MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Pediatric Bipolar Disorder

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Disclosures

Dr. Janet Wozniak has recently received consultation fees from Bristol Myers Squibb and Otsuka.
She has received research support from Demarest Lloyd, Jr. Foundation, the Baszucki Brain Research Fund, Johnson and Johnson, McNeil, Merck/Schering-Plough, Pfizer, and Shire as well as the National Institute of Mental Health (NIMH) of the National, Institutes of Health (NIH) and PCORI.
She is the author of the book, “Is Your Child Bipolar” published May 2008, Bantam Books.
Her spouse receives royalties from UpToDate; consultation fees from Emalex, Noctrix, Disc Medicine, Haleon, Alexza , Azurity and research support from Merck, American Regent, the RLS Foundation, and the Baszucki Brain Research Fund. In the past, he has received honoraria, royalties, research support, consultation fees or speaker’s fees from: Otsuka, Cambridge University Press, Advance Medical, Arbor Pharmaceuticals, Axon Labs, Boehringer-Ingelheim, Cantor Colburn, Covance, Cephalon, Eli Lilly, FlexPharma, GlaxoSmithKline, Impax, Jazz Pharmaceuticals, King, Luitpold, Novartis, Neurogen, Novadel Pharma, Pfizer, SanofiAventis, Sepracor, Sunovion, Takeda, UCB (Schwarz) Pharma, Wyeth, Xenoport, Zeo

Can children really have bipolar disorder?

Pediatric bipolar disorder affects a small percentage of youth (1-3%)

Lifetime Prevalence of Mental Disorders in U.S. Adolescents: Results from the National Comorbidity Survey Replication–Adolescent Supplement (NCS-A)

Kathleen Ries Merikangas, Ph.D., Jian-ping He, M.Sc., Marcy Burstein, Ph.D., Sonja A. Swanson, Sc.M., Shelli Avenevoli, Ph.D., Lihong Cui, M.Sc., Corina Benjet, Ph.D., Katholiki Georgiades, Ph.D., Joel Swendsen, Ph.D.

Objective: To present estimates of the lifetime prevalence of *DSM-IV* mental disorders with and without severe impairment, their comorbidity across broad classes of disorder, and their sociodemographic correlates. Method: The National Comorbidity Survey–Adolescent Supplement NCS-A is a nationally representative face-to-face survey of 10,123 adolescents aged 13 to 18 years in the continental United States. *DSM-IV* mental disorders were assessed using a modified version of the fully structured World Health Organization Composite International Diagnostic Interview. Results: Anxiety disorders were the most common condition (31.9%), followed by behavior disorders (19.1%), mood disorders (14.3%), and substance use disorders

Acad. Child Adolesc. Psychiatry, 2010;49(10):980–989. Key Words: epidemiology, adolescents, mental disorders, National Comorbidity Survey, correlates

2.9% Pediatric Bipolar in Study of 10,000+ US Adolescents
1.8% Pediatric Bipolar Disorder in Meta-Analysis of International Studies
8.7% ADHD

THE JOURNAL OF CLINICAL PSYCHIATRY

Results: The overall rate of bipolar disorder was 1.8% (95% CI, 1.1%–3.0%). There was no significant difference in the mean rates between US and non-US studies, but the US studies had a wider range of rates. The highest estimates came from studies that used broad definitions and included bipolar disorder not otherwise specified. Year of enrollment was negatively correlated with prevalence ($r = -0.04$) and remained nonsignificant when controlling for study methodological differences.

Conclusions: Mean rates of bipolar disorder were higher than commonly acknowledged and not significantly different in US compared to non-US samples, nor was there evidence of an increase in rates of bipolar disorder in the community over time. Differences in diagnostic criteria were a main driver of different rates across studies.

J Clin Psychiatry 2011;72(9):1250–1256

Merikangas 2010; Van Meter J Clin Psych 2011

Bipolar Disorder is now considered in the differential diagnosis for youngsters with mood symptoms

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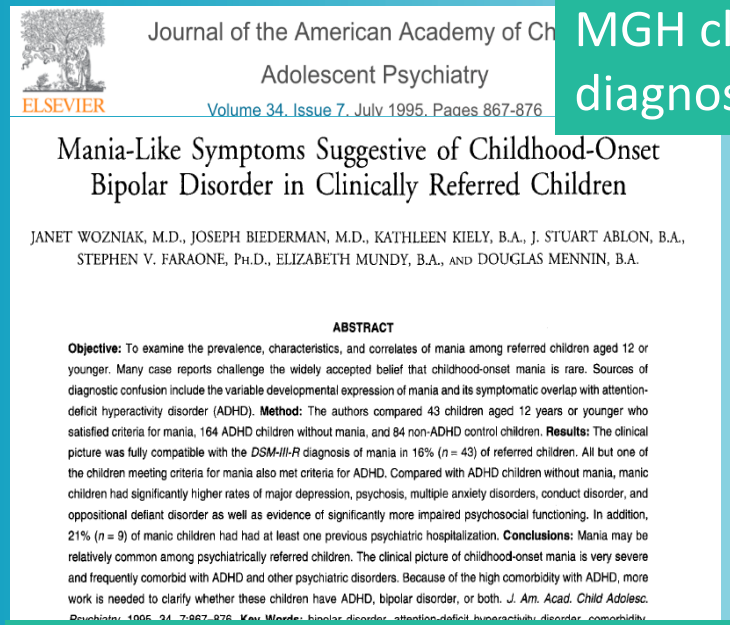


Journal of the American Academy of Ch
Adolescent Psychiatry
Volume 34, Issue 7, July 1995, Pages 867-876

ELSEVIER

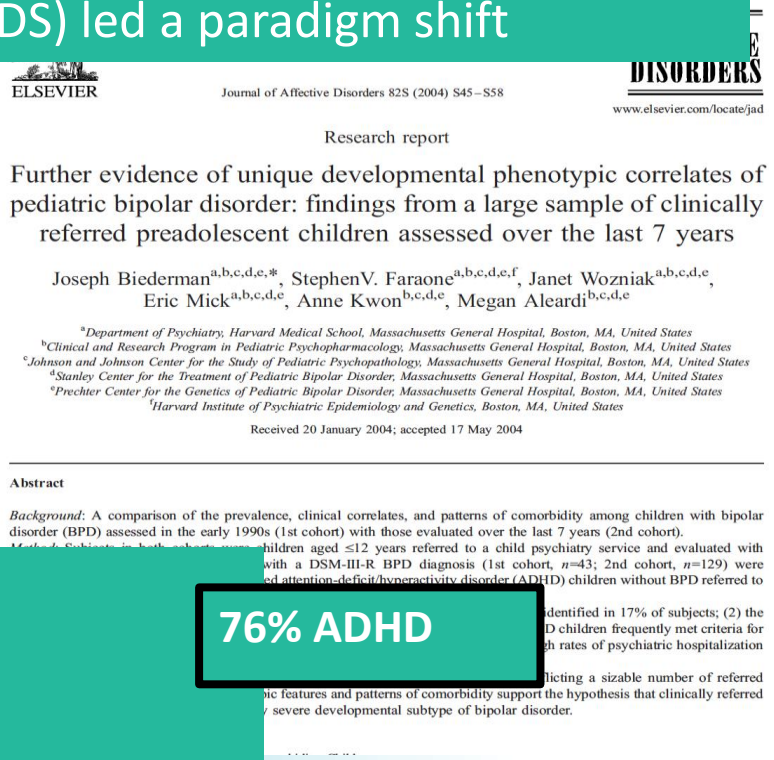
Mania-Like Symptoms Suggestive of Childhood-Onset Bipolar Disorder in Clinically Referred Children

JANET WOZNIAK, M.D., JOSEPH BIEDERMAN, M.D., KATHLEEN KIELY, B.A., J. STUART ABLON, B.A., STEPHEN V. FARAONE, PH.D., ELIZABETH MUNDY, B.A., AND DOUGLAS MENNIN, B.A.

ABSTRACT

Objective: To examine the prevalence, characteristics, and correlates of mania among referred children aged 12 or younger. Many case reports challenge the widely accepted belief that childhood-onset mania is rare. Sources of diagnostic confusion include the variable developmental expression of mania and its symptomatic overlap with attention-deficit hyperactivity disorder (ADHD). **Method:** The authors compared 43 children aged 12 years or younger who satisfied criteria for mania, 164 ADHD children without mania, and 84 non-ADHD control children. **Results:** The clinical picture was fully compatible with the *DSM-III-R* diagnosis of mania in 16% ($n = 43$) of referred children. All but one of the children meeting criteria for mania also met criteria for ADHD. Compared with ADHD children without mania, manic children had significantly higher rates of major depression, psychosis, multiple anxiety disorders, conduct disorder, and oppositional defiant disorder as well as evidence of significantly more impaired psychosocial functioning. In addition, 21% ($n = 9$) of manic children had had at least one previous psychiatric hospitalization. **Conclusions:** Mania may be relatively common among psychiatrically referred children. The clinical picture of childhood-onset mania is very severe and frequently comorbid with ADHD and other psychiatric disorders. Because of the high comorbidity with ADHD, more work is needed to clarify whether these children have ADHD, bipolar disorder, or both. *J. Am. Acad. Child Adolesc. Psychiatry*, 1995, 34, 7:867-876. **Key Words:** bipolar disorder, attention-deficit hyperactivity disorder, comorbidity

MGH clinical studies using structured interview diagnoses (KSADS) led a paradigm shift



ELSEVIER

Journal of Affective Disorders 82S (2004) S45–S58

DISORDERS

www.elsevier.com/locate/jad

Research report

Further evidence of unique developmental phenotypic correlates of pediatric bipolar disorder: findings from a large sample of clinically referred preadolescent children assessed over the last 7 years

Joseph Biederman[a,b,c,d,e,*], StephenV. Faraone[a,b,c,d,e,f], Janet Wozniak[a,b,c,d,e], Eric Mick[a,b,c,d,e], Anne Kwon[b,c,d,e], Megan Aleardi[b,c,d,e]

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[f]*Harvard Institute of Psychiatric Epidemiology and Genetics, Boston, MA, United States*

Received 20 January 2004; accepted 17 May 2004

Abstract

Background: A comparison of the prevalence, clinical correlates, and patterns of comorbidity among children with bipolar disorder (BPD) assessed in the early 1990s (1st cohort) with those evaluated over the last 7 years (2nd cohort).
Methods: Subjects in both cohorts were children aged ≤12 years referred to a child psychiatry service and evaluated with ... with a DSM-III-R BPD diagnosis (1st cohort, n=43; 2nd cohort, n=129) were ... ed attention-deficit/hyperactivity disorder (ADHD) children without BPD referred to ...
... identified in 17% of subjects; (2) the ... D children frequently met criteria for ... h rates of psychiatric hospitalization ...
... licting a sizable number of referred ... ic features and patterns of comorbidity support the hypothesis that clinically referred ... severe developmental subtype of bipolar disorder.

Consecutively referred children ≤ 12 years:

1991-1995 16% Bipolar Disorder (N=262)
1995-2002 17% Bipolar Disorder (N=768)

76% ADHD

Wozniak 1995; Biederman 2004

The symptoms of mania are the same in children and adults*

A. A *distinct period* of abnormally and persistently elevated, expansive or irritable mood and persistently increased goal-directed activity or energy

B. At least 3/7 (4/7 if mood is irritable)

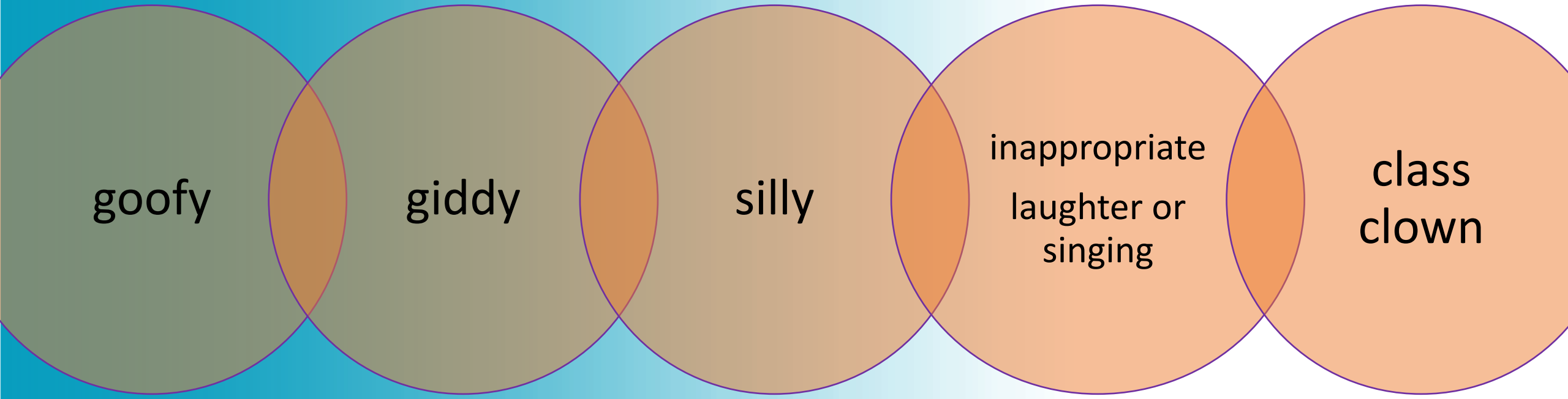
1) D Distractibility
2) I Increased activity/psychomotor agitation
3) G Grandiosity or inflated self-esteem
4) F Flight of ideas or racing thoughts
5) A Activities with painful consequences
6) S Sleep decreased
7) T Talkative or pressured speech

Diagnostic and Statistical Manual (DSM-5).

***taking development into consideration**

Isn’t ‘euphoria’ and ‘grandiosity’ part of childhood?

Euphoria in children can be difficult to distinguish from developmentally normal behaviors



Grandiosity can appear as flagrant disregard for adult authority

Biederman JAACAP 1996

MGH PEDIATRIC MANIA SYMPTOM CHECKLIST©

GUIDELINES FOR RATING

- Rate each of the following items for the past week
- Rate items relative to subject's baseline or what's expected for age / developmental level
- Assess behavior based on report from caretaker, subject and rater observation
- Assess composite severity based on frequency and intensity of the behavior

SYMPTOMS	FREQUENCY			INTENSITY			COMPOSITE SEVERITY			
Start each item by saying - "In the last week did s/he have difficulties with…"	< ½ a week (< 4 days)	> ½ a week (≥ 4 days)	All week (Daily)	Mild	Moderate	Severe				
	1	2	3	1	2	3				
1. MOOD BEING *EUPHORIC* Score	1	2	3	1	2	3	0	1	2	3
as suggested by sustained periods of: ○ **happy** or **excited** mood ○ **silly**, **giddy**, **goofy** mood ○ **laughing** [illegible] **talk**										
2. MOOD BEING *IRRITABLE* Score	1	2	3	1	2	3	0	1	2	3
as suggested by sustained periods of: ○ extremely **irritable**, **angry**, **cranky**, **grouchy** moods ○ extremely **threatening**, **destructive**, or **assaultive** behaviors ○ extreme **anger outbursts** / meltdowns / rage										
3. INCREASED ENERGY OR ACTIVITY Score	1	2	3	1	2	3	0	1	2	3
as suggested by: ○ engaging in activities in an **urgent**, **pressured**, **rushed** way, or at a **faster pace** than expected *(does not slow down)* ○ working on **big projects** that are beyond the capacity of what is typical for age ○ **extreme involvement** in an activity of interest (*engages at earliest opportunity; difficult to disengage*)										
4. LACK OF SLEEP Score	1	2	3	1	2	3	0	1	2	3
as suggested by sleeping fewer hours than expected										
5. DISTRACTIBILITY Score	1	2	3	1	2	3	0	1	2	3
as suggested by: ○ inability to stay on task ○ being highly **inattentive** ○ inability to **concentrate**										
6. TALKATIVENESS Score	1	2	3	1	2	3	0	1	2	3
as evidenced by: ○ talking **loud**, **fast** or **too much** ○ **pressured speech** that is difficult to **interrupt**										
7. STAYING ON TOPIC / RACING THOUGHTS Score	1	2	3	1	2	3	0	1	2	3
as suggested by: ○ **jumping from topic to topic** or talking about many different topics at the same time ○ reporting **racing thoughts** or **mind being too active**										

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Ask about symptoms appropriate to developmental stage

MGH PEDIATRIC MANIA SYMPTOM CHECKLIST©

SYMPTOMS		FREQUENCY			INTENSITY			COMPOSITE SEVERITY			
Start each item by saying - "In the last week did s/he have difficulties with…"		< ½ a week (< 4 days)	> ½ a week (≥ 4 days)	All week (Daily)	Mild	Moderate	Severe				
		1	2	3	1	2	3				
8. Increased Interest / Preoccupation With Sex	*Score*	*1*	*2*	*3*	*1*	*2*	*3*	**0**	**1**	**2**	**3**
as suggested by: ○ sexual remarks or bathroom humor ○ touching, rubbing, or exposing self ○ touching or sexual play involving others											
9. Poor Judgment	*Score*	*1*	*2*	*3*	*1*	*2*	*3*	**0**	**1**	**2**	**3**
as suggested by: ○ **reckless** or **daredevil** behaviors putting self or others in trouble ○ excessive and/or unrealistic **demands** or insists on **buying** ○ excessively **friendly** with strangers											
10. Inflated Self-esteem (Over-estimating Oneself)	*Score*	*1*	*2*	*3*	*1*	*2*	*3*	**0**	**1**	**2**	**3**
as suggested by: ○ **bragging** and/or acting **stronger and smarter** than others *(overestimating oneself)* ○ extremely **bossy** and/or **controlling** behaviors *(extreme entitlement)* ○ flagrant disregard for **rules**, **chores**, and/or **adult authority** *(as if above rules)*											
11. Unusual Experiences	*Score*	*1*	*2*	*3*	*1*	*2*	*3*	**0**	**1**	**2**	**3**
as evidenced by: ○ reporting **hearing voices or seeing things** that don't exist ○ **grandiose**, **suspicious** or **paranoid** behaviors that are out of touch with reality ○ **bizarre** behaviors											
12. Personal Care & Appearance	*Score*	*1*	*2*	*3*	*1*	*2*	*3*	**0**	**1**	**2**	**3**
as suggested by: ○ **poor hygiene**: refuses to shower, brush teeth or change clothes; unkempt or disheveled ○ excessive indulgence in **personal care** (grooming, bathing or makeup) ○ **inappropriately dressed:** for the situation/weather, strange/odd, sexually provocative or under/over dressed											
13. Awareness Of Behavioral Difficulties	*Score*	*1*	*2*	*3*	*1*	*2*	*3*	**0**	**1**	**2**	**3**
as evidenced by: ○ denying having **problem** ○ refusing to take **medications** or **see doctor** ○ expressing no **regret, remorse, apology** or **guilt** for misbehaviors											

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Ask about symptoms appropriate to developmental stage

Here's what we learned about children with mania

IRRITABLE
- The major mood disorder chief complaint of the parents was **severe irritability** (rather than euphoria)

MIXED
- The children had mostly **mixed states** (mania and depression overlapped in time)

CHRONIC
- The children were **seldom well** due to mixed states, many cycles and comorbidity (chronicity)

Wozniak 1995; Biederman 2004

How can you say that irritability is a symptom of mania?

A new disorder was created called DMDD grouped under ‘depressive disorders’

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Diagnosing DMDD does not inform management

A clinical decision must be made

Is the illness:

- **a form of depression?**
- **a form of bipolar disorder?**

Risperidone and aripiprazole are FDA approved for irritability in autism

The symptoms of mania are the same in two cohorts of pre-adolescent age youth with bipolar disorder

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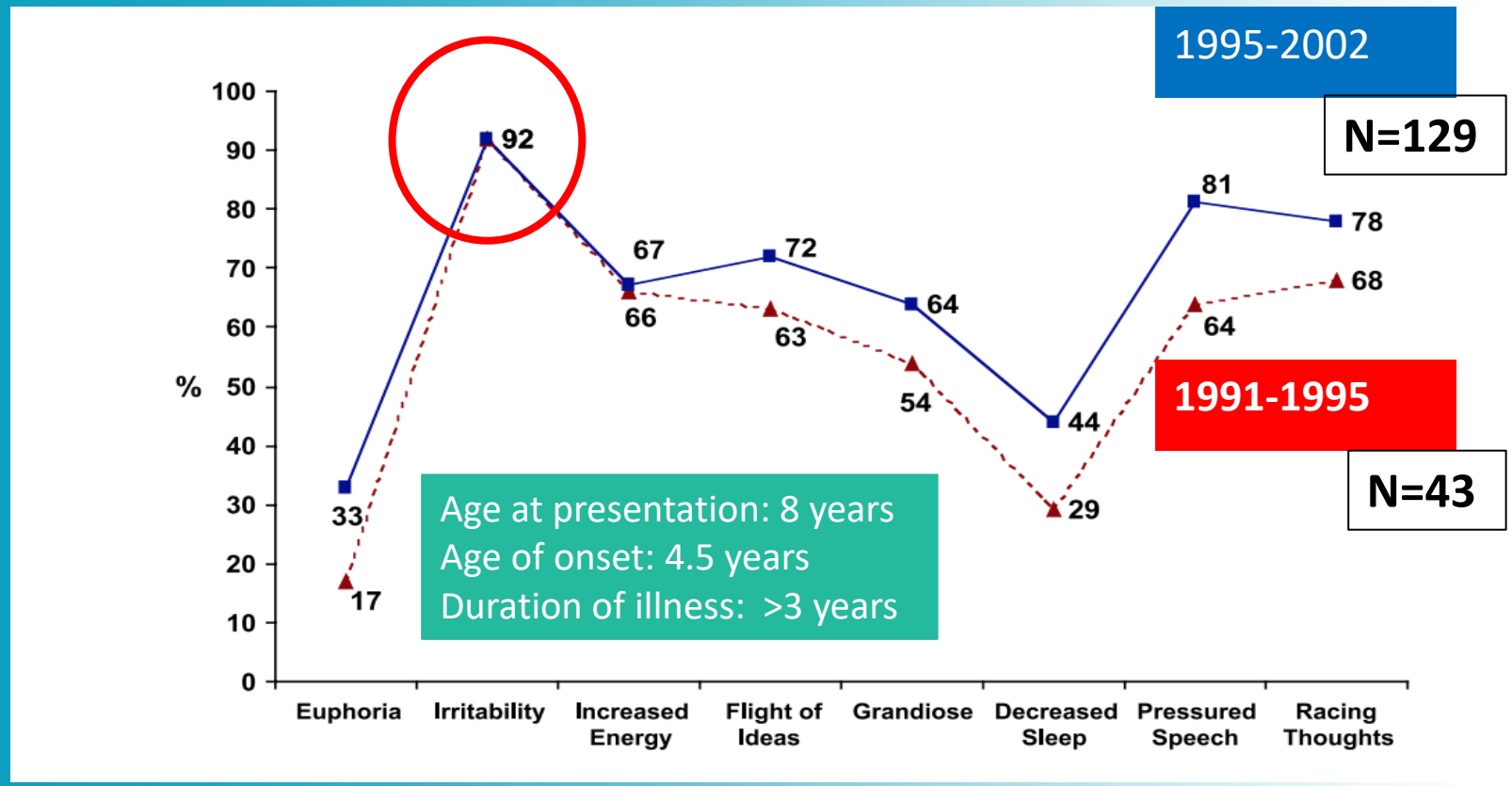
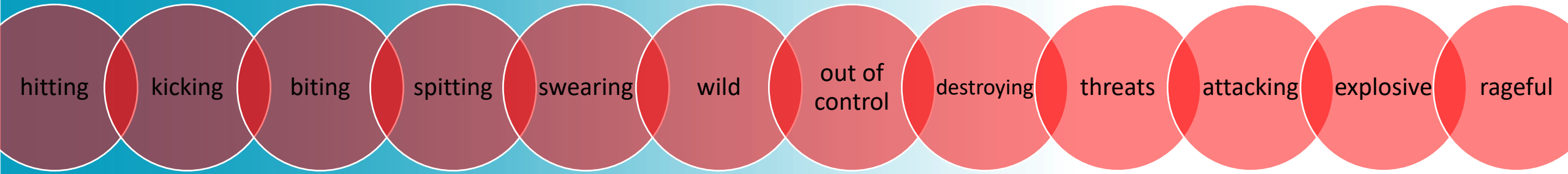
Irritability is the most common and impairing complaint in this referred sample



Wozniak 1995; Biederman 2004

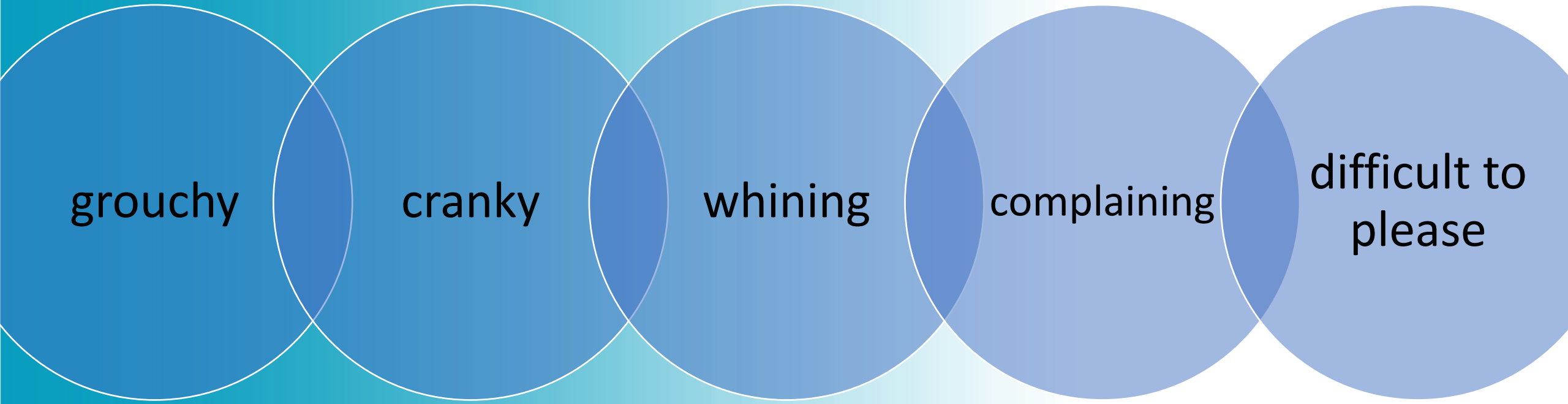
The type of irritability observed in manic children is very severe with a flagrant disregard for adult authority



Dangerous outbursts can be daily or more than daily and long lasting, 30-60+ minutes

Biederman JAACAP 1996

Irritability is also a symptom of depression

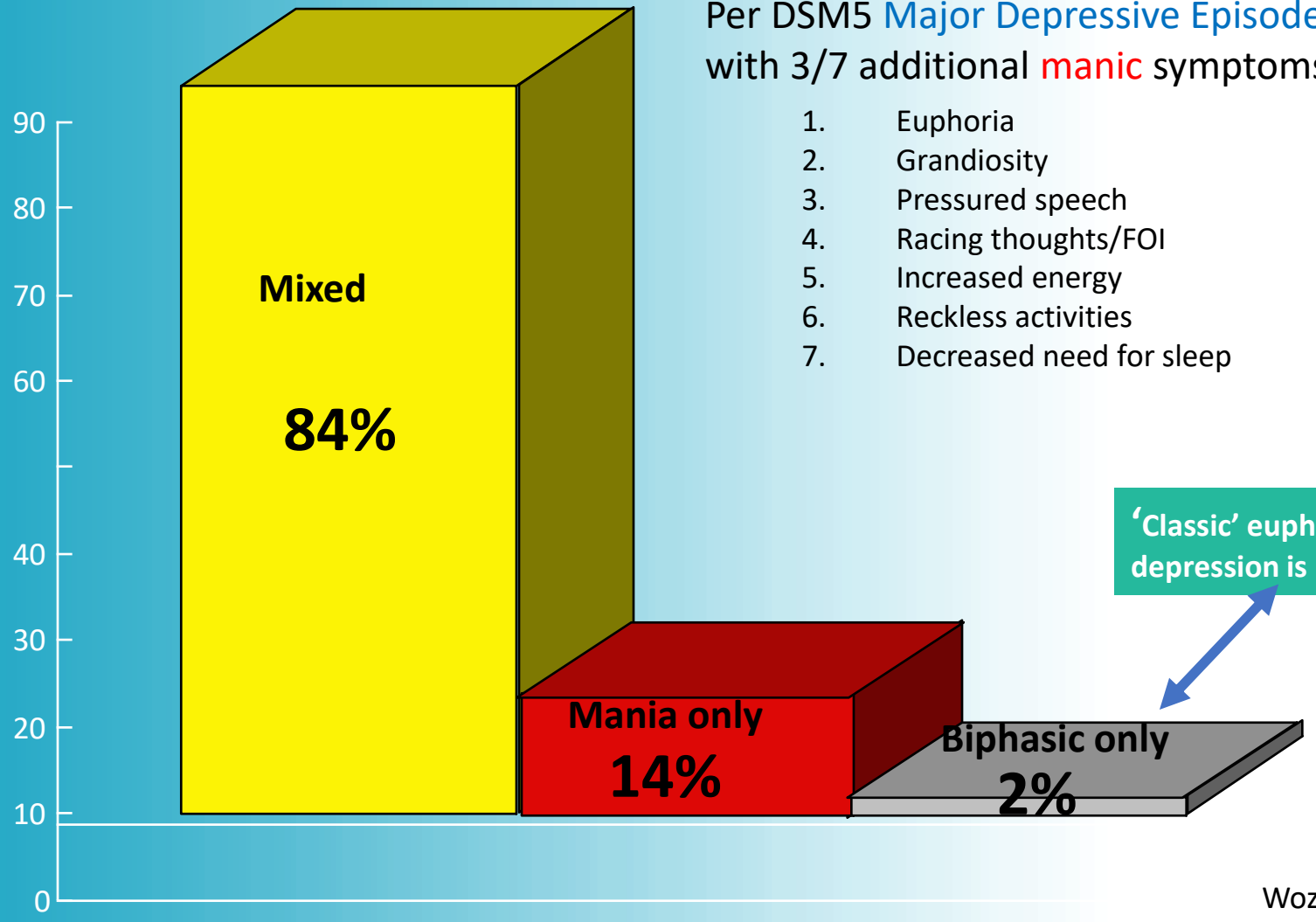


Mixed states are common making it difficult to know if the child needs more anti-manic treatment or an anti-depressant treatment

Biederman JAACAP 1996

Doesn’t bipolar disorder have to have clear ‘cycles?’

Mixed presentations are common



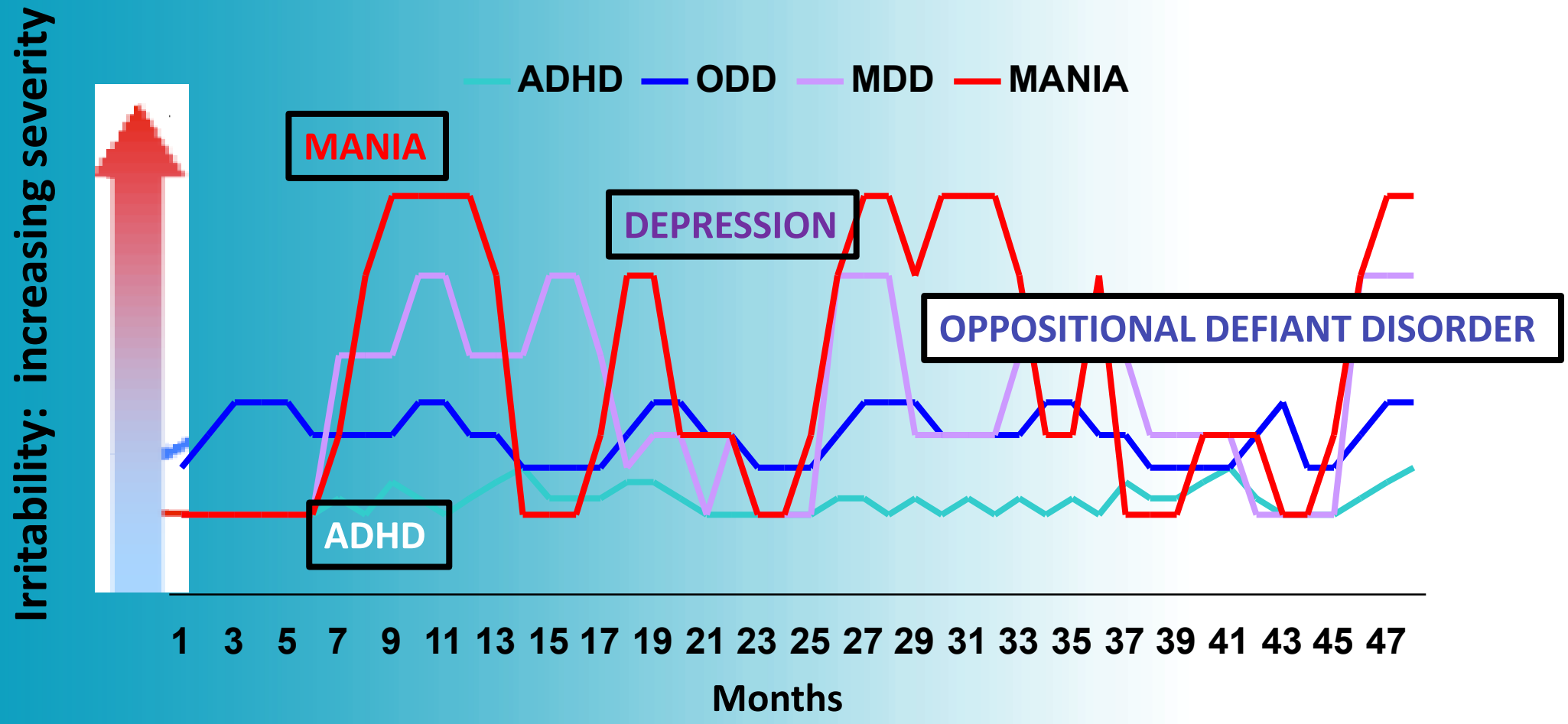
Per DSM5 Major Depressive Episode is "mixed" with 3/7 additional manic symptoms

1. Euphoria
2. Grandiosity
3. Pressured speech
4. Racing thoughts/FOI
5. Increased energy
6. Reckless activities
7. Decreased need for sleep

'Classic' euphoric mania alternating with depression is rare in pediatric bipolar disorder

Wozniak 1995; Biederman 2004

Different forms of irritability can co-exist and overlap, leading to a 'never well' condition



Mick 2007

You say these manic children have hyperactivity, talkativeness, impulsivity, irritability, defiance and chronicity.

How can I be convinced that these children don't just have a severe form of ADHD?

Here's what we learned about children with mania

IRRITABLE
- The major mood disorder chief complaint of the parents was severe irritability (rather than euphoria)

MIXED
- The children had mostly mixed states (mania and depression overlapped in time)

CHRONIC
- The children were seldom well due to mixed states, many cycles and comorbidity (chronicity)

ADHD
- **Almost all of them had ADHD**

(especially when the onset of mania was prior to age 12)

Wozniak 1995; Biederman 2004

Mania and ADHD share symptoms, but ADHD is not a mood disorder

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Mania:

A. A *distinct period (7 days=mania; 4 days=hypomania)* of abnormally and persistently elevated, expansive, or irritable mood and persistently increased goal-directed activity or energy

B. At least 3/7 (4/7 if mood is irritable)

ADHD sx in blue

1) D Distractibility
2) I Increased activity/psychomotor agitation
3) G Grandiosity or inflated self-esteem
4) F Flight of ideas or racing thoughts
5) A Activities with painful consequences (impulsivity)
6) S Sleep decreased
7) T Talkative or pressured speech

Diagnostic and Statistical Manual (DSM-5)

Pediatric bipolar disorder symptoms overlap with ADHD symptoms, but requires mood symptoms to diagnose

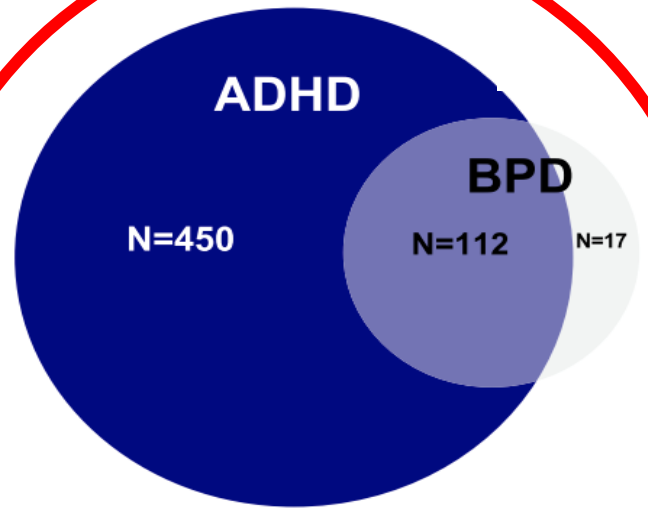
There are overlapping symptoms between ADHD and BPD

- Distractibility
  - very severe in bipolar disorder
- Hyperactivity
  - vs. increased energy/activity in bipolar disorder
- Talkativeness
  - vs. pressured speech in bipolar disorder
- Bipolar disorder requires severe mood symptoms:
  - euphoria/irritability/melancholy

Biederman JAACAP 1996

There is a substantial bi-directional overlap between bipolar disorder and ADHD-
Bipolar disorder+ADHD has higher rates of comorbidity than ADHD alone

	MANIA	ADHD
Depression	**86%**	38%
Psychosis	**16%**	0
Defiance (ODD)	**88%**	48%
Conduct Disorder	**37%**	15%
Anxiety	**56%**	26%
Hospitalization	21%	2%
Functioning	Very poor	fair
Learning Disability	42%	14%



Most young children with bipolar disorder also have comorbid ADHD

Wozniak 1995; Biederman 2004

Adults with ADHD have higher rates of bipolar disorder than adults without ADHD

The National Epidemiologic Survey on Alcohol and Related Conditions

N=34,000 adults

2.5% ADHD

34% ***with* ADHD** had bipolar disorder

versus

6% *without* ADHD had bipolar disorder

The National Comorbidity Survey Replication

N=3199 adults

4.4% ADHD

19% ***with* ADHD** had bipolar disorder

versus

3% *without* ADHD had bipolar disorder

Bernardi Psychol Med 2012
Kessler Am J Psych 2006

Is this the same bipolar disorder that adults have?

Do children develop ‘classic’ bipolar disorder?

Most adults in this large clinic sample report pediatric onset of their bipolar disorder with greater morbidity

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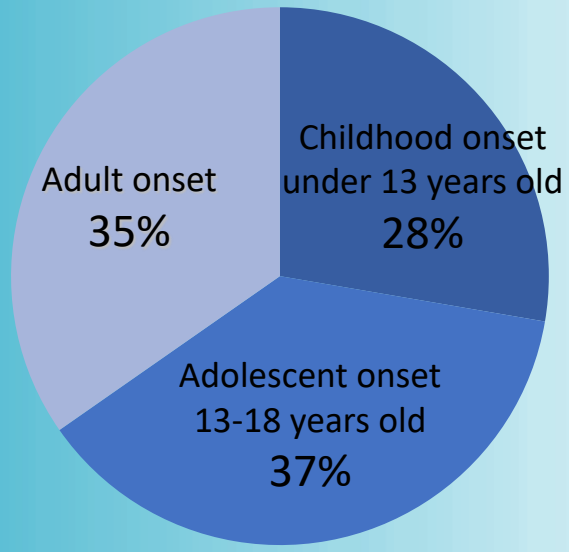
STEP-BD (N=983)



65% Report Pediatric Onset of Bipolar Disorder

Earlier onset associated with:

- Higher rates of comorbid anxiety and substance abuse
- More recurrences
- Shorter periods of euthymia
- Greater likelihood of suicide attempts
- Greater likelihood of violence

Perlis Biol Psych 2004

Adults with Bipolar Disorder + ADHD have clinical correlates similar to that seen in pediatric bipolar disorder

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9.5% lifetime prevalence comorbid ADHD in adult STEP-BD (N=983)

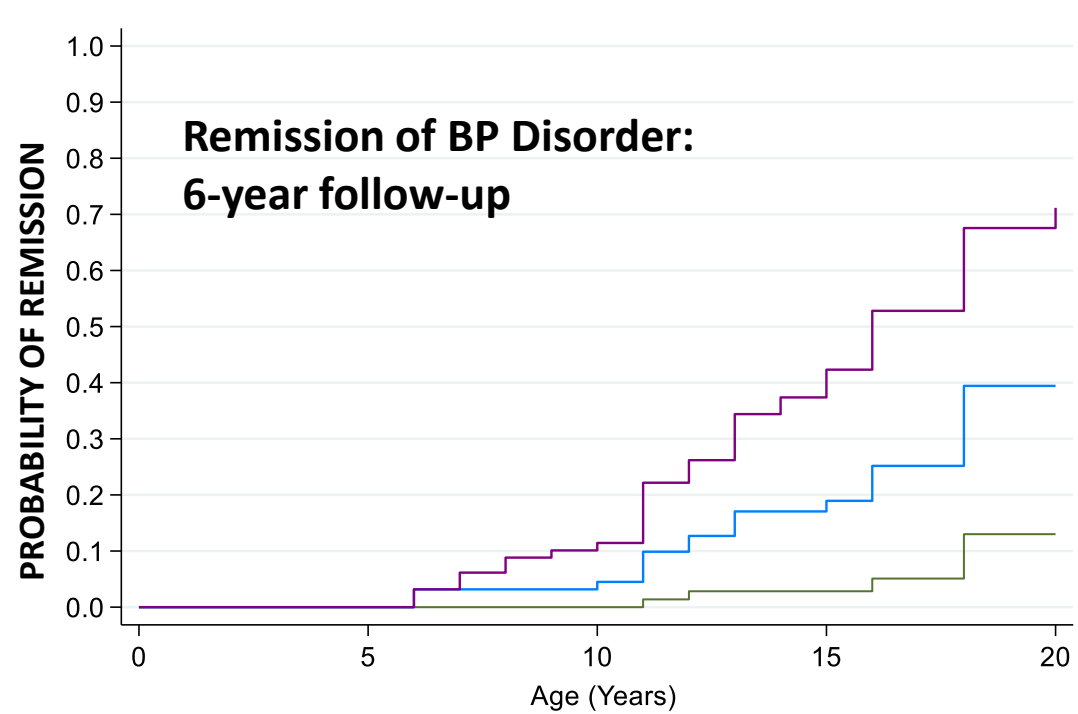
BPD+ADHD Adult patients:

- had earlier onset BPD by 5 years
- had shorter periods of wellness (chronic)
- had more comorbidity (anxiety and substance)
- were more likely to be male
- were more likely to have Bipolar I
- had more days irritable and more days elated
- had lower GAF
- more suicide attempts
- more violence
- more legal problems (conduct disorder?)

Nierenberg Biol Psych 2005

Are you labeling these children with this highly stigmatized extremely serious disorder for the rest of their lives?

Pediatric Bipolar Disorder is persistent; full remission is rare



Most common: Has symptoms and impaired functioning

No symptoms, but functioning impaired

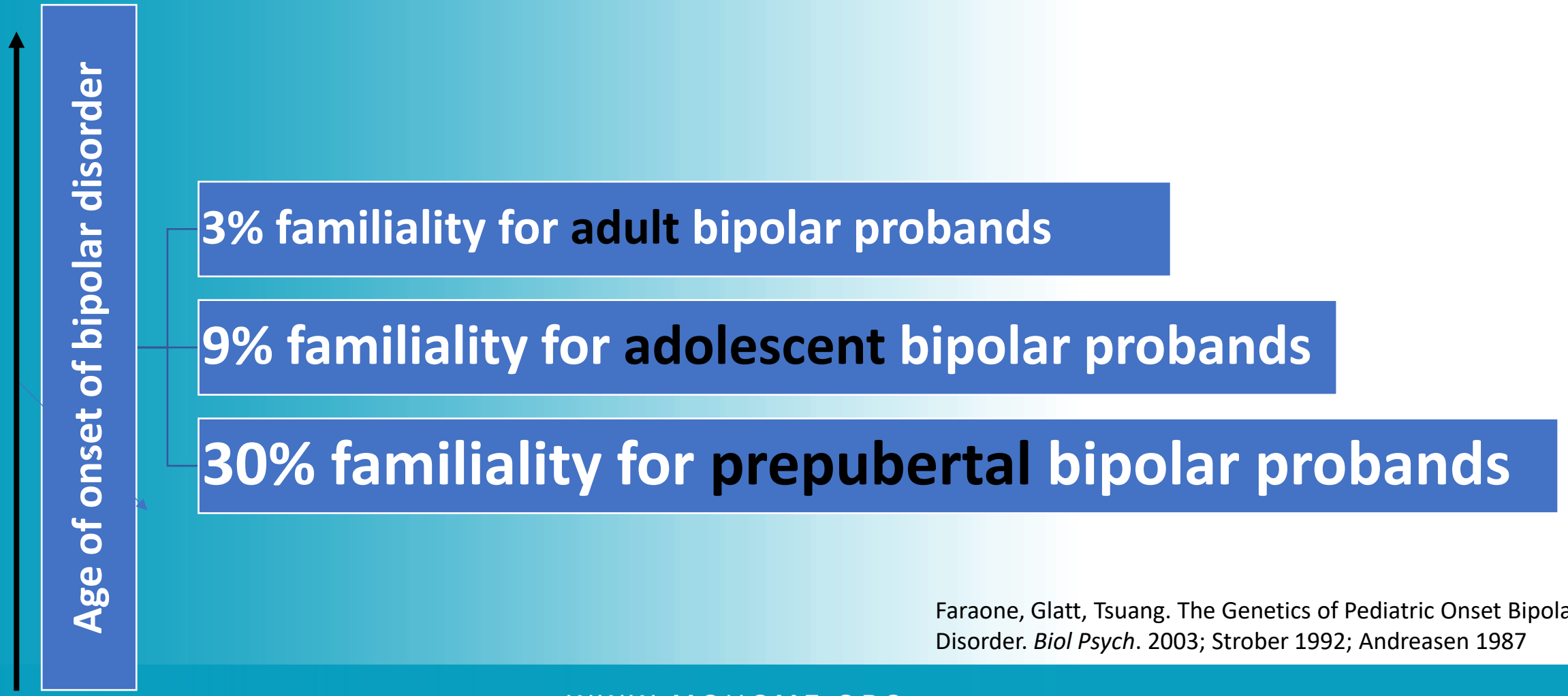
Least likely: full recovery with no symptoms and good functioning

Functional remission is least likely outcome
Symptoms and poor functioning found at follow-up

Wozniak 2020

Does bipolar disorder run in families?

Family studies support a larger genetic contribution to early-onset cases



Faraone, Glatt, Tsuang. The Genetics of Pediatric Onset Bipolar Disorder. *Biol Psych*. 2003; Strober 1992; Andreasen 1987

Familial risk of bipolar I disorder is greatest in first-degree relatives of BP-I versus ADHD and control probands

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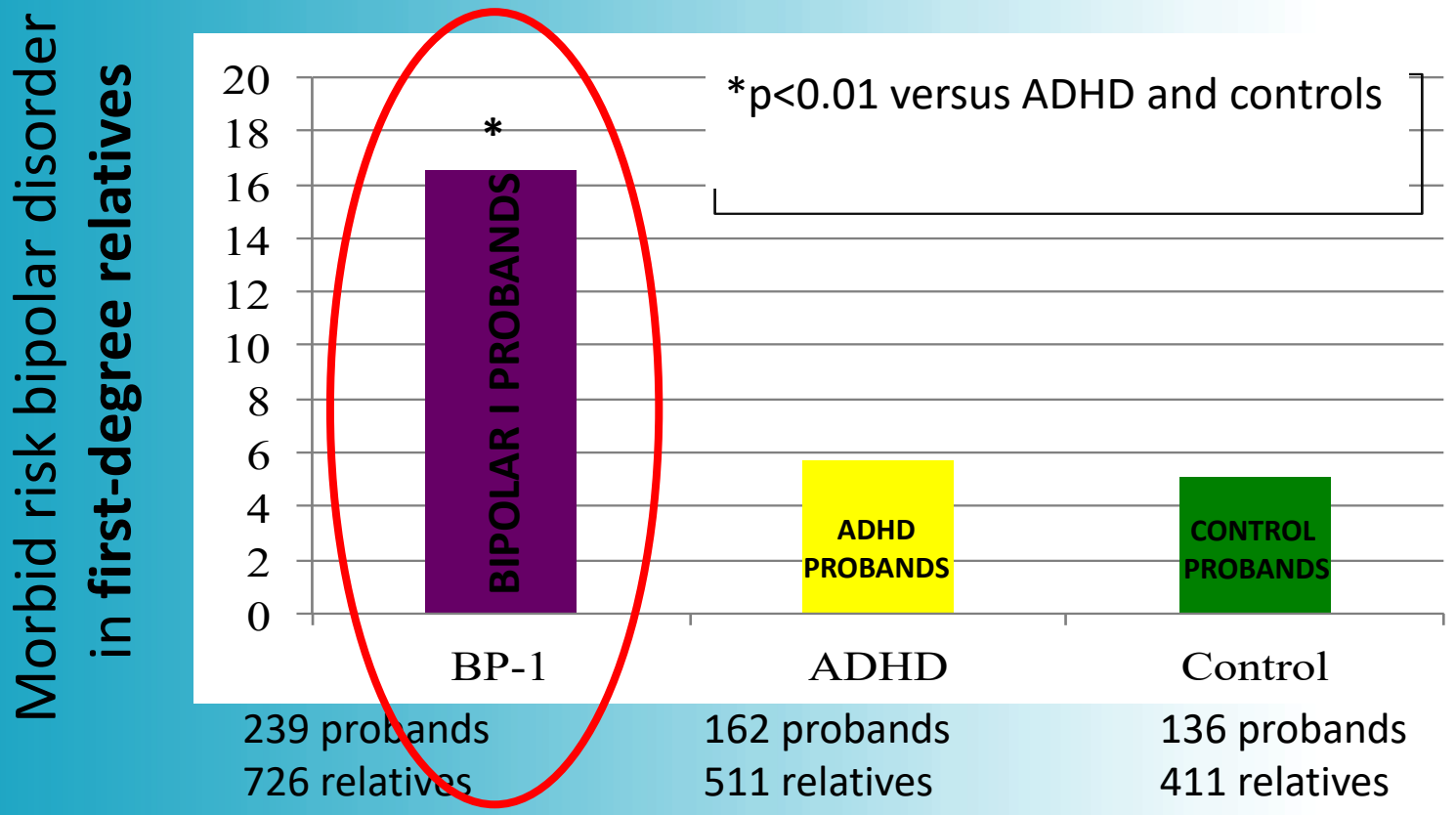
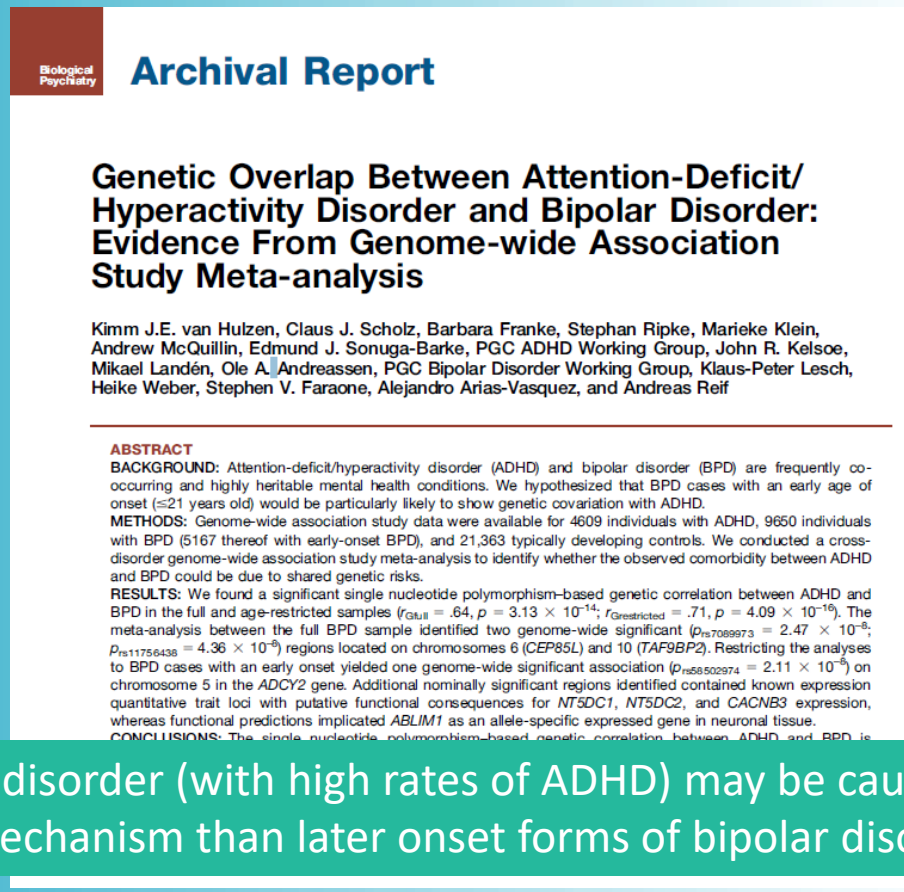
The MGH Pediatric Bipolar Disorder study is the largest controlled family study



Wozniak.*J Clin Psych.*2012

Genome wide association study (GWAS) supports the idea that bipolar + ADHD is an early onset genetic subtype of bipolar



Biological Psychiatry

Archival Report

Genetic Overlap Between Attention-Deficit/ Hyperactivity Disorder and Bipolar Disorder: Evidence From Genome-wide Association Study Meta-analysis

Kimm J.E. van Hulzen, Claus J. Scholz, Barbara Franke, Stephan Ripke, Marieke Klein, Andrew McQuillin, Edmund J. Sonuga-Barke, PGC ADHD Working Group, John R. Kelsoe, Mikael Landén, Ole A. Andreassen, PGC Bipolar Disorder Working Group, Klaus-Peter Lesch, Heike Weber, Stephen V. Faraone, Alejandro Arias-Vasquez, and Andreas Reif

ABSTRACT

BACKGROUND: Attention-deficit/hyperactivity disorder (ADHD) and bipolar disorder (BPD) are frequently co-occurring and highly heritable mental health conditions. We hypothesized that BPD cases with an early age of onset (≤21 years old) would be particularly likely to show genetic covariation with ADHD.

METHODS: Genome-wide association study data were available for 4609 individuals with ADHD, 9650 individuals with BPD (5167 thereof with early-onset BPD), and 21,363 typically developing controls. We conducted a cross-disorder genome-wide association study meta-analysis to identify whether the observed comorbidity between ADHD and BPD could be due to shared genetic risks.

RESULTS: We found a significant single nucleotide polymorphism–based genetic correlation between ADHD and BPD in the full and age-restricted samples ($r_{Gfull} = .64$, $p = 3.13 \times 10^{-14}$; $r_{Grestricted} = .71$, $p = 4.09 \times 10^{-16}$). The meta-analysis between the full BPD sample identified two genome-wide significant ($p_{rs7089973} = 2.47 \times 10^{-8}$; $p_{rs11756438} = 4.36 \times 10^{-8}$) regions located on chromosomes 6 (*CEP85L*) and 10 (*TAF9BP2*). Restricting the analyses to BPD cases with an early onset yielded one genome-wide significant association ($p_{rs58502974} = 2.11 \times 10^{-8}$) on chromosome 5 in the *ADCY2* gene. Additional nominally significant regions identified contained known expression quantitative trait loci with putative functional consequences for *NT5DC1*, *NT5DC2*, and *CACNB3* expression, whereas functional predictions implicated *ABLIM1* as an allele-specific expressed gene in neuronal tissue.

CONCLUSIONS: The single nucleotide polymorphism–based genetic correlation between ADHD and BPD is

Early onset bipolar disorder (with high rates of ADHD) may be caused by a different genetic mechanism than later onset forms of bipolar disorder

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