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PSYCHIATRY ACADEMY

Juvenile Mania: Pediatric Bipolar Disorder Occurs (and Co-Occurs with ADHD)

Janet Wozniak, MD

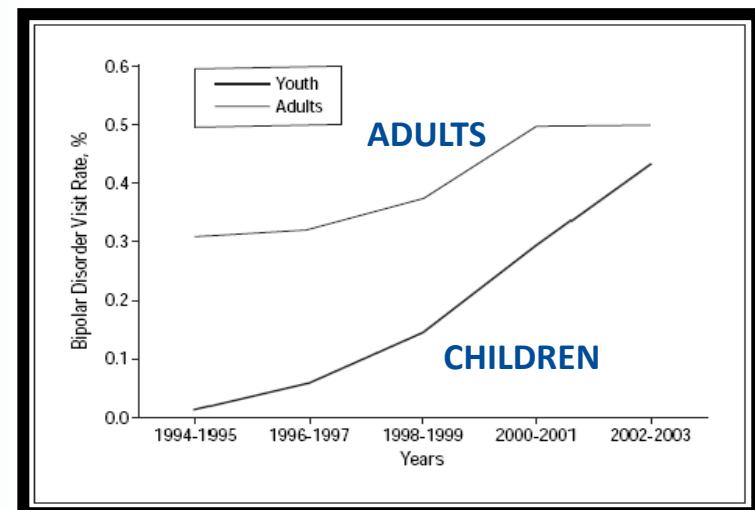
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Rising Rates of Pediatric Bipolar Disorder





Disclosures

My spouse/partner and I have the following relevant financial relationships with commercial interests to disclose:

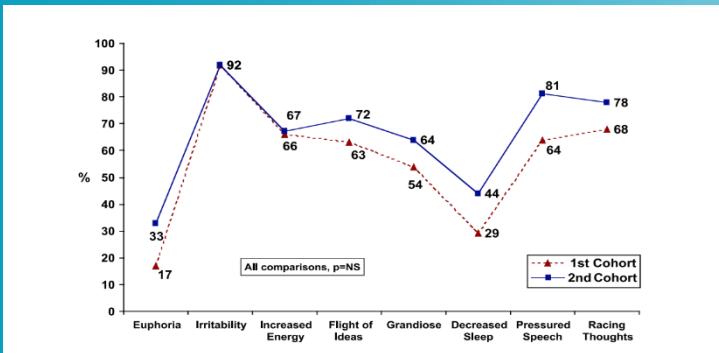
Dr. Janet Wozniak receives research support from the Baszucki Brain Research Fund, PCORI and Demarest Lloyd, Jr. Foundation. In the past, Dr. Wozniak has received research support, consultation fees or speaker's fees from Eli Lilly, Janssen, Johnson and Johnson, McNeil, Merck/Schering-Plough, the National Institute of Mental Health (NIMH) of the National Institutes of Health (NIH), Pfizer, and Shire. She is the author of the book, *"Is Your Child Bipolar"* published May 2008, Bantam Books.

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Overview:

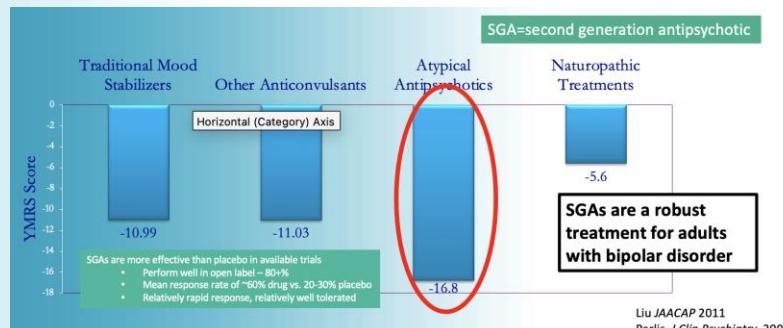
Pediatric Bipolar Disorder Is a highly morbid, valid condition that affects a significant minority of young children and is often comorbid with ADHD

Scope: Pediatric Bipolar Disorder is now in the differential diagnosis for moody children



Diagnostic description: Pediatric bipolar disorder can be reliably diagnosed and is often mixed and irritable and comorbid with ADHD.

Treatment: SGAs are the most effective mood stabilizers





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



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

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. FARAOONE, 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: 867-876. **Key Words:** bipolar disorder, attention deficit hyperactivity disorder, comorbidity.

Consecutively referred children ≤ 12 years:

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

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



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



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,*}, Stephen V. 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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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).

Method: Children with a history of mania and/or hypomania were identified in the 1st cohort (1991-1995) among children aged ≤ 12 years referred to a child psychiatry service and evaluated with a structured interview (KSADS) for a DSM-III-R BPD diagnosis (1st cohort, $n=43$; 2nd cohort, $n=129$) were compared with children without BPD referred to the same service during the same time period.

76% ADHD

identified in 17% of subjects; (2) the 17% of children without BPD frequently met criteria for ADHD, and (3) the 17% of children without BPD had significantly higher rates of psychiatric hospitalization

than the 17% of children with BPD. These findings support the hypothesis that clinically referred children with BPD have a high rate of comorbidity with ADHD and other psychiatric disorders.

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



*taking development into consideration

Diagnostic and Statistical Manual (DSM-5).

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

Here's what we learned about children with mania



- The major mood disorder chief complaint of the parents was severe irritability (rather than euphoria)
- The children had mostly mixed states (mania and depression overlapped in time)
- The children were seldom well due to mixed states, many cycles and comorbidity (chronicity)
- **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

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



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

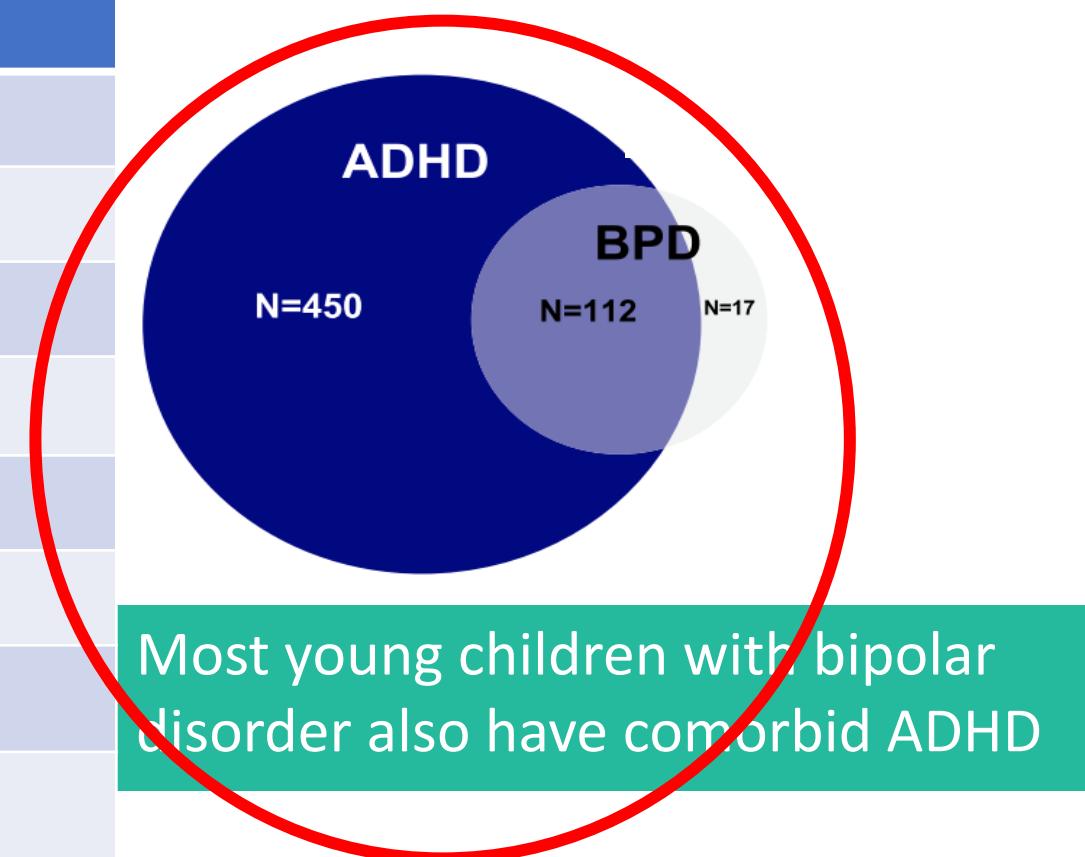
Talkativeness
vs. pressured
speech in
bipolar disorder

Bipolar disorder requires
severe mood symptoms:
euphoria/irritability/melancholy

Biederman JAACAP 1996

There is a substantial bi-directional overlap between bipolar disorder and ADHD

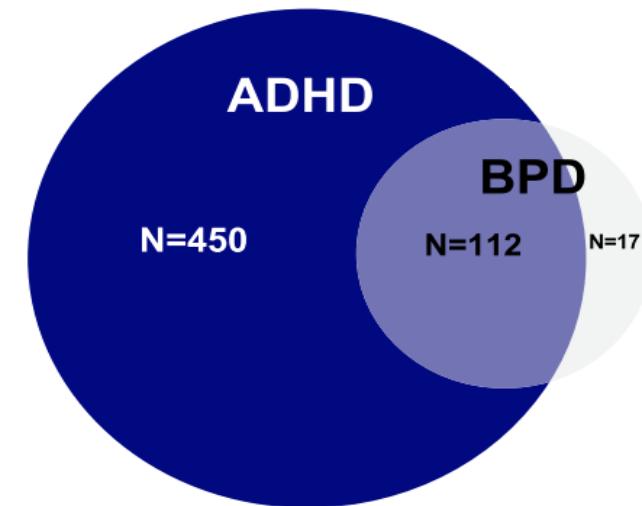
	MANIA	ADHD
Depression	86%	38%
Psychosis	16%	0
Defiance (ODD)	88%	48%
Conduct Disorder	37%	15%
Anxiety	56%	26%
Hospitalization	21%	2%
Functioning	Very poor	fair
Learning Disability	42%	14%



Wozniak 1995; Biederman 2004

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%
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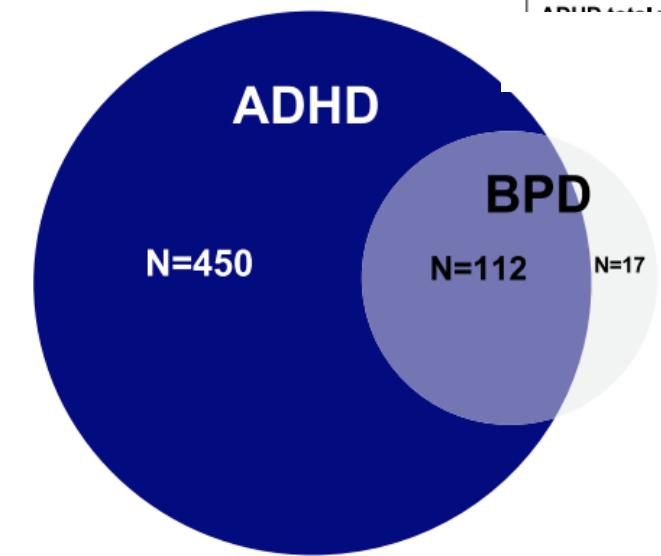


Most children with bipolar disorder
also have comorbid ADHD

Wozniak 1995; Biederman 2004

Bipolar disorder+ADHD is associated with very poor functioning

	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
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Most 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



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

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

meta-analysis between the full BPD sample identified two genome-wide significant ($p_{n=7089973} = 2.47 \times 10^{-8}$; $p_{n=1756438} = 4.36 \times 10^{-9}$) 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 ($p_{n=58502974} = 2.11 \times 10^{-5}$) 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 *ABLM1* as an allele-specific expressed gene in neuronal tissue.

CONCLUSIONS: The single nucleotide polymorphism-based genetic correlation between ADHD and BPD is substantial, significant, and consistent with the existence of genetic overlap between ADHD and BPD, with potential differential genetic mechanisms involved in early and later BPD onset.

Keywords: Attention-deficit/hyperactivity disorder, bipolar disorder, cross-disorder meta-analysis, genetic correlation, genetic overlap, GWAS

<http://dx.doi.org/10.1016/j.biopsych.2016.08.040>

van Hulzen Biol Psych 2017



Despite rise in rate, pediatric bipolar disorder affects a *minority of youth*, and ADHD is more common

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 (11.4%), with approximately 40% of participants with one class of disorder also meeting

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

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

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Editorial

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
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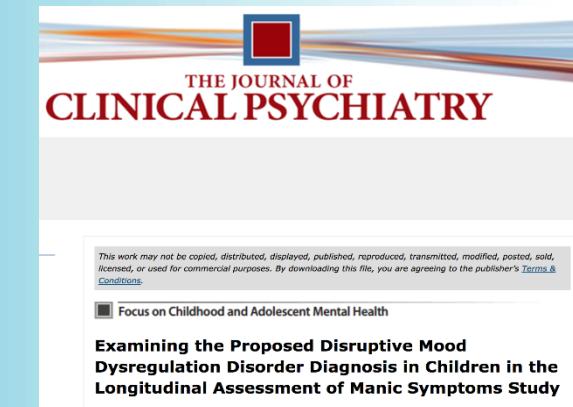
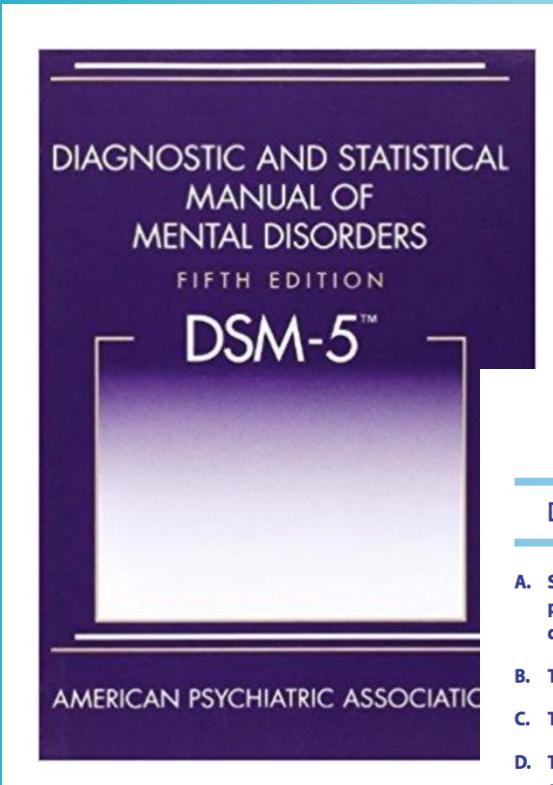
Merikangas 2010; Van Meter J Clin Psych 2011

To 'decrease the # of bipolar diagnoses' in children, a new disorder was created called DMDD (Disruptive Mood Dysregulation Disorder)



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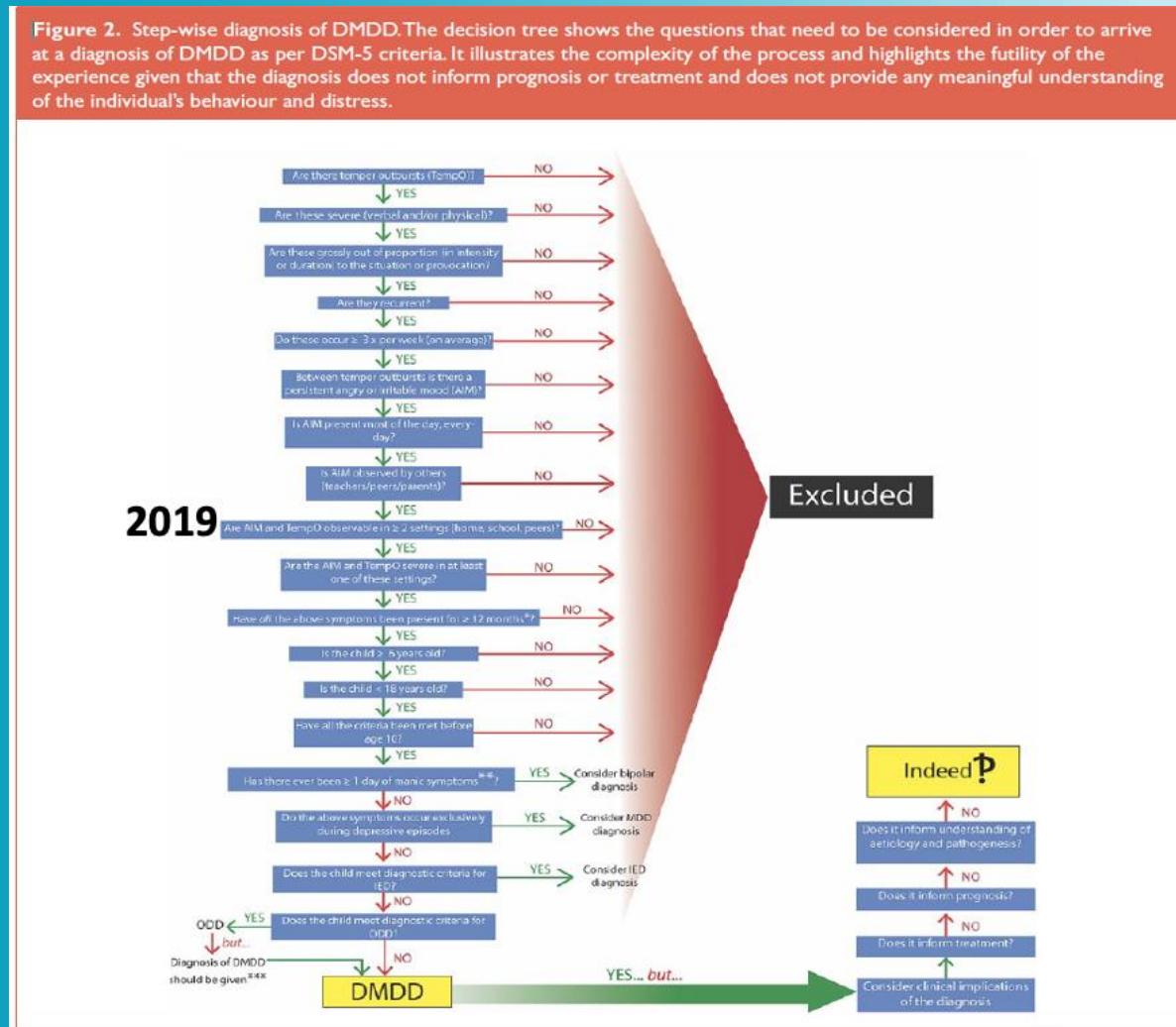
DSM-5™ Diagnostic Criteria

Disruptive Mood Dysregulation Disorder 296.99 (F34.8)

- 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).

Diagnosing DMDD is a “complex and futile” convoluted process that does not inform management

Figure 2. Step-wise diagnosis of DMDD. The decision tree shows the questions that need to be considered in order to arrive at a diagnosis of DMDD as per DSM-5 criteria. It illustrates the complexity of the process and highlights the futility of the experience given that the diagnosis does not inform prognosis or treatment and does not provide any meaningful understanding of the individual's behaviour and distress.



“This convoluted process – many aspects of which are clearly unrealistic – would at least be theoretically acceptable were it not for the fact that successfully *making a diagnosis of DMDD does not inform management*”

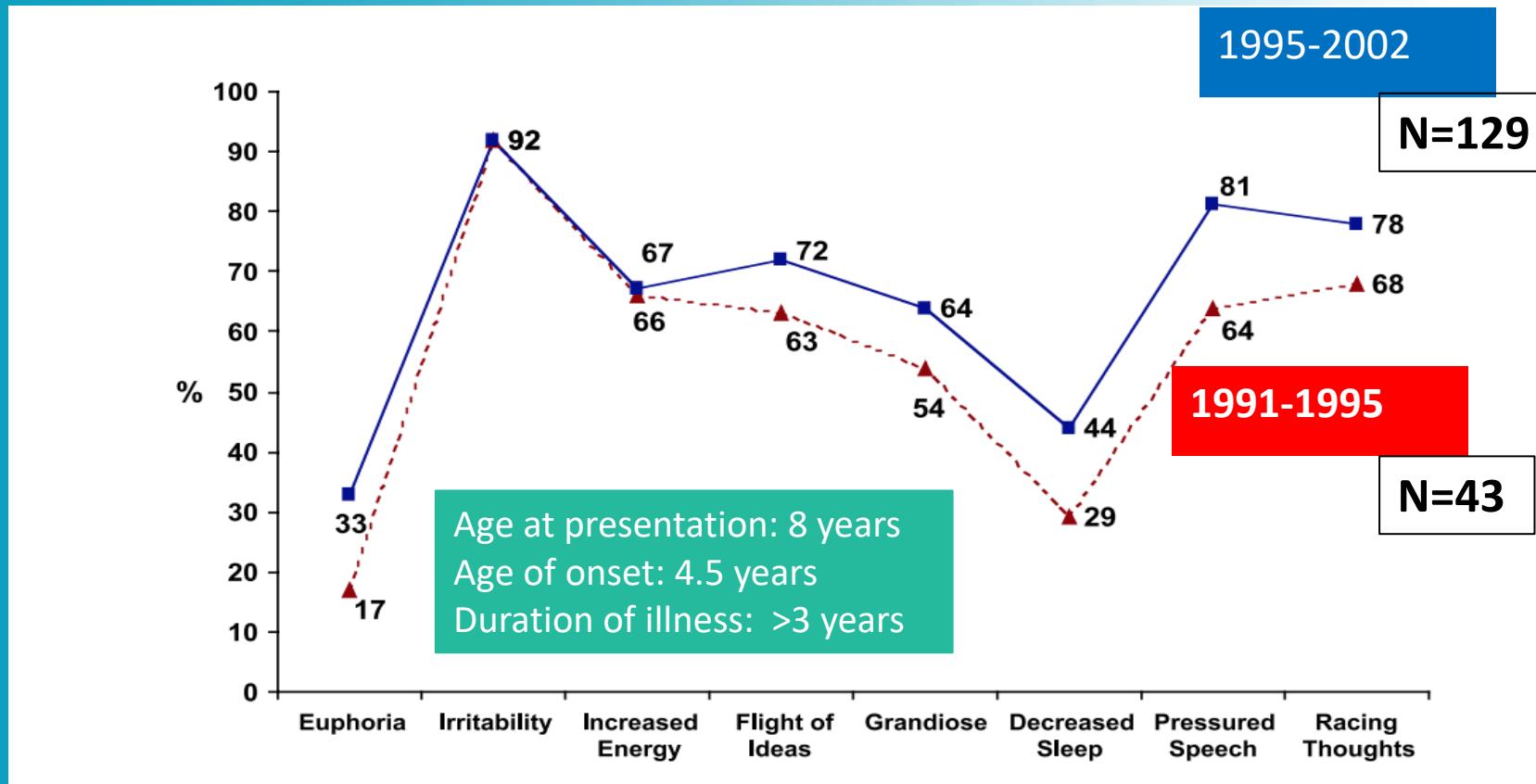
A clinical decision must be made

Is the illness:

- a form of depression or
- a form of bipolar disorder

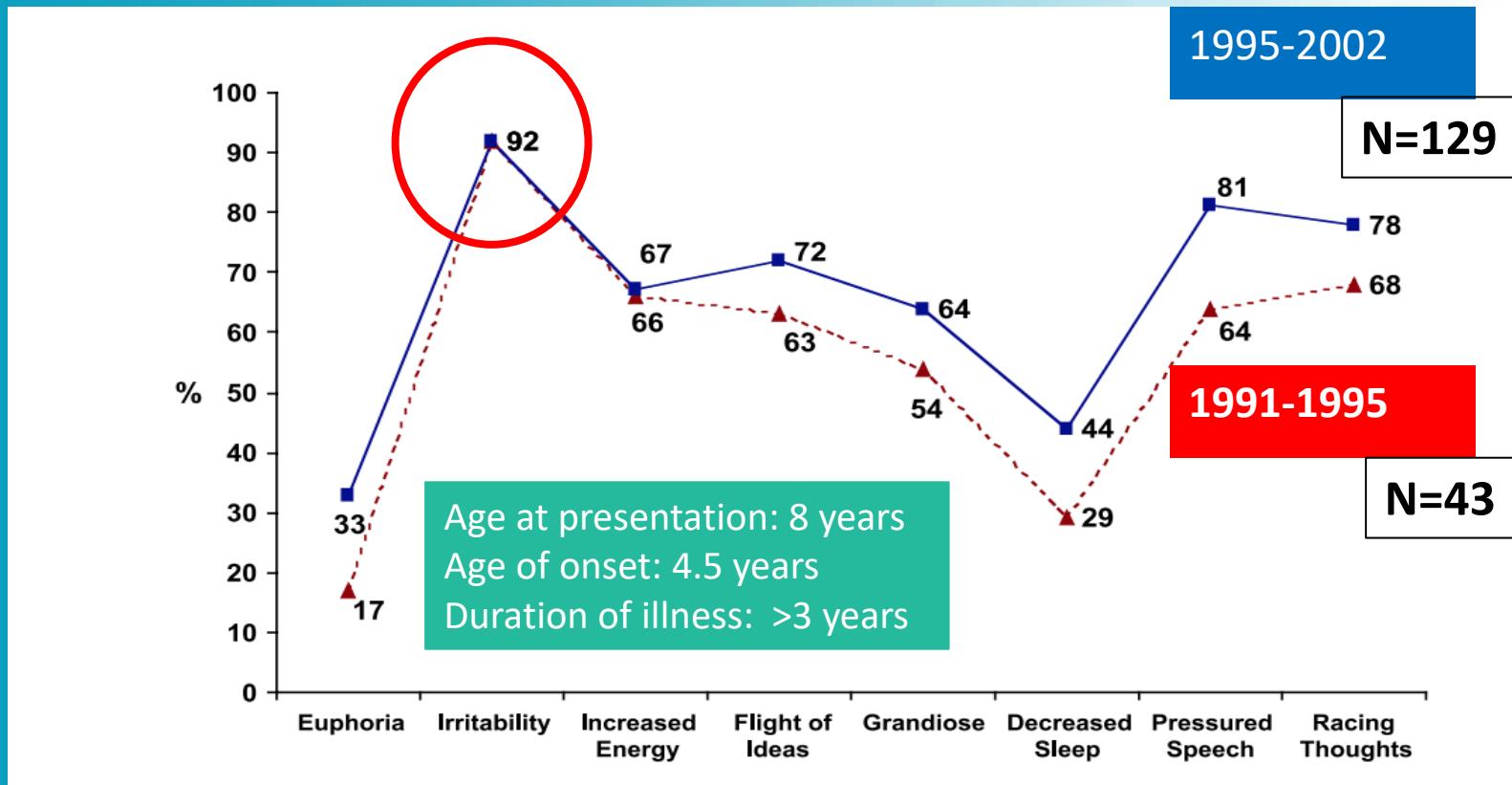
Malhi Australian & New Zealand Journal of Psychiatry 2019

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



Wozniak 1995; Biederman 2004

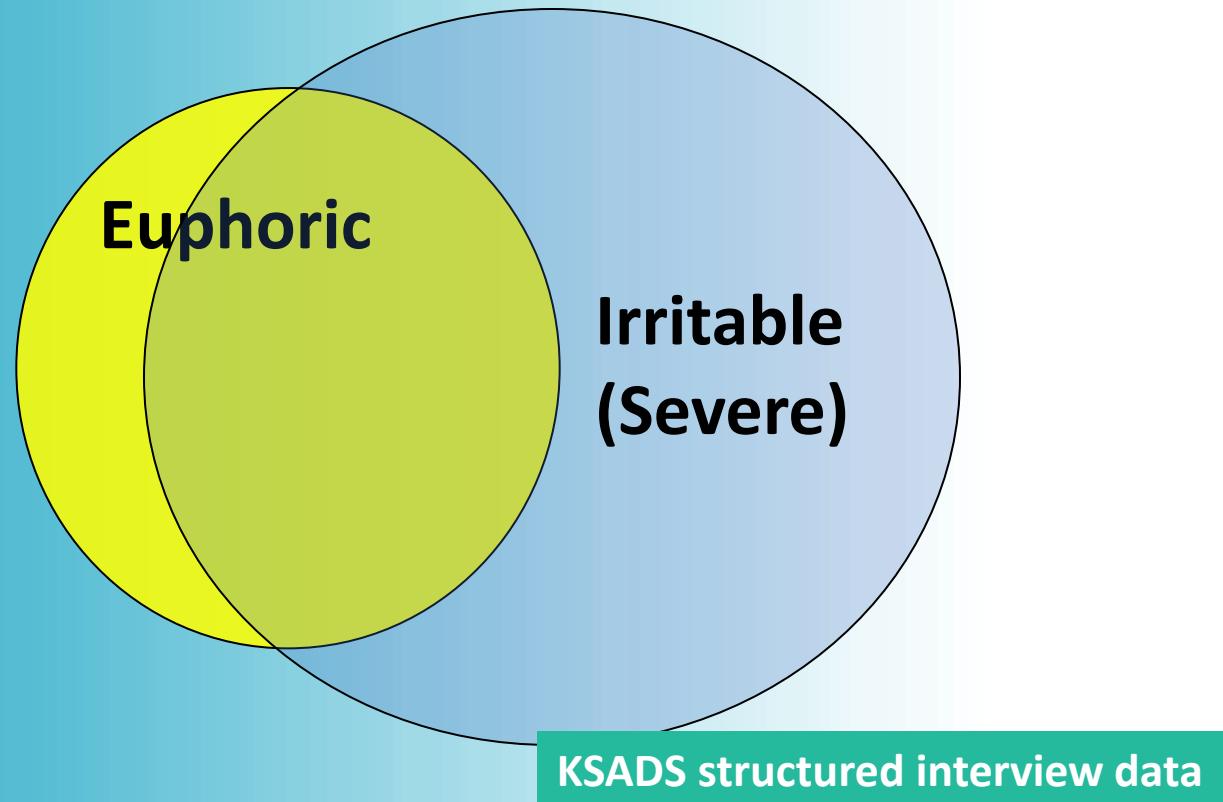
Irritability is the most common and impairing complaint



Wozniak 1995; Biederman 2004

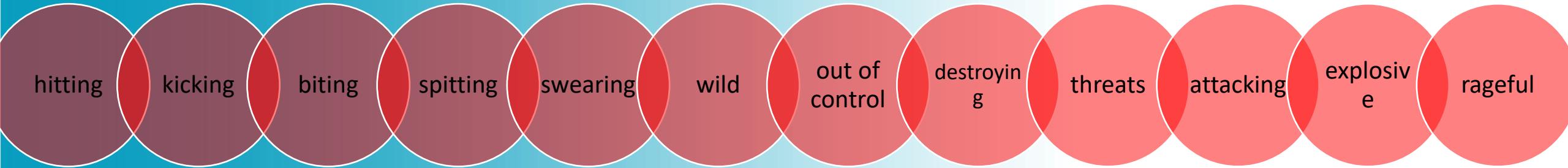


**Irritability is more common than euphoria in bipolar youth
(lasting 7 days or longer, most of the day, almost every day)**



Wozniak 1995; Biederman 2004

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



hitting

kicking

biting

spitting

swearing

wild

out of
control

destroyin
g

threats

attacking

explosiv
e

rageful

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

grouchy

cranky

whining

complaining

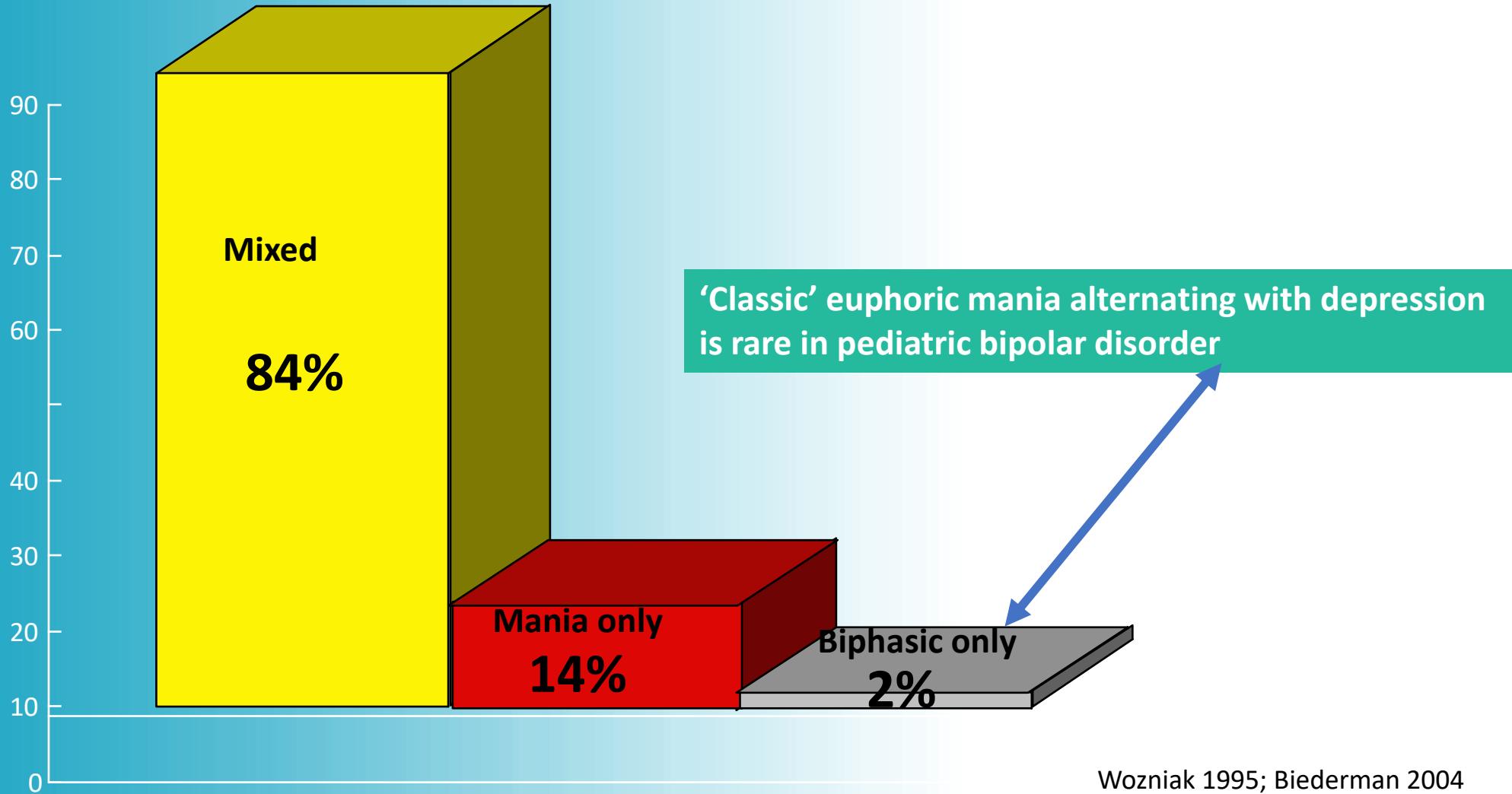
difficult to
please

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

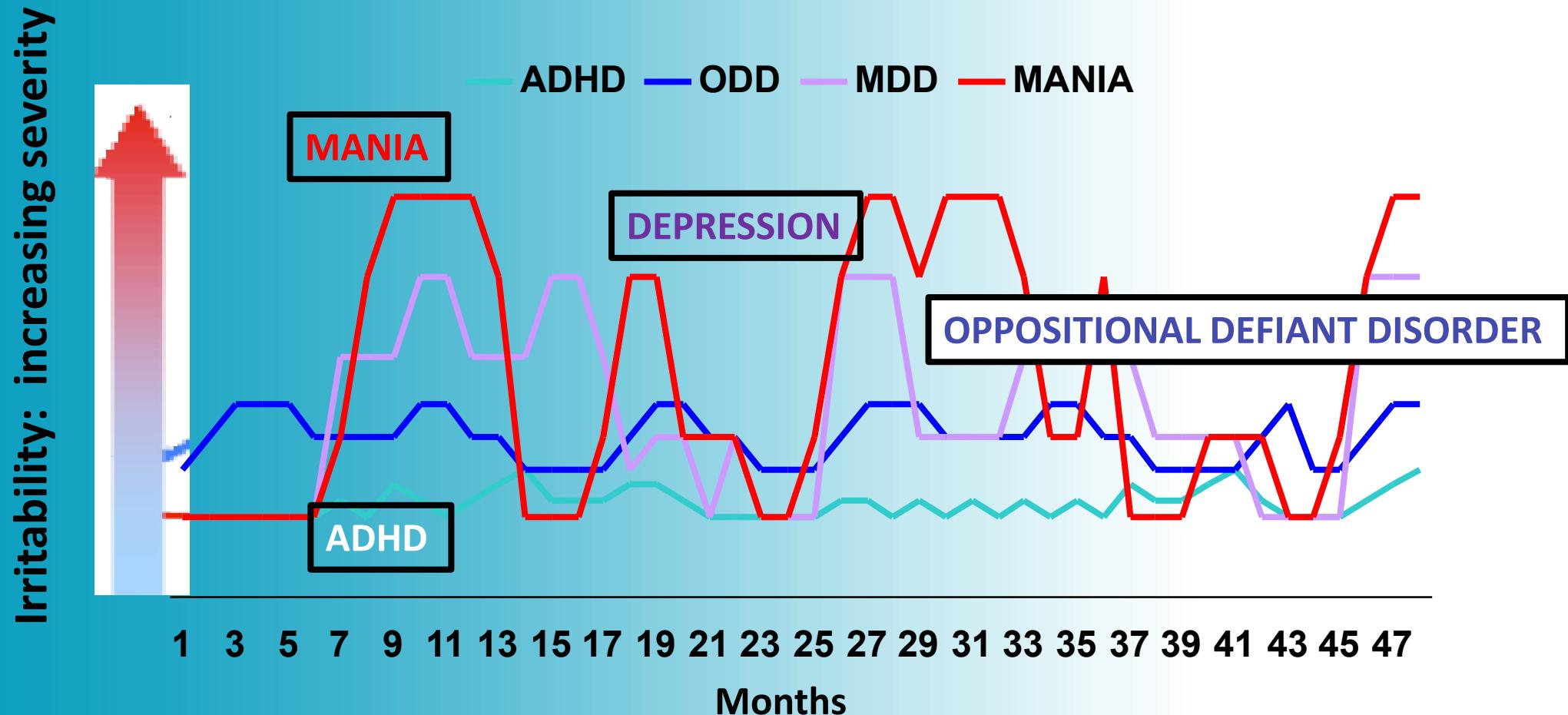
Biederman JAACAP 1996



Mixed presentations are common

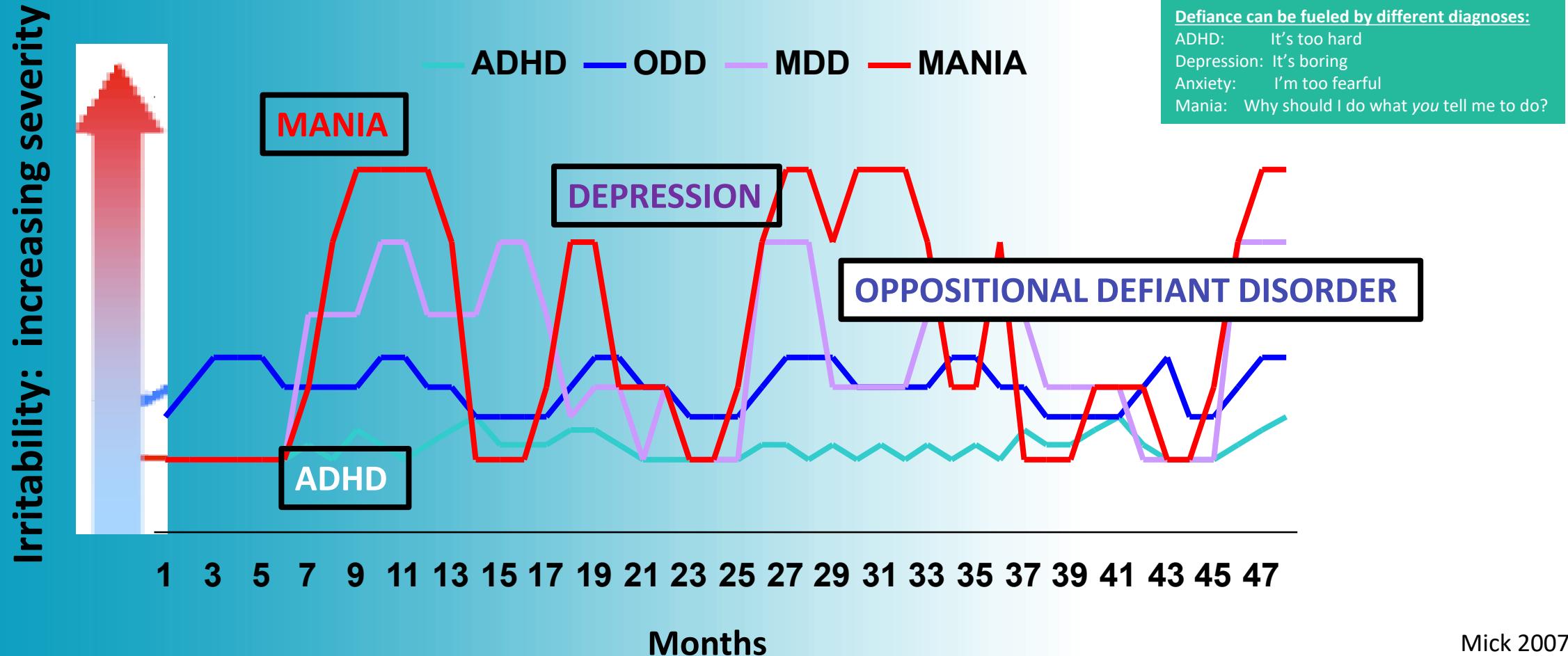


Different forms of irritability can co-exist and overlap, leading to a 'never well' condition



Mick 2007

Irritability and defiance can have qualitatively and quantitatively different forms



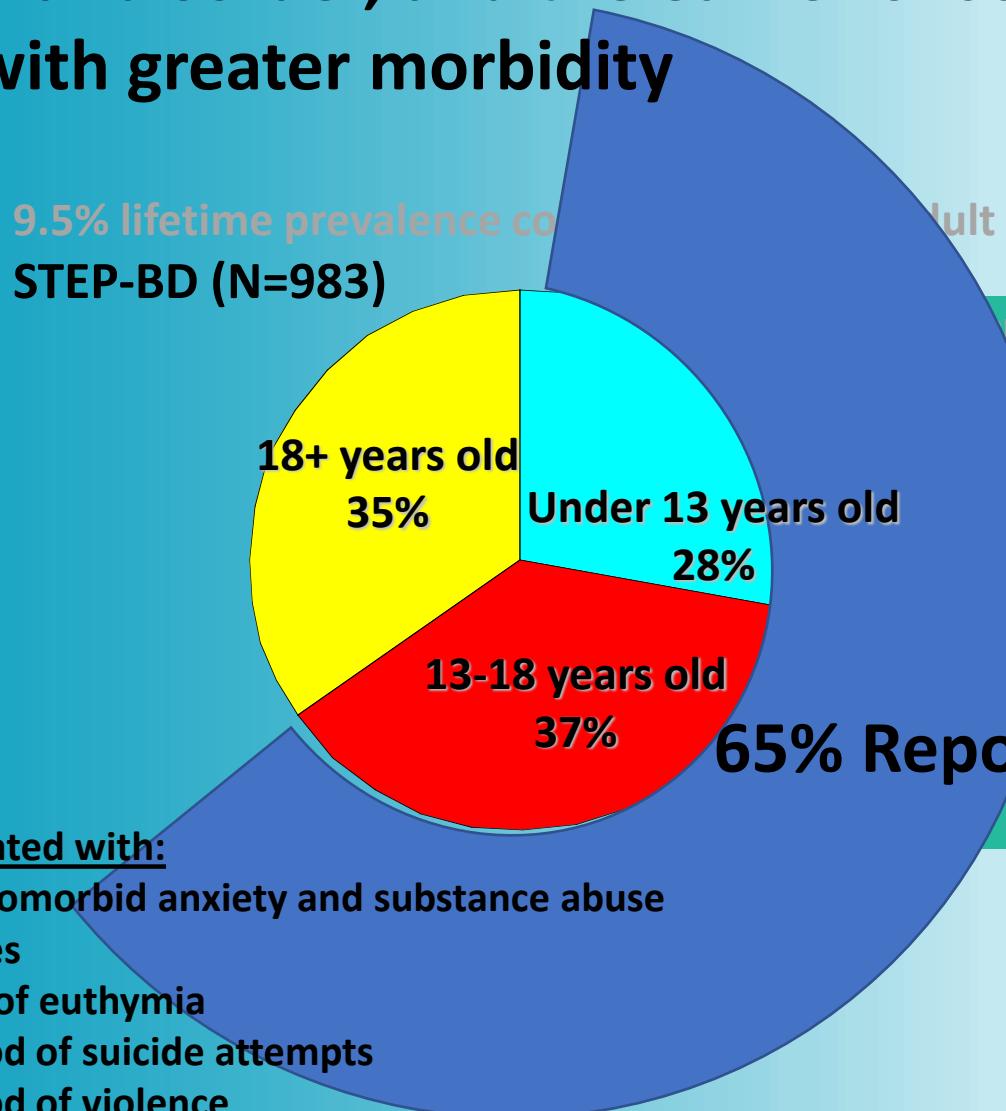
Mick 2007

Most adults in this large clinic sample report pediatric onset of their bipolar disorder, and the earlier onset cases are associated with greater morbidity



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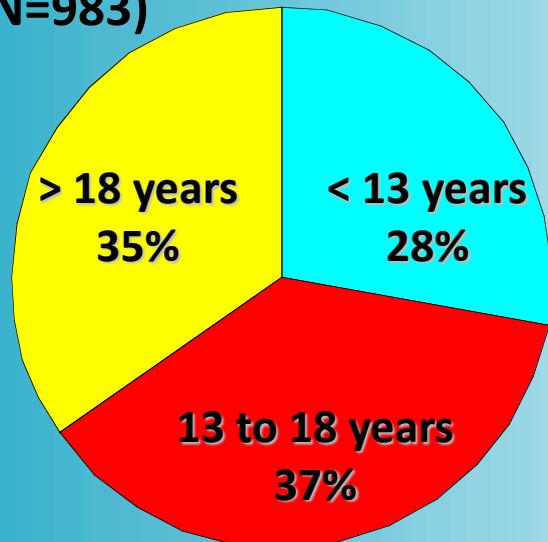


D+ADHD Adult patients:
had earlier onset BPD by 5 years
had shorter periods of wellness (chronic)
had more comorbidity (anxiety and substance)
were more likely to be male
were more likely to have Bipolar I
had more days irritable and more days elated
had lower GAF
more suicide attempts
more violence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

Perlis Biol Psych 2004

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

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



Earlier onset associated with:

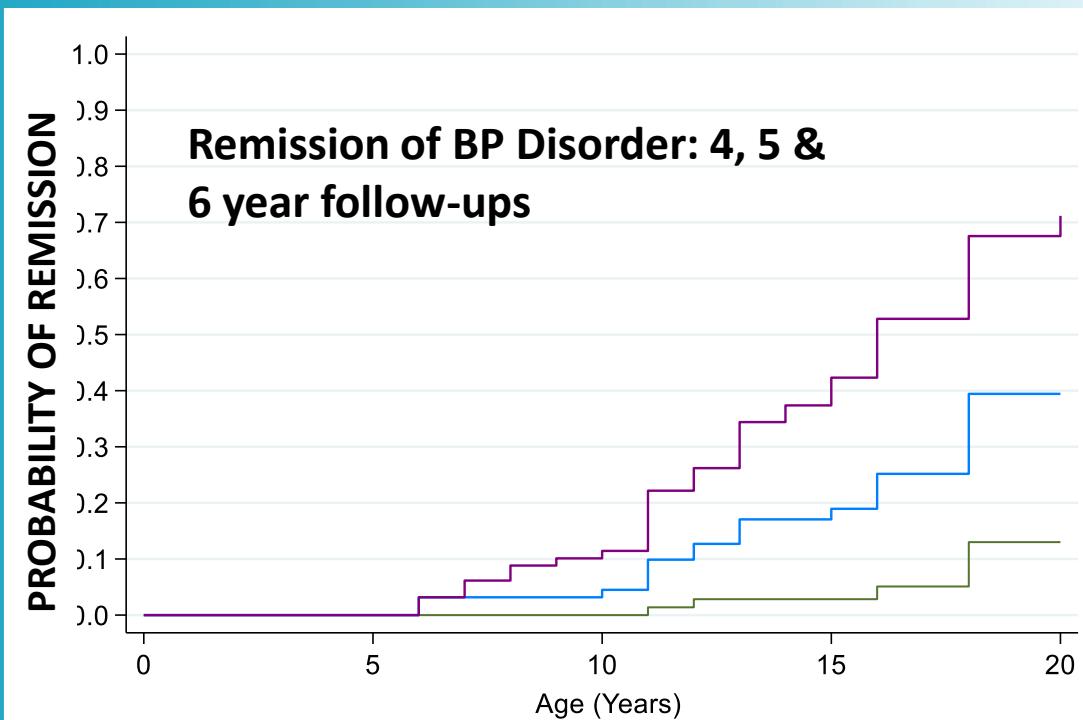
- Higher rates of comorbid anxiety and substance abuse
- More recurrences
- Shorter periods of euthymia
- Greater likelihood of suicide attempts
- Greater likelihood of violence

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

Pediatric Bipolar Disorder is persistent; full remission is rare



Syndromatic Remission

*No longer full syndrome,
Has symptoms and functioning impaired*

Symptomatic Remission

No symptoms, but functioning impaired

Functional remission

*Least likely: full recovery with
no symptoms and good functioning rare*

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

Wozniak 2020

We have many FDA approved treatments for youth with emotional dysregulation



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Lithium: manic or mixed states, patients age 13-17

Risperidone 2007: manic or mixed states, age 10-17

Aripiprazole 2008: manic or mixed states, age 10-17

Olanzapine 2008: manic or mixed states, age 13-17

Quetiapine 2009: monotherapy or adjunct to lithium or divalproex sodium, manic states, age 10-17

Asenapine Saphris 2015: manic or mixed episodes in BPD I, age 10-17

Lurasidone Latuda 2018: pediatric bipolar depression

Olanzapine-fluoxetine 2013: pediatric bipolar depression

Fluoxetine: depression and OCD age 8+

Escitalopram 2002: depression age 12+

Sertraline, fluvoxamine, anfranil: pediatric OCD

Duloxetine Cymbalta: GAD 7+

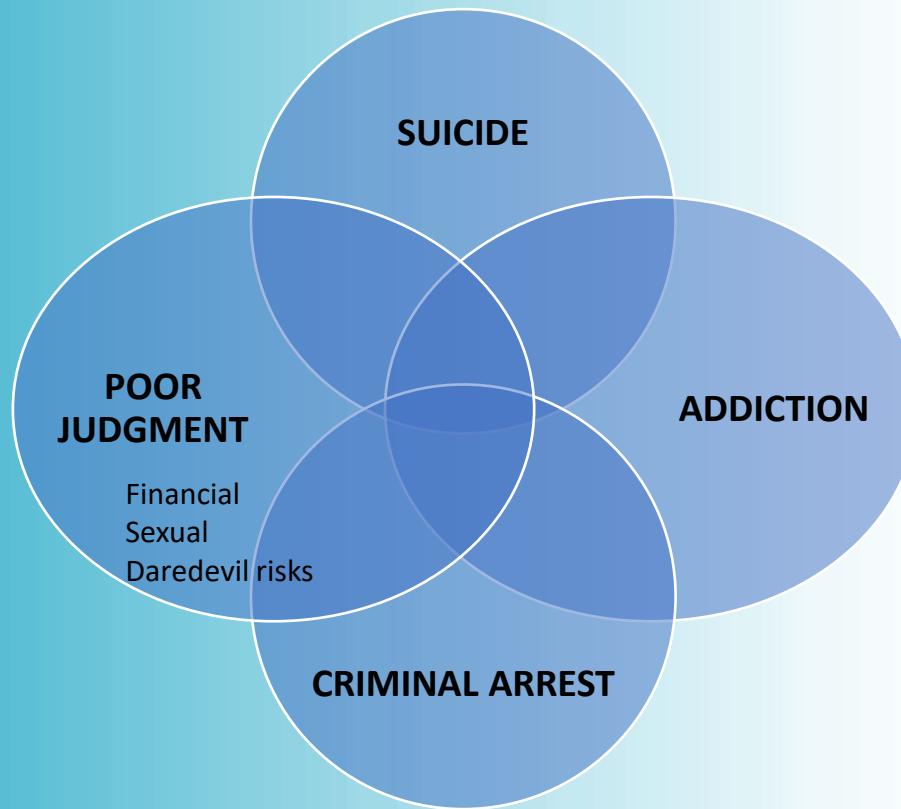
Risperidone 2006: irritability associated with autism age 5-16

Aripiprazole 2009: irritability associated with autistic disorder age 6-17

All have serious and annoying side effects

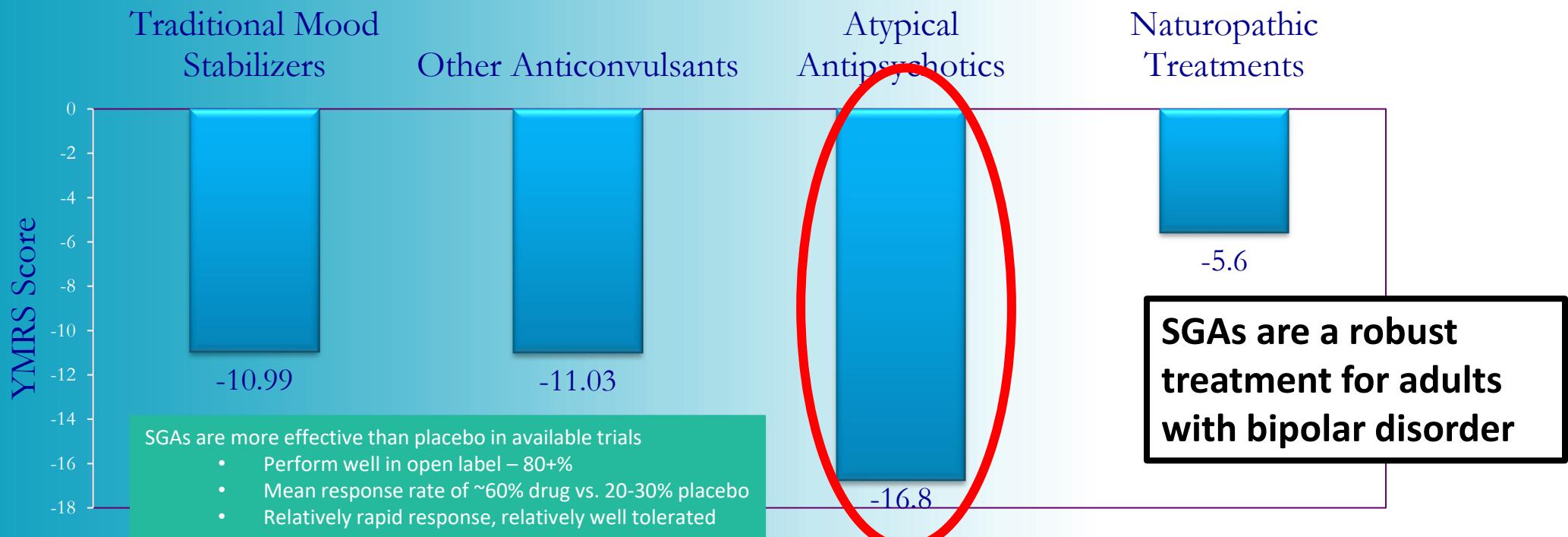


The risk-benefit analysis of treatment must include the risks associated with not treating bipolar disorder



The mean decrease in YMRS in pediatric studies is much greater for the SGAs than for other agents

SGA=second generation antipsychotic



Liu JAACAP 2011
Perlis J Clin Psychiatry 2006

Lithium, divalproex sodium, carbamazepine can be used for pediatric bipolar disorder but are not as effective as SGAs



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SGA=second generation antipsychotic



Trials notable for:

- high drop out rates
- need for rescue medications

Kowatch AACAP 2000

SGAs perform better than valproate for pediatric bipolar disorder



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SGA=second generation antipsychotic

3 double blind RCTs
1 chart review

Valproate versus second generation antipsychotics

more rapid
onset of effect

greater
reduction of
manic
symptoms

Chen 2014



SGAs performed better than mood stabilizers with less discontinuations and less need for augmentation

N=7423

mean age 12.73

57% adolescents

54% males

66.60% SGA

33.40% mood stabilizer

(valproate/oxcarbazepine/lithium)

Comparable
risk of
psychiatric
hospital
admission
186 days

Patients who
initiated on
SGA were
**less likely to
discontinue
the treatment**

SGA=second generation antipsychotic

Retrospective Medicaid claims study of pediatric bipolar disorder patients who initiated a new treatment episode for bipolar disorder on either an SGA or mood stabilizer, followed for 12 months

Chen 2014

Lithium has long been FDA-approved for pediatric bipolar disorder, but the first double blind RCT study for pediatric BP-I was in 2015



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Lithium in the Acute Treatment of Bipolar I Disorder: A Double-Blind, Placebo-Controlled Study

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BACKGROUND: Lithium is a benchmark treatment for bipolar disorder in adults. Definitive studies of lithium in pediatric bipolar I disorder (BP-I) are lacking.

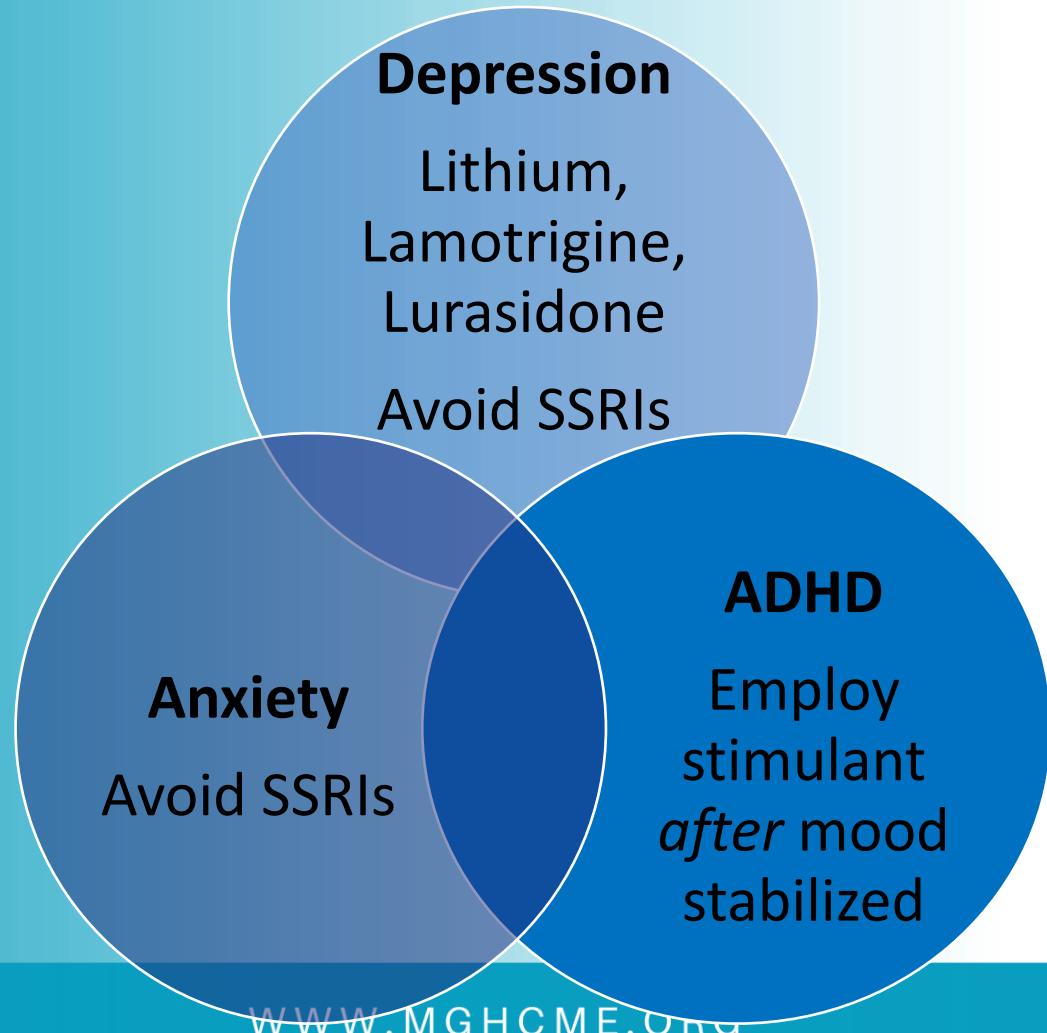
METHODS: This multicenter, randomized, double-blind, placebo-controlled study of pediatric participants (ages 7–17 years) with BP-I/manic or mixed episodes compared lithium ($n = 53$)

47% lithium vs 21% placebo “much/very much improved”

RESULTS: The change in YMRS score was significantly larger in lithium-treated participants (5.51 [95% confidence interval: 0.51 to 10.50]) after adjustment for baseline YMRS score, age group, weight group, gender, and study site ($P = .03$). Overall Clinical Global Impression-Improvement scores favored lithium ($n = 25$; 47% very much/much improved) compared with placebo ($n = 6$; 21% very much/much improved) at week 8/ET ($P = .03$).



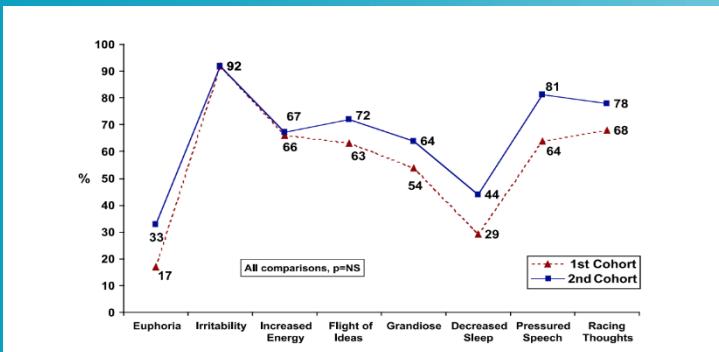
Comorbidity must be addressed in addition to mania



Overview:

Pediatric Bipolar Disorder Is a highly morbid, valid condition that affects a significant minority of young children and is often comorbid with ADHD

Scope: Pediatric Bipolar Disorder is now in the differential diagnosis for moody children



Diagnostic description: Pediatric bipolar disorder can be reliably diagnosed and is often mixed and irritable and comorbid with ADHD.

Treatment: SGAs are the most effective mood stabilizers

