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Family Genetics of Pediatric Bipolar Disorder

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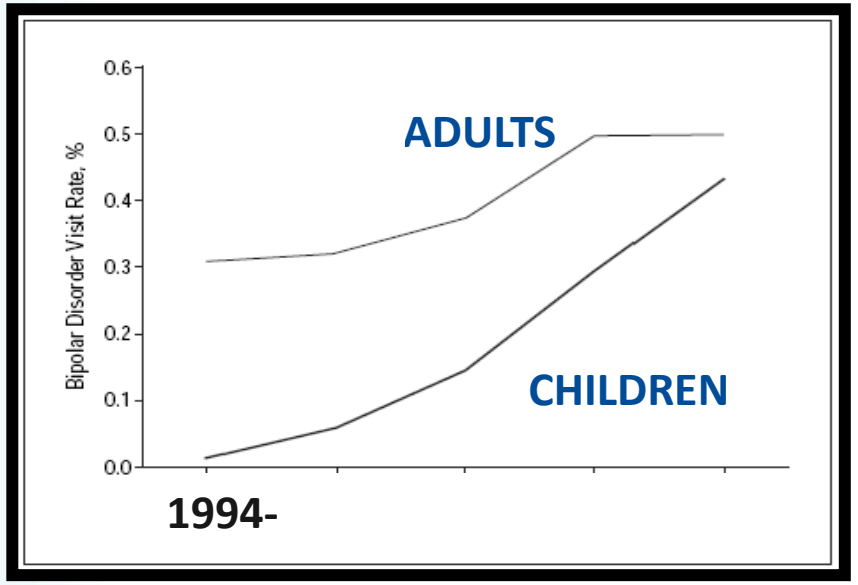
Harvard Medical School and Massachusetts General Hospital



Disclosures

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My spouse and I have the following financial relationship with a commercial interest 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.

Her spouse receives royalties from UpToDate; consultation fees from Emalex, Noctrix, Disc Medicine, Avadel, HALEO, OrbiMed, and CVS; and research support from Merck, NeuroMetrix, American Regent, NIH, NIMH, 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, Sanofi-Aventis, Sepracor, Sunovion, Takeda, UCB (Schwarz) Pharma, Wyeth, Xenoport, Zeo.

Overview:
This presentation is about the familiality of Full Syndrome and Subsyndromal Pediatric Bipolar Disorder

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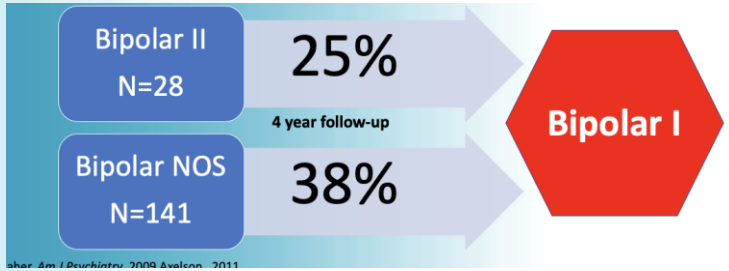
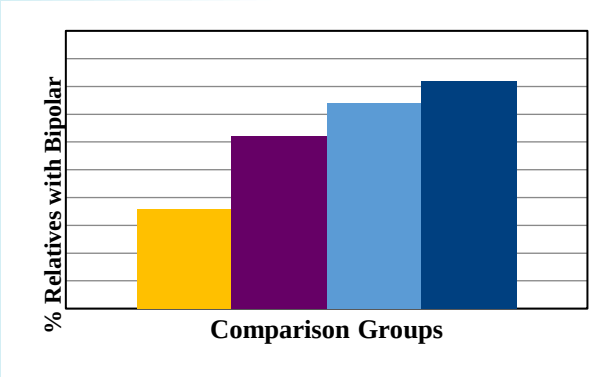
Scope: Bipolar disorder whether full or subthreshold is a highly morbid condition that affects a significant minority of young children



1. Clinical description
2. Laboratory Studies
3. Delimitation
4. Follow-up Study
5. Family Study

Familiality: Familiality is a measure that is external to the clinical picture and therefore supports diagnostic validity of controversial conditions

Full and subthreshold pediatric-onset bipolar disorder: both types of bipolar disorder are familial, suggesting diagnostic continuity and validity



The rapid increase in pediatric bipolar diagnoses led to need for reliability studies

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2007

ORIGINAL ARTICLE

National Trends in the Outpatient Diagnosis and Treatment of Bipolar Disorder in Youth

Carmen Moreno, MD; Gonzalo Laje, MD; Carlos Blanco, MD, PhD; Huiping Jiang, PhD; Andrew B. Schmidt, CSW; Mark Olfson, MD, MPH

Context: Although bipolar disorder may have its onset during childhood, little is known about national trends in the diagnosis and management of bipolar disorder in young people.

Objectives: To present national trends in outpatient visits with a diagnosis of bipolar disorder and to compare the treatment provided to youth and adults during those visits.

Design: We compare rates of growth between 1994-1995 and 2002-2003 in visits with a bipolar disorder diagnosis by individuals aged 0 to 19 years vs those aged 20 years or older. For the period of 1999 to 2003, we also compare demographic, clinical, and treatment characteristics of youth and adult bipolar disorder visits.

Setting: Outpatient visits to physicians in office-based practice.

Participants: Patient visits from the National Ambulatory Medical Care Survey (1999-2003) with a bipolar disorder diagnosis (n=962).

Main Outcome Measures: Visits with a diagnosis of bipolar disorder by youth (aged 0-19 years) and by adults (aged ≥20 years).

Results: The estimated annual number of youth office-based visits with a diagnosis of bipolar disorder increased from 25 (1994-1995) to 1003 (2002-2003) visits per 100 000 population, and adult visits with a diagnosis of bipolar disorder increased from 905 to 1679 visits per 100 000 population during this period. In 1999 to 2003, most youth bipolar disorder visits were by males (66.5%), whereas most adult bipolar disorder visits were by females (67.6%); youth were more likely than adults to receive a comorbid diagnosis of attention-deficit/hyperactivity disorder (32.2% vs 3.0%, respectively; $P<.001$); and most youth (90.6%) and adults (86.4%) received a psychotropic medication during bipolar disorder visits, with comparable rates of mood stabilizers, antipsychotics, and antidepressants prescribed for both age groups.

Conclusions: There has been a recent rapid increase in the diagnosis of youth bipolar disorder in office-based medical settings. This increase highlights a need for clinical epidemiological reliability studies to determine the accuracy of clinical diagnoses of child and adolescent bipolar disorder in community practice.

Arch Gen Psychiatry. 2007;64(9):1032-1039

Why there is any disbelief that children can suffer from mania is unclear

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The NEW ENGLAND JOURNAL of MEDICINE

about features is a new diagnostic category for children: temper dysregulation disorder with dysphoria (TDD). The addition has been praised by some as a verdict on one of the hottest questions in child psychiatry: Is the dramatic increase in the number of children with a diagnosis of bipolar disorder appropriate? The answer appears to be no. But the creation of this new category raises another question: Will the TDD diagnosis advance what everyone agrees should be the ultimate goal of psychiatric classification — helping troubled children to flourish? Sadly, the answer to the second question is also no, unless

pediatric mental
The hallmark
order in adults
sode a distinct
mal y and persi
exp nsive, or irri
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at le st 1 week. I
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that most childr
diso der do not h
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chro nic and very
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aggressive outbu
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Perspective

MAY 20, 2010

Pediatric Mental Health Care Dysfunction Disorder?

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

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

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

dysregulation disorder with dys-

order in adults is a manic epi-

No one disputes that these

2010

"Is the dramatic increase in the number of children with a diagnosis of bipolar disorder appropriate?.....No."

Backlash and disbelief can be powerfully stated, discouraging pediatric clinicians from making bipolar diagnoses

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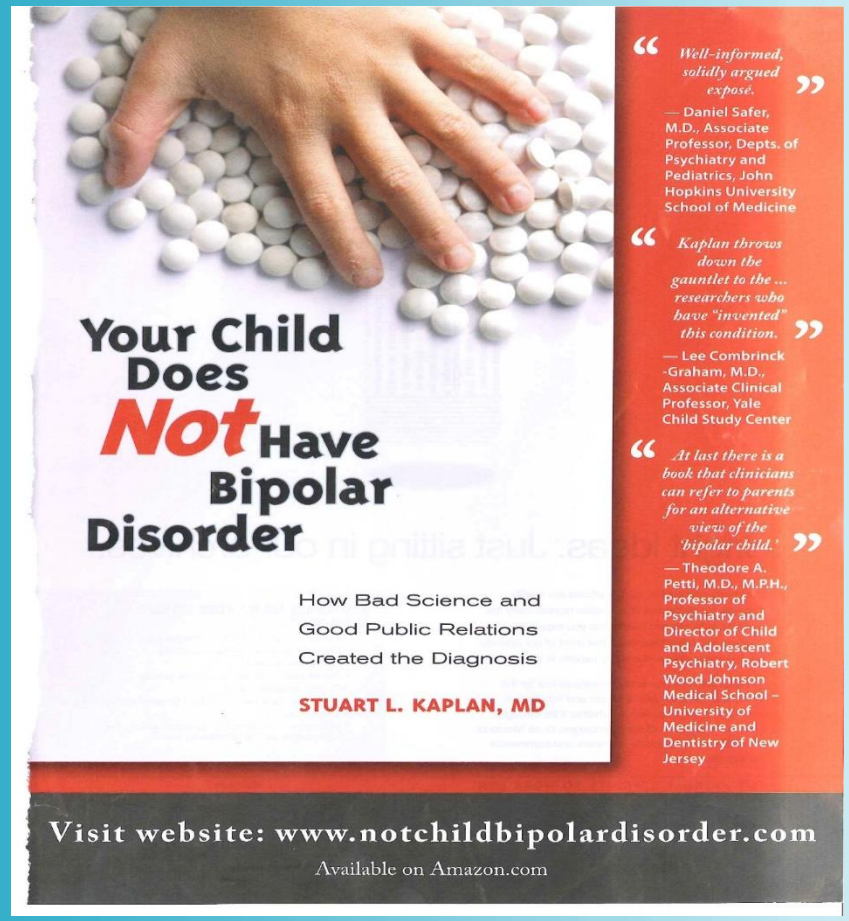
2011



Disruptive Mood Dysregulation Disorder was added to the DSM despite a competing agenda among adult psychiatrists to expand bipolar diagnoses

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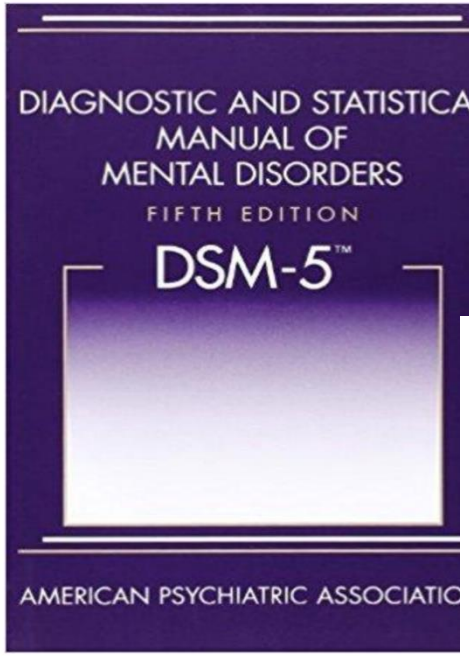
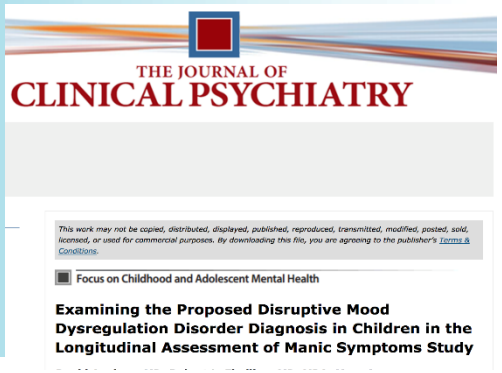
2013





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.

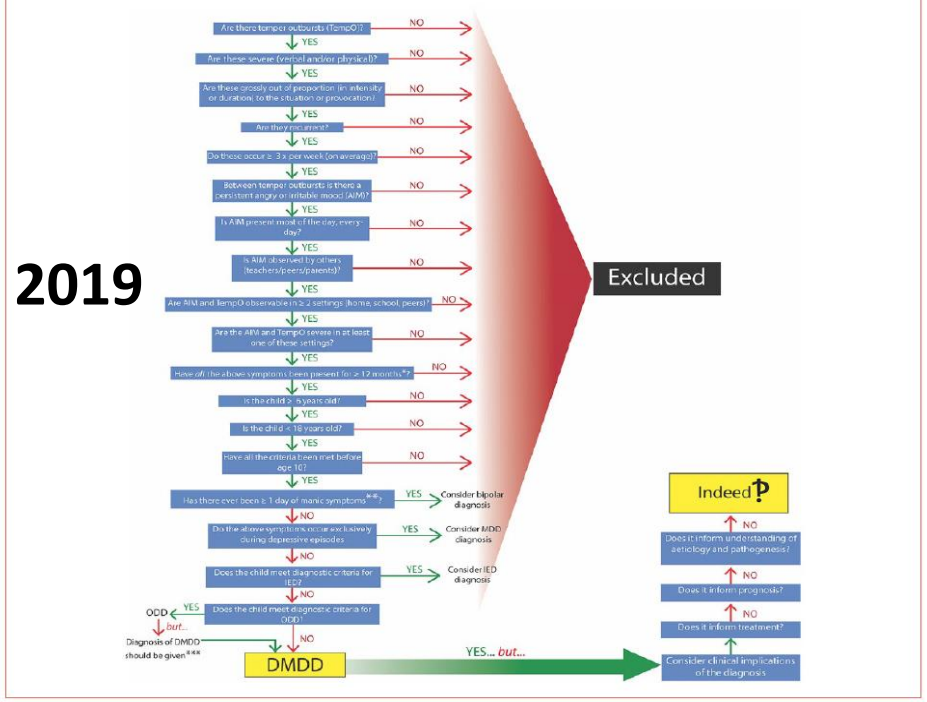
C. The temper outbursts occur, on average, three or more times per week.

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).

Child WorkGroup Mission: REDUCE THE NUMBER OF BIPOLAR DIAGNOSES IN CHILDREN
Adult WorkGroup Mission: ENSURE BIPOLAR DISORDER IS NOT MISDIAGNOSED AS DEPRESSION

The step-wise "complex and futile" diagnosis of DMDD is a 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*"

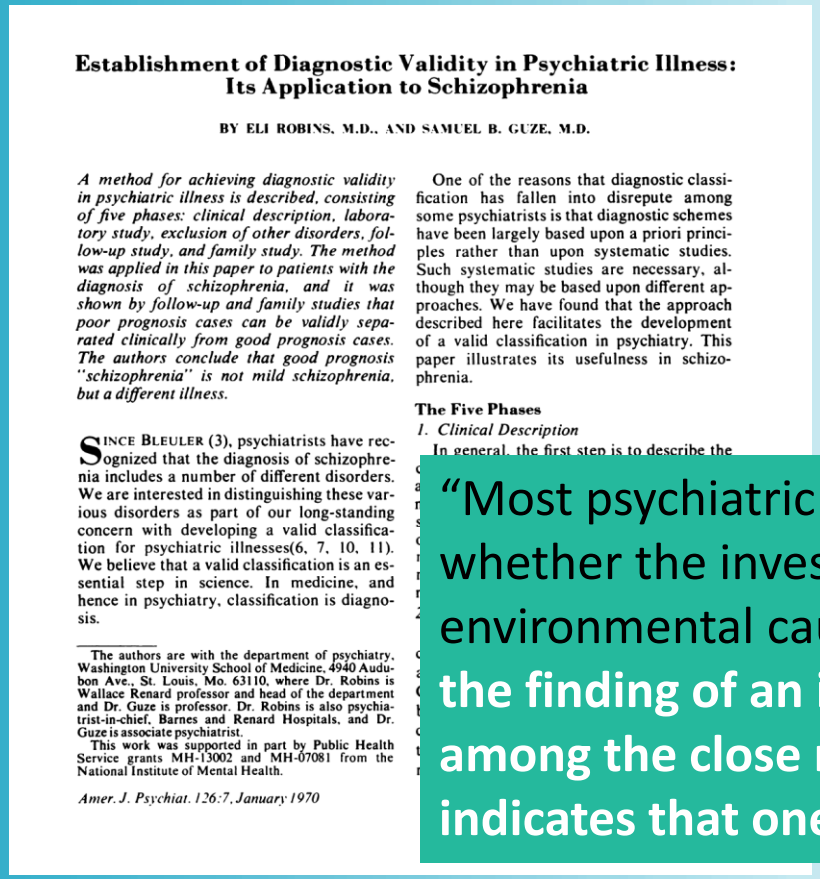
The clinical decision must be made

Is the mood dysregulation

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

Malhi *Australian & New Zealand Journal of Psychiatry* 2019

A framework for the validation of psychiatric disorders can be applied to pediatric-onset 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.

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

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.

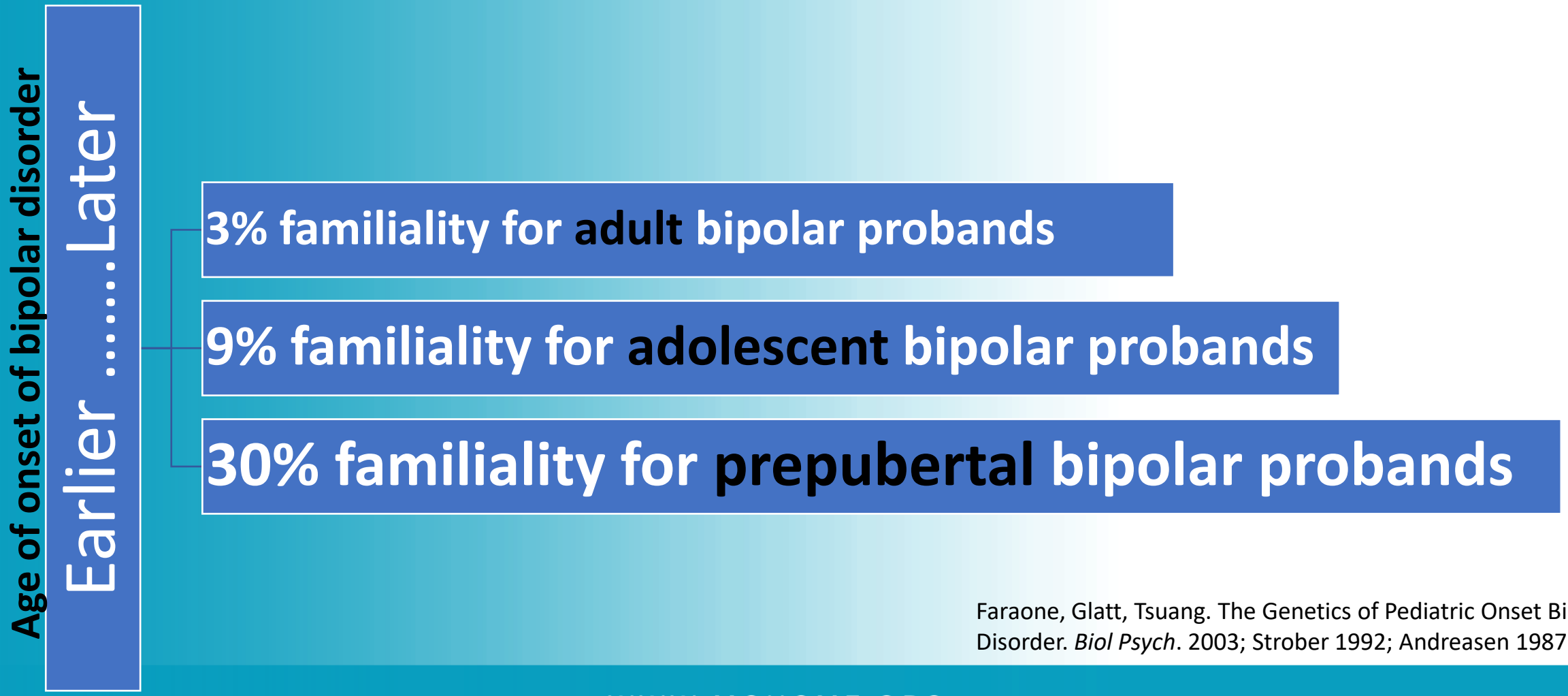
Amer. J. Psychiat. 126:7, January 1970

1. Clinical description
2. Laboratory Studies
3. Delimitation
4. Follow-up Study
5. Family Study

"Most psychiatric illnesses have been shown to run in families, whether the investigations were designed to study hereditary or environmental causes. Independent of the question of etiology…… **the finding of an increased prevalence of the same disorder among the close relatives of the original patients strongly indicates that one is dealing with a valid entity**"

Robins & Guze *Am J Psych* 1970

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

These are the controlled family studies of pediatric Bipolar-I Disorder

Kutcher. Affective disorders in first-degree relatives of adolescent onset bipolars, unipolars, and normal controls. *J Am Acad Child Adolesc Psychiatry*. 1991;30(1):75-78.

Wozniak. A pilot family study of childhood-onset mania. *J Am Acad Child Adolesc Psychiatry*. 1995;34(12):1577-1583.

Faraone. Attention-deficit hyperactivity disorder with bipolar disorder: a familial subtype? *J Am Acad Child Adolesc Psychiatry*. 1997;36(10):1378-1387.

Geller. Controlled, blindly rated, direct-interview family study of a prepubertal and early-adolescent bipolar I disorder phenotype: morbid risk, age at onset, and comorbidity. *AGP*. 2006 Oct;63(10):1130-1138.

Wozniak. A controlled family study of children with DSM-IV bipolar-I disorder and psychiatric co-morbidity. *Psychol Med*. 2010 Jul;40(7):1079-1088.

- **1991-2010**
- examined rates of bipolar-I disorder in all first-degree relatives
- included age and sex matched controls

Familiality of BP-I in BP-I Probands is consistently greater than in controls across 5 studies

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Study	BP-I probands/ relatives (N)	FAMILIALITY	
		BP-I probands	controls
Kutcher 1991	N=23/ 81	15%	1%
Wozniak 1995	N=16/ 46	13%	3%
Faraone 1997	N=15/ 51	16%	3%
Geller 2006	N=95/ 284	28%	4%
Wozniak 2010	N=157/ 487	18%	5%

NO EVIDENCE OF HETEROGENEITY IN MAGNITUDE OF FAMILIAL TRANSMISSION

Wozniak *J Clin Psych.* 2012

Familiality is used to determine genetic risk and is different from family history

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Familiality → $\frac{\text{\# relatives with bipolar}}{\text{\# total relatives}}$

Family History → $\frac{\text{\# probands with bipolar relative}}{\text{\# total probands}}$

This very large controlled family study of pediatric Bipolar I Disorder includes 239 probands and 726 first degree relatives

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Table 1. Clinical and Demographic Characteristics (N = 2,185)[a]

	Bipolar I Families	ADHD Families	Control Families	Statistics		
				Test Result	*P*	
Probands	n = 239	n = 162	n = 136			*
Age, y	10.7 ± 3.3	10.6 ± 3.0	10.7 ± 3.0	$F_{2,536} = 0.03$	1.0	*
Gender, n (%) male	99 (72)	121 (75)	99 (73)	$\chi^2_2 = 0.21$	.9	
Past GAF score	40.7 ± 5.8	50.7 ± 7.3	70.5 ± 8.5	$F_{2,534} = 778.5$	< .001	
Current GAF score	46.6 ± 5.9	57.4 ± 8.2	73.3 ± 7.3	$F_{2,534} = 628.35$	< .001	
Parents	n = 476	n = 323	n = 269			*
Age, y	42.2 ± 6.7	41.3 ± 6.4	41.6 ± 5.8	$F_{2,1064} = 2.0$	.1	*
Gender, n (%) male	225 (47)	161 (50)	133 (49)	$\chi^2_2 = 0.6$	.7	
Past GAF score	51.7 ± 9.8	56.9 ± 12.6	63.5 ± 12.4	$F_{2,1064} = 93.5$	< .001	*
Current GAF score	63.2 ± 7.8	68.5 ± 9.5	72.9 ± 7.9	$F_{2,1064} = 117.1$	< .001	
Siblings	n = 250	n = 188	n = 142			*
Age, y	12.3 ± 4.6	13.7 ± 5.9	12.9 ± 5.1	$F_{2,577} = 4.71$	< .01	*
Gender, n (%) male	116 (46)	103 (55)	74 (52)	$\chi^2_2 = 3.2$	.20	
Past GAF score	57.6 ± 9.7	61.8 ± 12.0	65.9 ± 10.7	$F_{2,577} = 27.9$	< .001	*
Current GAF score	62.9 ± 7.8	67.9 ± 10.8	71.1 ± 8.4	$F_{2,576} = 41.1$	< .001	
Total	n = 965	n = 673	n = 547			*
Socioeconomic status[b]	1.8 ± 0.9	1.8 ± 1.0	1.5 ± 0.8	$\chi^2_2 = 9.33$	.01	
Race/ethnicity, n (%)						
White	916 (95)	667 (99)	536 (98)	$\chi^2_6 = 39.39$	< .001	
African-American	32 (3)	6 (1)	7 (1)			
More than 1	15 (2)	0 (0)	0 (0)			
Unknown	2 (< 1)	0 (0)	4 (1)			

[a]Values expressed as mean ± SD unless otherwise noted.
[b]For socioeconomic status, 1 = most advantaged, 5 = most disadvantaged.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, GAF = Global Assessment of Functioning.

Wozniak *J Clin Psych* 2012

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

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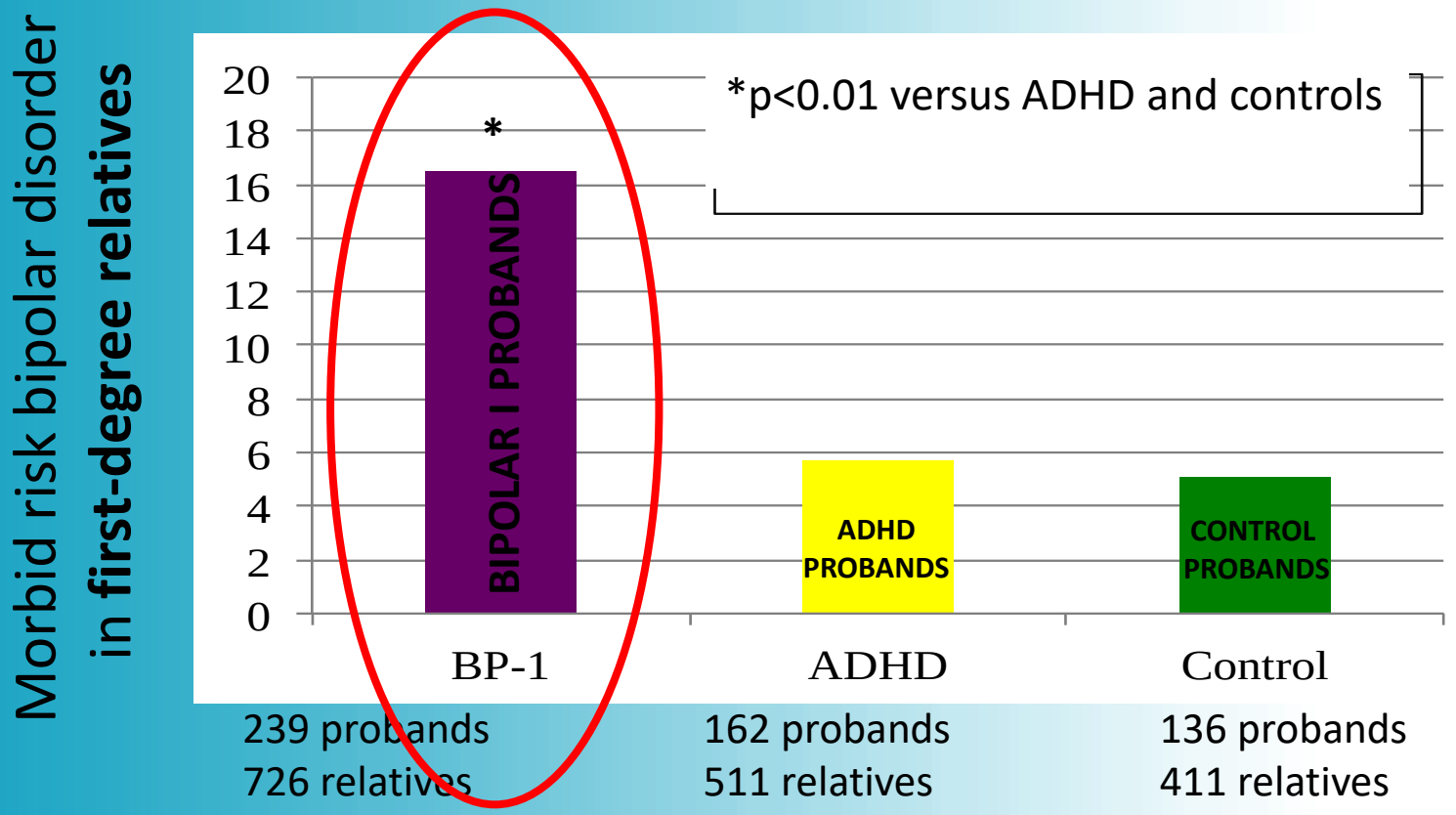
The MGH Pediatric Bipolar Disorder study is the largest controlled family study



Wozniak.*J Clin Psych.*2012

In a study of 10,000+ US adolescents, the rate of pediatric bipolar disorder was 2.9%
In a meta-analysis of international studies, the rate of pediatric bipolar disorder was 1.8%

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.,

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

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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 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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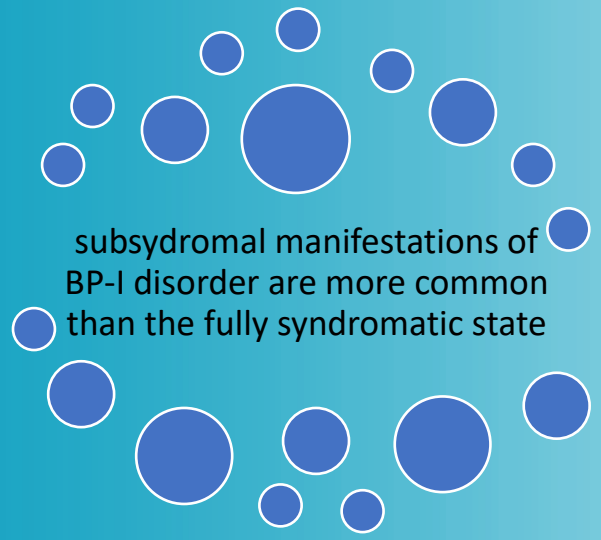
The prevalence of SUBTHRESHOLD BIPOLAR DISORDER in epidemiological samples of adolescents ranges from 1.2%–13.3%

Merikangas 2010; Van Meter *J Clin Psych* 2011

High risk offspring of bipolar parents often have subsyndromal presentations

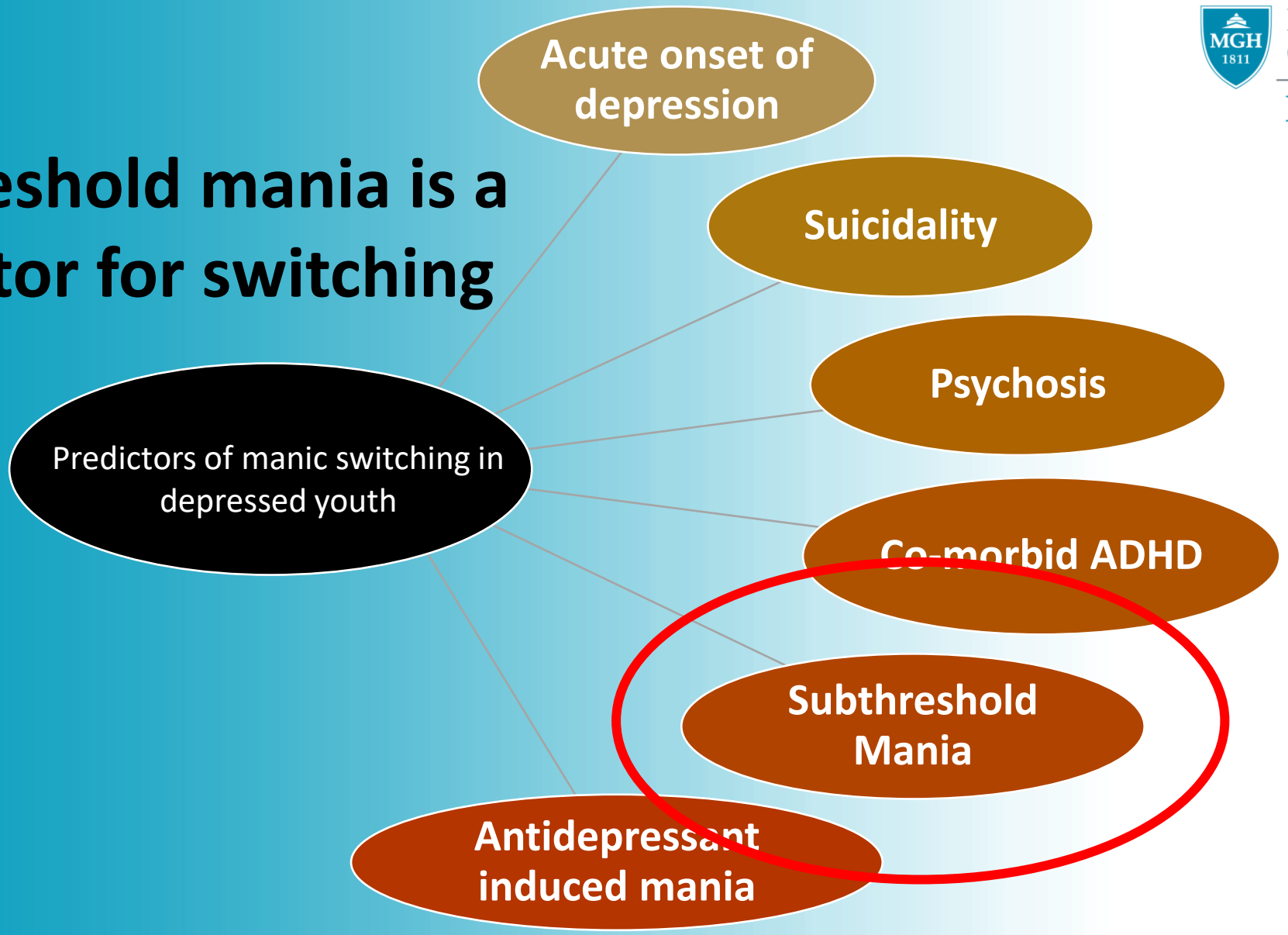
Children with bipolar parents



subthreshold states herald a compromised outcome and should be the focus of clinical assessment and treatment

Axelson *Am J Psych* 2015

Subthreshold mania is a risk factor for switching



Strober 1982, 1994. Biederman 2009, 2013. Uchida 2014

ST manifestations of BP-I disorder evolved into full syndromatic status over COBY 4-year follow-up

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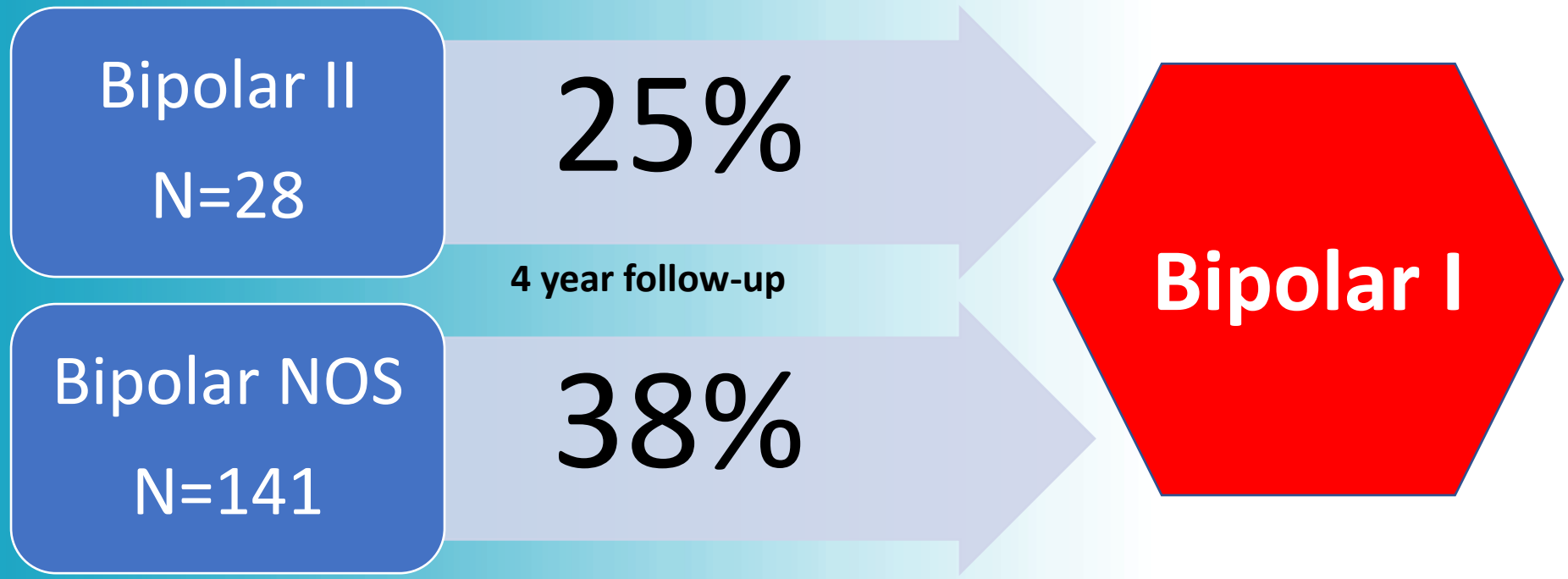
Four-Year Longitudinal Course of Children and Adolescents with Bipolar Spectrum Disorders:
Course and Outcome of Bipolar Youth (COBY) Study



Birmaher Am J Psychiatry 2009; Axelson 2011

COBY Bipolar NOS is defined liberally

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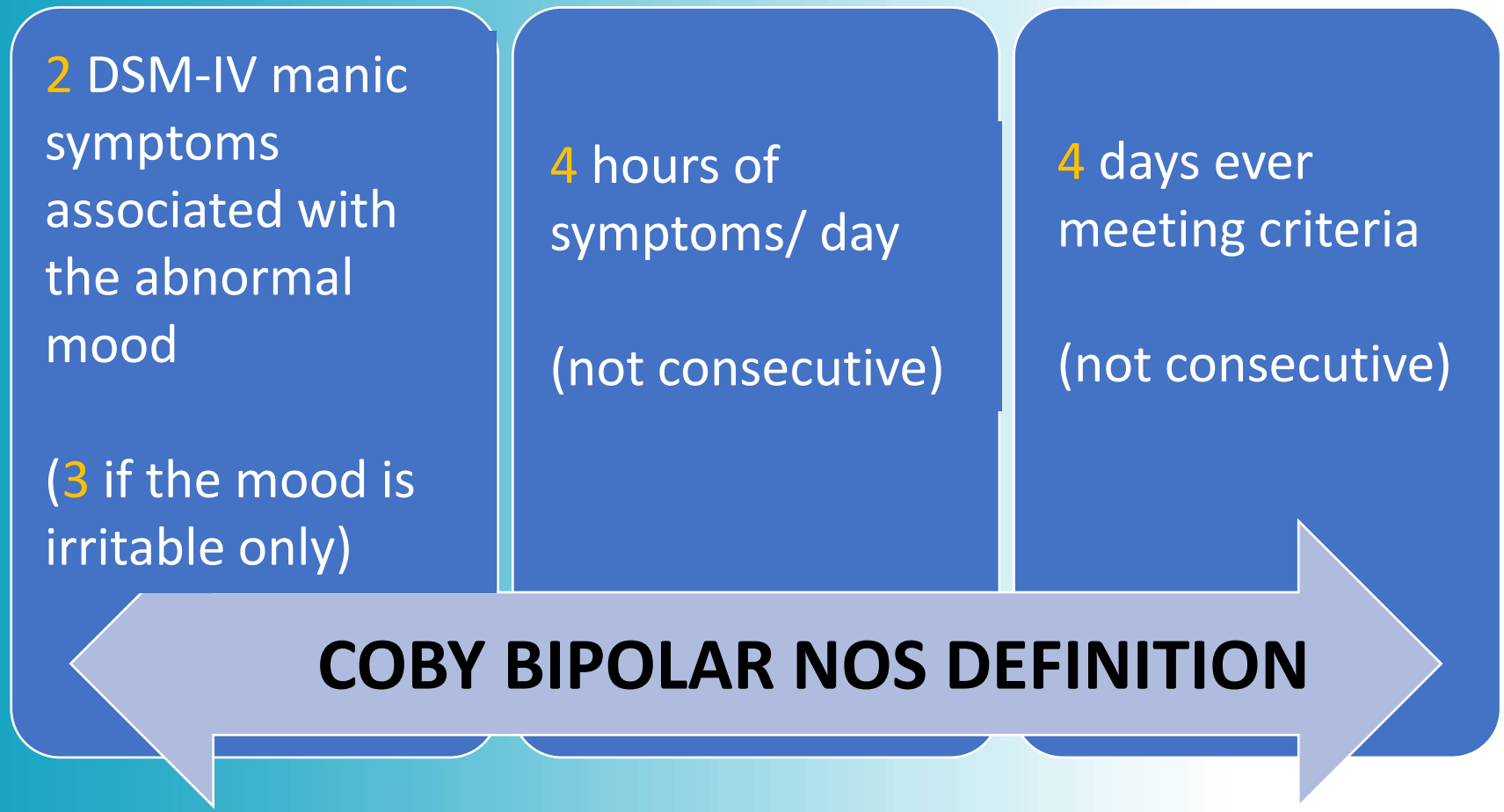
Elevated, expansive or irritable mood with change in functioning:



Axelson 2012

BP-NOS frequently evolved into bipolar I or II at COBY 5-year follow-up

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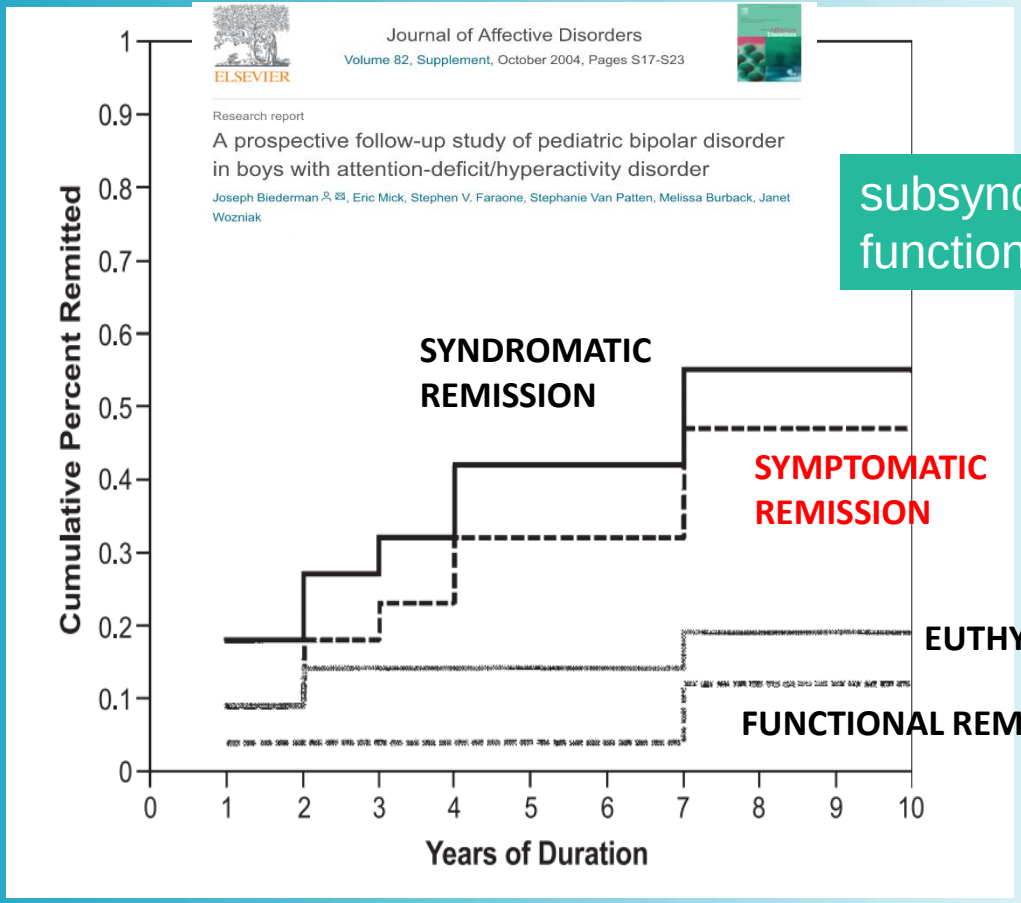
Course and Outcome of Bipolar Youth (COBY) Study

Axelson 2011

4-year follow-up of 22 ADHD boys with bipolar disorder found a high rate of persistence, including subsyndromal states (N=128)



subsyndromal states and functioning assessed

Baseline age: 10.5±3.0
Bipolar age onset: 6.3±4.7

Biederman J Affec Dis 2004

High rate of persistence reported at 5-year follow-up including ST mania

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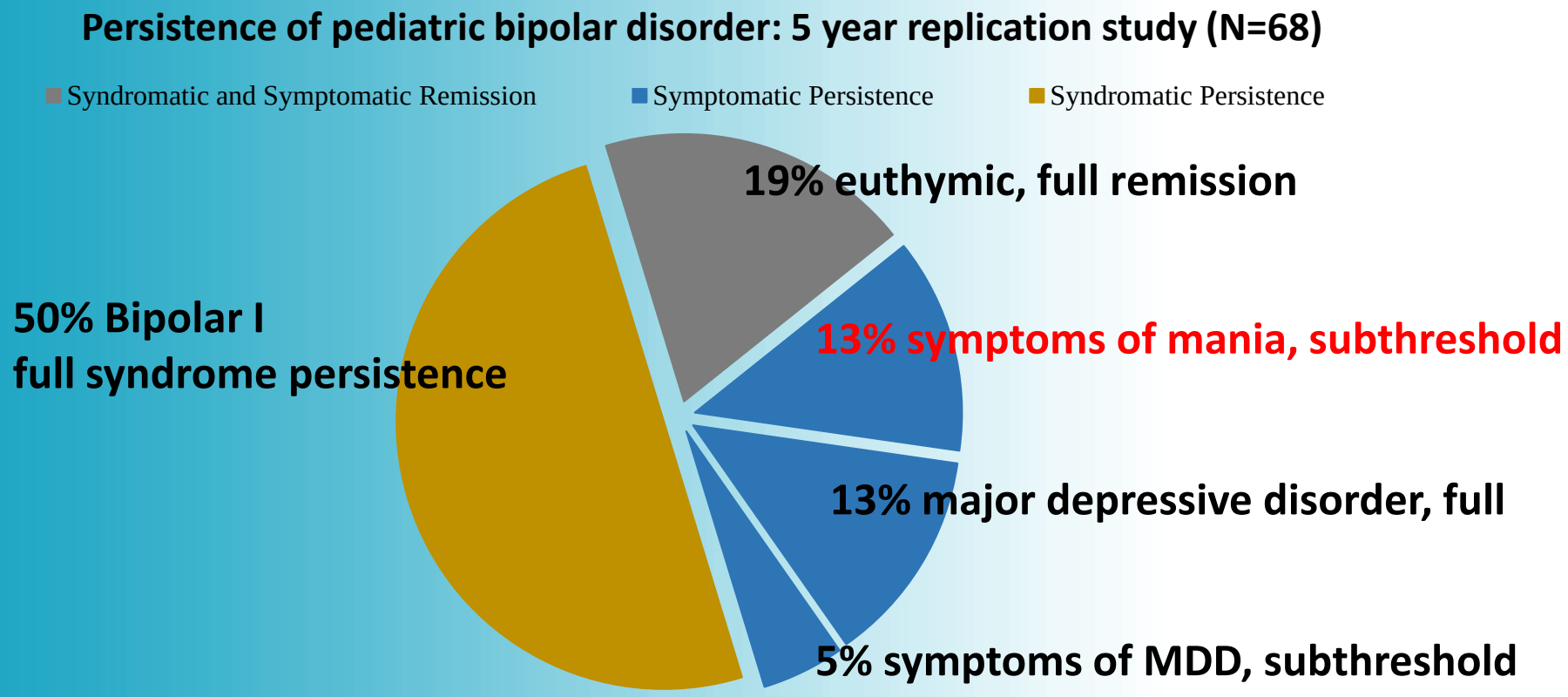

Wozniak SJCAPP 2018

ST bipolar disorder is more common and as impairing as full syndrome bipolar disorder in adolescents

Adolescent Epidemiological Sample N=1709

6% ST bipolar disorder

1% full syndrome BP-I

STs had similar or more

- **Impairment**
- **Comorbidity**
- **Suicide attempts**

Lewinsohn 1995, 2000, 2002, 2003

Subthreshold bipolar disorder is prevalent and highly impairing in adults

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Angst J JAD 2003
Toward a re-definition of subthreshold bipolarity: epidemiology and proposed criteria for bipolar-II, **minor bipolar disorders** and hypomania

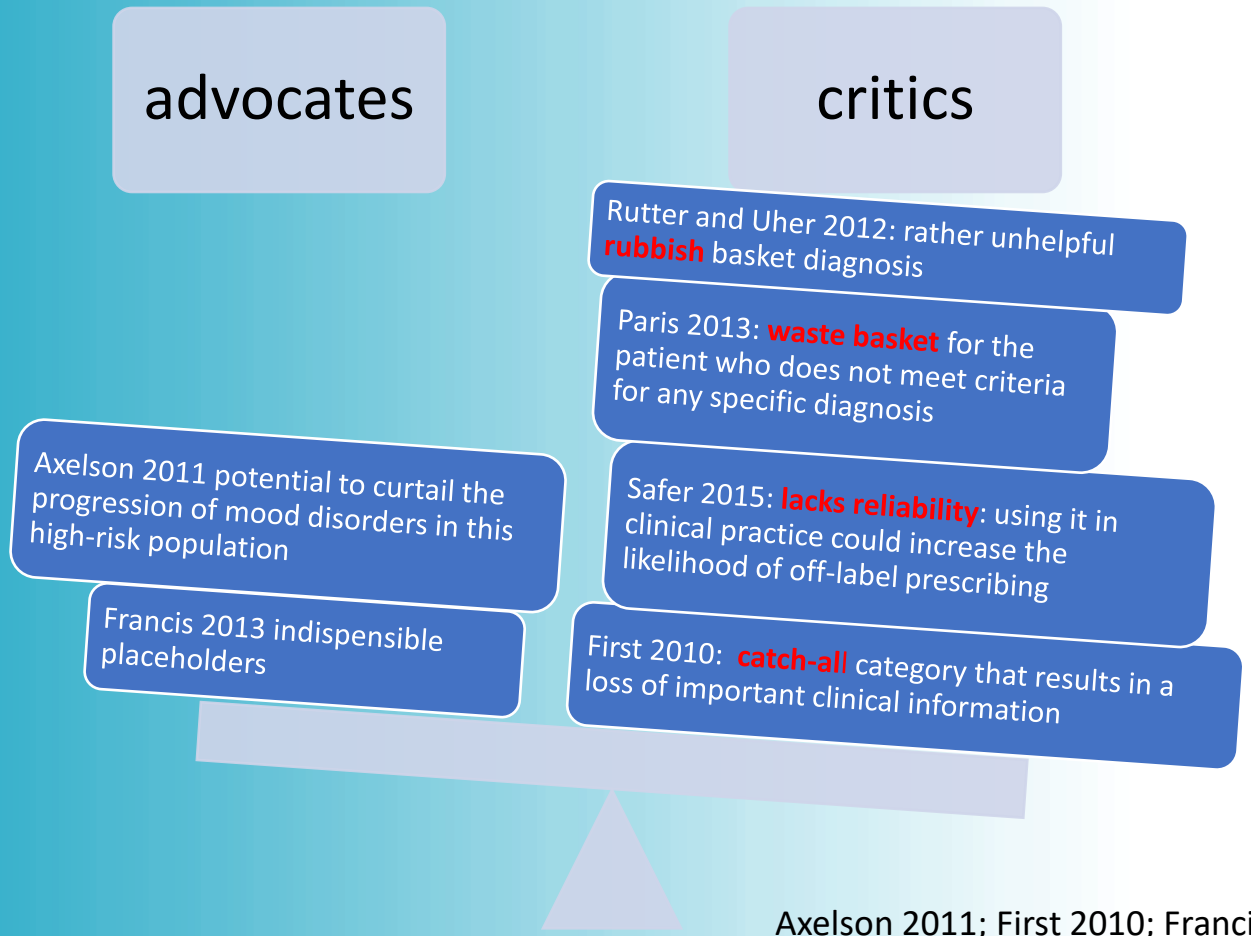
Judd LL JAD 2003
The prevalence and disability of bipolar spectrum disorders in the US population: re-analysis of the ECA database taking into account **subthreshold** cases

Merikangas AGP 2007
Lifetime and 12-month prevalence of **bipolar spectrum disorder** in the National Comorbidity Survey replication

Failure to recognize bipolar spectrum disorder delays treatment and worsens prognosis

Angst JAD 2003; Judd JAD 2003; Merikangas AGP 2007

Subthreshold diagnoses have been hailed as useful and the subject of criticism



Axelson 2011; First 2010; Francis 2013; Paris 2013; Rutter 2012; Safer 2015

Gene expression (inferred from family history) can result in full or partial (ST) manifestations

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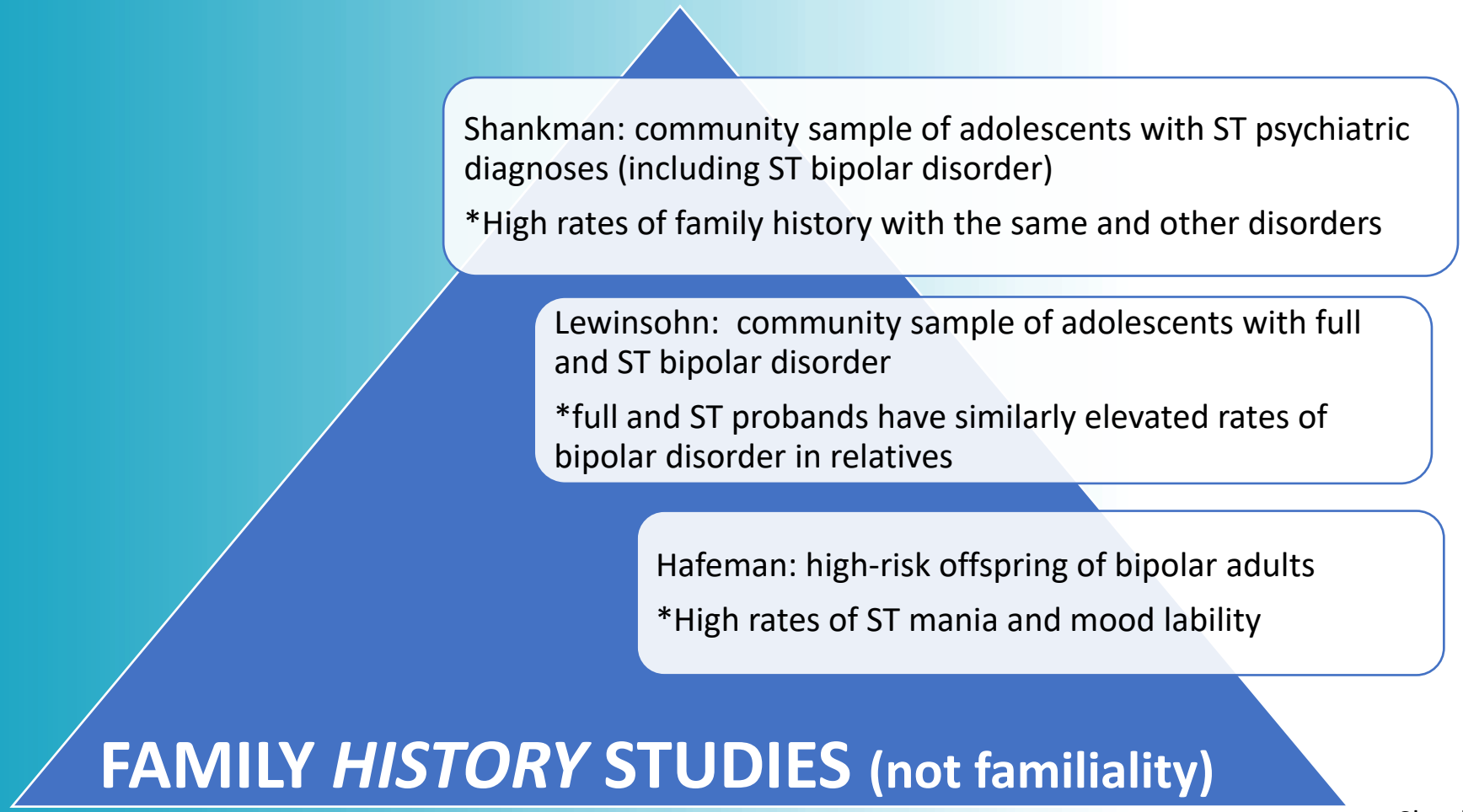
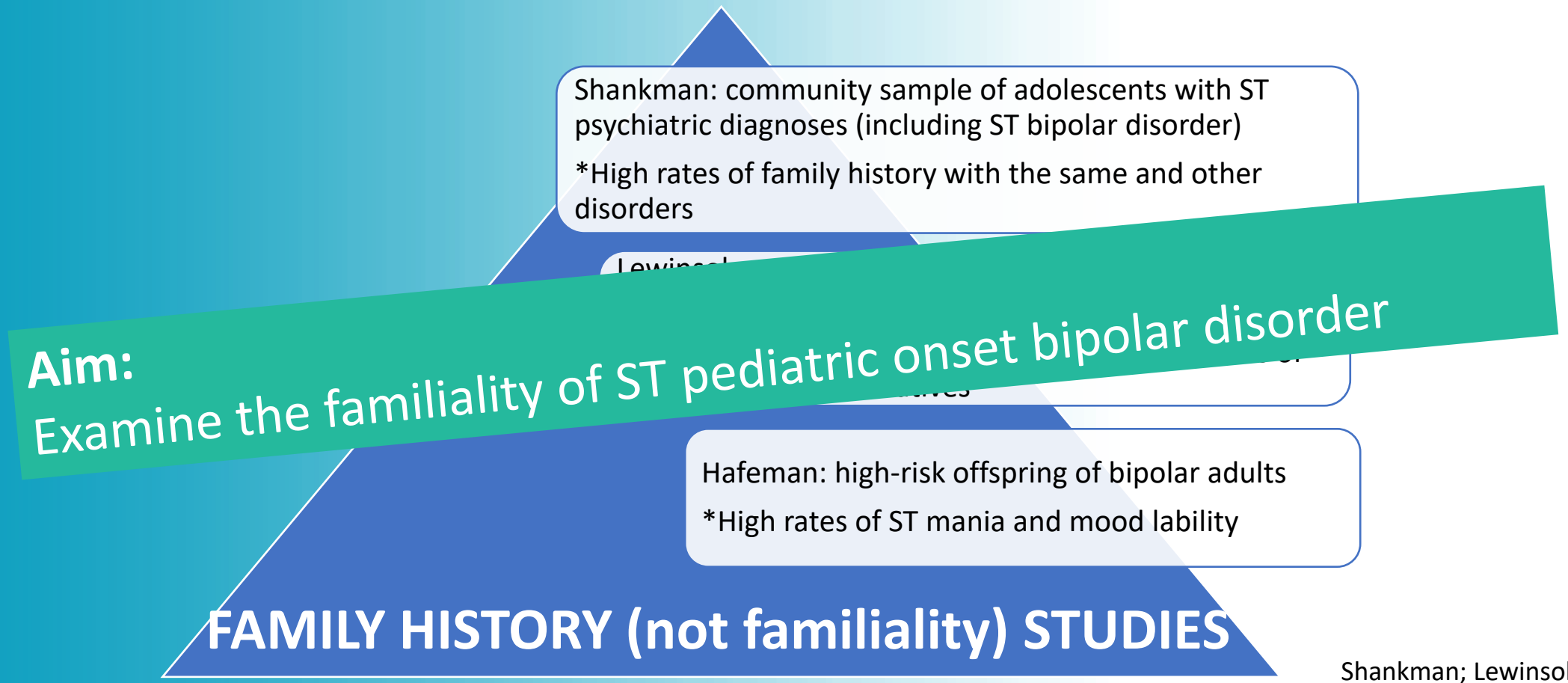


Shankman; Lewinsohn; Hafemar

Family studies can help verify the validity of ST pediatric onset bipolar-I disorder



Aim:
Examine the familiality of ST pediatric onset bipolar disorder

Shankman; Lewinsohn; Hafeman

The symptoms of mania are the same in children and adults

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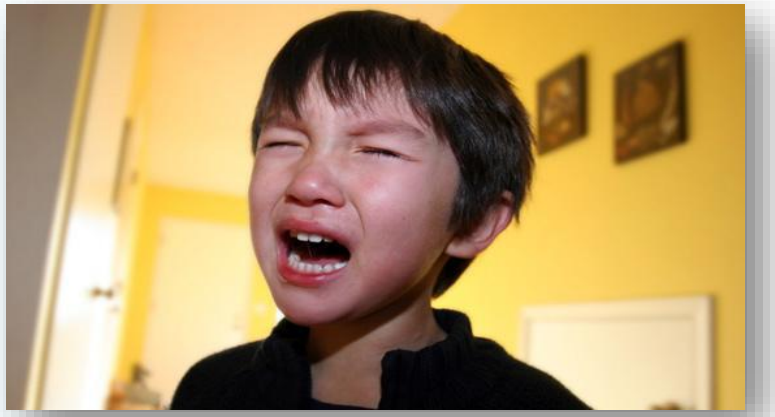
Full criteria for Bipolar I

A. A *distinct period (7+ days)* 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)

We define subsyndromal as bipolar II or bipolar NOS

Bipolar I

Criterion A:
extreme persistent elevated/ expansive/ irritable

Lasting at least 7 days

PLUS

Criterion B:
3 of 7 symptoms during the mood disturbance
(4 if the mood is irritable only)

Bipolar II

Criterion A:
extreme persistent elevated/ expansive/ irritable

Lasting at least 4 days

PLUS

Criterion B:
3 of 7 symptoms during the mood disturbance
(4 if the mood is irritable only)

Bipolar NOS

Criterion A:
extreme persistent elevated/ expansive/ irritable

Lasting <4 days

AND/OR

Criterion B:
2 of 7 symptoms during the mood disturbance
(3 if the mood is irritable only)

ST pediatric bipolar disorder is also familial

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Pediatric ST and Full syndrome bipolar probands have similar rates of familiality of BPI (and both are different from ADHD/controls)

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ORIGINAL ARTICLE

WILEY BIPOLAR DISORDERS

Similar familial underpinnings for full and subsyndromal pediatric bipolar disorder: A familial risk analysis

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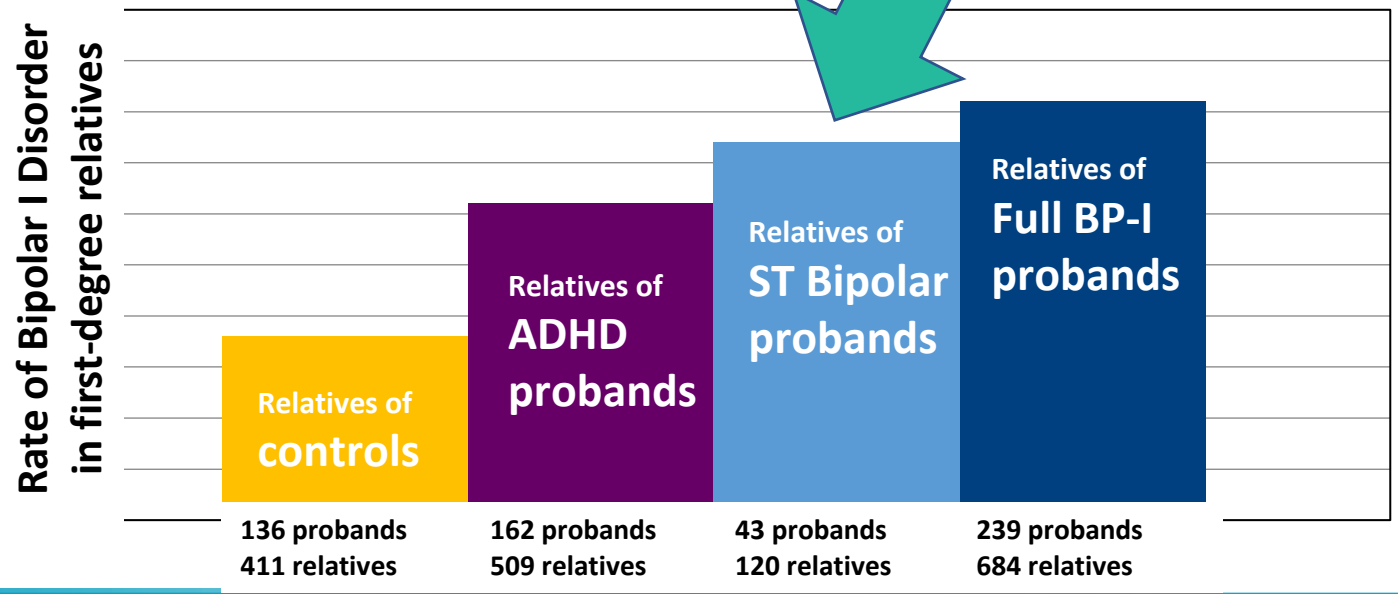

And the rate of MDD among relatives of *subthreshold* BP-I, *full* BP-I and ADHD probands is significantly different from controls

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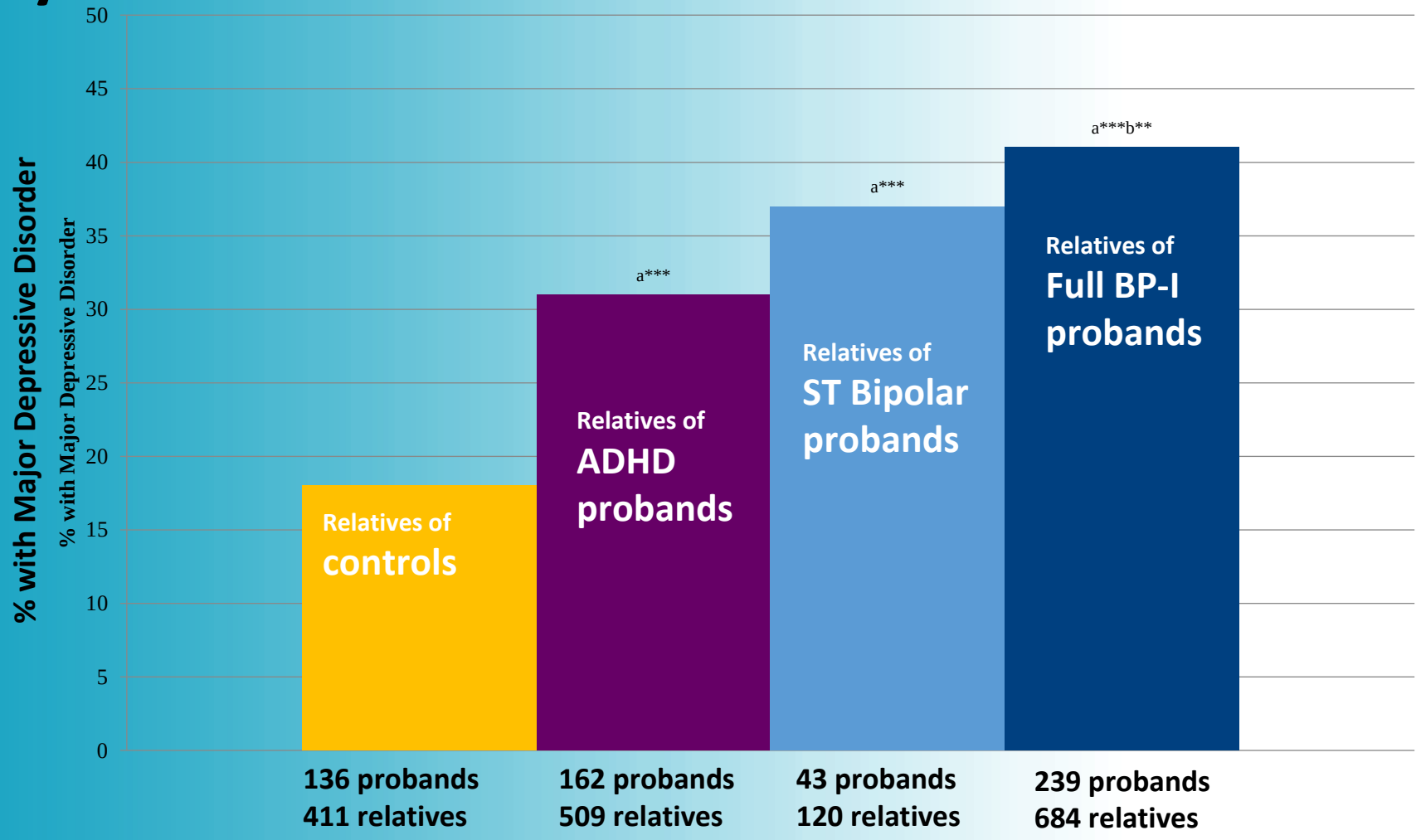

Wozniak 2017

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Conclusion:
Subsyndromal conditions are important to diagnose

Genetic conditions throughout medicine present pleomorphically with variable symptomatic expression that may be above or below arbitrary thresholds set forth by our nosology

The finding of shared familial risk between subsyndromal and syndromal forms of pediatric BP-I disorder is consistent with the expected way that genetic risk factors manifest themselves

Conclusion:
Family studies provide useful information given the absence of identified genes

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By providing information that is one step removed from a diagnosis in an affected child, **family study methodology is useful for the validation** of complex psychiatric disorders such as pediatric bipolar disorder

By documenting that *subthreshold* pediatric bipolar disorder probands have high rates of familiality with full BP-I disorder, our study provides **support for the validity of subthreshold** pediatric bipolar disorder

These findings support the **diagnostic continuity** between subsyndromal and fully syndromatic states of pediatric BP-I disorder

Overview:
This presentation is about the familiality of Full Syndrome and Subsyndromal Pediatric Bipolar Disorder

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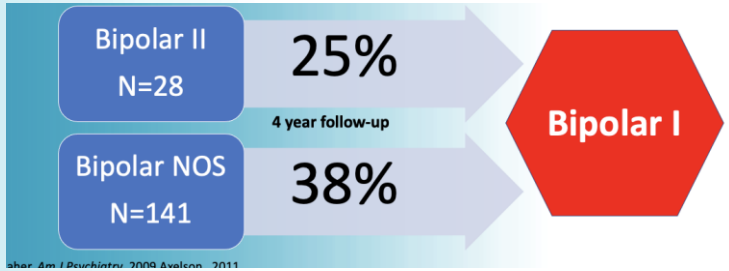
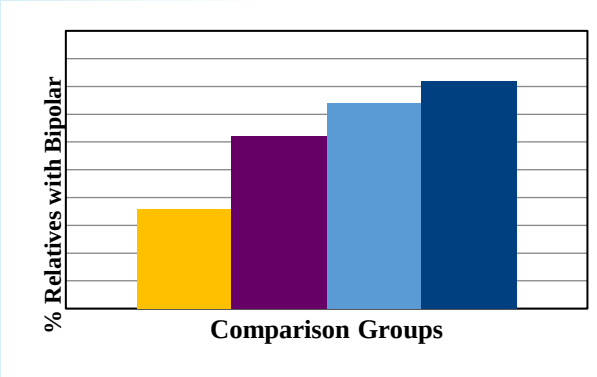
Scope: Bipolar disorder whether full or subthreshold is a highly morbid condition that affects a significant minority of young children



1. Clinical description
2. Laboratory Studies
3. Delimitation
4. Follow-up Study
5. Family Study

Familiality: Familiality is a measure that is external to the clinical picture and therefore supports diagnostic validity of controversial conditions

Full and subthreshold pediatric-onset bipolar disorder: both types of bipolar disorder is familial, suggesting diagnostic continuity and validity



QUESTIONS?