Pediatric Bipolar Disorder and Mood Disorders

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Disclosure and potential conflicts

My spouse and I have the following financial relationship with a commercial interest to disclose:

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Pediatric-Onset Bipolar Disorder & Differentiating Unipolar vs Bipolar Depression in Children

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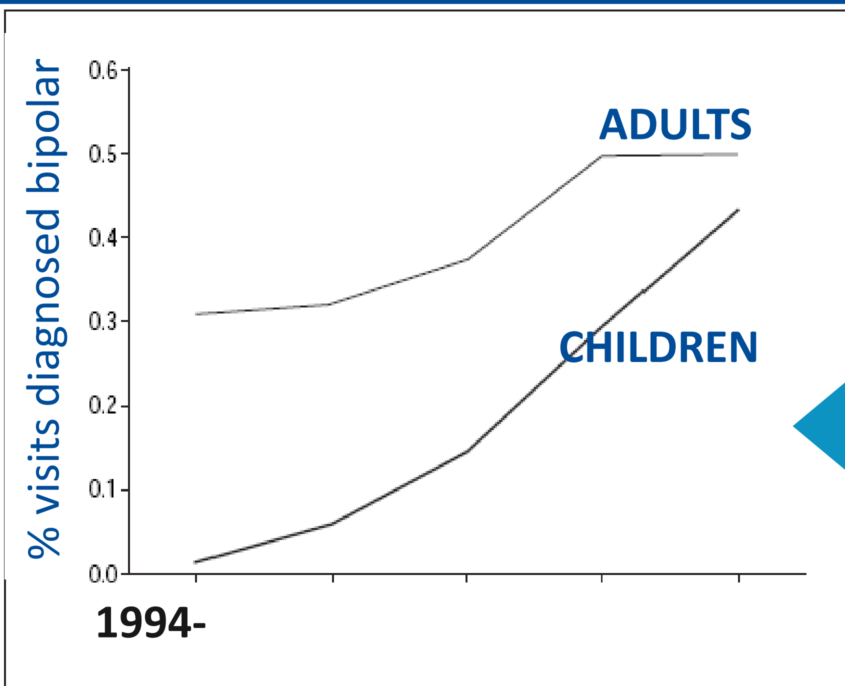


ANTI-DEPRESSANTS?

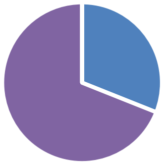
treat depression

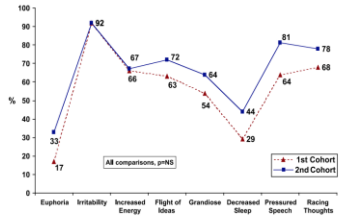
destabilize mania

Overview:

Switch from pediatric depression to bipolar disorder is common.
Children with bipolar disorder spend much time in mixed or depressive states.
Pediatric-onset bipolar disorder is a severely impairing disorder which persists into late adolescence; treatment usually necessary

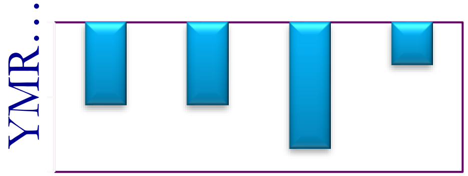
Children with MDD often switch: Early depression is a predictor of bipolar disorder

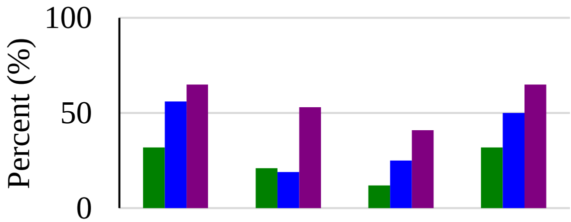




Pediatric Bipolar disorder is a highly morbid condition that affects a significant minority of young children, is familial and persists over time

Treatment: Pharmacologic treatment often with SGAs is generally required for pediatric mood disorders: use antidepressants with caution





Natural Treatments hold promise in the treatment of pediatric bipolar disorder

We use the same diagnostic criteria (developmentally appropriate) for depression in children as adults

<u>Major Depression</u>:

A. 2 weeks of depressed mood (irritable, grumpy, easily annoyed, bored or sad/melancholic)

B. 4/8 of following symptoms:

1. <u>S</u> Sleep (insomnia/ hypersomnia)
2. <u>I</u> Interest (loss of interest)
3. <u>G</u> Guilt (excessive guilt or feelings of worthlessness)
4. <u>E</u> Energy (loss of energy/ physical complaints)
5. <u>C</u> Concentration (making decisions)
6. <u>A</u> Appetite (change in appetite or weight)
7. <u>P</u> Psychomotor agitation or retardation
8. <u>S</u> Suicidal thoughts

We use the same diagnostic criteria (developmentally appropriate) for mania in children as adults

<u>Mania:</u>

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

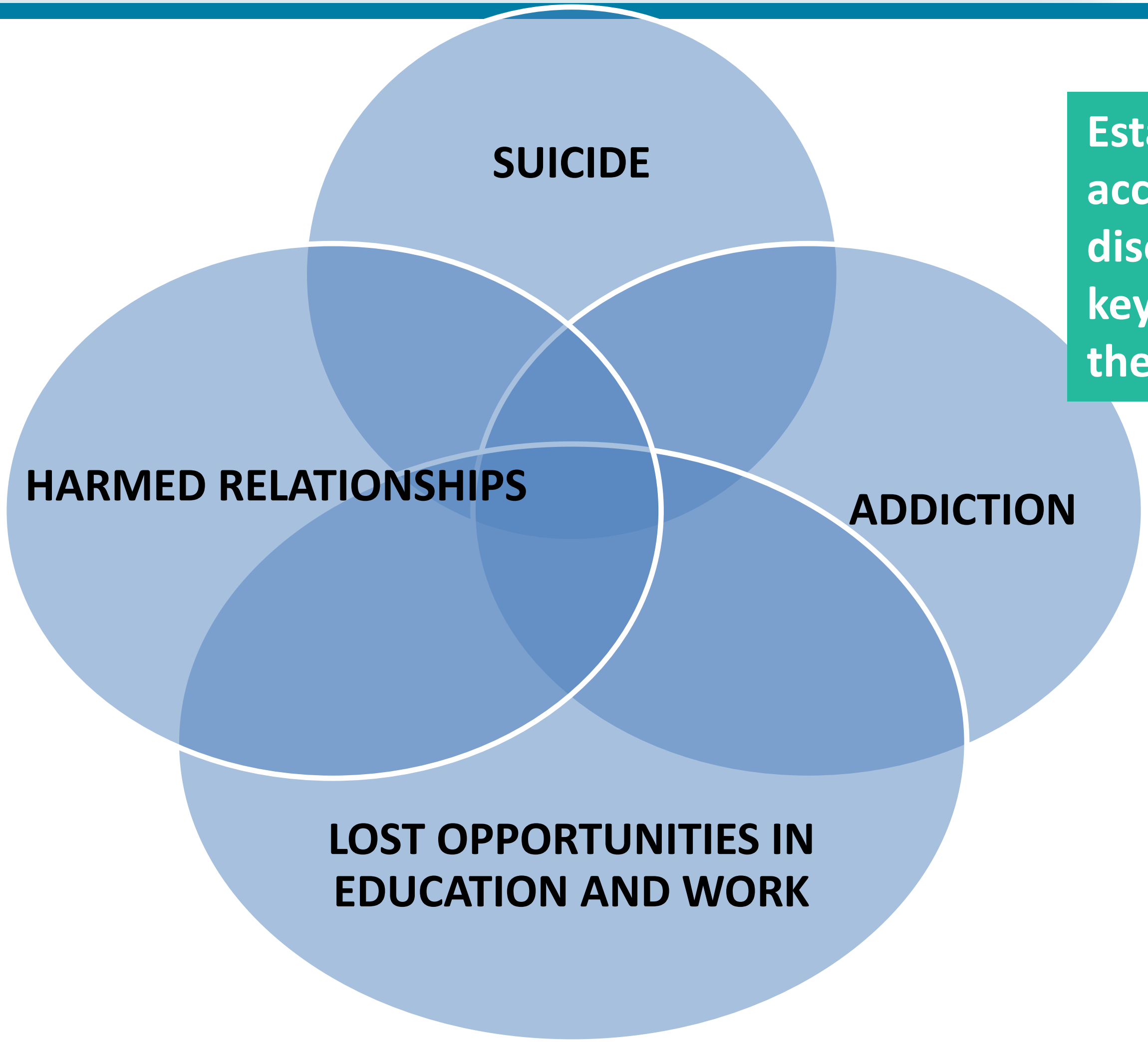
B. At least 3/7 (4/7 if mood is irritable)

ADHD sx in blue

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

Diagnostic and Statistical Manual (DSM-5)

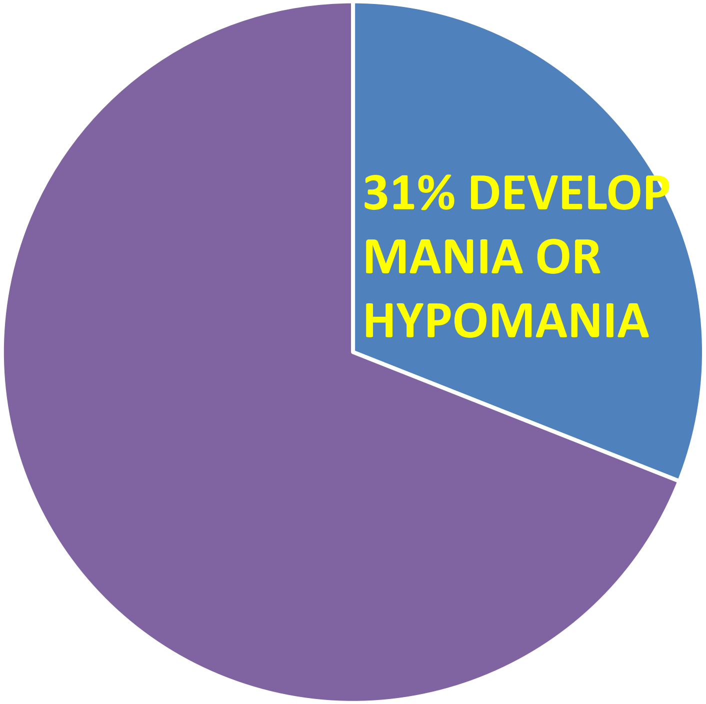
The risk-benefit analysis of treatment must include the risks associated with not treating a mood disorder.



Establishing an accurate mood disorder diagnosis is key, or could worsen the clinical picture

Children with MDD often switch

CHILDREN WITH MDD

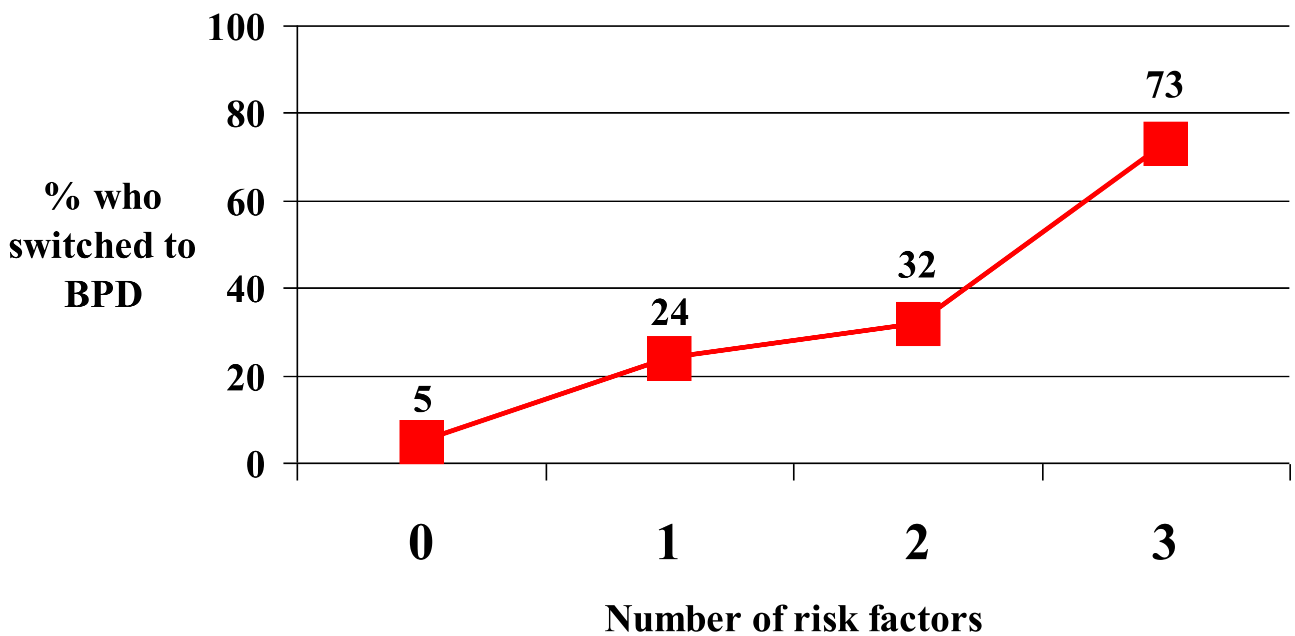


Adult literature has consistently reported that "early onset" (< 25 years) depression poses a risk of switching

Weissman 1999; Geller 1994

There is a 'dose response' of multiple risk factors contributing to manic switch

- conduct disorder
- school behavior problems
- parental mood disorder



Biederman 2009

Other predictors of manic switching

- Acute onset of depression
- Suicidality
- Psychosis
- Co-morbid ADHD
- Subthreshold Mania
- Antidepressant induced mania

Strober 1982, 1994; Biederman 2009, 2013

Antidepressants play a negative role in switching, use with caution

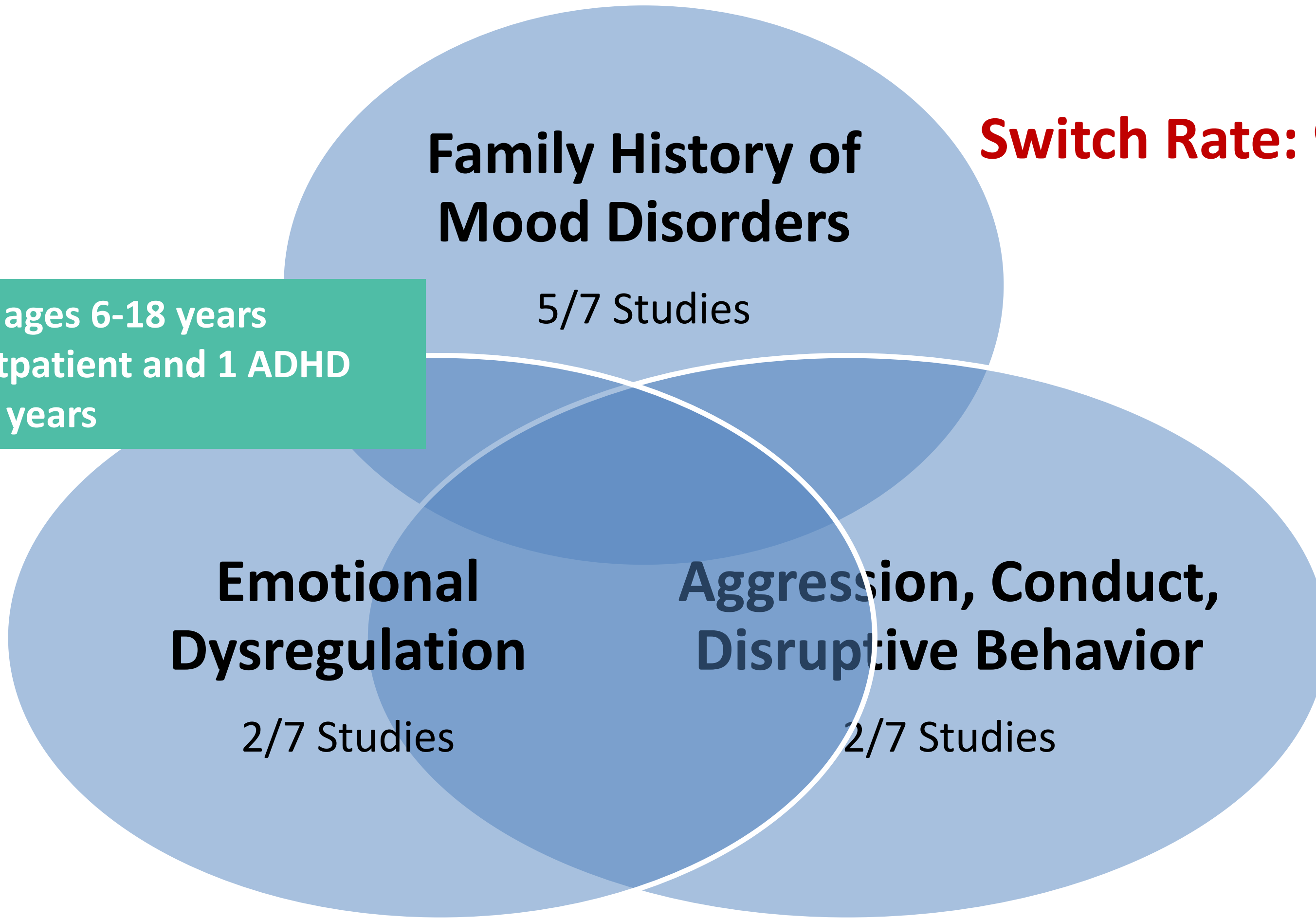
- pharmacologically induced hypomania was a predictor of a bipolar course
- antidepressant induced mood change was seen more in BP MDD
- rate of switching higher in subjects with history of receiving antidepressants especially in children

Strober; Shon; Martin

Top features of pediatric depression found which predict subsequent switch to bipolar disorder from 7 prospective studies (4 samples)

Switch Rate: 9% - 43%

N= 985 subjects, ages 6-18 years
2 inpatient, 1 outpatient and 1 ADHD
Follow up: 1 - 11 years



Strober 1982,1993; Geller 1994,2001; Kochman 2005; Biederman 2009, 2013

In a meta-analysis of international studies, the rate of pediatric bipolar disorder was 1.8%

THE JOURNAL OF
CLINICAL PSYCHIATRY

Zealand).

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

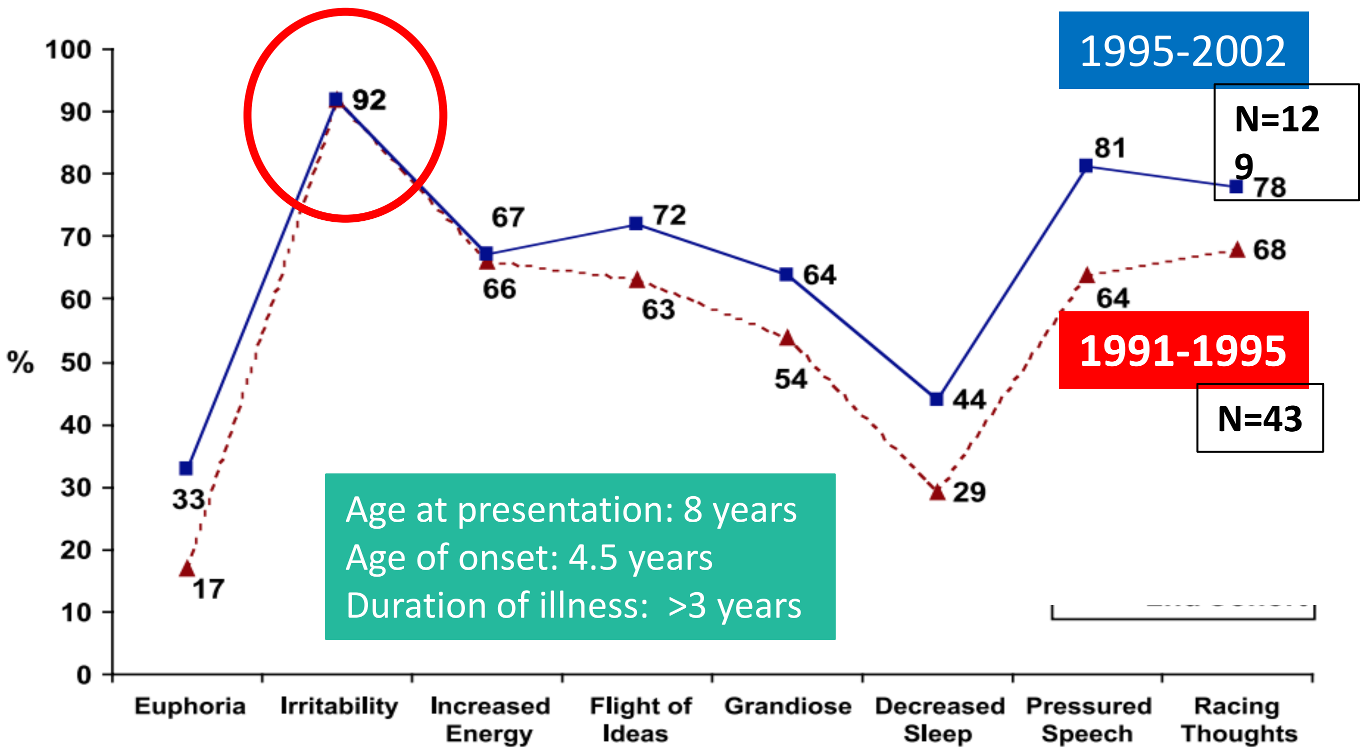
Bipolar Disorder affects 1.8% children worldwide

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

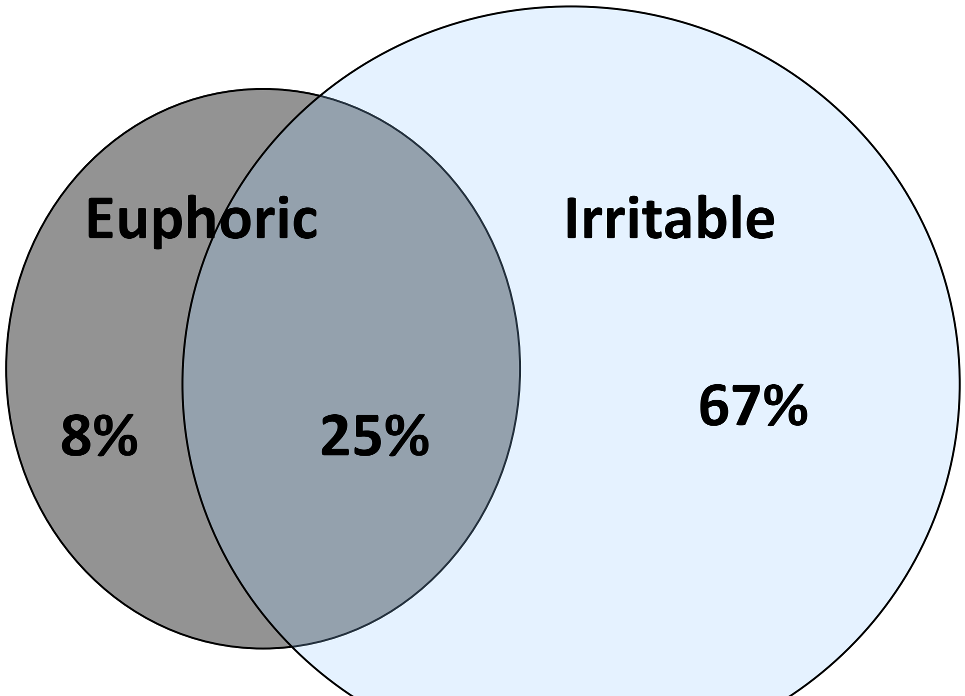
Van Meter J Clin Psych 2011

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



Wozniak, 1995; Biederman, 2004

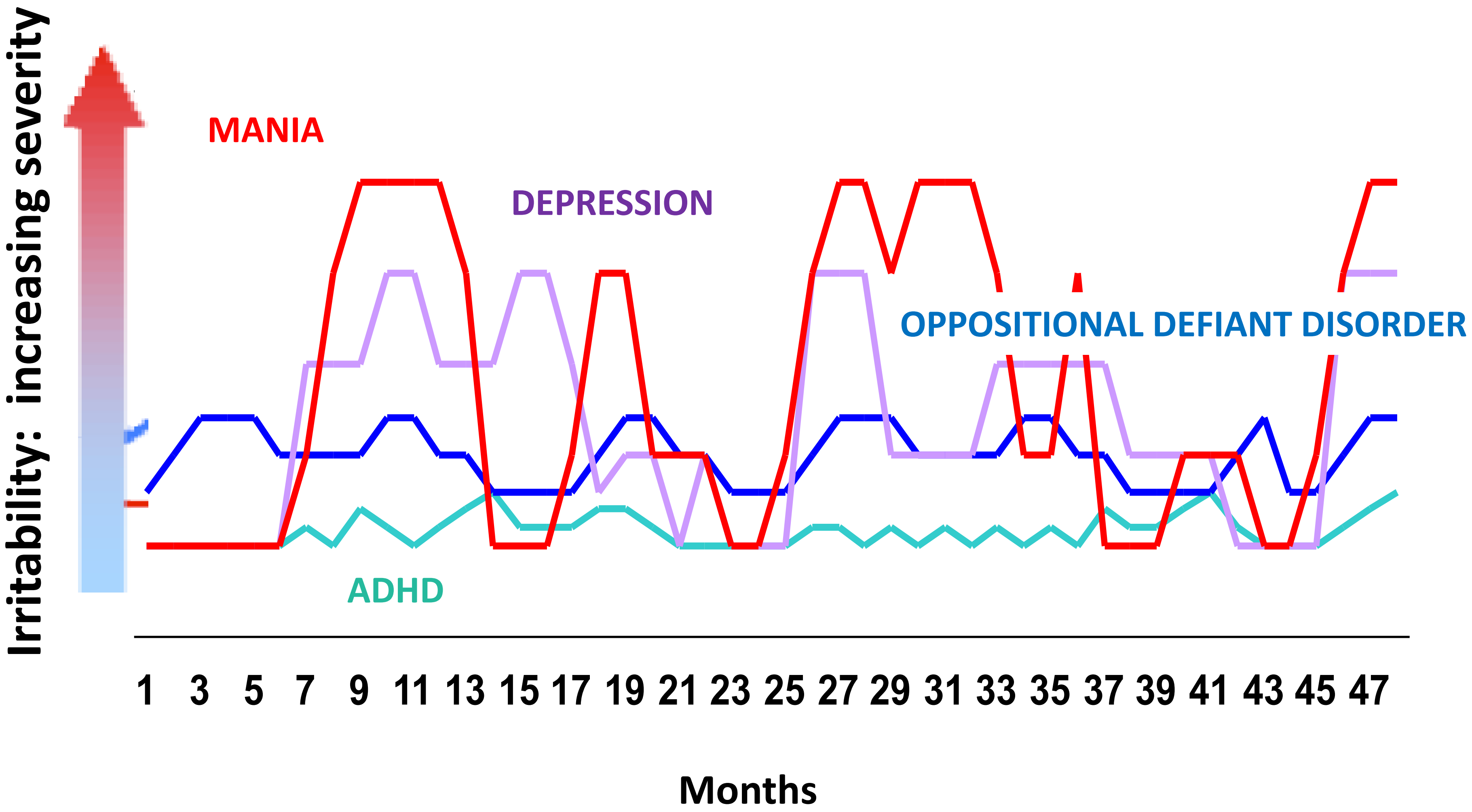
Severe aggressive and destructive irritability is a common feature of pediatric mania: kicking, hitting, biting, spitting



Bipolar disorder has 'highs' and 'lows,' with euphoric mania and melancholy depression, but irritability is common and highly impairing

Wozniak, 1995; Biederman, 2004

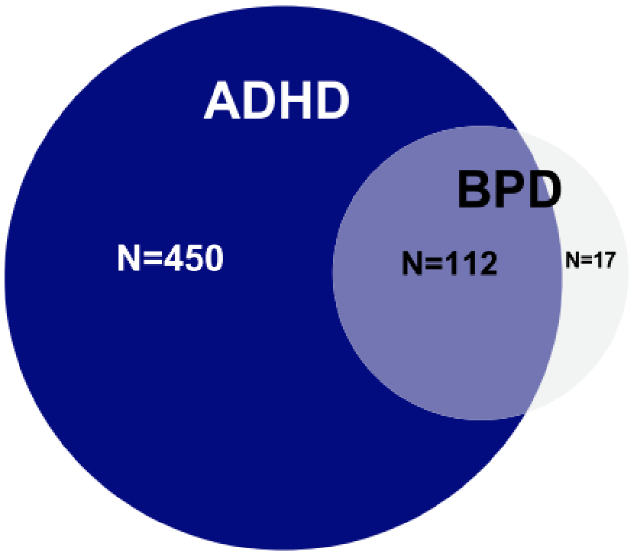
Children with bipolar disorder are seldom completely well and different types of irritability may be present



Mick 2007

Bipolar disorder + ADHD is a different and more impairing condition from ADHD alone

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

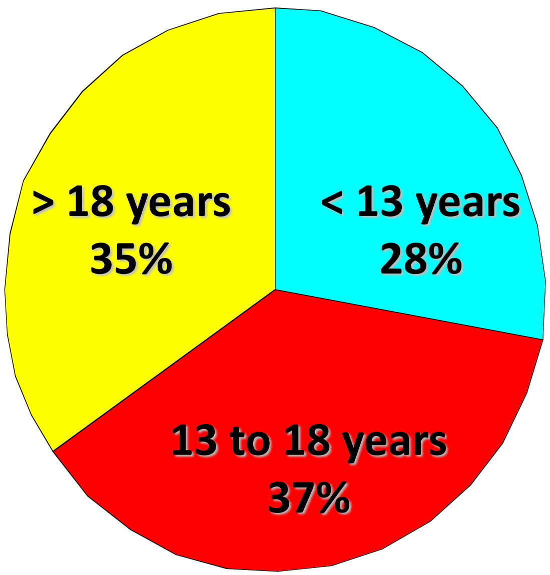


Most children with bipolar disorder also hav comorbid ADHD

Wozniak, 1995; Biederman, 2004

Bipolar adults with ADHD have clinical correlates similar to that seen in pediatric bipolar disorder.

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



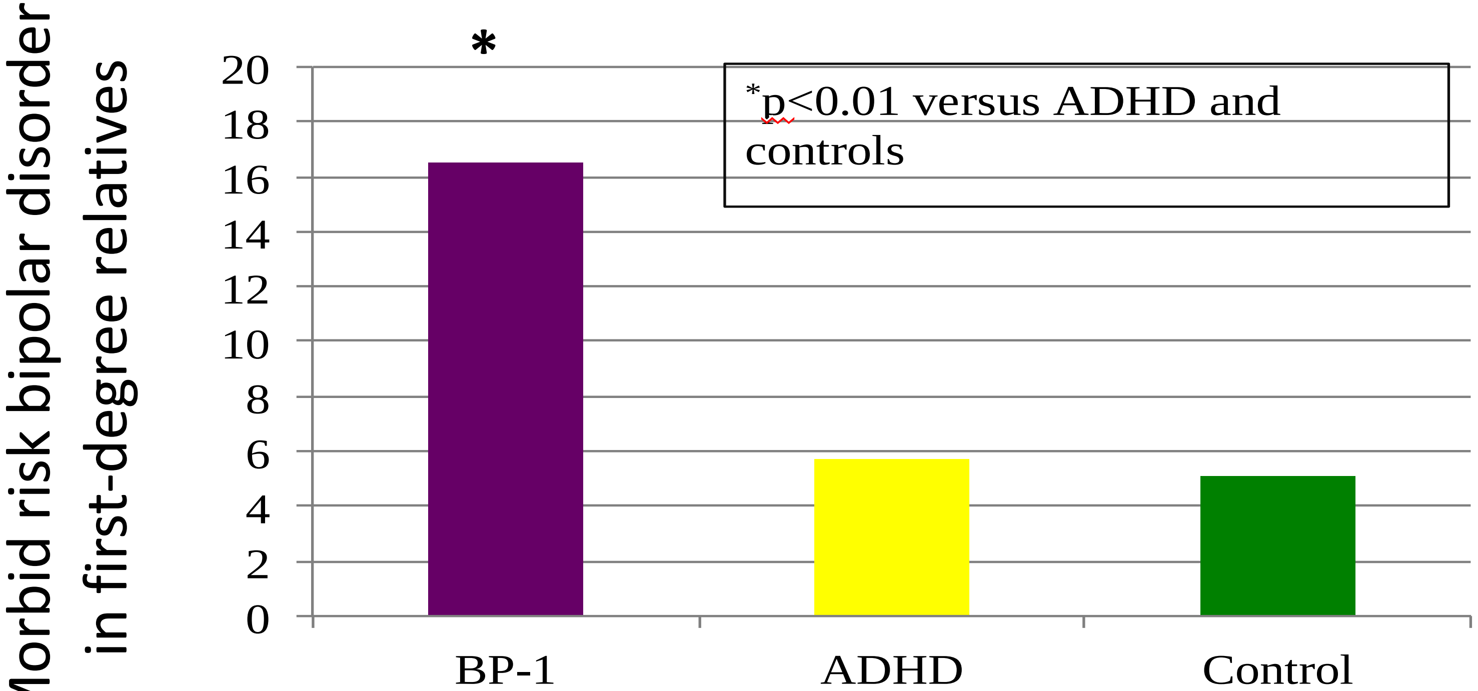
BPD+ADHD Adult patients:

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

Perlis Biol Psych 2004; Nierenberg 2005

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



BP-1	ADHD	Control
239 probands	162 probands	136 probands
726 relatives	511 relatives	411 relatives

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Wozniak J Clin Psych 2012

Subsyndromal pediatric bipolar disorder is also familial and highly impairing

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WILEY BIPOLAR DISORDERS

ORIGINAL ARTICLE

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

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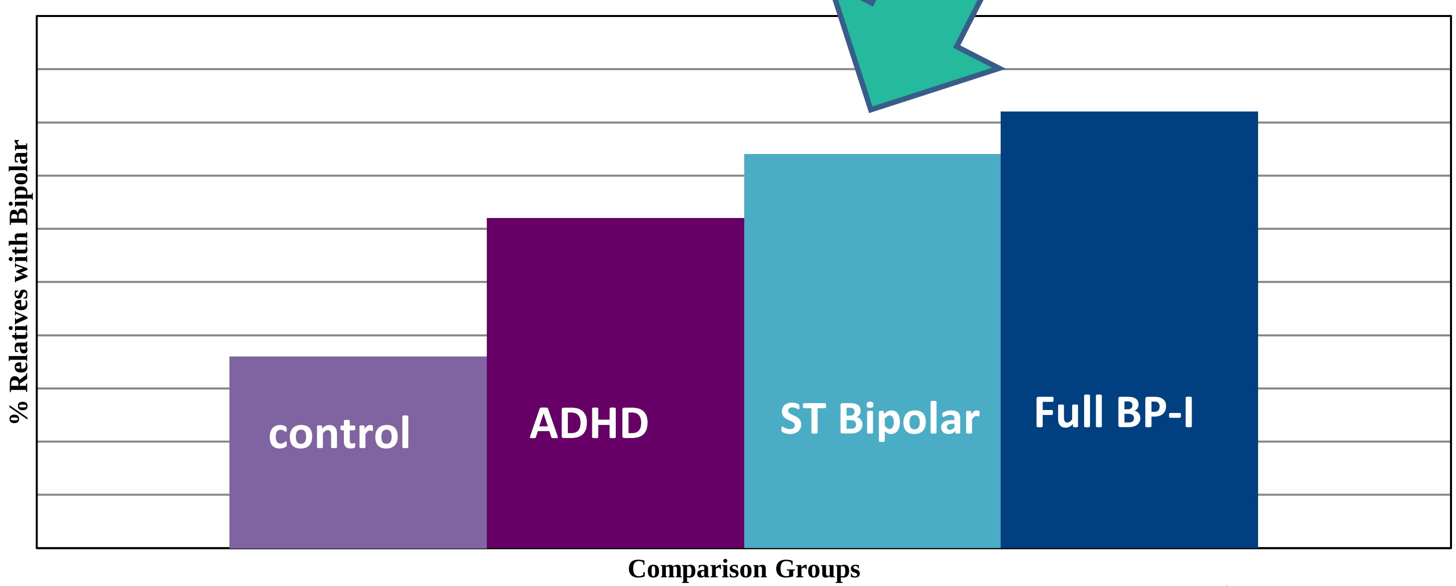
Pediatric probands with subthreshold bipolar disorder have rates of familiality similar to full syndrome probands



Wozniak 2017

Epidemiological Version (KSADS-E) and Structured Clinical Interview for DSM-IV

Persistence of pediatric-onset bipolar disorder has been documented in St Louis and Pittsburgh samples

Geller, 2008:

<u>WashU KSADS (modified criteria) study</u>

In grown-up subjects with child BP-I, identified using the, the **44.4% frequency of manic episodes was 13 to 44 times higher than population prevalences**, strongly supporting continuity

Birmaher, 2009:

<u>The Course and Outcome of Bipolar Youth (COBY) Study</u>

25% of BPDII and 38% of BPD NOS converted to BPI

Subjects symptomatic on average for 60% of the follow-up period

Geller ArchGenPsychiatry 2008
Birmaher AmJPsychiatry 2009

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

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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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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 high levels of morbidity and disability. Persistence of subsyndromal forms of bipolar disorder was also associated with dysfunction and morbidity

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

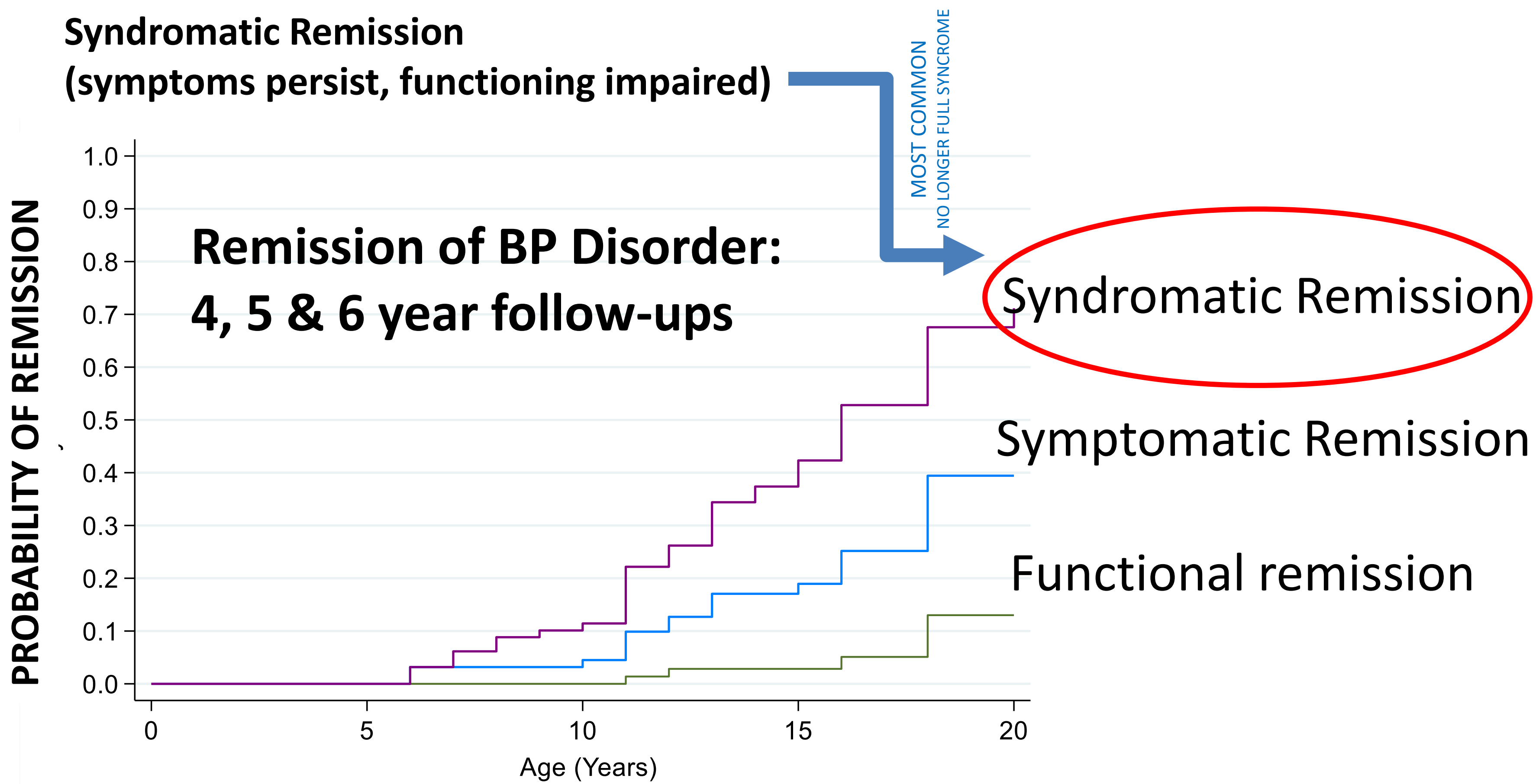
- **Baseline age 10 years**
- **76% male**
- **Age of onset bipolar disorder: 5 years**
- **Duration of BPD at baseline: 7 years**

Wozniak JPsychiatrRes 2011

Functional Remission
(no symptoms, good functioning) ***is less likely than***

Symptomatic Remission
(no symptoms, functioning impaired) which ***is less likely than***

Syndromatic Remission
(symptoms persist, functioning impaired)

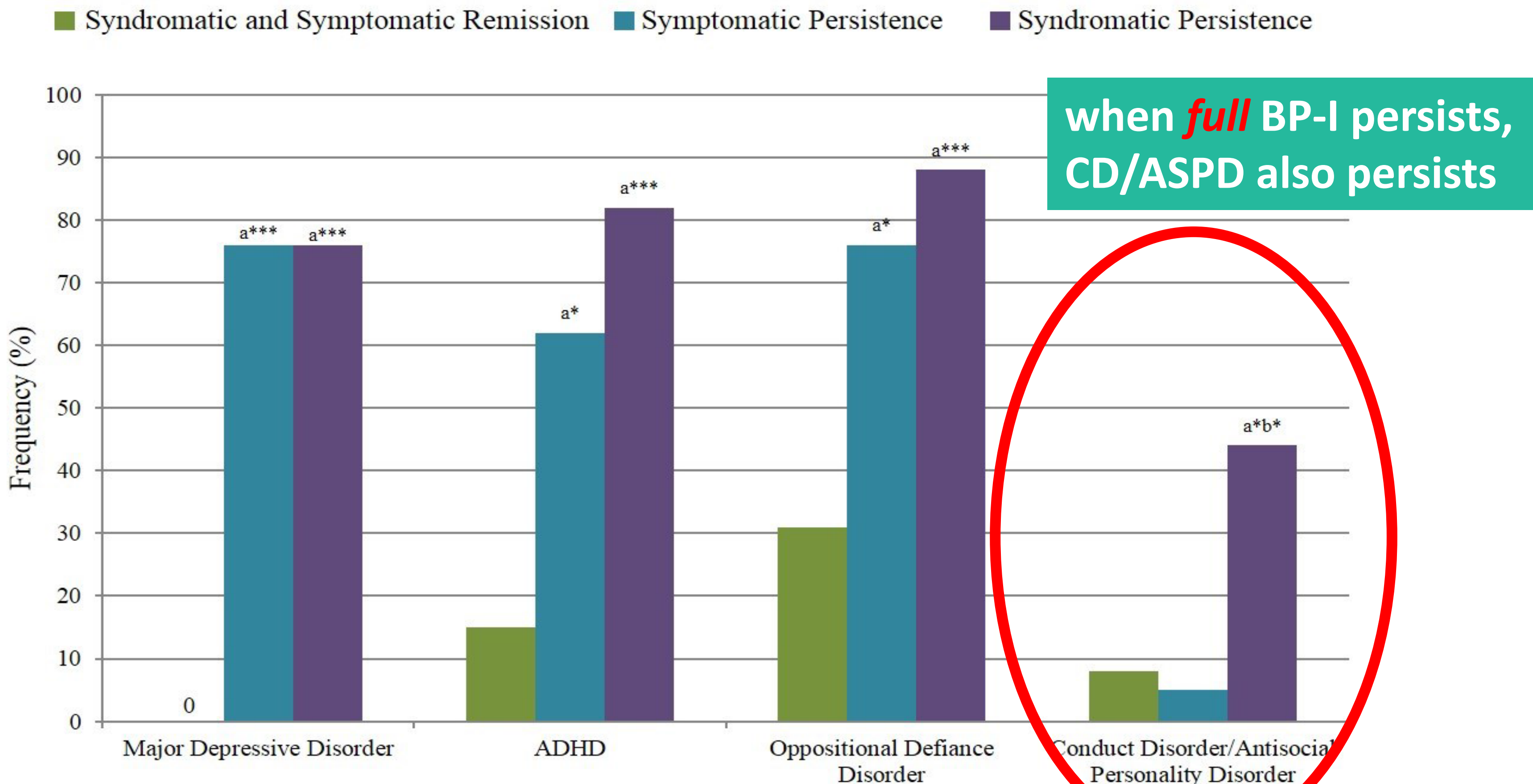


Symptoms and poor functioning found at follow-up

Wozniak 2020

Comorbid diagnoses at 5-year follow-up are high and similar in both persistent groups versus full remission (except CD/ASPD)

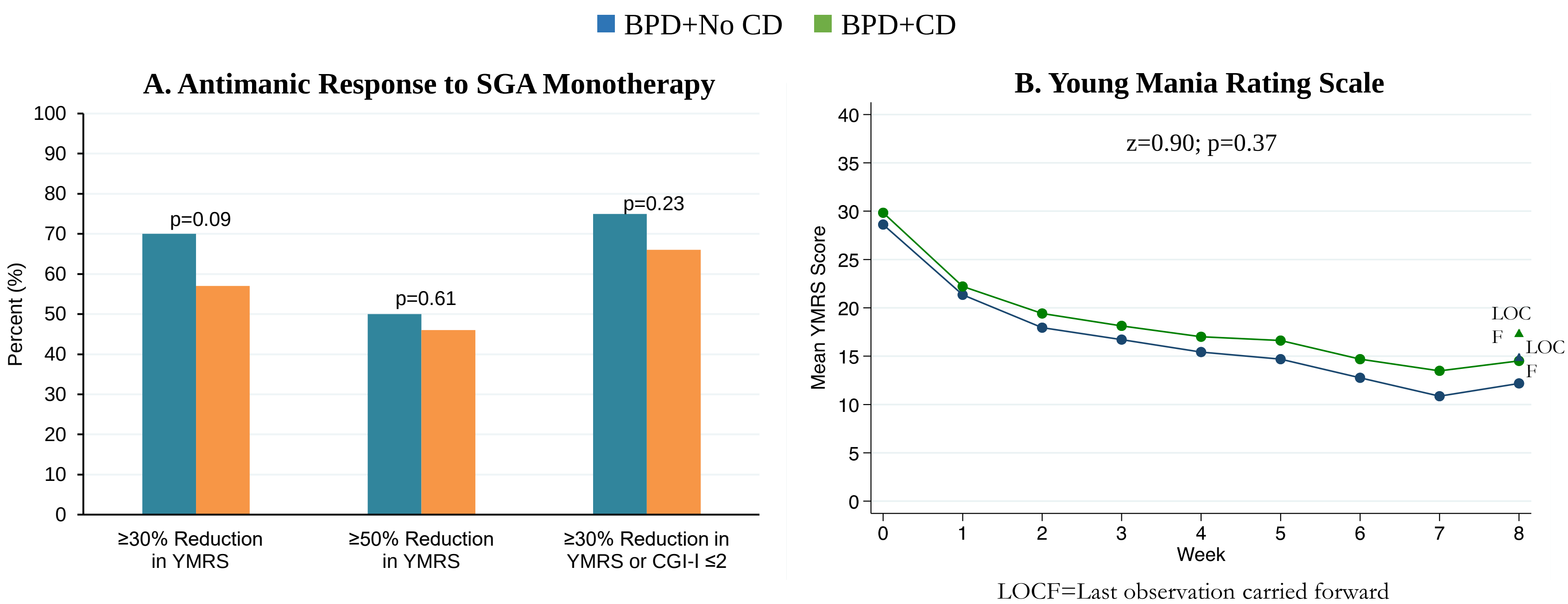
Figure 2. One-year prevalences of comorbid psychiatric disorders.
[a] Compared to syndromatic and symptomatic remission. [b] Compared to symptomatic persistence. *P<0.05, **P<0.005, ***P<0.001



Wozniak 2018

SGAs can successfully treat bipolar disorder even in the setting of CD comorbidity (and CD remits for many subjects only when BPD remits)

Figure 1. (A) Antimanic response to SGA monotherapy and (B) YMRS scores over the course of the 8-week trials in youth with bipolar disorder with and without comorbid conduct disorder.



Of the 57 BP + CD with antimanic response to SGA treatment,

18 (32%) had CGI-CD-I scores ≤ 2 at endpoint (very much or much improved)

Of the 32 BP + CD with no antimanic response to SGA treatment,

3 (9%) had CGI-CD-I scores ≤ 3 at endpoint (very much or much or improved)

We have many FDA approved treatments for youth with emotional dysregulation

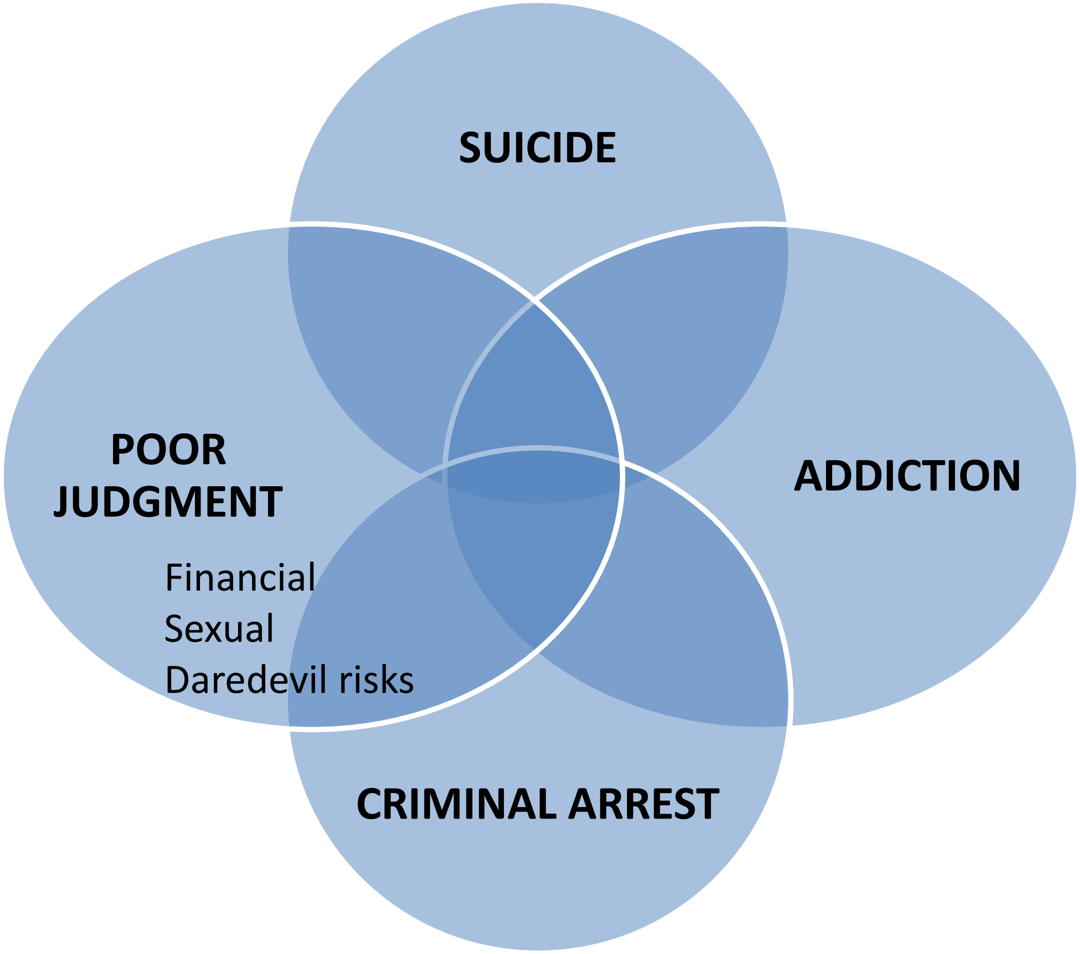
Lithium: manic or mixed states, patients age 13-17

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

Fluoxetine: depression and OCD age 8+
Escitalopram: depression age 12+
Sertraline,fluvoxamine, anfranil: pediatric OCD

Aripiprazole: irritability associated with autistic disorder age 6-17
Risperidone: irritability associated with autism age 5-16

The risk-benefit analysis of treatment must include the risks associated with *not* treating a serious mood disorder



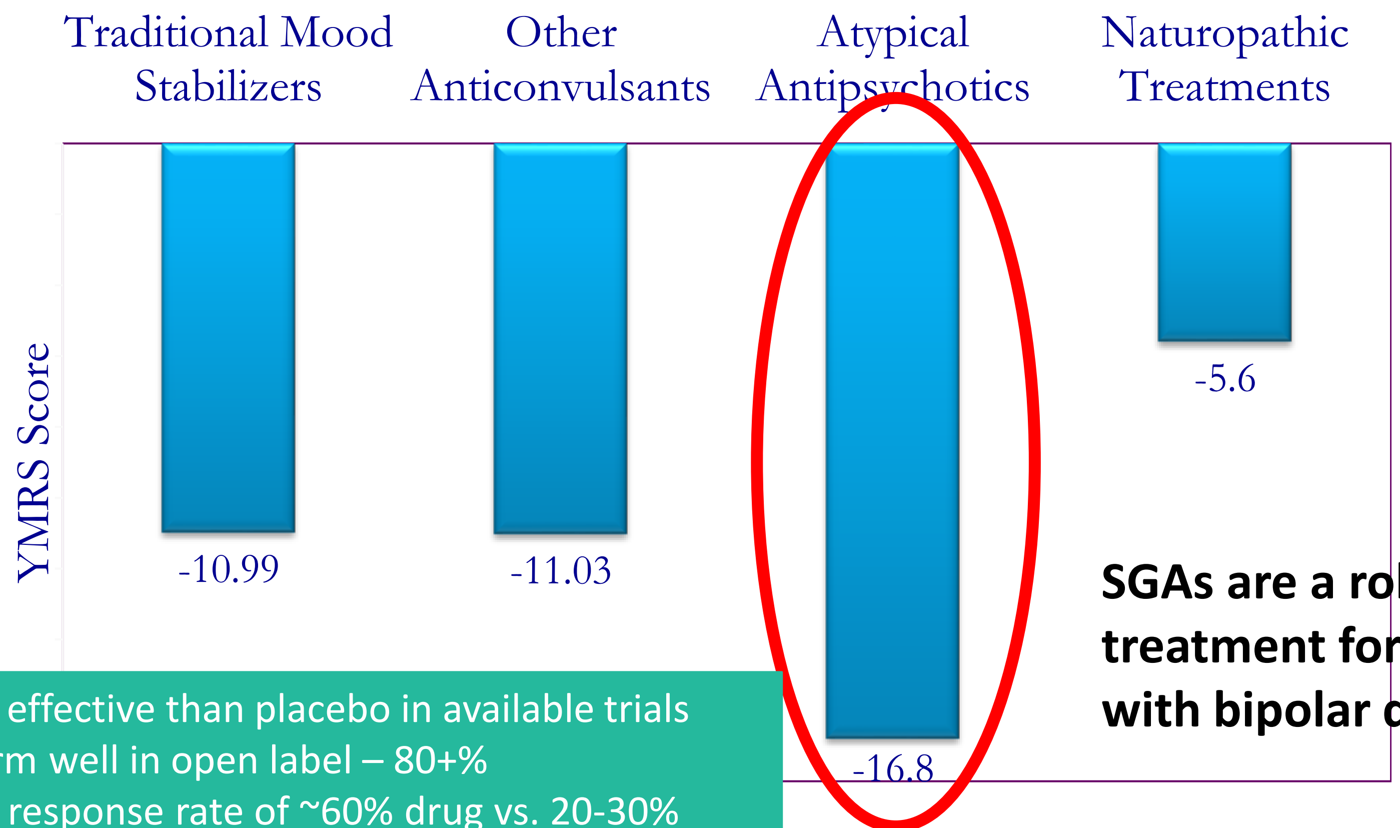
Pediatric bipolar disorder is difficult to treat

50% of adults and adolescents with mania require augmentation with another agent/combination therapy

Kowatch 2003, 2005

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

SGA=second generation antipsychotic



SGAs are a robust treatment for adults with bipolar disorder

SGAs are more effective than placebo in available trials

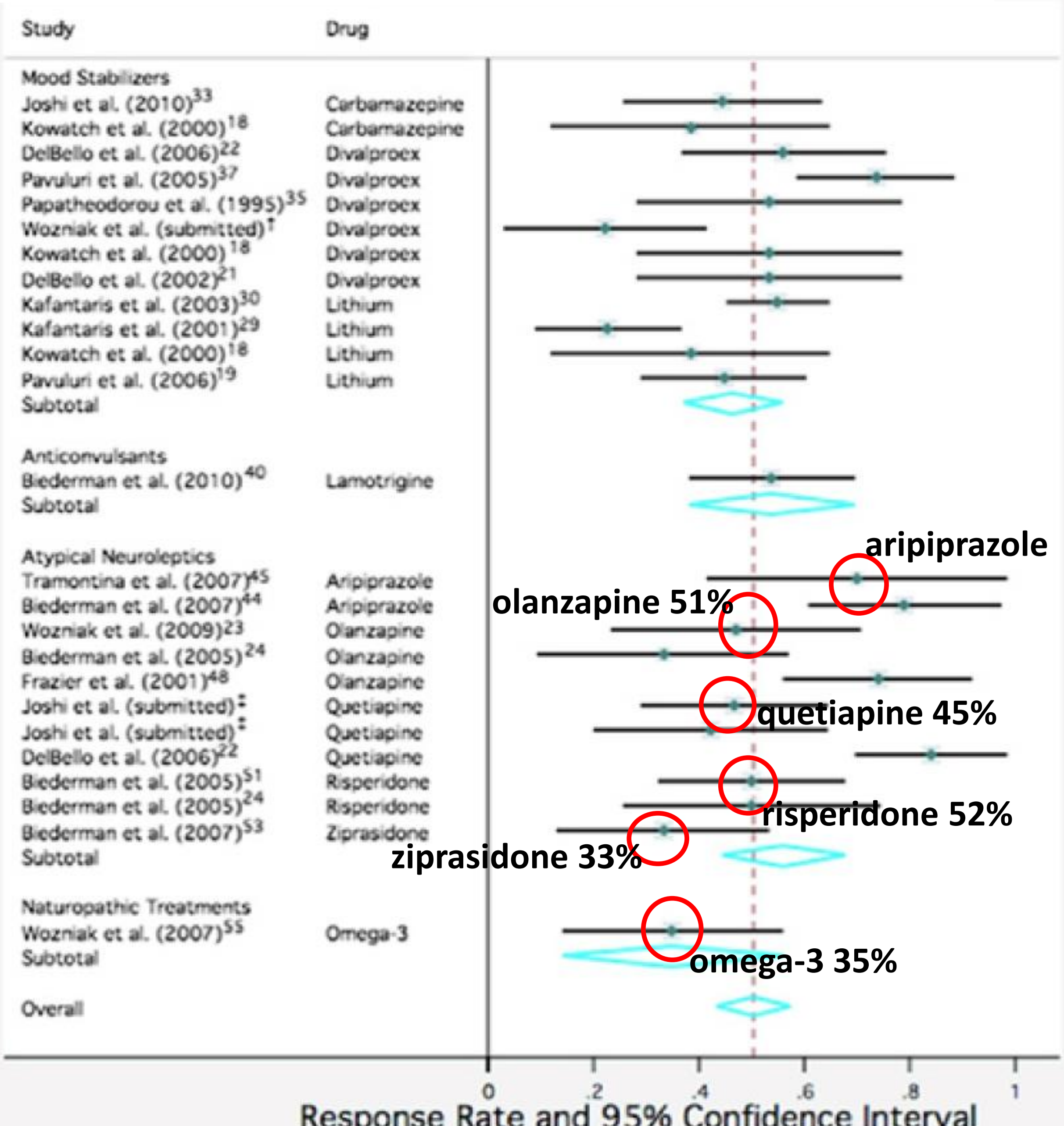
- Perform well in open label – 80+%
- Mean response rate of ~60% drug vs. 20-30% placebo
- Mean decrease in YMRS ranged from 14.2 to 18.5 in medication group vs. 8.2 to 9.99 for placebo
- Relatively rapid response, relatively well tolerated

Liu JAACAP 2011; Perlis J Clin Psychiatry 2006

Response Rates (50%+ decrease in YMRS) Open Label Trials

aripiprazole 70%
risperidone 52%
olanzapine 51%
quetiapine 45%
ziprasidone 33%

omega-3 35%



Liu JAACAP 2011;50(8):749-762

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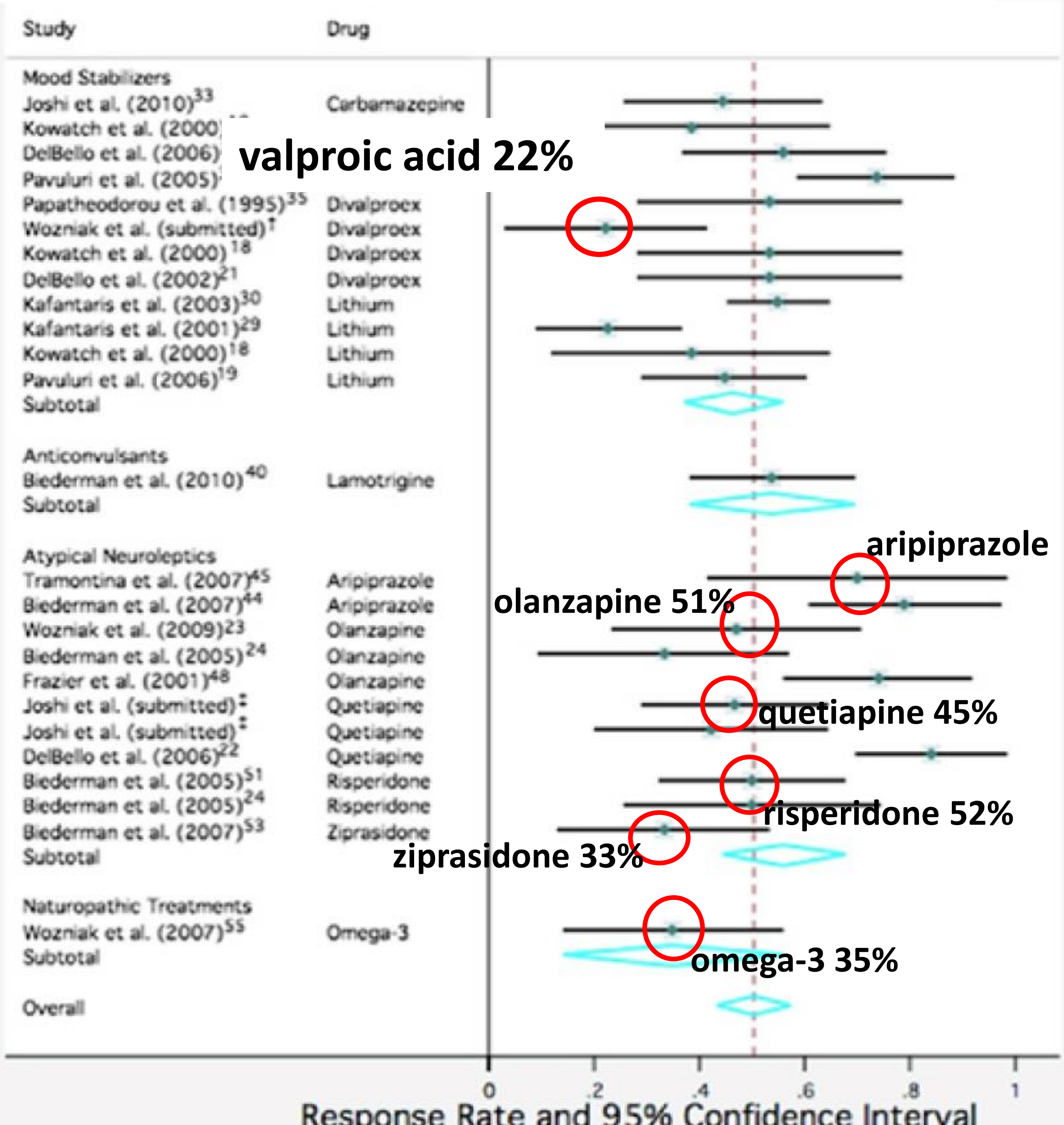
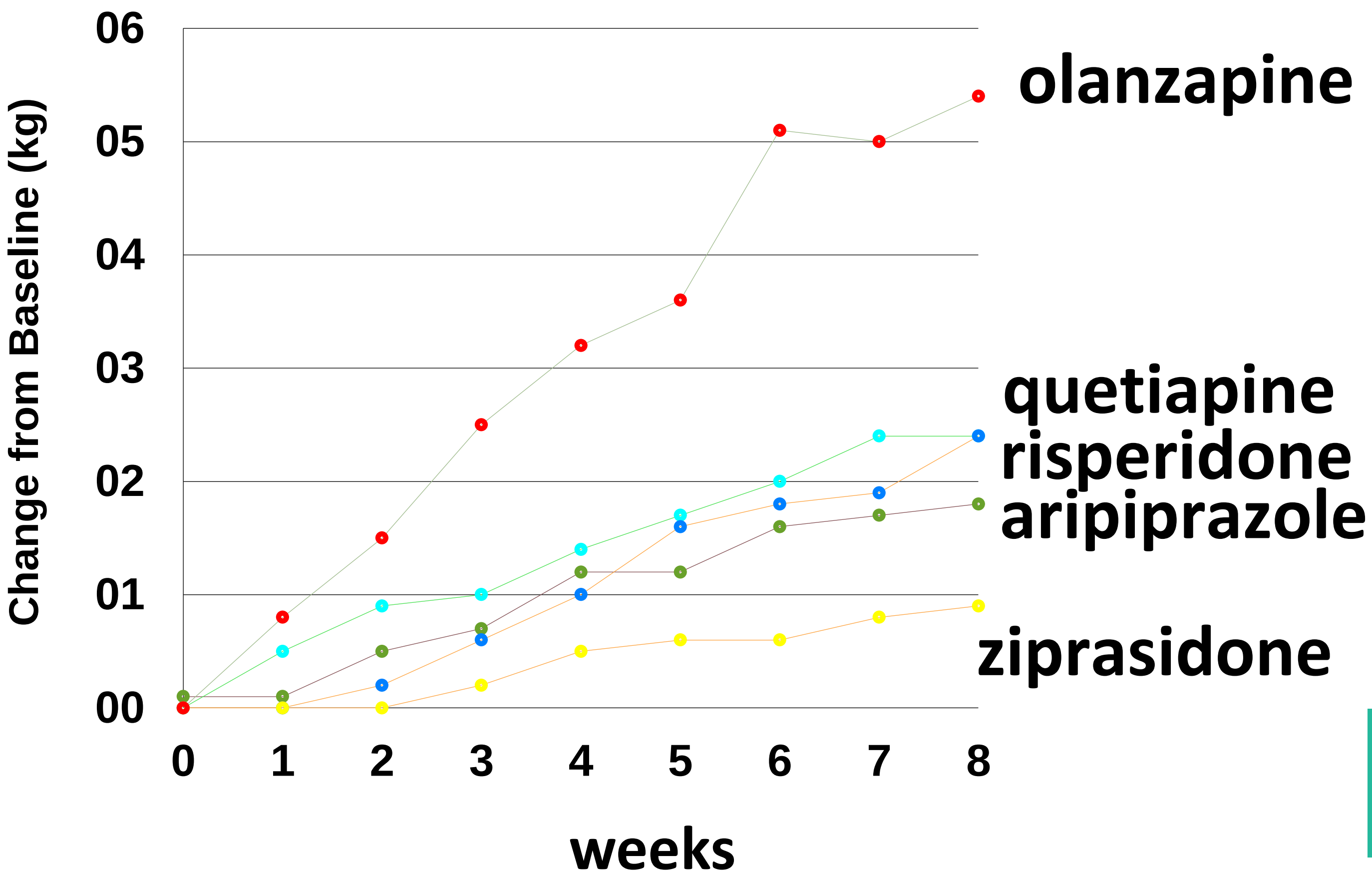


Liu JAACAP 2011;50(8):749-762

Unfortunate weight gain noted in 8-week open label trials of SGA monotherapy in children with bipolar disorder

SGA=second generation antipsychotic



Parallel trials
Total N=116

Biederman 2007 AACAP Boston

Tardive dyskinesia is dreaded, but 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):

0% children

0.8% adult

6.8% adult and elderly

first generation?

5.4% adults haloperidol

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

There is a lower risk for tardive dyskinesia associated with SGAs versus first generation antipsychotics

Correll AmJPsych 2004

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

SGA=second generation antipsychotic

divalproex sodium	lithium	carbamazepine
53%	38%	38%

RESPONSE RATES FAIR

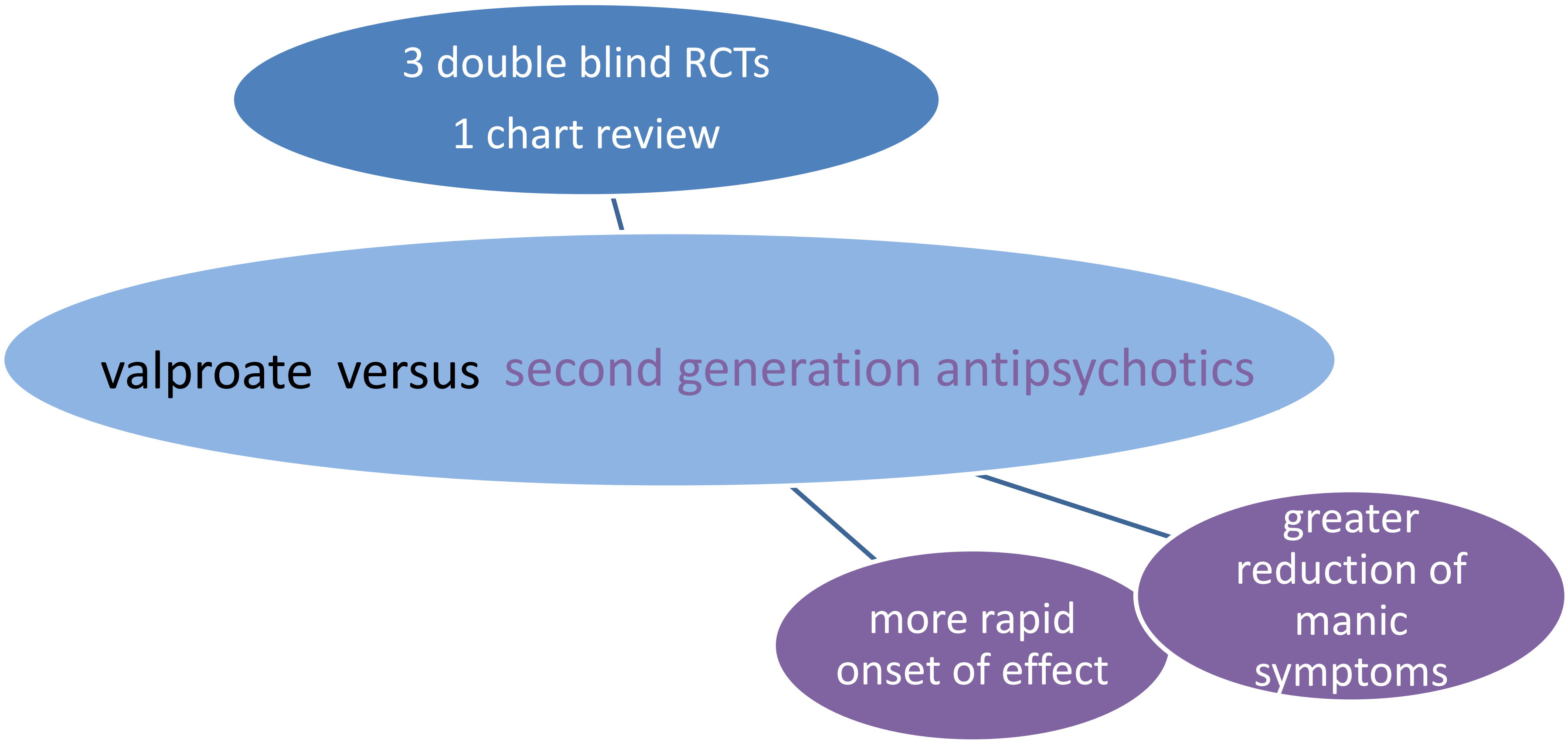
Trials notable for:

- high drop out rates
- need for rescue medications

Kowatch JAACAP 2000

SGAs perform better than valproate for pediatric bipolar 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

Lithium has long been FDA-approved for pediatric bipolar 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

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abstract

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

Newer mood stabilizers hold promise for the treatment of mania in children with bipolar disorder

Prospective open-label trial of

lamotrigine

monotherapy

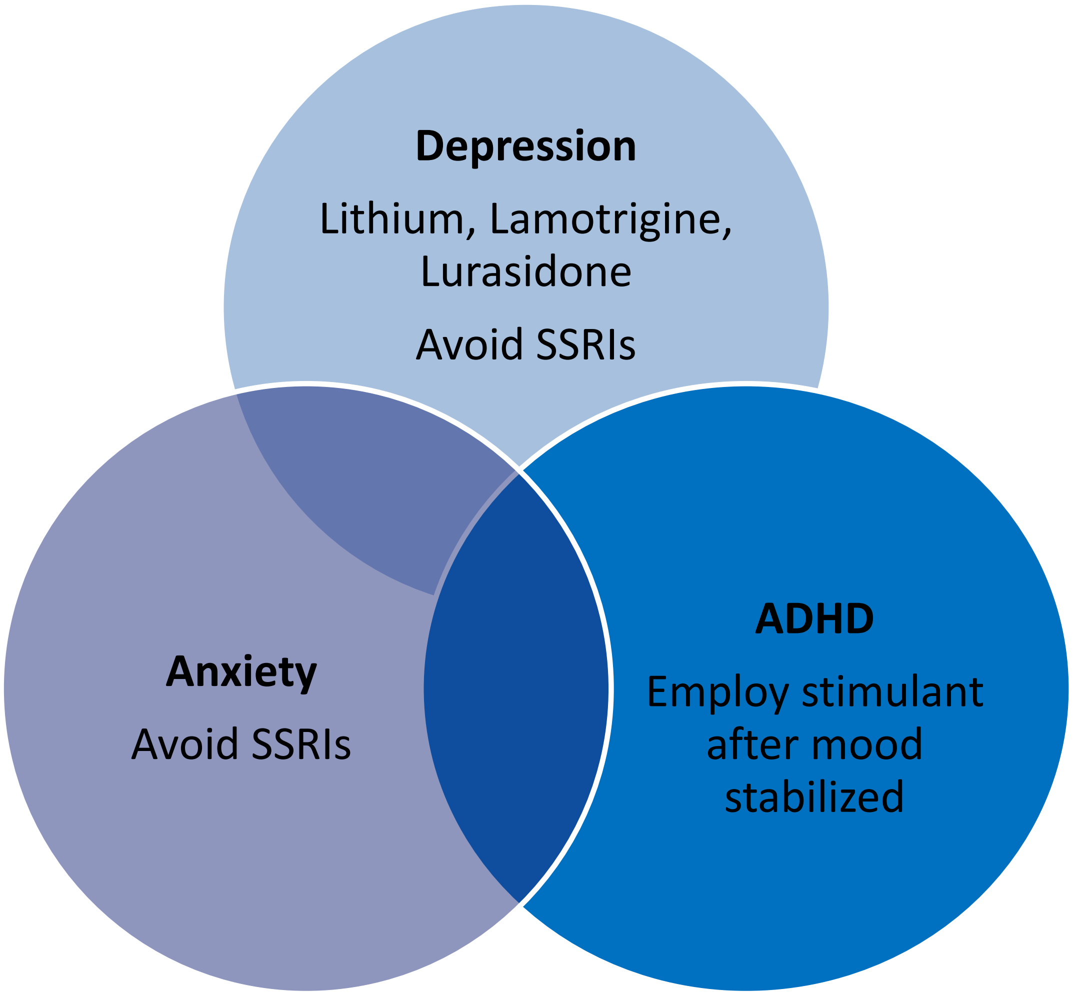
Prospective open-label trial of

extended-release carbamazepine

monotherapy

Joshi JCAP 2010

Comorbidity must be addressed in addition to mania



Joshi 2009

Depressive symptoms are often more persistent and debilitating in pediatric bipolar disorder

4-year longitudinal study pediatric bipolar I disorder

50% time met criteria for
- major depression
- minor depression
- dysthymia

2-year follow-up study of youth with

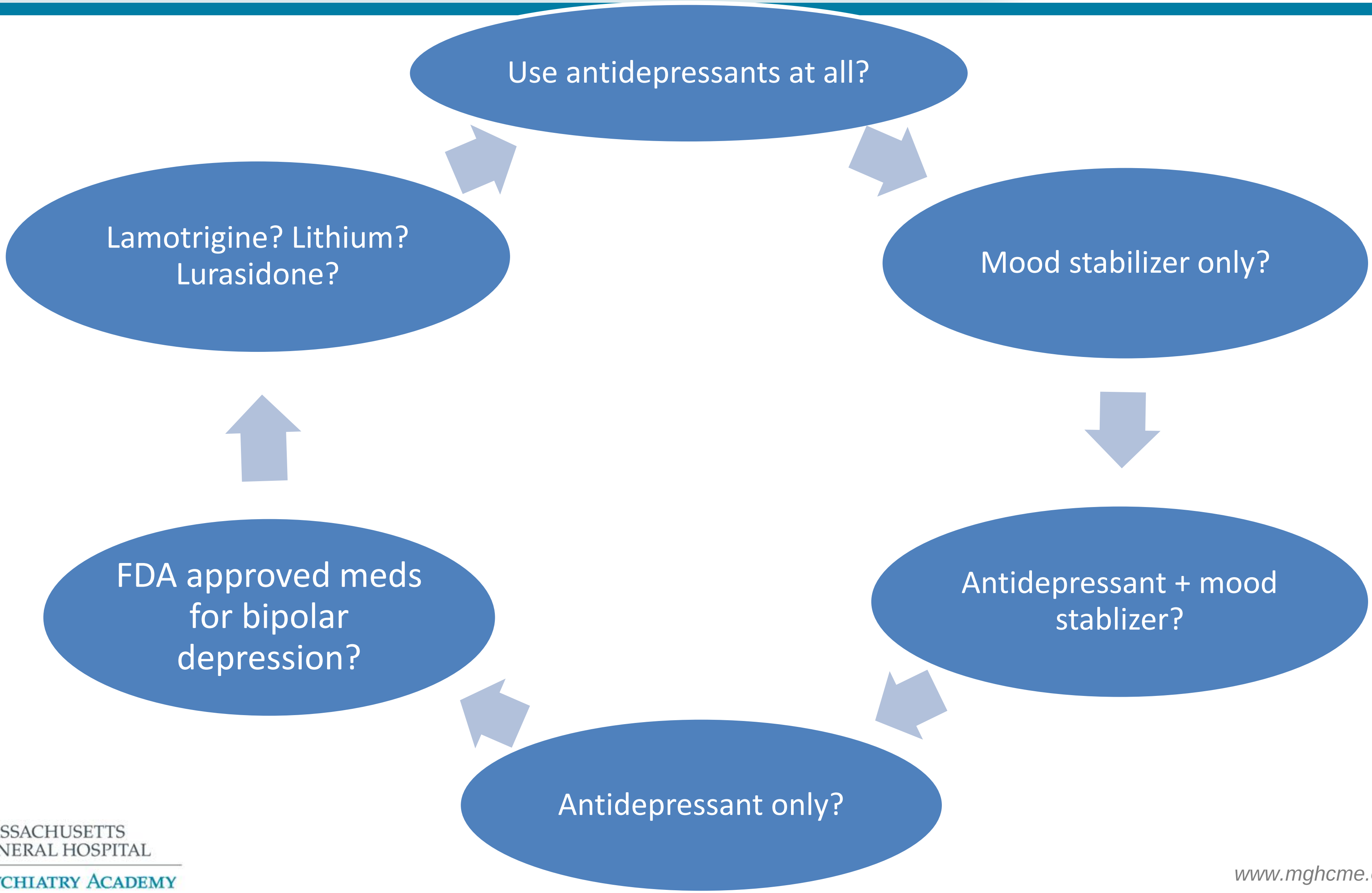
bipolar spectrum disorders

60% of the time with
- depressive symptoms
- mixed symptoms
- repeated changes in symptom polarity

"Successful long-term management of pediatric bipolar disorder requires a medication that treats both mania and

Chen 2014; Wozniak 2005; Birmaher 2006

Pharmacologic management of bipolar depression is very difficult



The double-edged sword of antidepressants for bipolar youth was noted in chart review

SSRIs led to the most improvement of BP MDD (versus mood stabilizers, typical neuroleptics or TCAs)

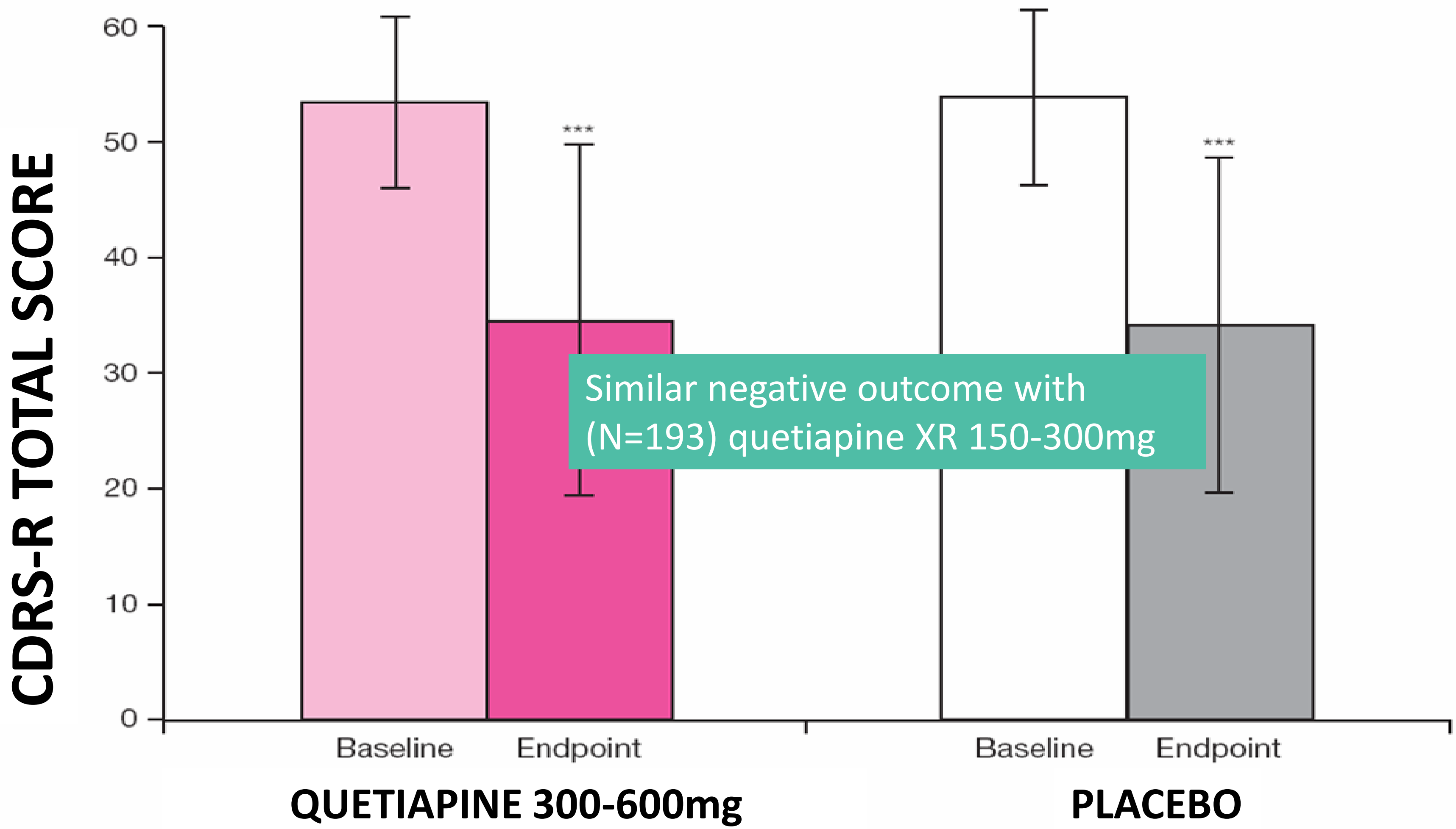
SSRIs led to the most destabilization with mania

Anti-depressants win the battle….. but lose the war

Biederman 2000

Quetiapine was not effective in adolescent bipolar 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 children and adolescents with Bipolar I Depression

placebo-controlled study

monotherapy with lurasidone

dose range of 20-80 mg/day,

minimal effects on weight and metabolic parameters

DelBello JAACAP 2017

Open label lamotrigine and lithium effective in adolescent bipolar depression (at least 50% decrease in CDRS)

Adjunctive or monotherapy lamotrigine
- N=20
- 63% responders

Monotherapy Lithium
- N=27
- 48% responders

Lithium has a narrow therapeutic window and requires intensive blood monitoring

lamotrigine is approved by FDA for use in those over the age of 16 years, due to increased risk of fatal side effects, such as Stevens–Johnson syndrome in the young age group.

Chang JAACAP 2006; Patel JAACAP 2006

SGAs have antidepressant qualities

FDA (2008) approved the use of aripiprazole in combination with antidepressant medication for the treatment of major depression in adults

RCT demonstrated increased antidepressant effect from the addition of risperidone to antidepressant monotherapy

Two reports with olanzapine N=18 adult patients found that 14 had positive response

Zarate 1998; Rothschild 1999; Mahmoud 2007

Treatment of ADHD in patients with bipolar disorder is feasible in the context of anti-manic treatment

Determine the risk of treatment-emergent mania associated with methylphenidate in patients with bipolar disorder

Swedish national registries 2006-14

N=2,307

Adults with bipolar disorder who initiated therapy with methylphenidate

TWO GROUPS

Those **WITH** concomitant mood-stabilizing treatment

Those **WITHOUT** concomitant mood-stabilizing treatment

Treatment emergent mania:

Hospitalization

New mood stabilizing medication

No association between methylphenidate and treatment-emergent mania among bipolar patients who were concomitantly receiving a mood-stabilizing medication

Rule out bipolar disorder before initiating methylphenidate as a monotherapy

Viktorin 2017

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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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

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Abstract

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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

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

disease. In treating this group, selective serotonin reuptake inhibitors and serotonin norepinephrine 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

Natural treatments are an appealing option for the treatment of bipolar disorder in children

Prescription medications have unknown effects on the developing brain

Intervening with supplementation during critical periods may enhance brain development

An agent with minimal effect on the adult brain could play a major role in the developing brain

Treatment for bipolar disorder involves antipsychotic medications and other mood stabilizers with significant side effects, fueling reluctance to diagnose

Funding/support: **This study was supported by a generous philanthropic donation from Kent and Elizabeth Dauten (Chicago, Illinois).**

THE JOURNAL OF
CLINICAL PSYCHIATRY

Focus on Childhood and Adolescent Mental Health

A Randomized Clinical Trial of High Eicosapentaenoic Acid Omega-3 Fatty Acids and Inositol as Monotherapy and in Combination in the Treatment of Pediatric Bipolar Spectrum Disorders:
A Pilot Study

Janet Wozniak, MD[a,b]; Stephen V. Faraone, PhD[c]; James Chan, MA[a]; Laura Tarko, MPH[a]; Mariely Hernandez, MA[a]; Jacqueline Davis, BA[a]; K. Yvonne Woodworth, BA[a]; and Joseph Biederman, MD[a,b,*]

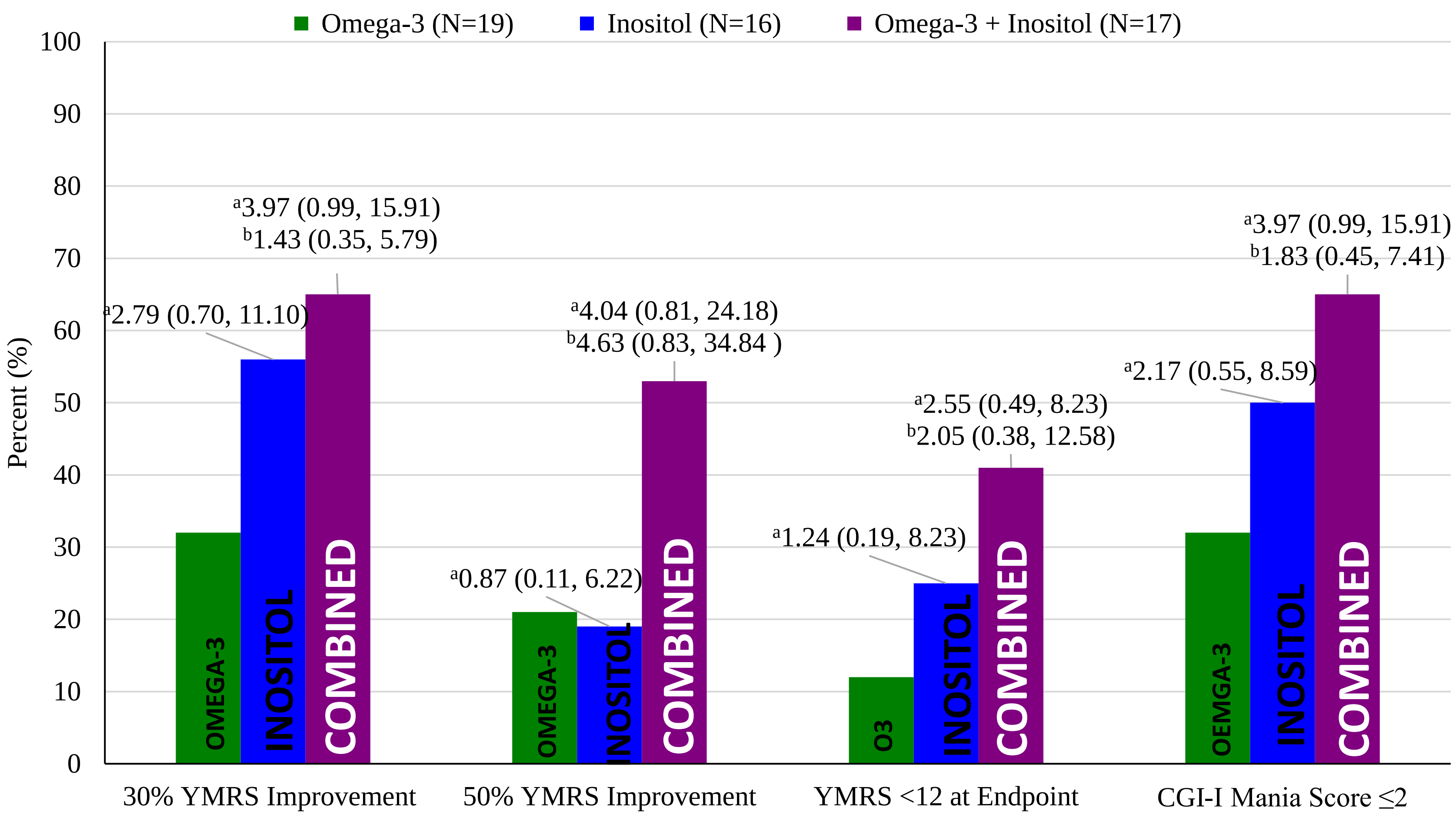
ABSTRACT

Objective: We conducted a 12-week, randomized, double-blind, controlled clinical trial to evaluate the effectiveness and tolerability of high eicosapentaenoic acid (EPA)/docosahexaenoic acid (DHA) omega-3 fatty acids and inositol as monotherapy and in combination in children with bipolar spectrum disorders

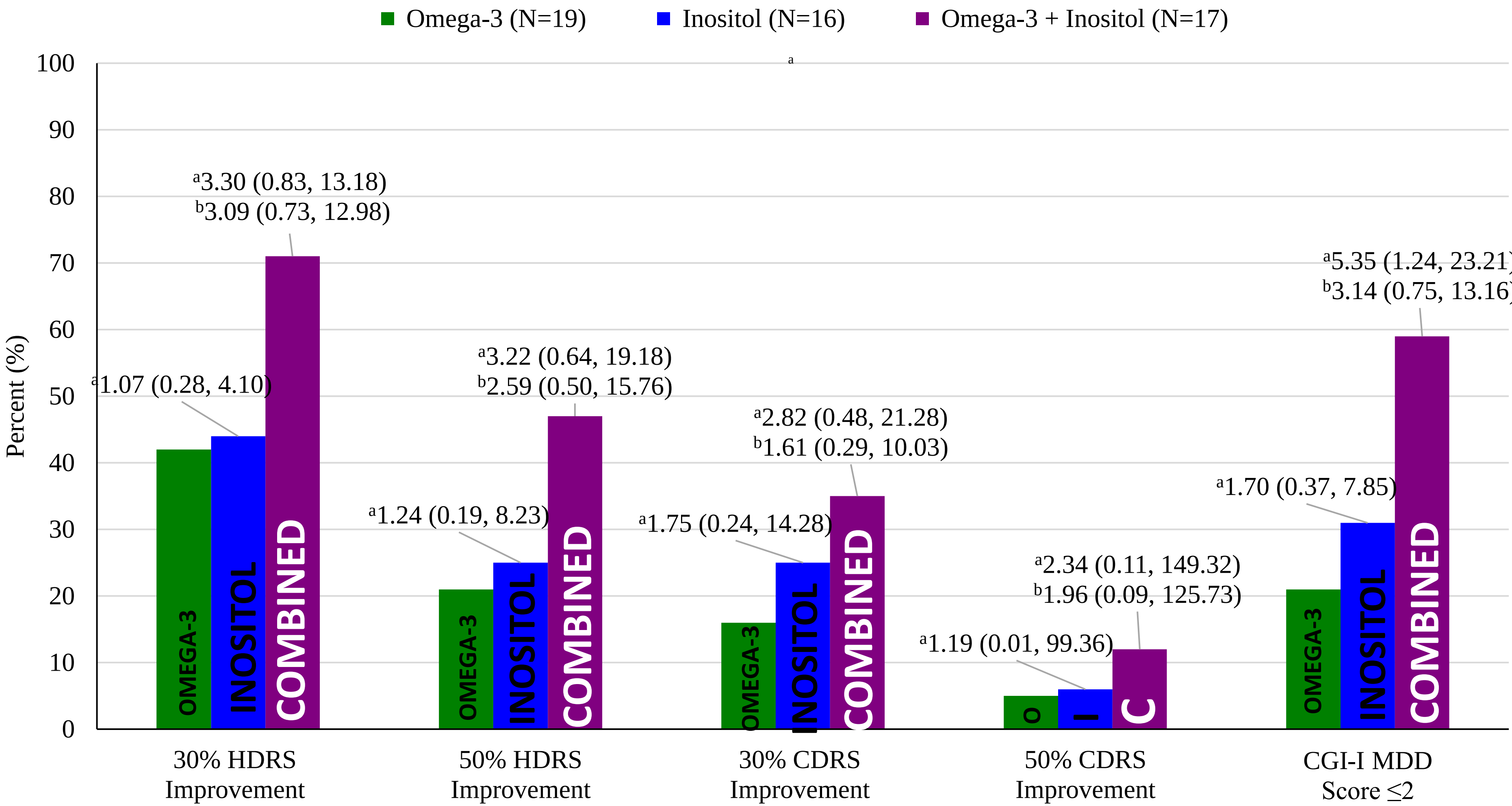
Pediatric bipolar disorder is increasingly recognized across the world as a prevalent and highly morbid disorder.[1–3] While several medications have received US Food and Drug Administration (FDA) approval for the treatment of pediatric bipolar disorder, their use is associated with significant and serious adverse effects, including weight gain, dyslipidemias, glycemic dyscontrol and risk for diabetes, and risk for tardive dyskinesia. This state of affairs supports the search for alternative safe and effective treatment to address the urgent

November 2015

Omega-3 + Inositol <u>combined</u> outperforms either used alone for mania (N=52)

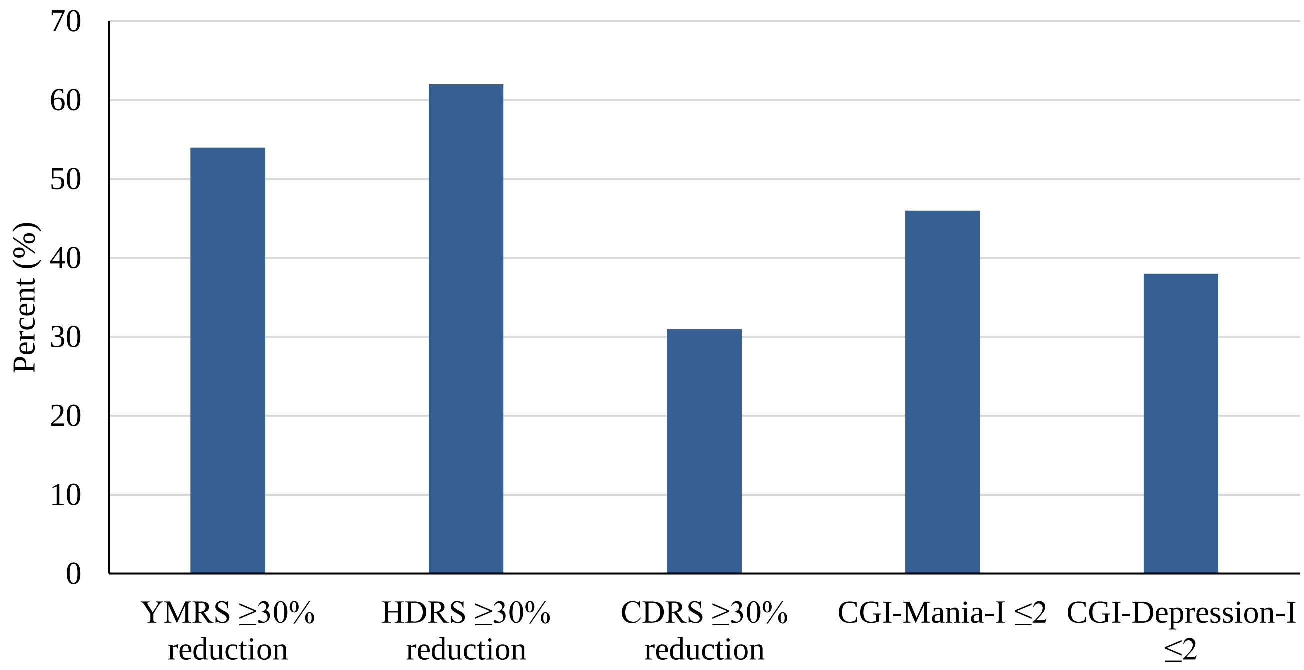


Omega-3 + Inositol ***combined*** outperforms either used alone for depression (N=52)



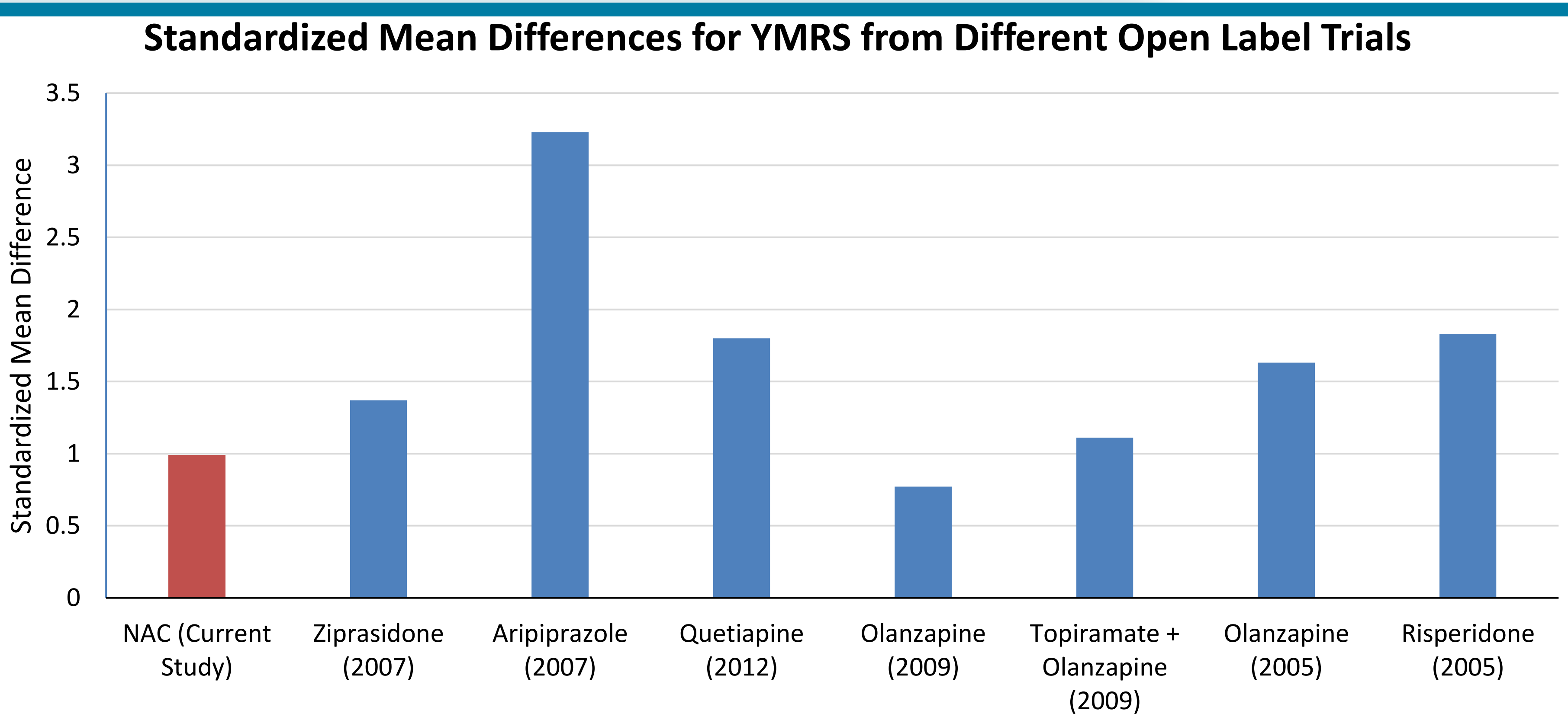
Funding/support: This study was supported by a generous philanthropic donation from Lisa and Philip Astley-Sparke (Boston, Massachusetts)

In open label trial NAC was useful for pediatric bipolar disorder with significant difference from baseline to endpoint YMRS, HDRS and CDRS



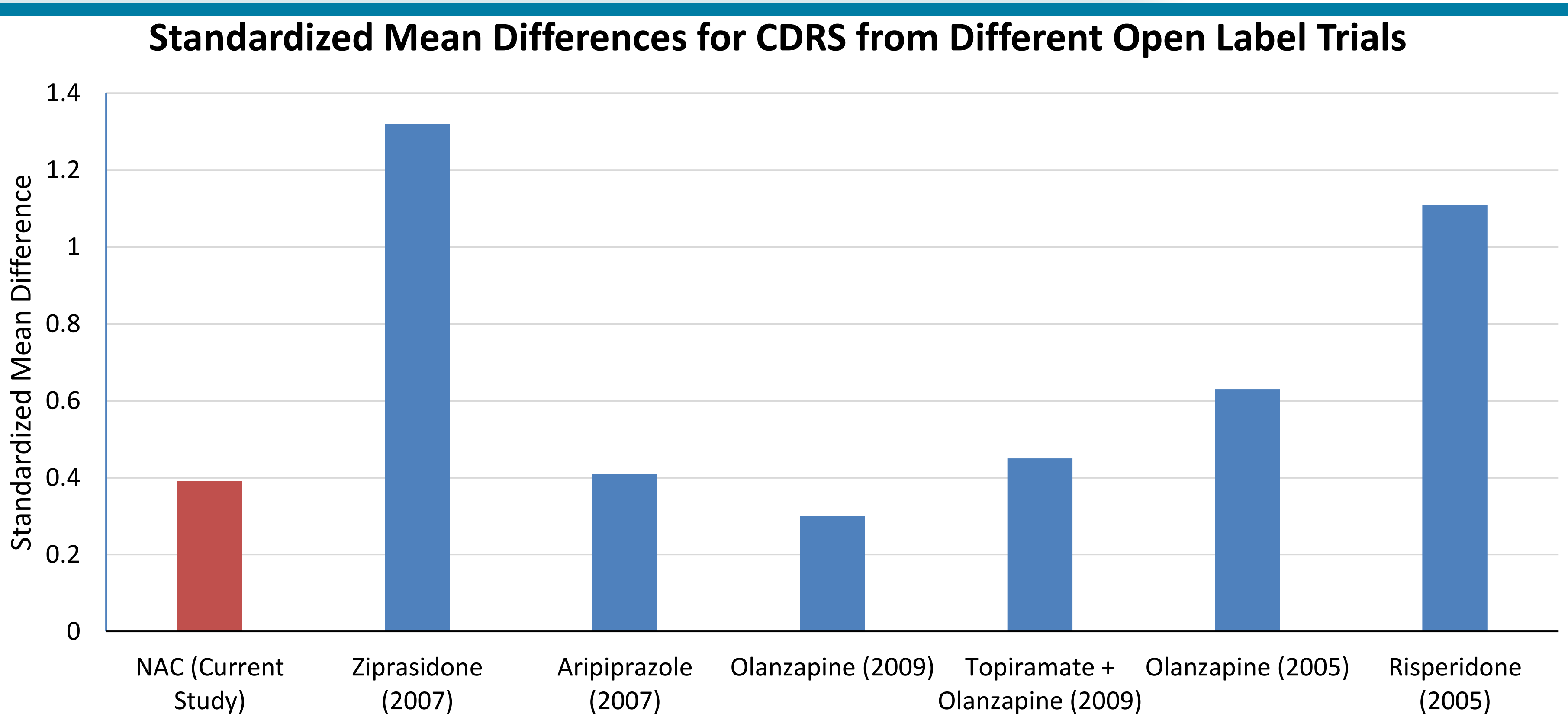
12 week open label
N=26
Average age 10 years
46% male

NAC has an effect size generally lower, but in the ballpark of the effect size of SGAs for mania



SMD is a summary statistic reflecting effect size, a method to to compare therapies across different studies in the absence of head-to-head trials

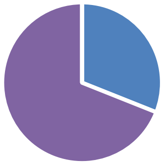
NAC has an effect size generally lower, but in the ballpark of the effect size of SGAs for mania

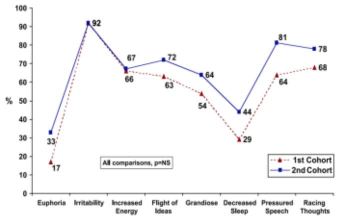


SMD is a summary statistic reflecting effect size, a method to to compare therapies across different studies in the absence of head-to-head trials

Overview: Switch from pediatric depression to bipolar disorder is common and children with bipolar disorder spend much time in mixed or depressive states. Pediatric-onset bipolar disorder is a severely impairing disorder which persists into late adolescence; treatment usually necessary

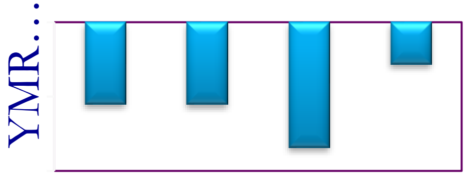
Children with MDD often switch: Early depression is a predictor of bipolar disorder

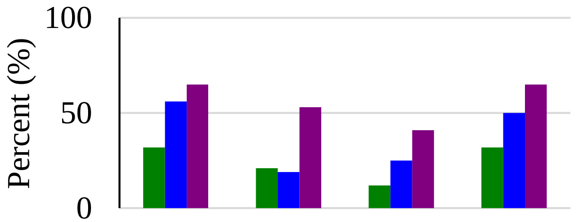




Pediatric Bipolar disorder is a highly morbid condition that affects a significant minority of young children, is familial and persists over time

Treatment: Pharmacologic treatment often with SGAs is generally required for pediatric mood disorders: use antidepressants with caution





Natural Treatments hold promise in the treatment of pediatric bipolar disorder

What questions do you have?