

# The Use of Medications for Pediatric Bipolar Disorder

Kiki D. Chang, M.D.

Associate Professor

Stanford University School of Medicine

# 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

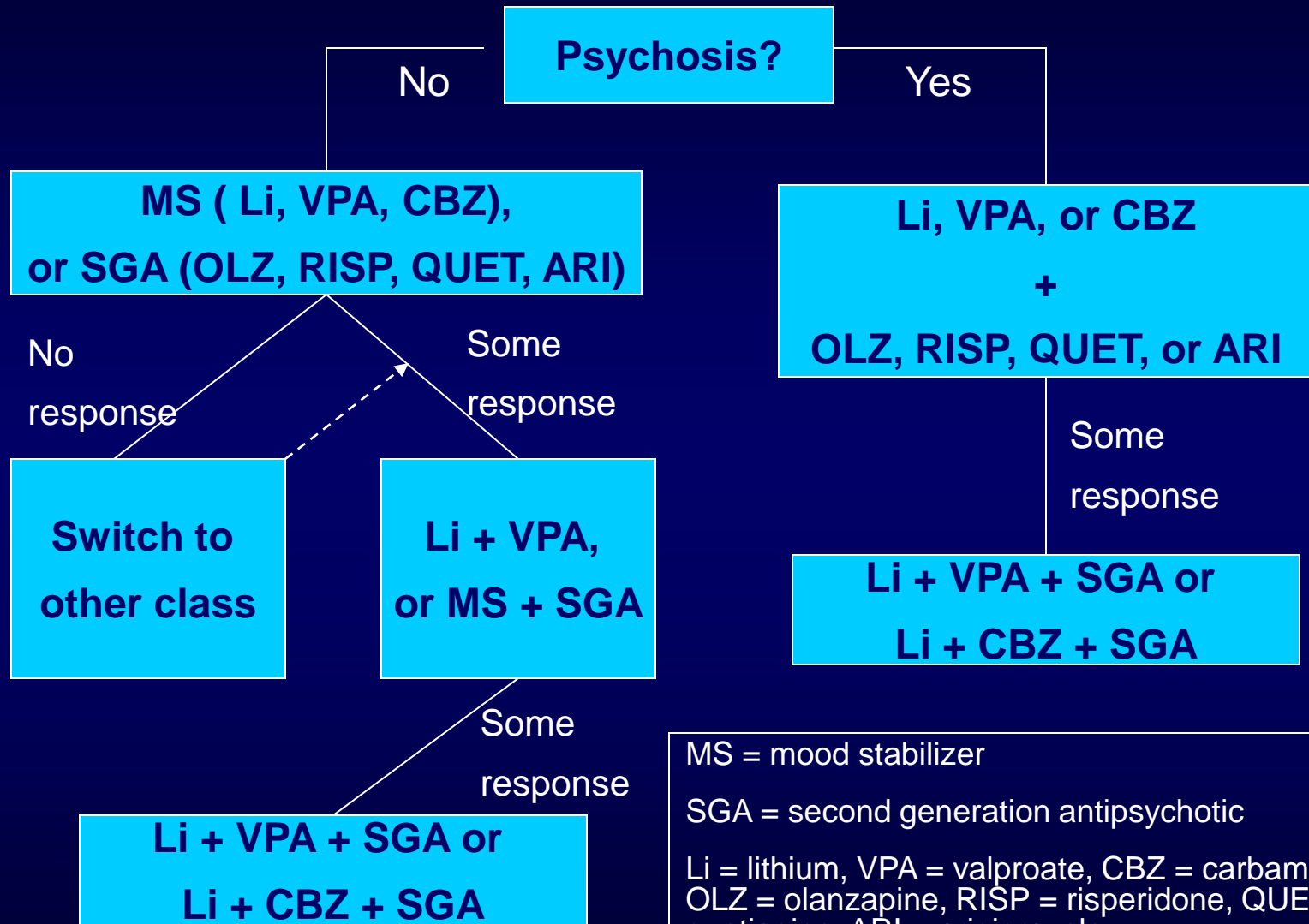
- Modafinil

- Alpha-2 agonists (clonidine, guanfacine)

## Anxiolytics

- Benzodiazepines (clonazepam, lorazepam, etc)

# Treatment of Acute Mania in Pediatric Bipolar Disorder



MS = mood stabilizer  
SGA = second generation antipsychotic  
Li = lithium, VPA = valproate, CBZ = carbamazepine,  
OLZ = olanzapine, RISP = risperidone, QUET =  
quetiapine, ARI = aripiprazole



# 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

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- 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

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- Adverse effects

	<u>DVPX</u>	<u>PLACEBO</u>
– 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](http://www.clinicalstudyresults.org/drugdetails/?company_id=1&sort=c.company_name&page=1&drug_id=1561). Accessed Aug. 20, 2007

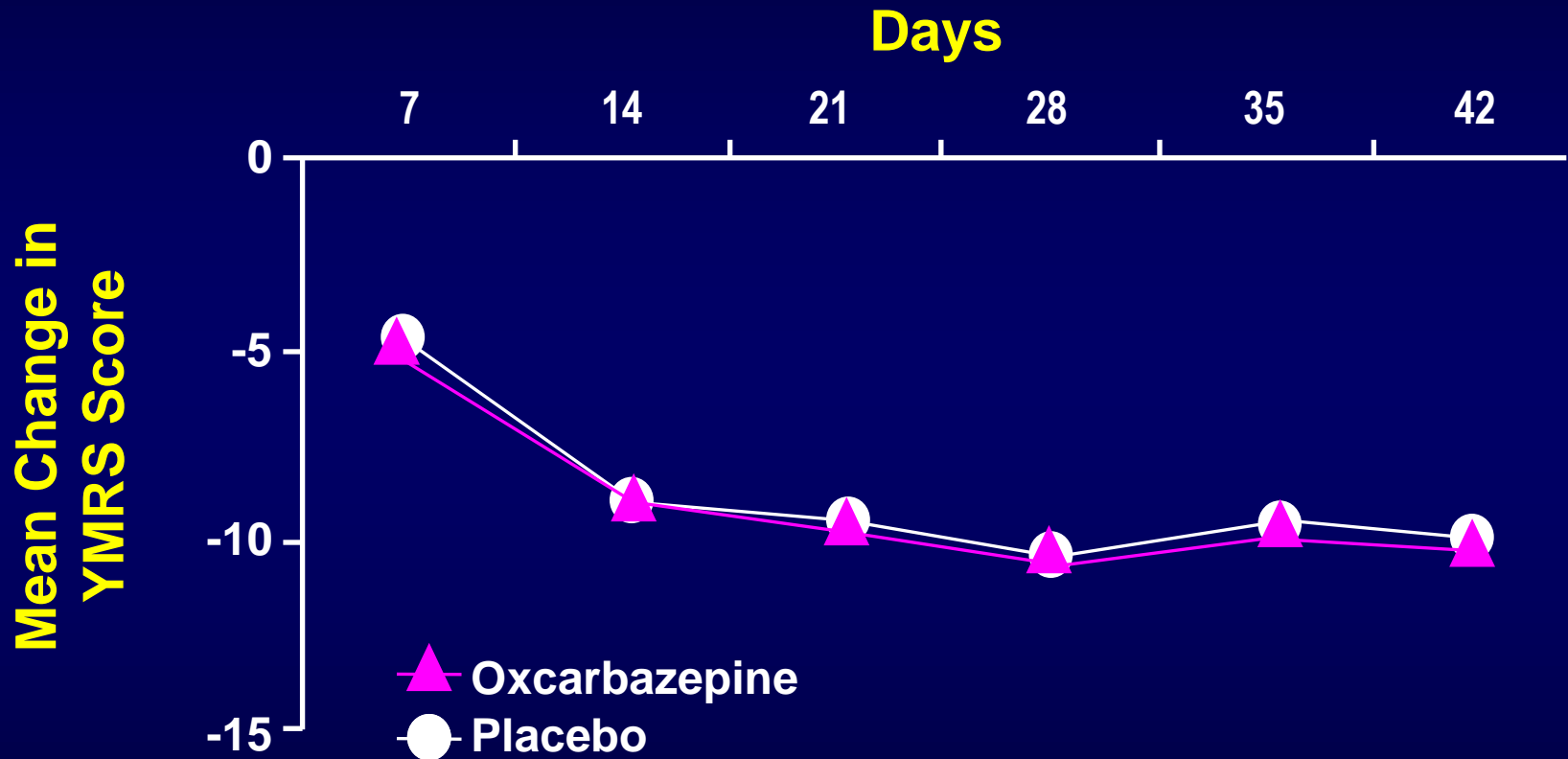
# Oxcarbazepine in Pediatric BD

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- 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:

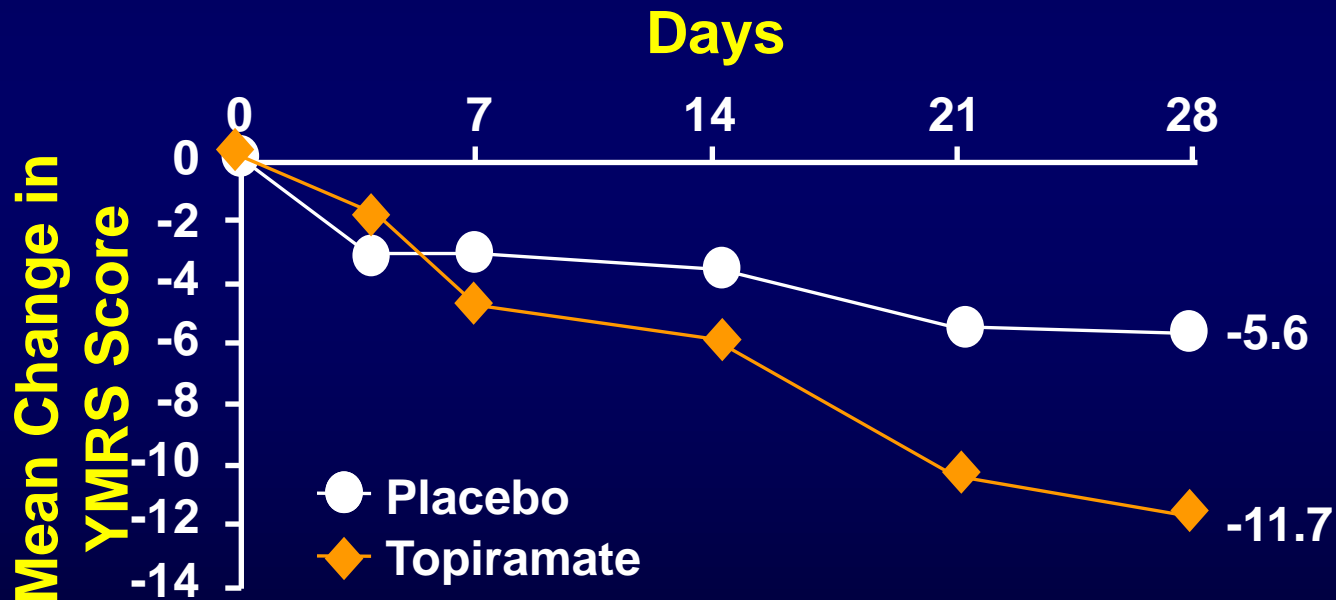
	<u>OXC</u>	<u>PLACEBO</u>	<u>p</u>
– Children	41%	17%	.029
– Adolescents	43%	40%	.86

# Oxcarbazepine in Pediatric BD



# Topiramate for Pediatric Bipolar I Disorder

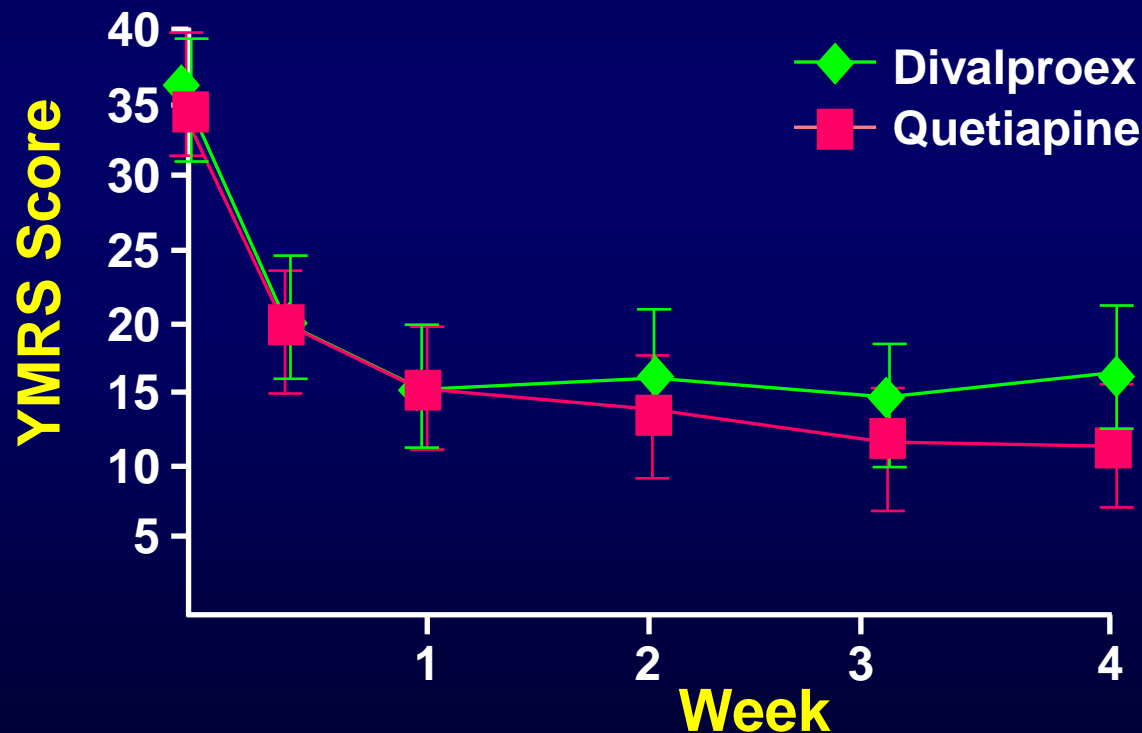
- 56 youths, ages 6-17, with bipolar I disorder, manic or mixed episodes
- Mean topiramate dose: 278 mg/day





# 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  $\mu\text{g/mL}$ ) for 4 weeks



# Omega-3 Fatty Acids in Pediatric BD

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- 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

# Omega-3 Fatty Acids in Pediatric BD

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- 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

# FDA Indications in Children

## Feb 2010

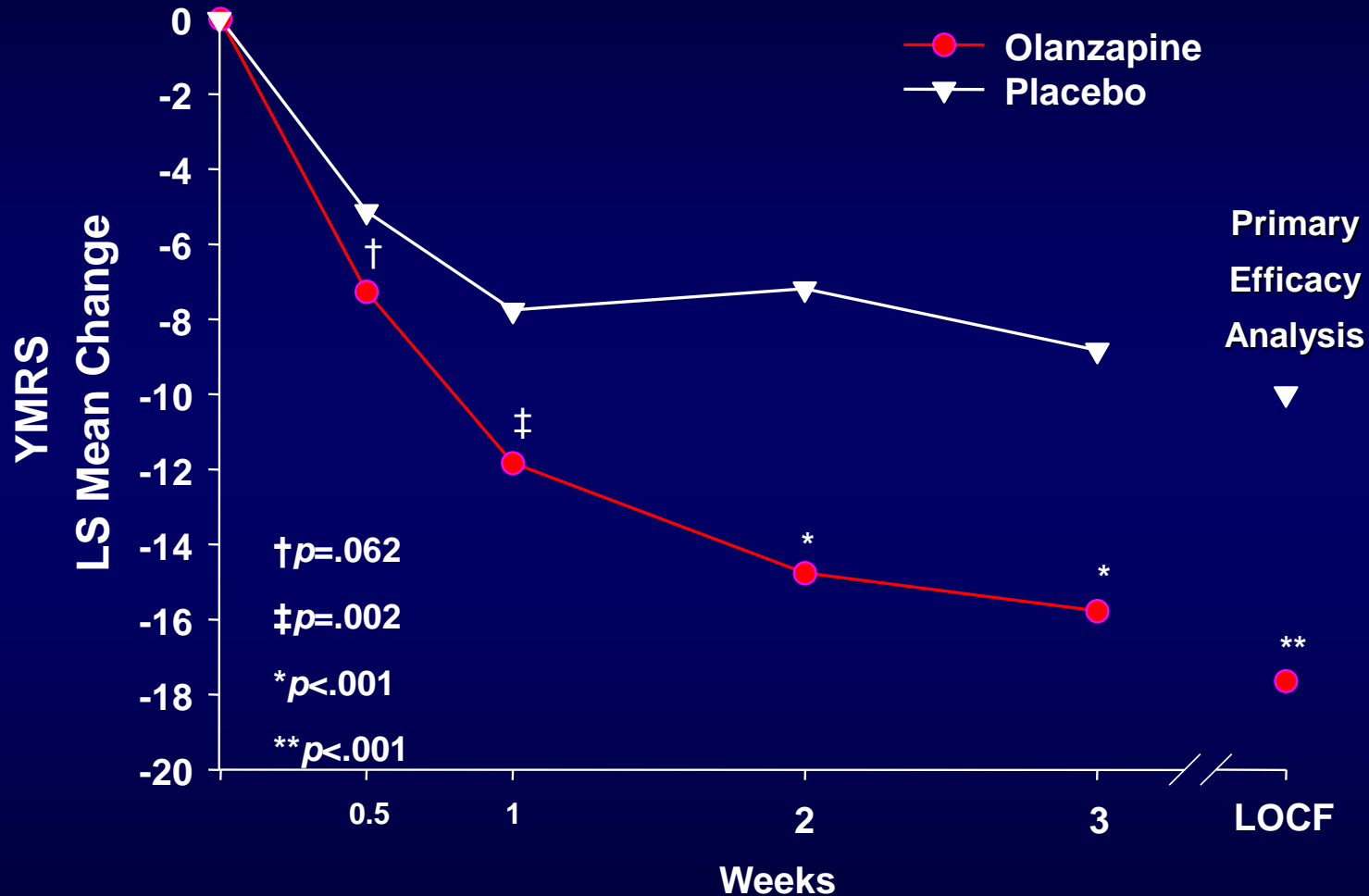
	<b>Bipolar Disorder (10-17 yo)</b>	<b>Schizophrenia (13-17 yo)</b>	<b>Irritability in Autism</b>
Clozapine			
Olanzapine	X (13-17 yo)	X	
Risperidone	X	X	X (5-16 yo)
Quetiapine	X	X	
Ziprasidone			
Aripiprazole	X	X	X (6-17 yo)
Paliperidone			
Asenapine			

# Olanzapine in Pediatric Bipolar Disorder

## Methods

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

# YMRS Change from Baseline: Olanzapine vs. Placebo



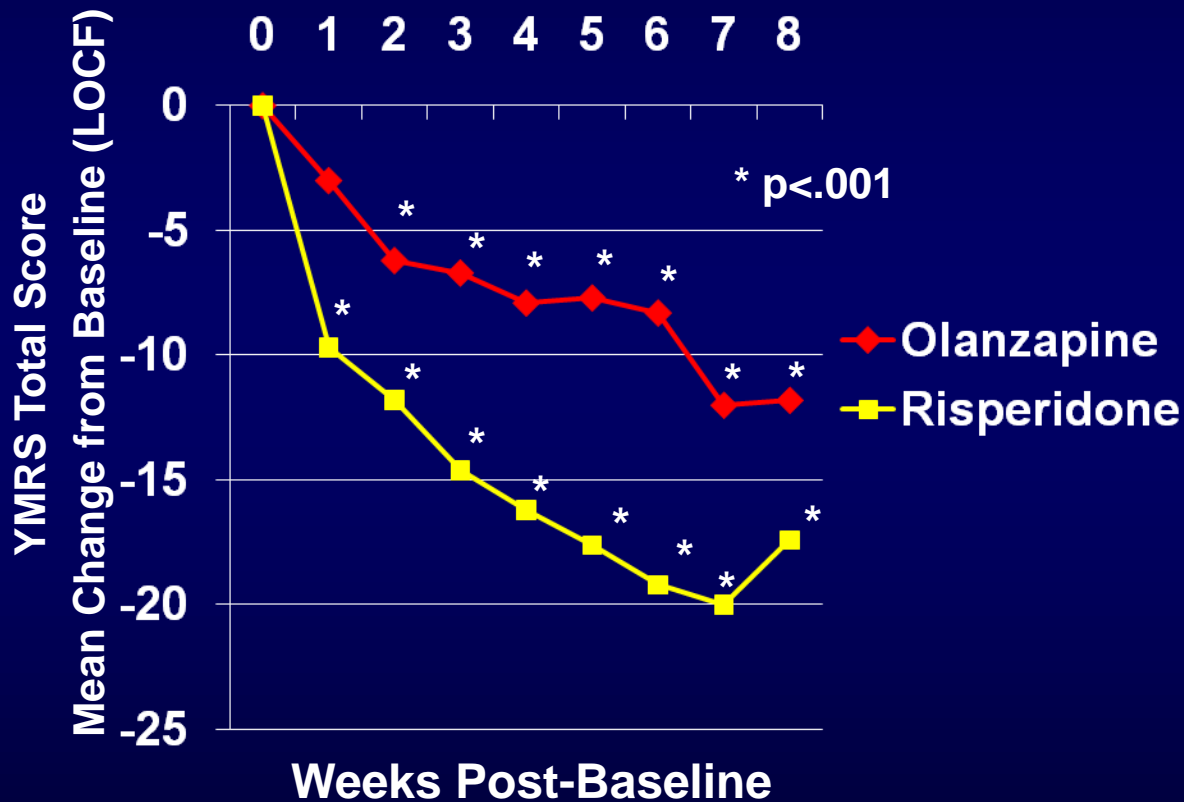
\* † Mixed ANCOVA Model: Change = Baseline Therapy Country Visit Therapy\*Visit.

\*\*TYPE III sum of Squares from ANCOVA: Model= Baseline Country Therapy.

# 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  $\leq 3$ )
- Weight gain =  $7.5 \pm 6.8$  kg
- $\geq 7\%$  inc in weight = 69%
- Inc prolactin = 71%

# 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)



# 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  $\leq 2$
- 70% responders (50% if using 50% criteria)
- Remission in 23% (YMRS < 10, CDRS < 29)
- YMRS: 28.0  $\rightarrow$  13.5
- Weight gain = 2.2 kg
- Prolactin = 4-fold elevation

# 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)

# 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.

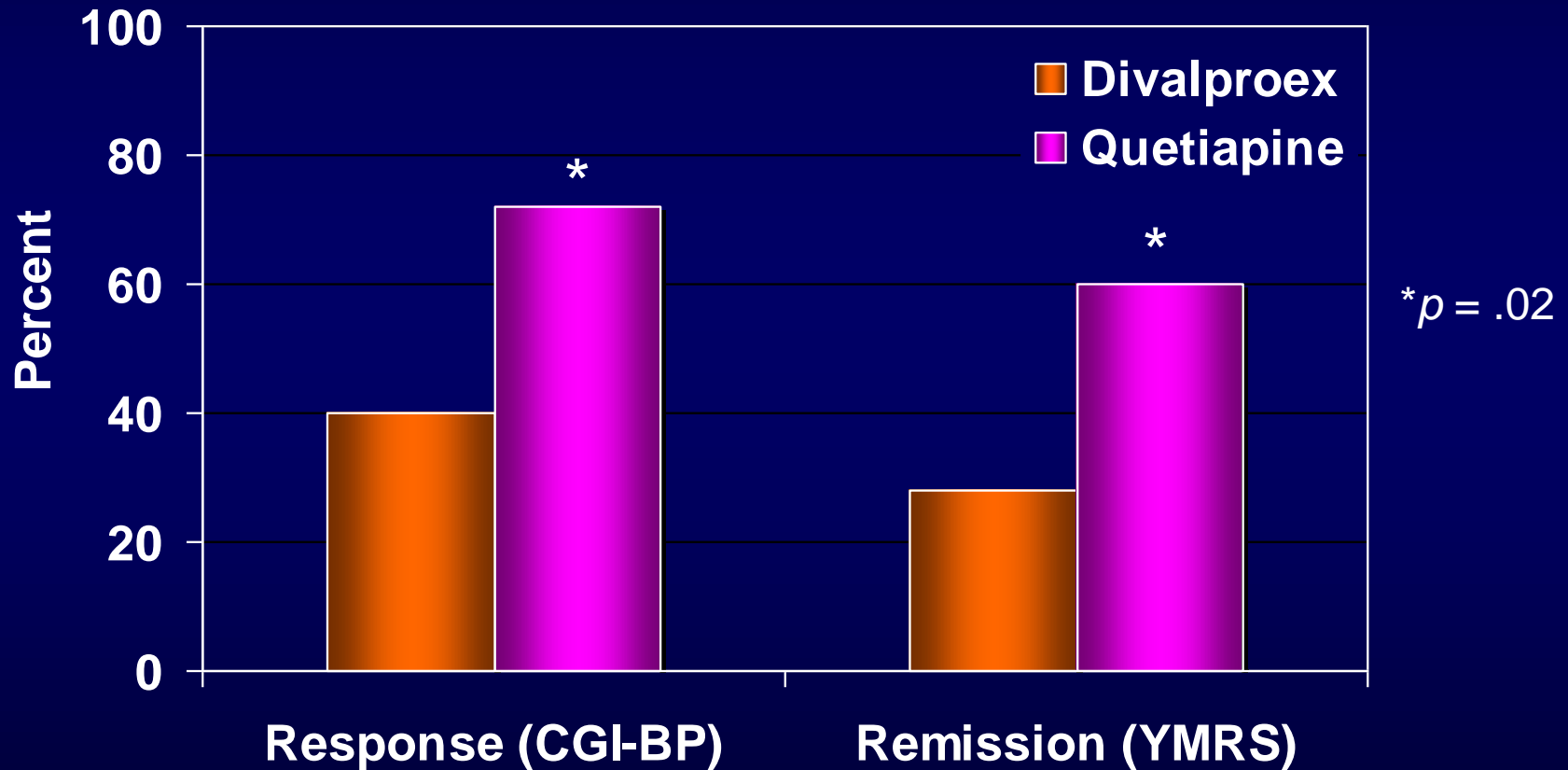
Available at: <http://www.fda.gov/bbs/topics/NEWS/2007/NEW01686.html>.

# Quetiapine vs. Divalproex in Pediatric Mania

- 50 adolescent ( $15 \pm 2$  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
  - $4.4 \pm 5.0$  kg (QUE) vs.  $3.6 \pm 6.0$  kg (DVP)

# Quetiapine vs. Divalproex in Pediatric Mania Response Rates

Response: CGI-BP-Improvement = 1 or 2  
Remission: YMRS  $\leq$  12



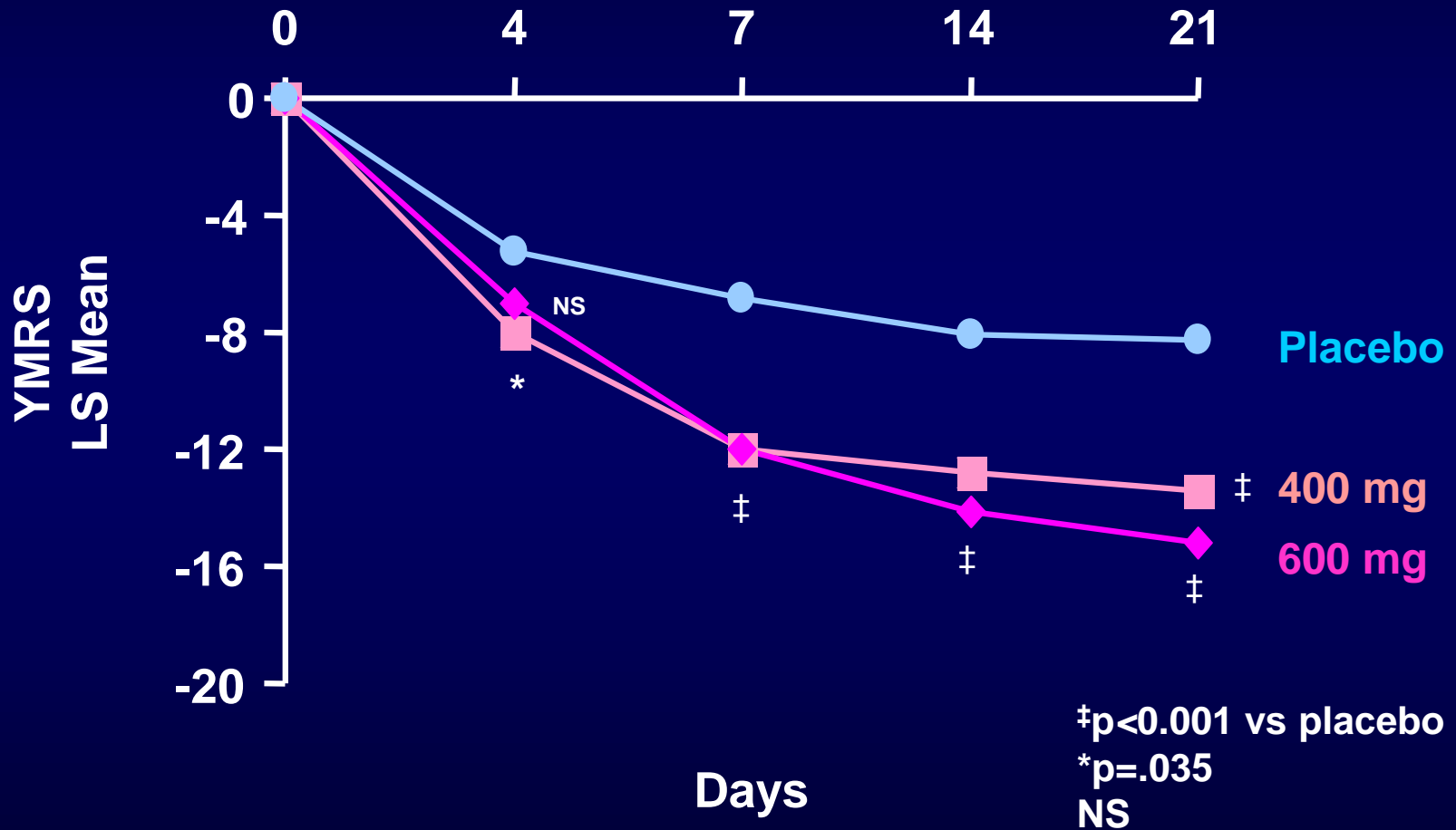
$\chi^2 = 4.7, df=1, p=0.03$

# 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

# YMRS Change from Baseline: Quetiapine vs. Placebo



# 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



# 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

# 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

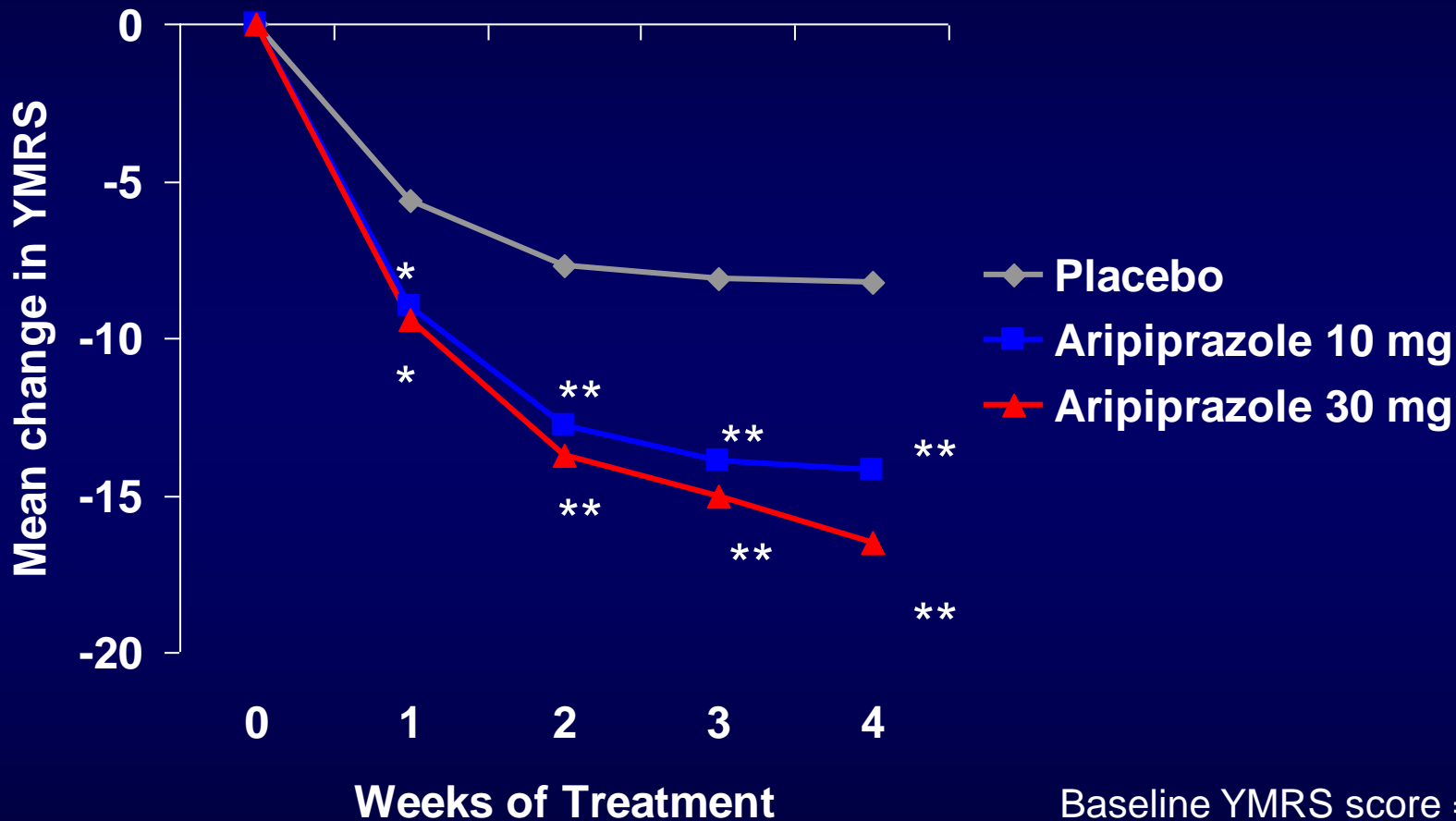
Dosing Schedule	Day						
	1	3	5	7	9	11	13
Low Dose, mg/day	2	5	10	10	10	10	10
High Dose, mg/day	2	5	10	15	20	25	30

# Aripiprazole for Pediatric Mania

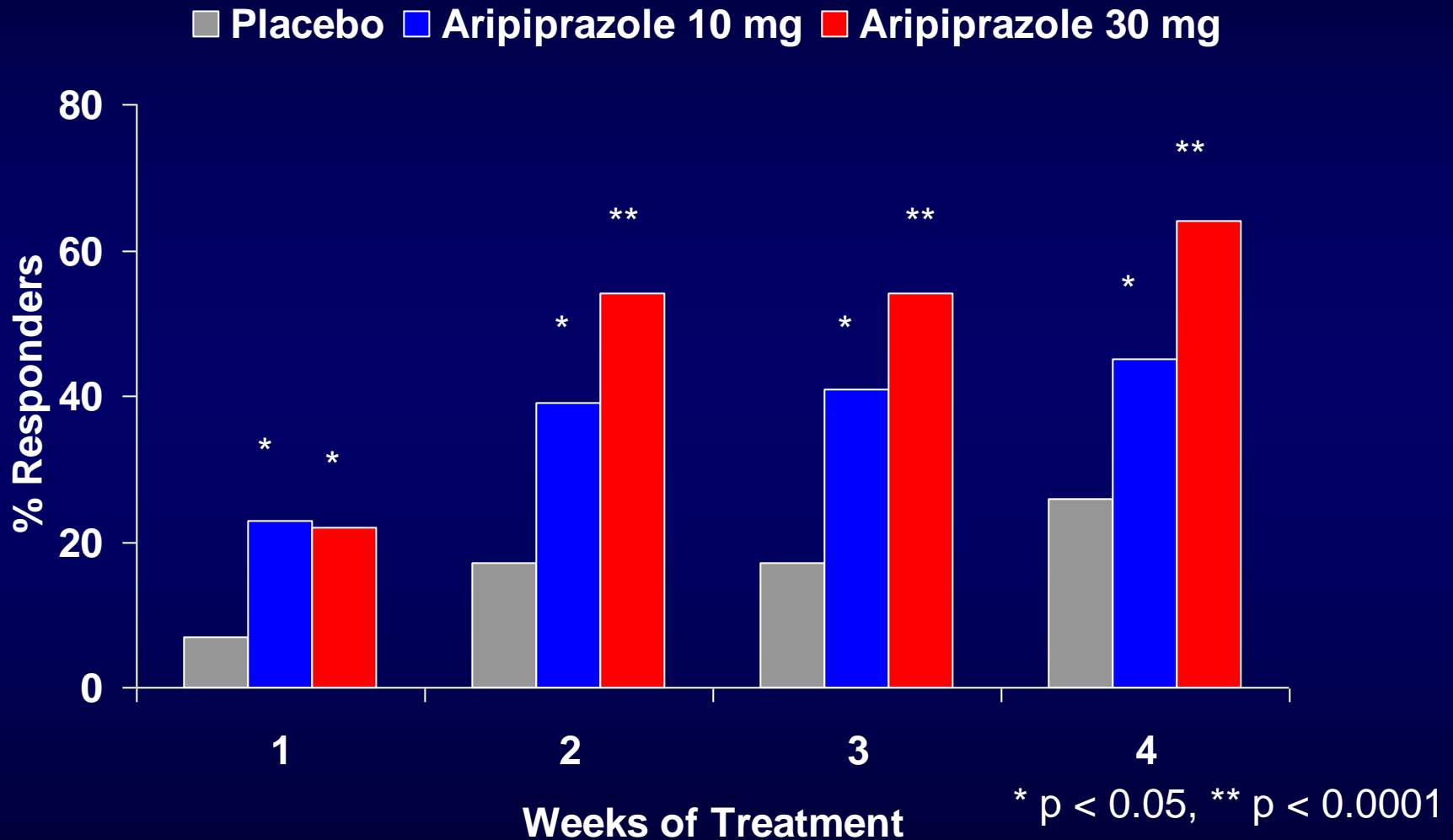
## Results

- 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  $\geq 7\%$  gain in body weight

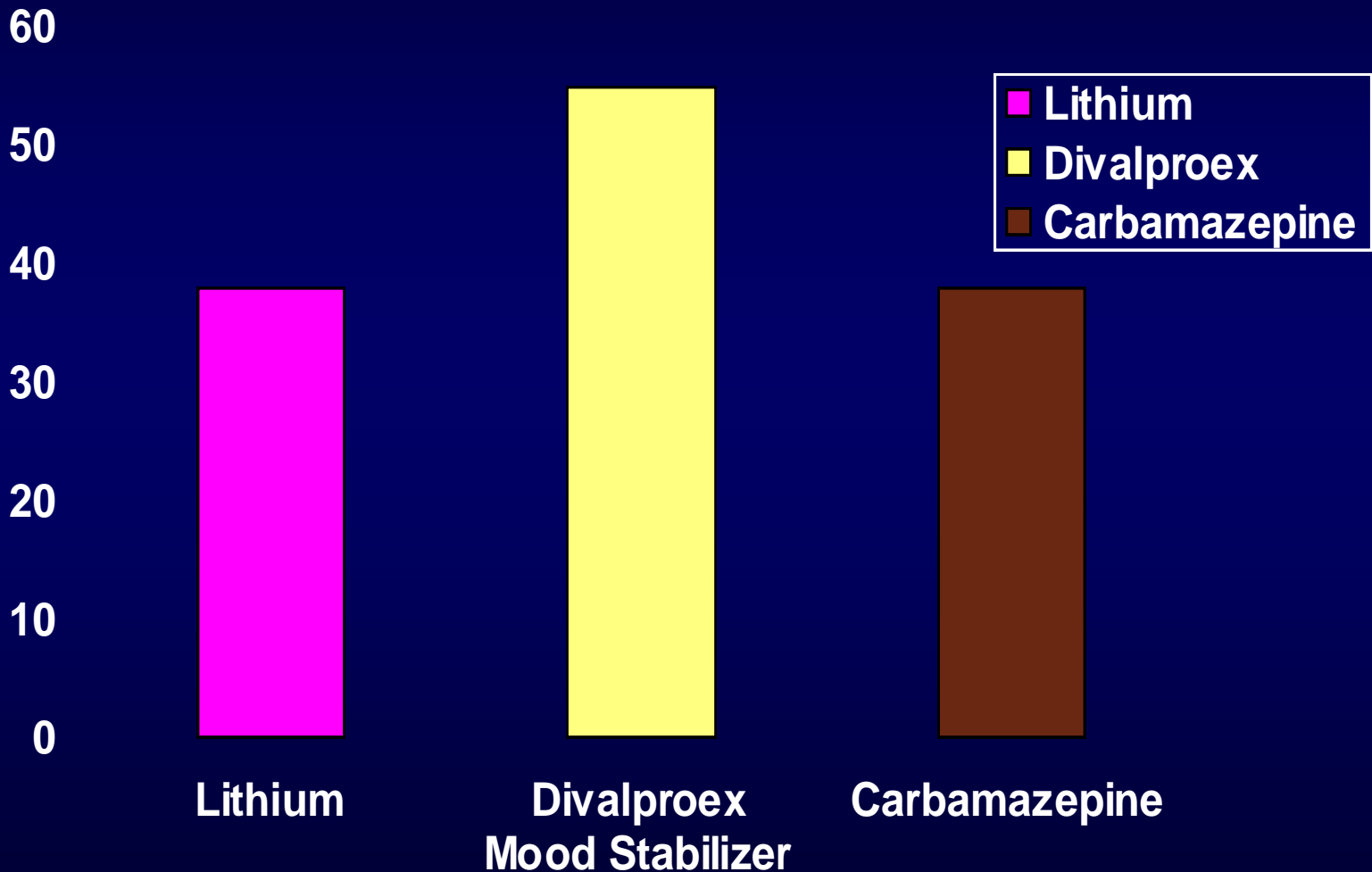
# Primary Endpoint: Mean Change in YMRS Score (LOCF)



# Response Rate (LOCF)



# 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

# 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

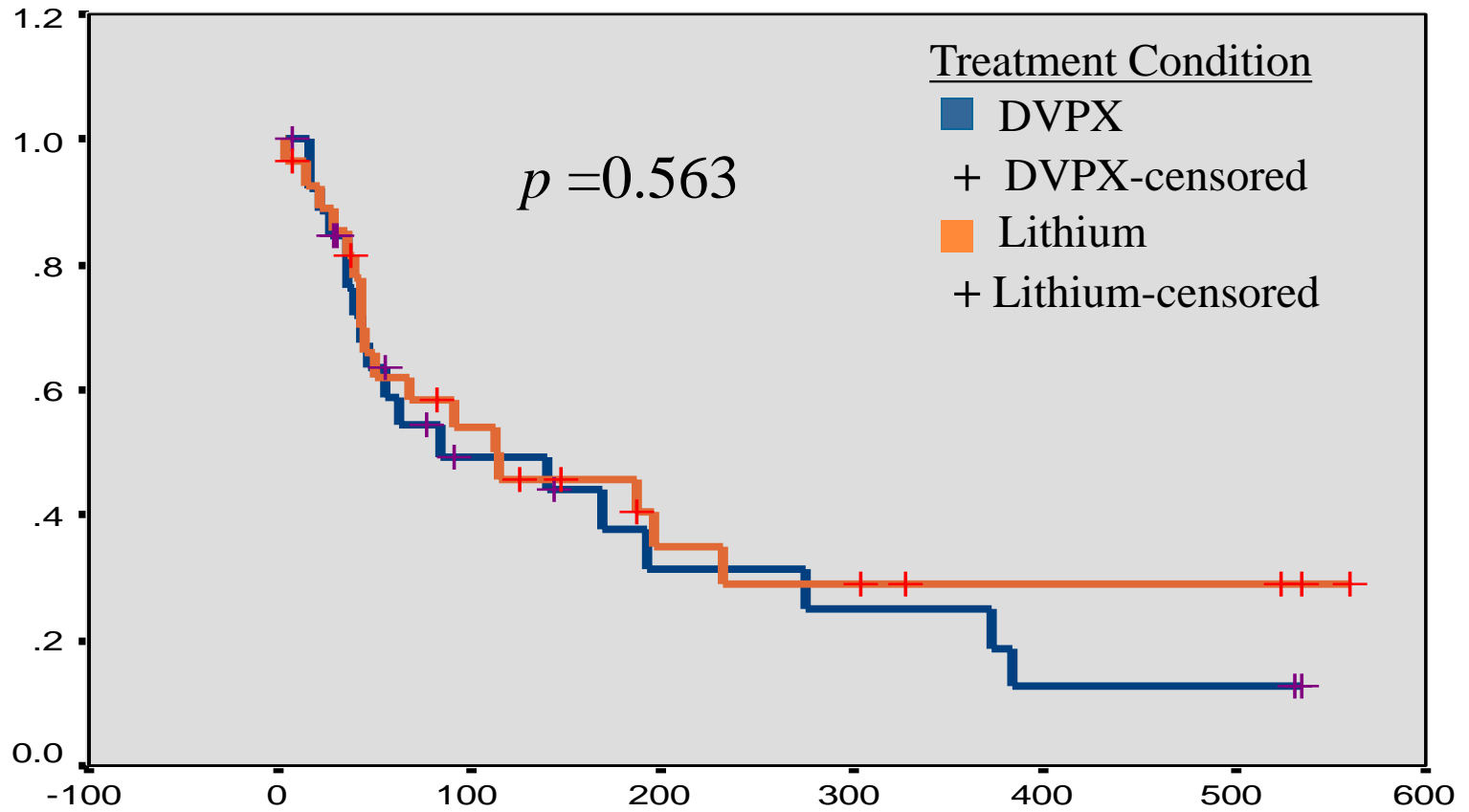
# DVPX + Lithium

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



Survival Analysis- number of days in phase 2

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.**

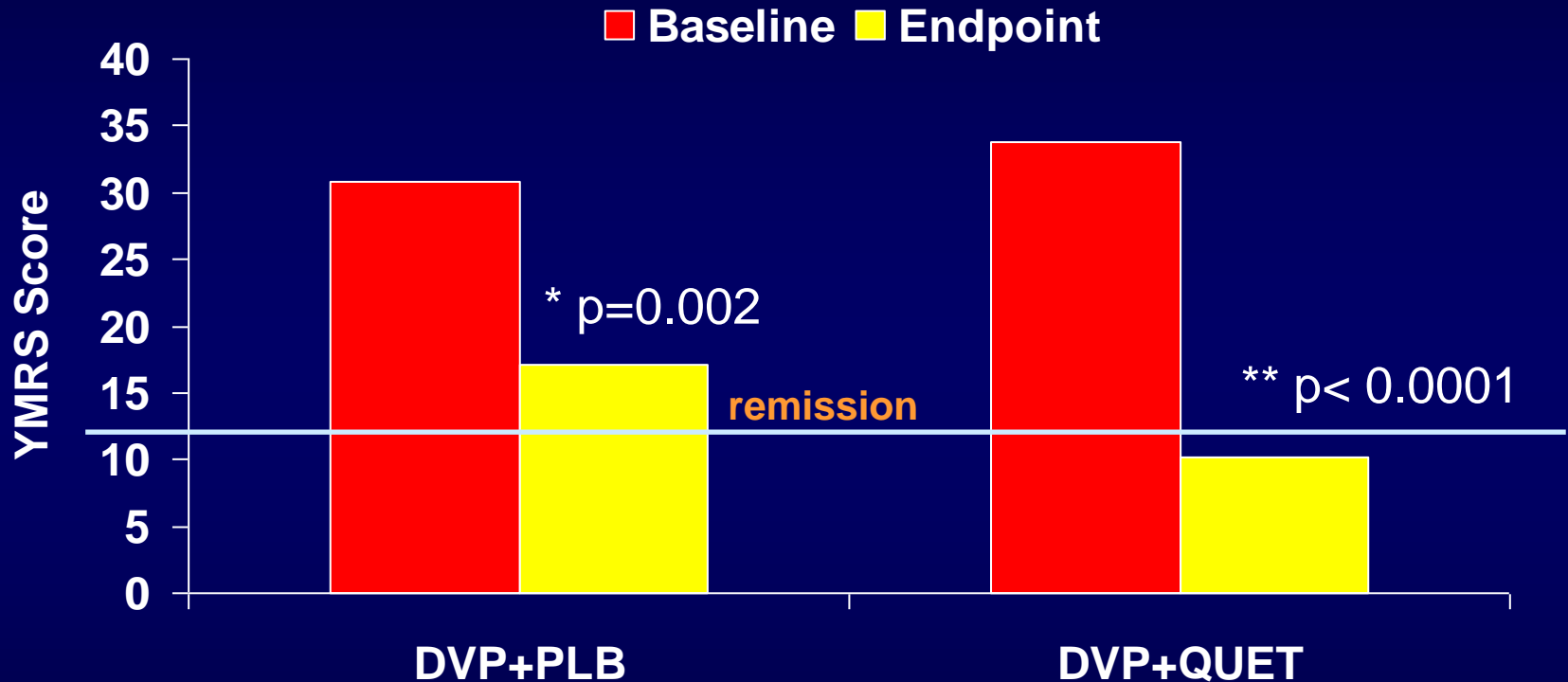
# Quetiapine + Divalproex in Adolescent Mania

- 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



# Quetiapine for Adolescent Mania

Change Baseline to Endpoint in YMRS



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

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

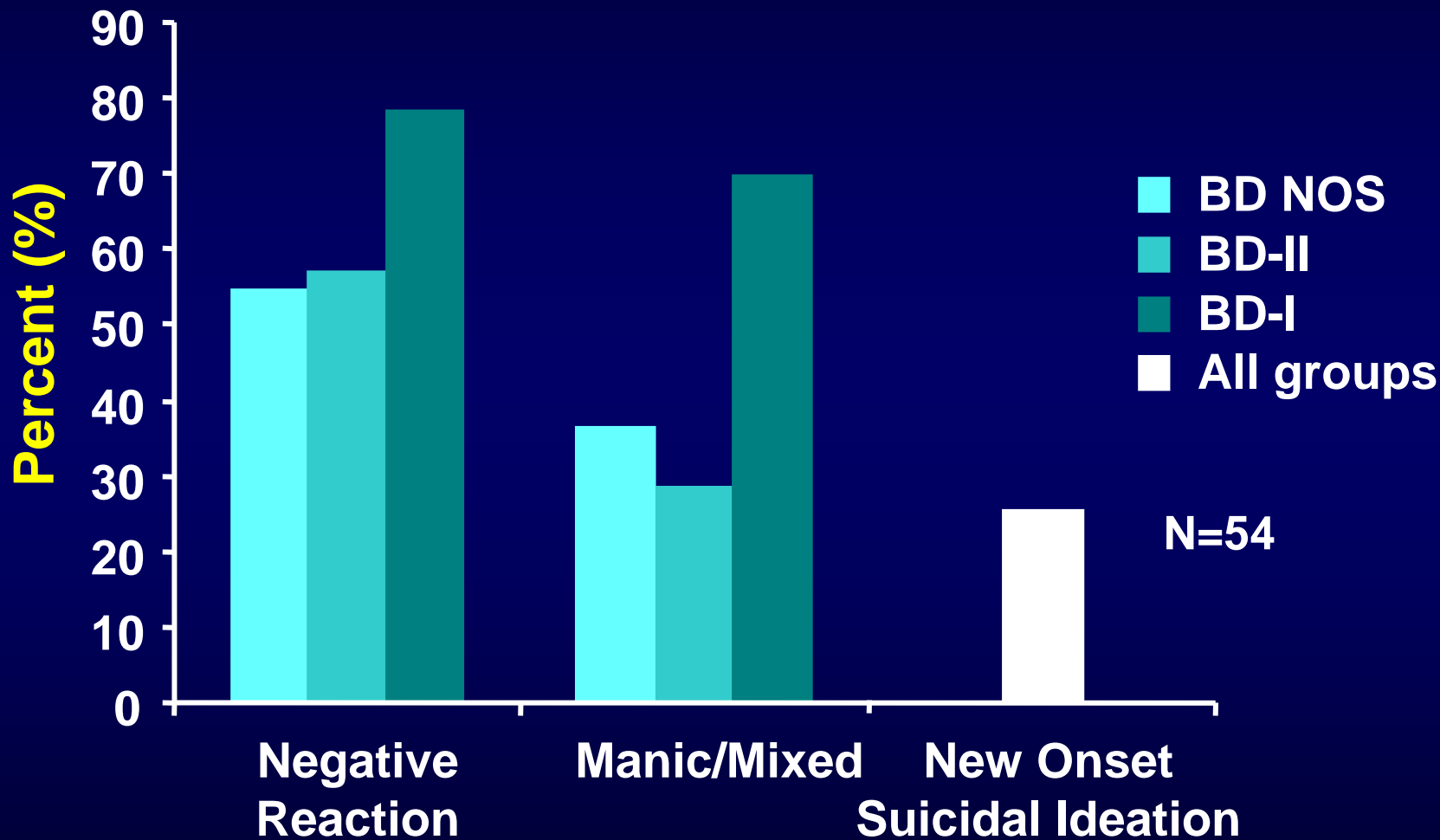
- Divalproex sodium monotherapy was safe and effective ( $p < .0001$ )
- 30 of 40 initial subjects were randomized.
- No subject withdrew due to side-effects.
- Most common side-effects were GI upset, hair loss (girls > boys), easy bruising (without decreased platelets).

## 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





# SSRI Induced Mania

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- 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?

# Treatment of Bipolar Depression

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- 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

# Lithium for Adolescent BP Depression

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- 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

# Sample Characteristics: Lithium Study

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<b>VARIABLE</b>	<b>BP depressed N=27</b>
Age, mean $\pm$ 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 (%)	<b>12 (44)</b>

# CDRS Score vs Time

QuickTime™ and a  
TIFF (Uncompressed) decompressor  
are needed to see this picture.

# Lamotrigine in Adolescent Bipolar Depression

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- 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)

# 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%)

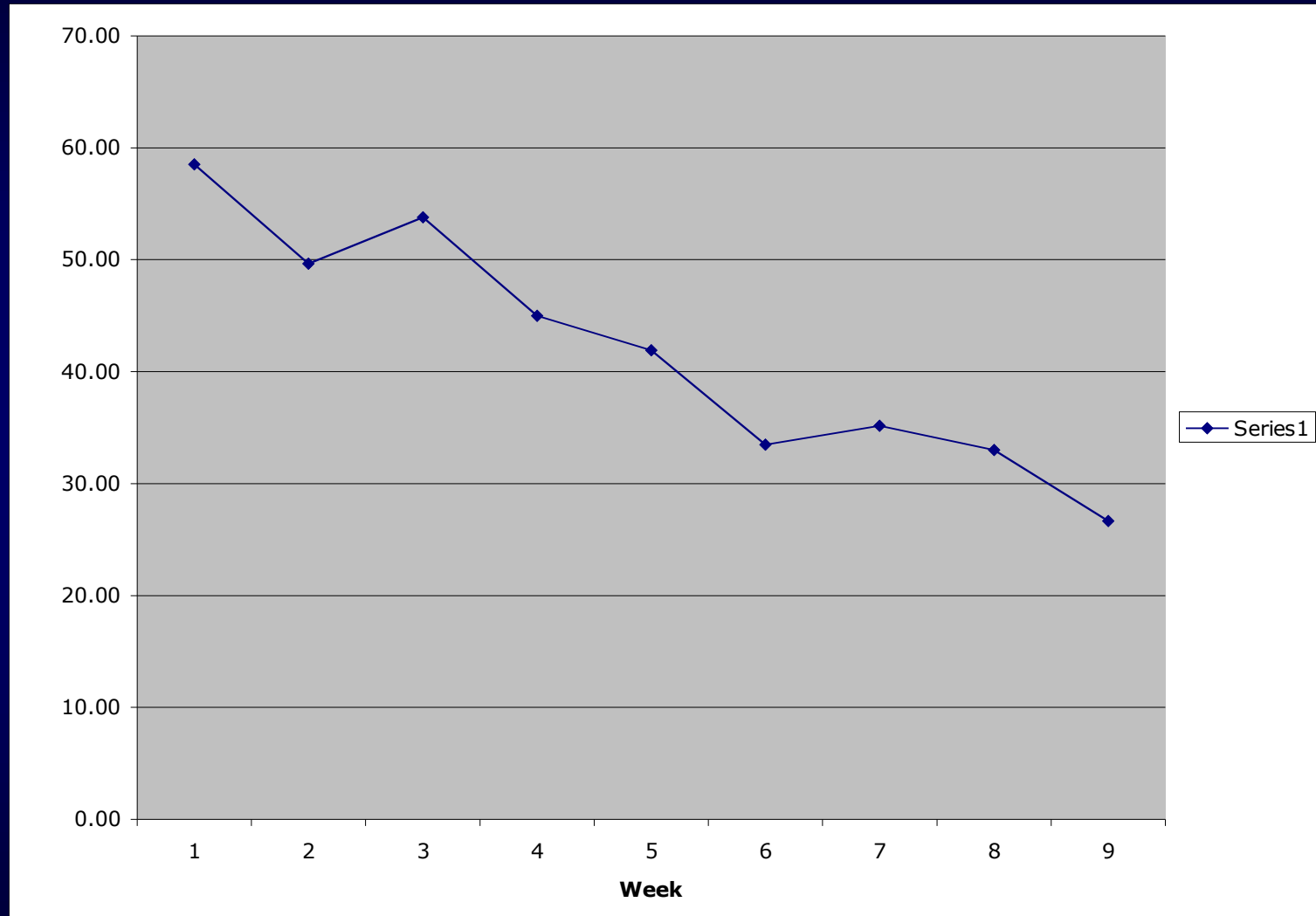
# Results (Completed Subjects)

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- 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%)



# CDRS-R Score by Week



# 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

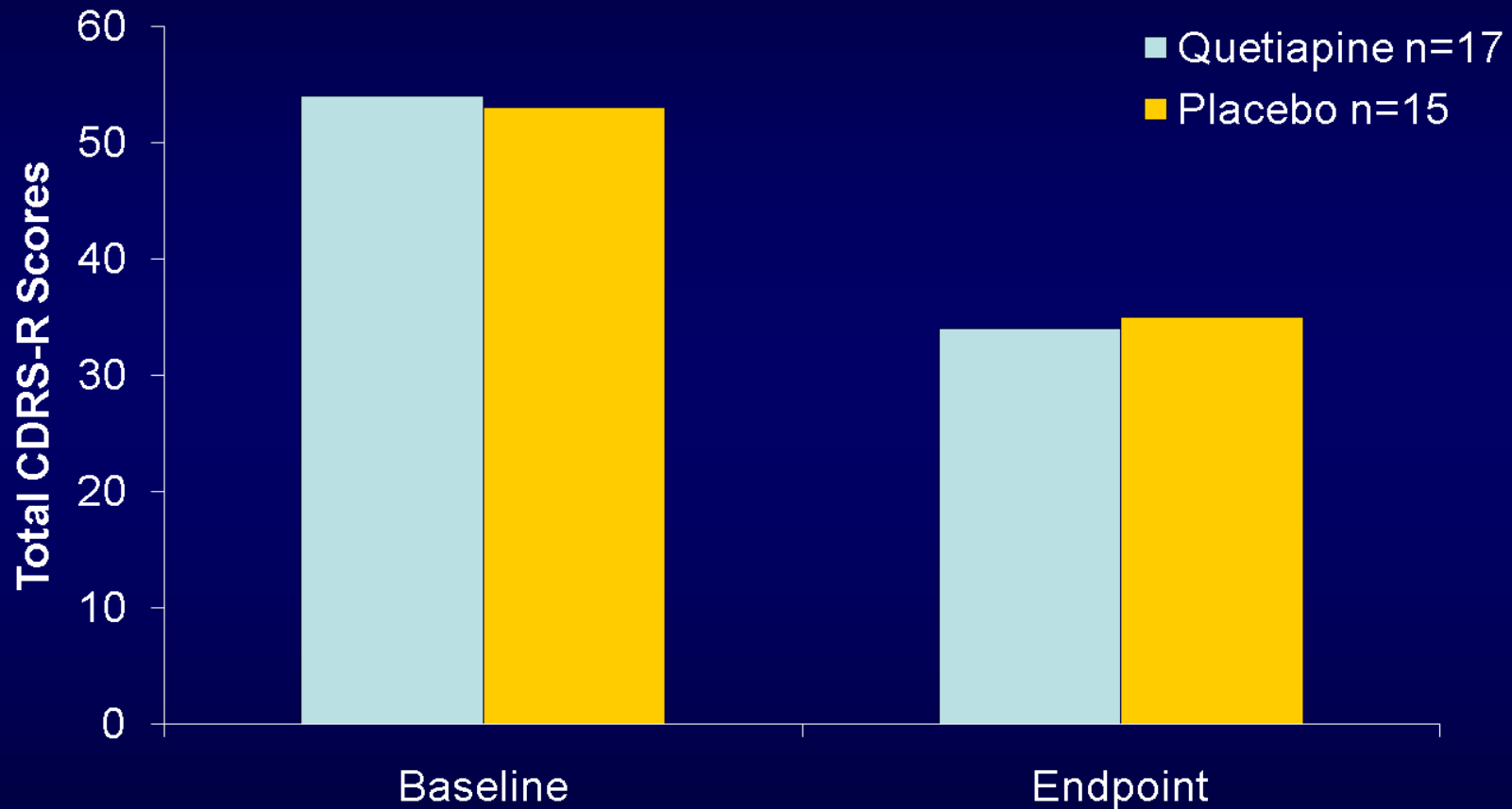
# Outcome Measures

- 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.

# 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)

# Change in CDRS-R from Baseline to Endpoint

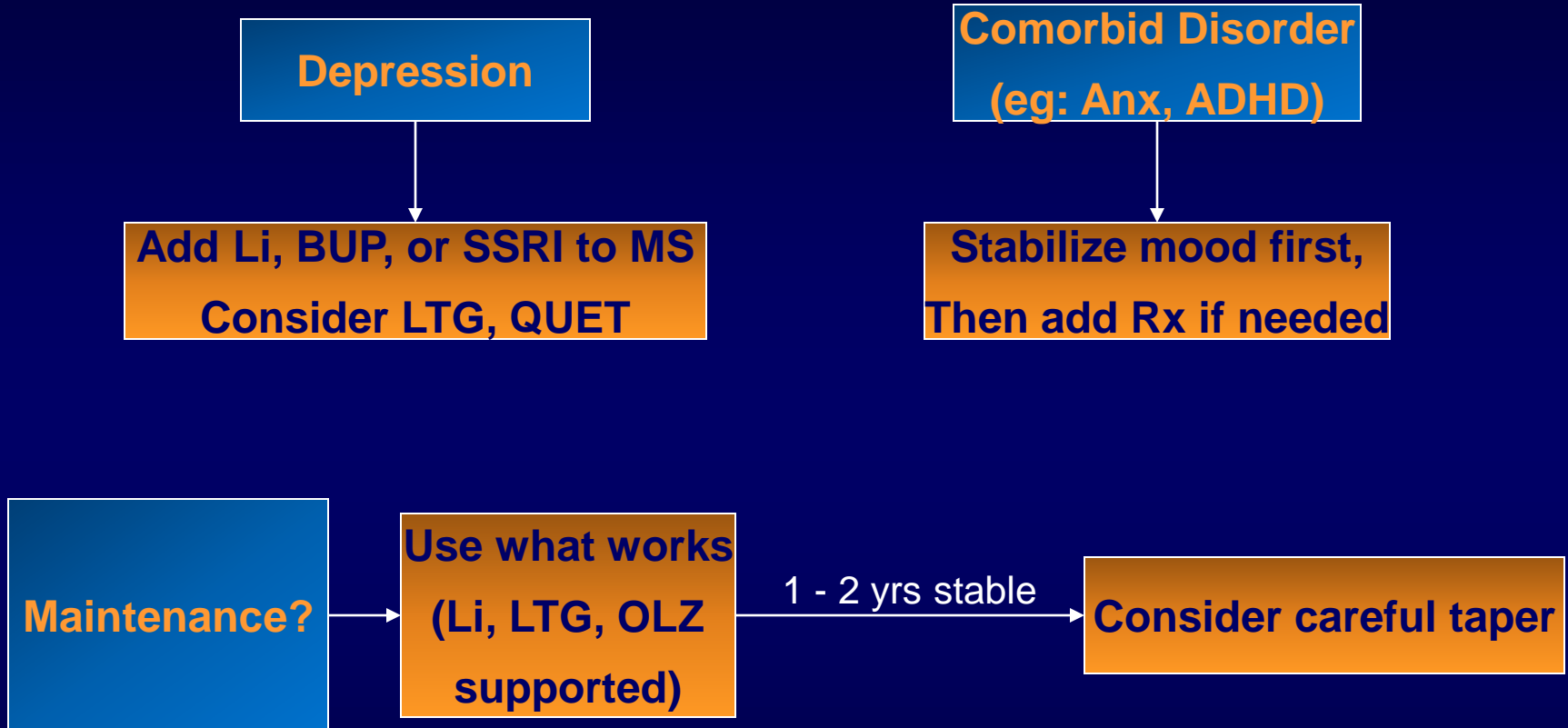


Group difference,  $t=-0.14$ ,  $df=30$ ,  $p=0.89$

# 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),  $p=1.0$ .

# Treatment Issues in Pediatric Bipolar Disorder



MS = mood stabilizer

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

# 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<sub>4</sub>
- 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

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- 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:  $5.6 \pm 4.3$   $\approx$  1 SD or  $\uparrow$  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)

# Lamotrigine - Risk of Rash

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

<sup>1</sup>Dooley, J, et al (1996) *Neurology* 46:240-242

<sup>2</sup>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<sup>1</sup>

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

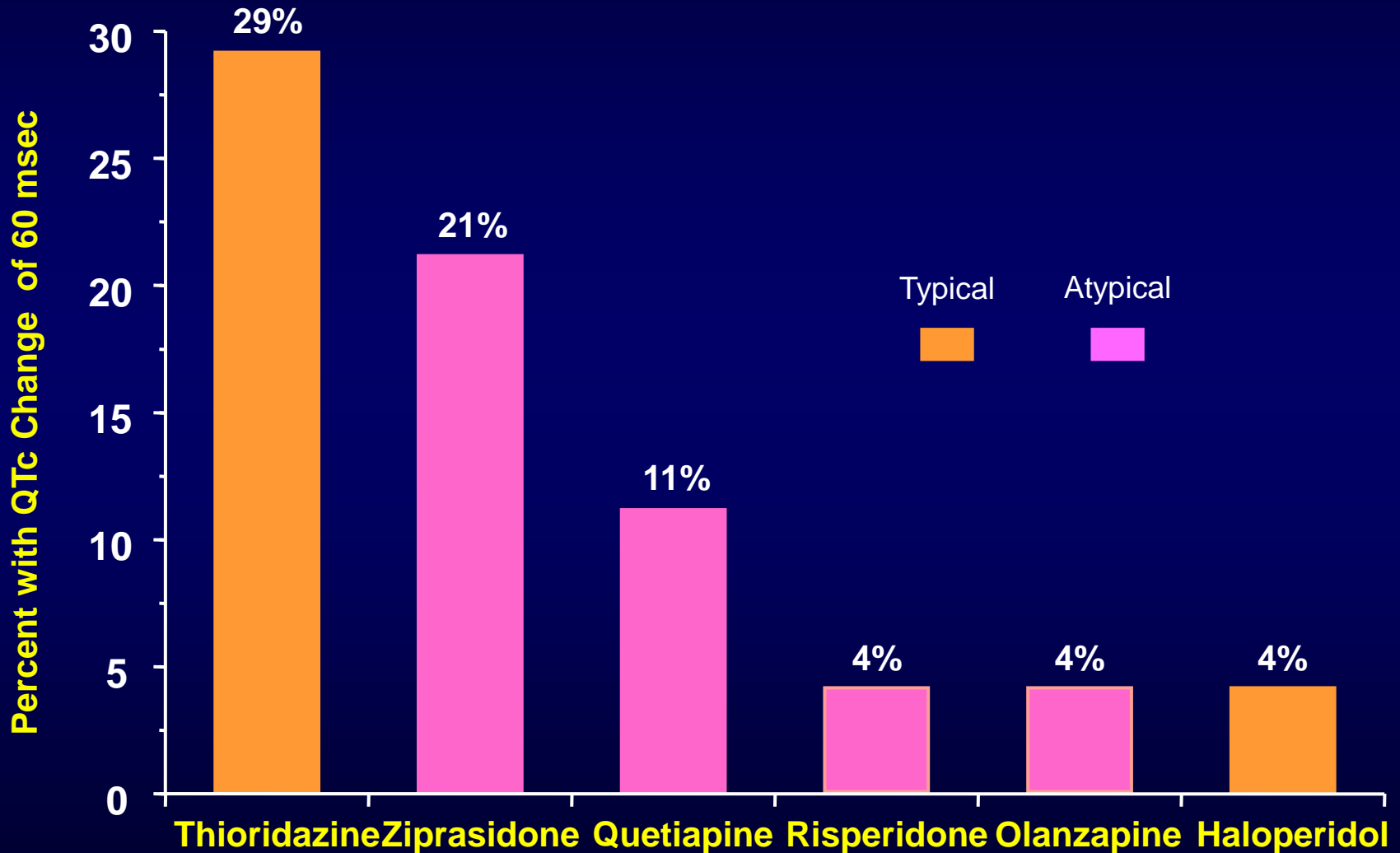
<sup>1</sup>Guberman, AH, et al (1999) *Epilepsia* 40:985-91

# Atypical Antipsychotics: Potential Adverse Effects

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



# Antipsychotic-Induced QTc Prolongation

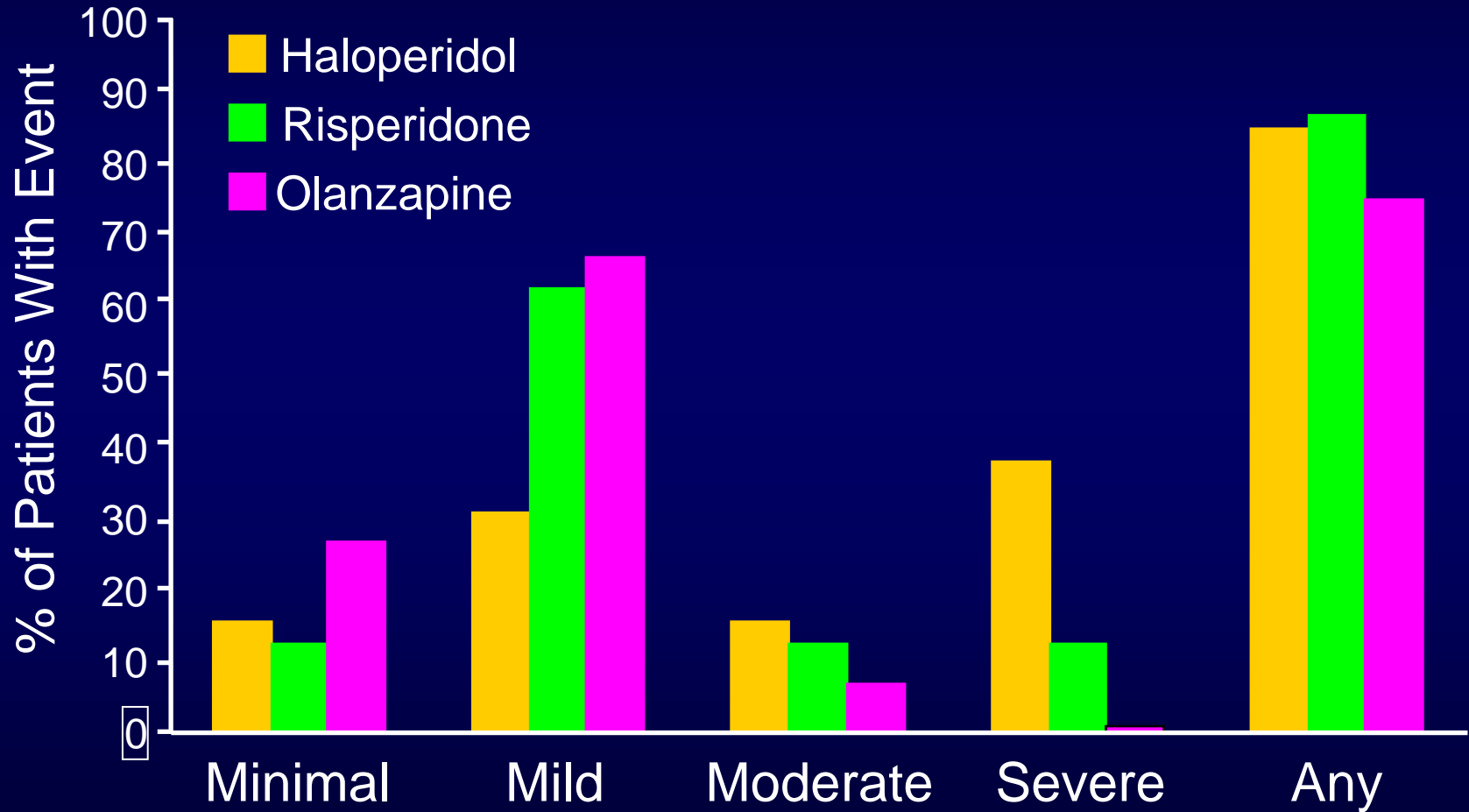


Adapted from: FDA Background on Ziprasidone 2000:5.

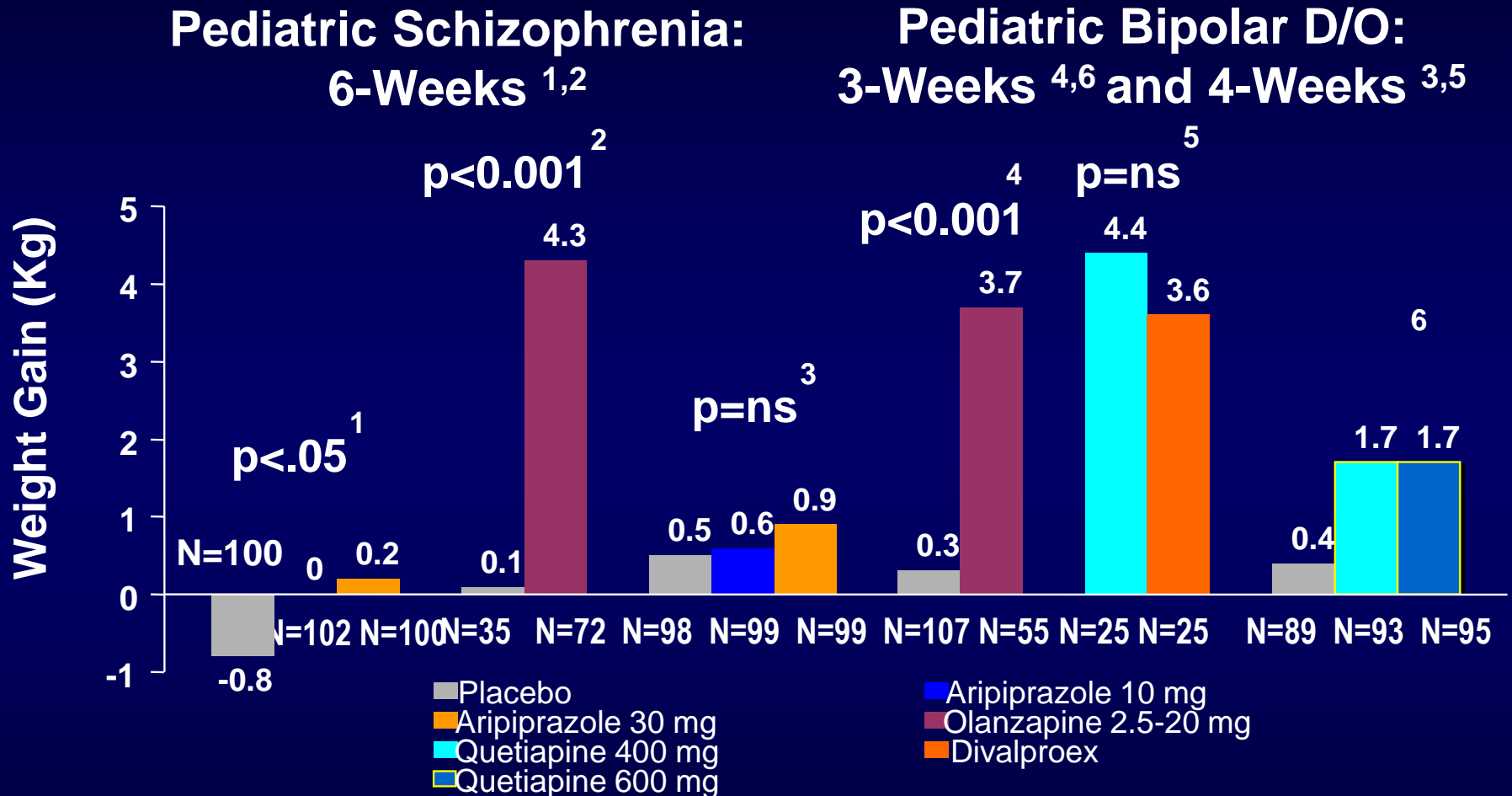
# Relative Potency of Antipsychotics in Elevating Serum Prolactin (PRL)

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

# Incidence and Severity of EPS with Antipsychotics in Psychotic Youth



# Weight Gain in in Pediatric Schizophrenia & Bipolar



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

<sup>4</sup> Tohen M et al. (2007), *Am J Psychiatry* 164(10):1547-56; <sup>5</sup> DelBello MP et al., *J Am Acad Child Adolesc Psychiatry*. 2006;45:305-13; <sup>6</sup> 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