

## **Update on Pediatric Bipolar Disorder**

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## Symptoms of Mania

- “A distinct period of abnormally and persistently elevated, expansive, or irritable mood”, plus:
  - Increased self-esteem, grandiosity
  - Decreased need for sleep
  - More talkative or pressure to keep talking
  - Racing thoughts, stream of ideas
  - Distractible
  - Increased purposeful activity
  - Risky, thrill-seeking behaviors

## Types of Bipolar Disorder

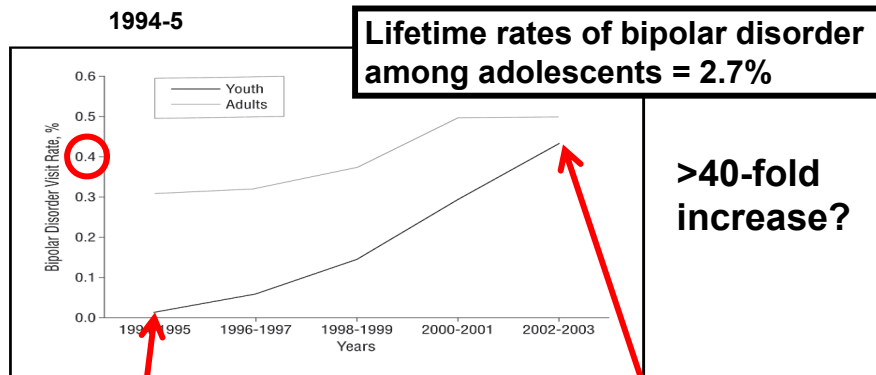
- Bipolar I Disorder
- Bipolar II Disorder
- Bipolar Disorder Not Otherwise Specified (NOS)
- Cyclothymic Disorder

### Severity of Early-onset Bipolar Disorder

- 32-65% of adults have onset  $\leq 18$  years old
- More anxiety, substance abuse
- More episodes and symptoms
- More suicidality, violence, psychosis
- Longer delay until treatment
- Greater functional impairment
- **Less time well**

Goldstein & Levitt, 2006; Leverich et al. 2007; Perlis et al. 2004

### Epidemic of Adolescent Bipolar Disorder?

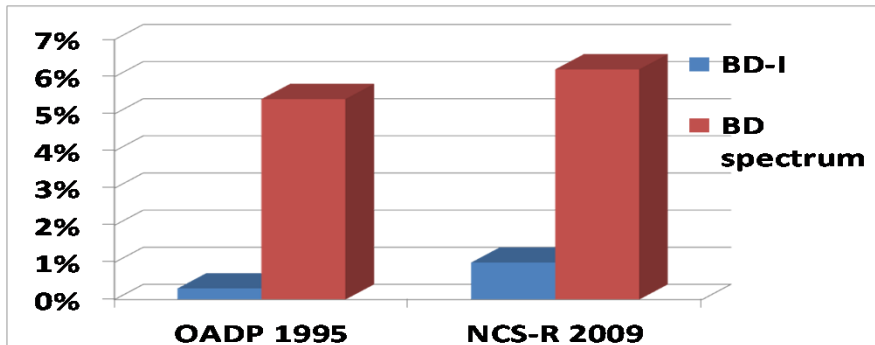


0.01% of MD visits  
0.42% of psychiatry visits

0.44% of MD visits  
6.67% of psychiatry visits

Moreno et al. Arch Gen Psychiatry 2007; Van Meter et al. J Clin Psych 2011

## Epidemic of Pediatric Bipolar Disorder?



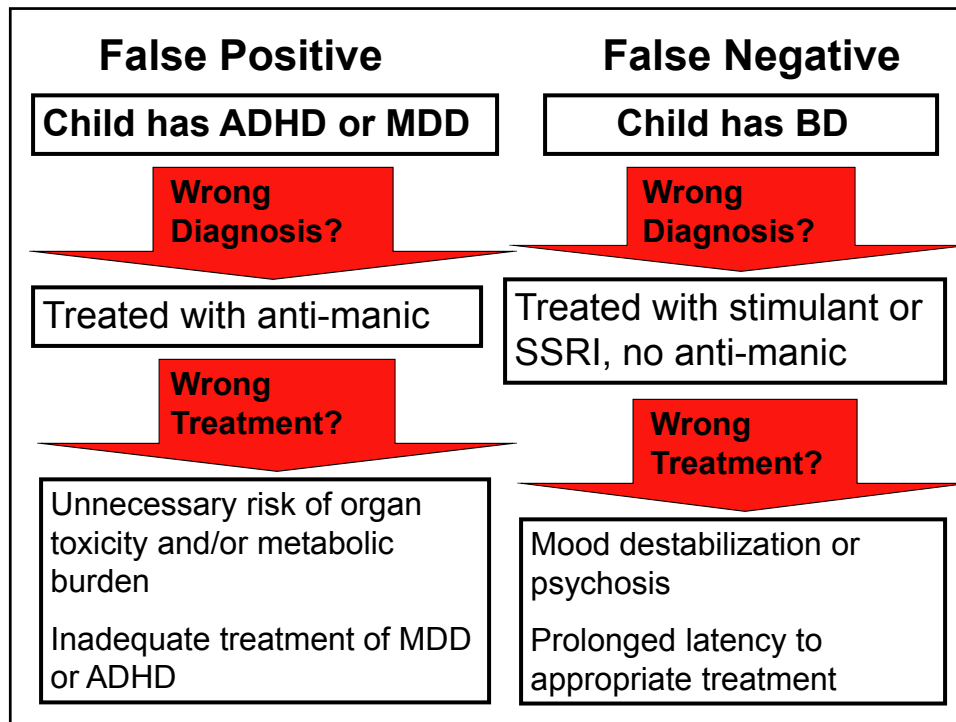
- Lifetime bipolar disorder in adolescents = 2.7%
- No significant increase over time
- No significant difference of U.S. vs. elsewhere

Lewinsohn et al, *JAACAP* 1995; Kessler et al, *JAACAP* 2009; Van Meter et al. *J Clin Psych* 2011

## Bipolar Disorder among 191 Canadian Adolescents and Young Adults

	15-18yo	19-24yo
Female	64.9%	52.3%
White	72.7%	77.7%
Anxiety disorder	41.8%	48.6%
Substance abuse	32.1%	46.0%
Suicidality	54.6%	48.6%
Received treatment	45.8%	60.3%

Kozloff et al, *J Affect Disord* 2010



### **Why is this a Challenging Diagnosis?**

- Symptom overlap with other disorders
- Less time well vs. adults
- More likely to have “mixed” states, involving both manic and depressive symptoms
- Historical recall affected by current mood
- Often need repeated visits, follow-up

## Clinical Pearls

- Establish a “baseline”
- Identify an episode
- Look for a change in trajectory
- Determine onset, including precipitants
- Ensure there’s “enough”:
  - Enough symptoms
  - Enough duration
  - Enough distress and/or functional impairment

## Recovery in COBY

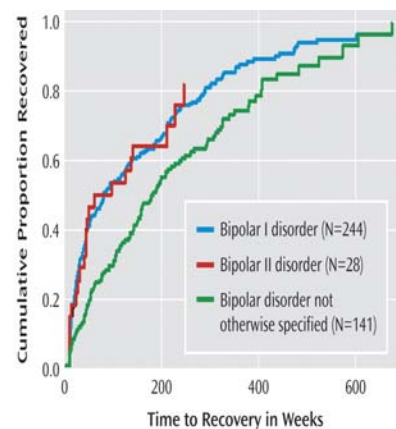
**After 2.5 years, 81.5% recovered**

**Less likely to recover if:**

**BD-NOS  
<12yo at intake  
Minority race  
Longer illness**

**More like to recover if:**

**Living with both parents  
and high SES**

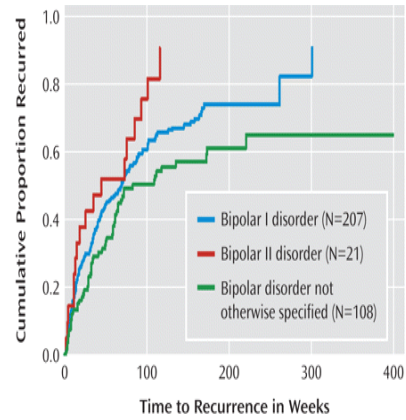


Birmaher et al, *Arch Gen Psychiatry* 2009

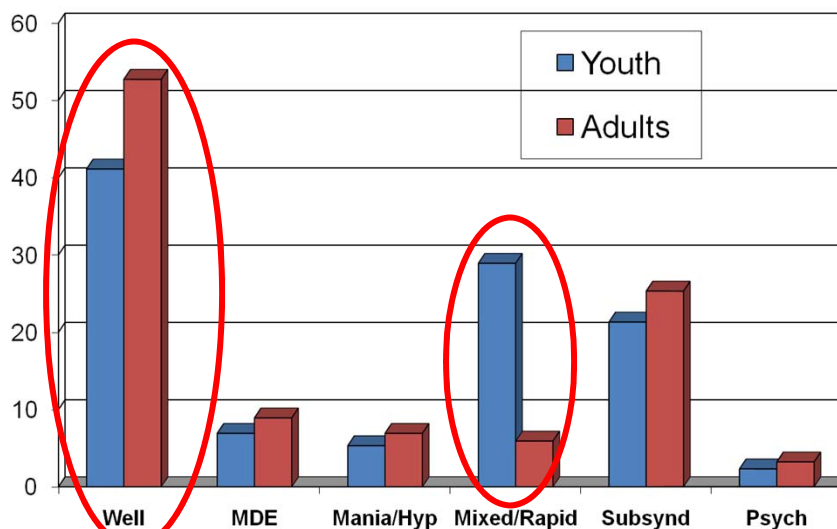
## Recurrence in COBY

Among recovered, 62.5% had  $\geq 1$  recurrence within 1.5 yrs  
 Polarity of index episode predicted polarity of recurrence

More likely to recur if:  
 BD-I or BD-II  
 Low SES  
 Family history of BD



Weekly Symptoms Status Comparing Youth with **BP-I** (Birmaher et al., 2006) vs. Adults with **BP-I** (Judd et al., 2002)



## Longitudinal Course of Bipolar Disorder

- 12-mo. follow-up of adolescents hospitalized for mania:
  - Psychotherapy predicts longer time to recurrence
  - Antidepressants, alcohol use disorders predict shorter time to recurrence
  - 86% syndromic recovery, ~40% functional recovery
  - Predictors of lack of recovery: ADHD, anxiety, DBD, non-adherence, low SES

DelBello et al, *Am J Psychiatry* 2007

## Longitudinal Course of Bipolar Disorder

- 8-yr. follow-up of childhood and early-adolescent BD-I:
  - 88% recovery, 73% relapse to mania
  - Low maternal warmth predicted relapse and more weeks ill
  - 34% developed new-onset substance use disorders
  - 44% of subject >18yo had manic episodes as adults

Geller et al, *Arch Gen Psychiatry* 2008



### Comorbidity in Large Clinical Samples

	Axelson et al, 2006 N=438	Biederman et al, 2005 N=299*	Findling et al, 2001 N=90	Geller et al, 2004 N=86
<b>Mean age</b>	<b>12.7y</b>	<b>~10.7y</b>	<b>10.8y</b>	<b>10.8y</b>
<b>Female</b>	<b>47%</b>	<b>36%</b>	<b>~33%*</b>	<b>38%</b>
<b>Anxiety</b>	<b>39%</b>	<b>49%</b>	<b>14%</b>	<b>17%</b>
<b>ADHD</b>	<b>60%</b>	<b>84%</b>	<b>68%</b>	<b>86%</b>
<b>ODD</b>	<b>40%</b>	<b>85%</b>	<b>47%</b>	<b>78%</b>
<b>CD</b>	<b>13%</b>	<b>42%</b>	<b>17%</b>	<b>13%</b>
<b>SUD</b>	<b>0%/16%</b>	<b>0%/22%</b>	<b>0%/18%</b>	<b>---</b>

\*Tabulated

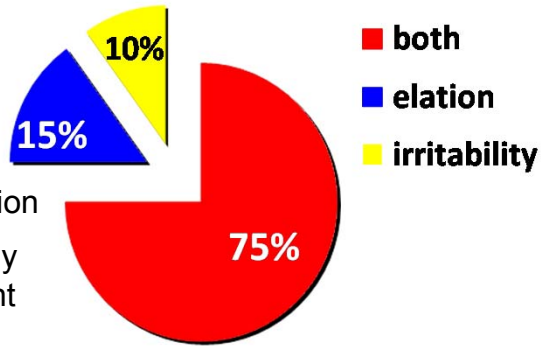
### Differential Diagnosis of Manic Symptoms

	Bipolar Mania/Hypomania	ADHD <sup>1</sup>	ODD <sup>2</sup>
<b>Elation</b>	Episodic, prolonged, pathological (inappropriate to context, uncharacteristic), associated with change in functioning, "travels" with ≥3 other manic symptoms	If present, not clearly episodic or pathological	If present, not clearly episodic or pathological
<b>Irritability</b>	Episodic, prolonged, pathological, associated with change in functioning, "travels" with ≥4 other manic symptoms	Can be an associated feature, related to stimulant rebound, or due to a comorbid illness (e.g. ODD)	Diagnostic criterion, lacks distinct prolonged episodes, does not "travel" with other manic symptoms
<b>Sleep</b>	Reduced <u>need</u> for sleep, i.e. significantly less sleep than usual without increased daytime fatigue or somnolence, mood-related	Insomnia, i.e. difficulty falling asleep, can be an associated feature or associated with stimulants, but need for sleep is unchanged	Not a symptom or common characteristic, may defy bedtime rules or routine
<b>Grandiosity</b>	Distinct uncharacteristic increase in confidence or self-importance, mood-related	Not a symptom or common characteristic	Defiance toward authority figures is common, but not necessarily mood-related
<b>Hyperactivity, Distractibility</b>	Episodic, if comorbid ADHD then distinctly "worse than usual", mood-related	Diagnostic criteria, non-episodic	Not prominent or episodic

### Irritability Without Elation in a Large Bipolar Youth Sample: Frequency and Clinical Description

**Irritability without elation:**

- Overall highly similar to those with elation
- Younger
- More family history of alcohol abuse, depression
- Conclusion: irritable-only hypo/mania is infrequent



Hunt et al, JAACAP 2009

### Neurocognitive Dysfunction in Pediatric Bipolar Disorder

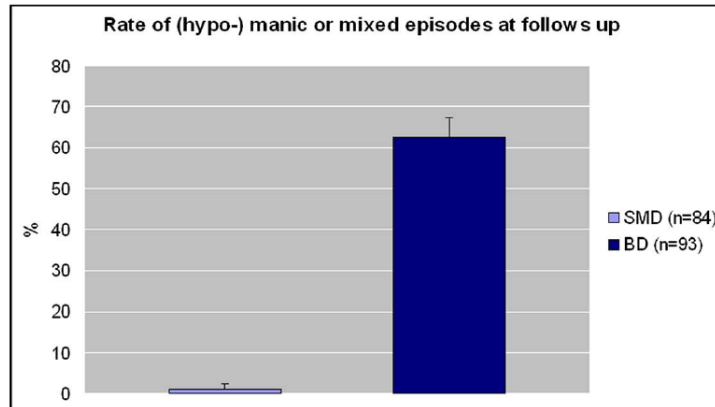
- Ten studies, N=352
- @50-80% with ADHD
- Mix of symptomatic and asymptomatic
- 60-90% medicated

Neurocognitive Domain	Effect Size
Full-scale IQ	0.32
Reading achievement	0.40
Attention	0.62
Motor speed	0.33
Executive function	0.55
Working memory	0.60
Verbal fluency	0.45
Visual-perceptual	0.48
Visual memory	0.51
Verbal memory	0.77

Joseph et al, *J Child Adoles Psychopharm* 2008

## Pediatric Bipolar Disorder Versus Severe Mood Dysregulation: Risk for Manic Episodes on Follow-Up

FIGURE 2 Bars with standard errors show the percentage of patients with either severe mood dysregulation (SMD) or bipolar disorder (BD) who developed a (hypo-)manic or mixed episode during the follow-up period.



Stringaris et al., JAACAP 2011

### Summary of Neurobiological Findings Regarding Bipolar Disorder vs. “Severe Mood Dysregulation”

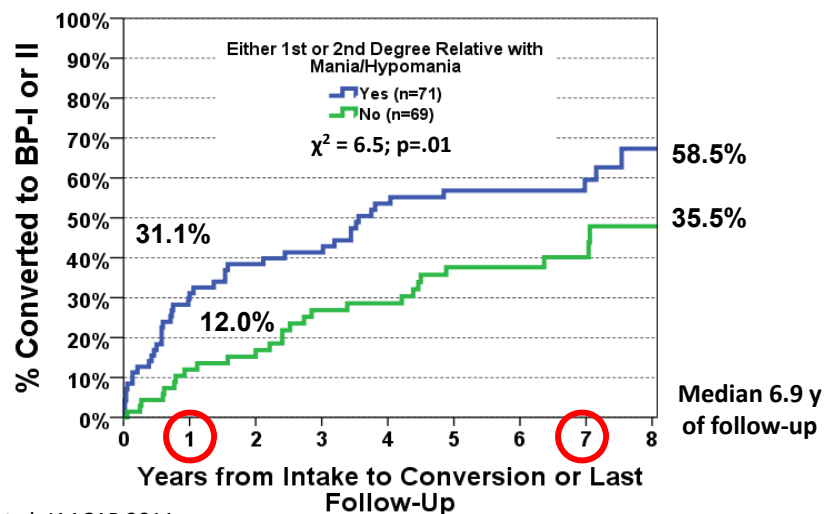
- Posner task accuracy: Control>BD>SMD
- Response reversal accuracy: Controls=BP>SMD (response reversal)
- Frustration P3: Control=SMD>BD
- Post-frustration reaction time: BD>Control=SMD
- Face emotion labeling: Control>BD=SMD
- Affective prosody labeling: Control>BD=SMD
- Neural activation during failed inhibition: BD<SMD=Control
- Neural activation to negative feedback: BD different, SMD=Control
- Attention interference of emotional stimuli: SMD<BD=Control
- Neural response to emotion processing of neural faces: SMD<BD=Control<ADHD

**Like the phenotypes, many behavioral and neural differences between SMD and BD, and many similarities**

### Who is at Highest Risk?

- Adolescents with Major Depression
  - With psychosis
  - With medication-induced mania
- Offspring of parents with bipolar disorder
  - With anxiety disorders
  - With disruptive behavior
  - With both parents affected
- Youth with BP-NOS (40% conversion)
  - With family history

### Family History at Intake associated with Progression to BP-I or II



Axelson et al, JAACAP 2011

### **The Child Behavior Checklist (CBCL) and the CBCL-Bipolar Phenotype Are Not Useful in Diagnosing Pediatric Bipolar Disorder**

- Compared youth with BP (N=157), MDD/Anx (N=101), DBD (N=127), and healthy controls (N=128)
- 41% of BP youth did not have elevated CBCL-PBD
- Sensitivity = 57%, specificity = 70-77%
- Accuracy (AUC) 0.72-0.78

Diler et al, *J Child Adolesc Psychopharm* 2009

### **Parent General Behavior Inventory, 10-item short form (PGBI-SF10)**

Example items:

- Has your child experienced **periods of several days or more** when, although he/she was feeling **unusually happy and intensely energetic** (clearly more than your child's usual self), he/she was also physically **restless**, unable to sit still, and had to keep moving or jumping from one activity to another?
- Have there been periods of **several days or more** when your child's friends or other family members told you that your child seemed **unusually happy** or high – **clearly different** from his/her usual self or from a typical good mood?
- Has your child's **mood or energy shifted rapidly** back and forth from happy to sad or **high to low**?

<http://www.whatsupdoc.us/Common/PCP/PGBI-sf10%20mania%20modified%20again.pdf>

### Likelihood of Having Bipolar Disorder Based on PGBI 10-item Mania Short Form

Score Range	Risk	Likelihood Ratio	Sensitivity (%)	Specificity (%)
0.0-0.9	Very low	0.01	100	0
1.0-4.9	Low	0.16	100	21
5.0-9.9	Low to neutral	0.56	94	54
10-14.9	Neutral	1.55	78	78
15.0-17.9	High	2.67	56	90
18.0-30.0	Very high	7.25	39	95

Youngstrom et al, *J Clin Psychiatry* 2008

### Mean Scores on PGBI 10-item Mania Short Form

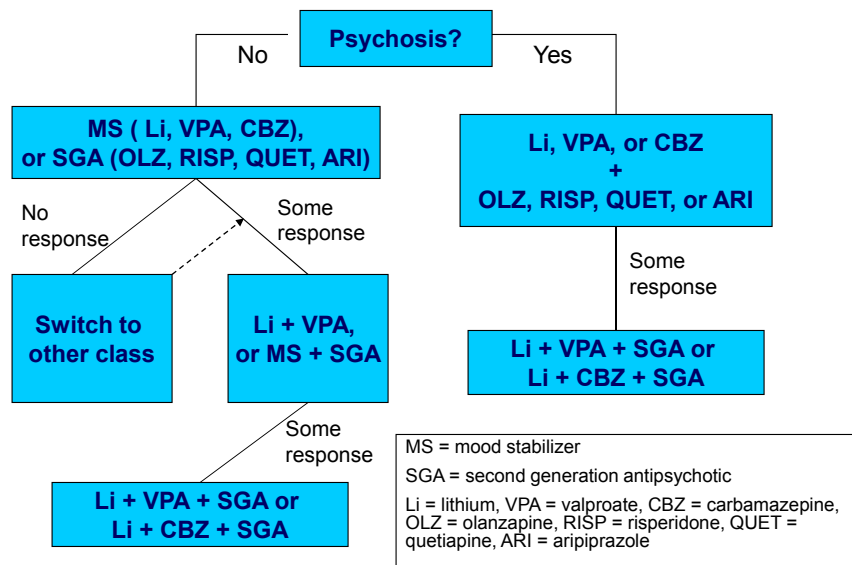
Group	N	Mean (SD)
Bipolar I	178	17.12 (6.86)
Other bipolar	116	12.90 (6.66)
Unipolar mood	131	6.10 (5.25)
ADHD/DBD	130	7.03 (6.03)
Residual diagnosis	19	6.63 (7.80)
No Axis I diagnosis	60	1.28 (3.82)
Total	637	10.17 (8.10)

Youngstrom et al, *J Clin Psychiatry* 2008

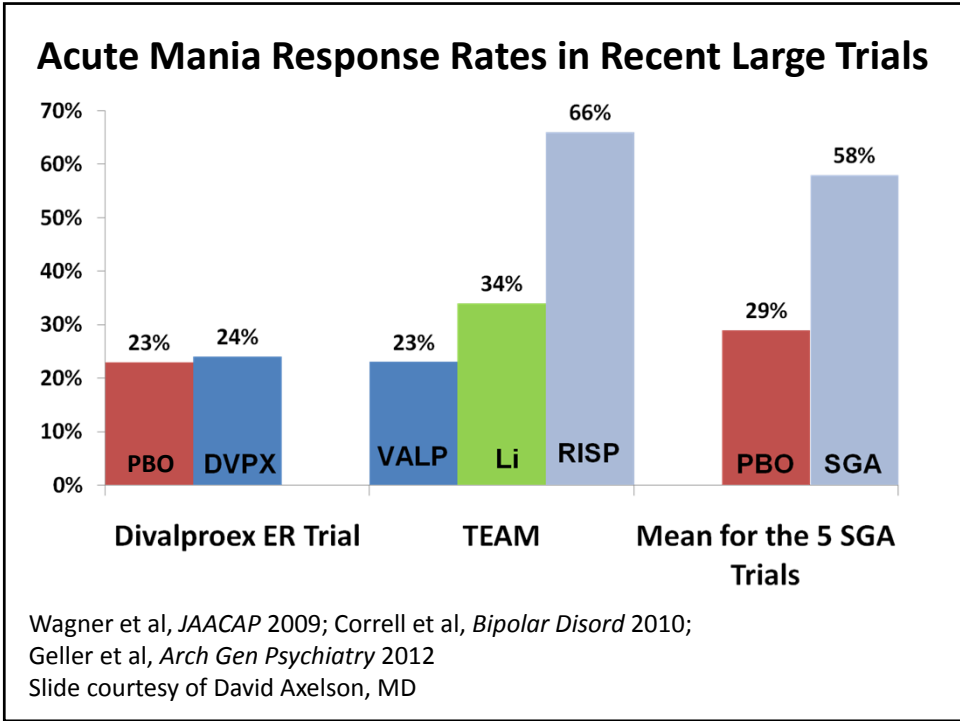
## Take-Home Messages

- Bipolar disorder among youth can be parsed from normal or comorbid disorders
- Difficult to diagnose (over- and under-diagnosed)
- Billing diagnoses have increased; prevalence has not
- Diagnosis and comorbidity has treatment implications
- Pediatric BD is a severe, impairing, familial illness, frequently complicated by multiple comorbidities
- Both neurobiological differences and similarities with chronic irritability

## AACAP Guidelines for Treatment of Acute Mania



Slide courtesy of Kiki Chang, MD, APA 2010



### Age Differences in Antipsychotic and Mood Stabilizer Efficacy and Tolerability in Acute Mania

	Adult RCTs	Youth RCTs
Sample size	N=3297 SGA N=2581 MS	N=1140 SGA N=469 MS
Effect size	SGA (0.48)=MS (0.46)	SGA (0.65) > MS (0.20)
Response, remission, dropout	SGA=MS	SGA=MS
Weight gain effect size	SGA (0.13)=MS (0.00)	SGA (0.53) > MS (0.10)

Correll et al, *Bipolar Disord* 2009



## Adolescent Bipolar Depression Open Studies

Lamotrigine:

- 8 wk, N=20, any BP subtype
- Mean 132mg/d; target 100-200mg (1/2 if VALP)
- Titration: wk 1-2=25mg→wk 3-4=50mg  
→wk 5=100mg; wk 6-8 increase 25mg/wk prn
- 63% response, 58% remitted
- Side effects: H/A 84%, fatigue 58%, nausea 53%

Chang et al, *JAACAP* 2006

## Adolescent Bipolar Depression Open Studies

Lithium:

- 6 wk, N=27, BP-I
- Titration: 30mg/kg/d (bid); 70% therapeutic<19d
- Mean level @ endpoint, 0.9mEq/L (1356mg/d)
- 48% response
- Side effects: H/A 74%, N/V 67%

Patel et al, *JAACAP* 2006

### Quetiapine vs. Placebo for Adolescent Bipolar Depression

- DBPC, N=32, two-sites (UC & Stanford)
- 8-weeks monotherapy (300-600mg/day, no changes after day 28) BP I, depressed
- Inpatients or outpatients, ages 12-18 years

Good News for Quetiapine!

- 71% response, 35% remission

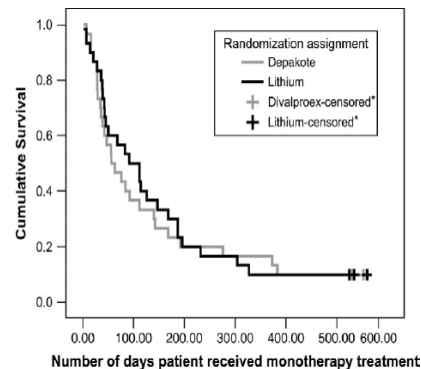
Good News for Placebo!

- 67% response, 40% remission

DelBello et al, *Bipolar Disord* 2009

### Double-Blind 18-Month Trial of Lithium Versus Divalproex Maintenance Treatment in Pediatric Bipolar Disorder

- BD-I or -II, stabilized on lithium/divalproex
- Randomized to one medication (N=30/group)
- No difference in relapse
  - 114 days for lithium
  - 112 days for divalproex



Findling et al, *JAACAP* 2005

### **Comorbid ADHD: AACAP Treatment Guidelines**

- Treat BD symptoms first
- Treat ADHD if impairing symptoms persist, stimulants are first-line in this setting
- Atomoxetine, stimulants, TCAs can induce switches to mania/cycling

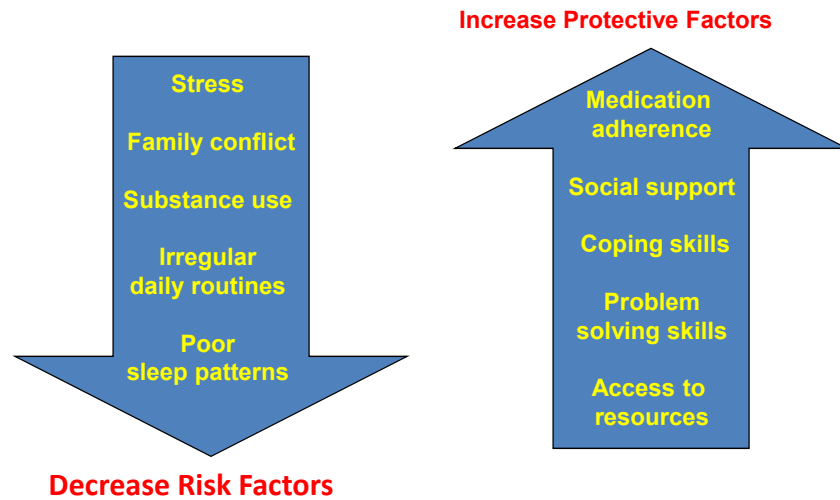
Kowatch et al, *JAACAP* 2005

### **Take-Home Messages**

- Response rates for acute manic and mixed episodes among youth are comparable to those among adults
- Less is known about combination, continuation, maintenance, depression, and some comorbidities
- Youth are highly responsive to SGAs, and especially sensitive to their metabolic side effects
- Use SSRIs with caution; consider psychosocial treatment first-line for bipolar depression or anxiety
- Once mood is stabilized, stimulant treatment of comorbid ADHD appears to be safe and effective

Goldstein, Sassi, Diler, *Child & Adol Psych Clinics* 2012

## What Are The Goals Of Psychotherapy For Adolescent Bipolar Disorder?



Psychotherapy slides courtesy of Tina R. Goldstein, PhD

## Promising Psychotherapies for Youth with Bipolar Disorder

### Individual Approaches

- Cognitive Behavioral Therapy (CBT; Danielson et al., 2004)
- Interpersonal & Social Rhythm Therapy (IPSRT-A; Hlastala & Frank, 2006)

### Family Approaches

- Family-Focused Therapy (FFT-A; Miklowitz et al., 2004)
- Child & Family-Focused CBT\* (Pavuluri et al., 2004)

### Group Approaches

- Multi-Family Psychoeducation Groups\* (MFPG; Fristad et al., 2003)

### Combination Approaches

- Dialectical Behavior Therapy (DBT-A; Goldstein et al., 2007)

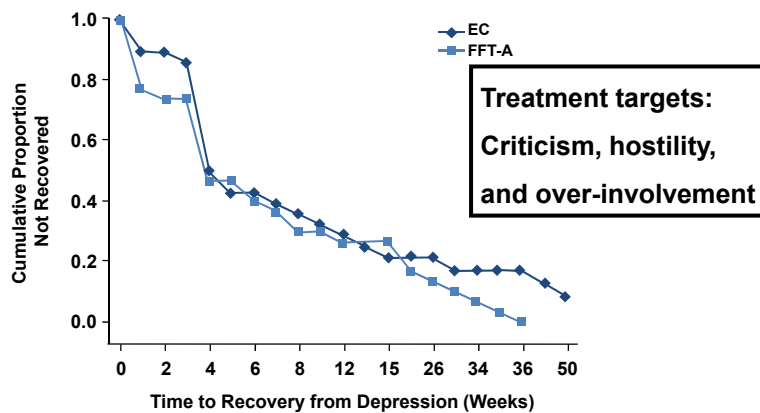
\*Focus on children <13yo

### Common Elements of Psychotherapies for Youth with Bipolar Disorder

- Psychoeducation about bipolar disorder
  - symptoms, course, treatment
- Sleep hygiene
- Medication adherence
- Mood Monitoring
- Skill Building
  - Communication
  - Problem Solving
  - Emotion Regulation
  - Impulse Control
- Enhance relationships
- Relapse prevention and safety planning

AACAP Treatment Guidelines for Children and Adolescents with Bipolar Disorder, 2005

### Family-Focused Treatment for Adolescents with Bipolar Disorder



$\chi^2_1=4.36$ .  $p=.04$ . HR=1.85. 95% CI 1.04-3.29.

EC=enhanced care. HR=hazard ratio. CI=confidence interval.  
Miklowitz DJ, et al. *Arch Gen Psychiatry*. 2008;65:1053-1061.

## Take-Home Messages

- There is strong evidence that specific psychotherapies are helpful for adults with bipolar disorder
- Psychotherapy is complementary to pharmacotherapy, and provides a forum for psychoeducation
- Benefits of psychotherapy may be most evident for depression and suicidality (vs. mania)
- Different psychotherapies share several core elements
- Youth-specific developmental considerations are key
- Involvement of families is suggested

## Bipolar SAQs

1. List three ways in which early-onset bipolar disorder can be considered a more severe variant than adult-onset bipolar disorder. Bipolar II Disorder

hospitalization, comorbidity, symptom burden, impairment, suicidality

2. List three factors that may contribute to the greater challenge of diagnosing bipolar disorder in youth as compared to adults.

symptom overlap with other diagnoses, less time well than adults, historical recall affected by current mood, more likely to have mixed states

## **Bipolar SAQs**

3. A 12 year-old girl presents with severe irritability accompanied by hyperactivity and distractibility. List three key aspects of the history that would be needed in order to rule in or rule out a diagnosis of bipolar disorder
  - Irritability is episodic
  - Irritability has sufficient duration (eg 4 days for hypomania)
  - Irritability episodes are accompanied by changes in at least 4 other manic symptoms

## **Bipolar SAQs**

4. List three neurocognitive deficits/problem areas that have been observed among youth with bipolar disorder
  - verbal memory
  - attention
  - working memory
  - executive function
  - face emotion recognition

## Bipolar SAQs

5. A 12 year-old girl presents with severe irritability accompanied by hyperactivity and distractibility. List three key aspects of the history that would be needed in order to rule in or rule out a diagnosis of bipolar disorder
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