MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Pediatric Bipolar Disorder: Assessment and Management

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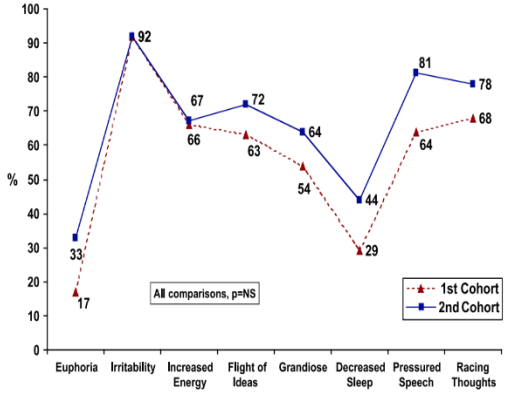
Disclosures 2020-2021

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

- *Research support:* Genentech, Headspace Inc., Pfizer Pharmaceuticals, Roche TCRC Inc., Sunovion Pharmaceuticals Inc., Takeda/Shire Pharmaceuticals Inc., and Tris.
- *Consulting fees:* Akili, Avekshan LLC, Jazz Pharma, and Shire/Takeda
- *Honorarium for scientific presentation:* Tris
- *Royalties paid to the Department of Psychiatry at MGH, for a copyrighted ADHD rating scale used for ADHD diagnoses:* Biomarin, Bracket Global, Cogstate, Ingenix, Medavent Prophase, Shire, Sunovion, and Theravance
- Through Partners Healthcare Innovation, I have a partnership with MEMOTEXT to commercialize a digital health intervention to improve adherence in ADHD.

Basic Overview

Scope: Pediatric Bipolar disorder is a highly morbid condition that affects a significant minority of young children



Diagnostic description: Pediatric bipolar disorder can be reliably diagnosed and is often mixed and highly irritable and sometimes violent

Persistence: Pediatric bipolar disorder persists over time

Pediatric Bipolar disorder should always be considered in the differential diagnosis of children with mood symptoms

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

Mania-Like Symptoms Suggestive of Childhood-O 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, children.

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

ELSEVIER
Journal of Affective Disorders 82S (2004) S45–S58
AFFECTIVE 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).
were children aged ≤12 years referred to a child psychiatry service and evaluated with
ildren with a DSM-III-R BPD diagnosis (1st cohort, n=43; 2nd cohort, n=129) were
, we used attention-deficit/hyperactivity disorder (ADHD) children without BPD referred to
ne period (1st cohort, n=164; 2nd cohort, n=450).
ndings, 2nd cohort results showed that (1) mania was identified in 17% of subjects; (2) the
rritable and mixed, and the course was chronic; (3) BPD children frequently met criteria for
s, and anxiety disorders; and (4) BPD children had high rates of psychiatric hospitalization
ired psychosocial functioning.
n that pediatric BPD is a severe clinical disorder afflicting a sizable number of referred
henotypic features and patterns of comorbidity support the hypothesis that clinically referred
s a very severe developmental subtype of bipolar disorder.
served.

Consecutively referred children ≤ 12 years:

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

Wozniak, 1995; Biederman, 2004

The symptoms of mania are the same in children and adults with presentations appropriate to developmental stage

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)

What Have We Learned About Children with Mania?

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

MIXED
- The children have mostly mixed states (mania and depression overlapping)

CHRONIC
- The children are seldom well with many cycles and chronic mood variability

- **Very high comorbidity with ADHD**

Wozniak, 1995; Biederman, 2004

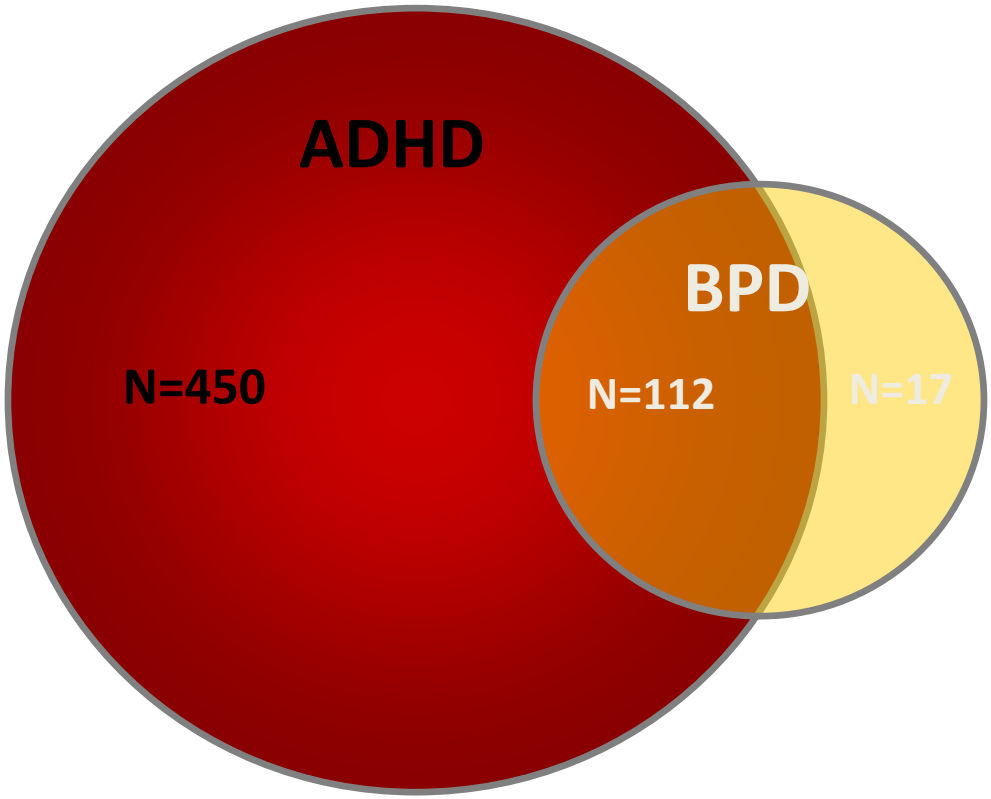
Problem: Large Overlap Between ADHD and Pediatric BP-I Disorder

Overlapping symptoms:

- Distractibility (very severe in BP disorder)
- Motoric hyperactivity (vs. agitation)
- Talkativeness (vs. pressured speech)

MGH Study of Pediatric BPD

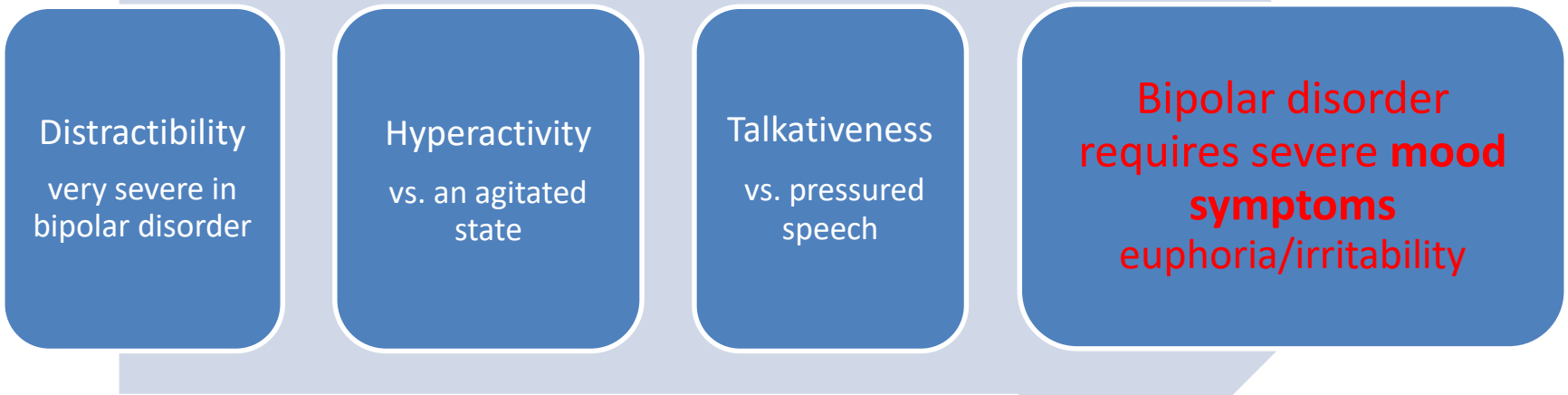
Diagnostic Overlap of BPD and ADHD [Second Cohort]



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

Despite overlapping symptoms between ADHD and Pediatric BP Disorder, Pediatric BP disorder requires mood symptoms to diagnose

Differentiating overlapping symptoms between ADHD and Pediatric BP Disorder



Biederman JAACAP 1996

Diagnosis of Bipolar Disorder Vs. ADHD

- KEY DISTINGUISHING FEATURE: Unlike ADHD, BP disorder requires the presence of both aberrant, persistent and severe mood symptoms (euphoria or irritability)

BP disorder in adults is Highly Comorbid with ADHD:

The National Epidemiologic Survey on Alcohol and Related Conditions

N=34,000 adults

2.5% ADHD

34% with ADHD had bipolar disorder vs. 6% without ADHD

The National Comorbidity Survey Replication

N=3199 adults

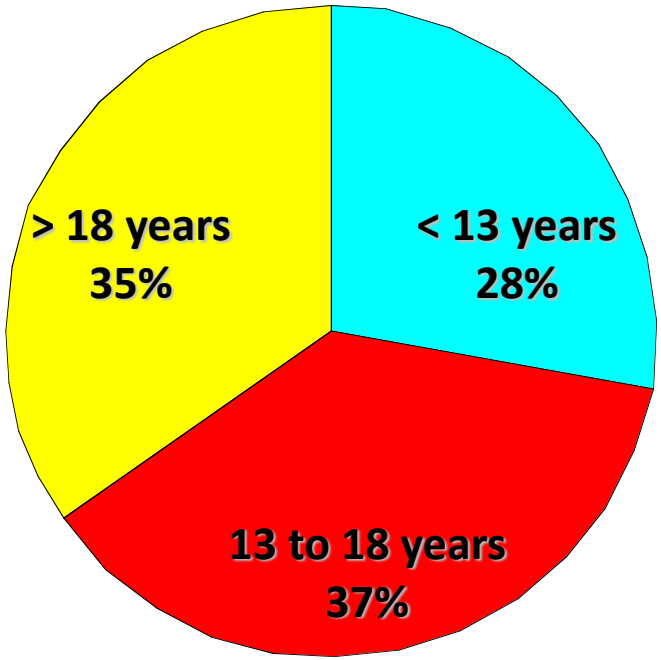
4.4% ADHD

19% with ADHD had BP disorder vs. 3% without ADHD

Bernardi, Psychol Med 2012; Kessler, Am J Psych 2006;

Most bipolar adults in STEP-BD (N=983) reported onset of their disorder in childhood or adolescence

Age of onset of bipolar disorder for bipolar adults



65% of bipolar adults had onset prior to age 18

28% of bipolar adults had age of onset prior to age 13

Perlis Biol Psych 2004

In study of 10,000+ US adolescents, 3% were BP and in a meta-analysis of international studies, the rate of pediatric bipolar disorder was 2%

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 criteria for another class of lifetime disorder. The overall prevalence of disorders with severe impairment and/or distress was 22.2% (11.2% with mood disorders, 8.3% with anxiety disorders, and 9.6% behavior disorders). The median age of onset for disorder classes was earliest for anxiety (6 years), followed by 11 years for behavior, 13 years for mood, and 15 years for substance use disorders. Conclusions: These findings provide the first prevalence data on a broad range of mental disorders in a nationally representative sample of U.S. adolescents. Approximately one in every four to five youth in the U.S. meets criteria for a mental disorder with severe impairment across their lifetime. The likelihood that common mental disorders in adults first emerge in childhood and adolescence highlights the need for a transition from the common focus on treatment of U.S. youth to that of prevention and early intervention. J. Am. Acad. Child Adolesc. Psychiatry, 2010;49(10):980–989. Key Words: epidemiology, adolescents, mental disorders, National Comorbidity Survey, correlates

THE JOURNAL OF CLINICAL PSYCHIATRY

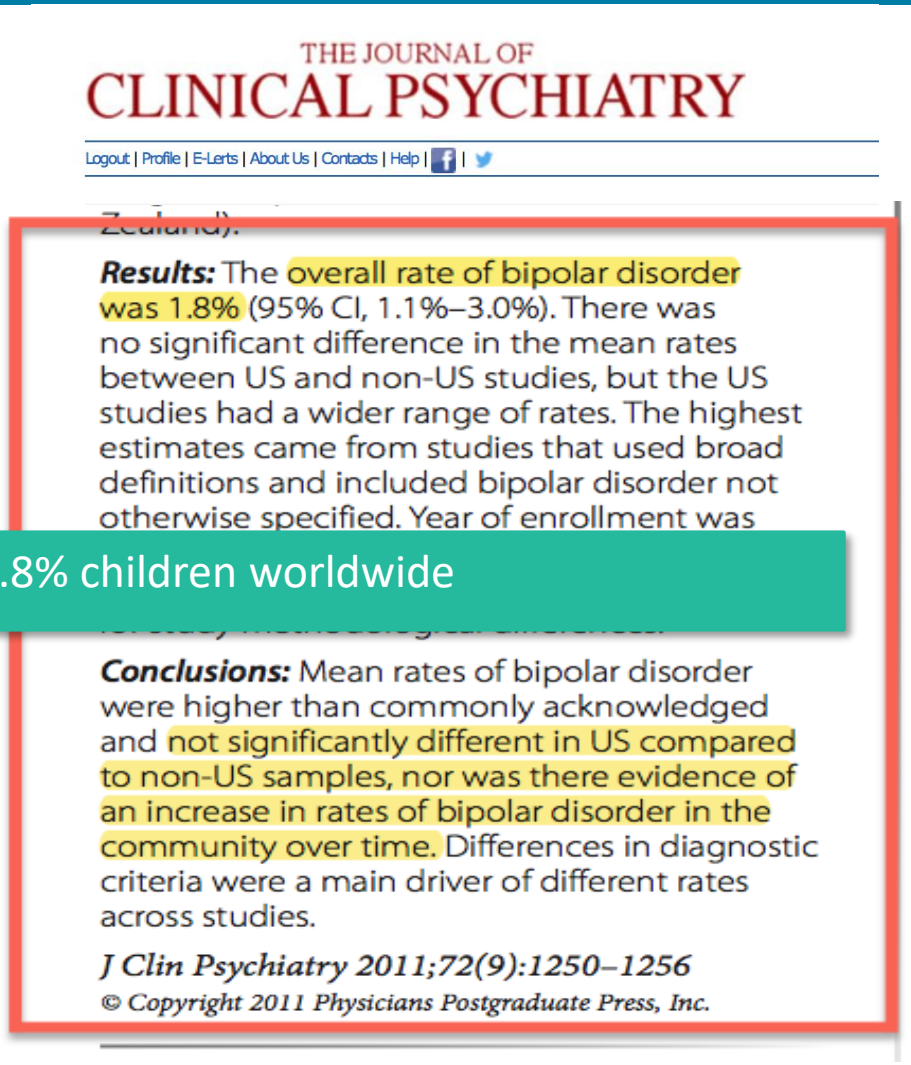
Results: The overall rate of bipolar disorder was 1.8% (95% CI, 1.1%–3.0%). There was no significant difference in the mean rates between US and non-US studies, but the US studies had a wider range of rates. The highest estimates came from studies that used broad definitions and included bipolar disorder 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

Pediatric BP disorder is prevalent across the world: In a meta-analysis of international studies, the rate of pediatric bipolar disorder was close to 2%



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Bipolar Disorder affects 1.8% children worldwide

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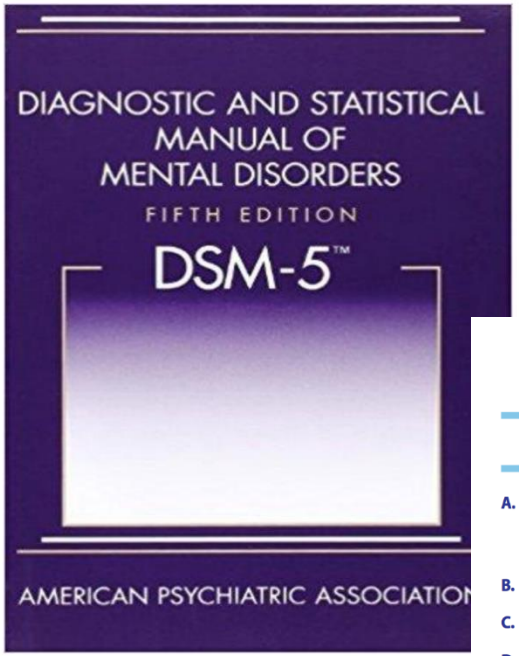
J Clin Psychiatry 2011;72(9):1250–1256

Van Meter J Clin Psych 2011

A new disorder was created in DSM V called Disruptive Mood Dysregulation Disorder to 'decrease the number of pediatric BP bipolar diagnoses'



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 in persistently irritable or angry most of the day, nearly every day, and is observable by others (e.g., parents, teachers, peers).

DMDD is "common, transient, difficult to distinguish from ODD and CD

Examining the Proposed Disruptive Mood Dysregulation Disorder Diagnosis in Children in the Longitudinal Assessment of Manic Symptoms Study

David Axelson, MD; Robert L. Findling, MD, MBA; Mary A. Fristad, PhD, ABPP; Robert A. Kowatch, MD, PhD; Eric A. Youngstrom, PhD; Sarah McCue Horwitz, PhD; L. Eugene Arnold, MD; Thomas W. Frazier, PhD; Neal Ryan, MD; Christine Demeter, MA; Mary Kay Gill, MSN; Jessica C. Hauser-Harrington, PhD; Judith Depew; Shawn M. Kennedy, MA; Brittany A. Gron, BS; Brieana M. Rowles, MA; and Boris Birmaher, MD

Conclusions: In this clinical sample, DMDD could not be delimited from oppositional defiant disorder and conduct disorder, had limited diagnostic stability, and was not associated with current, future-onset, or parental history of mood or anxiety disorders. These findings raise concerns about the diagnostic utility of DMDD in clinical populations.

J Clin Psychiatry 2012;73(10):1342–1350

- **Temper outbursts ≥3 per week**
- **Persistently irritable mood**
- present for 12 or more months. Throughout that time, the person has not had 3 or more consecutive months when they were without the symptoms

Exclusionary:
Euphoria for 1+ day with 3/7 B criteria
During MDD episode
History of (hypo)mania

Axelson JClinPsych 2012

How Valid is the Dx of Pediatric BP-Disorder? A framework for the validation of psychiatric disorders can be applied to pediatric bipolar disorder

Establishment of Diagnostic Validity in Psychiatric Illness: Its Application to Schizophrenia

BY ELI ROBINS, M.D., AND SAMUEL B. GUZE, M.D.

A method for achieving diagnostic validity in psychiatric illness is described, consisting of five phases: clinical description, laboratory study, exclusion of other disorders, follow-up study, and family study. The method was applied in this paper to patients with the diagnosis of schizophrenia, and it was shown by follow-up and family studies that poor prognosis cases can be validly separated clinically from good prognosis cases. The authors conclude that good prognosis "schizophrenia" is not mild schizophrenia, but a different illness.

SINCE BLEULER (3), psychiatrists have recognized that the diagnosis of schizophrenia includes a number of different disorders. We are interested in distinguishing these various disorders as part of our long-standing concern with developing a valid classification for psychiatric illnesses(6, 7, 10, 11). We believe that a valid classification is an essential step in science. In medicine, and hence in psychiatry, classification is diagnosis.

The authors are with the department of psychiatry, Washington University School of Medicine, 4940 Audubon Ave., St. Louis, Mo. 63110, where Dr. Robins is Wallace Renard professor and head of the department and Dr. Guze is professor. Dr. Robins is also psychiatrist-in-chief, Barnes and Renard Hospitals, and Dr. Guze is associate psychiatrist.

This work was supported in part by Public Health Service grants MH-13002 and MH-07081 from the National Institute of Mental Health.

One of the reasons that diagnostic classification has fallen into disrepute among some psychiatrists is that diagnostic schemes have been largely based upon a priori principles rather than upon systematic studies. Such systematic studies are necessary, although they may be based upon different approaches. We have found that the approach described here facilitates the development of a valid classification in psychiatry. This paper illustrates its usefulness in schizophrenia.

The Five Phases

1. Clinical Description

In general, the first step is to describe the clinical picture of the disorder. This may be a single striking clinical feature or a combination of clinical features thought to be associated with one another. Race, sex, age at onset, precipitating factors, and other items may be used to define the clinical picture more precisely. The clinical picture thus does not include only symptoms.

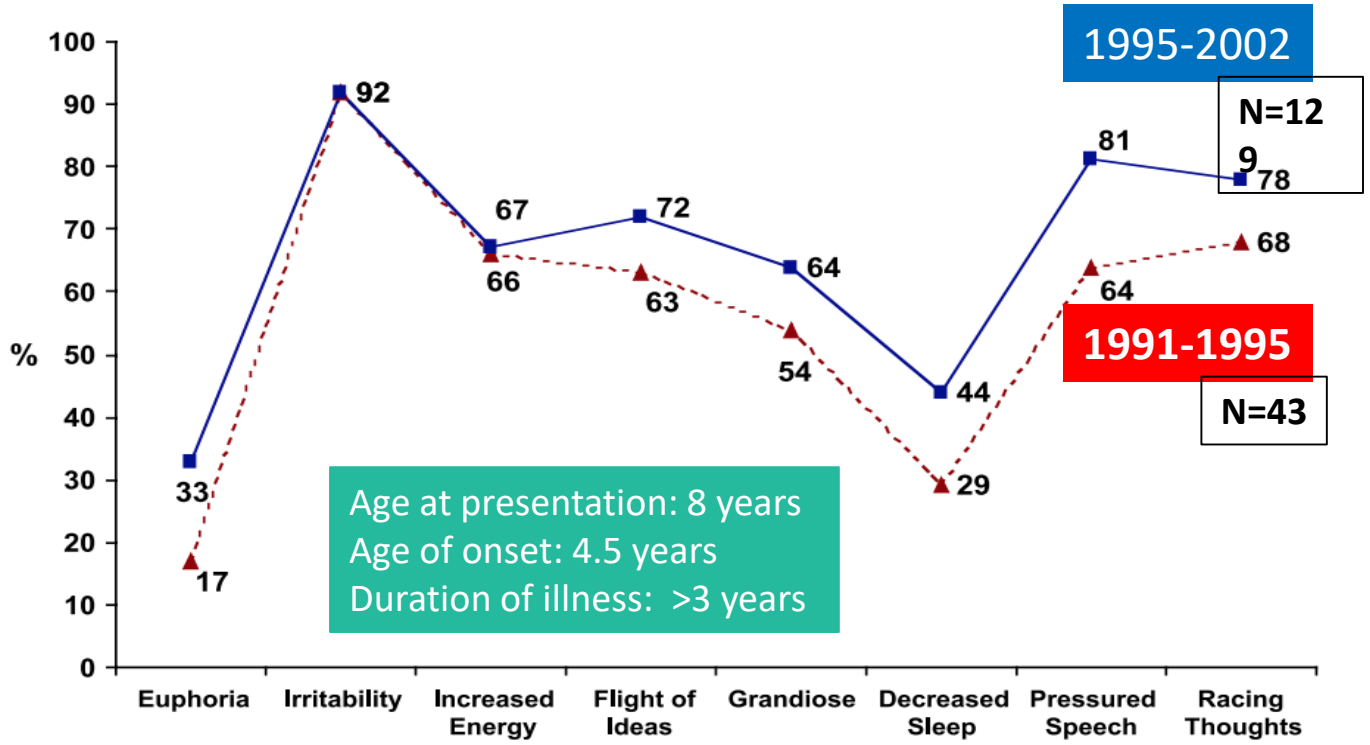
2. Laboratory Studies

Included among laboratory studies are chemical, physiological, radiological, and anatomical (biopsy and autopsy) findings. Certain psychological tests, when shown to be reliable and reproducible, may also be considered laboratory studies in this context. Laboratory findings are generally more reliable, precise, and reproducible than are

1. *Unique Clinical characteristics*
2. *Familiality*
3. *Course*
4. *Unique Pharmacological Responsivity*
5. *Laboratory Studies/Biomarkers*

Robins & Guze, Am J Psych 1970

The symptoms of mania are the same in two cohorts of pre-adolescent age (<12 years) youth with BP disorder



Wozniak, 1995; Biederman, 2004

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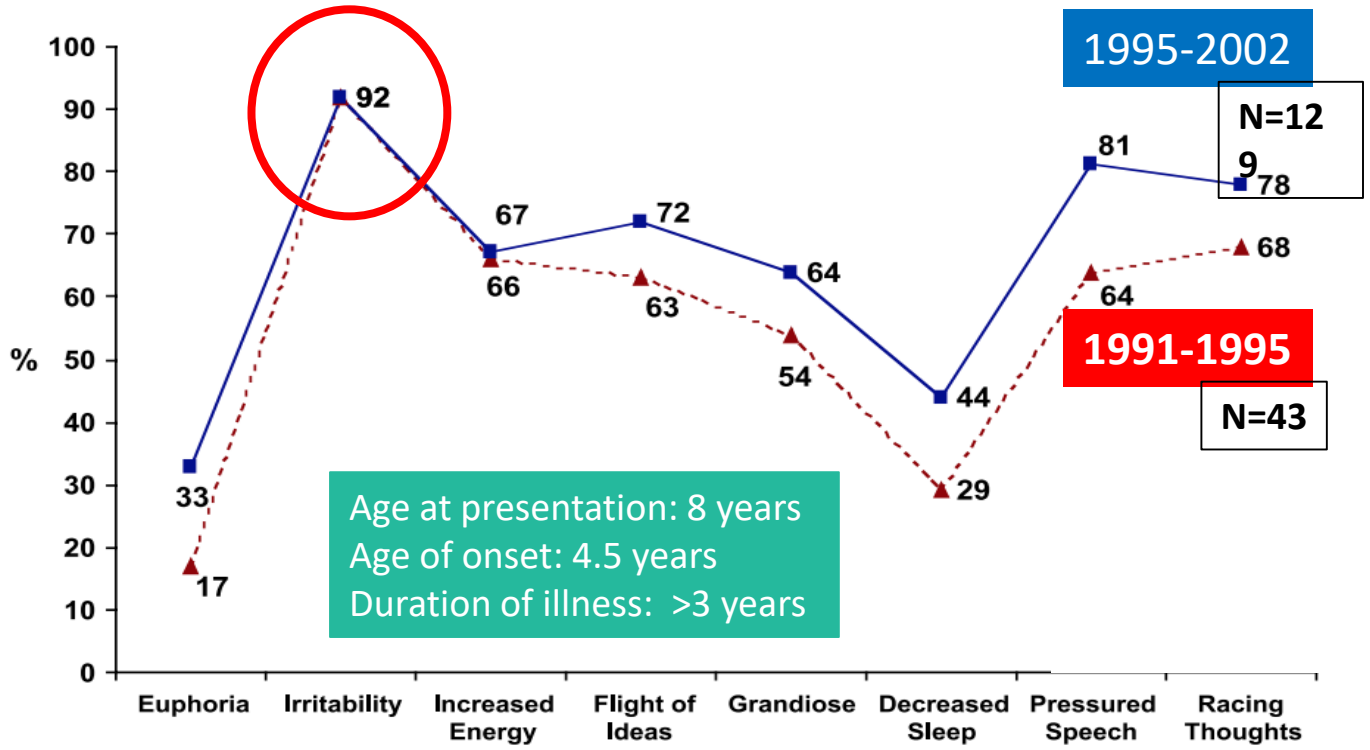
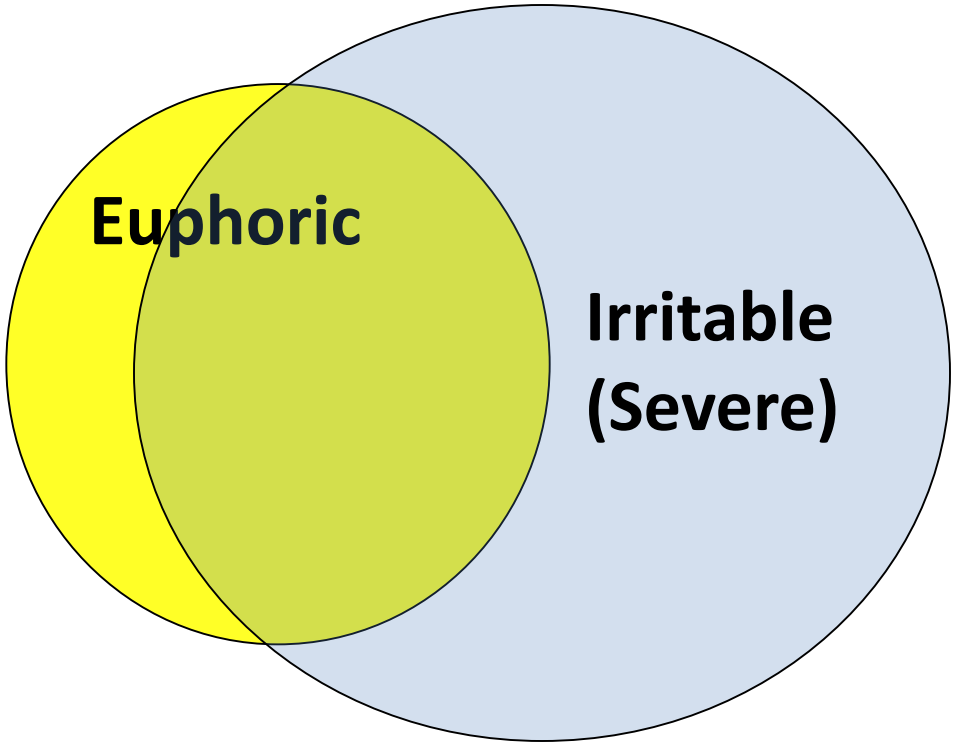


Wozniak, 1995; Biederman, 2004

Euphoria and Irritability in BPD Youth



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

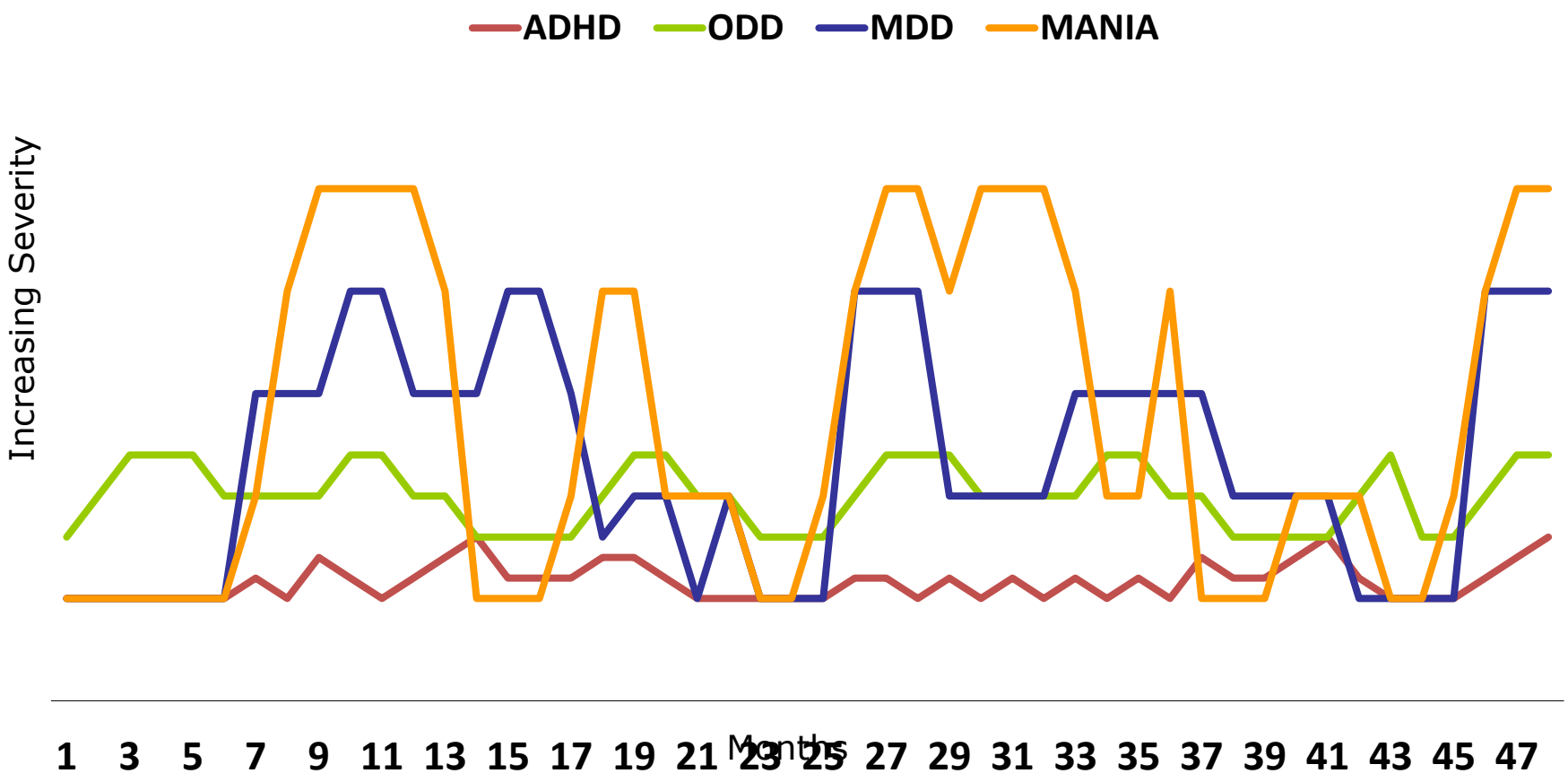
B. At least 3/7 (4/7 if mood is irritable)

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

Are All Forms of Irritability the Same?

Heterogeneity of Irritability

Heterogeneity of Irritability in Children



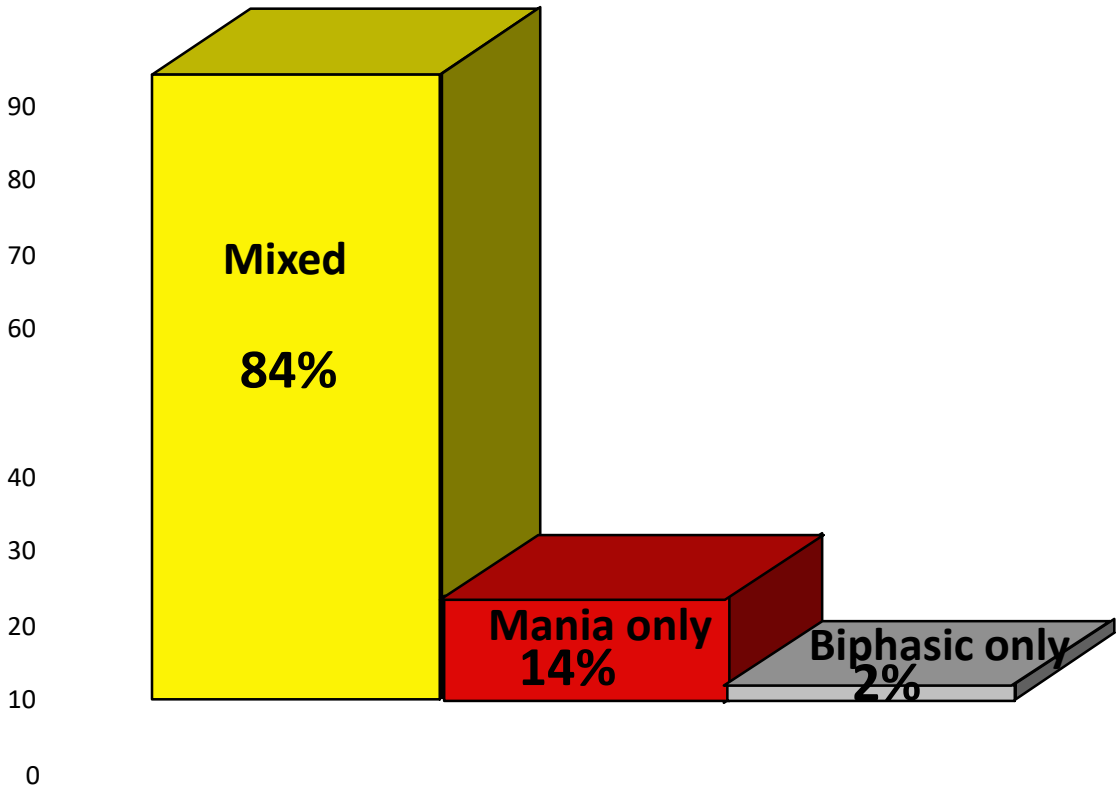
Mick et al, 2007

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.

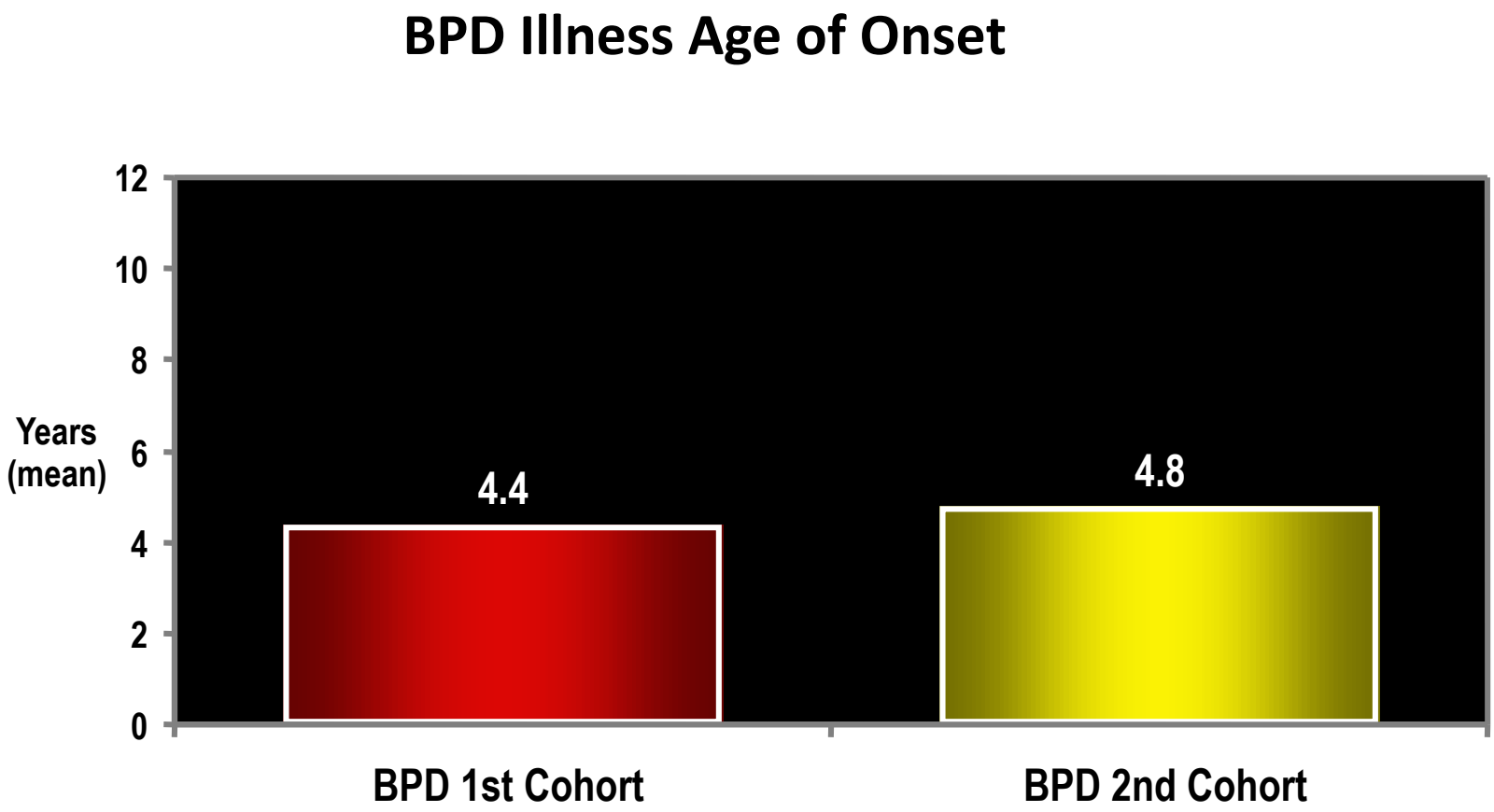
Biederman et al. *J Am Acad Child Adolesc Psychiatry*. 1996; 35(8): 997-1008.

Mixed presentations are the most common mood abnormality in pediatric BP disorder



Wozniak, 1995; Biederman, 2004

MGH Study of Pediatric BPD



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

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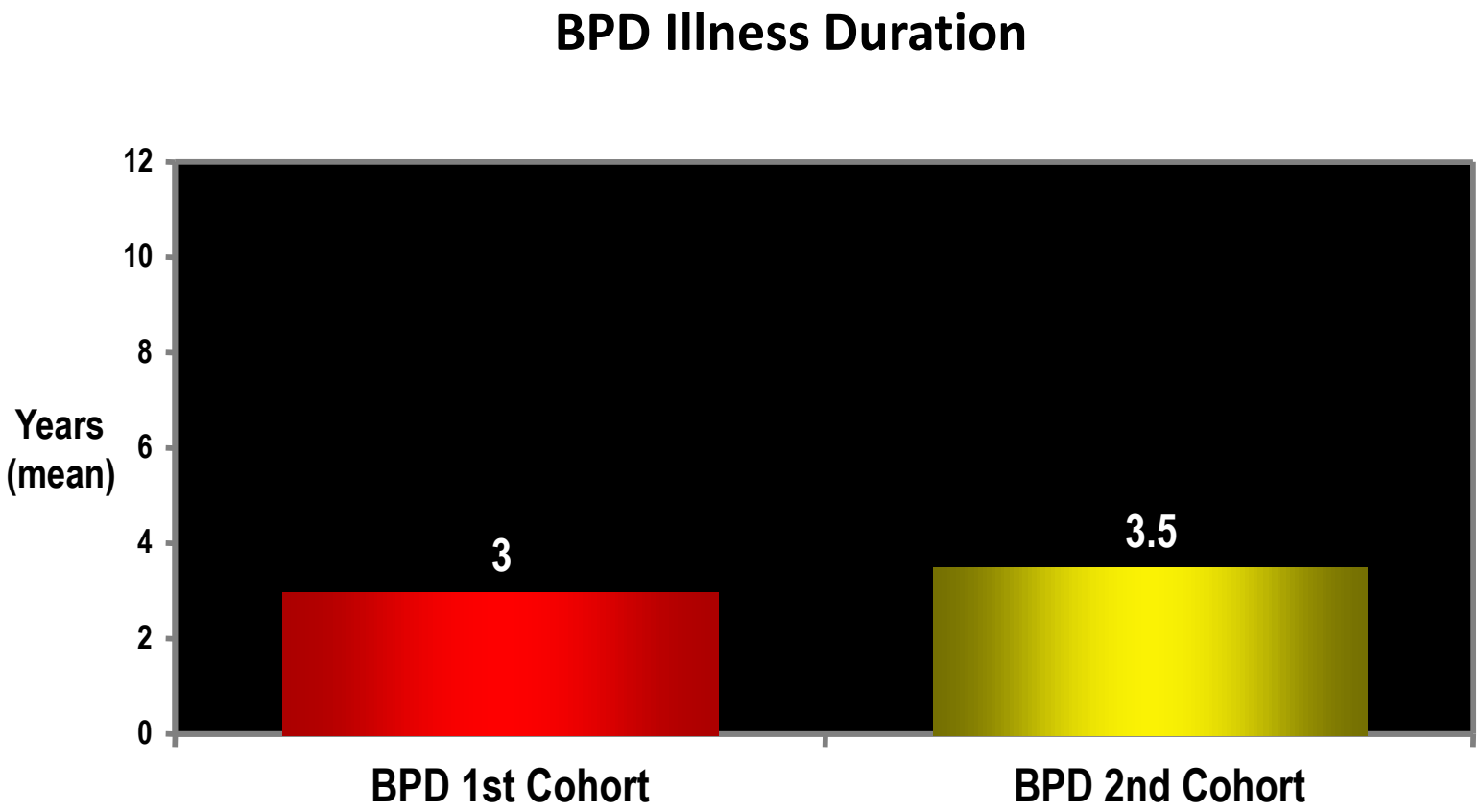

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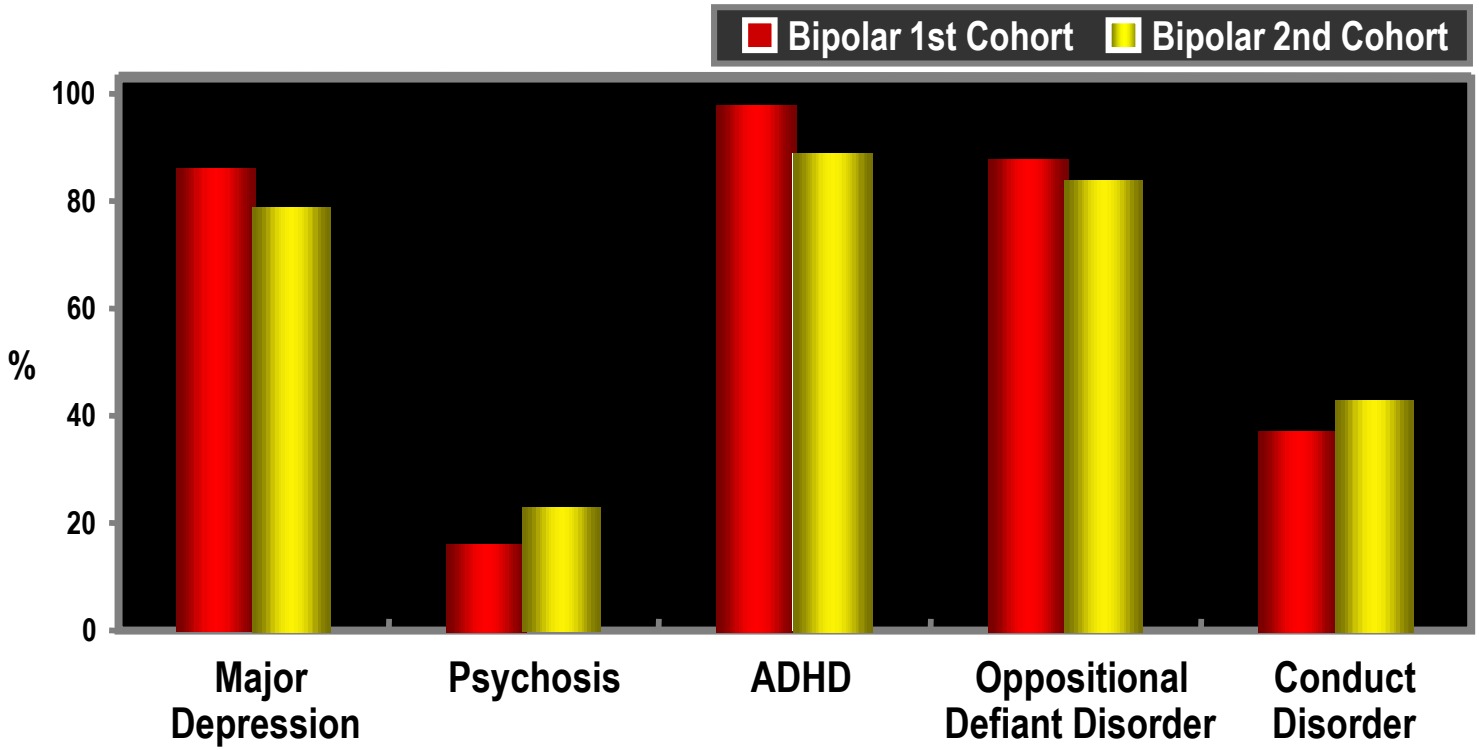
MGH Study of Pediatric BPD

Comorbid Disorders by Bipolar Cohort



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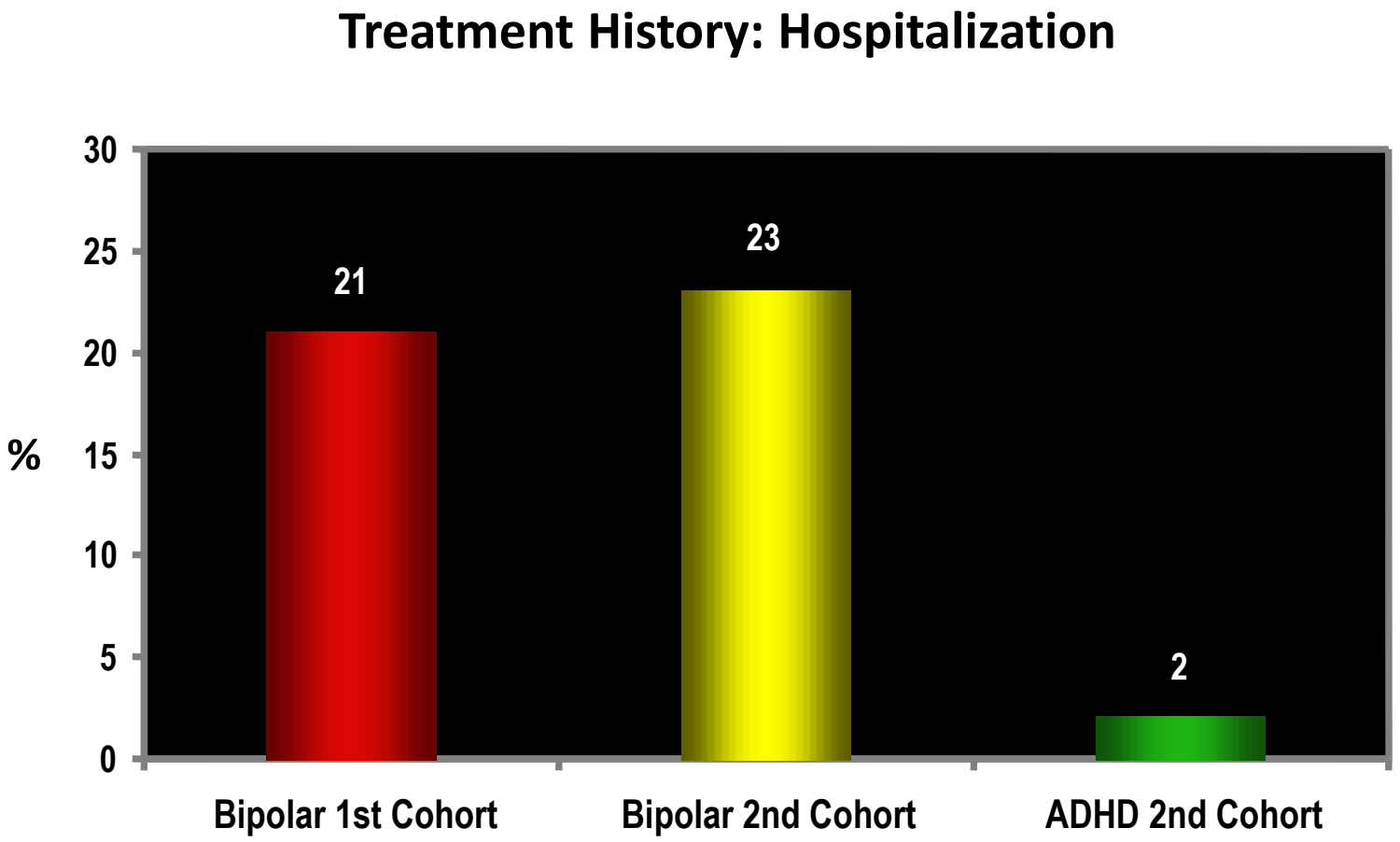
MGH Study of Pediatric BPD



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

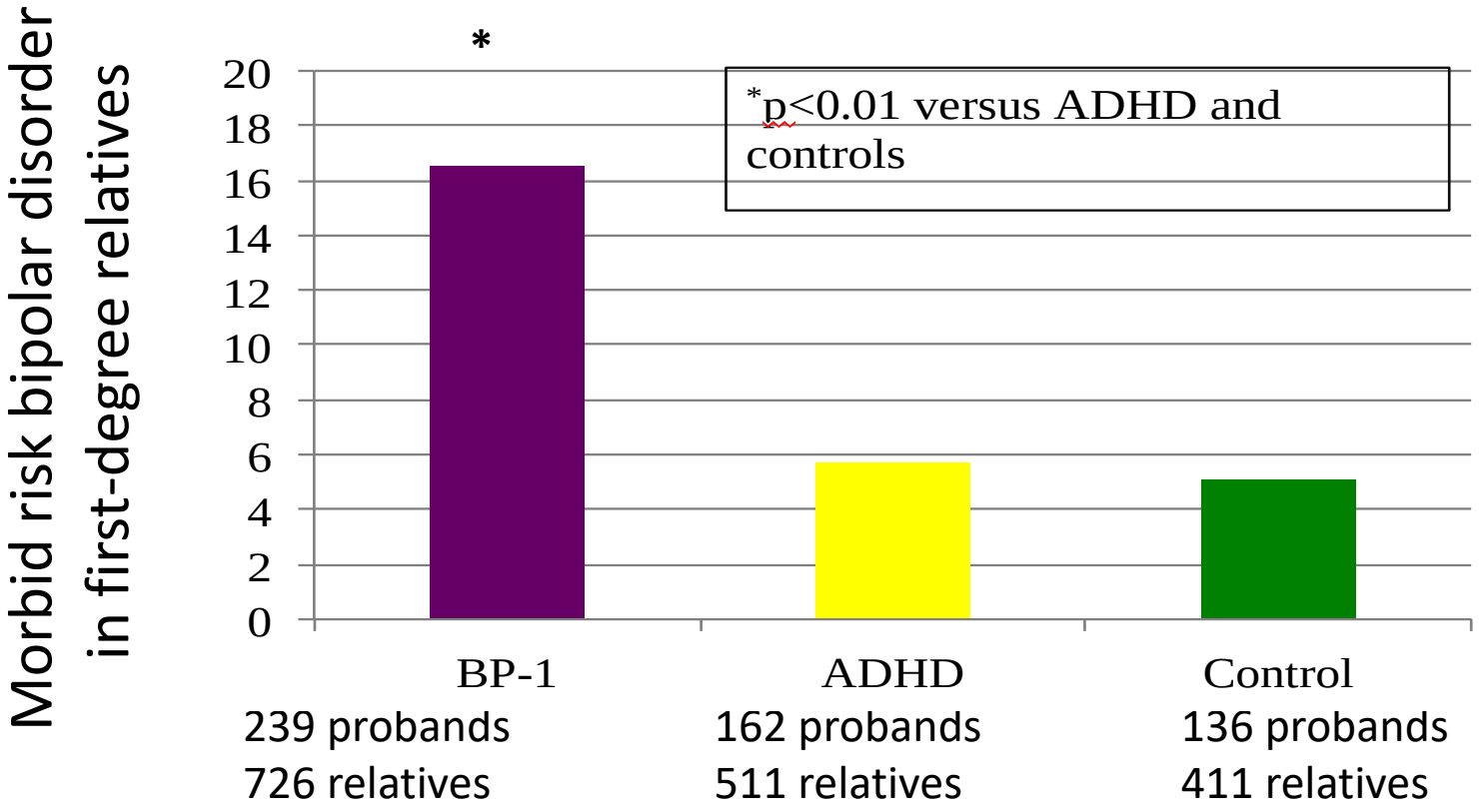
Summary of Clinical Presentation

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

Is Pediatric BP-I Disorder Familial?

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

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



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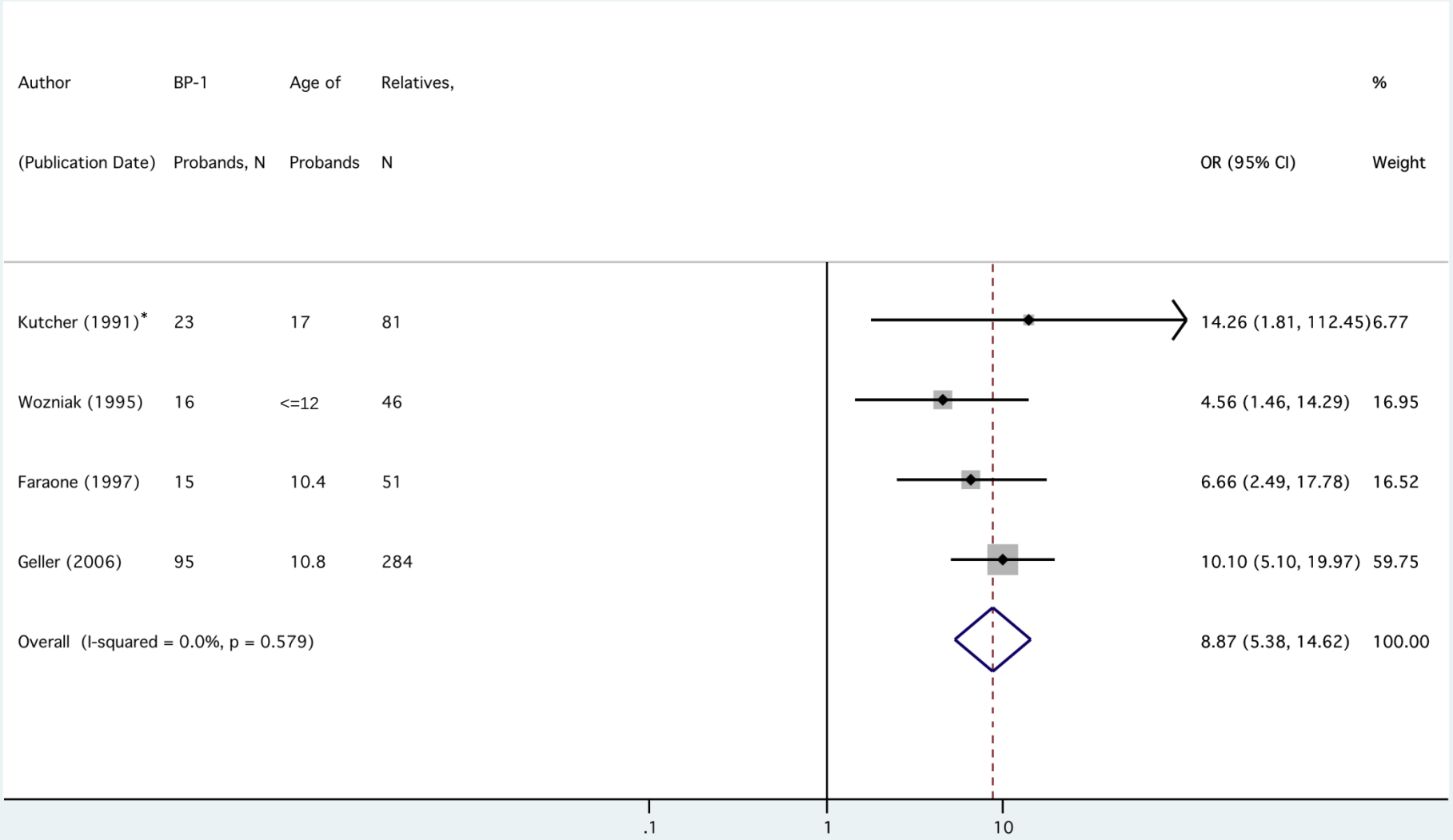
Wozniak J Clin Psych 2012

Meta-analysis of previous family studies



*It is important to note that Kutcher et al. only included probands who were referred from an inpatient or outpatient treatment at a medical center

Does Pediatric BPD have a unique course?

We followed-up children ascertained for a family study of pediatric-onset bipolar disorder to assess persistence

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

High level of persistence of pediatric bipolar-I disorder from childhood onto adolescent years: A four year prospective longitudinal follow-up study

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[b] Department of Psychiatry at Harvard Medical School, SUNY Upstate Medical University, United States
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ABSTRACT

Objective: To examine the longitudinal course of pediatric bipolar (BP)-I disorder in youth transitioning from childhood into adolescence.

Methods: We conducted a four year prospective follow-up study of 78 youth with BP-I disorder 6–17 years old at ascertainment followed up into adolescent years (13.4 ± 3.9 years). All subjects were comprehensively assessed with structured diagnostic interviews, neuropsychological testing, psychosocial, educational and treatment history assessments. BP disorder was considered persistent if subjects met full criteria for DSM-IV BP-I disorder at follow-up.

Results: Of 78 BP-I participating youth subjects, 57 (73.1%), continued to meet full diagnostic criteria for BP-I Disorder. Of those with a non-persistent course, only 6.4% ($n = 5$) were euthymic (i.e., syndromatic and symptomatic remission) at the 4-year follow-up and were not receiving pharmacotherapy for the disorder. The other non-persistent cases either continued to have subthreshold BP-I disorder ($n = 5$, 6.4%), met full ($n = 3$, 3.8%) or subthreshold ($n = 1$, 1.3%) criteria for major depression, or were euthymic but were treated for the disorder ($n = 7$, 9.0%). Full persistence was associated with higher rates of major depression and disruptive behavior disorders at the follow-up assessment and higher use of stimulant medicines at the baseline assessment. Non-Peristent BP-I was also characterized by high levels of dysfunction and morbidity.

Conclusions: This four year follow-up shows that the majority of BP-I disorder youth continue to experience persistent disorder into their mid and late adolescent years and its persistence is associated with

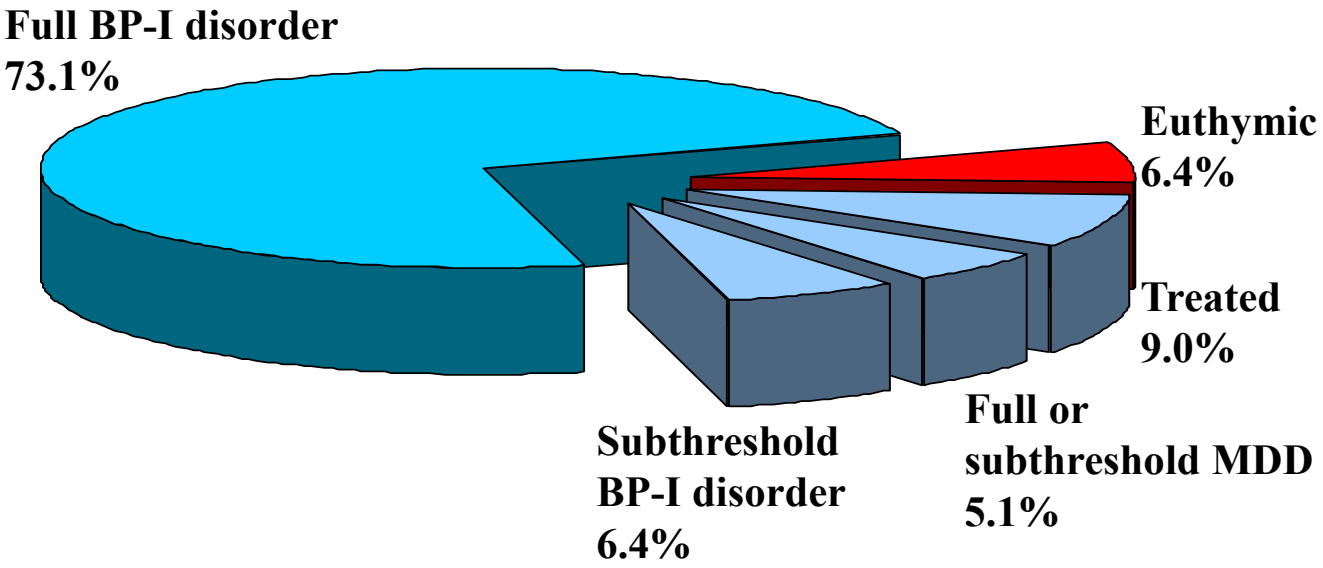
78 of 105 youth with Bipolar I Disorder participating in family study followed-up after 4 years

- **Baseline age 10 years**
- **76% male**
- **Age of onset bipolar disorder: 5 years**
- **Duration of BPD at baseline: 7 years**

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Wozniak JPsychiatrRes 2011

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

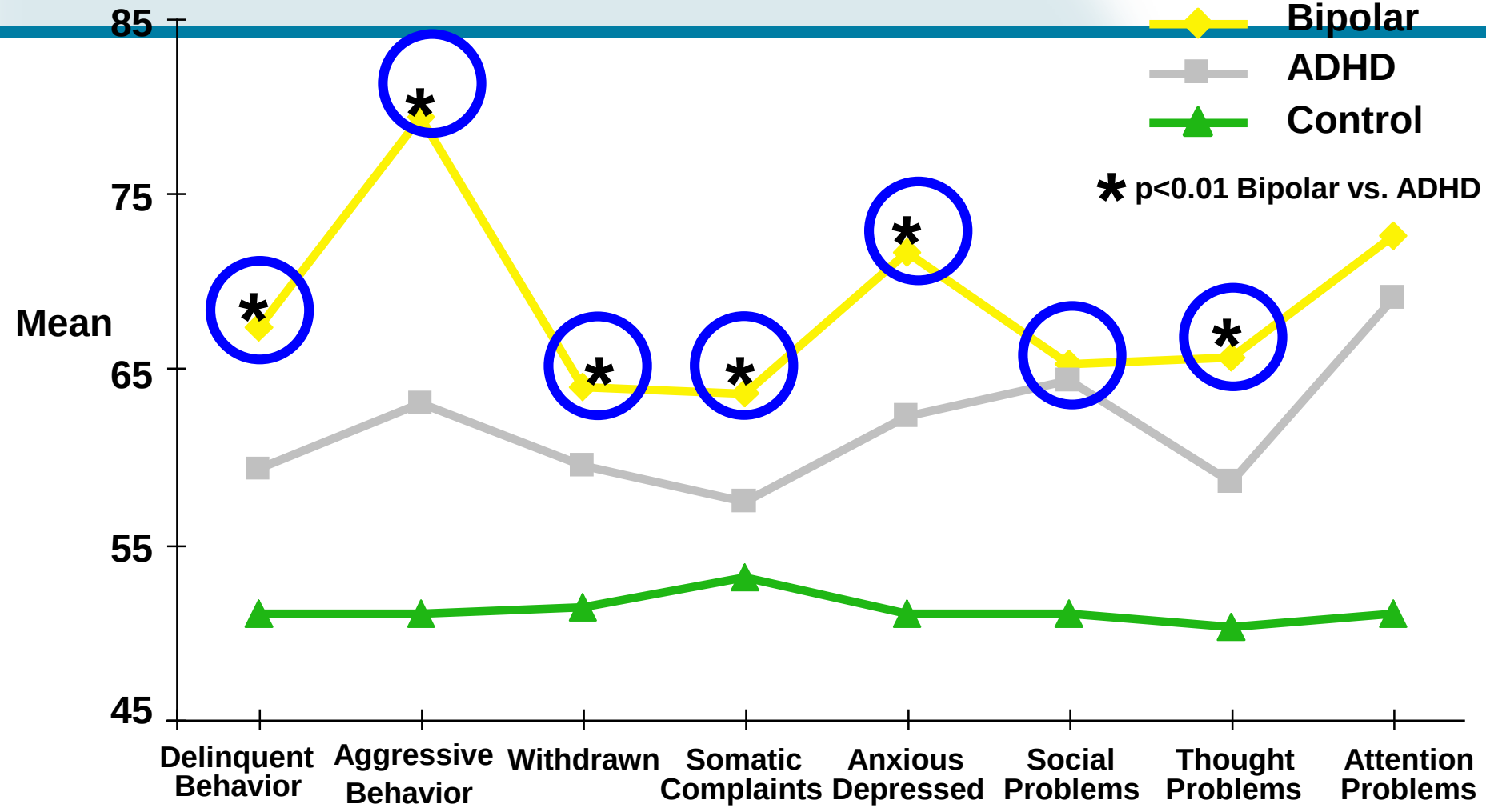


Wozniak, Biederman et al. 2012

Can We Screen for Pediatric BP Disorder?: The CBCL

CBCL Clinical Scales

(Biederman et al., JAACAP, 1995)



Significantly elevated in children of BPD parents (Wals et al., JAACAP, 2001)

The CBCL avoids cultural differences or methodological factors that could account for regional diagnostic differences

More diagnoses made in the US sample using the **KSADS-PL than in Holland**

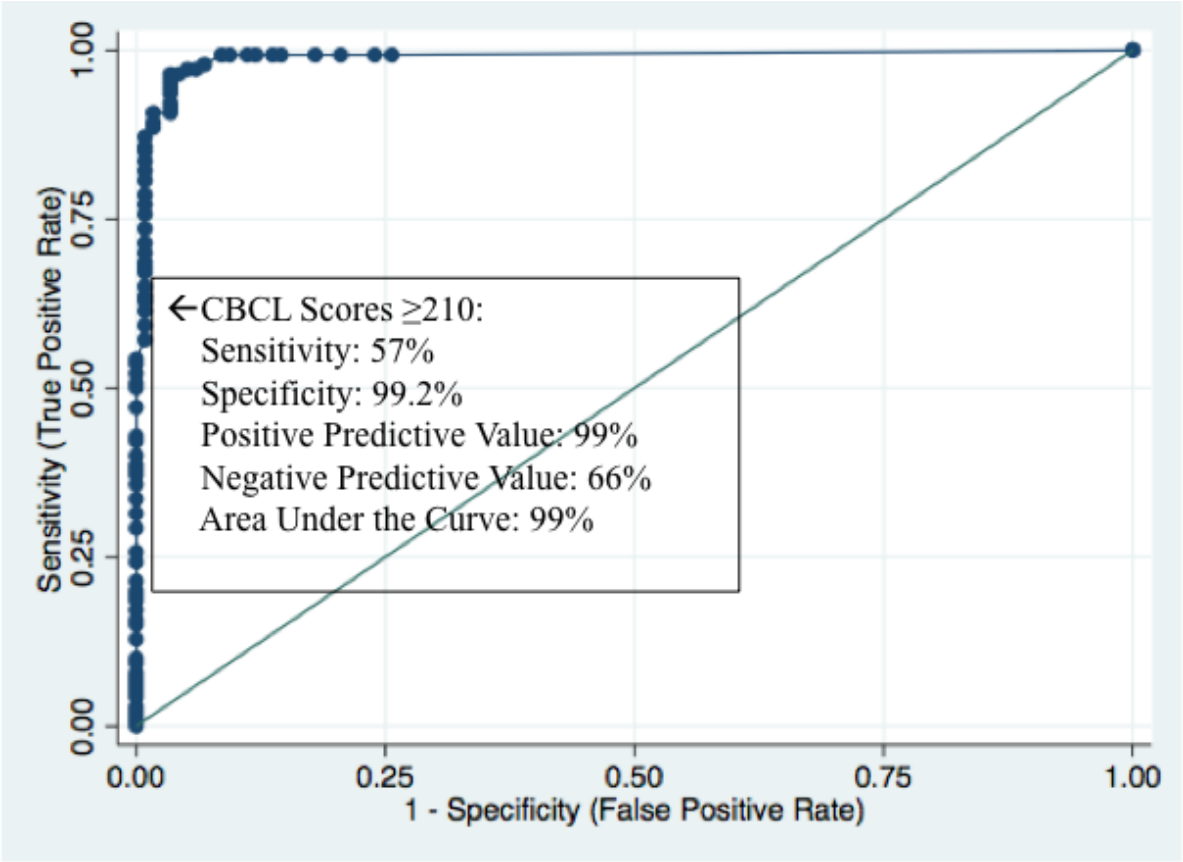
However No significant overall differences in parent CBCL report

Dutch Bipolar Offspring Study (N=136)

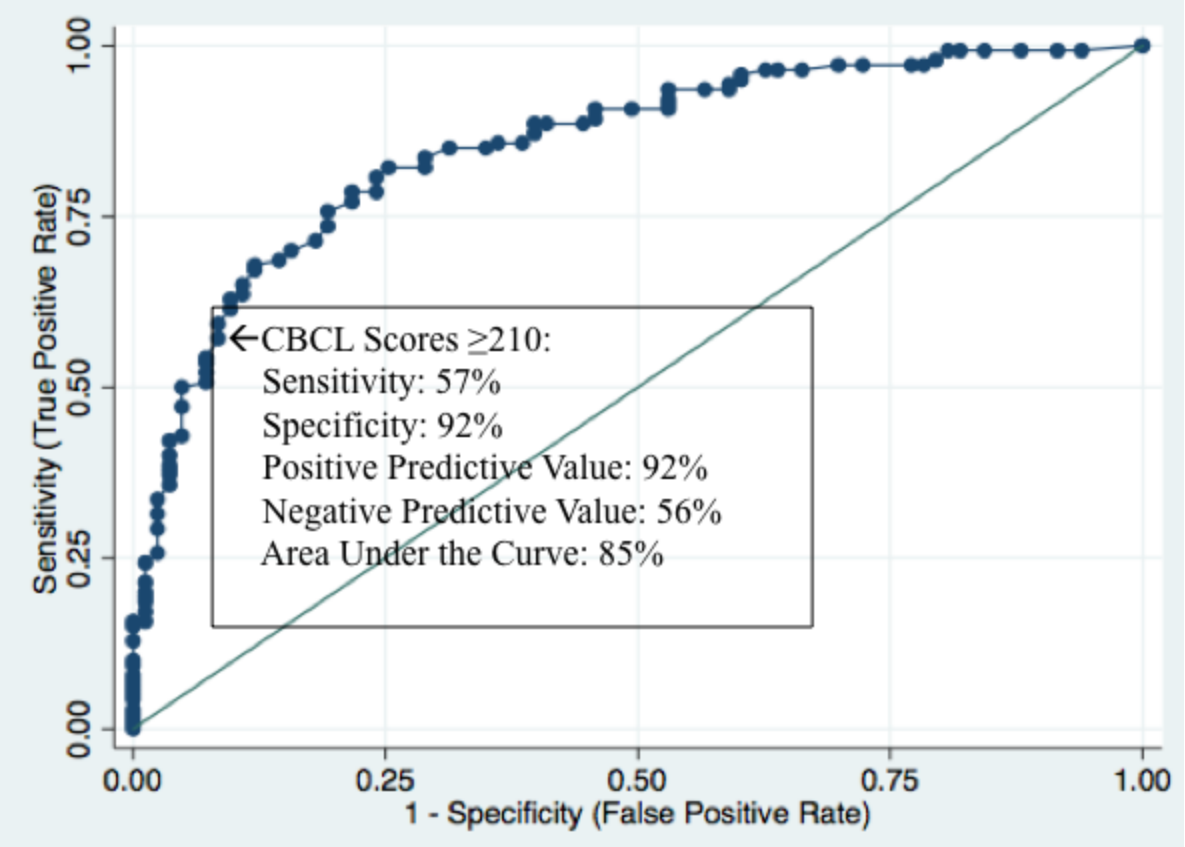
Pittsburgh Bipolar Offspring Study (N=224)

Mesman 2016

ROC analysis: BP-I probands & Controls



ROC analysis: BP-I probands & ADHD probands

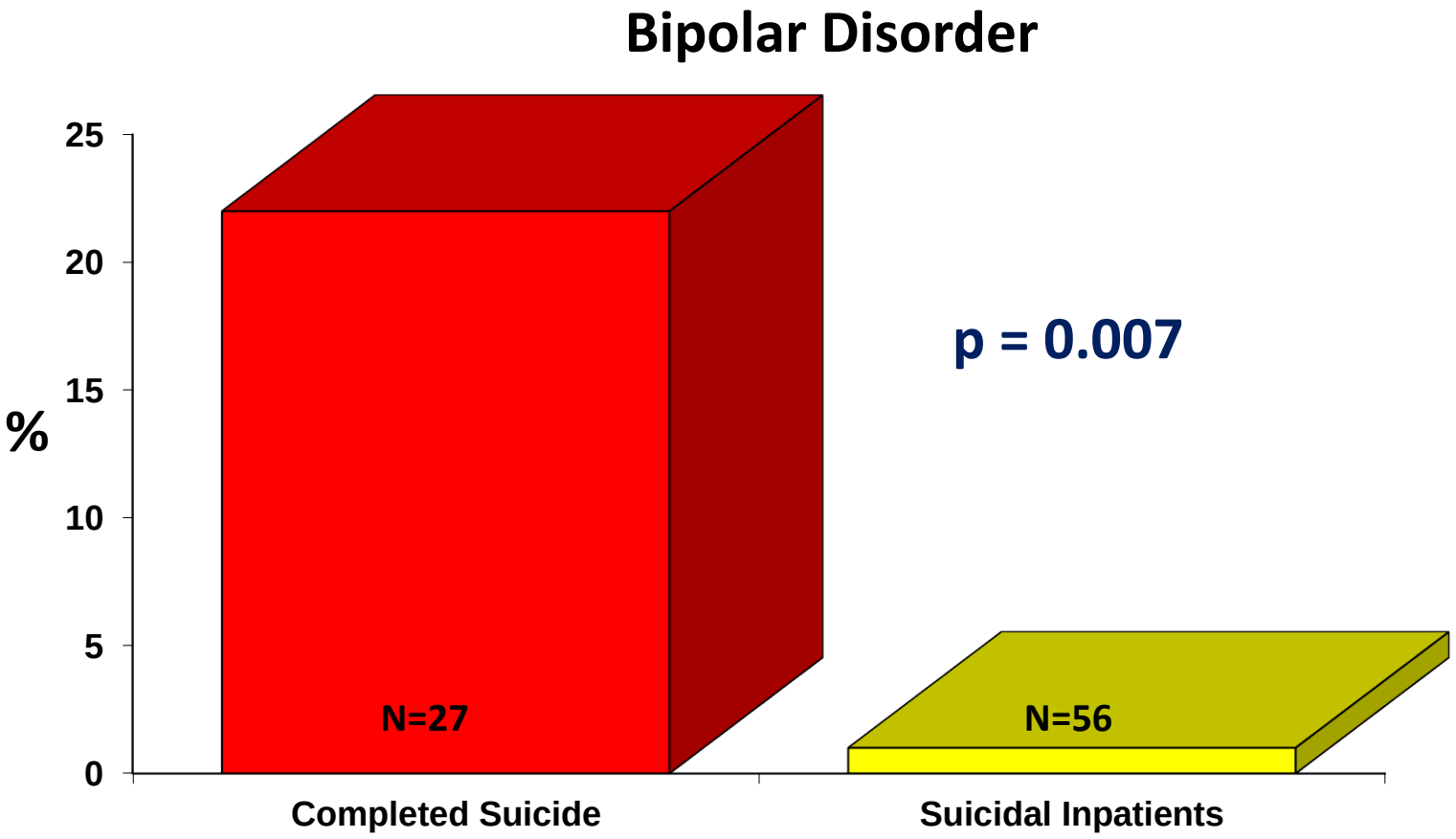


Does It Matter?

Risk for Completed Suicide

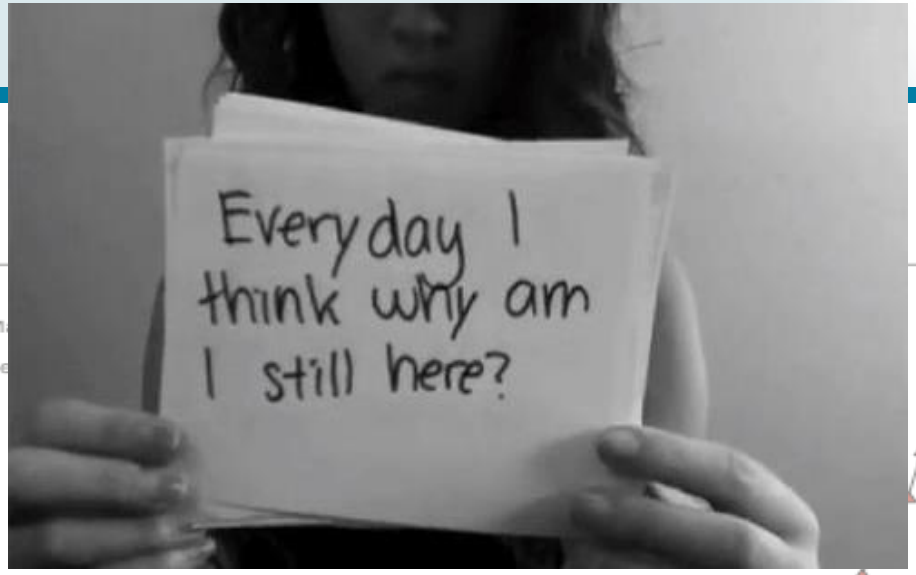
Risk Factors for Adolescent Suicide

Brent et al. AGP, 1988



20TH-CENTURY - CHANGES IN YOUTH SUICIDE RATES

— UNITED STATES, AGES 15–24 —



Bipolar adults with childhood and adolescent onset have more lifetime suicide attempts

Research

JAMA Psychiatry | Original Investigation

Association of Childhood Irritability and Depressive/Anxious Mood Profiles With Adolescent Suicidal Ideation and Attempts

Massimiliano Orri, PhD; Cedric Galera, MD, PhD; Gustavo Turecki, MD, PhD; Alberto Forte, MD; Johanne Renaud, MD, MSc, FRCPC; Michel Boivin, PhD; Richard E. Tremblay, PhD; Sylvana M. Côté, PhD; Marie-Claude Geoffroy, PhD

Supplemental content

IMPORTANCE Suicidal ideation and suicide attempt (suicidality) are common in adolescence and a public health concern. Childhood depression is a key risk factor for later suicidality and often co-occurs with irritability. No study to date has examined the joint association of depressive mood and irritability during childhood with later suicidality.

CONCLUSIONS AND RELEVANCE Children with high irritability and depressive/anxious mood and, to a lesser extent, with moderate irritability only had a higher suicidal risk during adolescence compared with children with low symptom levels. Early manifestation of chronic irritability during childhood, especially when combined with depressive/anxious mood, may be associated with an elevated risk for adolescent suicidality. The putatively causal role of irritability should be investigated.

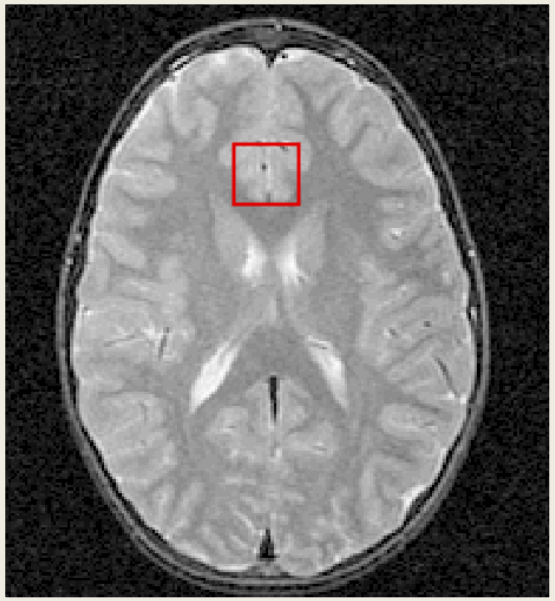
mood were assessed using teacher report 5 times from 6 to 12 years of age.

Orri et al. *JAMA Psychiatry*. 2018;75(5):465-473.

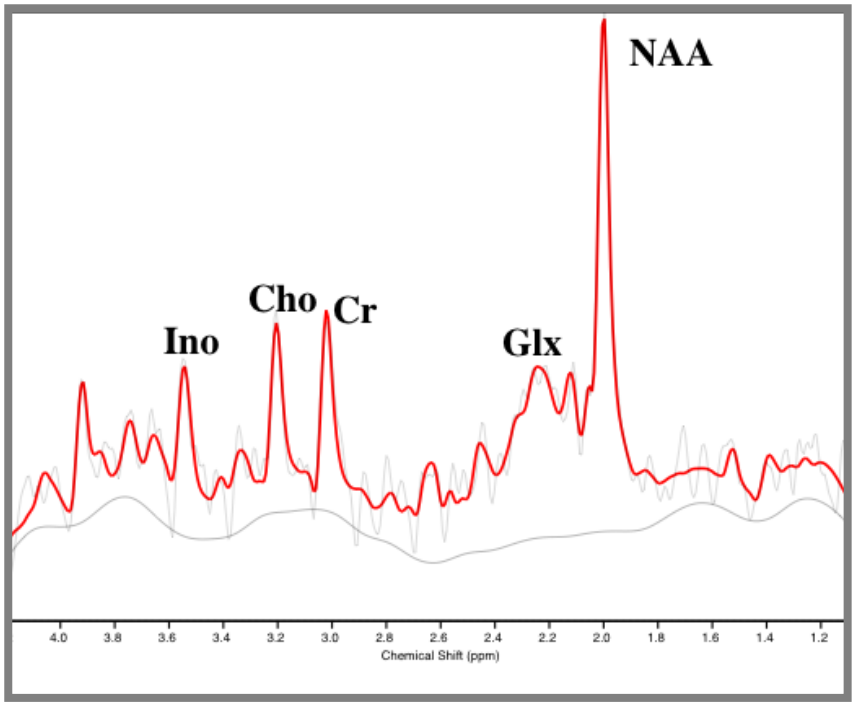
Does Pediatric BP Disorder have Unique Biomarkers?

Risk for Completed Suicide

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

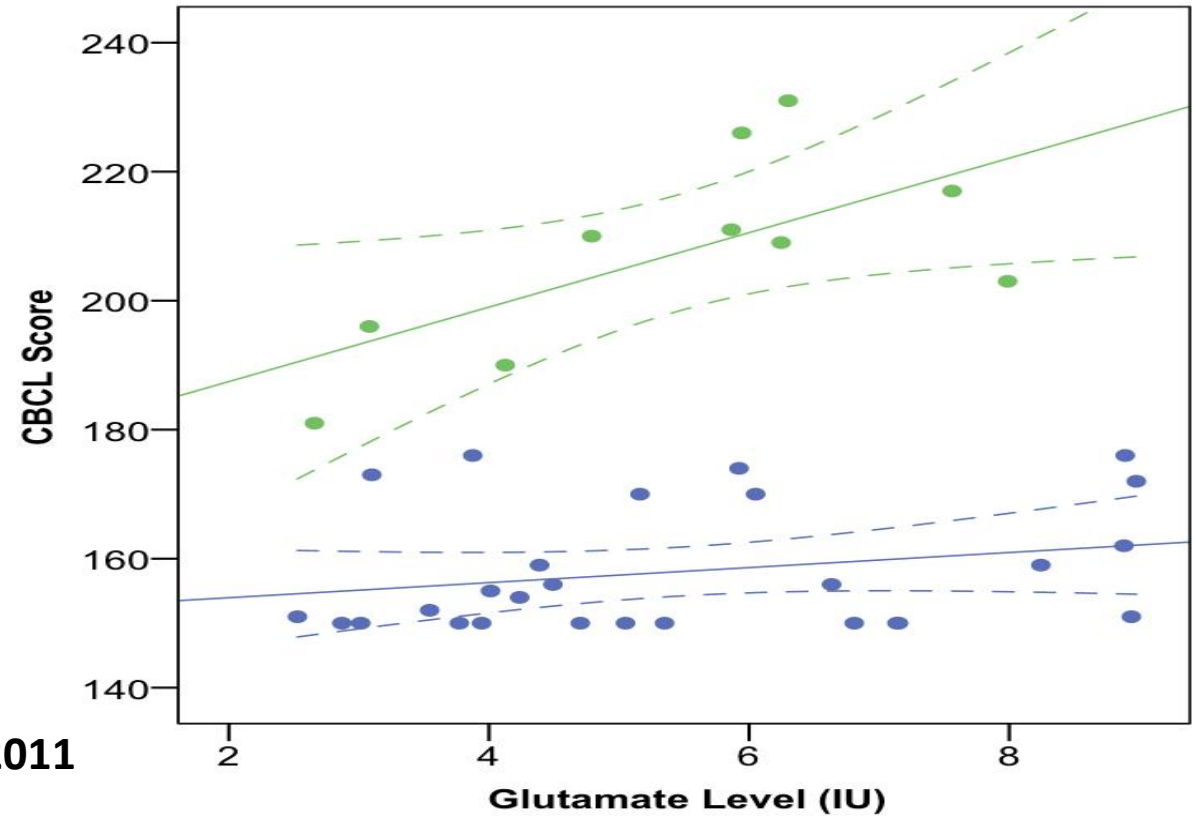


Ino: myo-Inositol
Cho: choline
Cr: creatine
Glx: glutamate and glutamine
NAA: N-acetyl aspartate



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

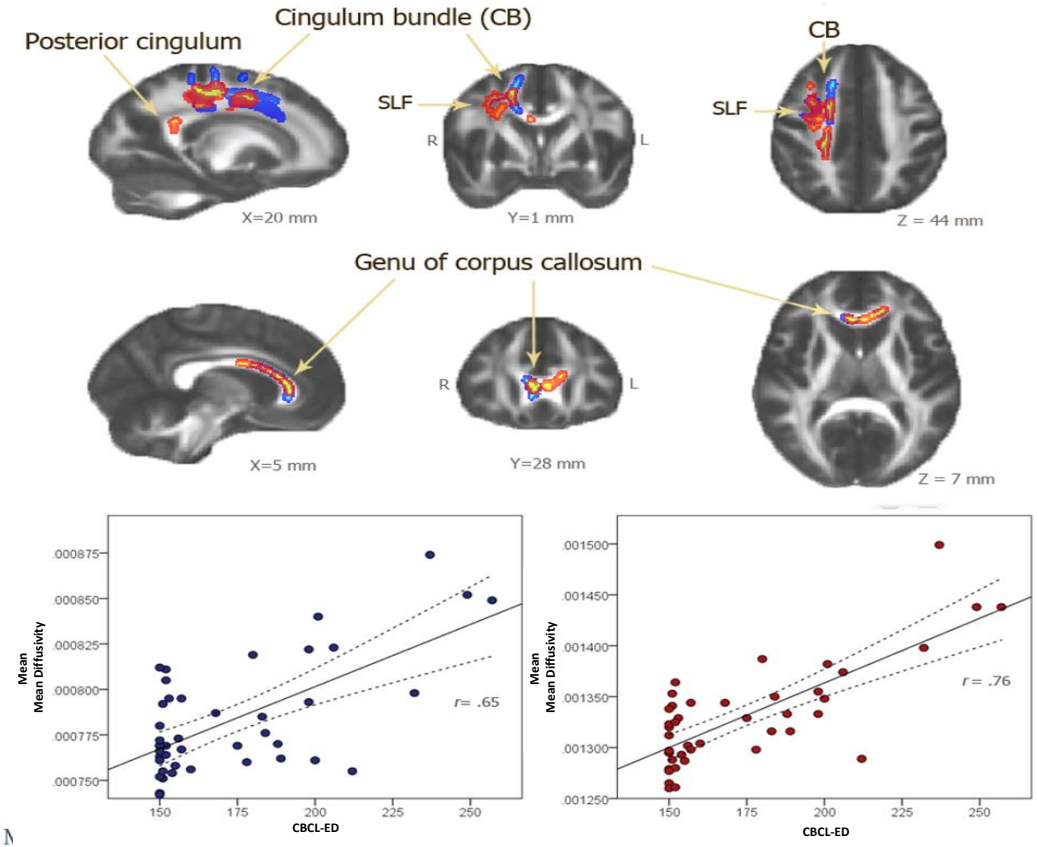
CBCL Scores vs Glutamate levels



Wozniak et al. 2011

Solid lines represent the linear fits to the low score group data (blue) and high score group data (green). Dashed lines represent 95% confidence intervals.

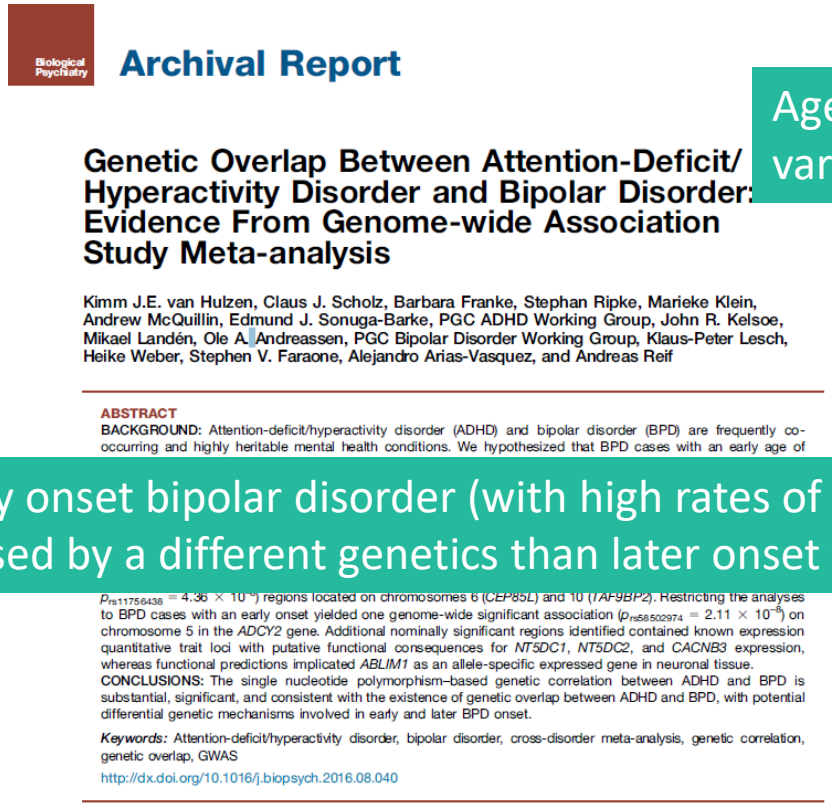
Significant Correlations Between CBCL-ED Score & Mean and Axial Diffusivity Surrounding the Cingulum Bundle



- Track-Based Spatial Statistics (TBSS) using voxelwise analysis showed a significant positive correlation between the CBCL-ED score and median diffusivity (MD; $p < 0.05$) and axial diffusivity (AD; $p < .05$,) overlapping in cingulum bundle areas, the genu of the corpus callosum, and the superior longitudinal fasciculus (SLF).

- Findings indicate that greater severity the emotional dysregulation as indexed through the CBCL-ED profile is associated with more impaired matter abnormalities in the cingulum bundle areas as indexed through mean diffusivity and axial diffusivity values.

Converging evidence from GWAS supports the notion that BP + ADHD is an early onset genetic subtype of either BP disorder or ADHD



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

$P_{rs11756438} = 4.36 \times 10^{-8}$) 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 ($p_{rs6502974} = 2.11 \times 10^{-8}$) 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 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

Age of onset is one source of the variance in what we call 'bipolar'

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

van Hulzen BiolPsych 2017

Biological Psychiatry

Archival Report

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

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.

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

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.

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.

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

Van Hulzen et al. *Biol Psychiatry* 2017.

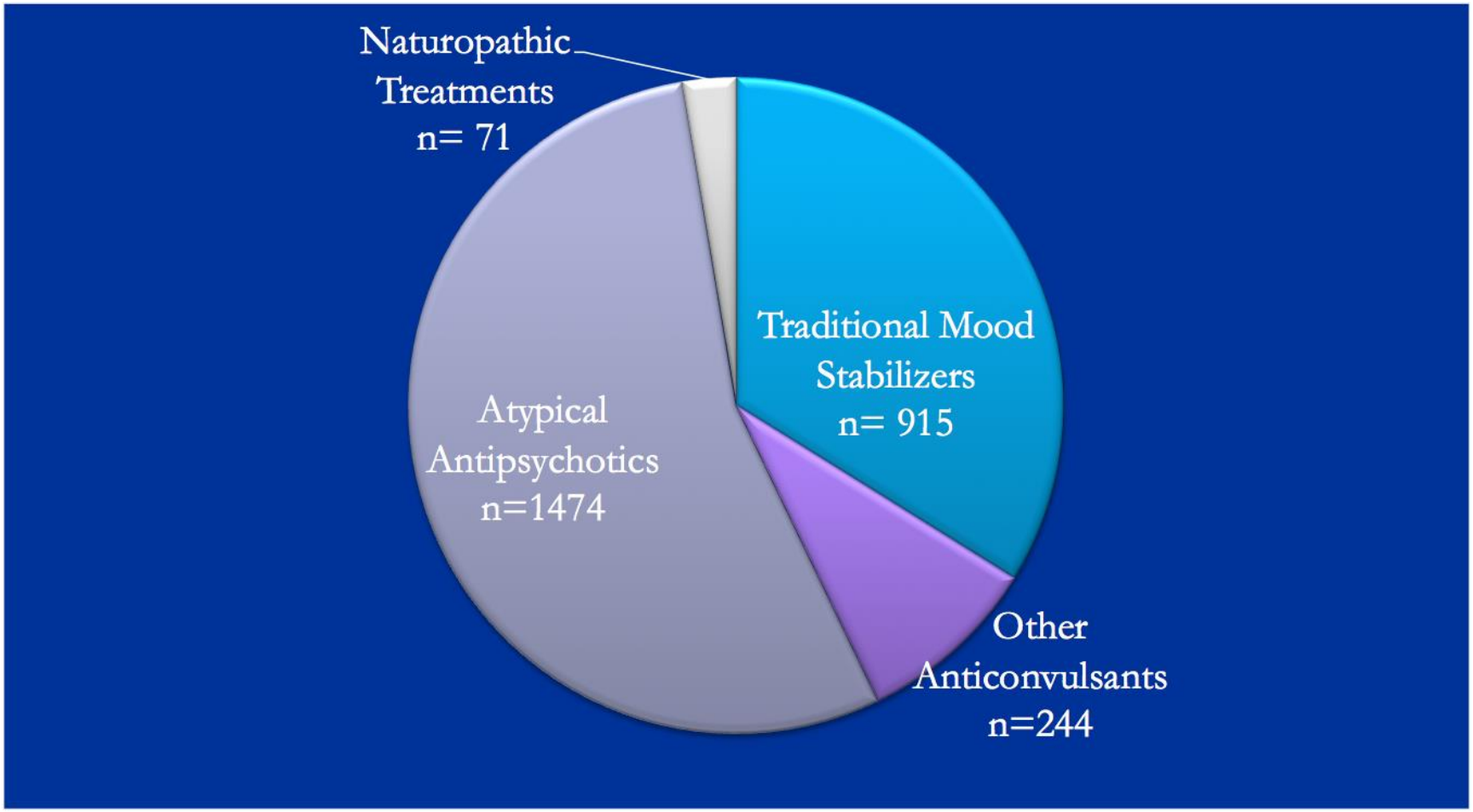
Unique Treatment Responsivity

Risk for Completed Suicide

FDA approved treatments for youth with BP Disorder

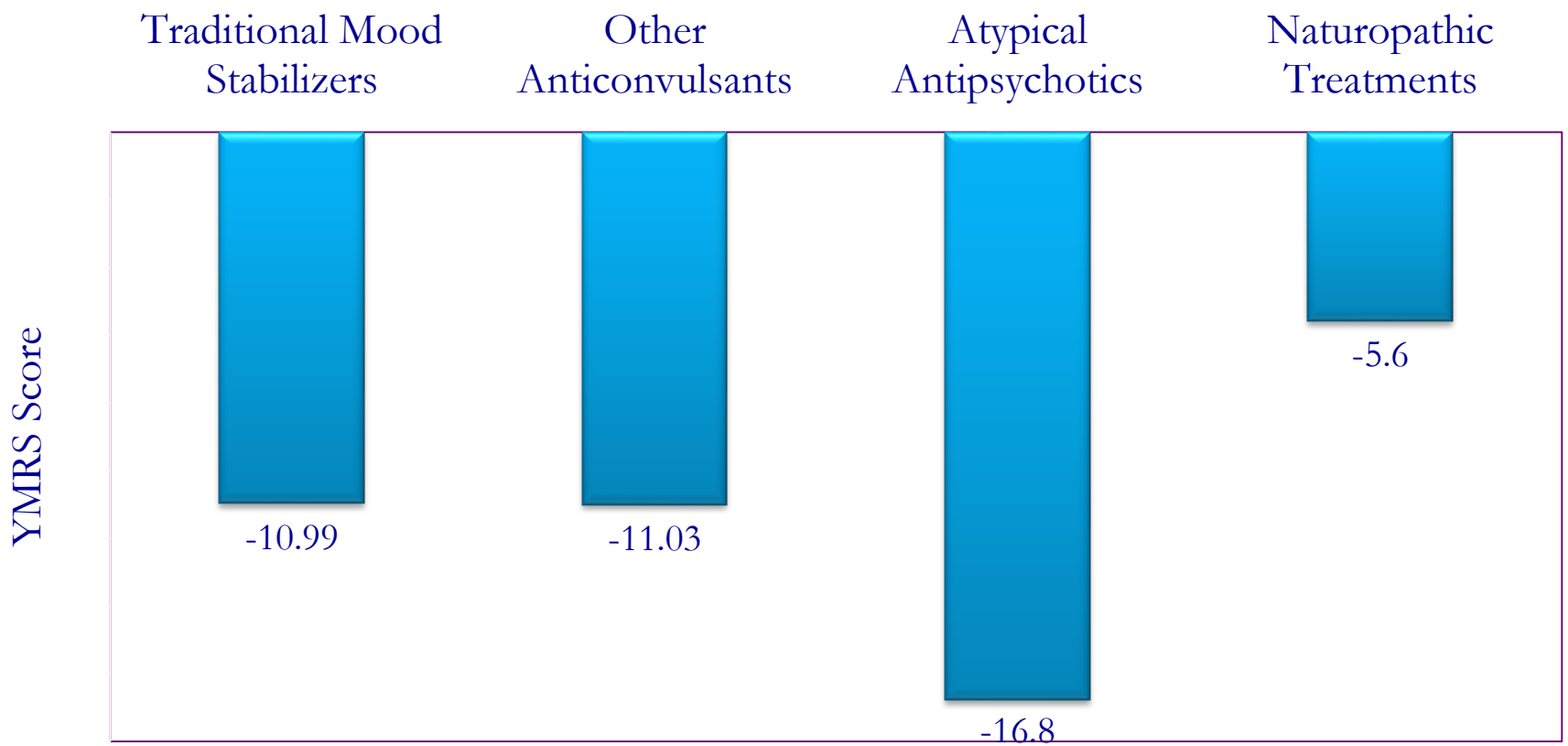
- Lithium: manic or mixed states, patients age 13-17
- Risperidone: manic or mixed states, age 10-17
- Aripiprazole: manic or mixed states, age 10-17
- Olanzapine: manic or mixed states, age 13-17
- Quetiapine: monotherapy or adjunct to lithium or divalproex sodium, manic states, age 10-17
- Asenapine manic or mixed episodes in BP-I, age 10-17
- Aripiprazole: irritability associated with autistic disorder age 6-17
- Risperidone: irritability associated with autism age 5-16

Large number of Youth participated in pediatric BP trials

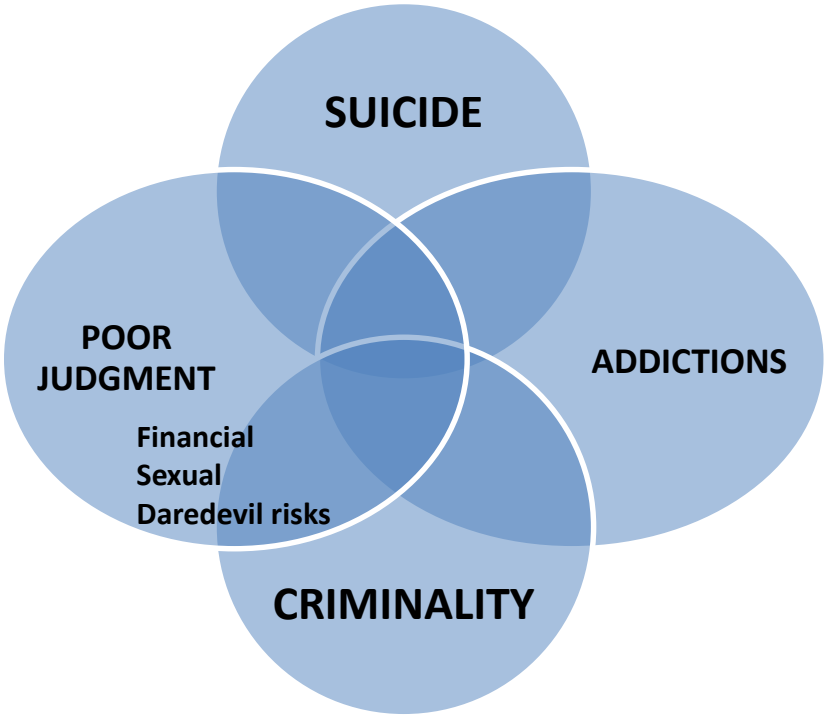


J Am Acad Child Adolesc Psychiatry, 2011;50(8):749-762.

The mean change in YMRS is much greater for the SGA's than for other agents



The risk-benefit analysis of treatment must include the risks associated with not treating Pediatric BP Disorder



Delaying treatment OFTEN leads to poor outcomes

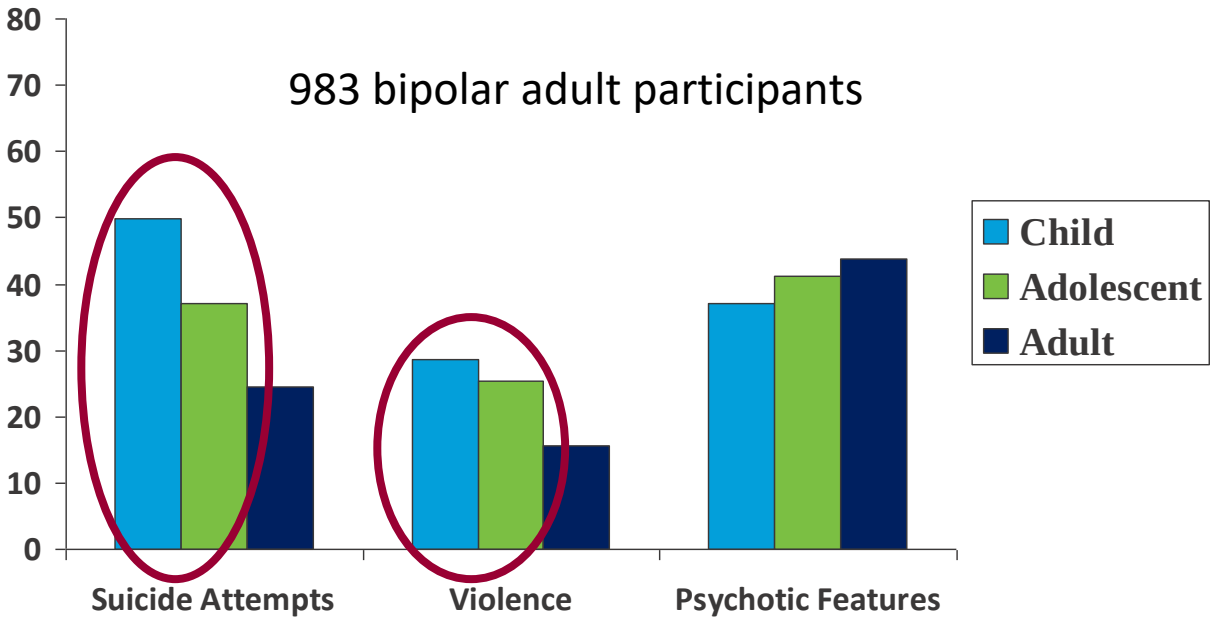
ultradian cycling, and fewer days euthymic (all $P < .05$).

Conclusions: These data converge with other evidence that onset of bipolar disorder in childhood is common and often associated with extraordinarily long delays to first pharmacologic treatment. Both childhood onset and treatment delay were associated with a persistently more adverse course of illness, respectively in adults. These data should help foster efforts to ensure earlier and more effective treatment of bipolar illness in children and adolescents. It is hoped that appropriate early intervention would result in a more benign illness and a better prognosis in adulthood.

J Clin Psychiatry 2010;71(7):864–872

Post, Leverich 2010

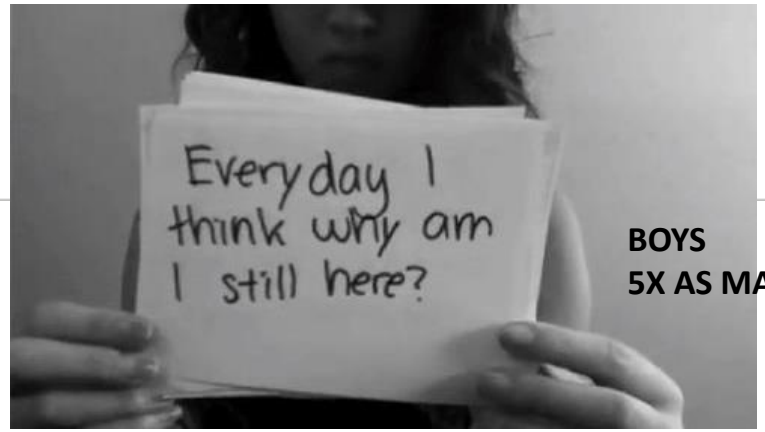
Not treating is not an option due to the severity of symptoms associated with early onset bipolar disorder



Perlis, Biol Psych 2004;55:875-881

20TH-CENTURY - RISING RATE OF SUICIDE IN YOUTH

UNITED STATES, AGES 15–24



BP adults with pediatric onset have more lifetime suicide attempts

SGAs are a robust treatment for adults with BP disorder

Atypical Antipsychotics in the Treatment of Mania: A Meta-Analysis of Randomized, Placebo-Controlled Trials

Roy H. Perlis, M.D.; Jeffrey A. Welge, Ph.D.; Lana A. Vornik, M.S.; Robert M. A. Hirschfeld, M.D.; and Paul E. Keck, Jr., M.D.

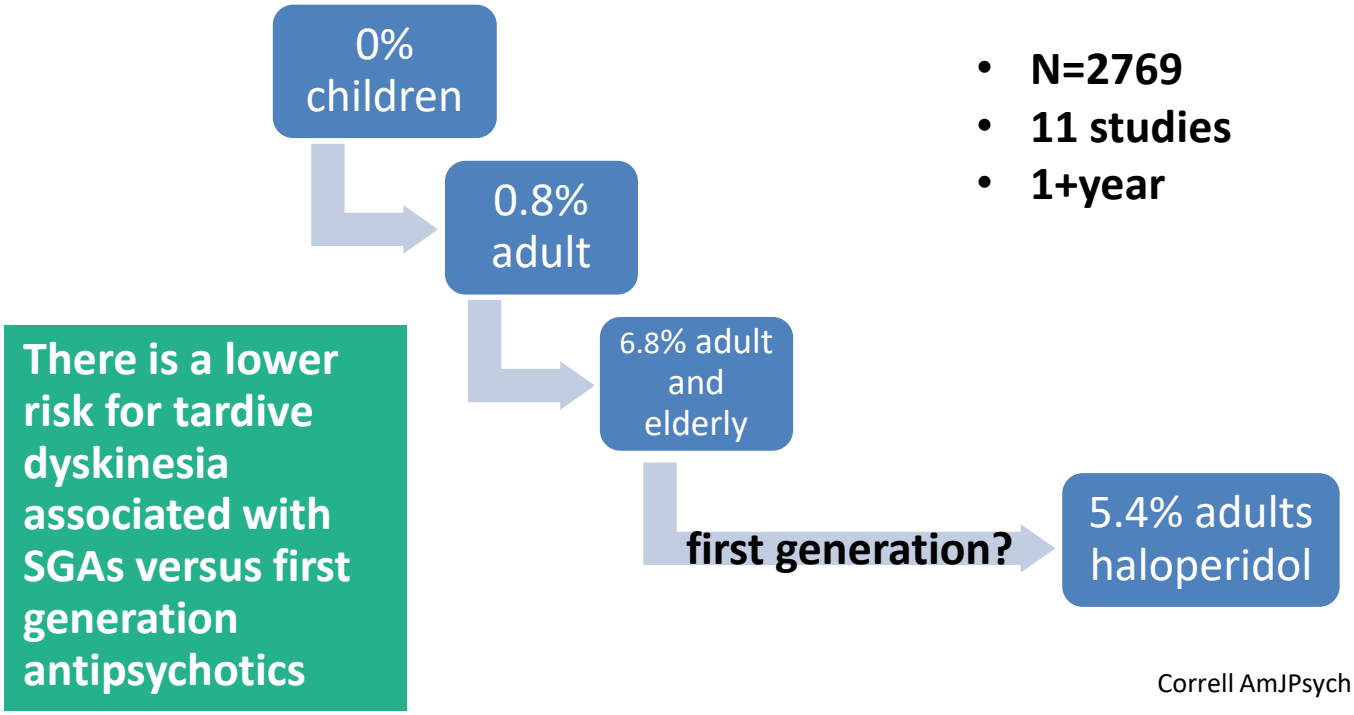
Data Synthesis: Data from 12 placebo-controlled monotherapy and 6 placebo-controlled adjunctive therapy trials involving a total of 4 ing 1750 placebo-treated subjects) with bipolar mania were obtained. Aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone all demonstrated significant efficacy in monotherapy (i.e., all confidence intervals exclude zero). However, after adjusting for multiple comparisons, pairwise comparisons of individual effects identified no significant differences in efficacy among antipsychotics. Magnitude of improvement was similar whether the antipsychotic was utilized as monotherapy or adjunctive therapy.

SGA=second generation antipsychotic

Perlis J Clin Psychiatry 2006; 64(4):509-516

Tardive dyskinesia is a dreaded complication of TX with SGAs, but children at low risk (although data limited by small sample sizes, low doses and limited durations)

The weighted mean annual incidence of tardive dyskinesia for second generation antipsychotics (SGA):

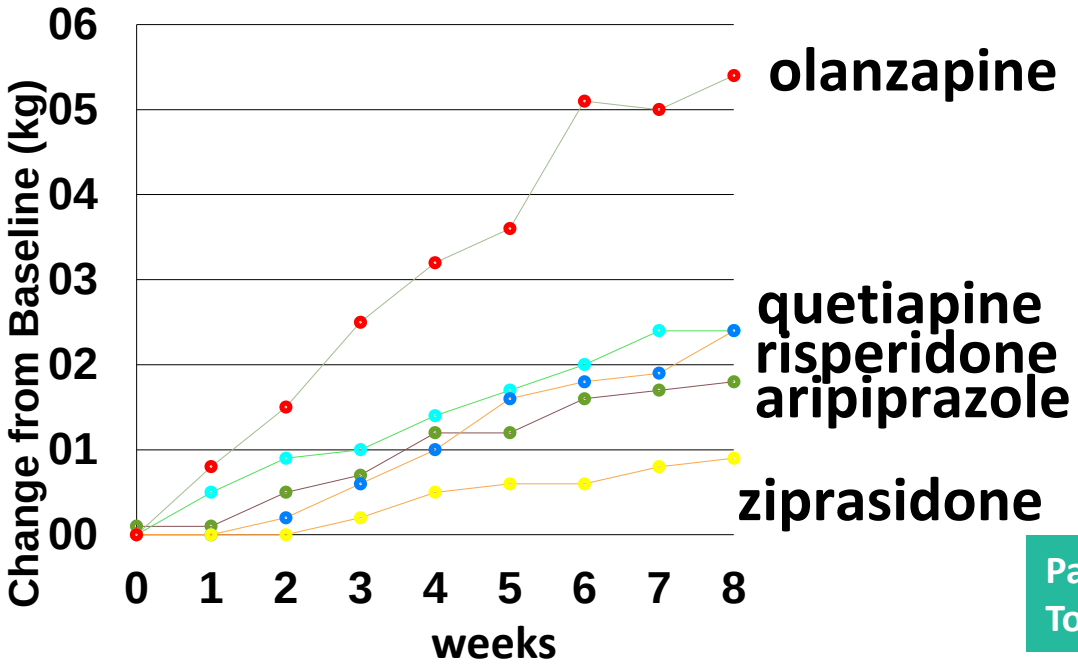


- **N=2769**
- **11 studies**
- **1+year**

Correll AmJPsych 2004

Unfortunately, weight gain is very common: Data from 8-week open label trials of SGA monotherapy in children with BP disorder

SGA=second generation antipsychotic

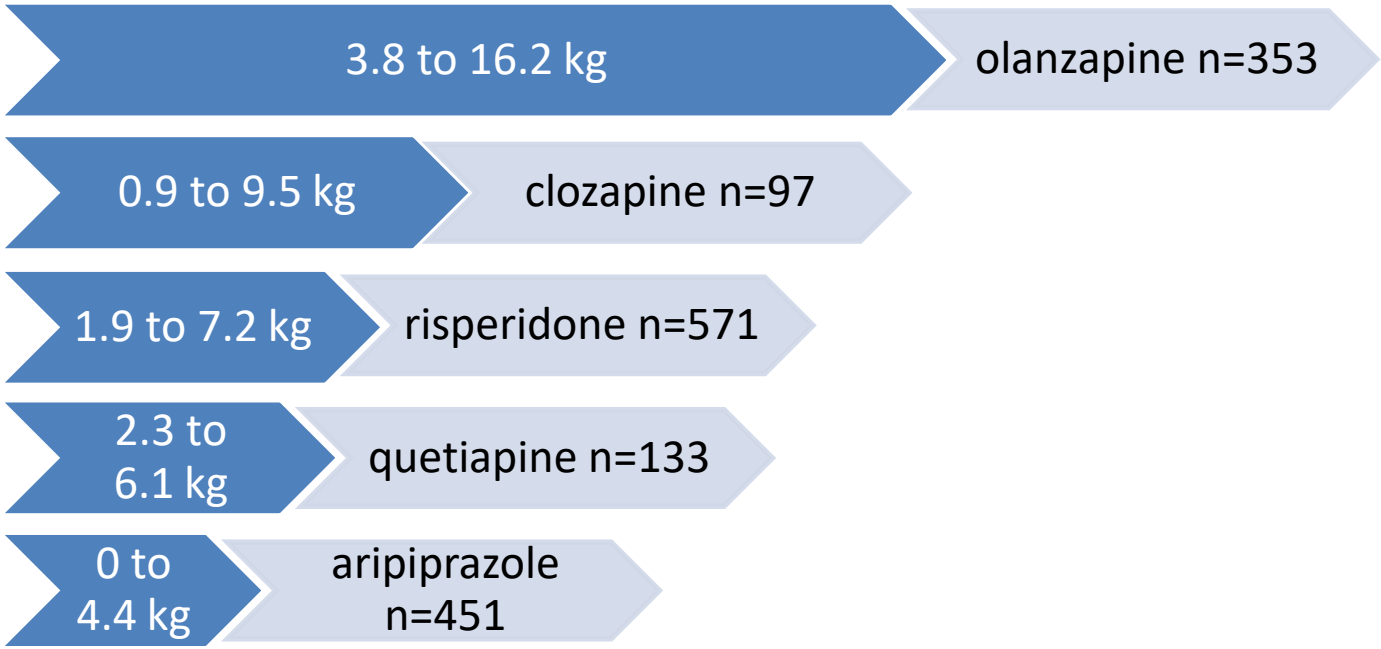


Parallel trials
Total N=116

Biederman 2007 AACAP Boston

Weight gain associated with SGA medications in Youth: Data from 34 studies

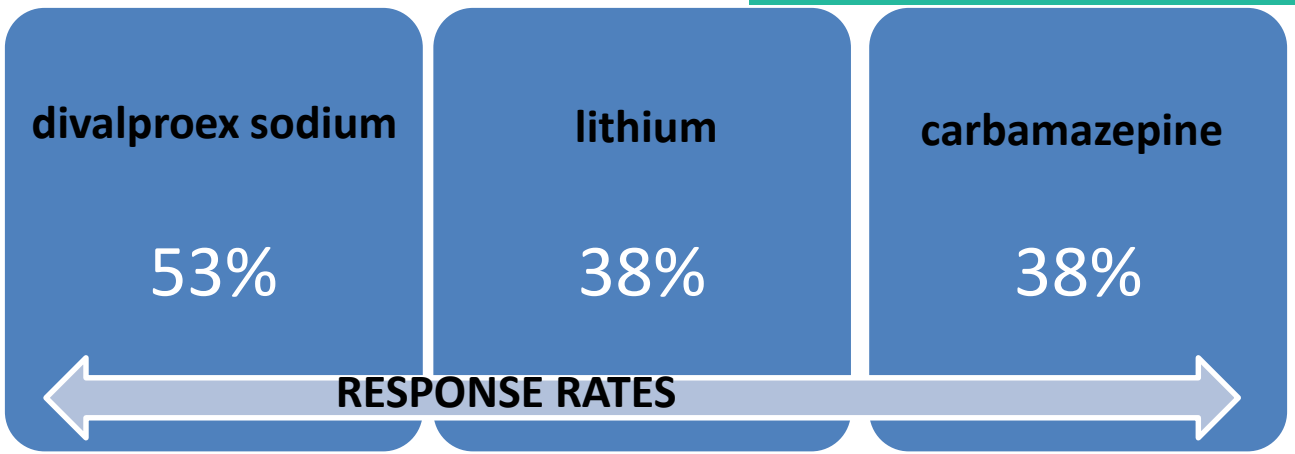
SGA=second generation antipsychotic



Correll JChildAdolescPsychopharm 2011

Lithium, divalproex sodium, carbamazepine are used for pediatric BP disorder bu they are not as effective than SGAs and can have serious AEs

SGA=second generation antipsychotic



Trials notable for:

- high drop out rates
- need for rescue medications

Kowatch JAACAP 2000

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

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

Robert L. Findling, MD, MBA[a], Adelaide Robb, MD[b], Nora K. McNamara, MD[c], Mani N. Pavuluri, MD, PhD[d], Vivian Kafantaris, MD[e], Russell Scheffer, MD[f], Jean A. Frazier, MD[g], Moira Rynn, MD[h], Melissa DelBello, MD[i], Robert A. Kowatch, MD, PhD[j], Brieana M. Rowles, MA[k], Jacqui Lingler, BS[c], Karen Martz, MS[l], Ravinder Anand, PhD[l], Traci E. Clemons, PhD[l], Perdita Taylor-Zapata, MD[m]

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) versus placebo (n = 28) for up to 8 weeks. The a priori primary efficacy measure was change

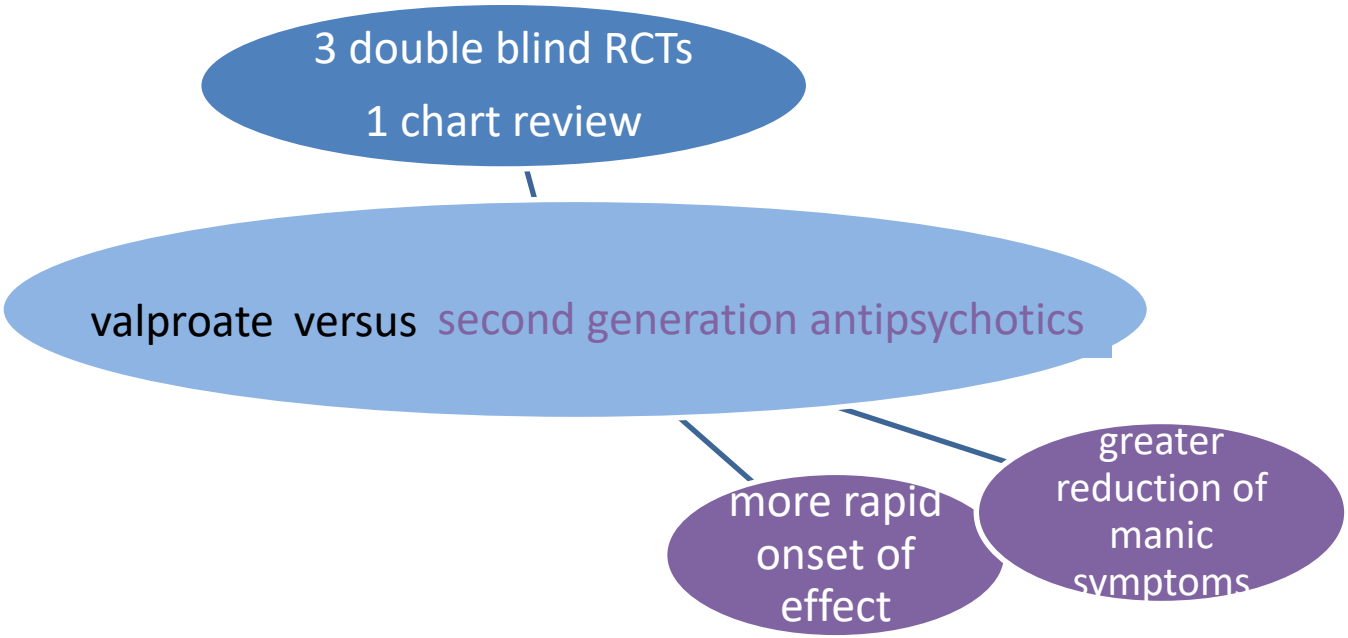
47% lithium vs 21% placebo "much/very much improved"

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). A statistically significant increase in thyrotropin concentration was seen with lithium

Findling Pediatrics 2015

SGAs perform better than valproate for pediatric BP disorder

SGA=second generation antipsychotic



Chen 2014

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

SGA=second generation antipsychotic

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

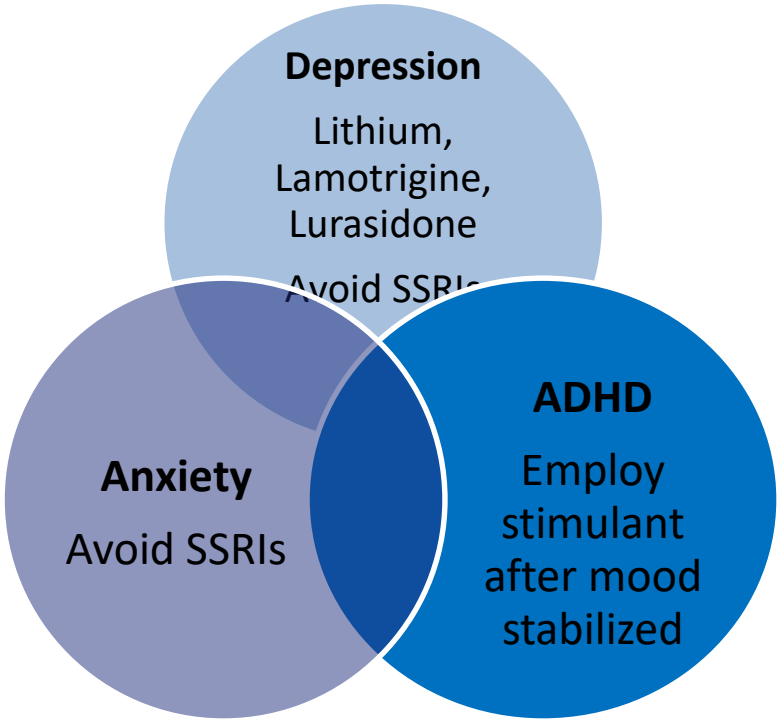
Patients who initiated on SGA were less likely to discontinue the treatment

Patients who initiated on SGA were less likely to receive treatment augmentation

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

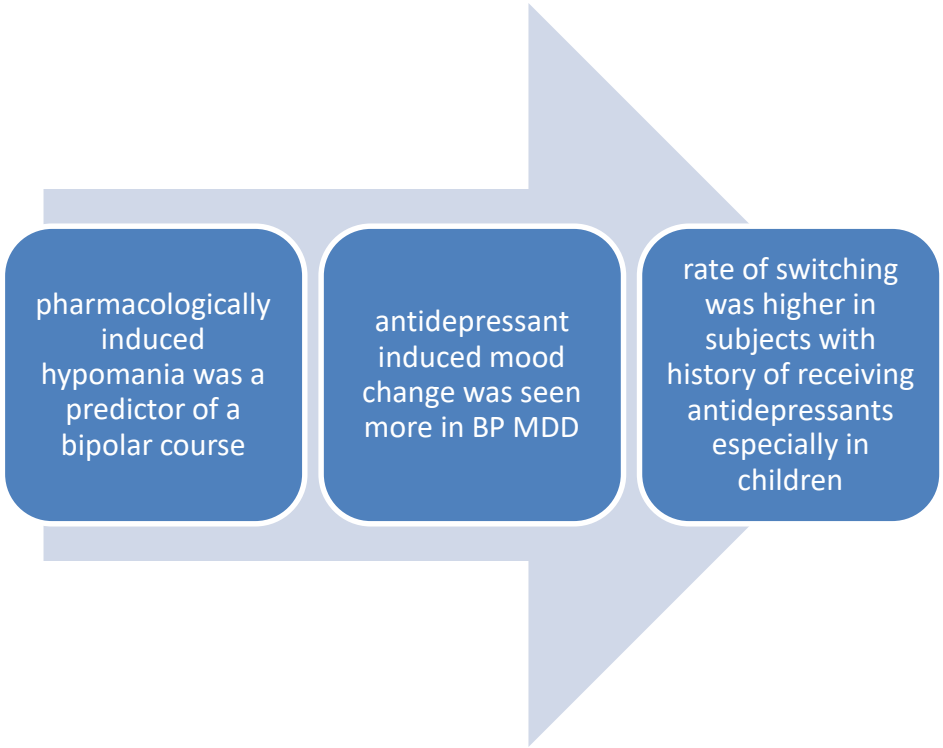
Chen 2014

Comorbidity must be addressed in the management of pediatric BP disorder



Joshi
2009

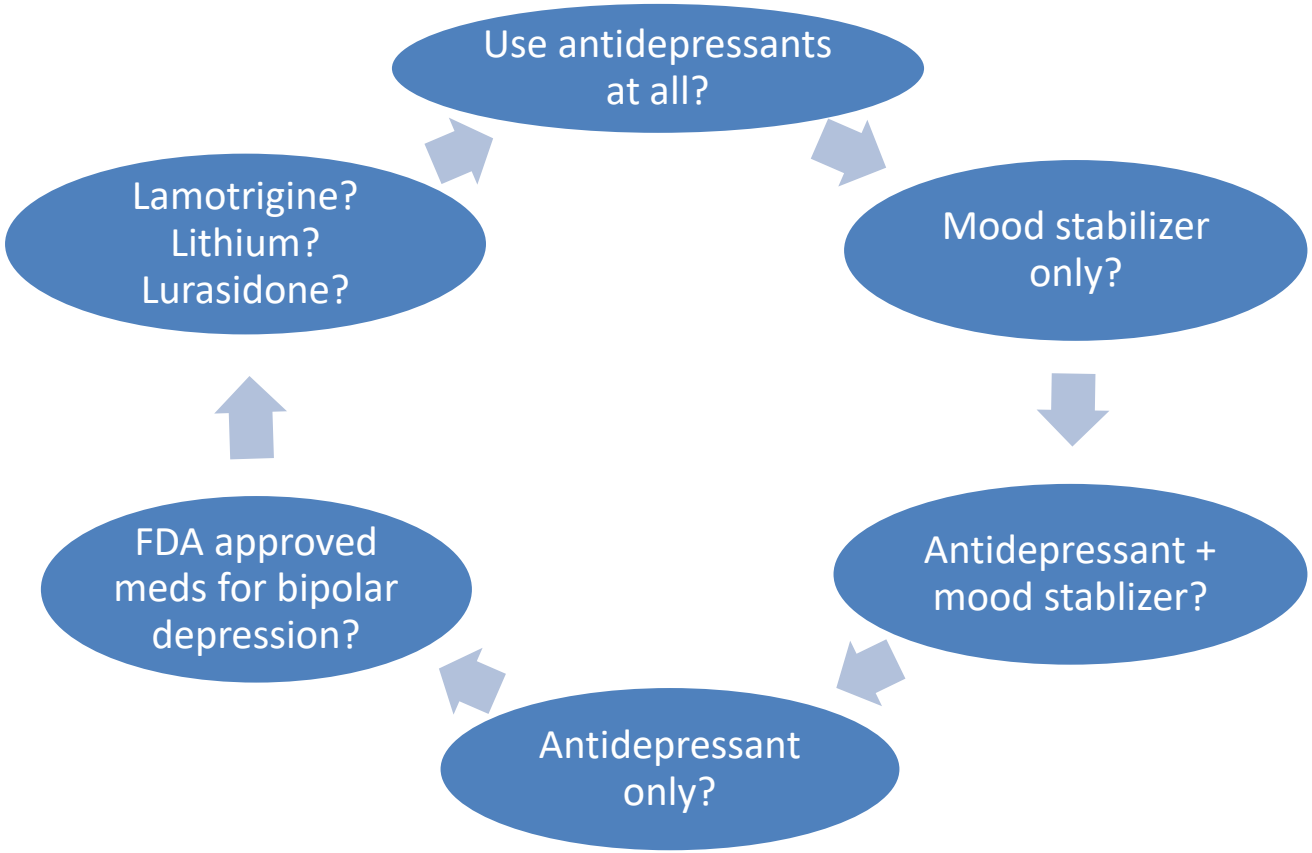
Antidepressants have a high risk for manic switching…….



ANTI-DEPRESSANTS

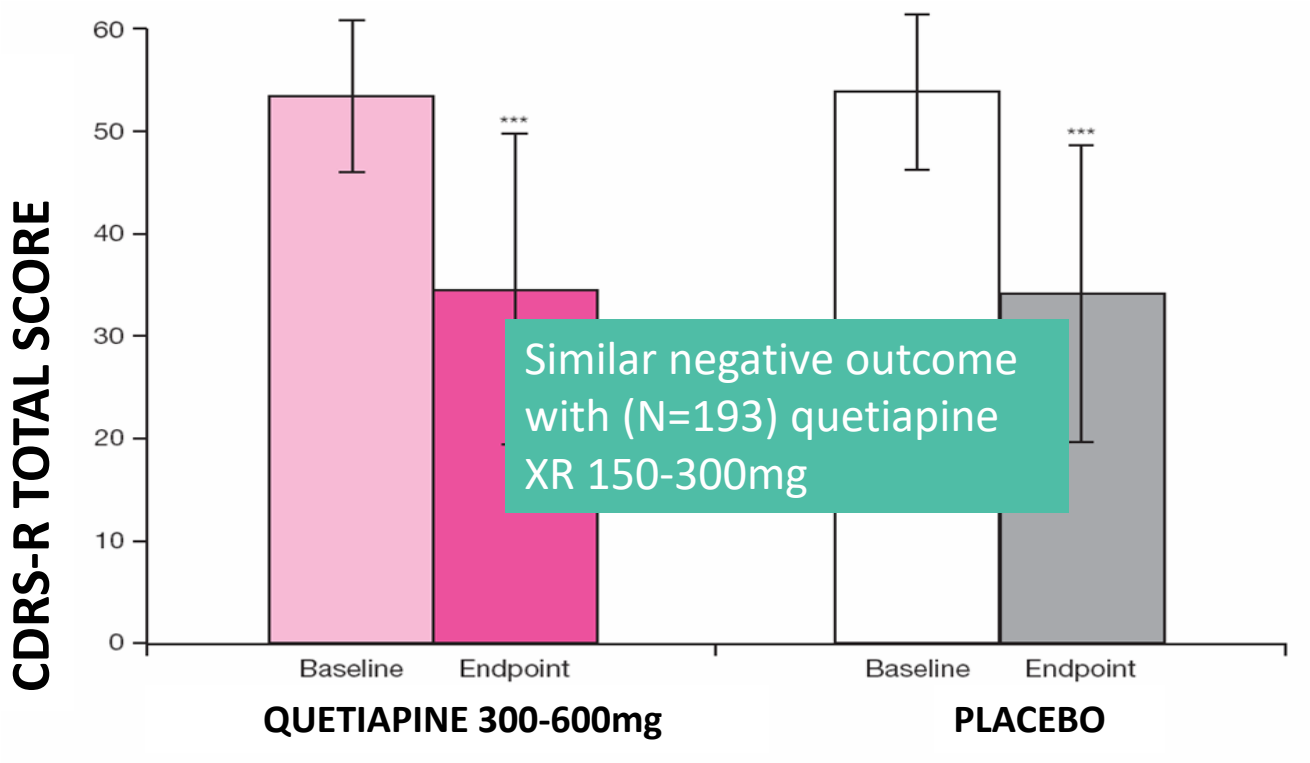
Strober; Shon; Martin

Pharmacologic management of pediatric BP depression is very difficult



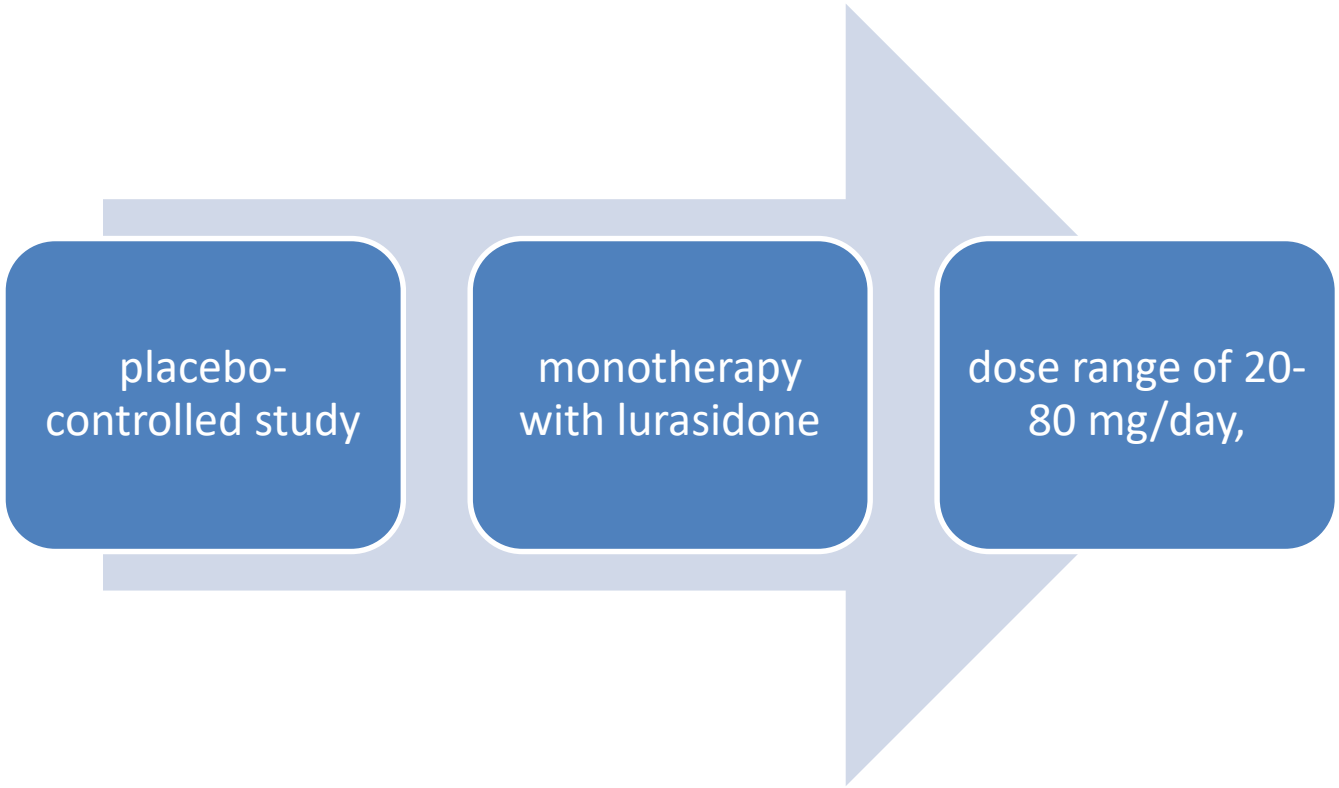
Quetiapine was not effective in adolescent BP depression, although the placebo response was very high

MEAN (SD) CHANGE IN CDRS-R SCORES FROM BASELINE TO ENDPOINT (8 weeks; N=32)



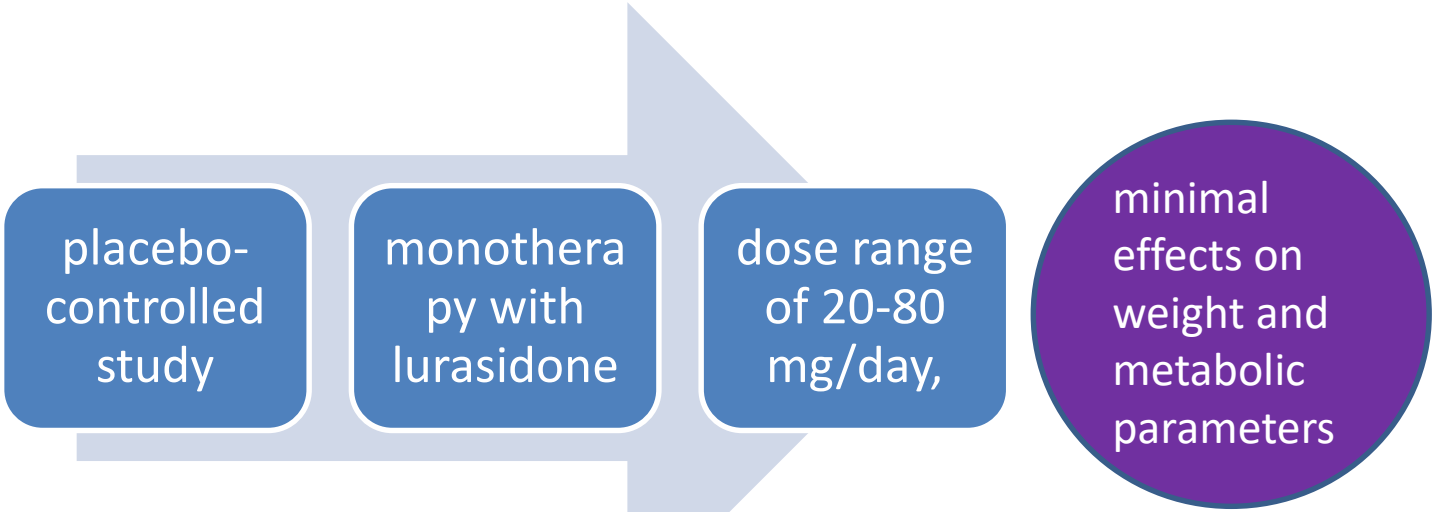
DelBello 2009; Findling 2014

Lurasidone significantly reduced depressive symptoms in youth with BP Depression



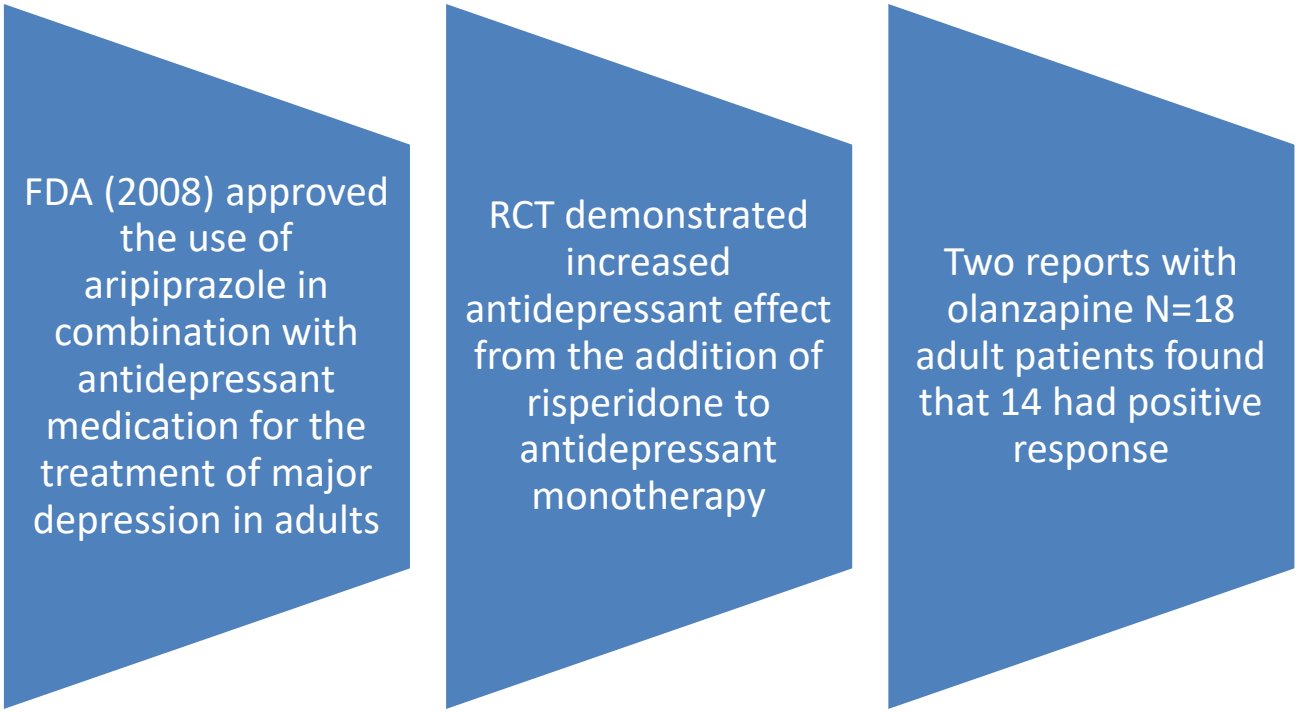
DelBello JAACAP 2017

Lurasidone significantly reduced depressive symptoms in youth with BP Depression



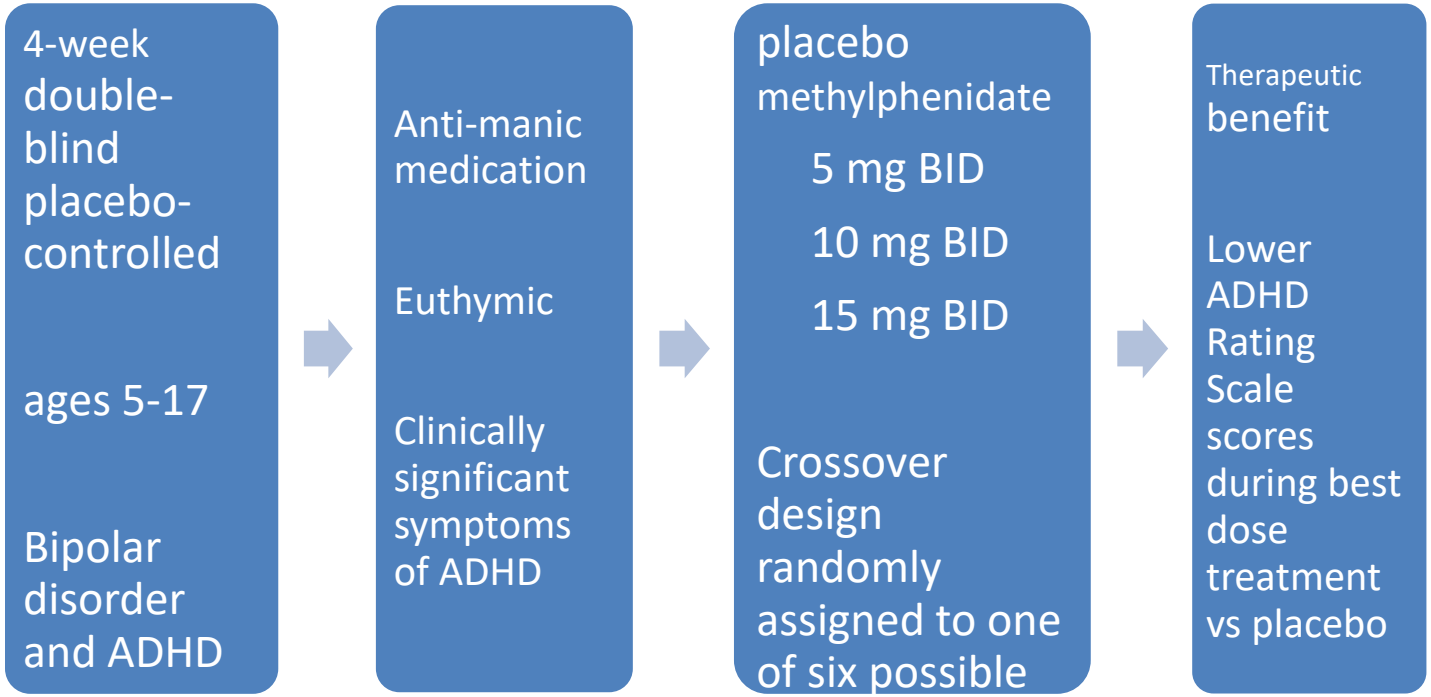
DelBello JAACAP 2017

SGAs have antidepressant qualities



Zarate 1998; Rothschild 1999; Mahmoud 2007

Euthymic youths with bipolar disorder and ADHD may benefit from concomitant treatment with stimulants



Findling 2007

Treatment for bipolar disorder involves antipsychotic medications with side effects, fueling reluctance to diagnose

Journal List › Prim Care Companion CNS Disord › v.16(2); 2014 › PMC4116292

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Prim Care Companion CNS Disord. 2014; 16(2): PCC.13r01599. PMCID: PMC4116292
Published online 2014 Apr 17. doi: 10.4088/PCC.13r01599

Mixed Specifier for Bipolar Mania and Depression: Highlights of *DSM-5* Changes and Implications for Diagnosis and Treatment in Primary Care

Jia Hu, MD, Rodrigo Mansur, MD, and Roger S. McIntyre, MD

Author information ▶ Article notes ▶ Copyright and License information ▶

Abstract Go to:

Bipolar disorder, while commonly encountered in the primary care setting, is often misdiagnosed or undiagnosed. In the *DSM-IV-TR*, patients could be diagnosed as being in a mixed state only if they had concurrent manic and depressive symptoms; while this occurs in some patients, many more experience subsyndromal mixed symptoms that would disqualify a "mixed state" diagnosis. The recently released

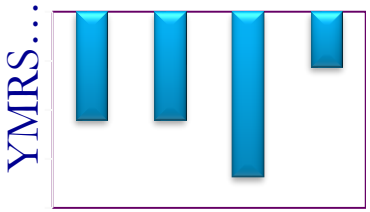
reuptake inhibitors remain first-line therapy, but augmentation with other therapies is often required. If a diagnosis of bipolar disorder is confirmed and the patient is experiencing a depressive phase, traditional antidepressants should be avoided. For those presenting with mania and mixed depressive symptoms, treatment with a combination of atypical antipsychotics and mood stabilizers is best.

Clinical Points

Traditional antidepressants should be avoided … treatment with a combination of atypical antipsychotics and mood stabilizers is best

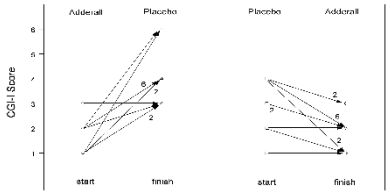
Overview: Pediatric Bipolar disorder is a highly morbid condition that usually requires pharmacologic treatment due to severity of illness. SGA's are the first line of treatment and comorbid conditions usually must be addressed.

Severity: Pediatric Bipolar Disorder is associated with suicidality, substance addiction and conduct disorder



Treatment: Pharmacologic treatment is generally required and SGAs are the first line of treatment

Comorbid Conditions: ADHD and depression and anxiety can be treated by sequencing appropriate treatments after the mania is stabilized



What questions would you like to ask?

Summary

- Pediatric BP is a prevalent and highly morbid disorder
- Strong evidence for validity
- High rates of comorbidity with MDD, ADHD, ODD and Anxiety disorders
- SGAs are the most effective treatments for mania
- Antidepressants should be avoided

Questions?