Is Pediatric Bipolar Disorder a Valid Disorder?

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Disclosures 2009-2011

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  - Eliminda, J&J, Shire, NIH, Philanthropy
- Honoraria:
  - Fundacion Areces, Medice, Spanish Child Psychiatry Association, Fundacion Cabral, Monterey Mexico, MGH Academy

Pediatric BPD: History of a Controversy

- 1960: Childhood mania exists but is rare (Anthony and Scott)
- 1970-1980: Childhood mania may be more common than we thought (Weller et al., Carlson et al.)
  - It may be under-diagnosed due to developmentally variable symptom expression
- 1990-2000: Childhood mania is a serious source of morbidity in child psychiatric clinics (Biederman et al., Geller et al.)
- 2000-2010: Childhood mania is over-diagnosed and over-treated (or is it?)

Pediatric Mania

NOVEMBER 3, 2003

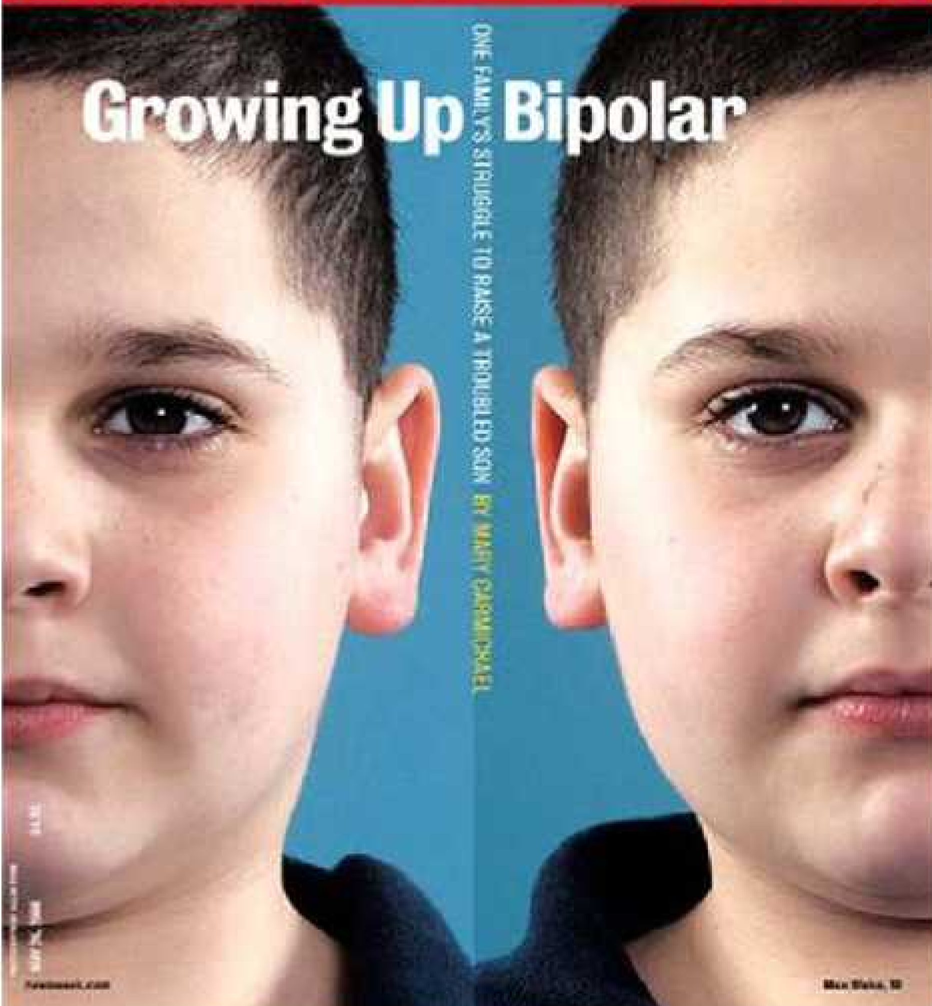
www.time.com AOL Keyword: TIME

TIME

ARE WE GIVING KIDS TOO MANY DRUGS?

A medicated generation is growing up with quick fixes for mood and behavior. Here are the benefits—and the risks

Jamari, 8, is being treated for what doctors believe is a mood disorder



May 26, 2008 issue

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

MAY 20, 2010

Pediatric Mental Health Care Dysfunction Disorder?

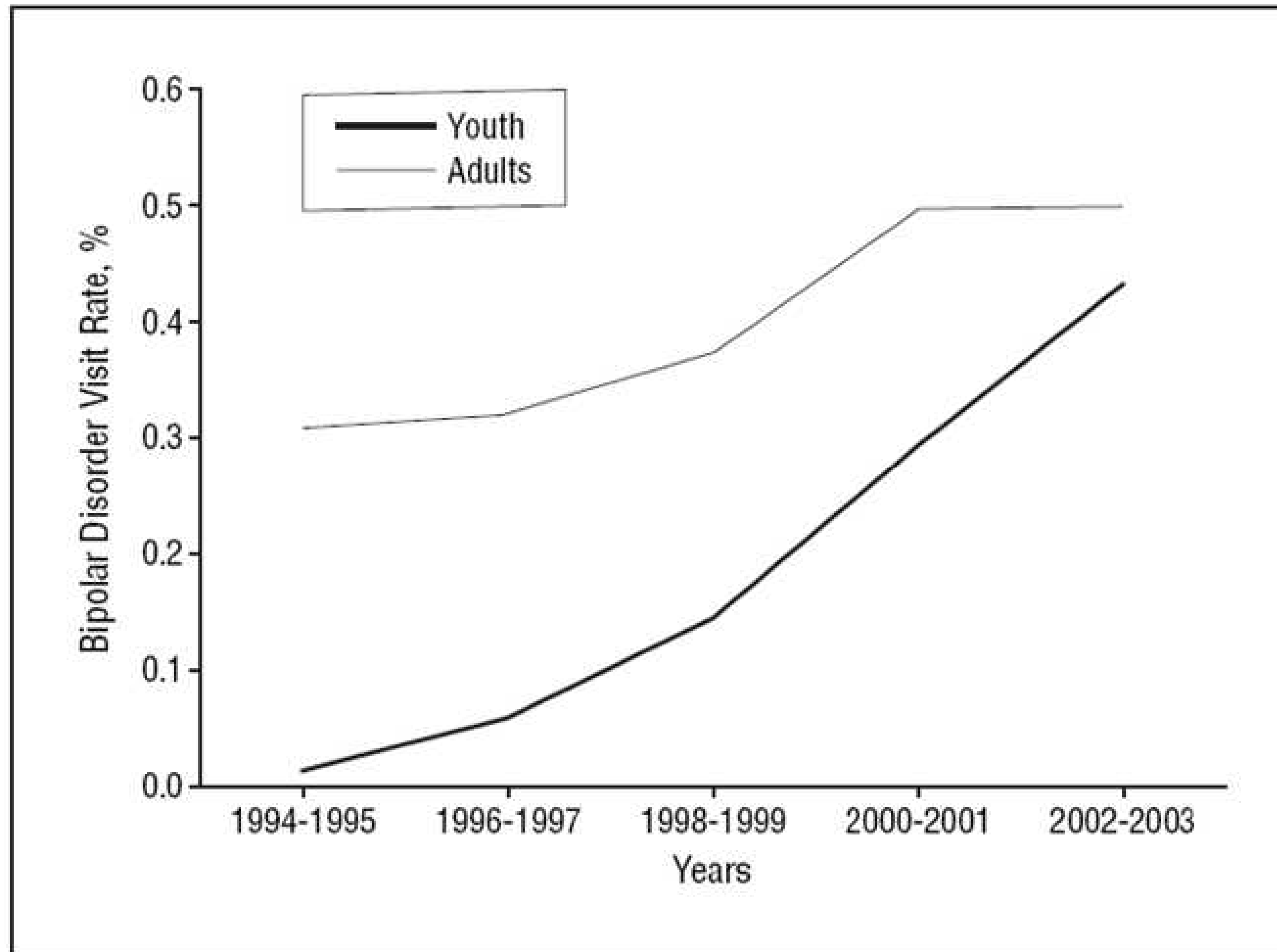
Erik Parens, Ph.D., Josephine Johnston, L.L.B., M.B.H.L., and Gabrielle A. Carlson, M.D.

In February, the American Psychiatric Association released draft revisions for the next iteration of its diagnostic manual (the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* [DSM-V]).

as reported by Moreno and colleagues,[1] the number of children with a diagnosis of bipolar disorder visiting outpatient clinics increased by a factor of 40. These children, some preschoolers, were

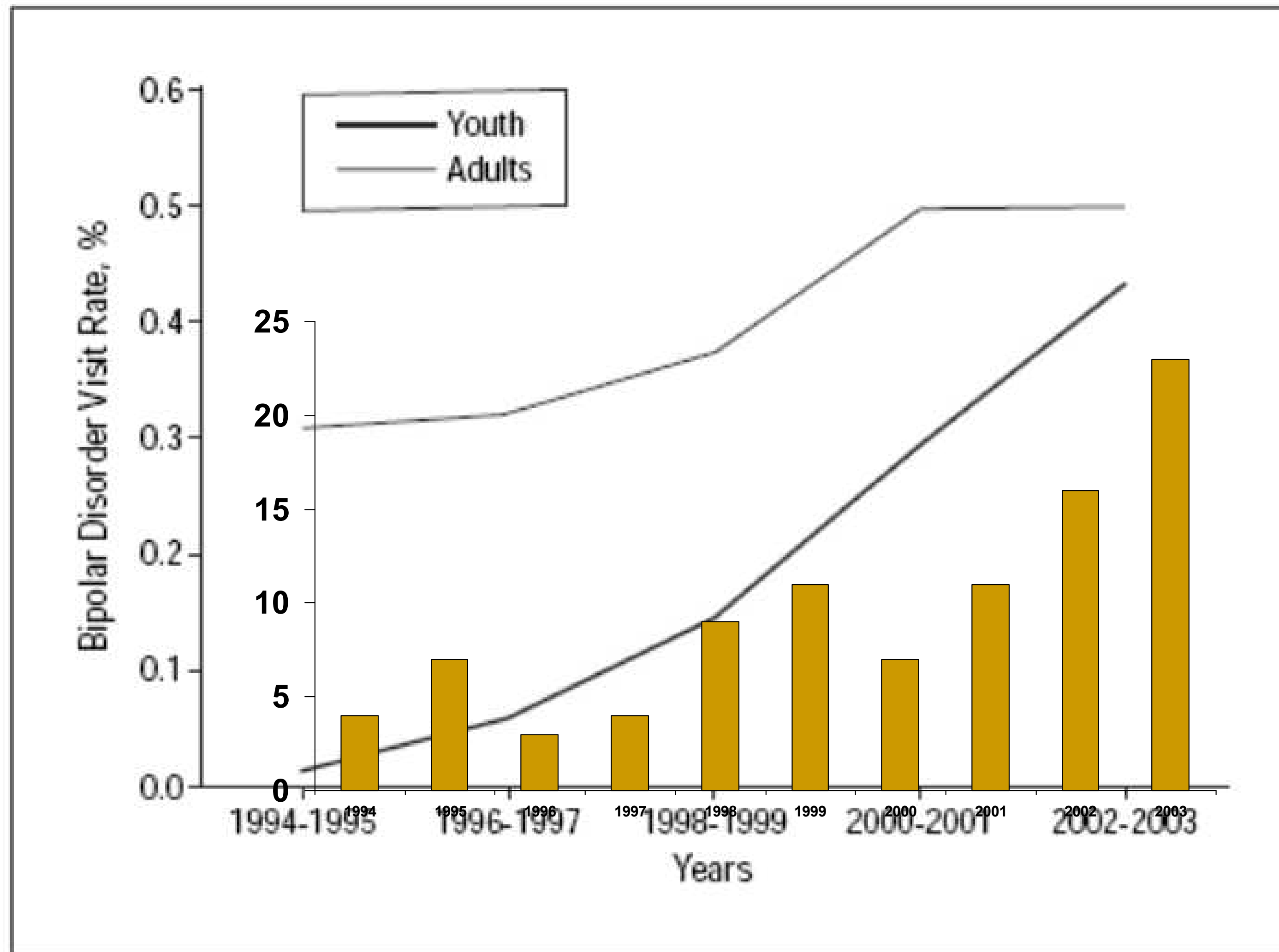
Parens et al. N Engl J Med. 2010 May 20;362(20):1853-5

National Trends in Visits with a Diagnosis of Bipolar Disorder as a Percentage of Total Office-Based Visits by Youth (aged 0-19 years) and adults (aged ≥20 years)



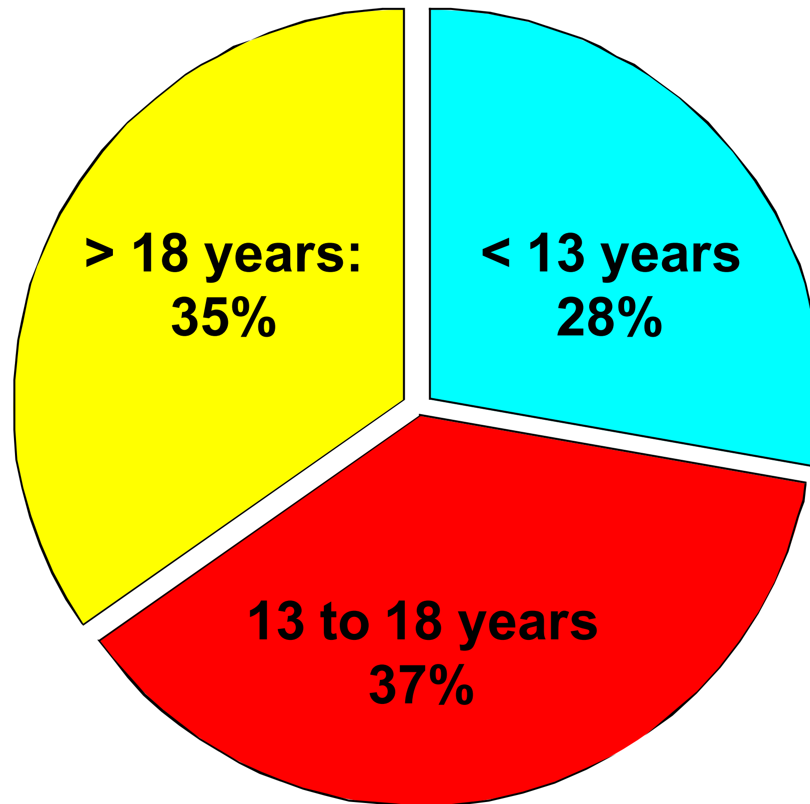
Moreno et al. ***Arch Gen Psychiatry*** **2007;64(9):1032-39**

National Trends in Visits with a Diagnosis of Bipolar Disorder as a Percentage of Total Office-Based Visits



Moreno et al., Arch Gen Psych, 2007)

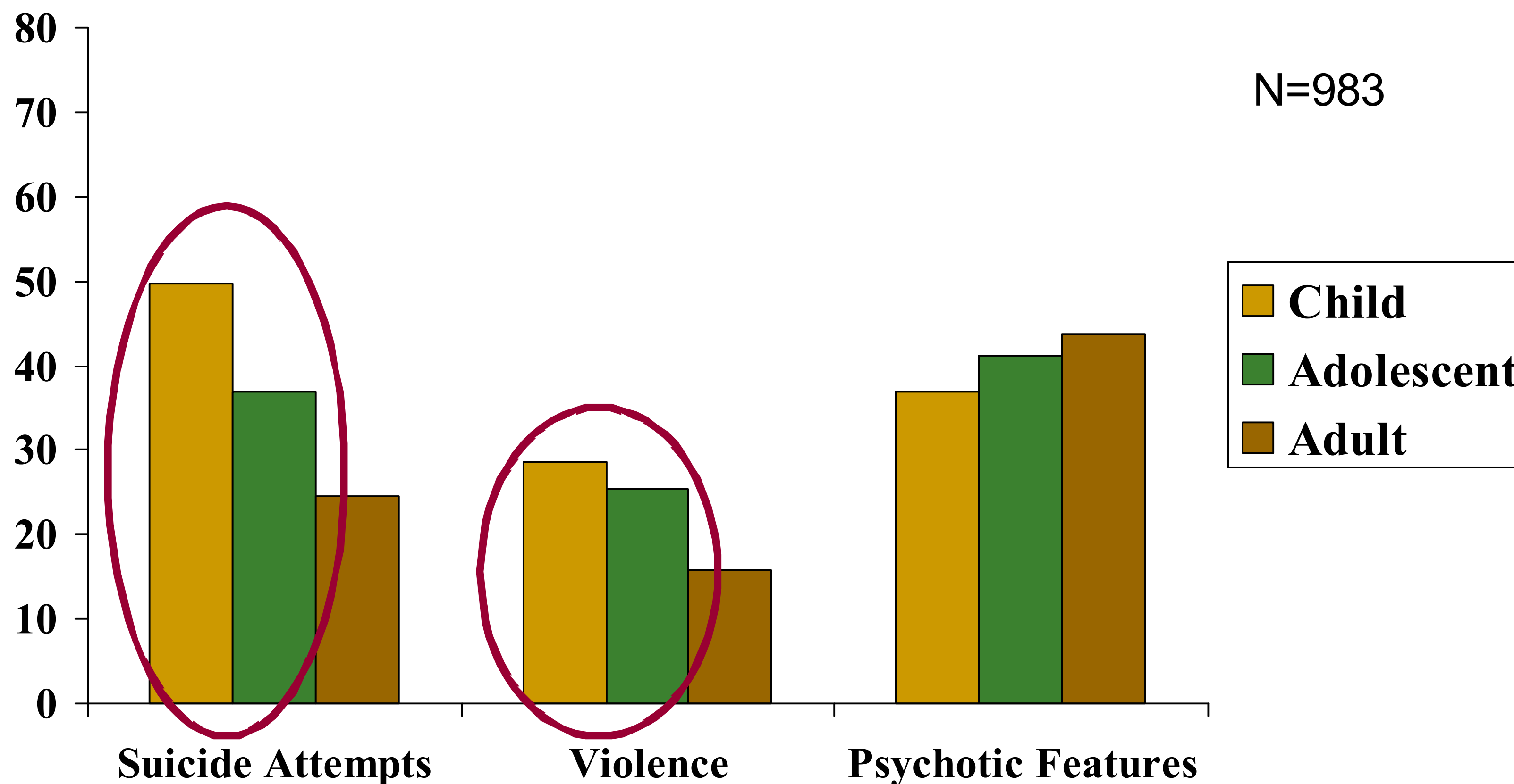
Most bipolar adults in STEP-BD reported onset in childhood or adolescence



- 65% of adults with onset < 18
- Almost a third with onset < 13

Perlis, Miyahara, Marangell, Wisniewski, Ostacher, DelBello, Bowden, Sachs, Nierenberg, Biol Psych 2004;55:875-881

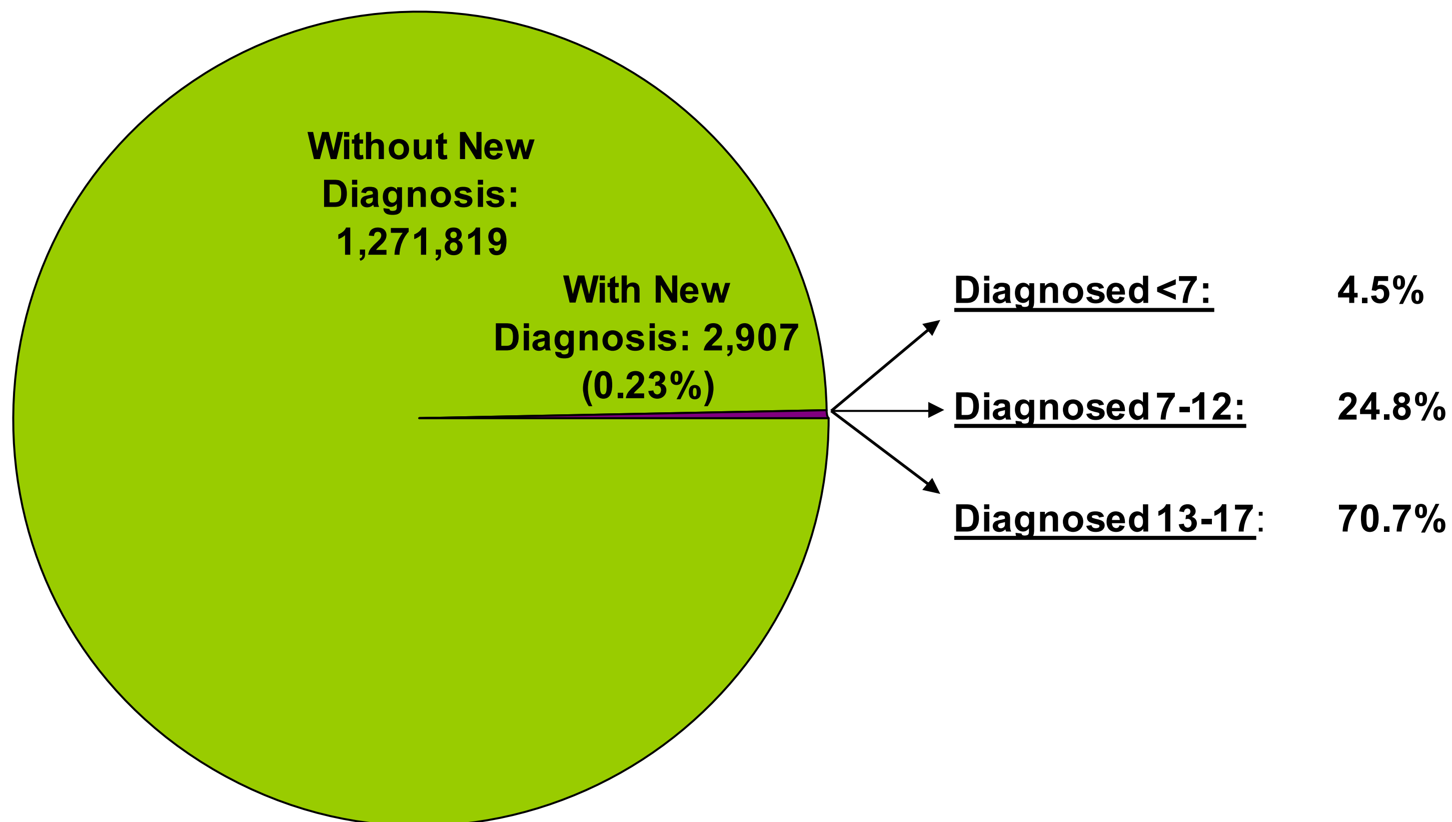
Bipolar adults with childhood and adolescent onset had more lifetime suicide attempts and violence



Perlis, Miyahara, Marangell, Wisniewski, Ostacher, DelBello, Bowden, Sachs, Nierenberg, Biol Psych 2004;55:875-881

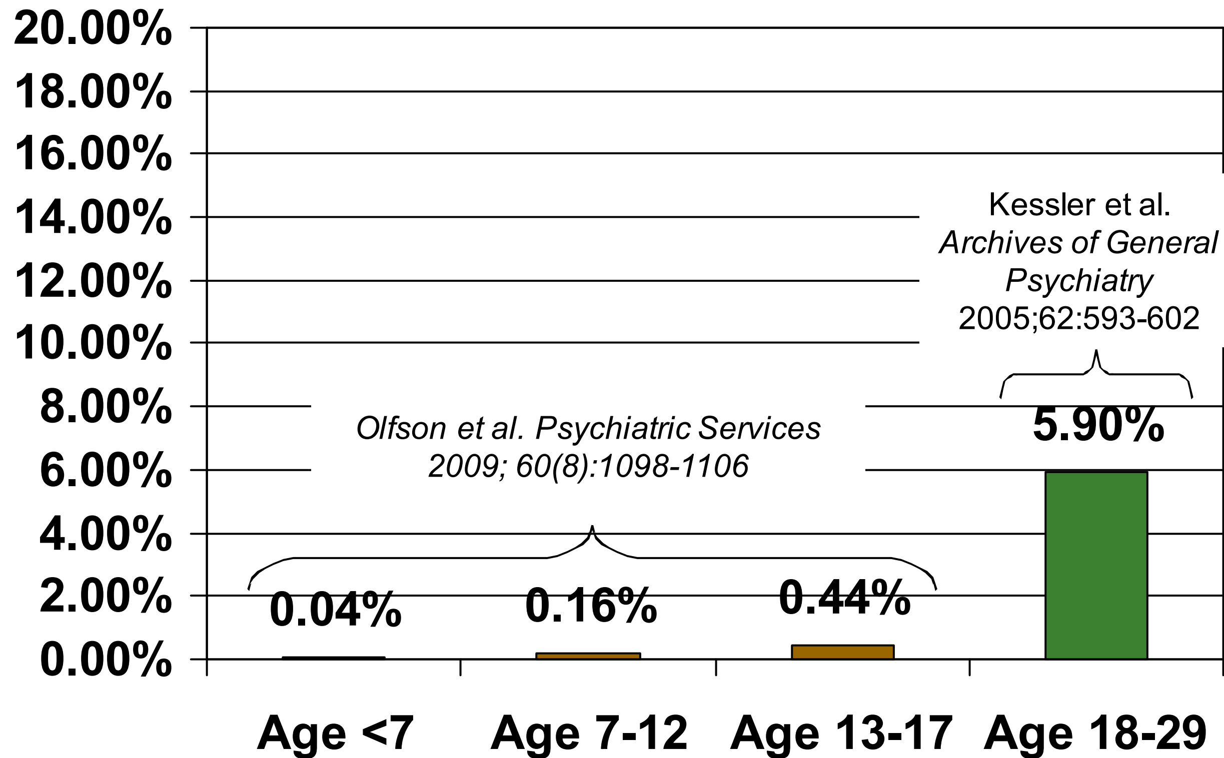
Population Studies of Bipolar Disorder and Severe Mood Dysregulation in Youth
Not USA: 1.9%*
USA: 1.7%*
Benjet 2009 Mexico
2.5
Lynch 2006 Ireland
0
Canals 1997 Spain
2.4
Kim-Cohen 2003 New Zealand
1.8
Stringaris 2010 UK
1.2
Holtzmann 2010 German
0.7
Verhulst 1997 Dutch
2.8
Costello 1996 USA
0
Kessler 2009 USA
6.3
Gould 1998 USA
1.3
Andrade 2006 USA
1.5
Kashani 1987 USA
0.7
Lewinsohn 1995 USA
1
Merikangas 2010 USA
2.9
0
2
4
6
8
Percent with Disorder
*from Van Meter et al., JCP, in press

Number of Patients with a New Diagnosis of Bipolar Disorder by Age Group



Olfson et al. *Psychiatric Services* 2009; 60(8):1098-1106.

Rates of New Bipolar Disorder Diagnoses by Age Group

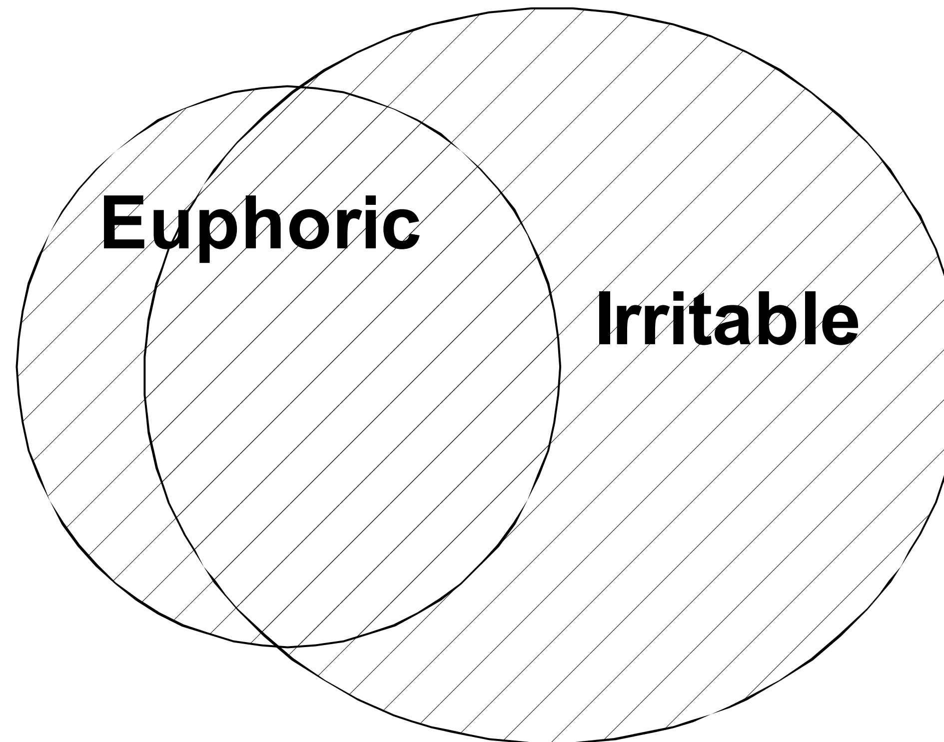


Robins & Guze Criteria for Validity of Psychiatric Diagnosis

- Clinical presentation
- Family history
- Treatment response
- Course and outcome
- Laboratory studies

Clinical Presentation

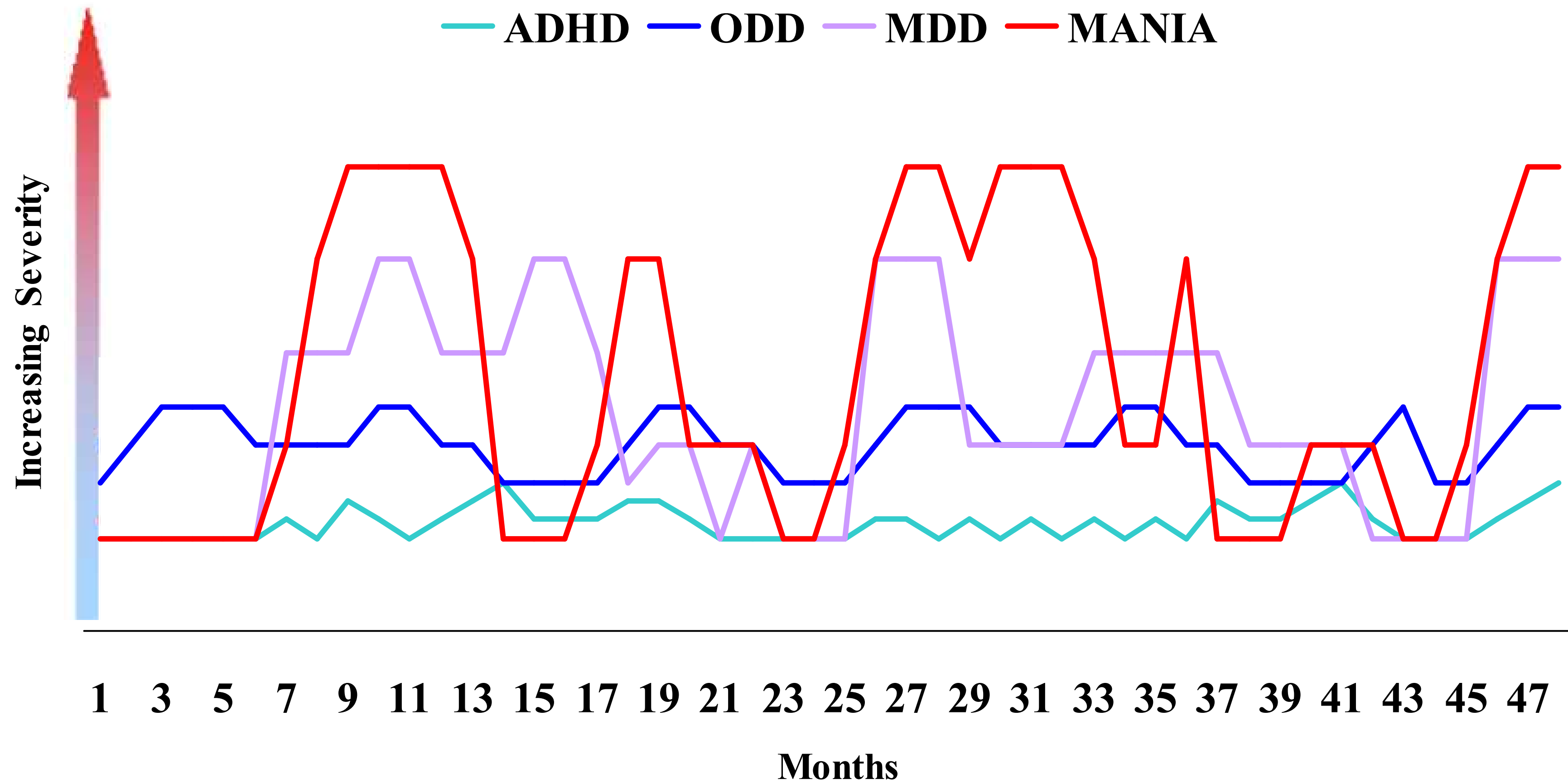
Euphoria and Irritability in BPD Probands



Are All Forms of Irritability the Same?

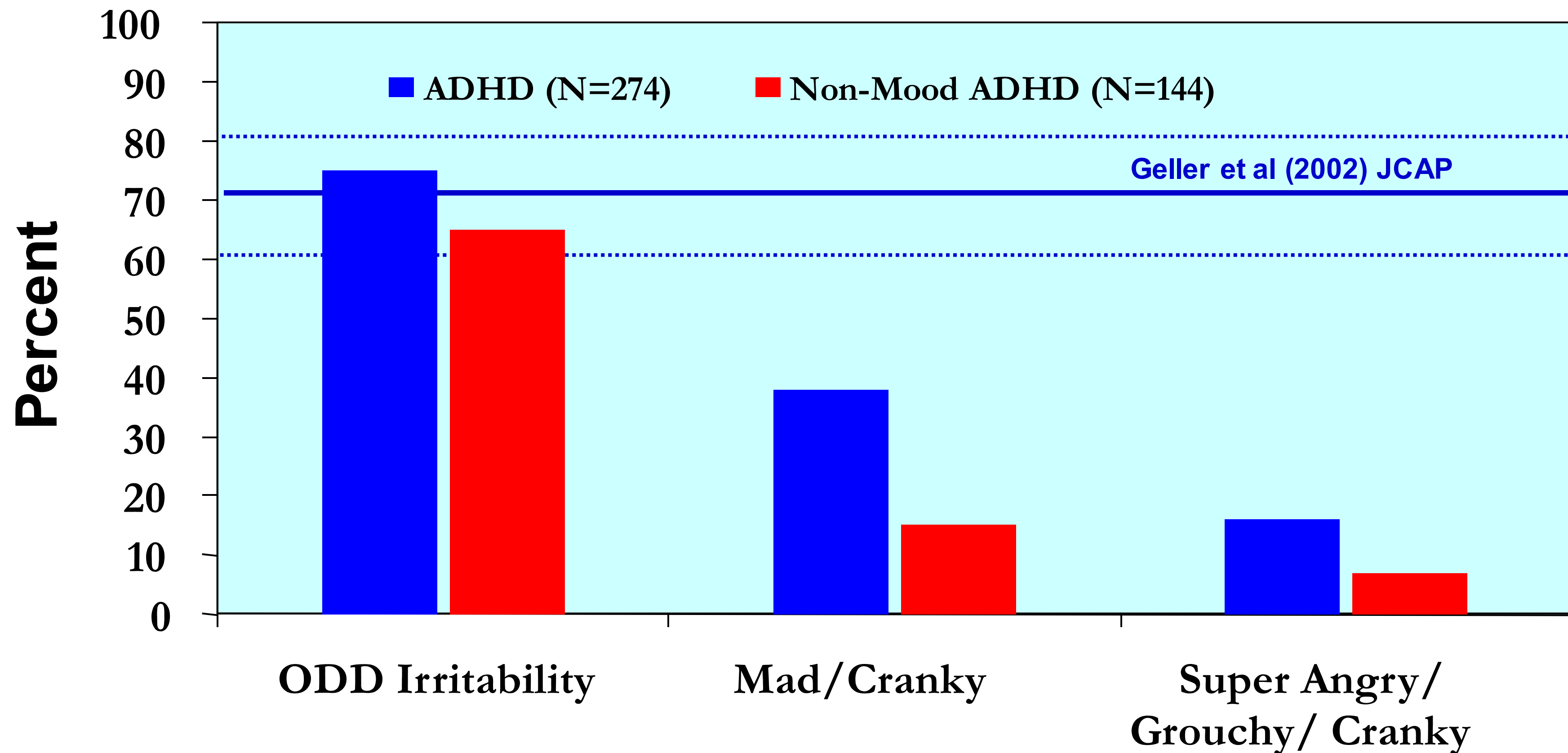
Heterogeneity of Irritability

Heterogeneity of Irritability in Children



Mick et al, 2007

Stratified Prevalence of Irritability in ADHD Subjects With and Without Mood Disorder



Mick et al. *Biological Psychiatry,* 2005; 58:576-582.

Juvenile Mania

- The type of irritability observed in manic children is very severe, persistent, and often violent.
- The outbursts often include threatening or attacking behavior towards others, including family members, other children, adults, and teachers.

Biederman et al. *J Am Acad Child Adolesc Psychiatry*. 1996; 35(8): 997-1008.

Heterogeneity of Irritability

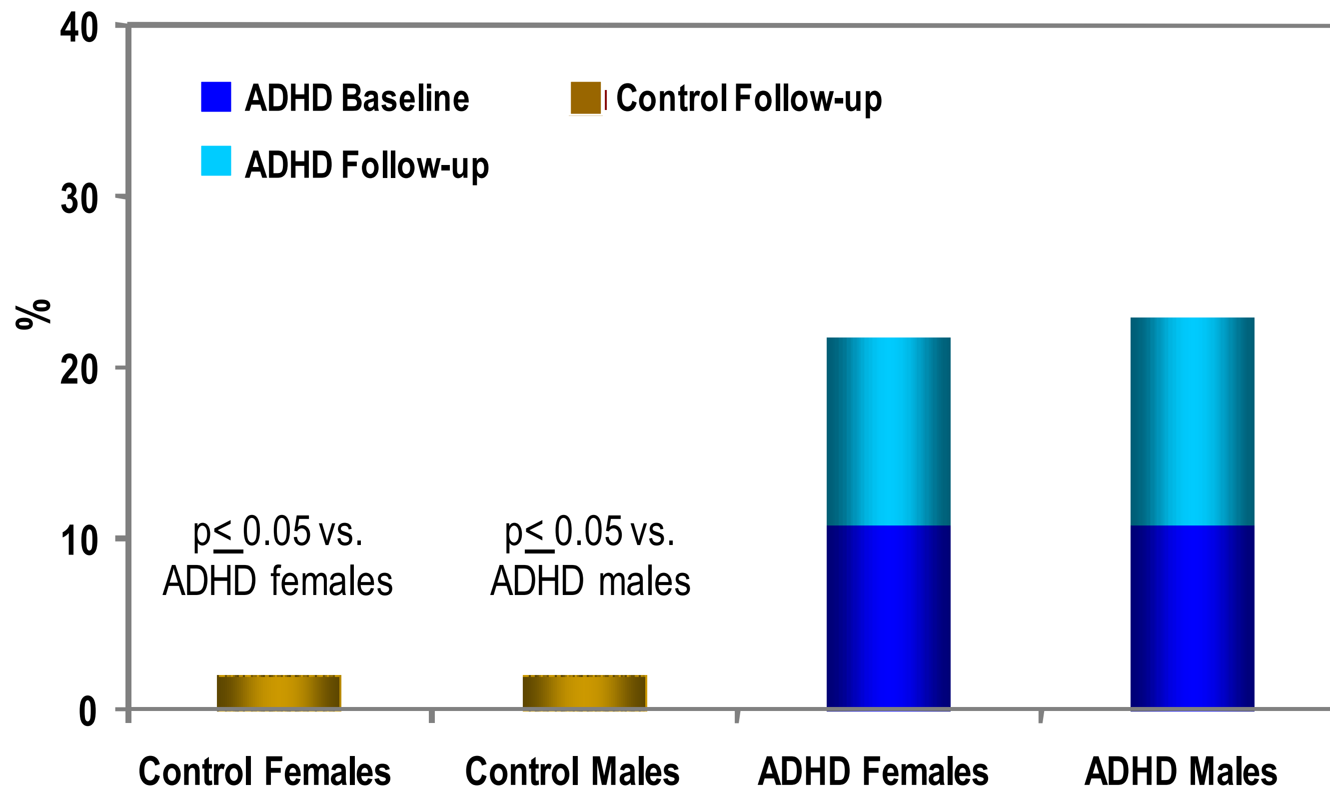
- Labile mood/hot temper: ODD
- Severe irritability: MDD
- Explosive/violent irritability: BPD

Mick et al. *Biological Psychiatry.* 2005; 58:576-582.

Differential Diagnosis with ADHD

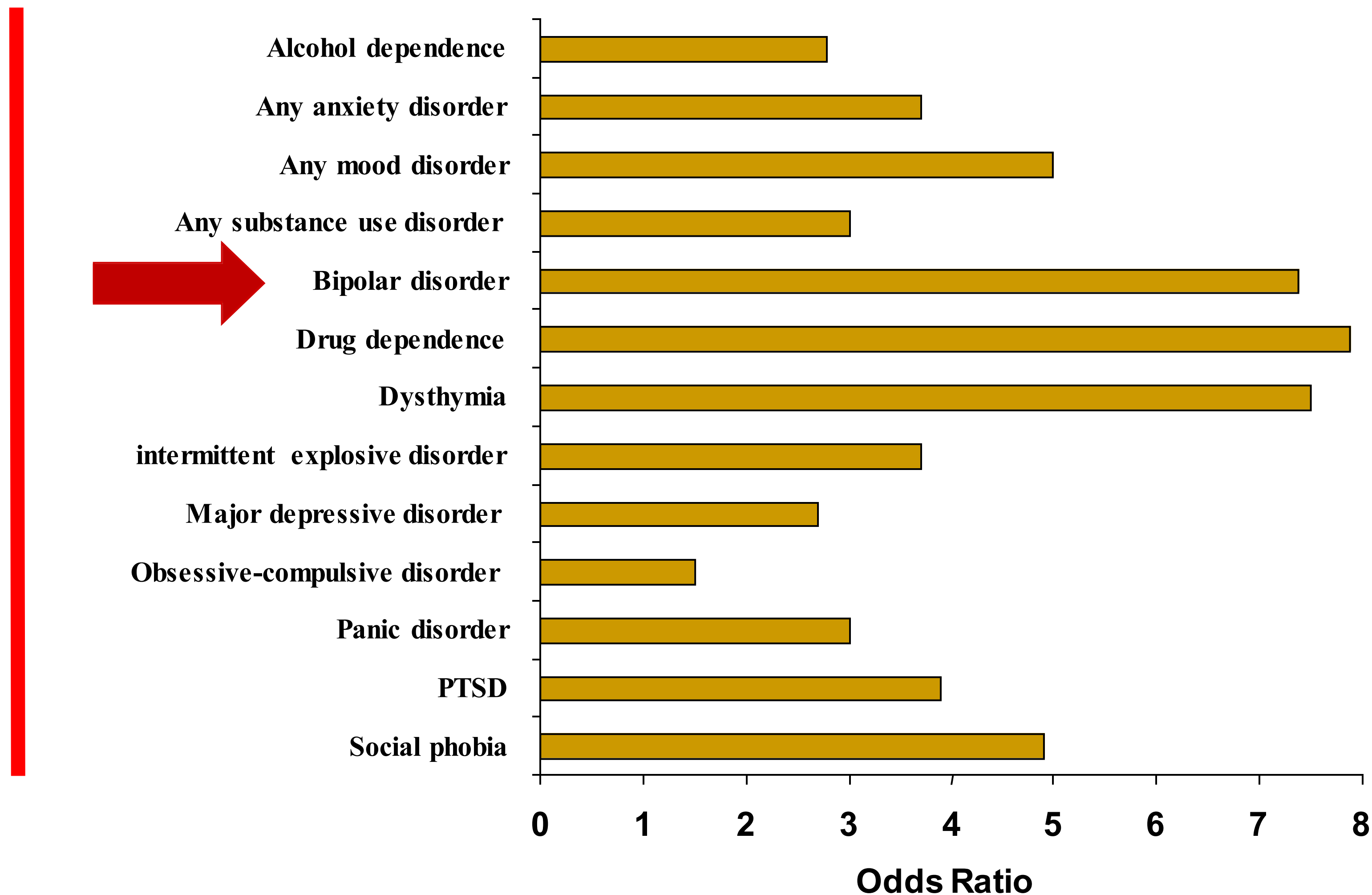
- Overlapping symptoms include:
  a) Distractibility
  b) Physical hyperactivity
  c) Talkativeness

Bipolar Disorder in Girls and Boys With and Without ADHD



Biederman et al. *Psychological Medicine*. 2006; 36: 167-179.
Biederman et al. *Biological Psychiatry.* 2006; 60: 1098-1105.

Patterns of Comorbidity in ADHD Adults



Kessler et at. *Am J Psychiatry*. 2006; 163:4

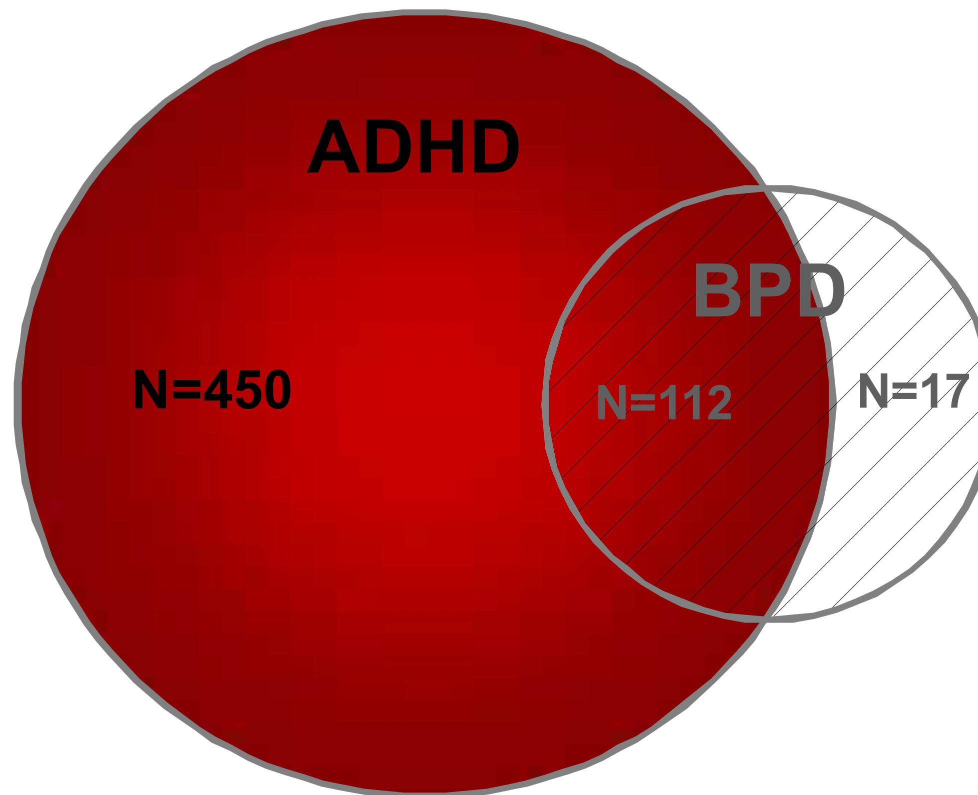
Clinical Presentation:

Two Cohorts

1) Assessed in the arly 1990's
2) Assessed 1995-2002

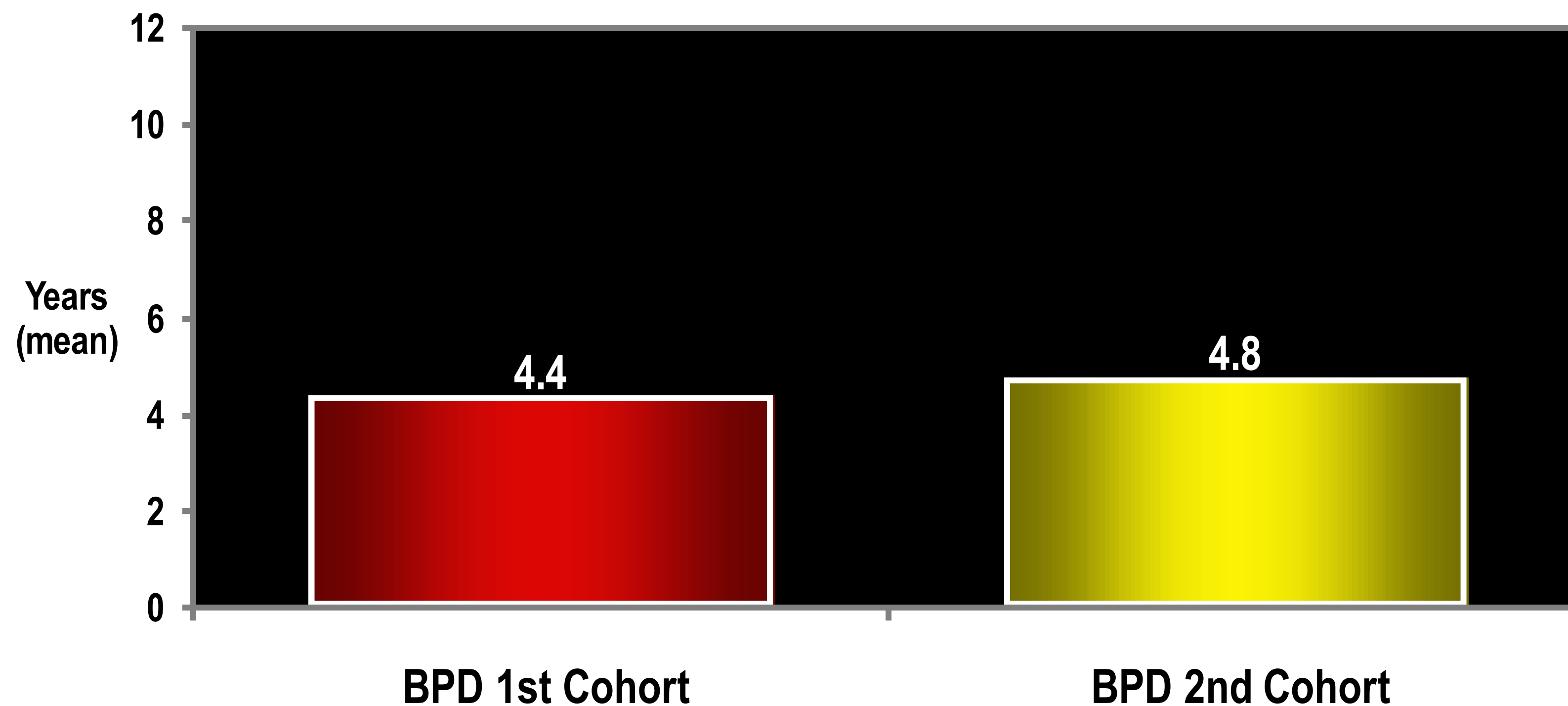
2002 MGH Study of Pediatric BPD

Diagnostic Overlap of BPD and ADHD [Second Cohort]



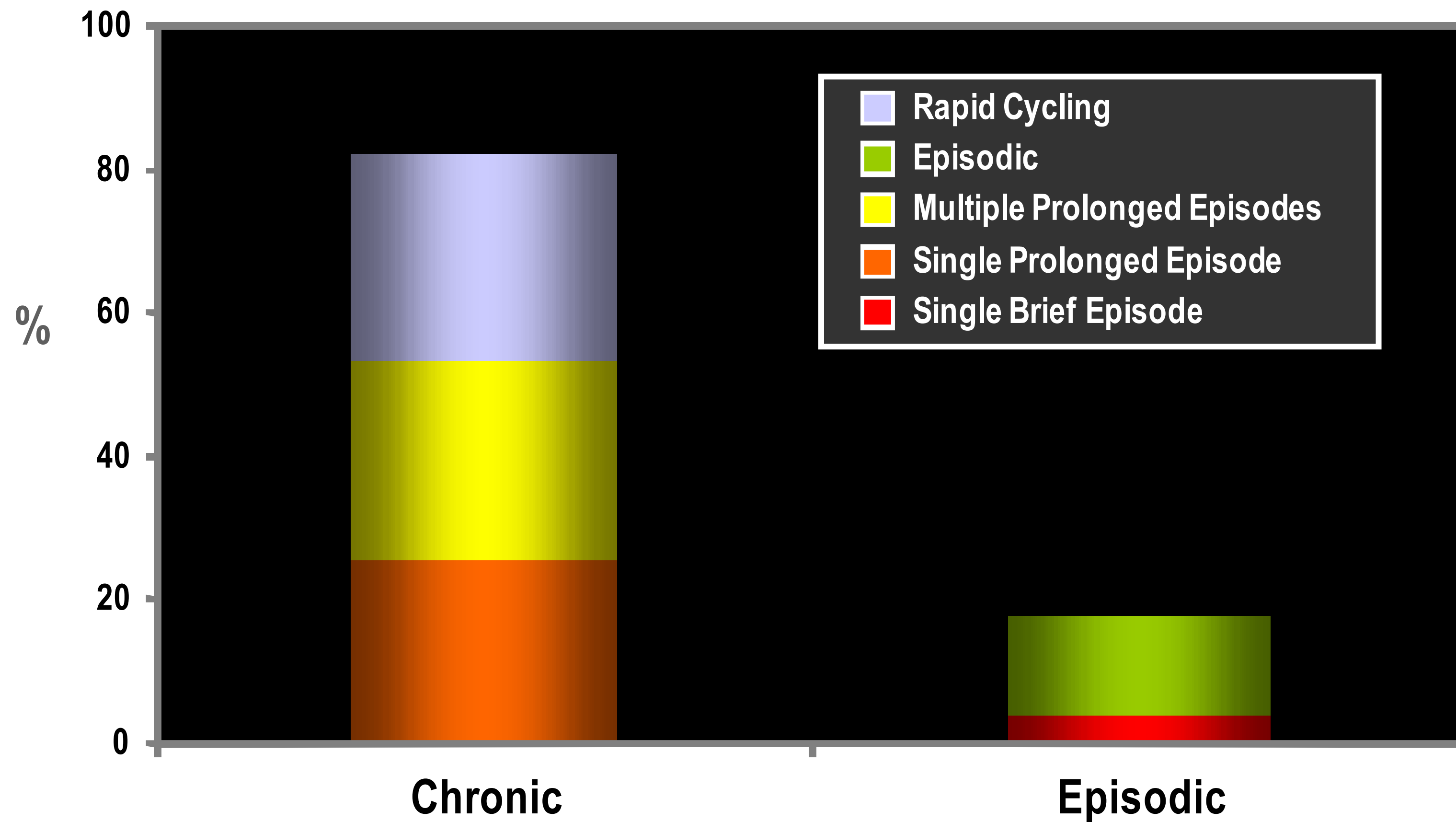
Biederman et al. *J of Affective Disorders*. 2004; S82:45-58.

2002 MGH Study of Pediatric BPD



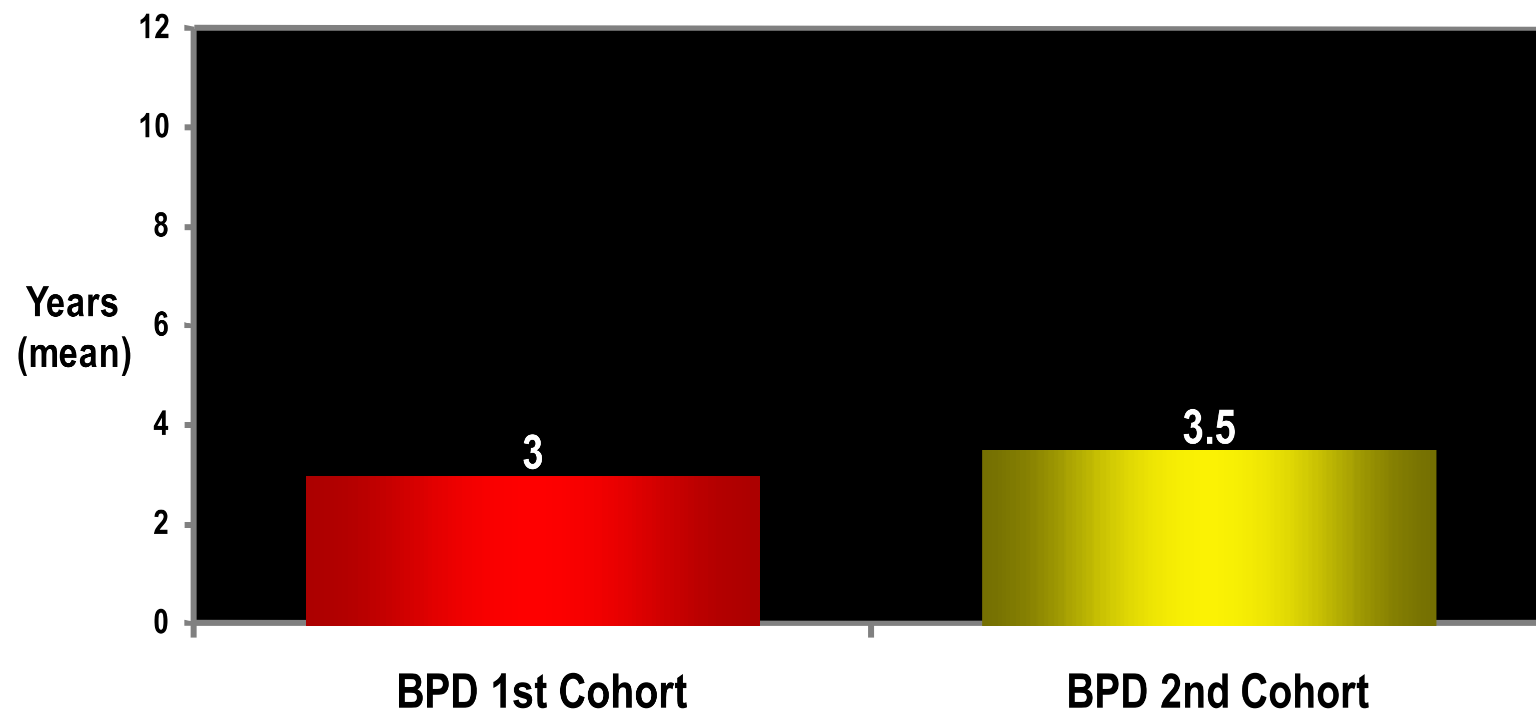
Biederman et al. *J of Affective Disorders*. 2004; S82:45-58.

2002 MGH Study of Pediatric BPD



Biederman et al. *J of Affective Disorders*. 2004; S82:45-58.

2002 MGH Study of Pediatric BPD



Biederman et al. *J of Affective Disorders*. 2004; S82:45-58.

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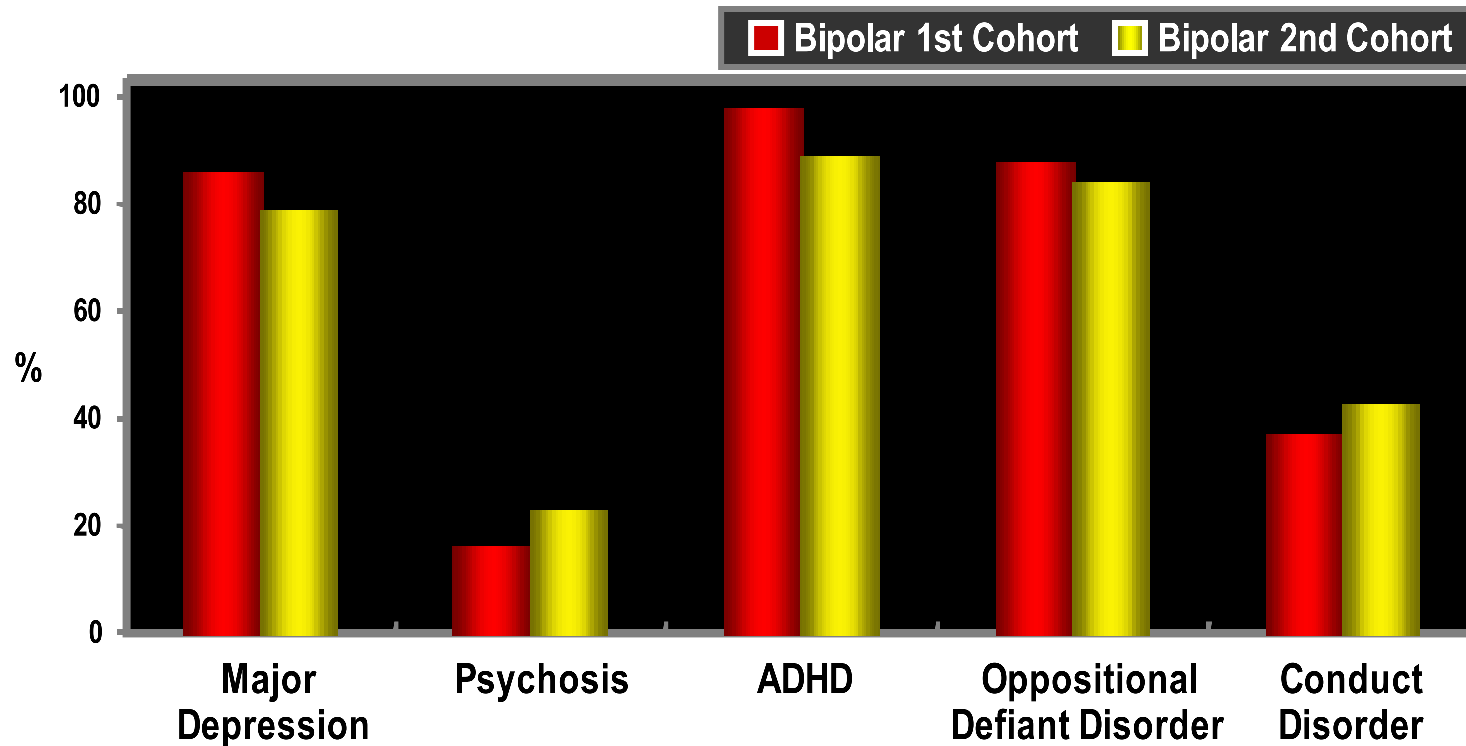

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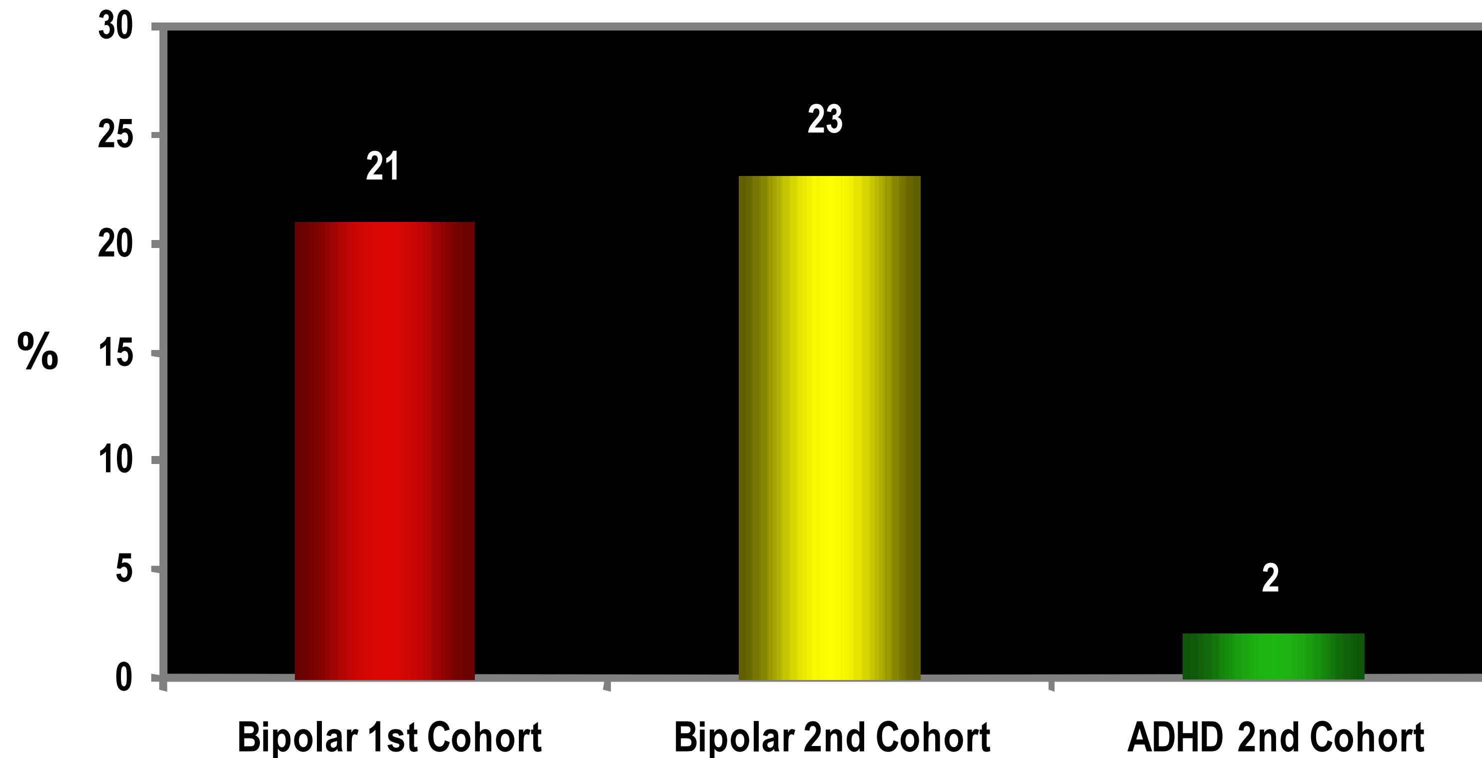


Biederman et al. *J of Affective Disorders*. 2004; S82:45-58.

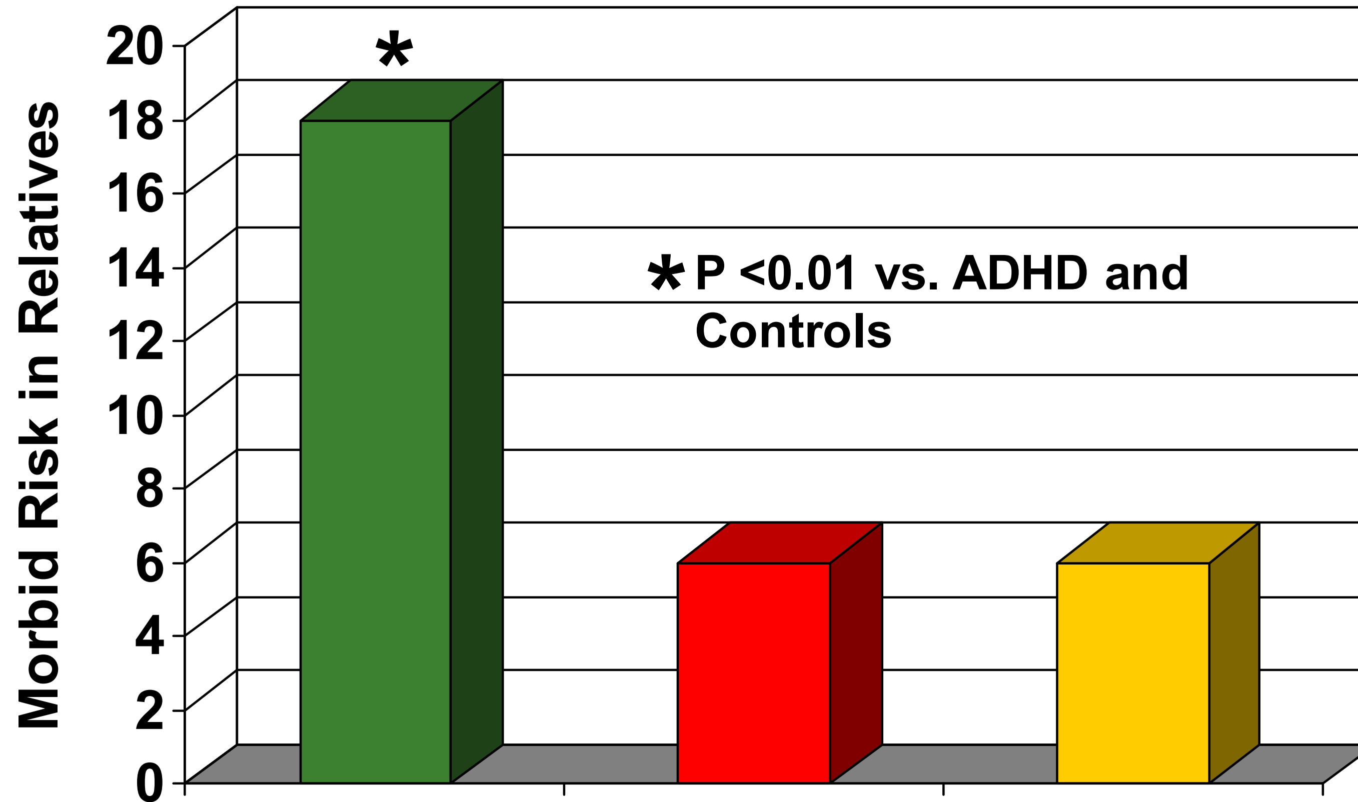
Clinical Presentation

- Frequently irritable
- Frequently non-episodic
- Frequently chronic
- Frequently mixed
- Highly comorbid with ADHD, ODD, CD, and anxiety

Robins & Guze Criteria for Validity of Psychiatric Diagnosis

Is Pediatric BPD Familial?

Familial Risk of BP-I Disorder in First Degree Relatives



	BP-I	ADHD	Control
Proband n=	157	162	136
Relative n=	508	511	411

Wozniak et al. In Press

Robins & Guze Criteria for Validity of Psychiatric Diagnosis

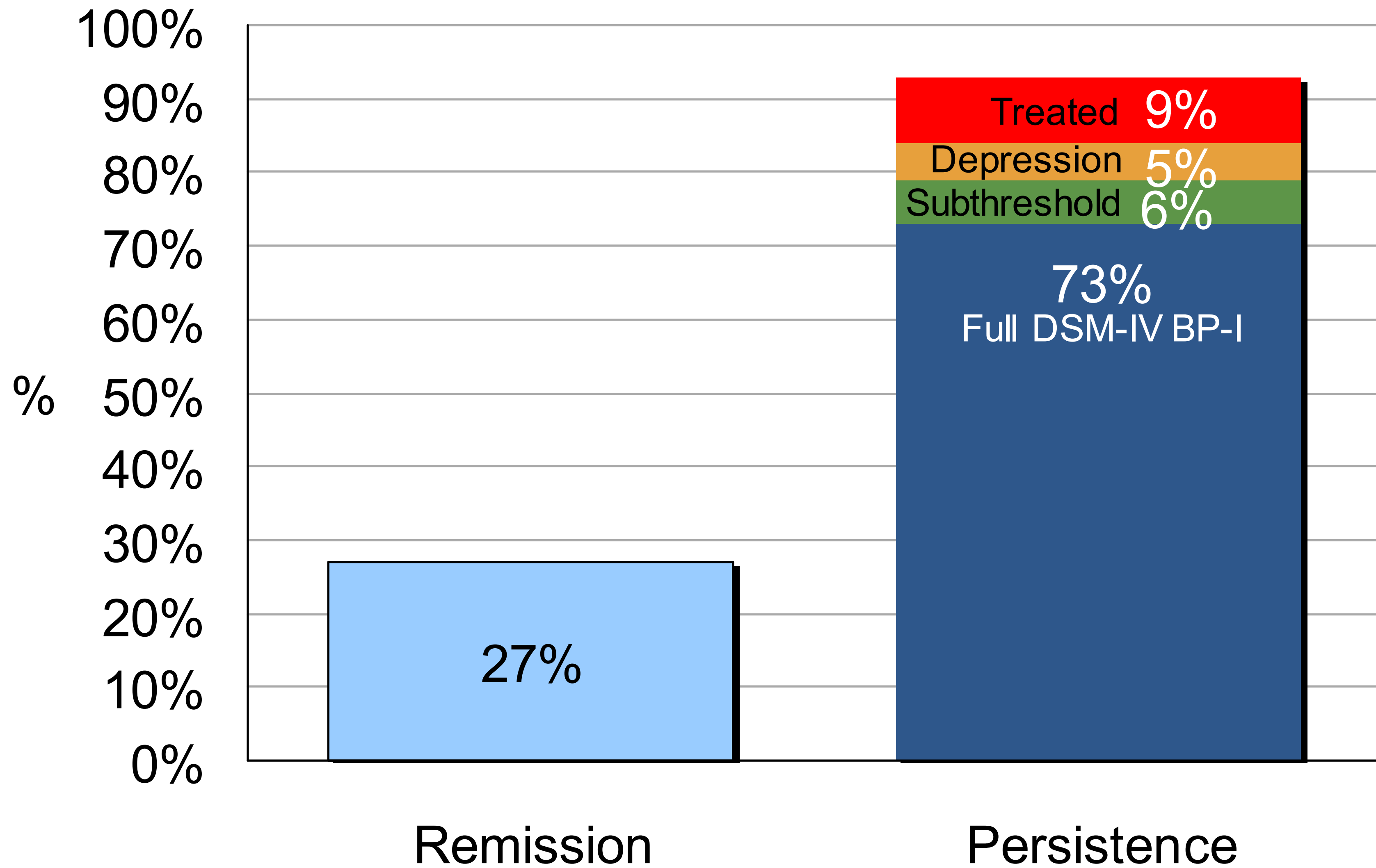
Does Pediatric BPD have a unique course?

Types of Remission

- Syndromatic Remission
  - Loss of full diagnostic status
- Symptomatic Remission
  - Loss of subthreshold diagnostic status
- Functional Remission
  - Loss of subthreshold diagnostic status with functional recovery

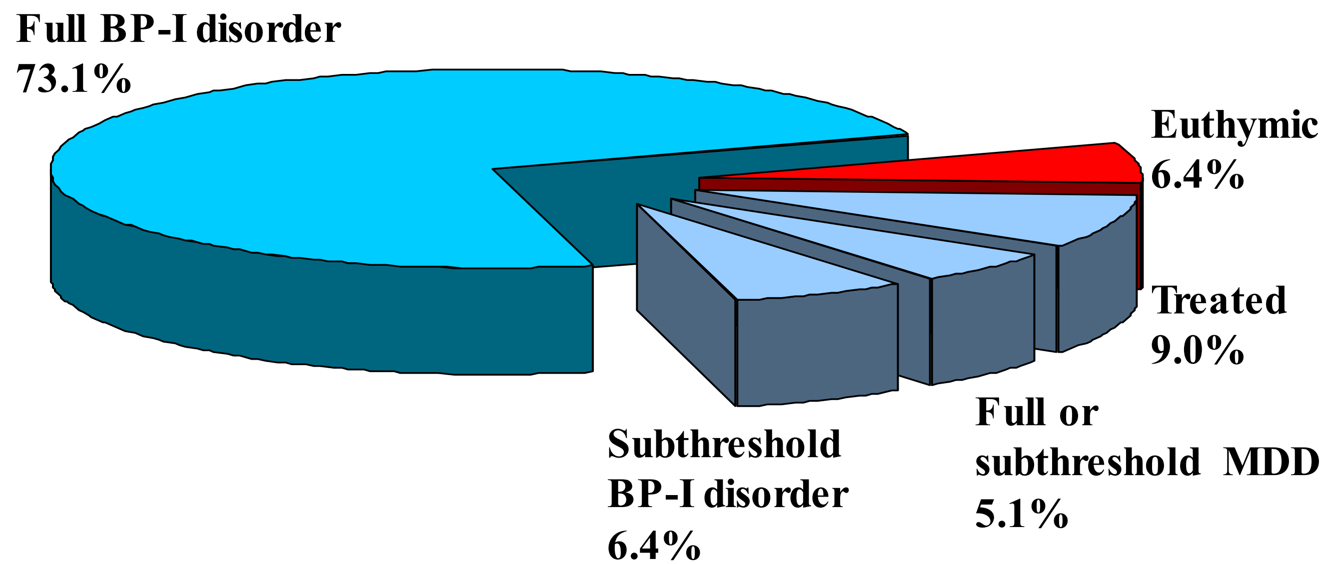
Keck et al. *American Journal of Psychiatry*. 1998:155:5.

Figure 1. Persistence of DSM-IV BP-I in youth at 4-year Follow-up



Wozniak, Biederman et al. 2010 in press

Persistence of DSM-IV BP-I in youth at 4-year Follow-up



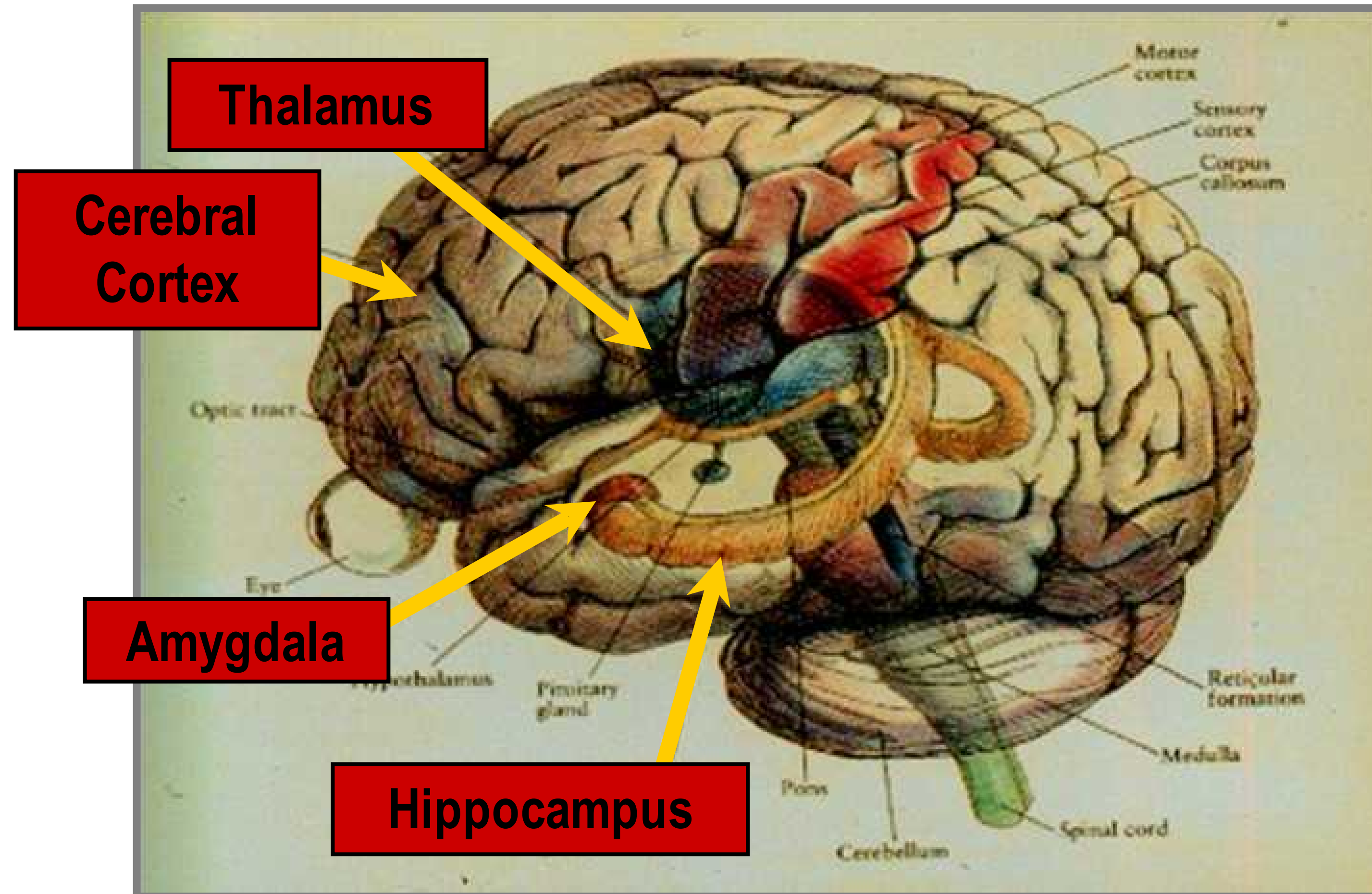
Wozniak, Biederman et al. 2010 in press

Robins & Guze Criteria for Validity of Psychiatric Diagnosis

Does Pediatric BPD have unique laboratory findings?

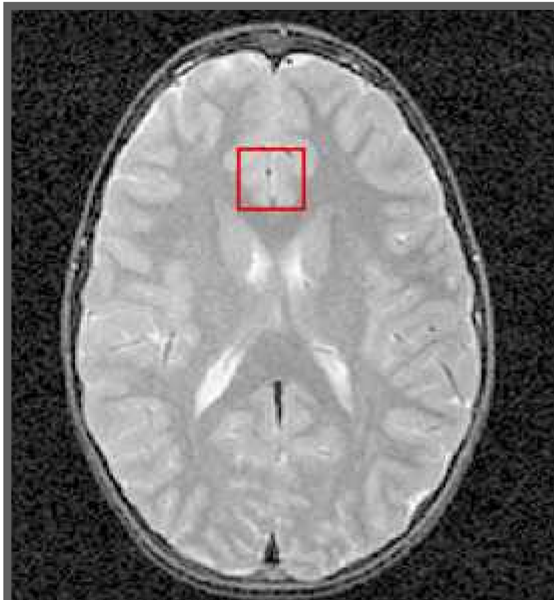
MRI Findings

Bipolar MRI Results

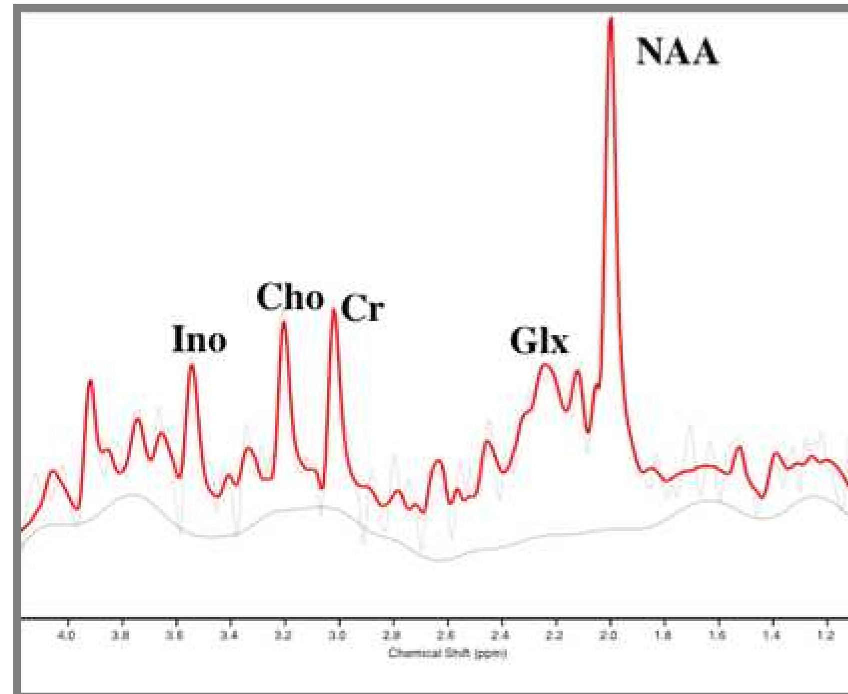


Frazier et al. 2003.

Proton Spectrum (b) acquired from the anterior cingulate cortex (a) of a child with bipolar disorder



Ino: myo-Inositol
Cho: choline
Cr: creatine
Glx: glutamate and glutamine
NAA: N-acetyl aspartate

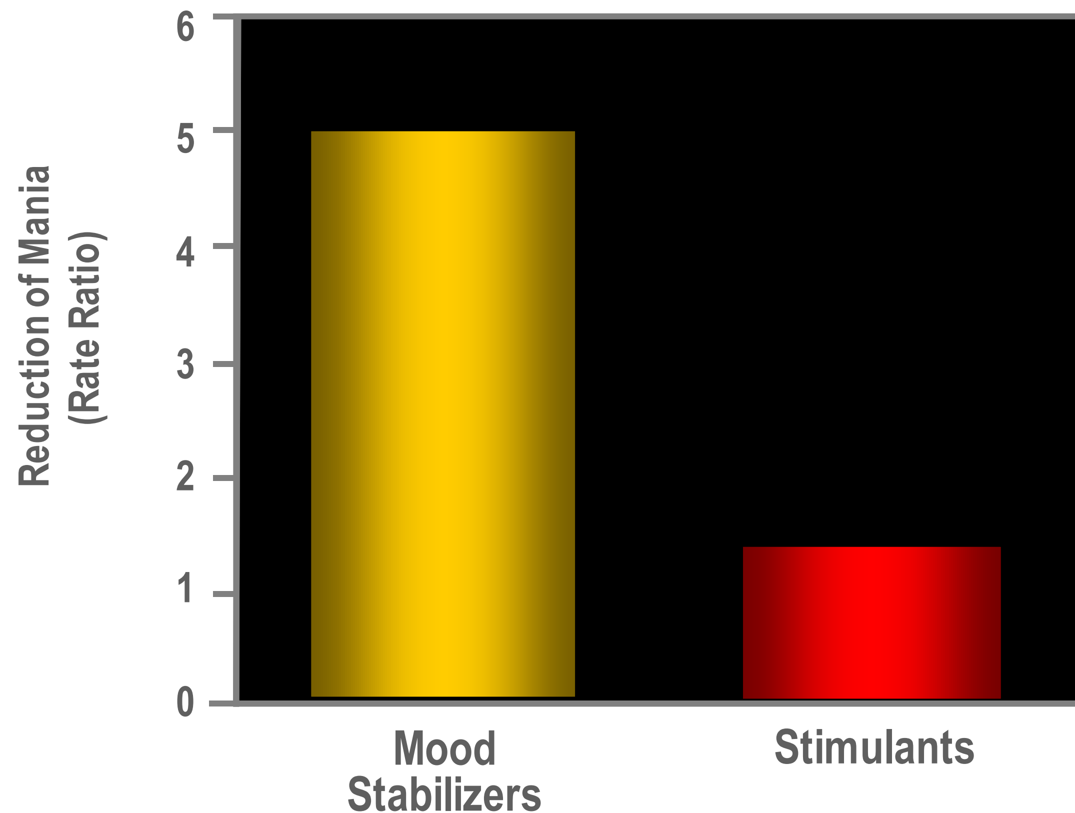


Moore et al. *Am J Psychiatry*. 2006; 163: 316-318.

Robins & Guze Criteria for Validity of Psychiatric Diagnosis

Does Pediatric BPD have a unique pharmacological response?

Pharmacologic Dissection Strategy: ADHD and BPD Naturalistic Study

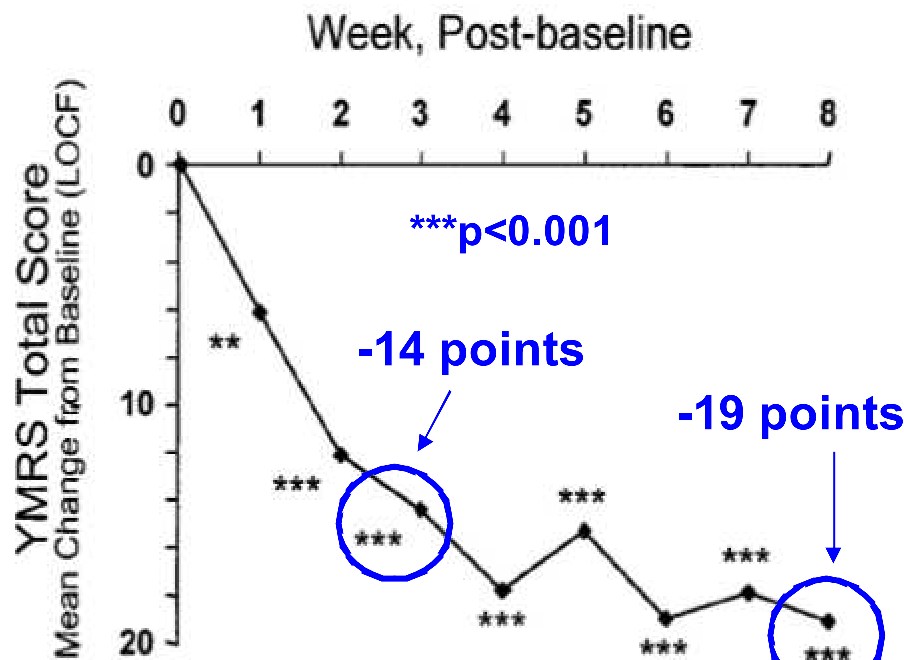


Biederman et al. *J Clin Psychiatry.* 1998; 59: 628-637.

Olanzapine in the Treatment of Pediatric Bipolar Mania: Change in YMRS Total Score from Baseline to Endpoint

OPEN LABEL 8-WEEK STUDY (n=23)

Mean dose: 9.6±4.3mg/day



CGI-S of Mania: 40% improvement, p<0.001

Mean Weight Gain: 5.0±2.3kg, p<0.001

Frazier et al. *J Child Adolesc Psychopharmacol* 2001 11(3): 239-250

DOUBLE BLIND 3-WEEK STUDY (n=161)

Mean dose: 8.9mg/day

-17.65 points, p<0.001

TABLE 2. Change in Symptom Severity Scores From Baseline to Endpoint

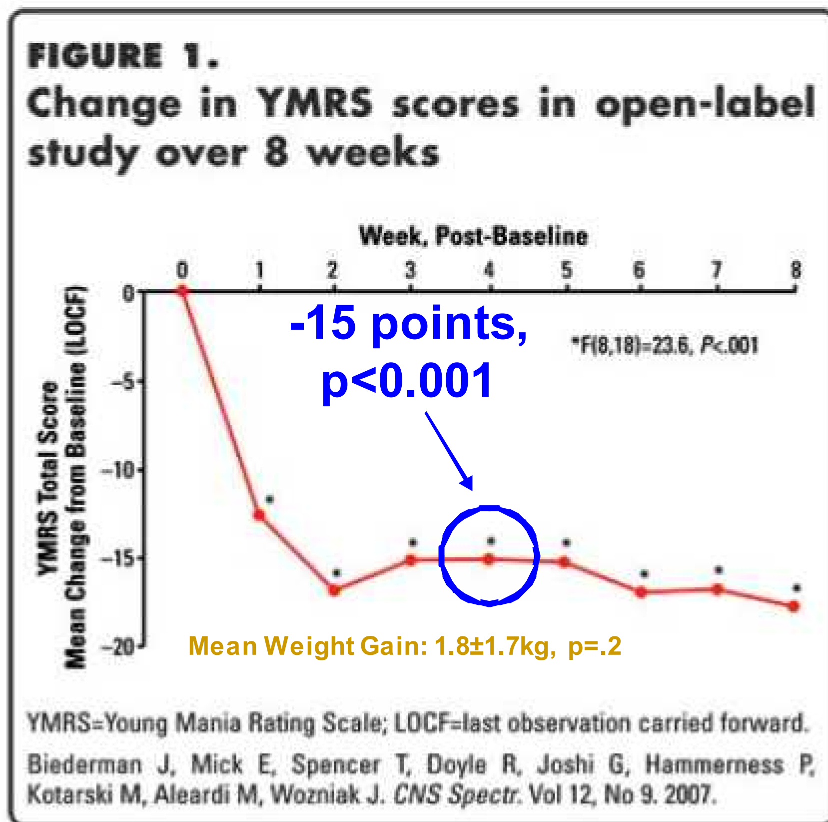
Scale	Olanzapine: Baseline (N=107) Mean	SD	Change From Baseline to Endpoint N	Mean	Placebo: Baseline (N=54) Mean	SD	Change From Baseline to Endpoint N	Mean	p
Young Mania Rating Scale Total score	33.08	6.55	105	–17.65	32.04	6.23	54	–9.99	<0.001
Elevated mood	2.79	0.99	105	–1.4	2.74	0.78	54	–0.69	<0.001
Increased motor activity/ energy	2.95	0.90	105	–1.21	2.80	0.76	54	–0.51	<0.001
Sexual interest	1.14	1.08	105	–0.72	1.33	1.13	54	–0.58	0.249
Sleep	2.42	1.08	105	–1.98	2.30	1.19	54	–1.26	<0.001
Irritability	5.48	1.32	105	–2.32	5.28	1.37	54	–1.4	0.004
Speech (rate and amount)	5.14	1.53	105	–2.96	4.69	1.66	54	–1.37	<0.001
Language thought disorder	2.24	0.58	105	–1.18	2.11	0.66	54	–0.71	<0.001
Content	3.41	2.29	105	–2.08	3.11	2.13	54	–1.35	0.019
Disruptive-aggressive behavior	4.84	1.37	105	–2.1	4.74	1.58	54	–1.18	0.006
Appearance	1.18	1.05	105	–0.61	1.24	1.10	54	–0.14	<0.001
Insight	1.49	1.39	105	–0.96	1.70	1.37	54	–0.77	0.268
Clinical Global Impressions Bipolar Version									
Severity overall	4.81	0.71	105	–1.63	4.83	0.75	54	–0.99	<0.001
Severity of mania	4.81	0.69	105	–1.73	4.81	0.75	54	–1.05	<0.001
Severity of depression	3.12	1.59	105	–0.89	2.65	1.60	54	–0.80	0.533
Children's Depression Rating Scale—Revised total score	40.43	15.60	100	–8.37	35.77	15.35	53	–9.50	0.508
ADHD Rating Scale-IV—Parent Version total score	29.03	13.84	99	–9.69	25.28	11.84	50	–6.33	0.048
Hyperactivity-impulsivity subtotal score	13.84	6.81	100	–5.29	11.56	5.39	50	–2.87	0.008
Inattention subtotal score	15.21	8.02	99	–4.43	13.67	7.49	51	–3.62	0.388
Overt Aggression Scale total score	6.34	3.67	100	–3.60	5.73	2.94	52	–1.90	<0.001
Verbal aggression total score	2.74	1.31	100	–1.43	2.73	1.21	52	–0.75	0.004
Physical aggression toward self total score	0.84	1.12	100	–0.54	0.58	0.85	52	–0.36	0.071
Physical aggression toward others total score	1.18	1.20	100	–0.65	1.00	1.12	52	–0.23	0.010
Physical aggression toward objects total score	1.58	1.14	100	–0.99	1.42	1.02	52	–0.63	0.026

Tohen et al. AJP 2007; 164:1547–1556

Aripiprazole in the Treatment of Pediatric Bipolar Mania: Change in YMRS Total Score from Baseline to Endpoint

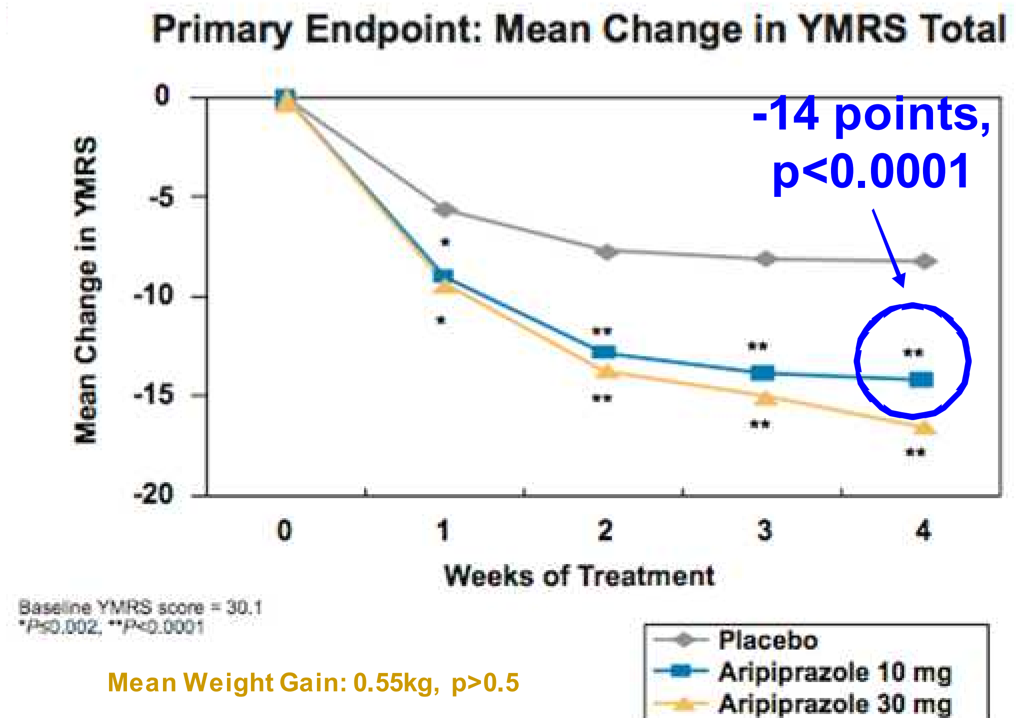
OPEN LABEL 8-WEEK STUDY (n=19)

Mean dose: 9.4±4.2mg/day



Biederman et al. *CNS Spectr* 2007; 12(9)

DOUBLE BLIND 4-WEEK STUDY (n=296)



Nyilas et al (2008) APA Meeting

Risperidone in the Treatment of Pediatric Bipolar Mania: Change in YMRS Total Score from Baseline to Endpoint

OPEN LABEL 8-WEEK STUDY (n=30)

Mean dose: 1.25 ± 1.5 mg/day

-14.4 points, p<0.0001

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 15, Number 2, 2005
Mary Ann Liebert, Inc.
Pp. 311–317

An Open-Label Trial of Risperidone in Children and Adolescents with Bipolar Disorder

Joseph Biederman, M.D.,[1-3] Eric Mick, Sc.D.,[1-3] Janet Wozniak, M.D.,[1,2]
Megan Aleardi, B.A.,[1,3] Thomas Spencer, M.D.,[1-3] and Stephen V. Faraone, Ph.D.[4]

TABLE 1. BASELINE AND ENDPOINT MEASURES OF MANIA, DEPRESSION, AND PSYCHOSIS

	Baseline Mean ± SD	Endpoint Mean ± SD	Statistic F (1,29)	Statistic p-value
YMRS	27.9 ± 9.2	13.5 ± 9.7	54.4	<0.0001
BPRS	43.3 ± 15.7	[illegible]	18.4	0.0002
Resistance (mania symptoms)	15.6 ± 5.8	8.2 ± 3.5	30.5	<0.0001
Positive symptoms	8.2 ± 3.9	6.4 ± 1.6	5.9	0.02
Negative symptoms	4.7 ± 3.1	5.1 ± 3.2	0.1	0.7
Psychological discomfort (anxiety/depression)	13.3 ± 6.8	9.9 ± 4.	16.7	0.2
CDRS	40.9 ± 11.5	30.7 ± 11.0	21.8	0.0001

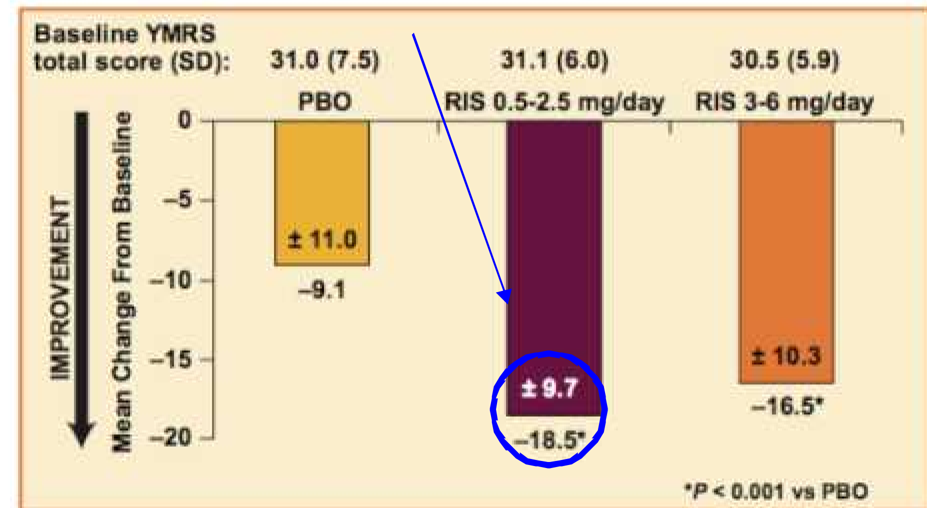
YMRS, Young Mania Rating Scale; BPRS, Brief Psychiatric Rating Scale; CDRS, Children's Depression Rating Scale.

Mean Weight Gain: 2.1±2.0kg; *p*<0.001

DOUBLE-BLIND 3-WEEK STUDY (n=137)

-18.5 points, p<0.001

Figure 2. YMRS Adolescent Version Total Scores: Change From Baseline to Endpoint (ITT Population, Last Observation Carried Forward Analysis).



YMRS = Young Mania Rating Scale; ITT = intent-to-treat; SD = standard deviation; PBO = placebo; RIS = risperidone.

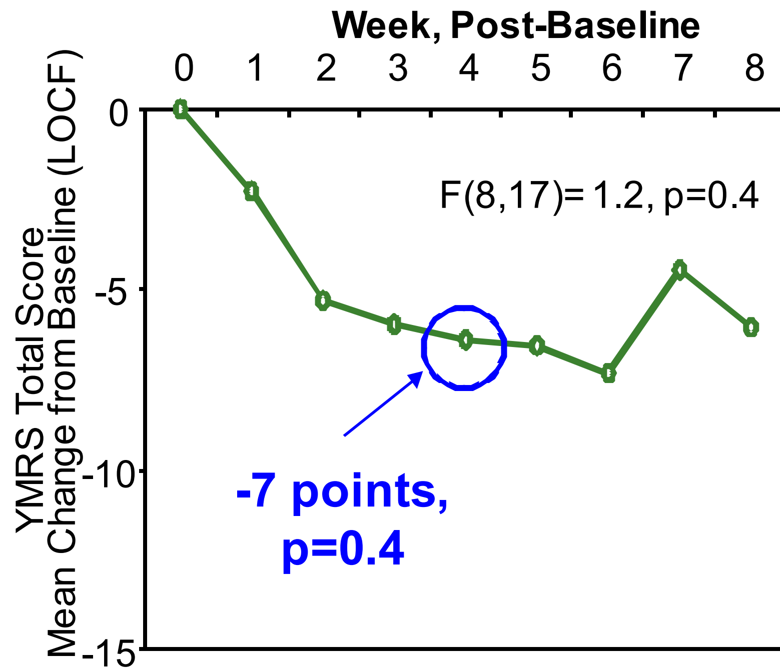
Mean Weight Gain: 1.9±1.7kg

Biederman et al. *J Child Adolescent Psychopharmacology* 2006; 15(2): 311-317

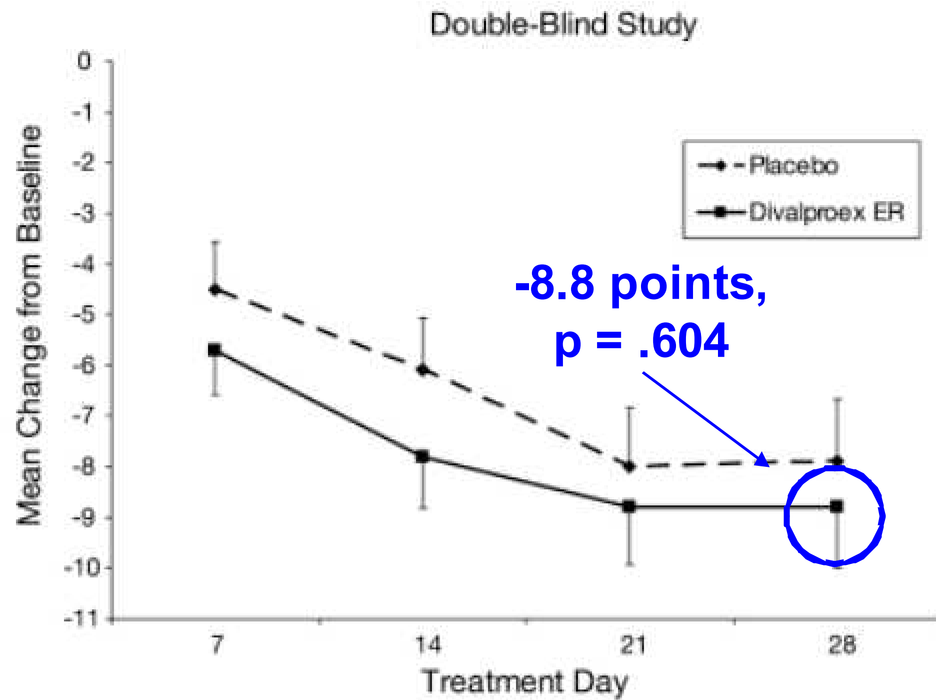
Pandina et al. (2007) AACAP Meeting

Divalproex ER in the Treatment of Pediatric Bipolar Mania: Change in YMRS Total Score from Baseline to Endpoint

OPEN LABEL 8-WEEK STUDY



DOUBLE BLIND 4-WEEK STUDY (n=229)



Mean Weight Gain: 1.0kg; $p>0.05$

Wozniak et al. *CNS Spectrums* 2008 submitted

Wagner et al., *JAACAP* 48:5, May 2009

Is Pediatric BPD Without the Distinct Episode Qualifier a Valid Clinical Entity?

- Fully satisfies Robins & Guze criteria for a valid clinical entity
- Severe and highly dysfunctional clinical presentation highly consistent with adult bipolar disorder
- Positive family history of BPD
- Selective treatment response to antimanic agents
- Compromised course and outcome

Is Mood Instability Characterized by Severe Irritability and Frequent Absence of Discrete Episodes in Children, BPD?

- Chronic and severe irritability and absence of discrete episodes may represent developmentally specific associated features of pediatric onset BPD.
- “Atypical” form is the most common presentation of BPD in children.

First scientific article to present a coherent conceptual perspective on Pediatric Bipolar Disorder as a developmental subtype of Bipolar Disorder

Pediatric Mania: A Developmental Subtype of Bipolar Disorder?

Joseph Biederman, Eric Mick, Stephen V. Faraone, Thomas Spencer, Timothy E. Wilens, and Janet Wozniak

Despite ongoing controversy, the view that pediatric mania is rare or nonexistent has been increasingly challenged not only by case reports, but also by systematic research. This research strongly suggests that pediatric mania may not be rare but that it may be difficult to diagnose. Since children with mania are likely to become adults with bipolar disorder, the recognition and characterization of childhood-onset mania may help identify a meaningful developmental subtype of bipolar disorder worthy of further investigation. The major difficulties that complicate the diagnosis of pediatric mania include: 1) its pattern of comorbidity may be unique by adult standards, especially its overlap with attention-deficit/hyperactivity disorder, aggression, and conduct disorder; 2) its overlap with substance use disorders; 3) its association with trauma and adversity; and 4) its response to treatment is atypical by adult standards. Biol Psychiatry 2000;48: 458–466 © *2000 Society of Biological Psychiatry*

Can a Subtype of Conduct Disorder Linked to Bipolar Disorder Be Identified? Integration of Findings from the Massachusetts General Hospital Pediatric Psychopharmacology Research Program

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Our intent was to investigate systematically the overlap between conduct disorder (CD) and bipolar disorder (BPD). We hypothesized that neither CD nor manic symptoms were secondary to the other disorder and that children with the two disorders would have correlates of both. Results from a series of programmatic studies examining phenotypic features of bipolar and conduct disorder alone or combined in probands and relatives were evaluated within and without the context of ADHD. Examination of the clinical features, patterns of psychiatric comorbidity, functioning in multiple domains, and familiality showed that children with CD and BPD had similar features of each disorder irrespective of the comorbidity with the other disorder. Our data suggest that when BPD and CD co-occur in children, both are correctly diagnosed. In these comorbid cases, CD symptoms should not be viewed as secondary to BPD, and manic symptoms should not be viewed as secondary to CD.
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"He's just doing that to get attention."