Diagnosis and Treatment of Children and Adolescents with Bipolar Disorder

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Disclosures: Christoph U. Correll

I have an interest in relation with one or more organizations that could be perceived as a possible conflict of interest in the context of this presentation. The relationships are summarized below:

Interest	Name of organization
Grants	**National Institute of Mental Health (NIMH), Patient Centered Outcomes Research Institute (PCORI), Takeda, Thrasher Foundation**
Shares	**No share holdings in pharmaceutical companies**
Paid positions, honoraria and advisory boards	**Alkermes, Bristol-Myers Squibb, Forum, Gerson Lehrman Group, IntraCellular Therapies, Janssen/J&J, LB Pharma, Lundbeck, Medavante, Medscape, Neurocrine, Otsuka, Pfizer, ProPhase, Sunovion, Supernus, Takeda, and Teva**

Overview

- Epidemiology
- Phenomenology
- Management of Pediatric Bipolar Disorder
  - Mania/mixed mania
  - Bipolar depression
  - Relapse prevention
- Adverse Effects
- Conclusions

Pediatric Bipolar Disorder

Epidemiology

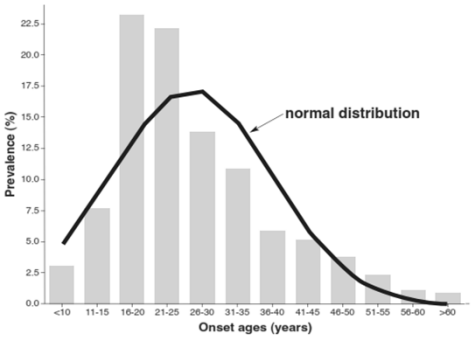
Severity of Adolescent Mood D/o's

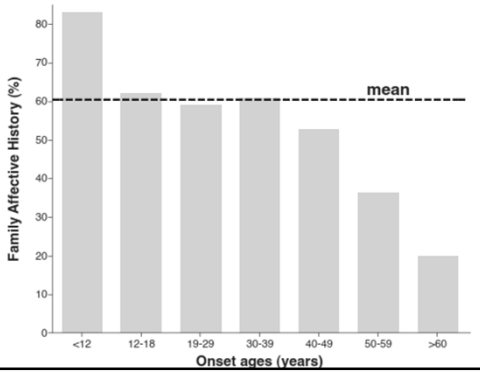
Disorder	Severity Distribution, % (SE)		
	Serious[b]	Moderate[b]	Mild[b]
Mood disorders			
Major depressive episode/dysthymia	35.6 (5.2)	31.0 (6.4)	33.4 (6.7)
Bipolar disorder[c]	30.5 (5.8)	26.5 (12.1)	43.1 (10.7)
Any mood disorder	32.4 (4.5)	29.8 (7.4)	37.8 (7.7)
Anxiety disorders			
Agoraphobia[d]	22.1 (7.4)	25.9 (15.5)	52.0 (15.9)
Generalized anxiety disorder	32.0 (8.6)	21.0 (8.9)	47.1 (9.0)
Social phobia	23.9 (5.1)	23.8 (9.3)	52.3 (9.0)
Specific phobia	19.6 (5.1)	16.8 (11.6)	63.7 (10.6)
Panic disorder[e]	35.4 (12.6)	21.2 (10.3)	43.4 (10.9)
Posttraumatic stress disorder	27.7 (7.0)	23.8 (11.1)	48.5 (10.4)
Separation anxiety disorder	25.0 (8.1)	25.5 (8.9)	49.5 (10.9)
Any anxiety disorder	18.4 (3.4)	19.6 (10.3)	62.0 (9.6)
Behavior disorders			
Attention-deficit/ hyperactivity disorder	35.4 (8.2)	40.6 (14.0)	24.0 (10.6)
Oppositional-defiant disorder	43.8 (7.8)	24.3 (6.8)	31.9 (8.9)
Conduct disorder	59.8 (8.4)	21.1 (9.4)	19.2 (8.6)
Eating disorders[f]	27.5 (10.0)	26.0 (15.1)	46.5 (16.6)
Any behavior disorder	33.6 (5.1)	30.2 (9.4)	36.2 (9.6)
Substance disorders			
Alcohol abuse[g]	26.4 (5.7)	21.4 (8.2)	52.1 (9.2)
Drug abuse[g]	33.8 (6.1)	19.2 (7.3)	47.0 (7.1)
Any substance disorder	29.1 (5.0)	19.2 (6.7)	51.7 (7.1)
No. of disorders			
Any disorder	18.8 (2.9)	22.9 (9.8)	58.2 (9.5)
Exactly 1 disorder	8.5 (3.8)	19.1 (12.4)	72.4 (12.1)
Exactly 2 disorders	12.1 (2.5)	25.3 (10.9)	62.5 (10.4)
≥3 Disorders	43.1 (6.2)	28.3 (7.1)	28.6 (7.0)

NCS-RA: n=6,483

Kessler RC et al. Arch Gen Psych. 2012; Apr;69(4):381-9.

Age at BP-I Onset & Outcomes (n=1,665)





Factors associated with juvenile onset: logistic regression

Factors	Odds ratio (95%CI)	χ^2	p
Poor functional outcome	2.00 (1.34 to 2.95)	8.82	0.003
More family history	1.71 (1.20 to 2.43)	5.86	0.015
More episodes/year	1.08 (0.89 to 1.33)	0.63	0.43

Factors associated with onset in childhood vs. adolescence: logistic regression

Factors	Odds ratio (95%CI)	χ^2	p
Poor functional outcome	2.70 (1.08 to 6.77)	4.51	0.03
More family history	4.65 (1.04 to 20.8)	4.04	0.04
More episodes/year	4.85 (1.05 to 22.4)	0.63	0.04

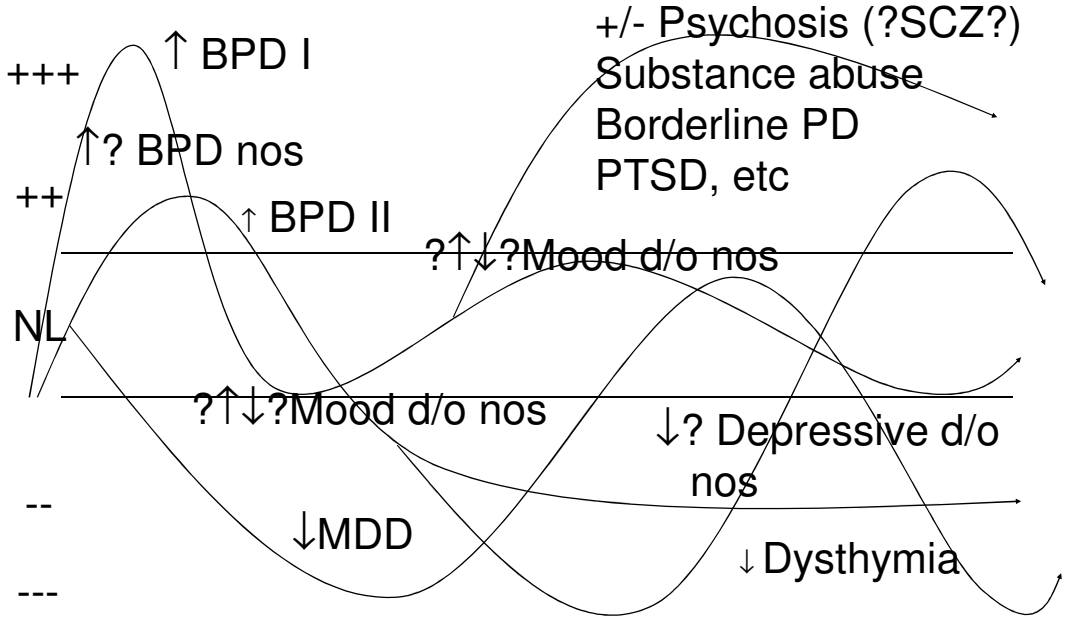
Factors associated with younger onset age: linear regression

Factors	β coefficient (95% CI)	t	p
More family history	2.78 (1.05 to 4.41)	3.35	0.001
Poor functional outcome	2.61 (1.01to 4.21)	3.20	0.001
Episodes/year	0.62 (–1.90 to 1.43)	1.50	0.13

Baldessarini R et al. World Psychiatry 2012;11(2):40-6

Phenomenology

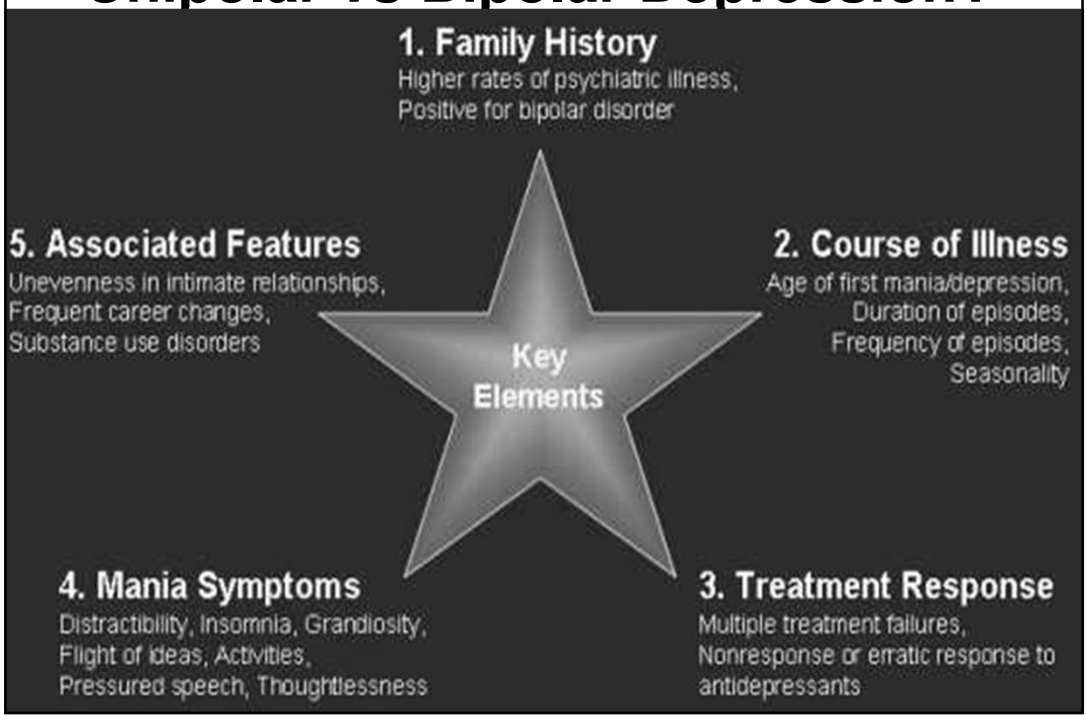
The Complex Bipolar Spectrum



DIAGNOSTIC CHALLENGES

- HETEROGENEITY
- Lack of biological illness markers
- Lack of normative data
- Non-specificity of symptoms
- Use of different definitions
- Fluctuating course of illness
- Developmental differences
- Role of psychosocial stressors
- Lack of data in large cohorts

Unipolar vs Bipolar Depression?



BIPOLAR CONTROVERSY 1

- Symptom overlap with other major childhood disorders:
  - Comorbidity
  - Developmental subtype
  - Risk factors (antidepressants, stimulants)

Manic Episode: Overlap With ADHD

Mania Criteria	Overlapping ADHD Criteria
Elevated or expansive mood	-
Irritable mood	[Common associated symptom related to frustrations and low frustration tolerance]
Grandiosity	[boastful compensation of limitations not uncommon]
Decreased need for sleep	[Insomnia secondary to psychostimulants not uncommon; careful distinction is needed]
Pressured speech	Talks excessively, blurts out answers, interrupts
Flight of ideas	Talks excessively
Distractibility	Loosing things, inattention, not listening, distractible, forgetful
Increased goal-directed activity or psychomotor agitation	Fidgets, leaves seat, runs/climbs excessively, “on the go”
Excessive involvement in pleasurable, but potentially painful activities	Carelessness, avoiding school work

Hauser M and Correll CU. Can J Psychiatry. 2013 Jan;58(1):22-31

Manic Episode: Overlap With ODD

ODD Criteria	Overlapping Mania Criteria
Is often spiteful and vindictive	-
Often loses temper	Irritable mood
Often argues with adults	Irritable mood, grandiosity
Often actively defies or refuses to comply with adults’ requests or rules	Grandiosity, excessive involvement in pleasurable activities that have a potential for painful consequences
Often deliberately annoys people	Irritable mood, grandiosity
Often blames other for his/her mistakes or misbehavior	Irritable mood, grandiosity
Often is touchy or easily annoyed by others	Irritable mood
Is often angry and resentful	Irritable mood

Hauser M and Correll CU. Can J Psychiatry. 2013 Jan;58(1):22-31

MANIA ITEM	BIPOLAR (n=93)	ADHD (n=81)
Irritable Mood	98%	72%
Grandiosity	86%*	7%
Elated Mood	89%*	14%
Daredevil Acts	65%	11%
Uninhibited People Seeking	66%	25%
Silliness/Laughing	63%	24%
Flight of Ideas/Racing Thoughts	71%*	10%
Accelerated Speech	97%	82%
Decreased Need For Sleep	40%*	6%
Increased Energy	100%	95%
Hypersexuality	43%*	6%
Distractibility	94%	97%

Geller et al., J Child Adol Psychopharmacol 2002

BIPOLAR CONTROVERSY 2

- Degree of continuity with adult disorder
- Requirement of hallmark symptoms
  - Specificity
- Episodic Instability
  - Level of resolution
- Cycle duration
  - Full criteria vs subsyndromal
  - Observable behavior vs subjective report

PEDIATRIC BIPOLAR PHENOTYPES

Criterion	Narrow	BAD NOS	Irritable (Hypo) Mania NOS	Broad*
Euphoria	+	+	-	-
Episodicity	+	+	-	-
Cycle Length	M: ≥7 d m: ≥4 d	≥1 d	≥1 d	-

*Chronic hyperarousal, poor frustration tolerance, chronic sxs, abnormal inter-episode mood states (anger, depr.), ≥2 settings

Leibenluft et al., Am J Psychiatry 2003

Disruptive Mood Dysregulation Disorder (DMDD) (1)

A. Severe recurrent temper outbursts manifested verbally (e.g., verbal rages) and/or behaviorally (e.g., physical aggression toward people or property) that are grossly out of proportion in intensity or duration to the situation or provocation.

B. The temper outbursts are inconsistent with developmental level.

C. The temper outbursts occur, on average, three or more times per week.

D. The mood between temper outbursts is persistently irritable or angry most of the day, nearly every day, and is observable by others (e.g., parents, teachers, peers).

APA 2013 - Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,

Disruptive Mood Dysregulation Disorder (DMDD) (2)

E. Criteria A–D have been present for ≥12 months and there has not been a period ≥3 consecutive months without all of the symptoms in Criteria A–D.

F. Criteria A and D are present in ≥2 of 3 settings (home, school, peers) and are severe in ≥1 of these.

G. The diagnosis should not be made for the first time before age 6 years or after age 18 years.

H. By history or observation, the age at onset of Criteria A–E is before 10 years.

I. There has never been a distinct period lasting >1 day during which the full symptom criteria, except duration, for a manic or hypomanic episode have been met.

APA 2013 - Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,

Disruptive Mood Dysregulation Disorder (DMDD) (3)

J. The behaviors do not occur exclusively during an episode of MDD and are not better explained by another mental disorder (e.g., ASD, PTSD, separation anxiety disorder, persistent depressive disorder [dysthymia]).

> **Note:** This diagnosis **cannot coexist with ODD, IED, or bipolar disorder**, though it can coexist with others, including MDD, ADHD, CD, and substance use disorders. **Individuals whose symptoms meet criteria for both DMDD and ODD should only be given the diagnosis of DMDD.** If an individual has e**ver experienced a manic or hypomanic episode**, the diagnosis of **DMDD should not be assigned**.

K. The symptoms are not attributable to the physiological effects of a substance or to another medical or neurological condition.

APA 2013 - Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,

BPD in Youth vs. Adults

Characteristic	Child and Adolescent Onset	Adult Onset
Family History of BP-I	Common, especially in prepubertal onset form	Not as common
Onset Pattern	Often more protracted	Often more abrupt
Cycle Length	Often short, frequent ultra-rapid and ultradian cycling (especially in prepubertal-onset form)	Often more demarcated episodes lasting week(s), rather than hours or days
Inter-episode Interval	Often impaired	Asymptomatic intervals not uncommon
Euphoria	Irritability > euphoria	Euphoria not uncommon
Mixed symptoms	Very common	Not as common
Psychosis	Common	Not as common
Substance Abuse Comorbidity	Less common	More common
ADHD Comorbidity	Common, especially in prepubertal-onset form	Uncommon
Aggression and Impulsivity	Common, especially in prepubertal-onset form	Less common

Hauser M and Correll CU. Can J Psychiatry. 2013 Jan;58(1):22-31

Course and Outcome of BD Youth (COBY)

- After 2.5 yrs 81.5% had fully recovered
- After 4 yrs, 62.5% had a syndromal recurrence, especially depression
- 1/3 had 1 syndromal recurrence, 30% had $\geq$2
- Polarity predicted subsequent episodes
- Participants were symptomatic 60% of follow-up period, + subsyndr. depression and mixed polarity
- 40% had sub-/syndromal sxs during 75% of follow-up
- 16% had psychotic sxs during 17% of follow-up
- Poor outcome predicted by early onset, BP-NOS, long illness duration, low SES and FxHx of mood d/o

Birmaher B et al., Am J Psychiatry 2009; 166:795–804

Sxs During Worst Mania Episode

Variable	BP-I (n = 220)†	BP-NOS (n = 116)†	
Symptom rated mild or higher			
Elated or expansive mood	91.8	81.9	*
Irritability or anger	84.5	80.2	
Decreased need for sleep	83.2	56.9	*
Grandiosity	75.5	62.1	*
Racing thoughts	75.5	65.5	
Unusual energy	91.8	82.8	
Increased goal-directed activity	61.4	56.9	
Accelerated speech	92.7	81.9	*
Flight of ideas	80.0	66.4	*
Poor judgment	85.0	71.6	*
Distractibility	86.0	74.1	*
Motor hyperactivity	94.1	87.1	
Hypersexuality	48.6	24.1	*
Mood lability	89.5	89.7	
Symptom rated moderate or higher			
Elated or expansive mood	86.4	61.2	*
Irritability or anger	77.3	62.9	*
Decreased need for sleep	77.7	37.9	*
Grandiosity	57.3	34.5	*
Racing thoughts	61.8	33.6	*
Unusual energy	89.5	71.6	*
Increased goal-directed activity	48.2	25.9	*
Accelerated speech	86.5	62.1	*
Flight of ideas	65.9	37.9	*
Poor judgment	75.0	44.0	*
Distractibility	67.3	45.7	*
Motor hyperactivity	87.3	75.0	*
Hypersexuality	29.1	7.8	*
Mood lability	82.3	66.4	*

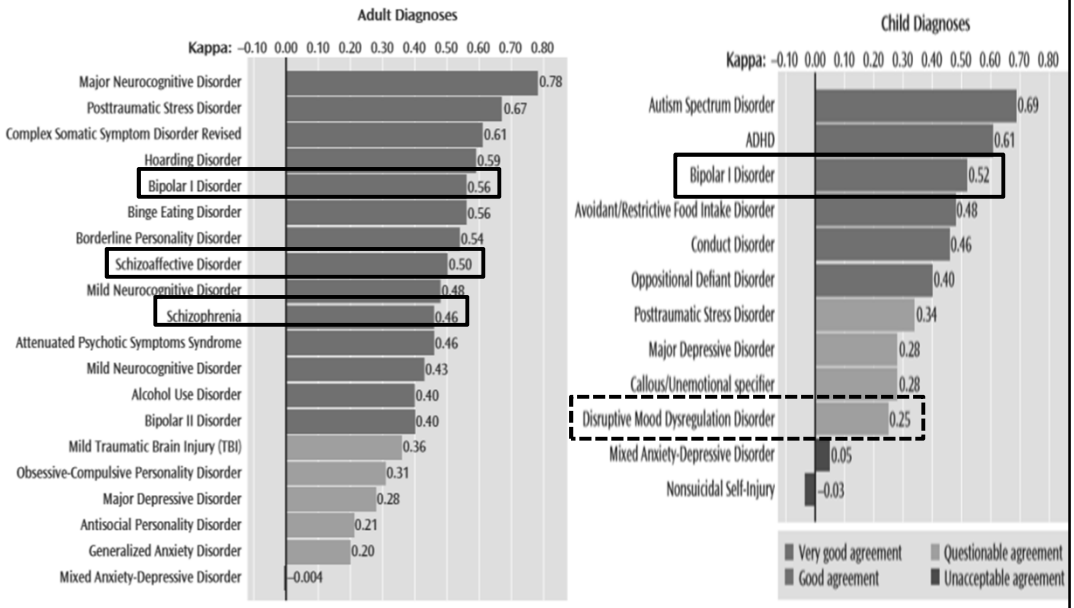
*** Significant difference between BP-I and BP-NOS** Axelson et al., Archives Gen Psychiatry 2007

8-Year Outcome in Prepubertal Onset BD (N=115)

- 87.8% recovered from mania, and 73.3% relapsed
- Like 1st mania episodes, 2nd and 3rd episodes were characterized by psychosis, daily cycling, and long duration (55.2 +40.0 wks), but were shorter than 1st.
- Mania relapse predicted by low maternal warmth predicted
- More weeks ill with mania predicted by low maternal warmth and younger baseline age
- 44% of 54 patients age $\geq$18 yrs had $\geq$1 manic relapse despite relatively brief f/u into adulthood
- 35.2% had substance use disorders.

Geller B et al., Arch Gen Psychiatry. 2008;65(10):1125-1133

Reliability of Psychiatric Diagnoses: DSM-5 Field Trials

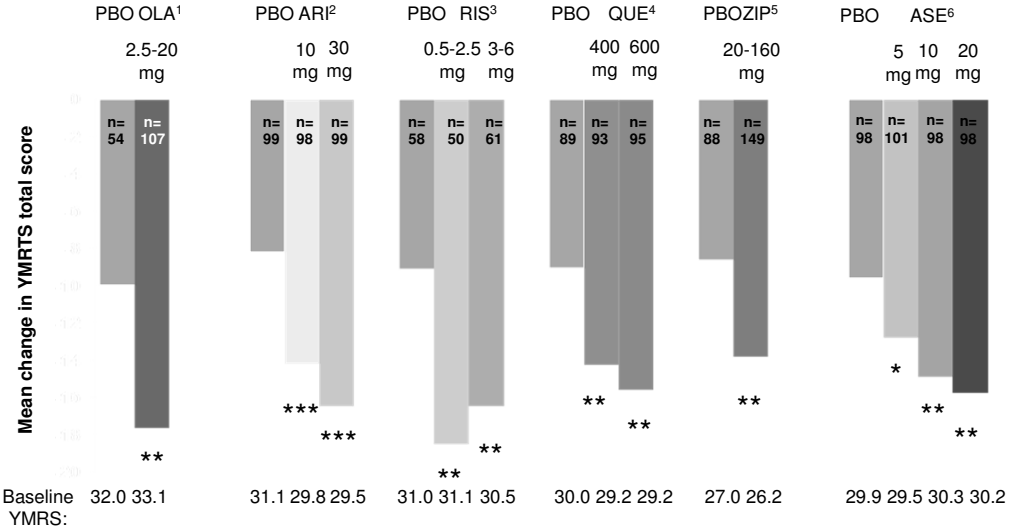


Freedman R, et al. *Am J Psychiatry 2013;170:1–5*

Pharmacologic Treatment of Pediatric Bipolar Disorder

Acute Efficacy for Mania/Mixed Episodes

SGAs: YMRS Total Improvement from 6 PBO-Controlled RCTs in Pediatric BPD (10–17 yrs)

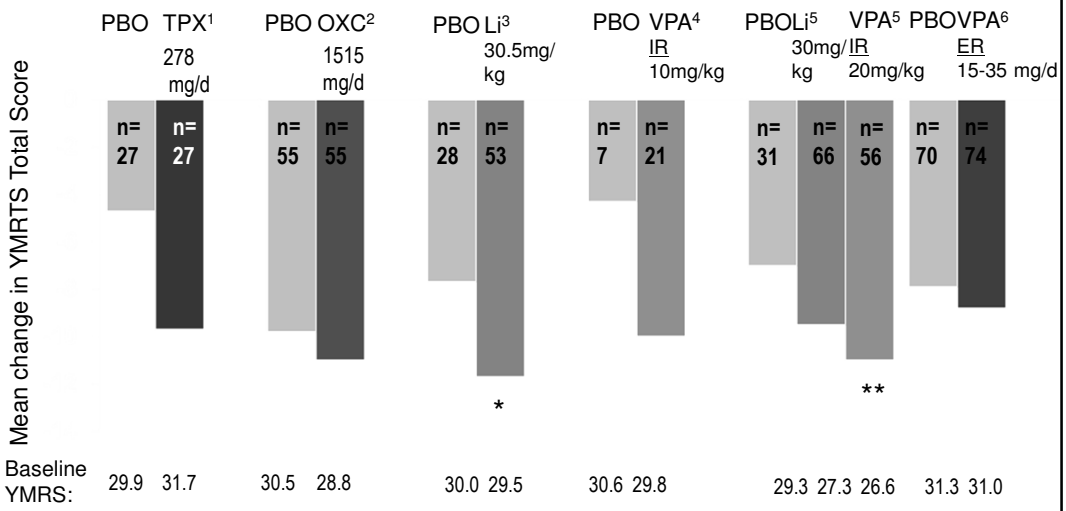


*p<0.01 vs placebo; **p<0.001 vs placebo; ***p<0.0001 vs placebo

1. Tohen M, *et al. Am J Psychiatry* 2007;164:1547–1556
2. Findling RL *et al. J Clin Psychiatry* 2009;70:1441–1451.
3. Haas M *et al. Bipolar Disord* 2009;11:687–700.
4. Pathak RL *et al.* J Clin Psychiatry. 2013 Jan;74(1):e100-9.
5. Findling RL *et al.* J Child Adolesc Psychoph. 2013;23(8):545-57.
6. Findling RL et al. J Am Acad Child Adolesc Psychiatry. 2015 Dec;54(12):1032-41.

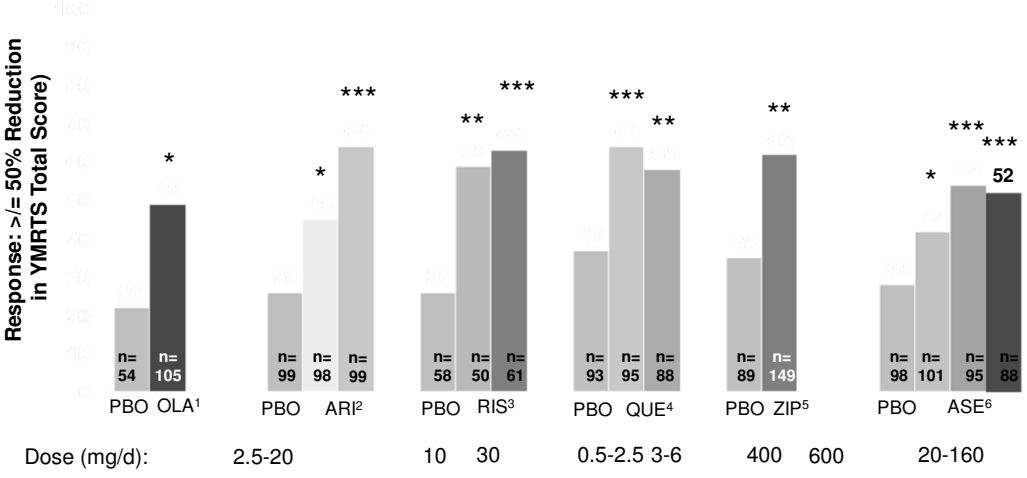
Adapted from Correll CU et al. J Clin Psychiatry. 2011 May;72(5):655-670.

Mood Stabilizers: YMRS Total Improvement from 5 PBO-Controlled RCTs in Pediatric BPD (6-17 Yrs)



1. DelBello MP et al J Am Acad Child Adolesc Psychiatry. 2005 Jun;44(6):539-47;
2. Wagner KD et al. Am J Psychiatry. 2006 Jul;163(7):1179-86;
3. Findling RL, et al. Pediatrics. 2015 Nov;136(5):885-94.
4. Kowatch RA et al. J Child Adolesc Psychopharmacol. 2015 May;25(4):306-13.
5. Kowatch R et al. AACAP Annual Meeting, October 27, 2007;
6. Wagner KD et al J Am Acad Child Adolesc Psychiatry. 2009 May;48(5):519-32.

SGAs: Response Rates (≥50%↓ in YMRS Total Score) in PBO-Controlled RCTs in Pediatric BPD: NNTs–3-6



*p<0.05 vs placebo; **p<0.005 vs placebo; ***p<0.001 vs placebo

1. Tohen M *et al. Am J Psychiatry* 2007;164:1547–1556.
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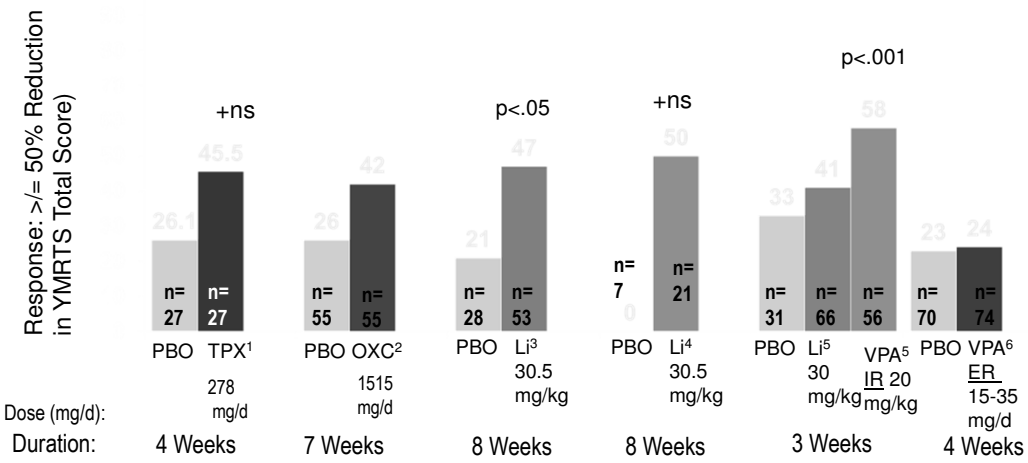
Adapted from Correll CU et al. J Clin Psychiatry. 2011 May;72(5):655-670.

Mood Stabilizers: Response Rates (≥50% Reduction in YMRS Total Score) in Pediatric Bipolar D/o: NNT=4-100



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+: response rate only given for CGI-I much or very much improved

Antipsychotics-PBO vs. Mood Stabilizer-PBO Differences in Efficacy

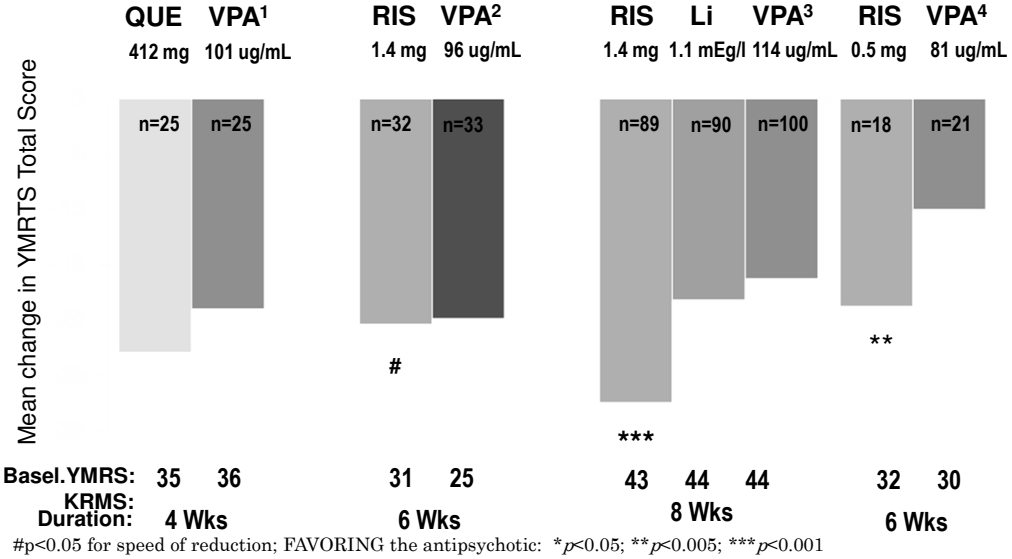
	Children and Adolescents				Significant Difference SGA vs MS in Youth
Outcome	***Second- Generation Antipsychotics N = 1,118***		***Mood Stabilizers N = 494***		
Continuous Outcome	***Effect Size***	***95% CI***	***Effect Size***	***95% CI***	
YMRS (including TPX among MS)	**0.65**	0.53– 0.78	**0.24**	0.06– 0.41	**SGA > MS**
YMRS (excluding TPX among MS)			**0.20**	0.02– 0.39	**SGA > MS**
CGI-BP Overall Illness (including TPX among MS)	**0.63**	0.50– 0.76	0.47[1]	-	N/A
Categorical Outcome	***NNT***	***95% CI***	***NNT***	***95% CI***	
Response: ≥ 50% ↓YMRS	4.0	3.3– 5.3	7.81	4.7– 24.4	NS
Remission: YMRS </ = 12	3.7	3.1– 4.7	-33.3**	-6.8– 10.0	NS
All-cause Discontinuation	**12.7**	7.5– 41.2	15.6**	-7.9–4.3	NS

*N = patients on medication or placebo

** = 95% confidence interval crosses 0, which indicates that the difference between treatment group and placebo is not statistically significant

Correll CU et al. Bipolar Disorders 2010;12(2):116-41.

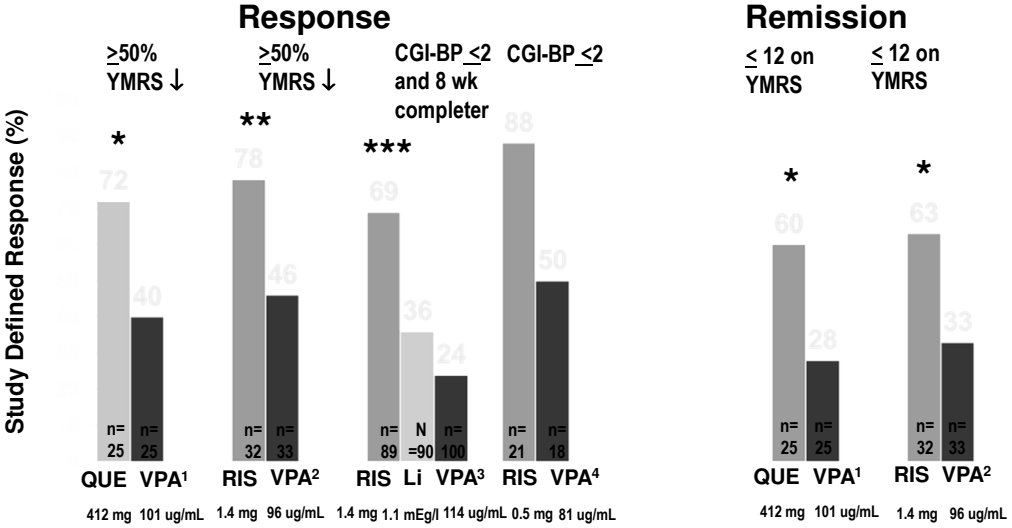
SGA vs VPA or Li: Mean Improvement in YMRS Total Score from 5 RCTs in Pediatric Bipolar D/o (6-17 Yrs)



#p<0.05 for speed of reduction; FAVORING the antipsychotic: *p<0.05; **p<0.005; ***p<0.001

1. DelBello MP, *et al. JAACAP 2006;54(3):305-13* – mean age: 15.0 years; 46% with psychosis
2. Pavuluri MN *et al. Bipolar Disord* 2010;12:593-605 – mean age: 10.9 years; 20% with psychosis
3. Geller B *et al. Arch Gen Psychiatry* 2012;69:515-28 – mean age: 10.1 years; 77% with psychosis
4. Kowatch RA et al. J Child Adolesc Psychopharmacol. 2015 May;25(4):306-13.; % with psychosis not reported

Response and Remission in 4 Trials Comparing Antipsychotics with Mood Stabilizers in PBD



* p<0.05; **p<0.01; ***p<0.001 favoring antipsychotic;

1. DelBello MP, *et al. JAACAP 2006;54(3):305-13* – mean age: 15.0 years; 46% with psychosis
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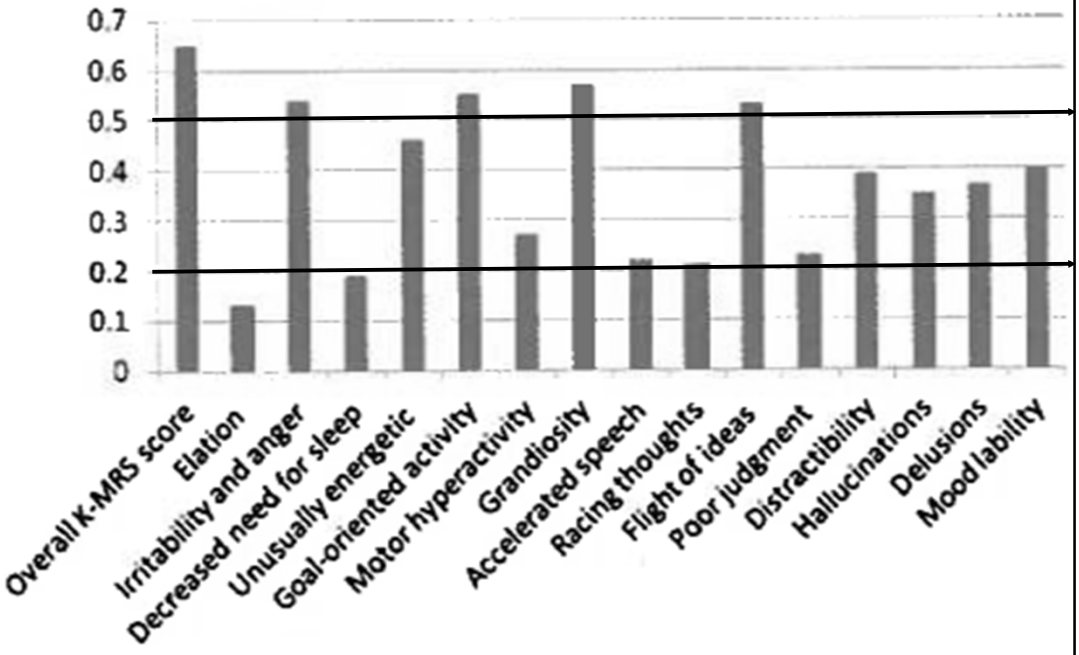
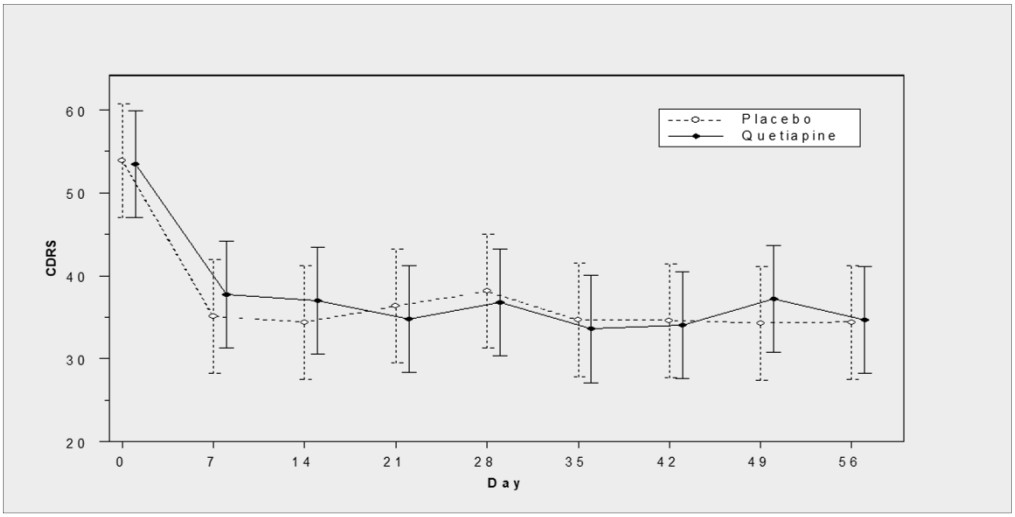
TEAM Study: Effect Sizes of Risperidone vs. Lithium *



* On KSADS-Mania Rating Scale Vitiello B et al. J Am Acad Child Adolesc Psychiatry. 2012;51(9):867-78.

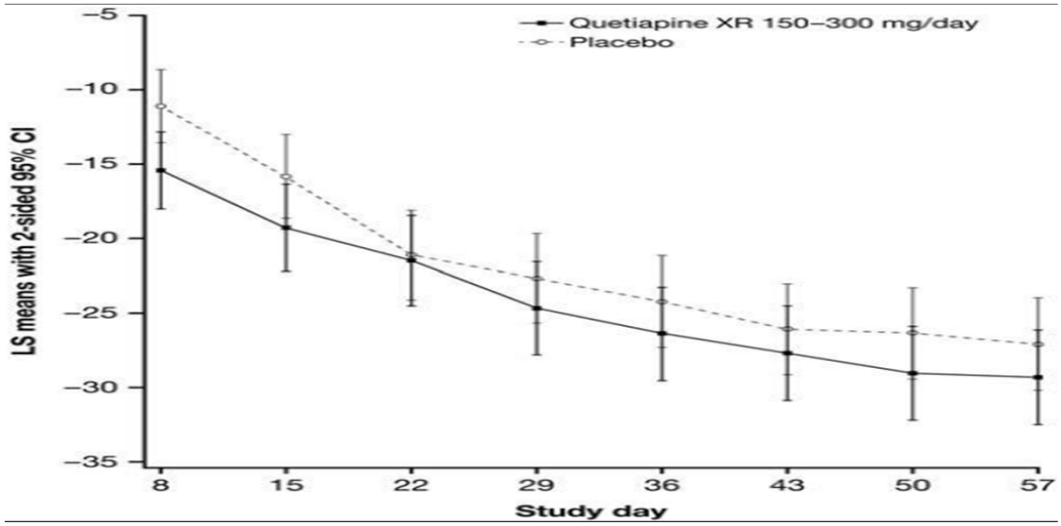
Acute Efficacy for Bipolar Depression

Quetiapine (n=17) vs. Placebo (n=15):
CDRS-R Change



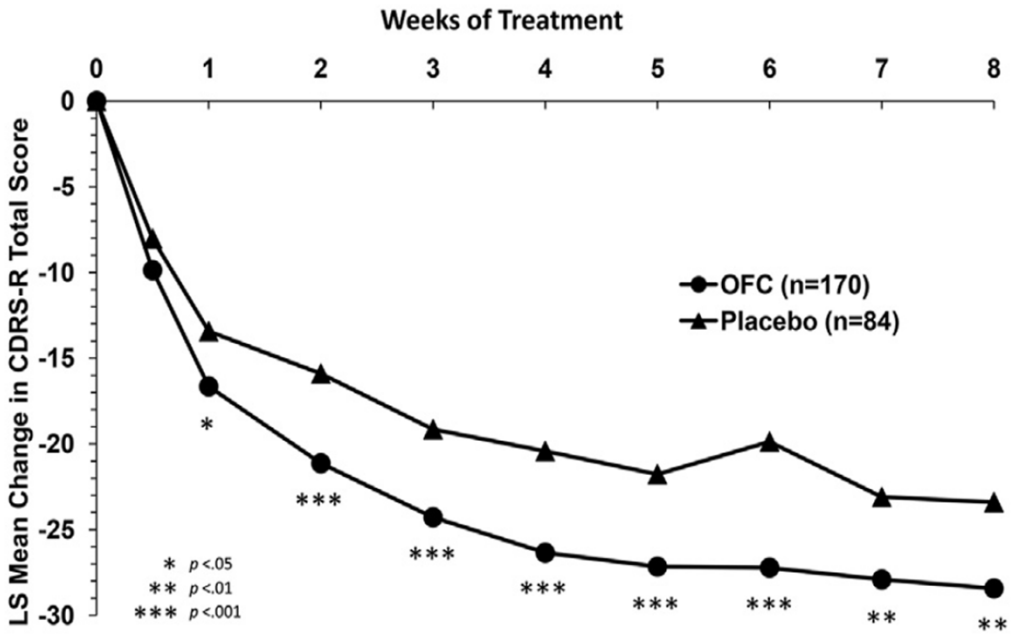
Age: 12-18 years (mean=15.5), females: 67%
Response: PBO=67% vs QUE: 71%; Remission: PBO: 40% vs QUE: 35%
DelBello MP et al. Bipolar Disord. 2009 Aug;11(5):483-93.

Quetiapine (n=93) vs. Placebo (n=100):
CDRS-R Change



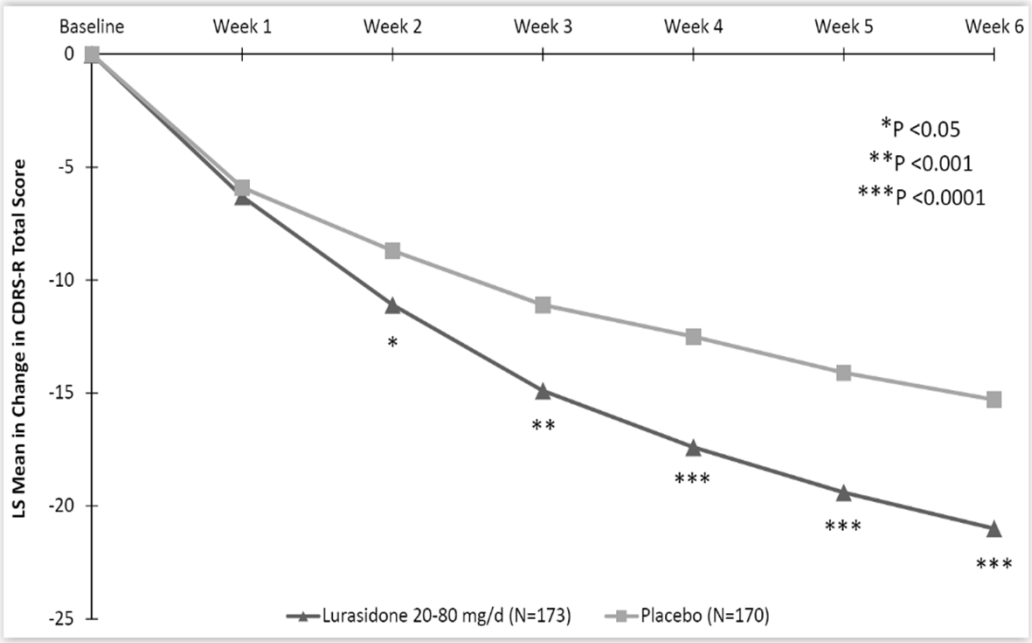
Age: 10-17 years (mean=14.0), females: 49.5%
Response: PBO=55.0% vs QUE: 63.0%; Remission: PBO: 34.0% vs QUE: 45.7%
Findling RL et M al. J Child Adolesc Psychopharmacol. 2014 Aug;24(6):325-35.

8-Week RCT of OLA/FLU vs PBO



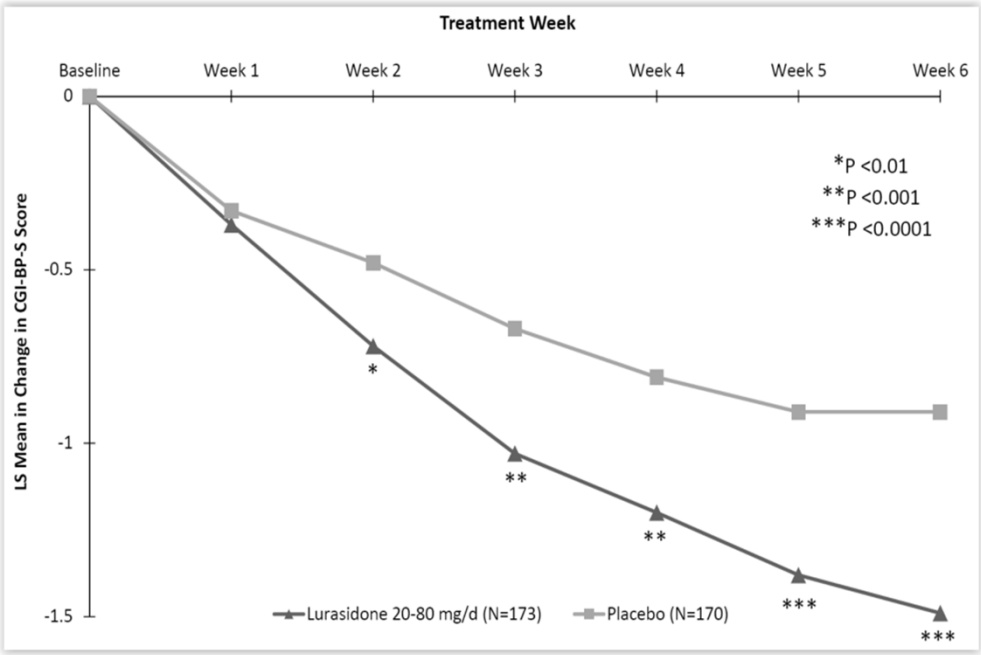
Detke H et al. J Am Acad Child Adolesc Psychiatry. 2015 Mar;54(3):217-24.

6-Week RCT of Lurasidone vs PBO: CDRS-R



DelBello M et al. J Am Acad Child Adolesc Psychiatry. 2017. Dec;56(12):1015–25.

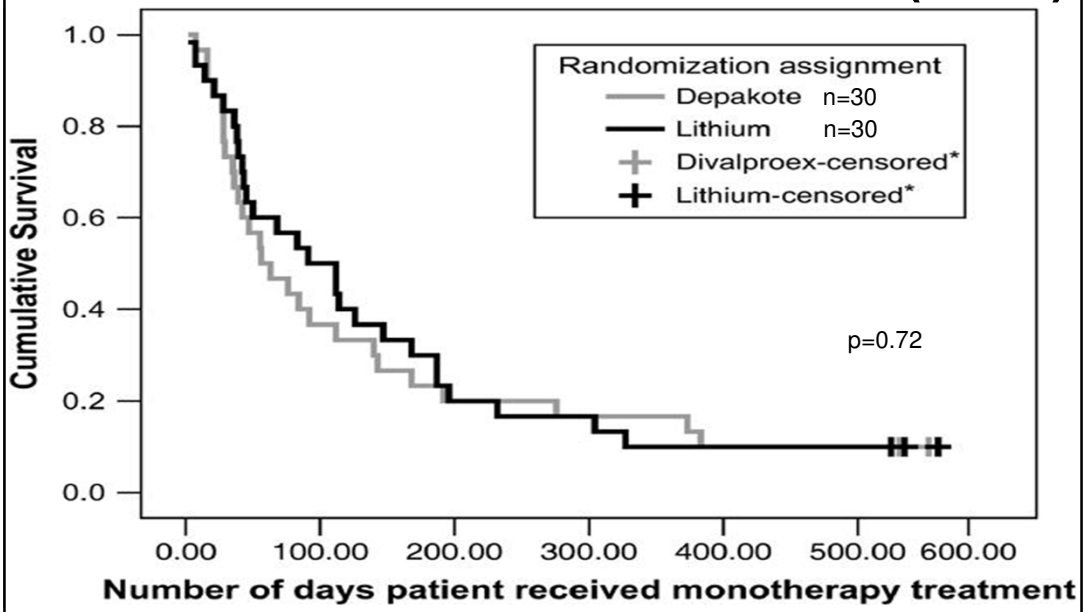
6-Week RCT of Lurasidone vs PBO: CGI-S



DelBello M et al. J Am Acad Child Adolesc Psychiatry. 2017. Dec;56(12):1015–25.

Bipolar Disorder Maintenance

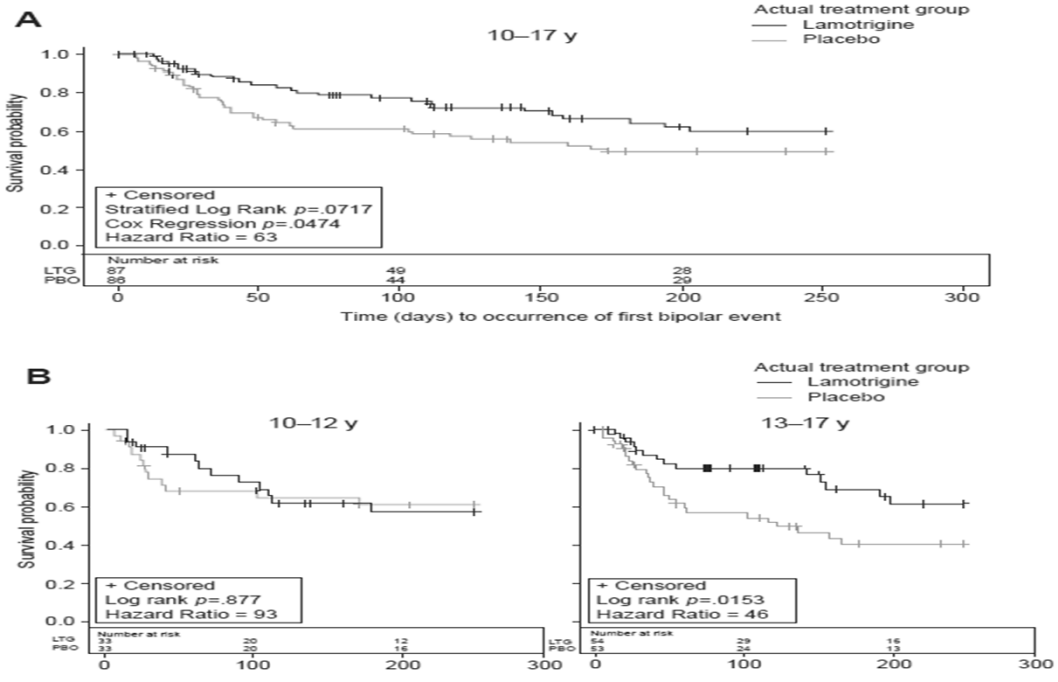
18 Mo Maintenance VPA or Li Trial (N=60)



139 youths (10.8±3.5 yrs) initially treated with Li+/DVPX for 10.7±5.4 weeks. Li+ and DVPX did not differ in survival time until emerging relapse (p=0.55) or all-cause discontinuation (p =0.72).

Findling et al., J Am Acad Child Adolesc Psychiatry. 2005 May;44(5):409-17.

Maintenance: Lamotrigine vs Placebo



Findling RL, et al. J Am Acad Child Adolesc Psychiatry. 2015 Dec;54(12):1020-1031.

Maintenance: Aripiprazole vs Placebo

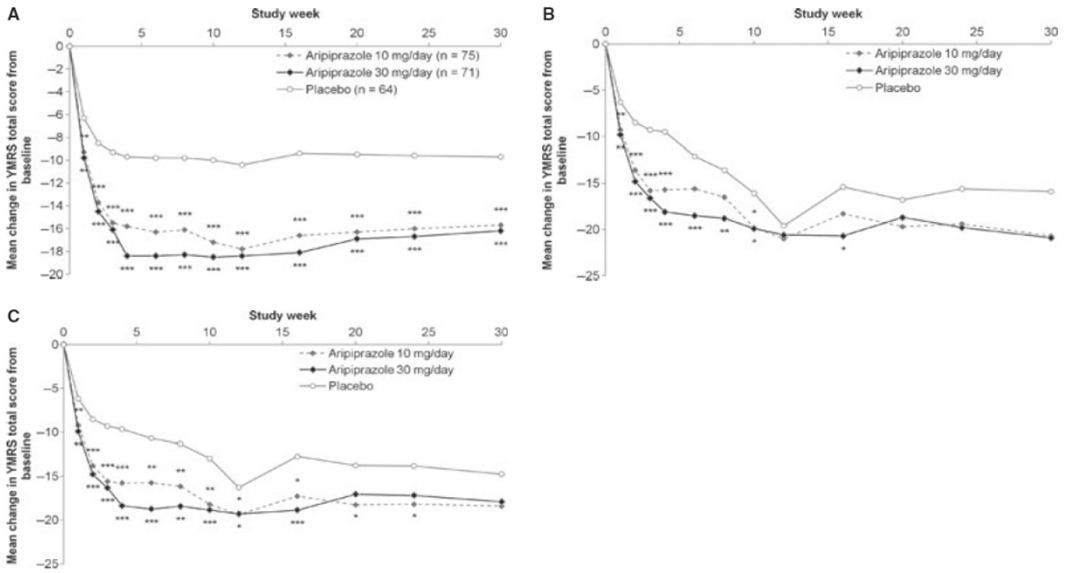


Fig. 2. Mean change from baseline in Young Mania Rating Scale (YMRS) total score (**A**) last observation carried forward (LOCF), (**B**) observed case (OC), and (**C**) mixed-models repeat measures (MMRM) analysis (extension phase sample). *p < 0.05 versus placebo; **p < 0.05 versus placebo; ***p ≤ 0.001 versus placebo. Baseline YMRS total scores: aripiprazole 10 mg/day = 30.3; aripiprazole 30 mg/day = 29.7; placebo = 30.4.

Findling RL, et al. Bipolar Disord. 2013 Mar;15(2):138-49.

Maintenance: Lithium with or without Adjunctive Treatments

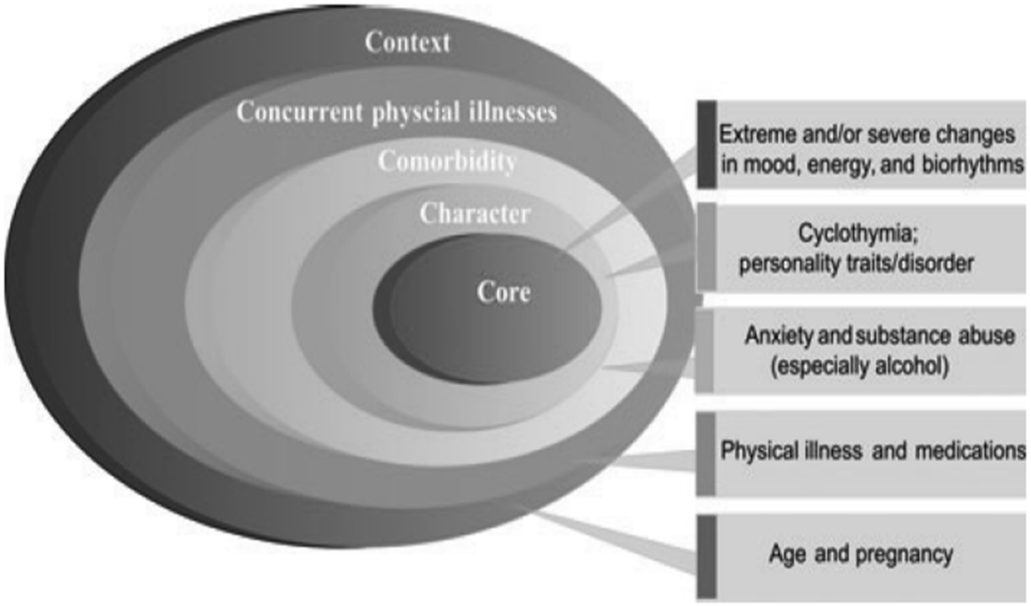
	No adjunctive psychotropic medications n = *16*		*Adjunctive psychotropic medications* n = *25*		*Mean difference in change scores*	
Measure	*Total participants*	p	*Total participants*	p	*Mean (SD)*	p
YMRS						
Phase II baseline score Mean (SD)	8.2 (5.4)		10.8 (6.8)			
EOS score Mean (SD)	8.7 (8.2)	0.76	9.9 (7.0)	0.56	1.4 (7.2)	0.55
Change score Mean (SD)	0.5 (6.8)		−0.9 (7.5)			
CDRS-R						
Phase II baseline score Mean (SD)	24.8 (5.1)		23.5 (5.4)			
EOS score Mean (SD)	23.6 (7.1)	0.49	22.4 (5.7)	0.35	−0.2 (6.3)	0.93
Change score Mean (SD)	−1.2 (7.1)		−1.1 (5.7)			
CGAS						
Phase II baseline score Mean (SD)	67.5 (14.4)		69.7 (14.2)			
EOS score Mean (SD)	69.2 (13.2)	0.48	68.9 (13.5)	0.55	0.5 (9.9)	0.86
Change score Mean (SD)	1.7 (9.8)		1.2 (10.0)			
CGI-S (Mania)						
Phase II baseline score Mean (SD)	2.2 (0.9)		2.4 (1.0)			
EOS score Mean (SD)	2.2 (1.1)	1.00	2.2 (1.1)	0.46	0.2 (0.9)	0.60
Change score Mean (SD)	0 (0.7)		−0.2 (1.1)			
CGI-S (Depression)						
Phase II baseline score Mean (SD)	1.9 (1.0)		1.7 (0.8)			
EOS score Mean (SD)	2.1 (0.9)	0.48	1.7 (0.9)	1.00	0.2 (1.0)	0.56
Change score Mean (SD)	0.2 (1.0)		0.0 (1.0)			
CGI-S (Overall Illness)						
Phase II baseline score Mean (SD)	2.4 (0.9)		2.4 (1.0)			
EOS score Mean (SD)	2.2 (1.1)	0.42	2.2 (1.1)	0.38	0.0 (1.0)	0.97
Change score Mean (SD)	−0.2 (0.9)		−0.2 (1.1)			

YMRS, Young Mania Rating Scale; CDRS-R, Child Depression Rating Scale Revised; CGAS, Children's Global Assessment Scale; CGI-S, Clinical Global Impressions-Severity; EOS, end of study.

Response: 68.3%; remission: 53.7% Findling RL, et al. J Child Adolesc Psychopharmacol. 2013 Mar;23(2):80-90.

Adverse Effects

Managing the Complexities in Bipolar Disorder



Malhi GS *et* al. Bipolar Disorders 2012: 14 (Suppl. 2): 66-89.

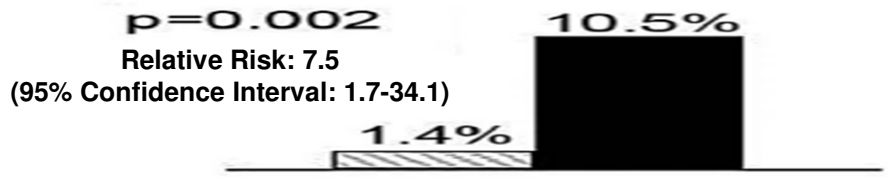
24% Incidence of Elevated TSH in Children and Adolescents During 20 Weeks of Combined Treatment with Lithium and Divalproex (N=82)

	Group 1 (TSH < 10.0, *n* = 62)	Group 2 (TSH ≥ 10.0, *n* = 20)
EOS lithium serum levels (mmol/L)		
Mean (SD)	0.76 (0.37)	1.0 (0.35)
Range	0.05–1.60	0.13–1.68
EOS divalproex sodium serum levels (μg/mL)		
Mean (SD)	70.7 (30.0)	85.8 (31.4)
Range	3–122	16–152
Baseline TSH levels (mU/L)		
Mean (SD)	2.05 (0.89)	2.97 (1.45)
Range	0.32–4.37	0.98–6.79
EOS TSH levels (mU/L)		
Mean (SD)	5.14 (2.04)	14.12 (3.69)
Range	0.86–9.47	10.61–25.01
EOS heart rate (bpm)		
Mean (SD)	91.93 (13.98)	89.8 (9.61)
Range	59–126	71–105

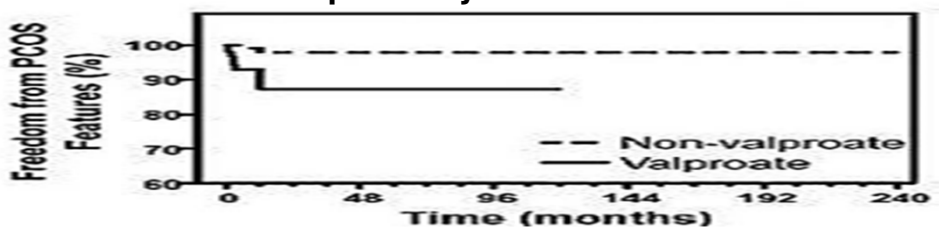
EOS= end of study

Gracious BL et al. J Am Acad Child Adolesc Psychiatry 43: 215-220

Prevalence and Time to Onset of Oligo-/Amenorrhea and Hyperandrogenism During Divalproex Treatment in 230 Women with Bipolar D/O (18-45 Yrs)



Kaplan-Meyer Survival Curve



Oligo-amenorrhea: <9 menstrual cycles in past year; Hyperandrogenism: hirsutism, acne, male pattern alopecia, elevated testosterone or free testosterone; Mean divalproex treatment: 17 months (median: 12, range: 1-223 months)

Joffe H. Biol Psychiatry 2006;59:1078–1086

Antiepileptics and Suicidal Ideation / Behavior in Youths age 5-17 (N=43,892)

Indication	Placebo Patients with Events Per 1000 Patients (N=27,863)	Drug Patients with Events Per 1000 Patients N=16,029	Relative Risk: Incidence of Events in Drug Patients/ Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	**1.0**	**3.5**	**3.6**	**2.5**
Psychiatric	**5.2**	**8.3**	**1.6**	**3.1**
Other	**0.8**	**2.0**	**2.3**	**1.1**
Total	**2.2**	**4.3**	**2.0**	**2.1**

Completed suicide: antiepileptics N=4 vs. PBO: N=0
Risk was apparent at 1-26 weeks, with few studies extending beyond 26 weeks
Antiepileptics Included in the analyses: Carbamazepine; Felbamate; Gabapentin; Lamotrigine; Levetiracetam; Oxcarbazepine; Pregabalin; Tiagabine; Topiramate; Valproate; Zonisamide
http://www.fda.gov/cder/drug/InfoSheets/HCP/antiepilepticsHCP.htm, last accessed: 08.08.2008

Comparison Mood Stabilizer-PBO vs Antipsychotic-PBO Differences in Tolerability

	Children and adolescents				
Outcome	SGA (n = 1,118)		MS (n^a = 494; n^b = 438)		SGA versus MS in youth
Continuous outcome	**ES**	**95% CI**	**ES**	**95% CI**	
Weight change[c]	**0.53**	0.41–0.66	0.10[e]	-0.12–0.33	**SGA > MS**
Weight change[d]			**0.48**	0.24–0.72	NS
Categorical outcome	**NNH**	**95% CI**	**NNHH**	**95% CI**	
≥7% weight gain	**10.0**	7.5–14.8	–	–	–
Somnolence	**4.7**	3.9–6.0	**9.5**	6.3–23.5	**SGA > MS**
Insomnia	100.0[e]	-47.1–24.0	15.1[e]	-15.3–5.0	NS
EPS	**7.5**	5.7–11.0	–	–	–
Akathisia	**20.4**	14.1–36.5	–	–	–
Hyperprolactinemia	**7.9**	6.1–11.1	–	–	–
Discontinuation due to intolerability	**20.4**	13.4–47.5	**9.2**	5.4–36.9	NS

[a]Based on data with aripiprazole and ziprasidone only.[b]Based on data with aripiprazole only.
[c]Including topiramate. [d]Excluding topiramate. Correll CU et al. Bipolar Disorders 2010;12(2):116-41.

8-Week RCT of OLA/FLU vs PBO

	OFC n = 170		Placebo n = 85		Between-Group *p* Value
	n	(%)	n	(%)	
Any adverse event	125	(73.5)	49	(57.6)	.015
Weight gain	34	(20.0)	1	(1.2)	<.001
Appetite increase	28	(16.5)	1	(1.2)	<.001
Headache	27	(15.9)	12	(14.1)	.854
Somnolence	27	(15.9)	2	(2.4)	<.001
Tremor	15	(8.8)	1	(1.2)	.025
Blood triglycerides increase	12	(7.1)	2	(2.4)	.151
Fatigue	11	(6.5)	6	(7.1)	1.00
Vomiting	11	(6.5)	6	(7.1)	1.00
Sedation	11	(6.5)	0	(0.0)	.018

Weight change (LOCF): OFC=4.4 kg, vs PBO=0.5 kg; MMRM: OFC=5.1 kg vs PBO=0.6 kg

•BMI: OFC=1.5 kg/m2 vs PBO=0.1 kg/m2, Gaining ≥7% body weight: OFC=52% vs PBO=4%, p<0.001), 15% of baseline body weight; ≥15 body weight: OFC=14% vs PBO=0%, p<0.001). Total cholesterol: OFC=16.3 mg/dL; LDL cholesterol: OFC=9.7 mg/dL; triglycerides: OFC=35.4 mg/dL, whereas PBO had small mean decreases (all between-group p values <0.001). Shifts OFC vs PBO: abnormal total cholesterol: 28.9% vs 8.2%; p<0.001), LDL cholesterol: 19.7% vs6.5%; p=0.010), triglycerides: 52.3% vs 27.3%; p=0.003); glucose= 11.0% vs 3.9% (p=0.085).

Detke H et al. J Am Acad Child Adolesc Psychiatry. 2015 Mar;54(3):217-24.

Conclusions

Conclusions

- Pediatric mood disorders are often severe illnesses, with frequent comorbidities and impairment
- Ongoing development and frequently co-occurring comorbidities complicate the diagnosis
- Antipsychotics seem to be more effective than conventional mood stabilizers, but combined use of several medications for core symptoms of bipolar disorder and for comorbid conditions is common
- Symptoms, timing/episodicity, co-occurrence, and functional impact require focused attention
- Diagnostic accuracy, openness and humility are needed, as are carefully chosen treatments.

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