

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

Question 4

The atypical antipsychotic that was recently approved by FDA for use in pediatric bipolar disorder is:

- A) Risperidone
- B) Olanzapine
- C) Quetiapine
- D) Ziprasidone
- E) Clozapine

Question 5

The mood stabilizer with a propensity to induce weight loss is:

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

Teaching points

- Bipolar disorder Not Otherwise Specified (BD-NOS) probably represents the largest group of bipolar disorder in the pediatric age group.
- Lithium is FDA approved for bipolar disorder in children > 12 years of age
- SSRI-induced mania may be seen in as many as 50% of children with bipolar disorder

Bipolar Medication Classifications

Lithium

Anticonvulsants

valproate (Depakote)

carbamazepine (Tegretol)

oxcarbazepine (Trileptal)

lamotrigine (Lamictal)

topiramate (Topamax)

gabapentin (Neurontin)

Antipsychotics

“Typical”: Haldol, Trilafon, Moban

“Atypical”: olanzapine (Zyprexa), risperidone (Risperdal), quetiapine (Seroquel), ziprasidone (Geodon), aripiprazole (Abilify), clozapine (Clozaril)

Bipolar Medication Classifications

Antidepressants

- TCAs (amitriptyline, etc)

- SSRIs (fluoxetine, sertraline, etc)

ADHD treatments

- Stimulants (methylphenidate, etc)

- Atomoxetine

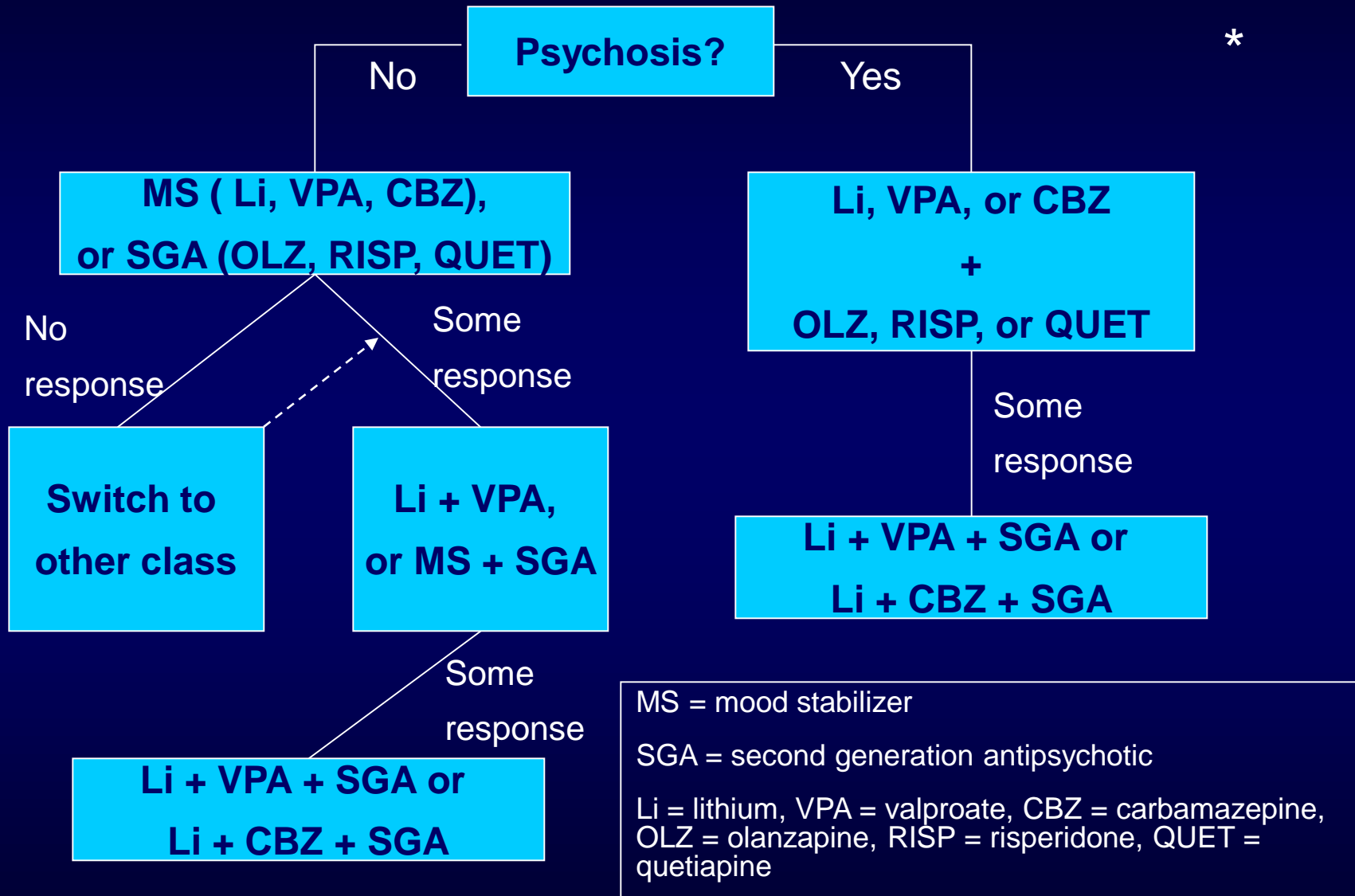
- Modafinil

- Alpha-2 agonists (clonidine, guanfacine)

Anxiolytics

- Benzodiazepines (clonazepam, lorazepam, etc)

Treatment of Acute Mania in Pediatric Bipolar Disorder



Emerging Data in Pediatric Bipolar Disorder*

| | Case Report | Case Series | Open Prospective | RCT |
|---------------|-------------|-------------|------------------|---------|
| Lithium | X | X | X | X |
| Valproate | X | X | X | X (Neg) |
| Carbamazepine | | X | X | |
| Lamotrigine | X | X | X | |
| Topiramate | | X | | X (Neg) |
| Oxcarbazepine | X | | | X (Neg) |
| Gabapentin | | X (Adjunct) | | |
| Clozapine | | X | | |
| Olanzapine | | X | X | X |
| Risperidone | | X | X | X |
| Quetiapine | | | X | X |
| Ziprasidone | X | | | P |
| 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

| | <u>DVPX</u> | <u>PLACEBO</u> |
|---|-------------|----------------|
| – Headache | 16% | 15% |
| – Vomiting | 13% | 8% |
| – Nausea | 9% | 1% |
| – Sig decreases in WBC, platelets, AST/ALT, cholesterol | | |
| – Sig increases 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

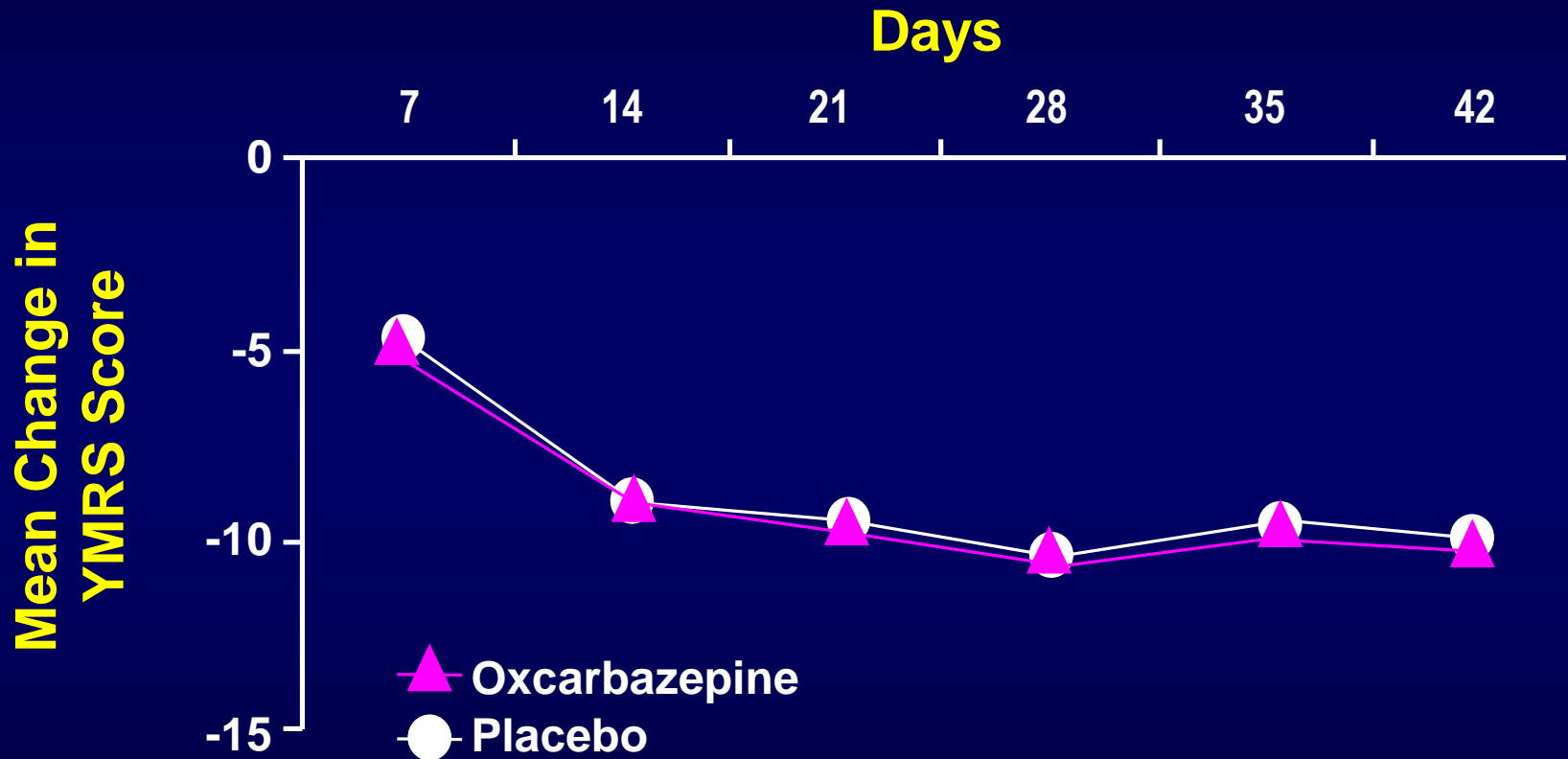
Oxcarbazepine in Pediatric BD

- 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 | <i>p</i> |
|---------------|------------|----------------|-----------------|
| – Children | 41% | 17% | .029 |
| – Adolescents | 43% | 40% | .86 |

Oxcarbazepine in Pediatric BD

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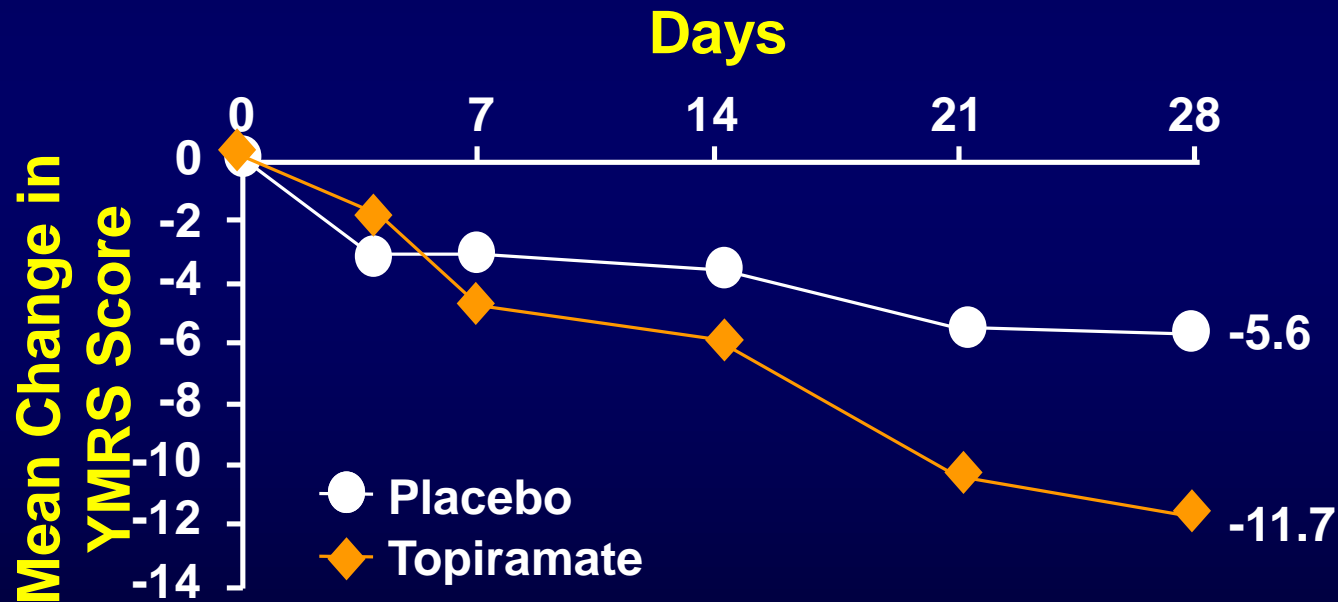


Wagner KD et al. (2006), Am J Psychiatry 163(7):1179-1186

Topiramate for Pediatric Bipolar I Disorder

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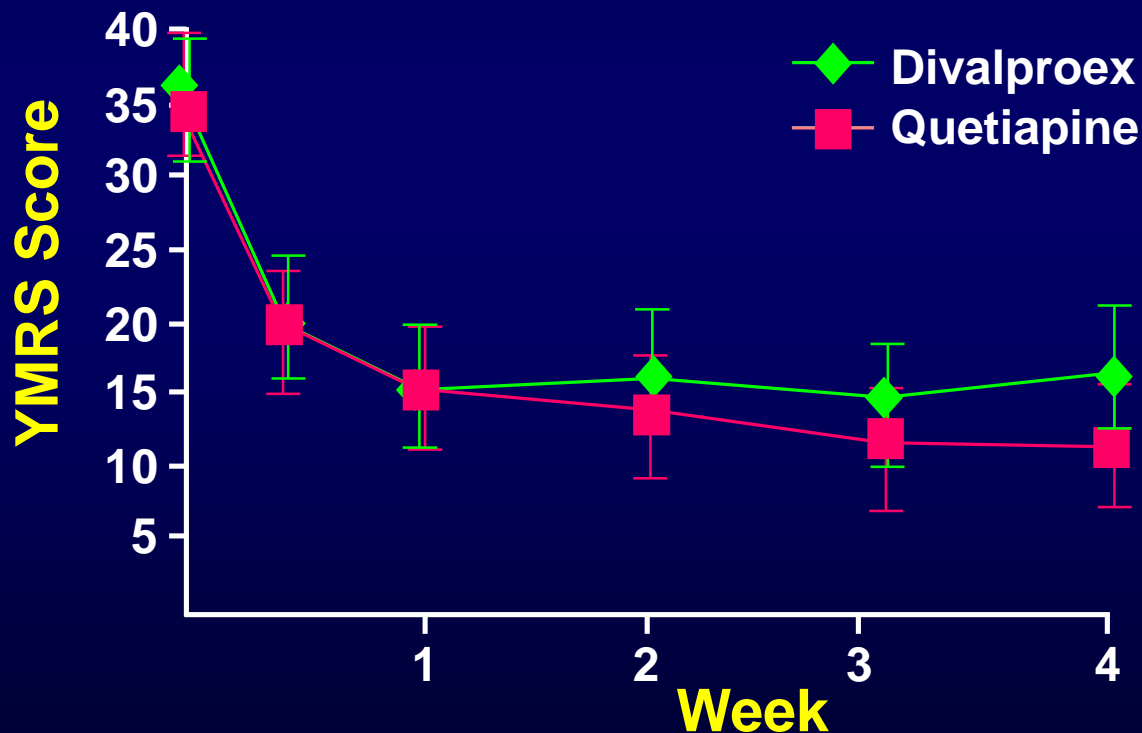
- 56 youths, ages 6-17, with bipolar I disorder, manic or mixed episodes
- Mean topiramate dose: 278 mg/day



Quetiapine vs. Divalproex for Adolescent Mania

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- 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



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

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

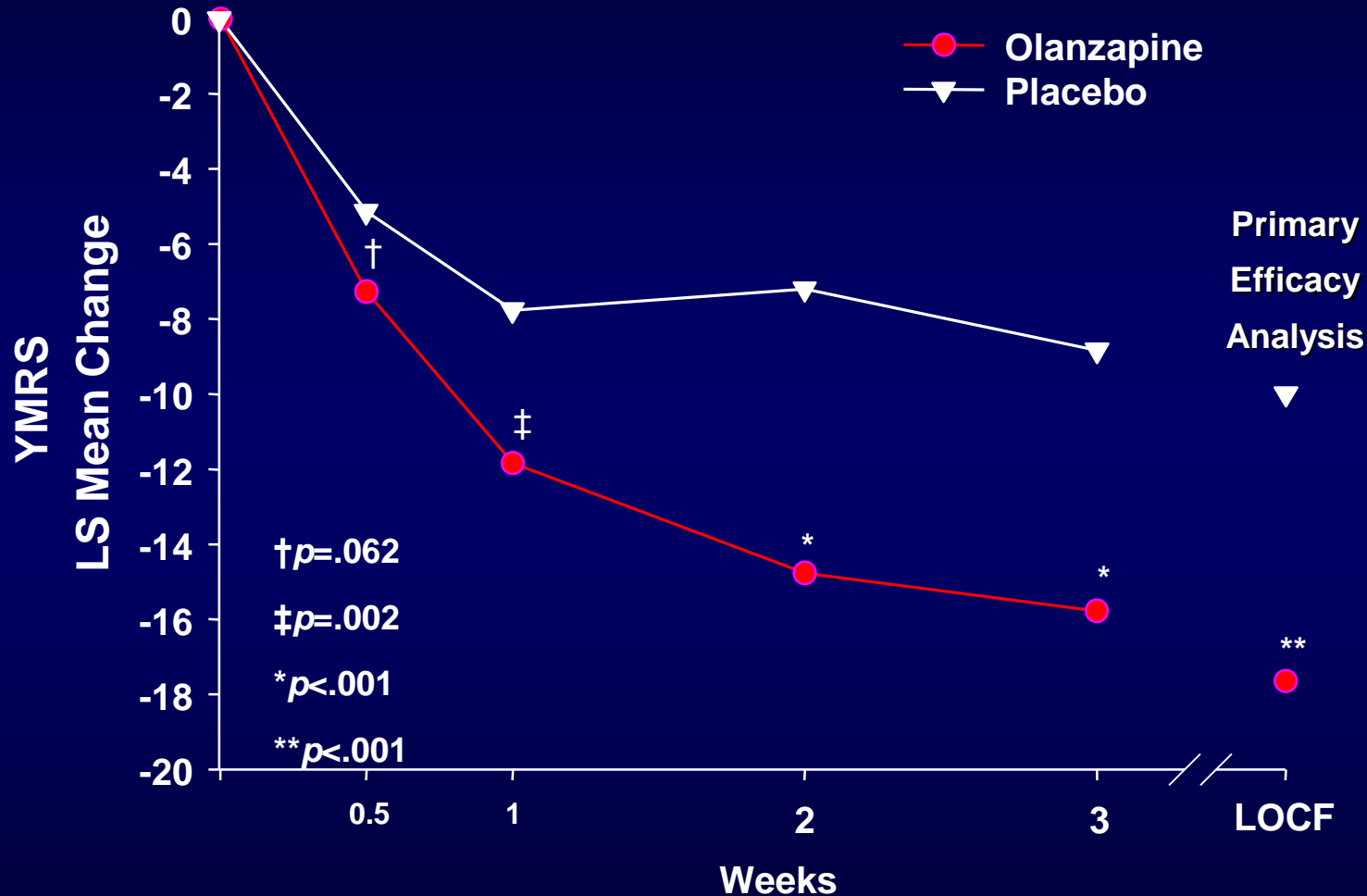
Olanzapine in Pediatric Bipolar Disorder

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.

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

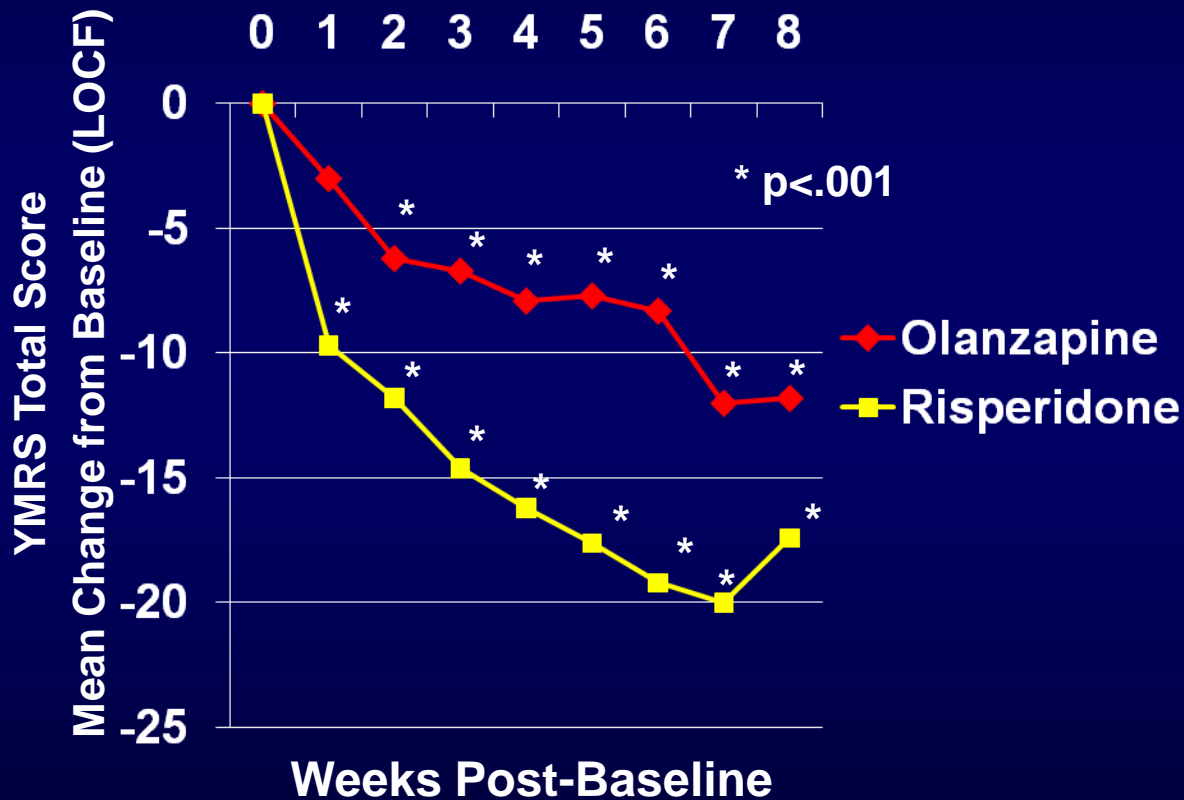
Open Label Olanzapine Extension Study

*

- 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
- $\geq 7\%$ inc in weight = 69%
- Inc prolactin = 71%

Olanzapine and Risperidone in Preschool Bipolar Disorder

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- 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 ≤ 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

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| | 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

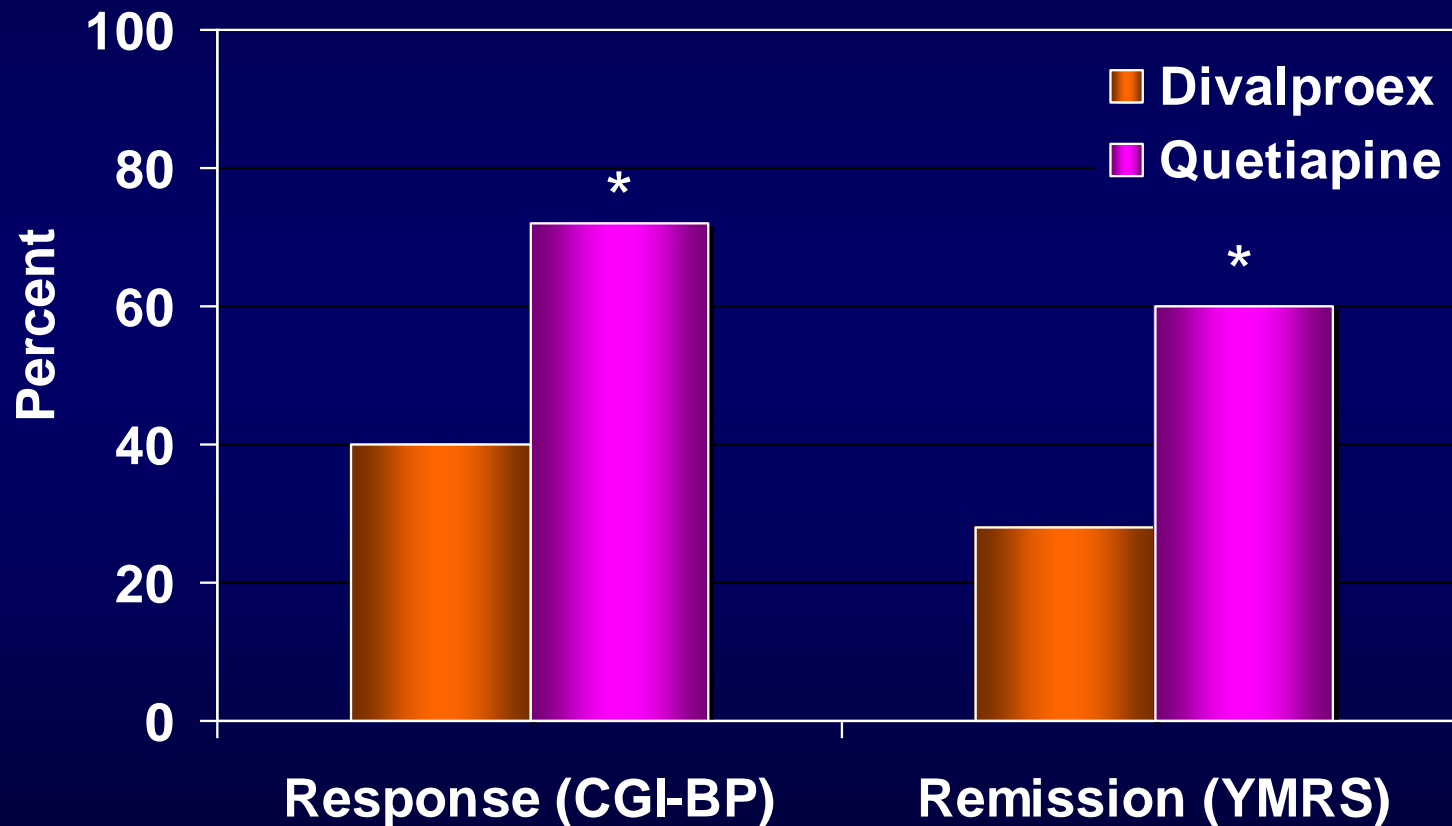
- 50 adolescent (15 ± 2 y.o.) inpatients
- Randomized:
 - DVPX: 80-120 ug/mL
 - QUET: 400-600 mg/d
- Similar side effect rates
 - Sedation: 60% (QUE) vs. 36% (DVP)
 - Dizziness: 36% vs. 36%
 - GI upset: 26% vs. 28%
- Similar weight increase
 - 4.4 ± 5.0 kg (QUE) vs. 3.6 ± 6.0 kg (DVP)

Quetiapine vs. Divalproex in Pediatric Mania

Response Rates

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



* $p = .02$

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

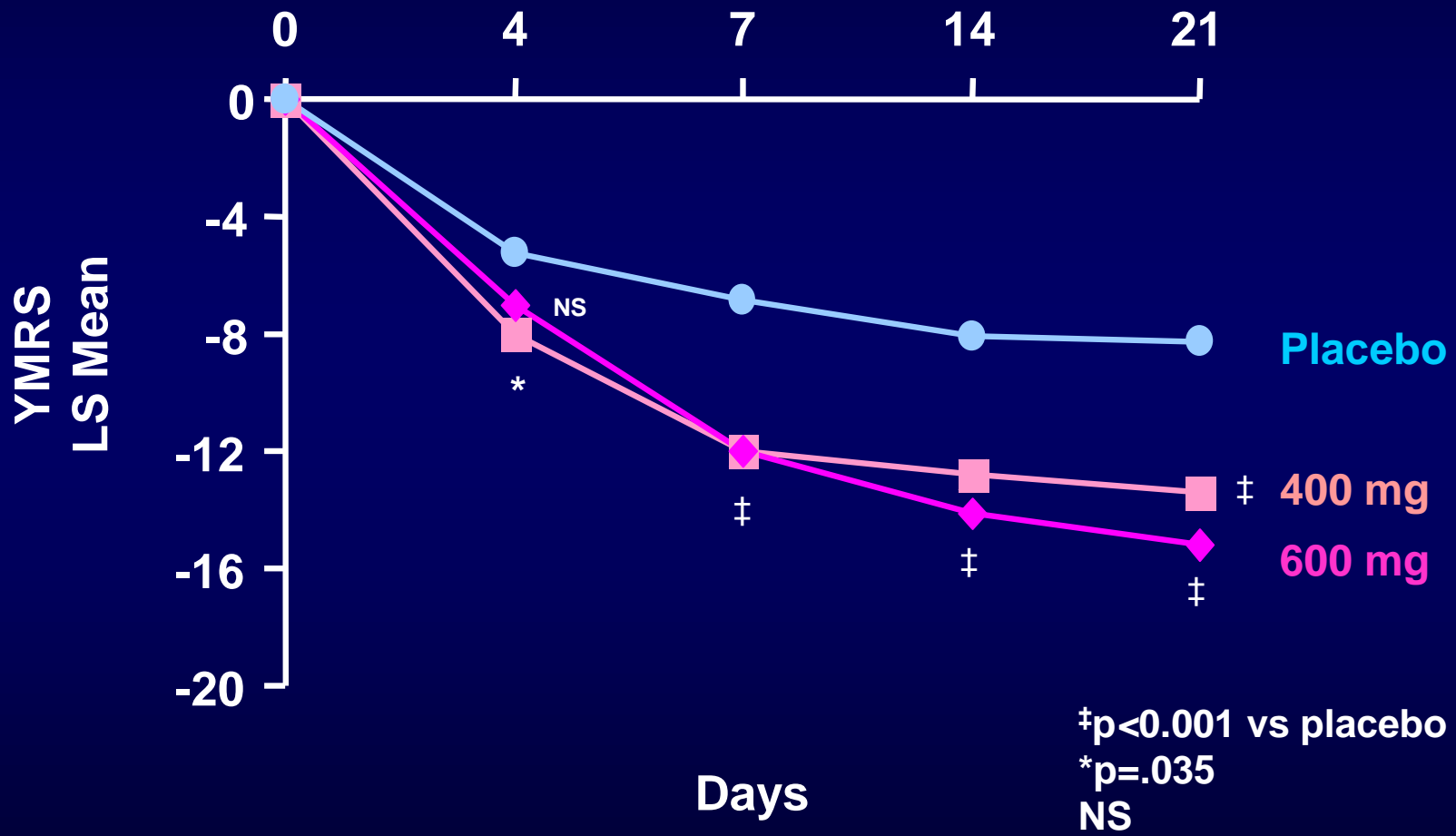
Quetiapine in Pediatric Mania

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

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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 |

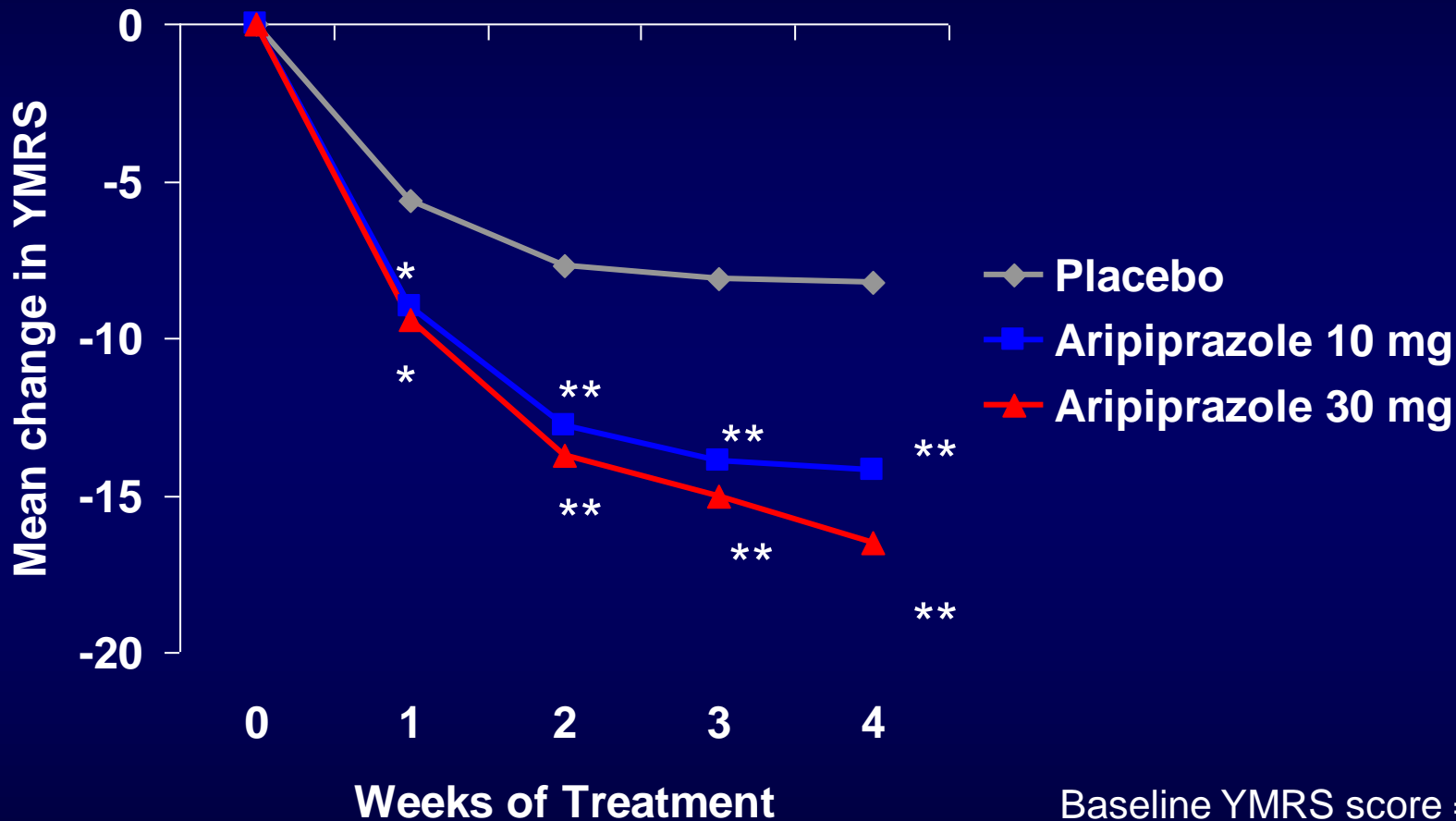
Aripiprazole for Pediatric Mania

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)

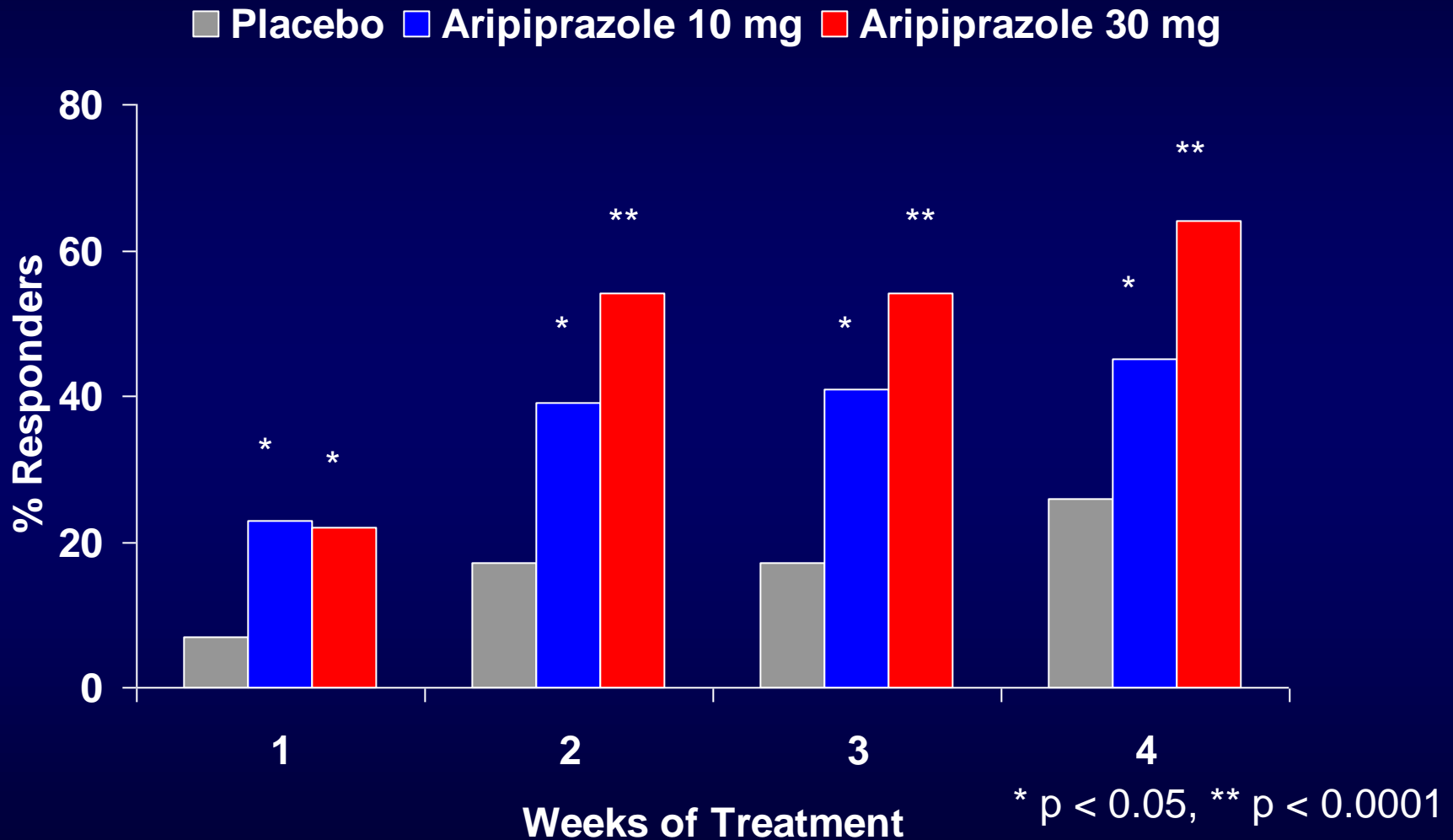
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Baseline YMRS score = 30.1

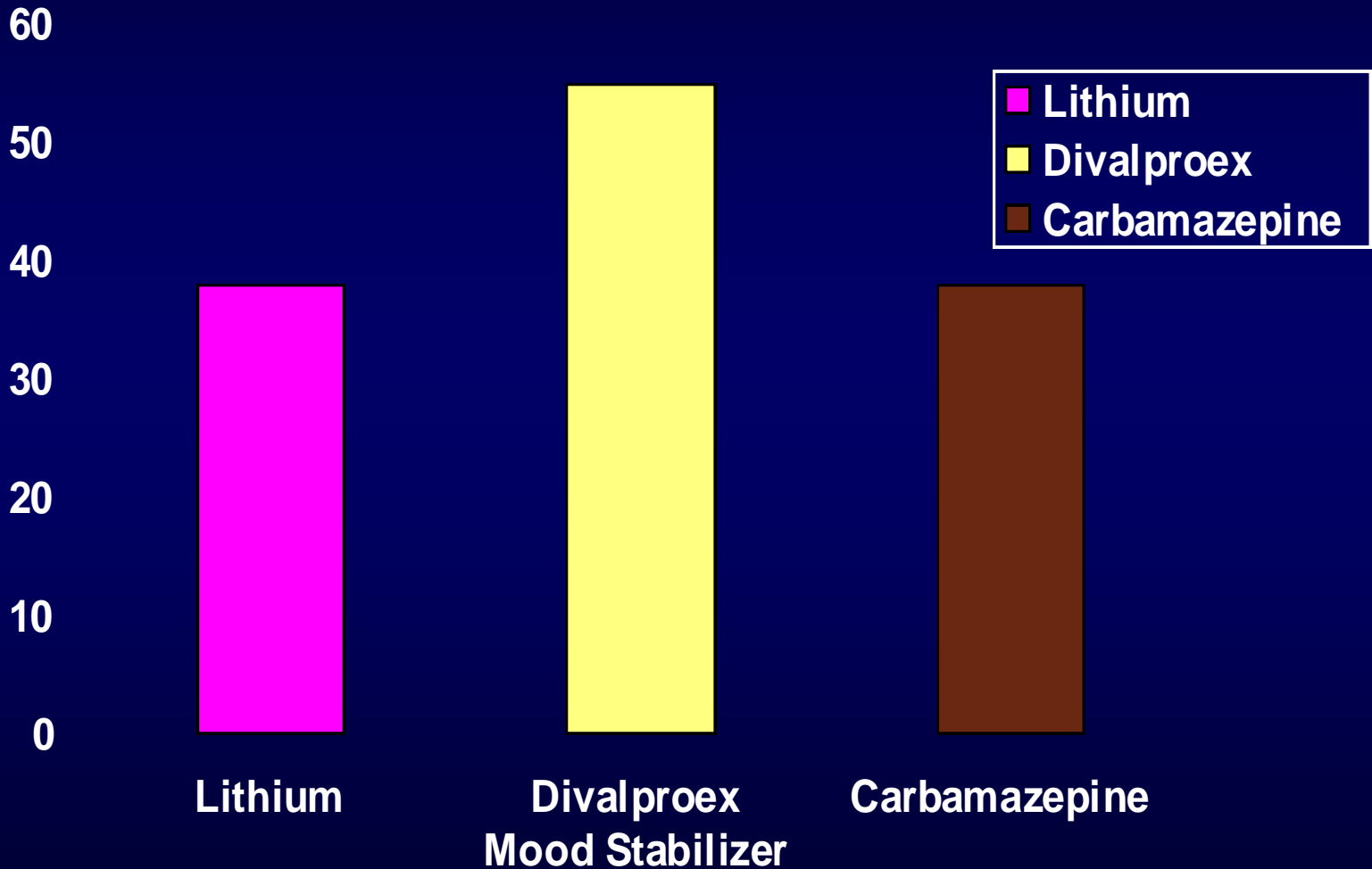
*p < 0.05, **p < 0.0001

Response Rate (LOCF)



Response Rate of Mood Stabilizers in Pediatric BD

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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

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- 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

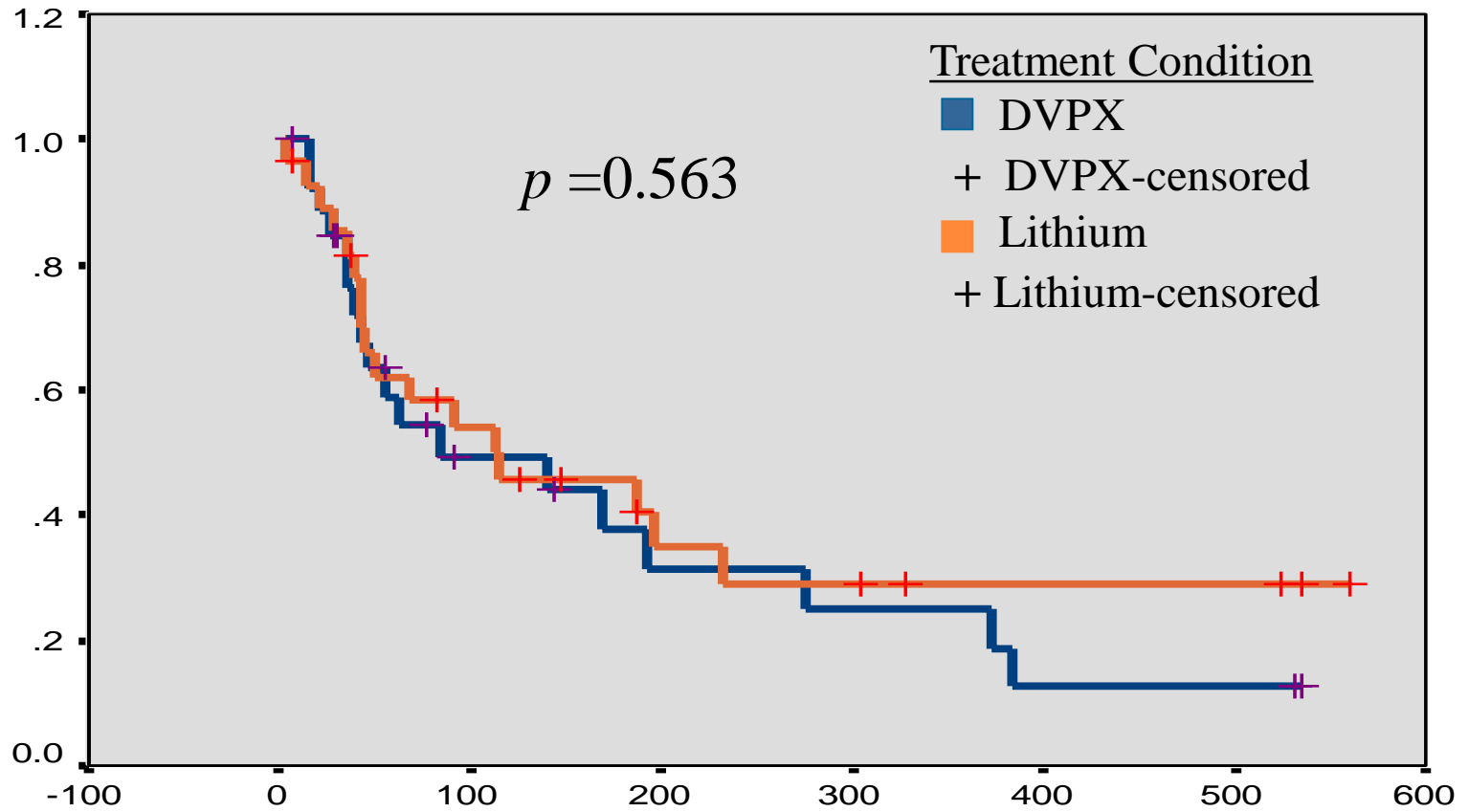
DVPX + Lithium

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

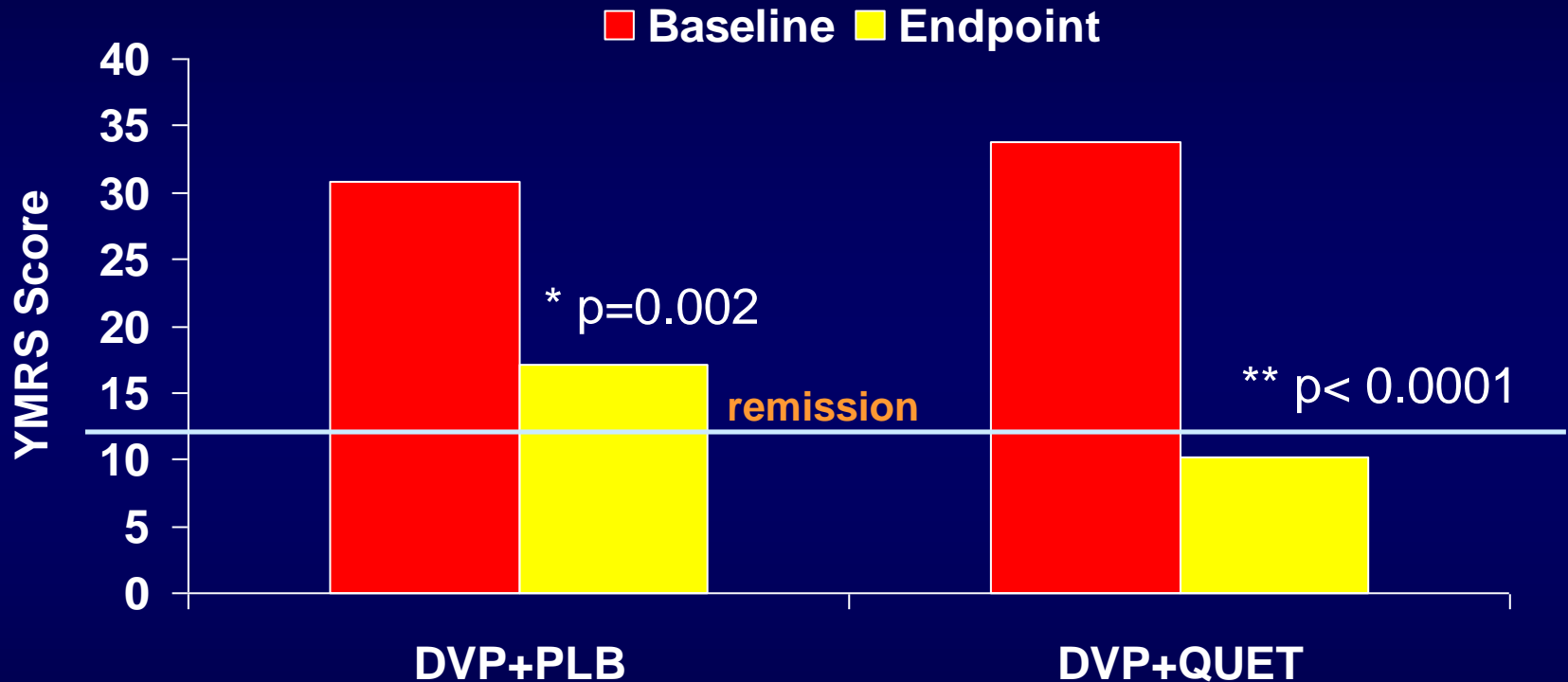
Chang, KD et al. (2000): Mood stabilizer augmentation with olanzapine in acutely manic children. *J Child Adolesc Psychopharmacol* 10:45-9.

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).

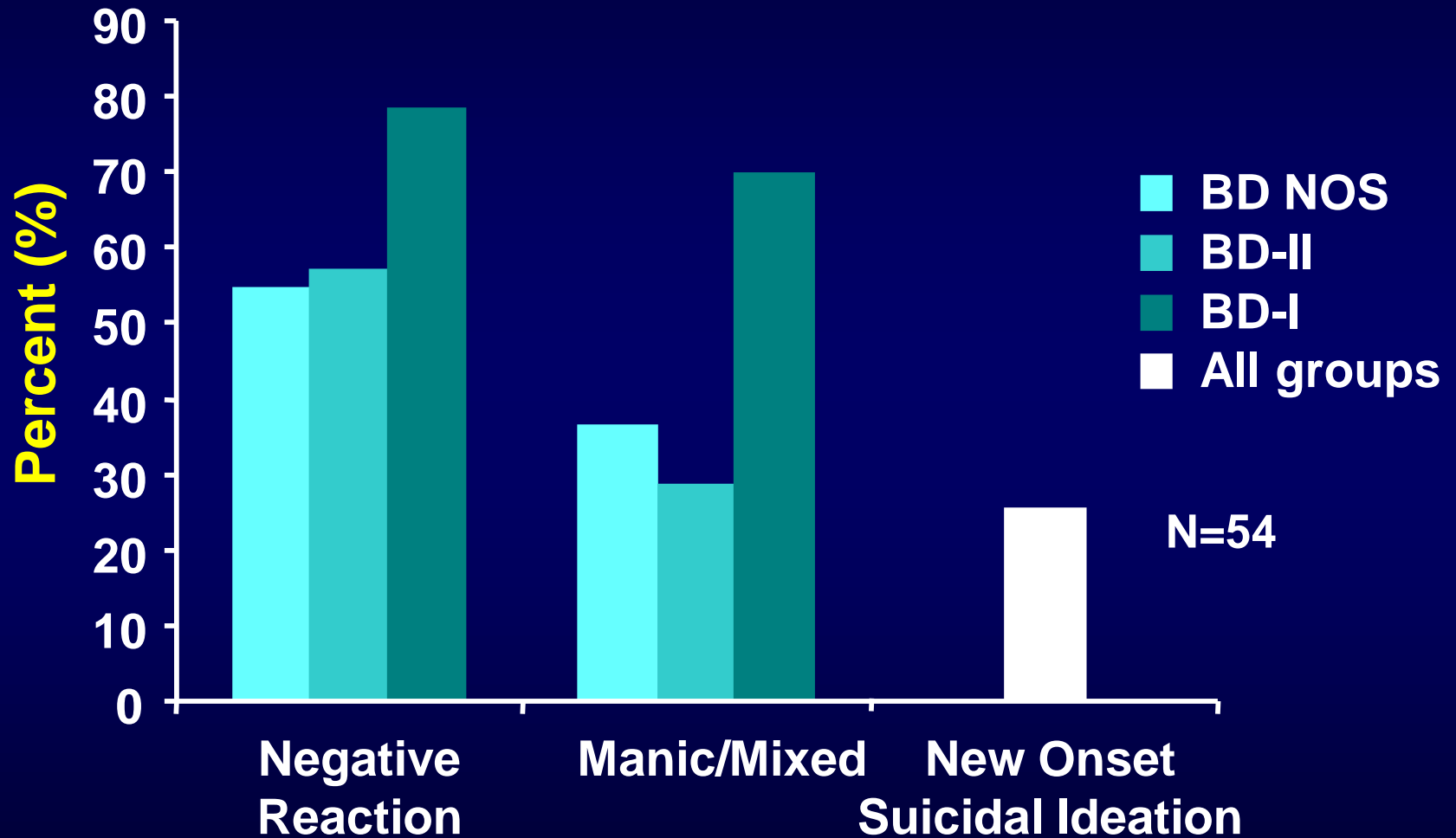
Results: Adderall vs. Placebo

- 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

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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?

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

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 ± 0.2 mEq/L

Sample Characteristics: Lithium Study

| VARIABLE | BP depressed N=27 |
|---------------------------|------------------------------|
| 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 (%) | 12 (44) |

CDRS Score vs Time

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

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)

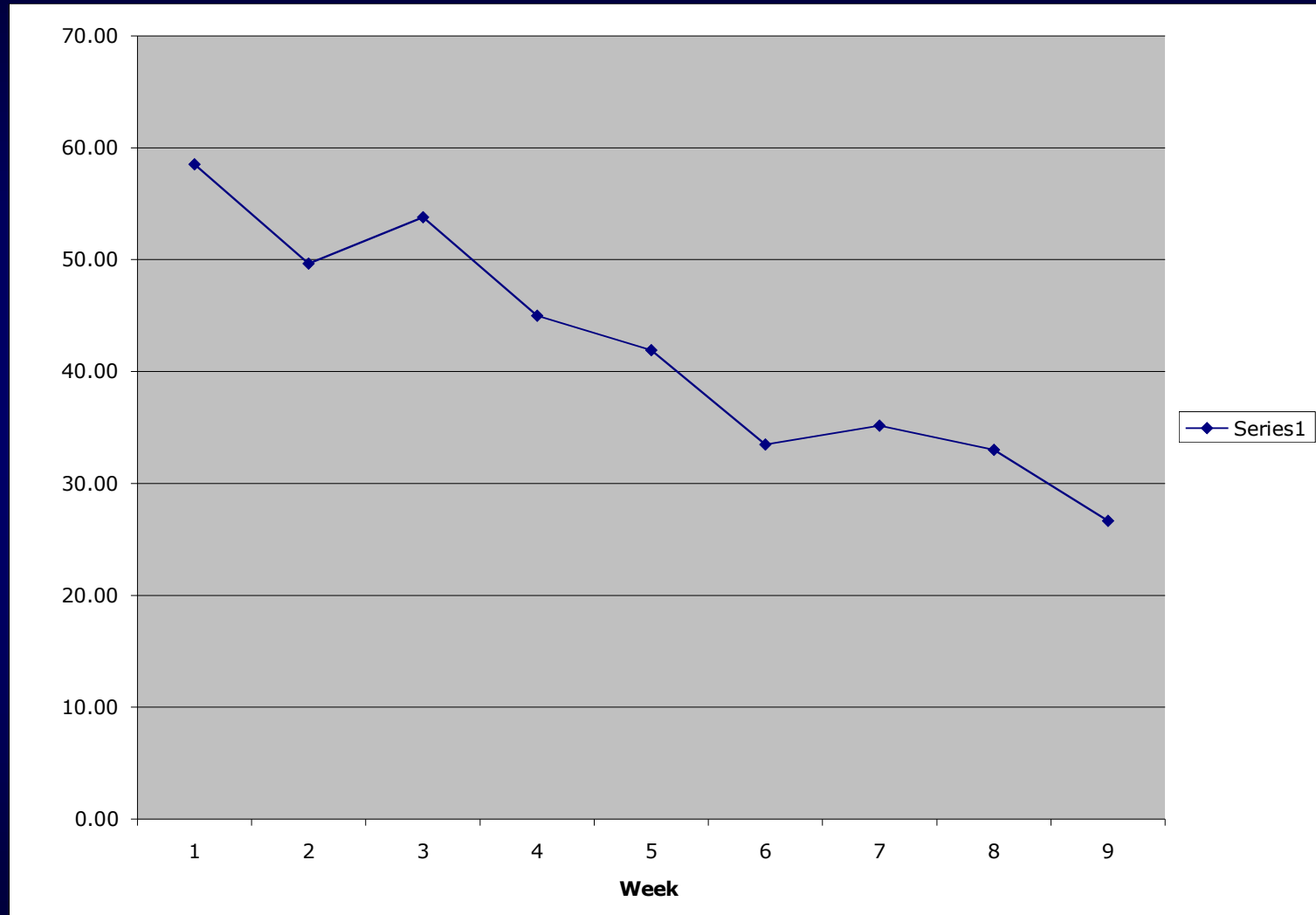
Cohort Characteristics

| | |
|---------------|------------------|
| 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)

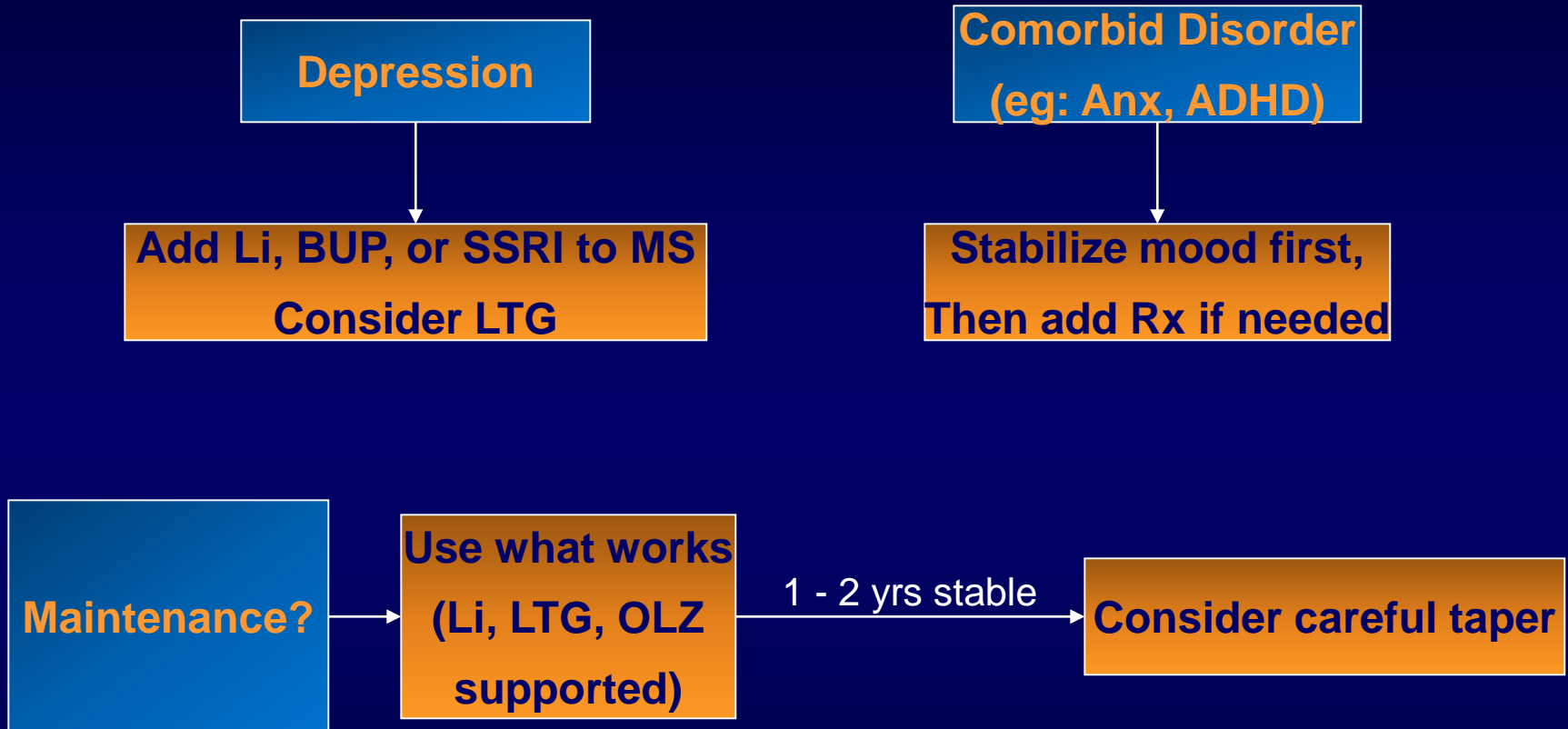
- One dropout, 19 completers
- 7 subjects with adjunct meds (2-DVPX, 1-ARI, 1-OLZ, 1-MPH, 1-ATX, 1-ALP, Li, 1-ATX, OROS-MPH, DVPX)
- Responders by CGI-C: 16/19 (84%)
- Responders by CDRS-R: 12/19 (63%)
- Remitters: 11/19 (58%)

CDRS-R Score by Week



Treatment Issues in Pediatric Bipolar Disorder

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MS = mood stabilizer

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

Treating Depressive Symptoms in Adolescent Bipolar Disorder

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- Check mood stabilizer levels, or increase dosage
- Add lithium
- Add lamotrigine
- Consider quetiapine
- Check TSH; if high, consider adding T₄
- Add/increase antidepressant—only if mood stabilizer on board!

Treating Depressive Symptoms in Bipolar Disorder (cont'd)

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

Conclusions

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- 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 $> 3 \times$ 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 \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 titration¹
 - Concomitant VPA administration^{1,2}
 - Definition of serious rash including any rash leading to discontinuation from trial²
- Regular tabs available in 25 mg, 100 mg, 150 mg, 200 mg
- Chewable tabs in 2 mg, 5 mg, 25 mg
- Antigen precautions

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

²Messenheimer, 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 - Dosing¹

| | <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 |

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

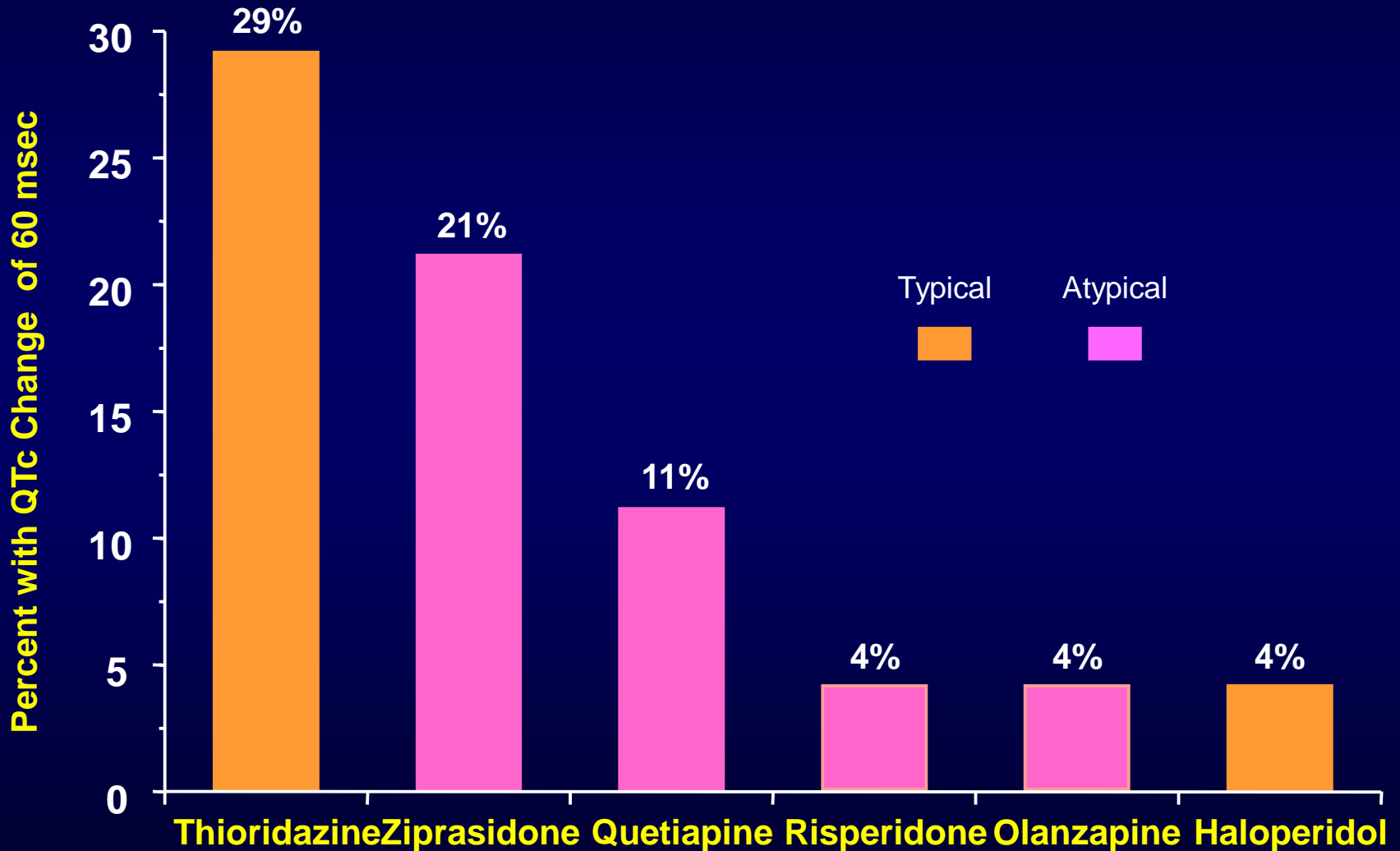
Atypical Antipsychotics: Potential Adverse Effects

*

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

Antipsychotic-Induced QTc Prolongation

*



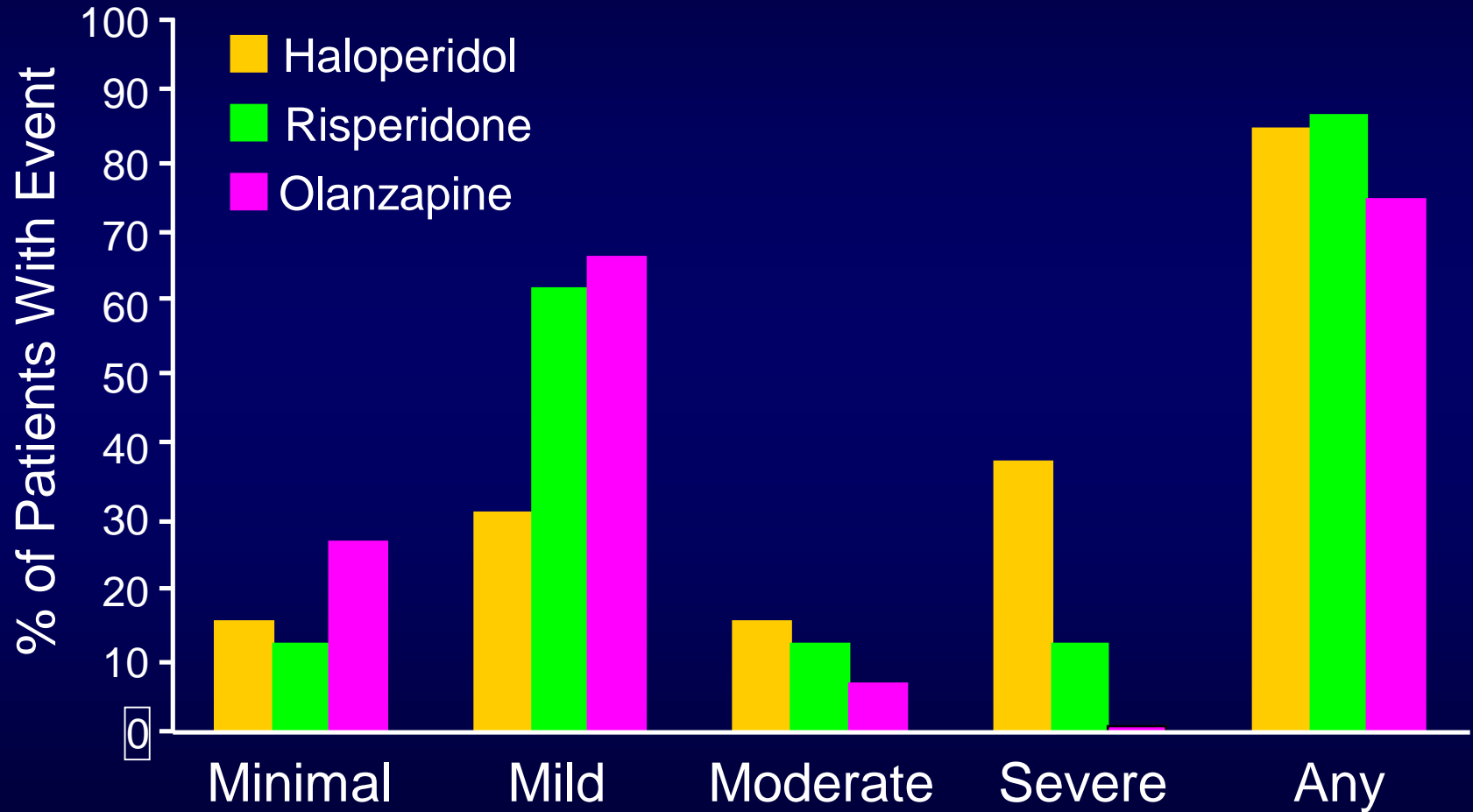
Adapted from: FDA Background on Ziprasidone 2000:5.

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

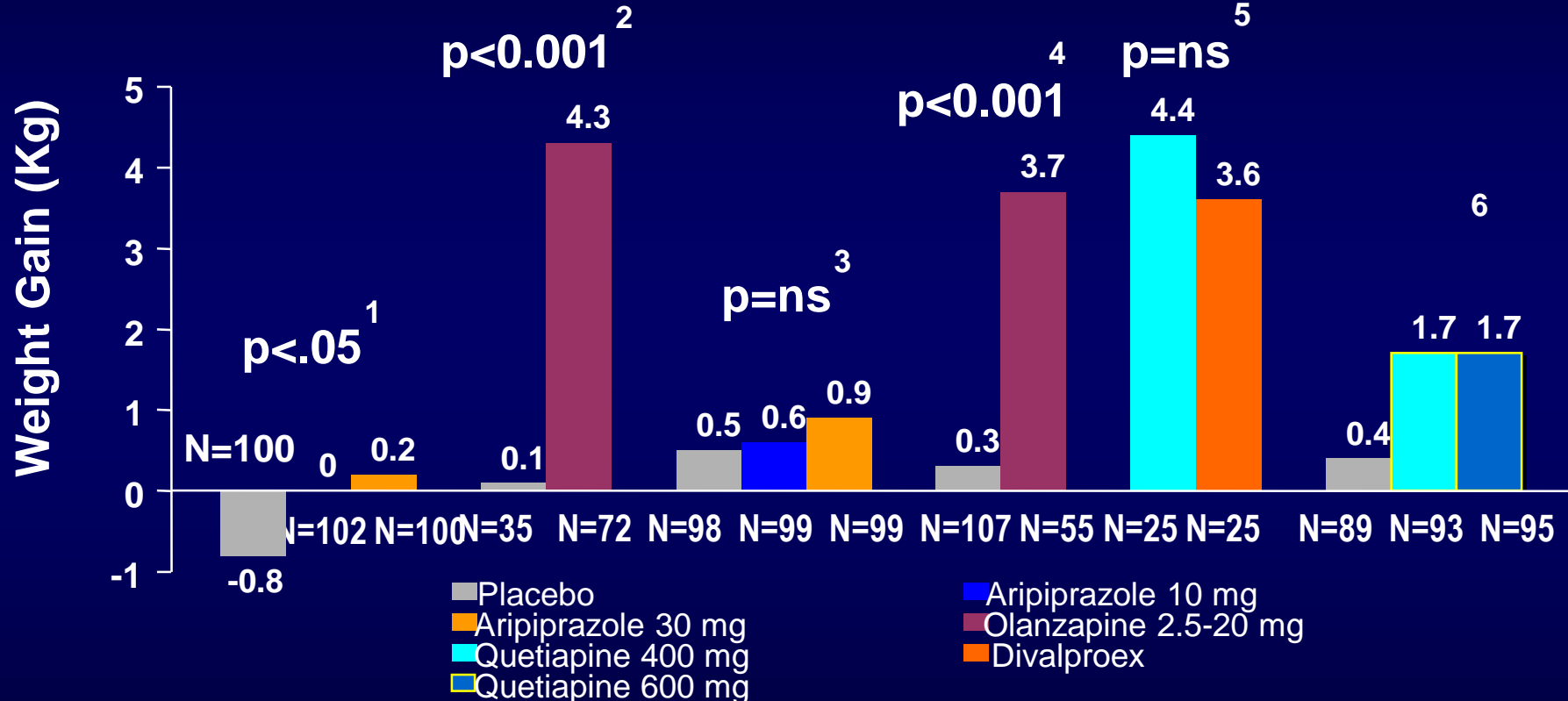
Incidence and Severity of EPS * with Antipsychotics in Psychotic Youth



Weight Gain in in Pediatric Schizophrenia & Bipolar *

**Pediatric Schizophrenia:
6-Weeks ^{1,2}**

**Pediatric Bipolar D/O:
3-Weeks ^{4,6} and 4-Weeks ^{3,5}**



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

Question 4

The atypical antipsychotic that was recently approved by FDA for use in pediatric bipolar disorder is:

- A) Risperidone
- B) Olanzapine
- C) Quetiapine
- D) Ziprasidone
- E) Clozapine

Question 5

The mood stabilizer with a propensity to induce weight loss is:

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

Answers

- 1 - A
- 2 - C
- 3 - D
- 4 - A
- 5 - E