., *Bipolar Disord*, 2009

Treatment Issues in Pediatric Bipolar Disorder



MS = mood stabilizer

Li = lithium, BUP = bupropion, SSRI = selective serotonin reuptake inhibitor, LTG = lamotrigine, OLZ = olanzapine, QUET = quetiapine

Adapted from Kowatch RA, et al. *J Am Acad Child Adolesc Psychiatry.* 2005;44:213-223.

Treating Depressive Symptoms in Adolescent Bipolar Disorder

- Check mood stabilizer levels, or increase dosage
- Add lithium
- Add lamotrigine
- Consider quetiapine
- Check TSH; if high, consider adding T_4
- Add/increase antidepressant—only if mood stabilizer on board!

Treating Depressive Symptoms in Bipolar Disorder (cont'd)

- Ensure adherence!
- Adolescents—no Accutane®!
- Consider hospitalization if severe
- If outpatient, decrease stress, optimize environment

Conclusions

- Definitive lithium data pending
- Valproate may be effective in higher serum levels, after longer treatment
- Antipsychotics demonstrating relatively high efficacy
- Remission should be goal of treatment
- Monotherapy is goal, but more often multiple medications is the reality

Conclusions

- Combination pharmacotherapy is an often necessary reality in treating pediatric BD
- Combinations should be logical, avoid redundancy
- Adjunctive atypical antipsychotics may speed up response
- Patients may need adjunctive stimulant therapy after mood stabilization
- Lamotrigine and lithium may be usefully adjunctively in bipolar depression

Bipolar Compounds on the Horizon

- Tamoxifen - PKC inhibitor, anti-glutamate
- Anti-glutamate: riluzole, amantadine - some efficacy in bipolar depression
- GABA-ergic
- VNS
- TMS
- New antipsychotics

Managing Adverse Effects of Medications

Kiki D. Chang, M.D.
Associate Professor
Stanford University School of Medicine

Lithium Adverse Effects

- Acne, psoriasis
- Weight gain
- Cognitive impairment
- Sedation, tremor, headache
- Gastrointestinal irritation
- Thyroid dysfunction
- Polyuria, polydipsia, enuresis
- Ebstein’s anomaly (1%)

Divalproex Adverse Effects

- Gastrointestinal irritation
- Thrombocytopenia (especially with levels > 100)
- Hepatic effects
  - Benign hepatic enzyme increases (common)
  - Hepatotoxicity (< 2 years age; with enzyme inducers)
  - Discontinue if LFTs > 3 x ULN
- Pancreatitis
- Neural tube defects (1%), cognitive delay
- Polycystic Ovarian Syndrome?

6-Month OL DVPX Trial in Mixed Mania (N=34)

Adverse Event	N (%)
Weight gain	20 (58.8)
Sedation	16 (47.1)
Increased appetite	16 (47.1)
Cognitive dulling	14 (41.2)
Nausea	9 (26.5)
Stomach pain	8 (23.5)
Agitation	6 (17.6)
Tremors	5 (14.7)

OL = open label; Mean age: 12.3 years; Mean weight gain: 5.6 ± 4.3 =~1 SD or ↑ from 50-70th BMI percentile; Pavuluri MN et al. (2005), Bipolar Disord 7(3):266-273

Polycystic Ovarian Syndrome

- First reported in female epilepsy population on valproate
- 80% of PCO cases treated before 20 y.o.
- May be secondary to obesity, hyperandrogenism
- Treat as any other side effect
- Avoid valproate use in adolescents females with risk factors for PCO

Carbamazepine Adverse Effects

- Leukopenia
  - Benign (1/10)
  - Aplastic anemia (1/100,000)
  - Discontinue if WBC < 3K, neutrophils < 1K
- Rash
  - Benign (1/10)
  - Stevens-Johnson(1/100,000)
  - Discontinue if any rash

Atypicals and EPS

- Less frequent than with typicals, but still happens
  - Reduce dose, add benztropine, or change to a different atypical agent
- Akathisia
  - Above measures; may need to add clonazepam or propranolol
- If anti-EPS agent used, attempt taper over several weeks to avoid anticholinergic side effects

Lamotrigine: Side Effects

- Sedation, ↓ concentration
- Mild weight gain: ↓ weight in adult bipolar studies
- Non-serious rash: 10% risk
  - ↑ risk with Valproate cotreatment; ↓ age; ↑ dose rate
- Serious rash
  - Adults with bipolar and other mood disorders
    - 0.08% (monotherapy); 0.13% (adjunctive therapy)
  - Adults with epilepsy: 0.3% (adjunctive therapy)
  - Patients <16 years with epilepsy: 0.8% (adjunctive Rx)

Package insert. Available at: www.accessdata.fda.gov

Lamotrigine - Risk of Rash

- Higher past incidence of rash due to
  - Higher initial dosing and faster titration[1]
  - Concomitant VPA administration[1,2]
  - Definition of serious rash including any rash leading to discontinuation from trial[2]
- Regular tabs available in 25 mg, 100 mg, 150 mg, 200 mg
- Chewable tabs in 2 mg, 5 mg, 25 mg
- Antigen precautions

[1]Dooley, J, et al (1996) *Neurology* 46:240-242
[2] Messenheimer, J (2002) *J Child Neurology* 17:2S34-42

Stanford Antigen Precautions

- During the initial 3 months: NO other new medicines or new foods, cosmetics, conditioners, deodorants, detergents, or fabric softeners
- Do not start lamotrigine within two weeks of having a rash, viral syndrome, or vaccination
- Avoid sunburn or poison oak exposure
- Any patient developing a rash accompanied by eye, mouth, or bladder discomfort -> ER
- Rashes with more benign presentations must be seen as soon as possible

Lamotrigine - Dosing[1]

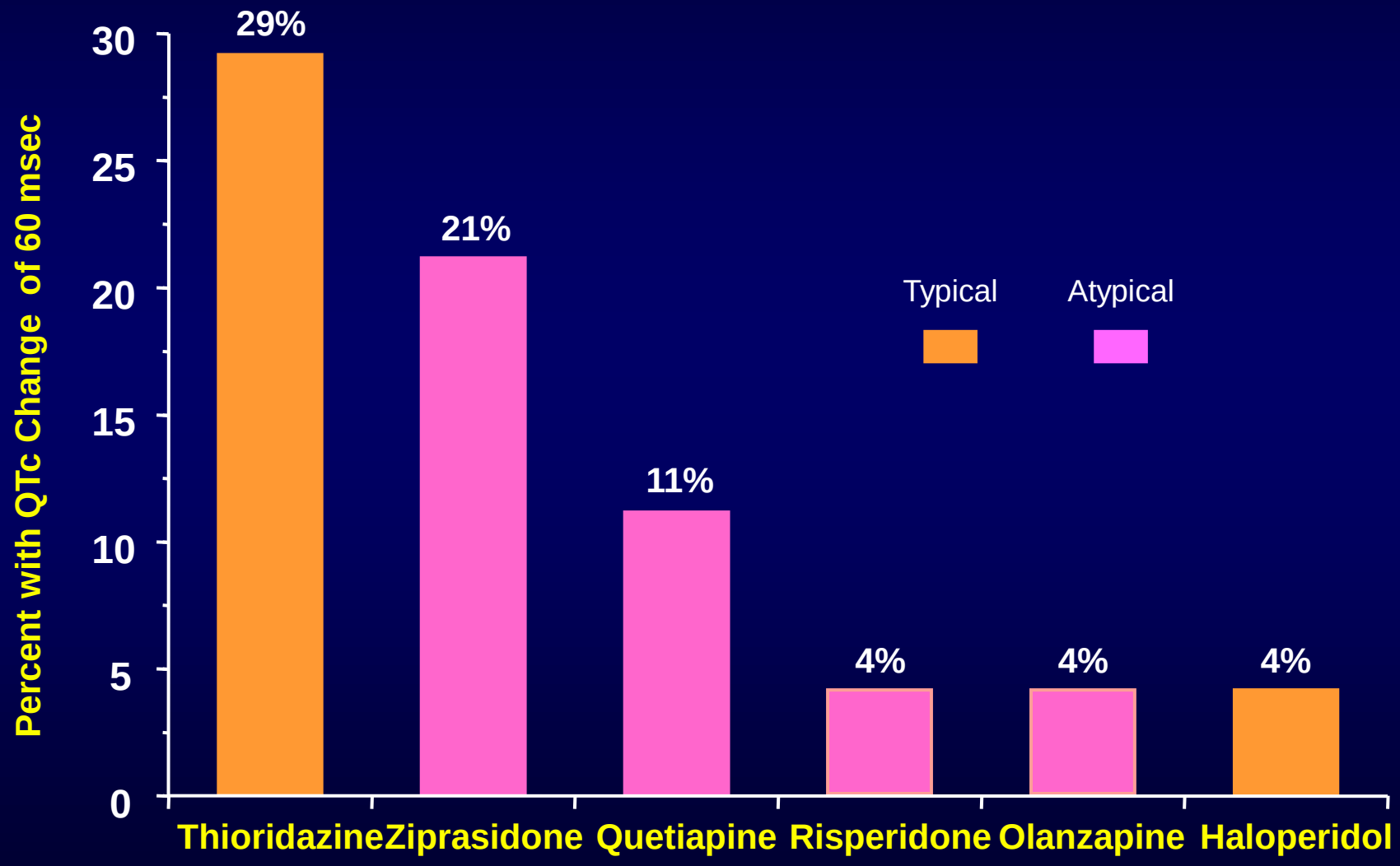
	Wk 1-2	Wk 3-4	Maintenance
Adults/adol :	25 mg	50mg	100-200mg/day
(> 12 yrs)			
+ VPA	1/2 x the dose		
+ Carb	2 x the dose		
Children :	0.6 mg/kg	1.2 mg/kg	1-5 mg/kg/day
(< 12 yrs)			
+ VPA	0.2 mg/kg	0.5 mg/kg	1-5 mg/kg/day
+ Carb	2 mg/kg	5 mg/kg	5-15 mg/kg

[1]**Guberman, AH, et al (1999) *Epilepsia* 40:985-91**

Atypical Antipsychotics: Potential Adverse Effects

- Sedation
- GI effects
- Hyperprolactinemia
- Extrapyramidal symptoms (EPS)
- Neuroleptic malignant syndrome (NMS)
- Weight gain
- Metabolic syndrome

Antipsychotic-Induced QTc Prolongation



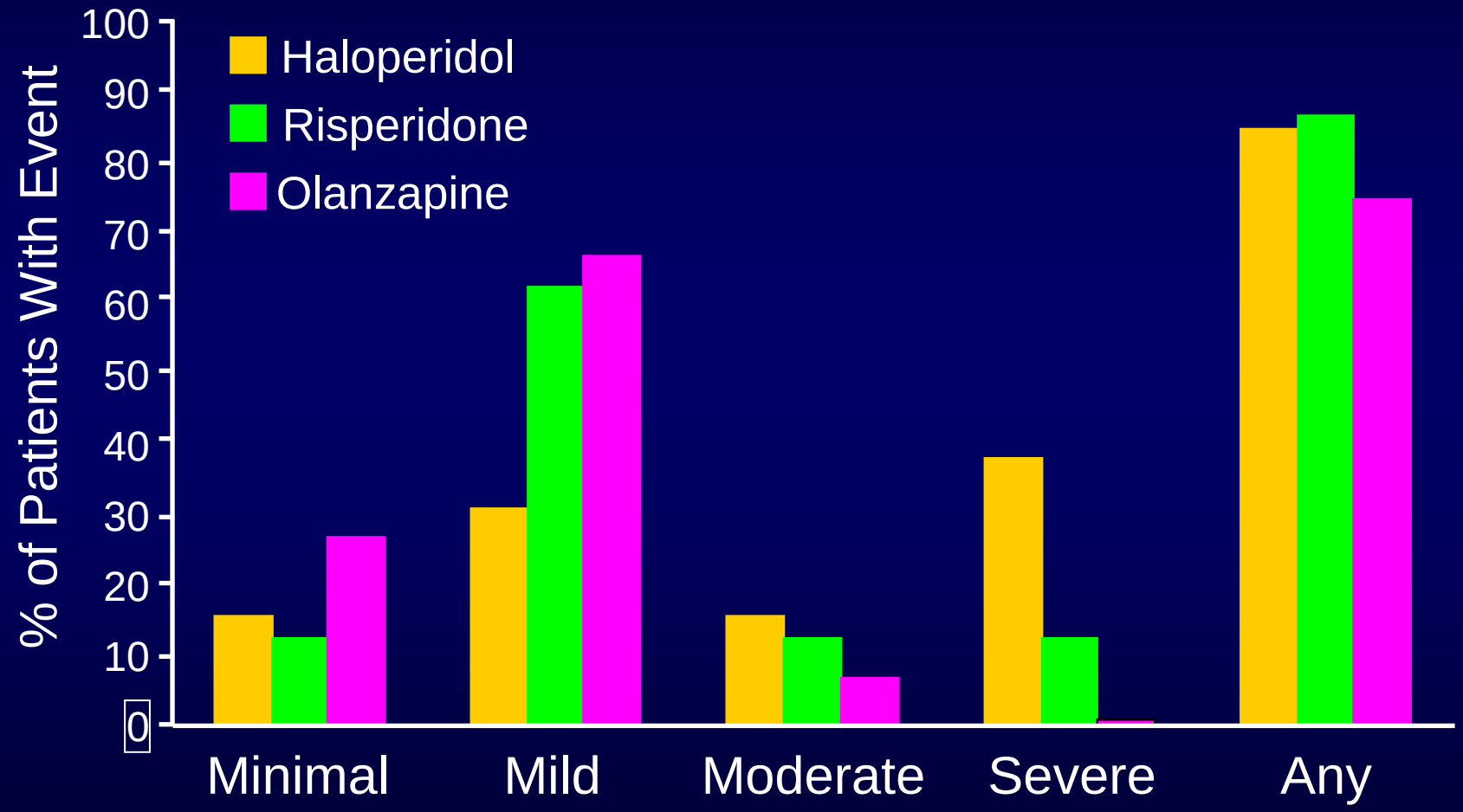
Adapted from: FDA Background on Ziprasidone 2000:5.

Relative Potency of Antipsychotics in Elevating Serum Prolactin (PRL)

- Risperidone > haloperidol > olanzapine > ziprasidone > quetiapine > clozapine > aripiprazole
- Aripiprazole has partial D2-DA agonist activity, and may suppress PRL below baseline levels

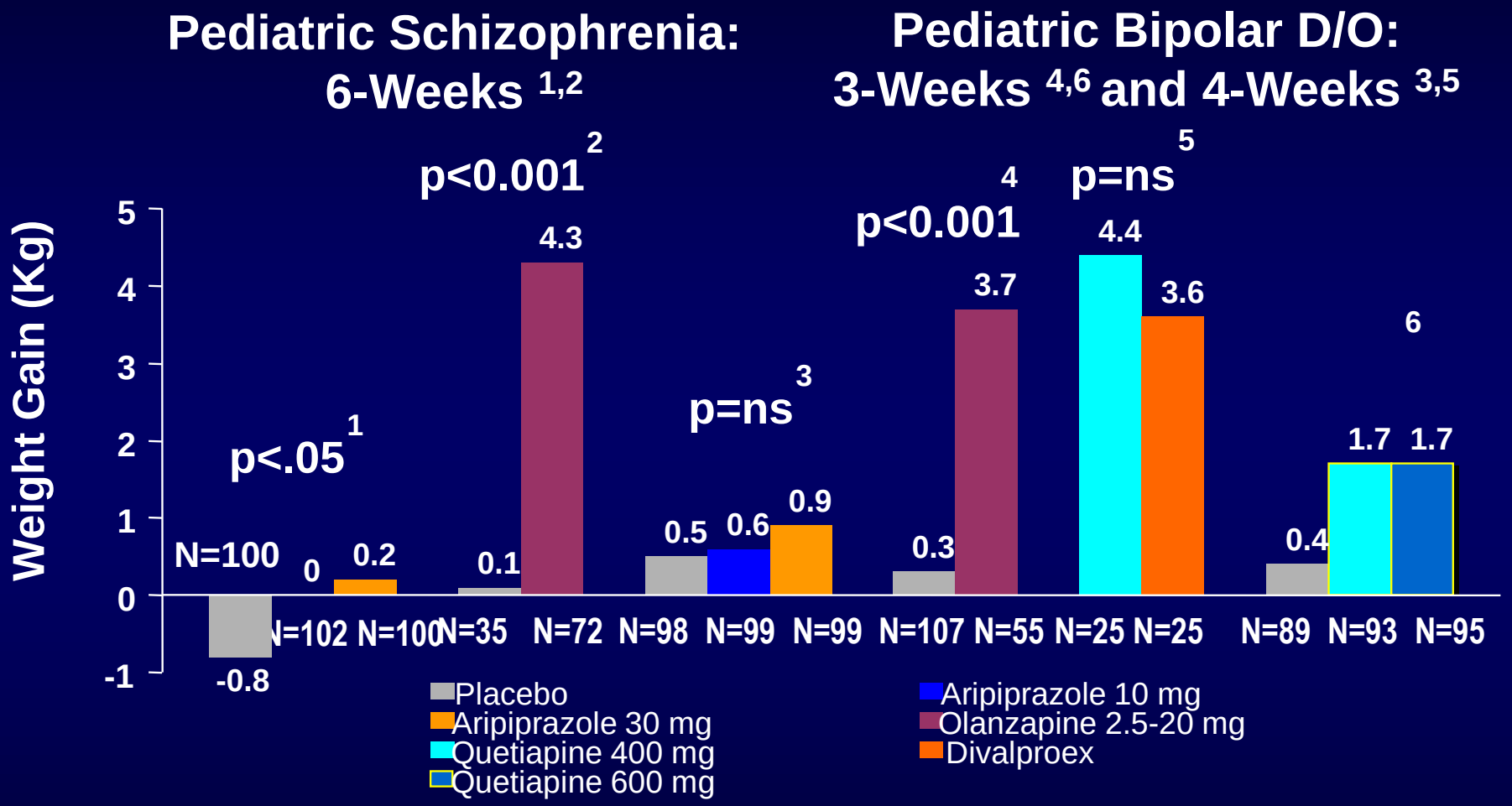
Correll CU, Carlson. *J Am Acad Child Adolesc Psychiatry*. 2006;45(7):771-791

Incidence and Severity of EPS with Antipsychotics in Psychotic Youth



Sikich L et al. Neuropsychopharmacology 2006;29(1):133-145

Weight Gain in in Pediatric Schizophrenia & Bipolar



[1] Findling RL et al., Poster presented at the APA meeting 2007, San Diego, CA; [2] Kryzhanovskaya L et al. Poster presented at ACNP meeting 2005, Waikoloa Beach, HI; [3] Correll CU et al., Poster presented at the AACAPP meeting 2007, Boston, MA;

[4] Tohen M et al. (2007), *Am J Psychiatry* 164(10):1547-56; [5]DelBello MP et al., *J Am Acad Child Adolesc Psychiatry*. 2006;45:305-13; [6] DelBello M et al., Poster presented at the AACAPP meeting 2007, Boston, MA.

Conclusions

- All medications have potential for adverse effects
- Maximize dose of single medication to avoid polypharmacy
- Obtain baseline laboratories, measures
- Use preventative measures (diet, exercise)
- Use rational combination treatment
- Emergencies: SJS, NMS

Question 1

Which of the following psychiatric disorders is most commonly comorbid with pediatric bipolar disorder:

- A) ADHD
- B) Conduct disorder
- C) Childhood schizophrenia
- D) Alcohol dependence
- E) Obsessive compulsive disorder

Question 2

The mood stabilizer that has been approved by FDA for treatment of bipolar disorder in adolescents is:

- A) Valproate
- B) Carbamazepine
- C) Lithium
- D) Oxcarbazepine
- E) Lamotrigine

Question 3

Which of the following is not a risk factor for SSRI induced manic episode in children?:

- A) Family history of bipolar disorder
- B) Psychomotor retardation
- C) Atypical depression
- D) Chronic, insidious onset
- E) Short allele of SERT gene

Answers

- 1 - A
- 2 - C
- 3 - D