Juvenile Mania: Diagnosis and Treatment 2 parts

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Disclosure and potential conflicts

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

Research support: PCORI
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Spouse research support: UCB Pharma, NeuroMetrix, Luitpold, NIMH, RLS Foundation

Juvenile Mania: Treatment part 2

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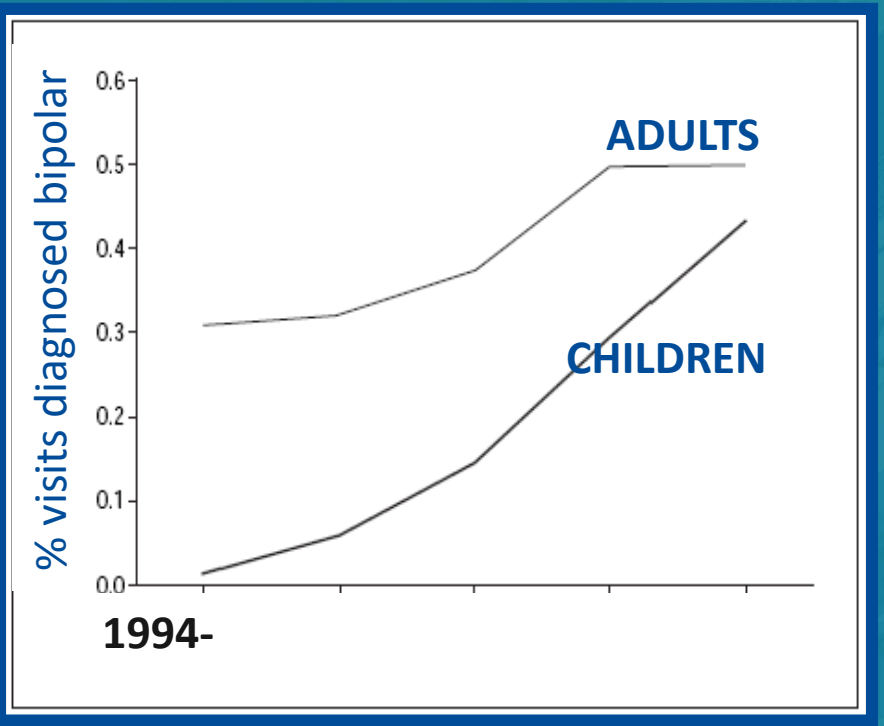


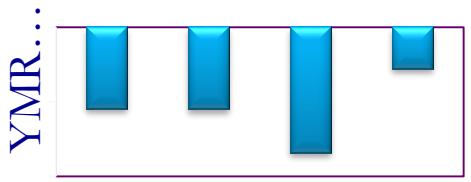
Overview: Switch from pediatric depression to bipolar disorder is common. Pediatric-onset bipolar disorder is a severely impairing disorder which persists into late adolescence.

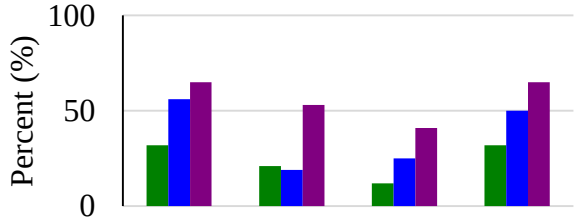
Antipsychotic medications are the most effective treatments for pediatric mania. Comorbid conditions must be addressed. Natural treatments hold promise.

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 with SGAs is generally required for pediatric bipolar disorder and comorbidities need separate treatment: use antidepressants with caution





Natural Treatments hold promise in the treatment of pediatric bipolar disorder

We have many FDA approved treatments for youth with emotional dysregulation

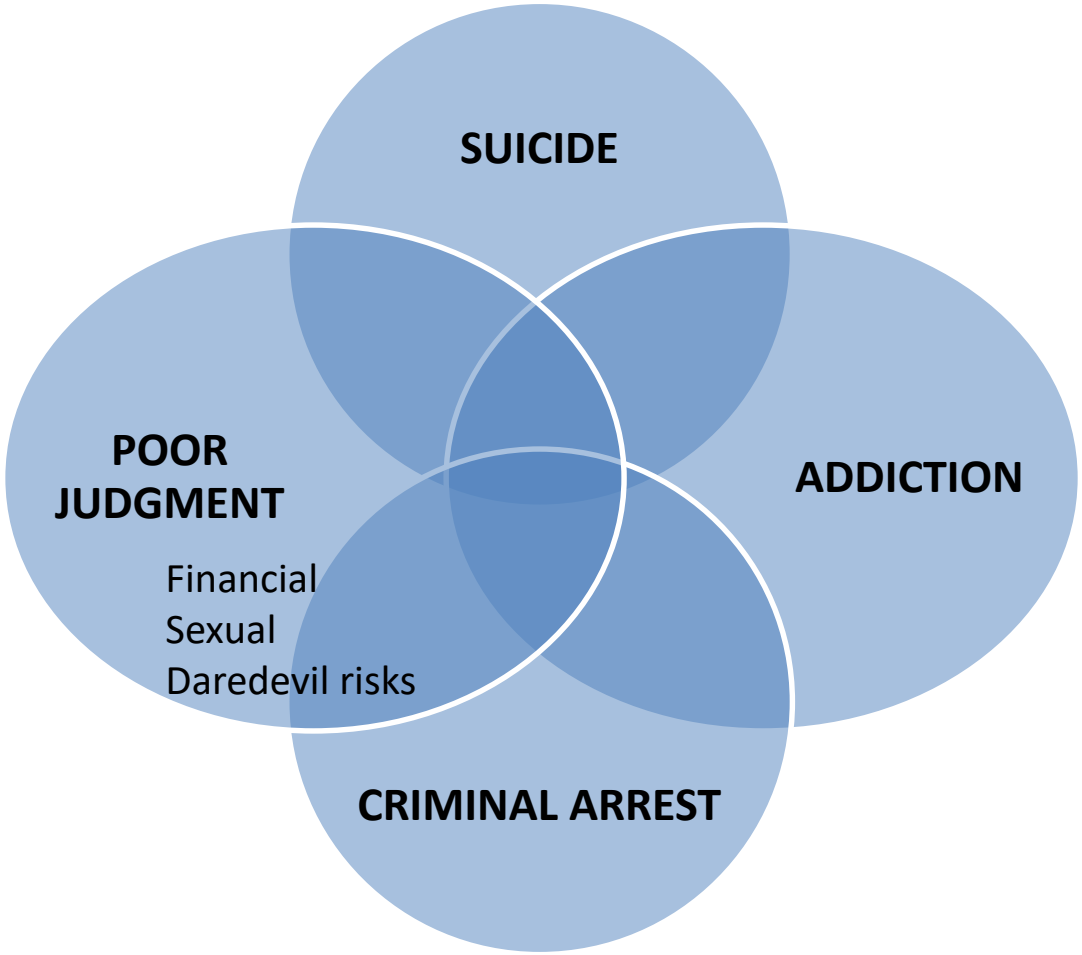
Lithium: manic or mixed states, patients age 13-17

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

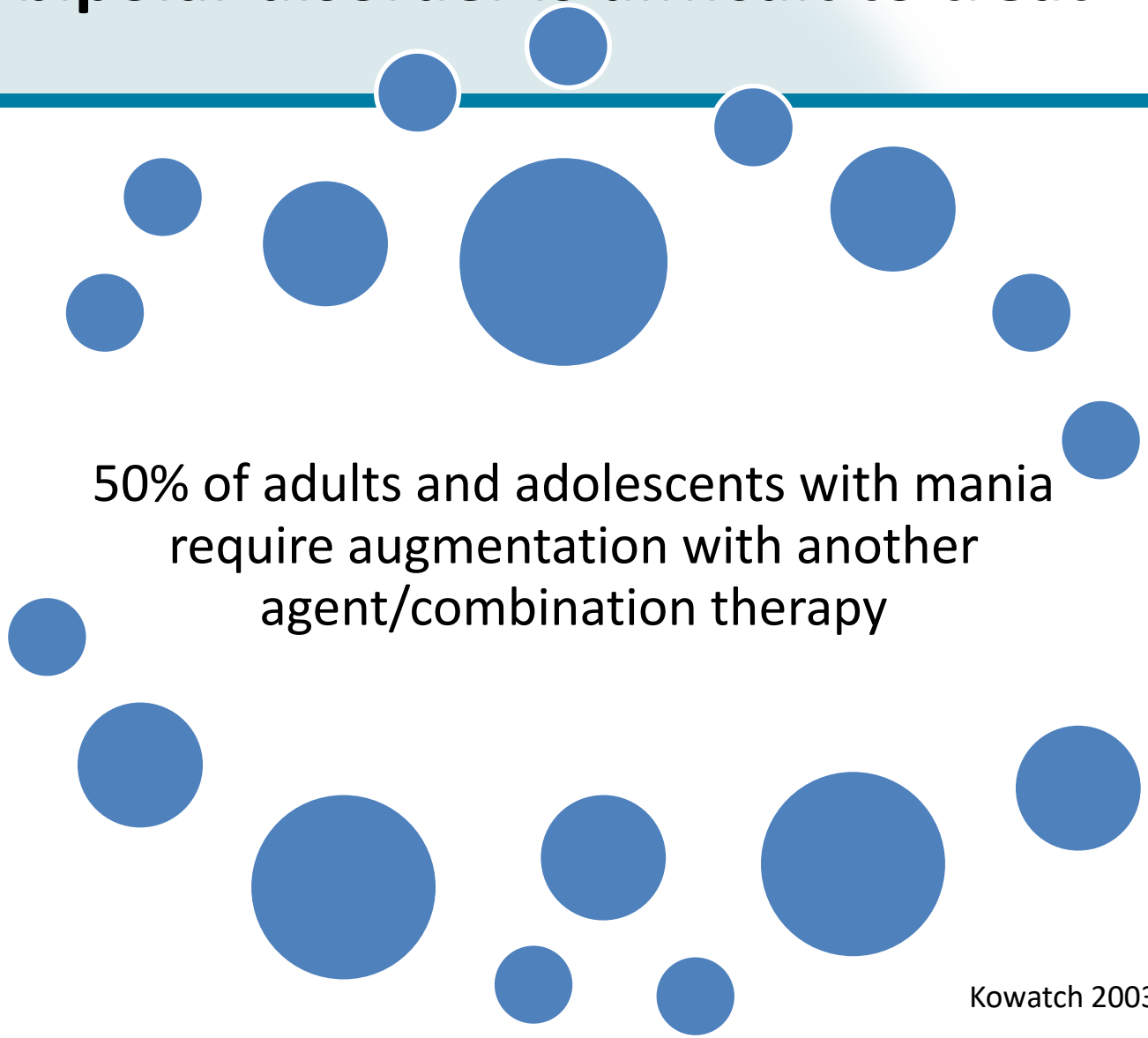
Fluoxetine: depression and OCD age 8+
Escitalopram: depression age 12+
Sertraline,fluvoxamine, anfranil: pediatric OCD

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 Bipolar Disorder



Pediatric bipolar disorder is difficult to treat

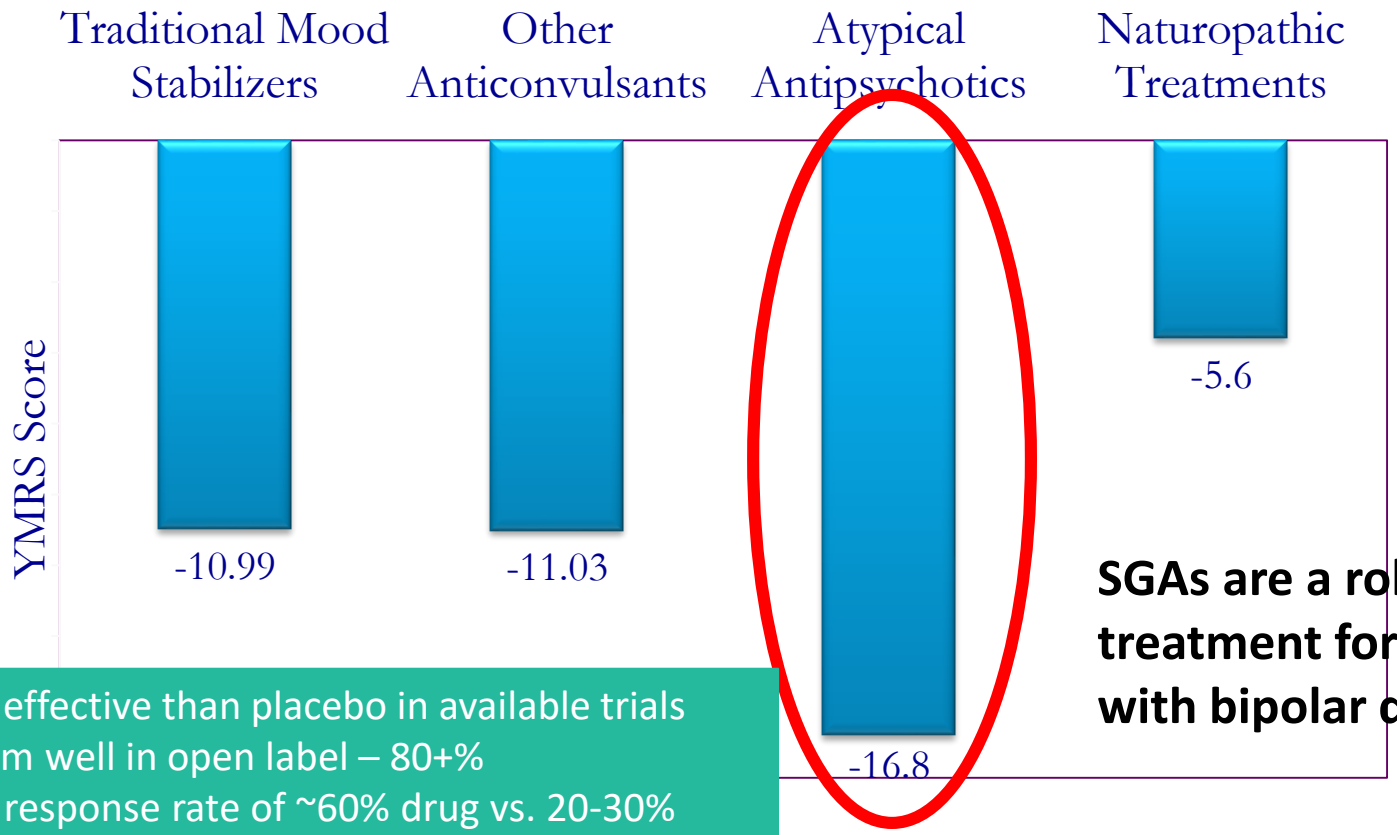


50% of adults and adolescents with mania require augmentation with another agent/combination therapy

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

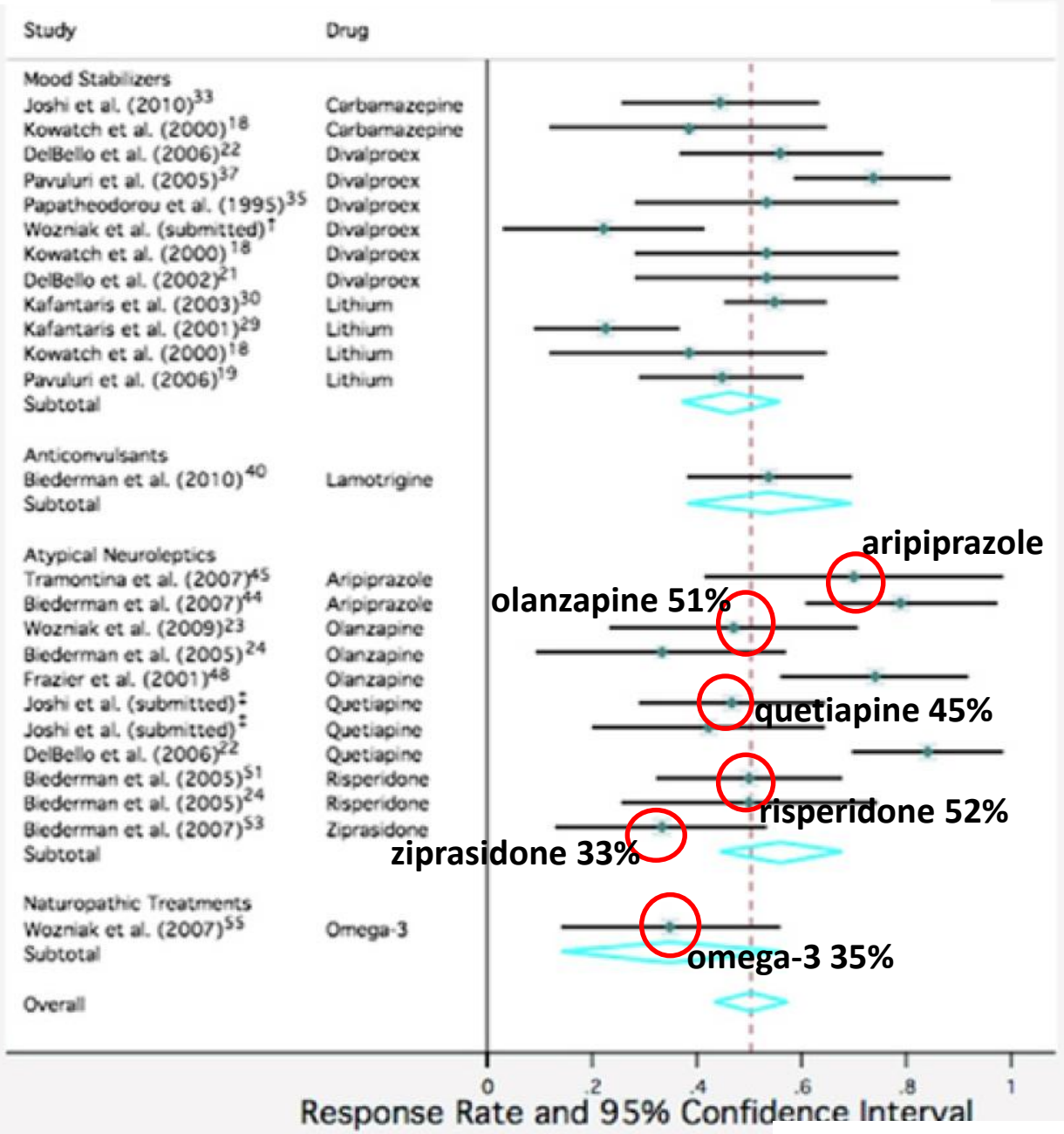
- Perform well in open label – 80+%
- Mean response rate of ~60% drug vs. 20-30% placebo
- Mean decrease in YMRS ranged from 14.2 to 18.5 in medication group vs. 8.2 to 9.99 for placebo
- Relatively rapid response, relatively well tolerated

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%



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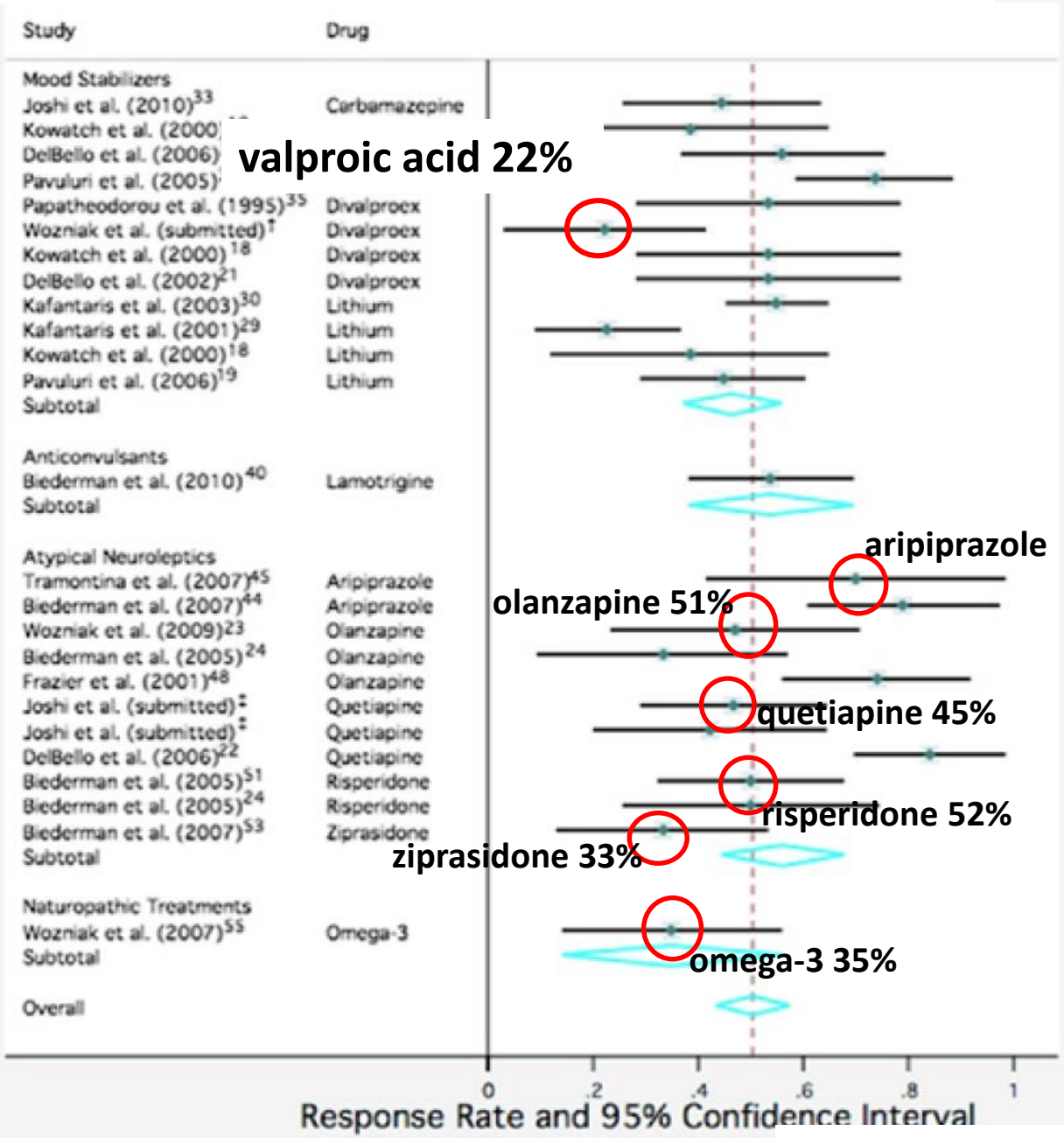
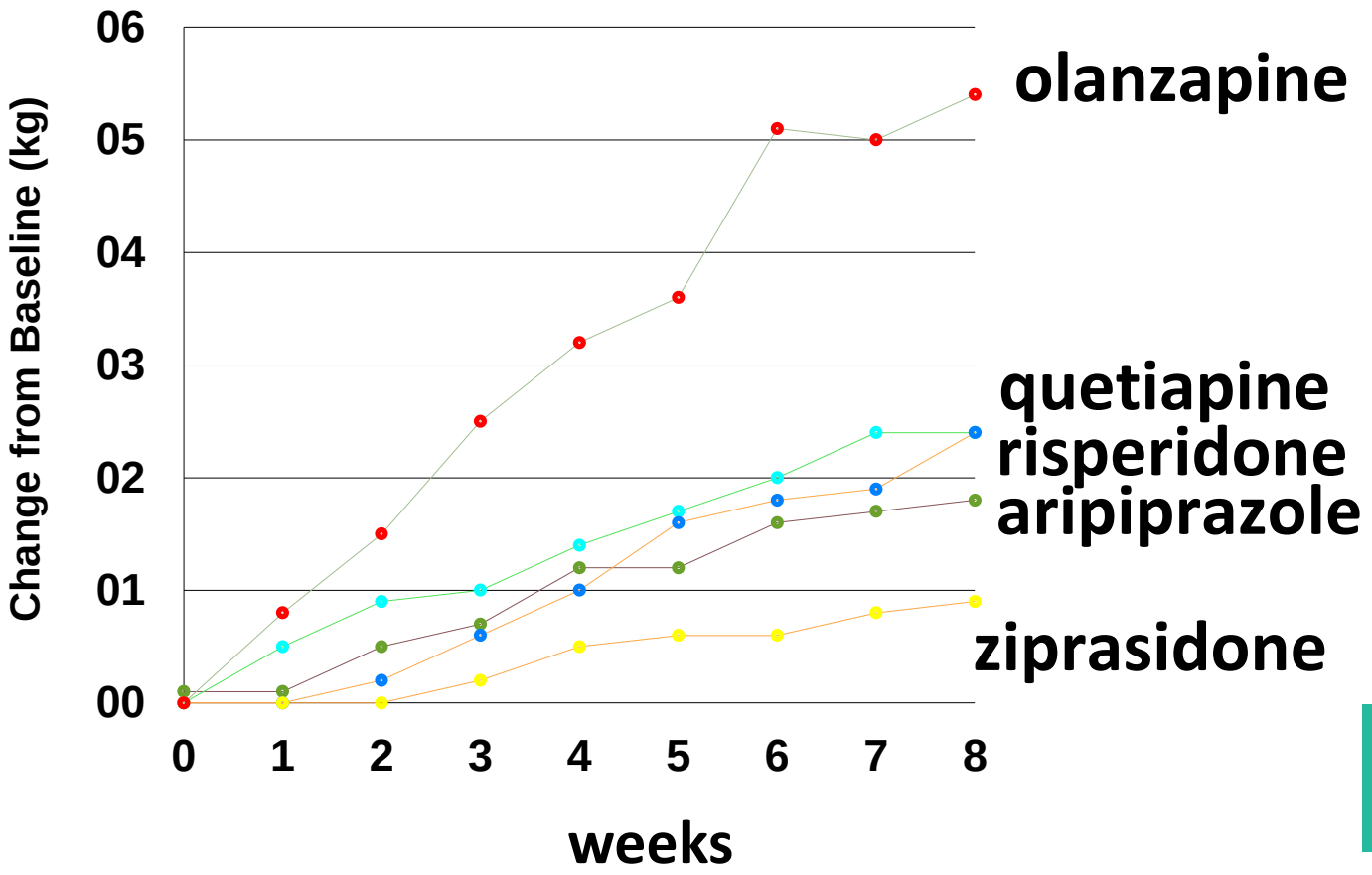


Liu JAACAP 2011;50(8):749-762

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

SGA=second generation antipsychotic

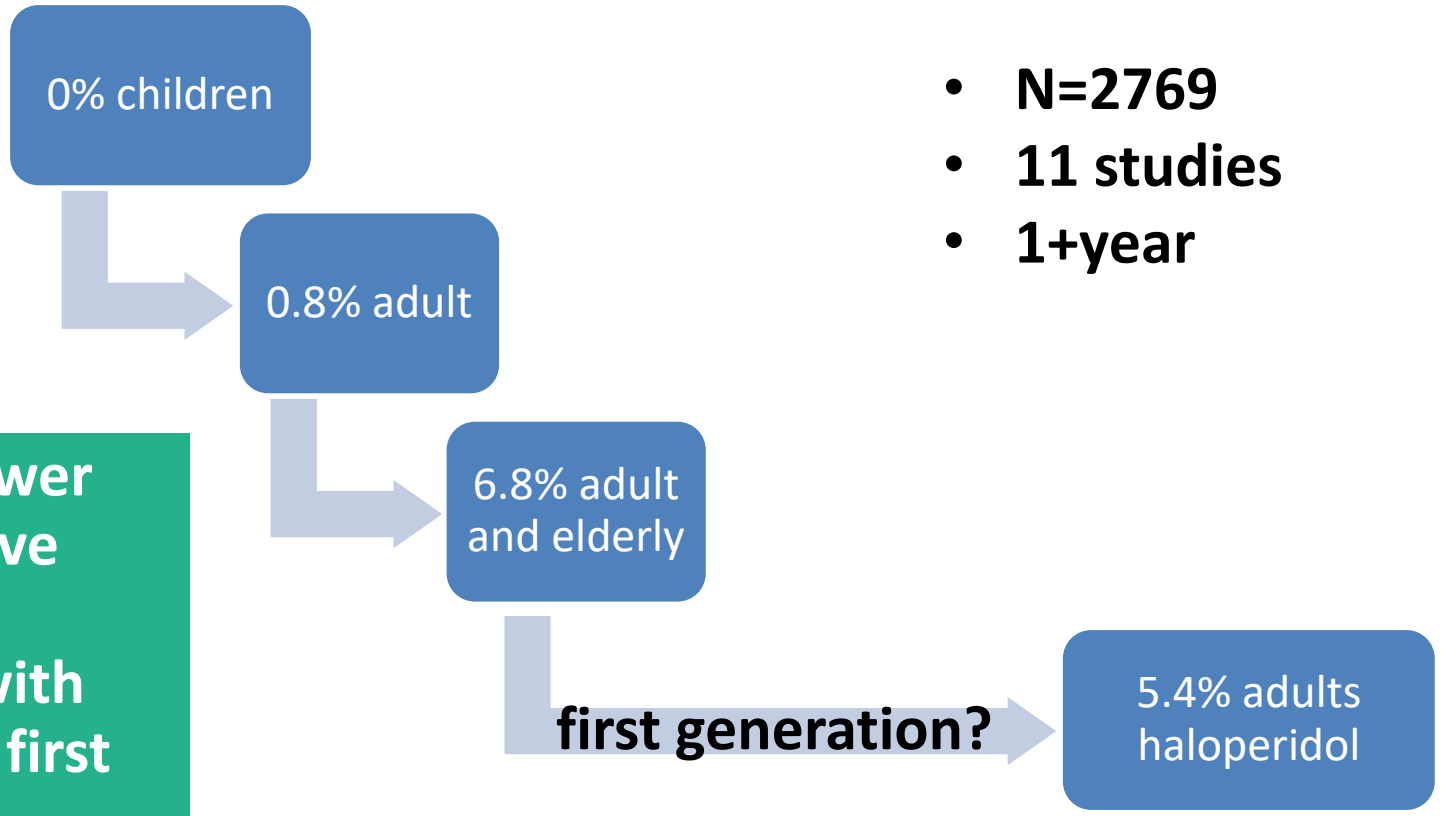


Parallel trials
Total N=116

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):**



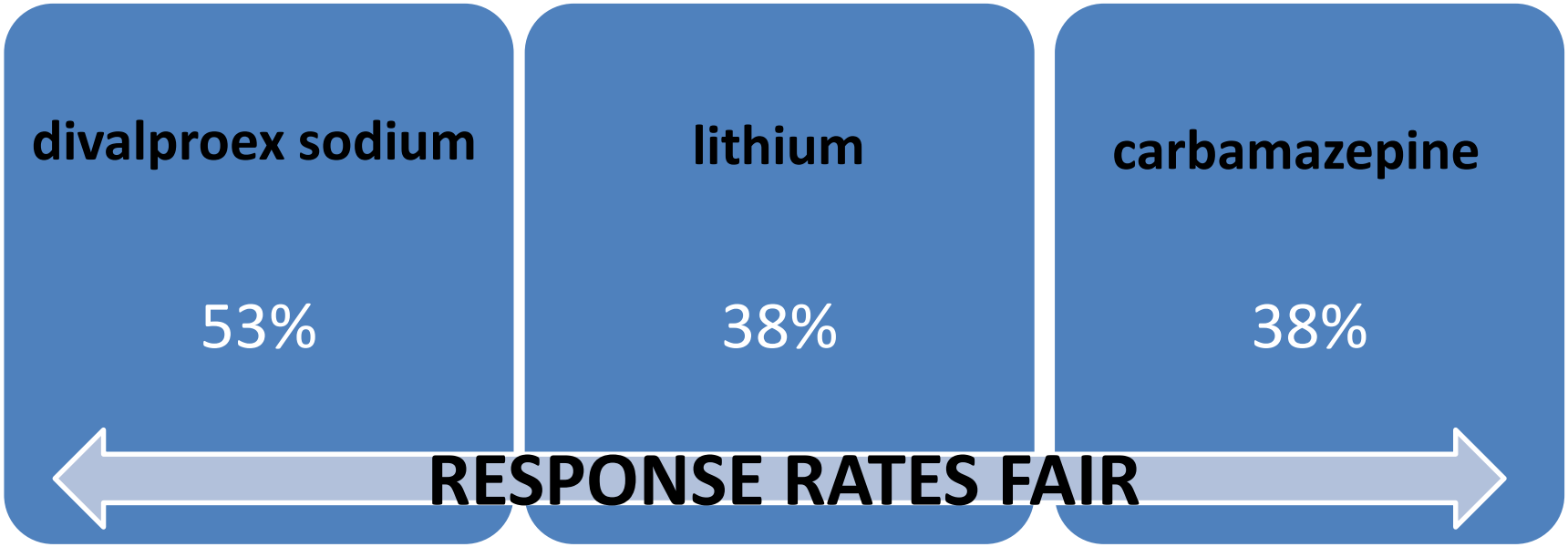
- **N=2769**
- **11 studies**
- **1+year**

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



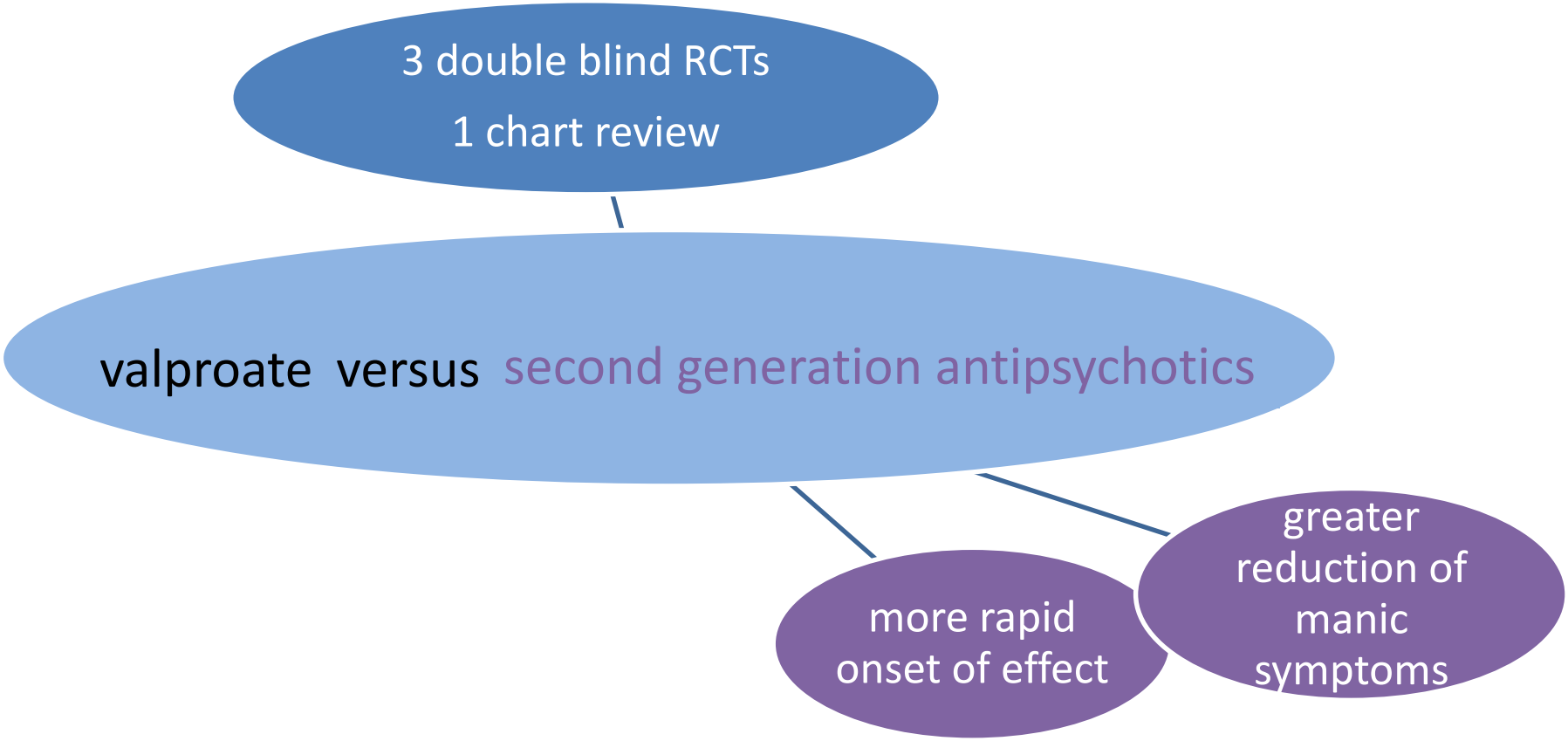
Trials notable for:

- 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

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]

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

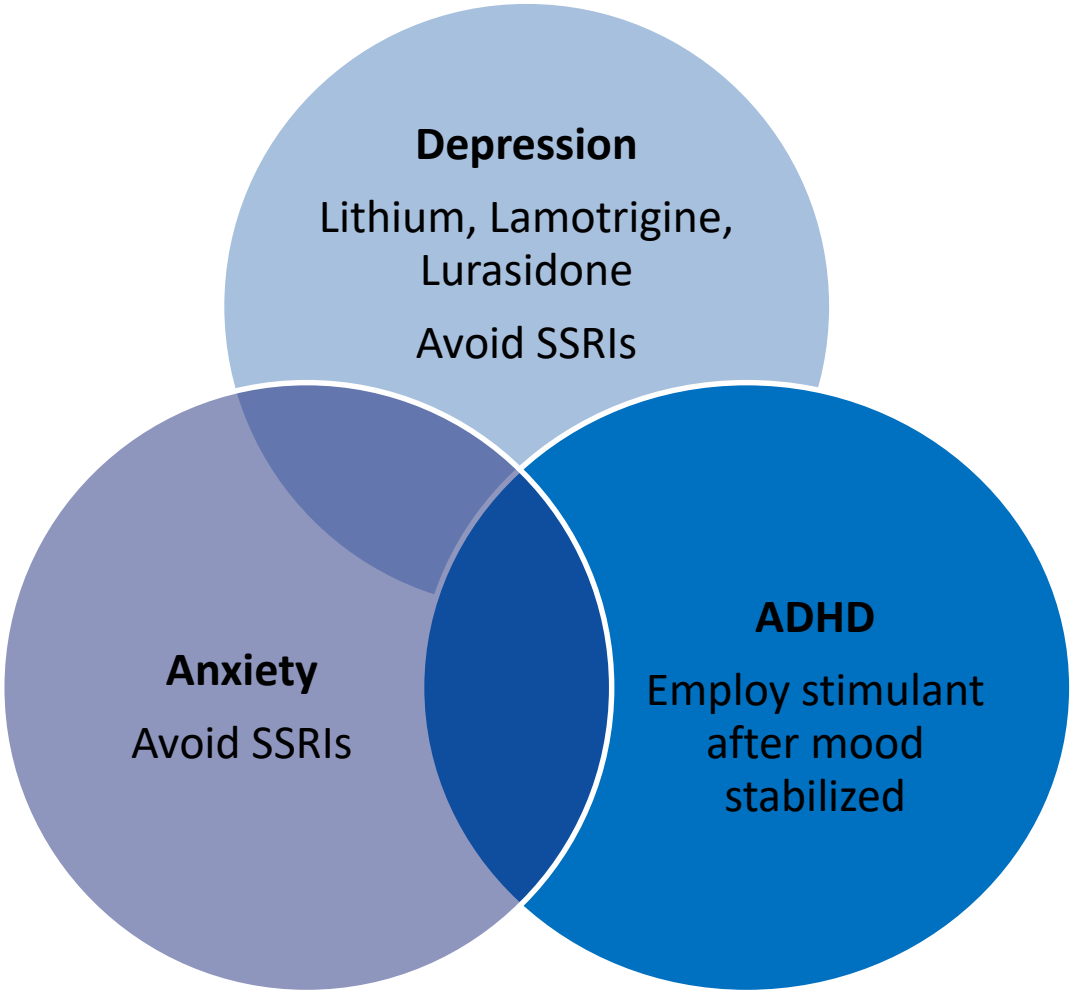
monotherapy

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

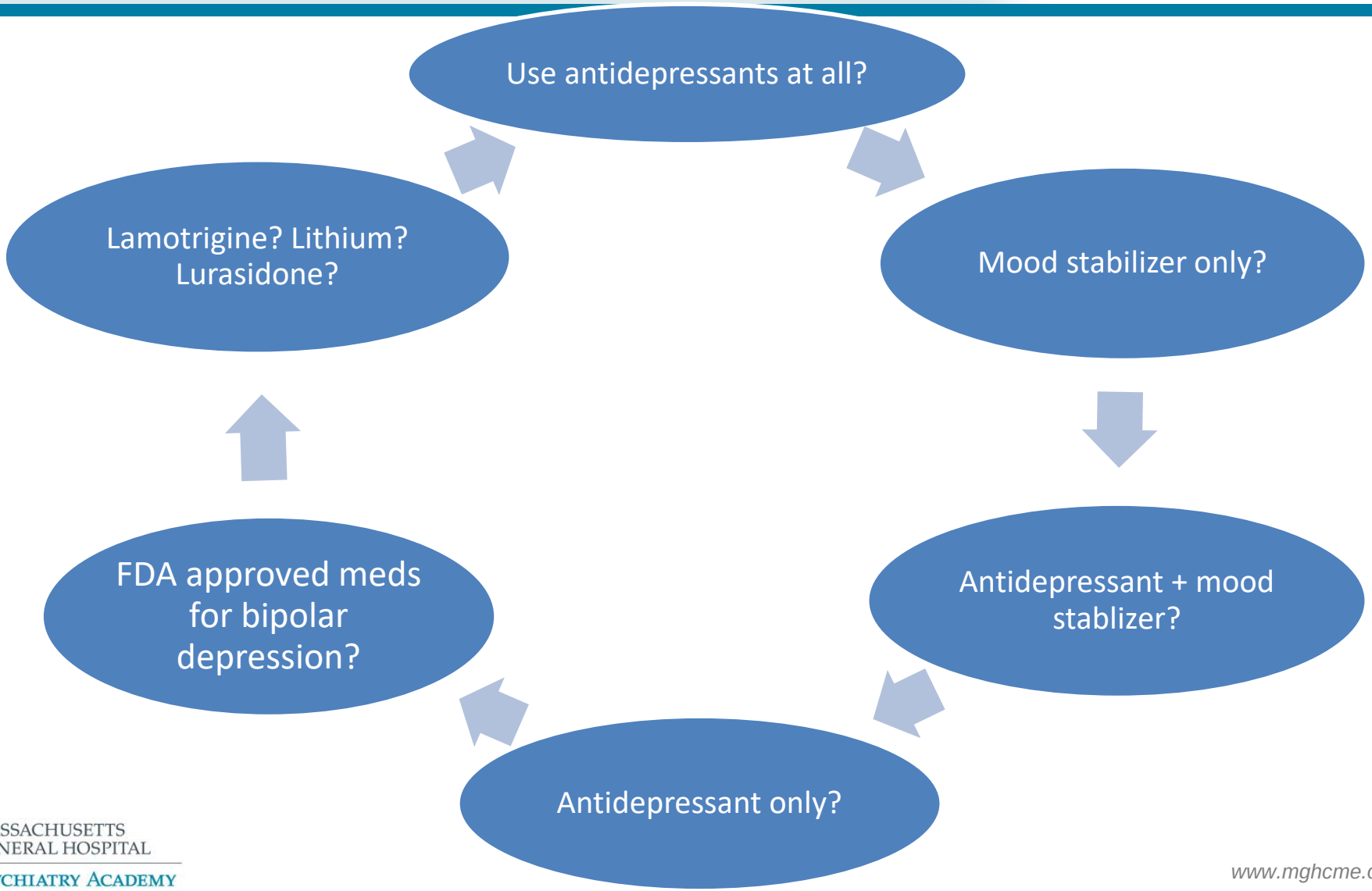
2-year follow-up study of youth with bipolar spectrum disorders

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 depression, without neglecting or exacerbating one phase for the sake of managing the other" (Chen 2014)

Chen 2014; Wozniak 2005; Birmaher 2006

Pharmacologic management of bipolar depression is very difficult



Antidepressants can lead to switching
Use with caution

pharmacologically induced hypomania was a predictor of a bipolar course

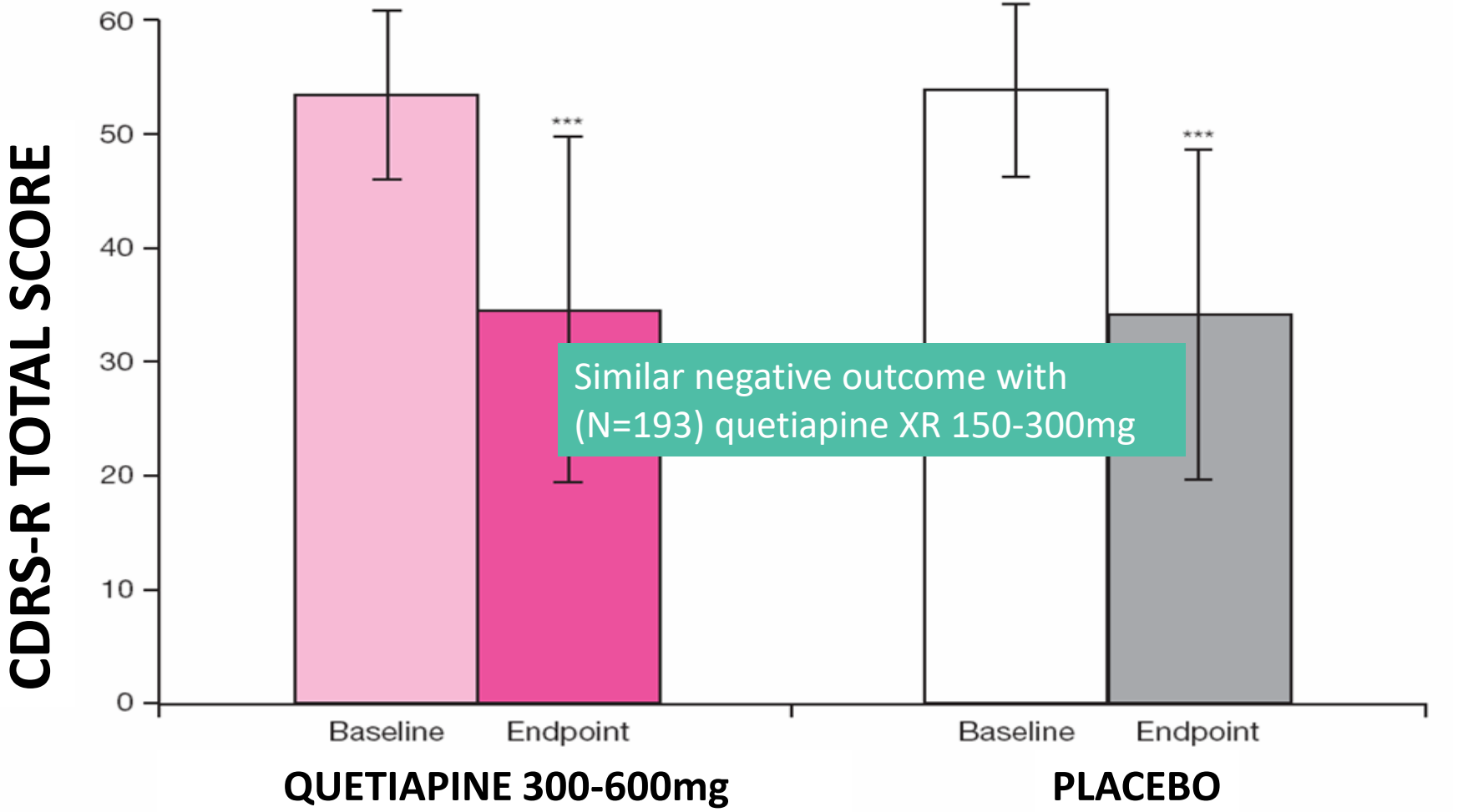
antidepressant induced mood change was seen more in BP MDD

rate of switching higher in subjects with history of receiving antidepressants especially in children

Strober; Shon; Martin

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)



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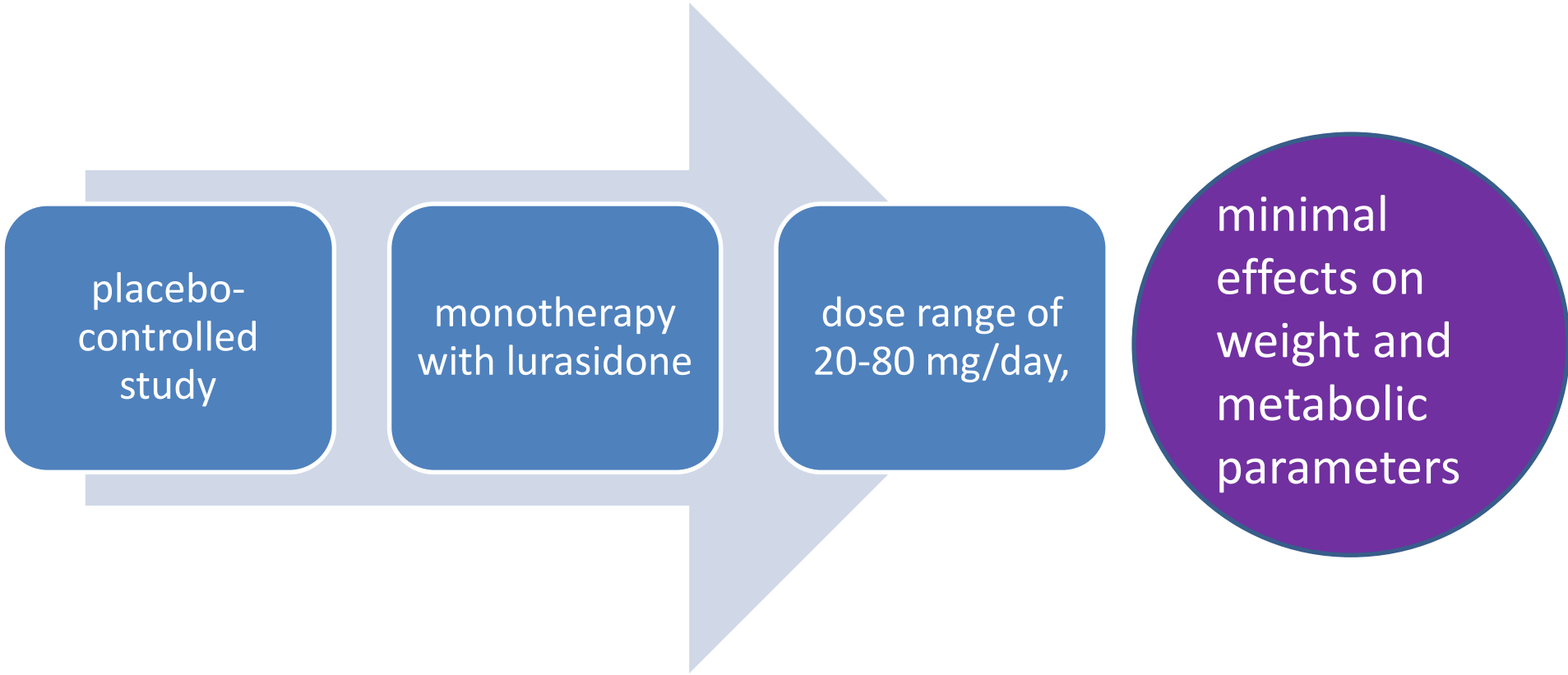
DelBello 2009; Findling 2014

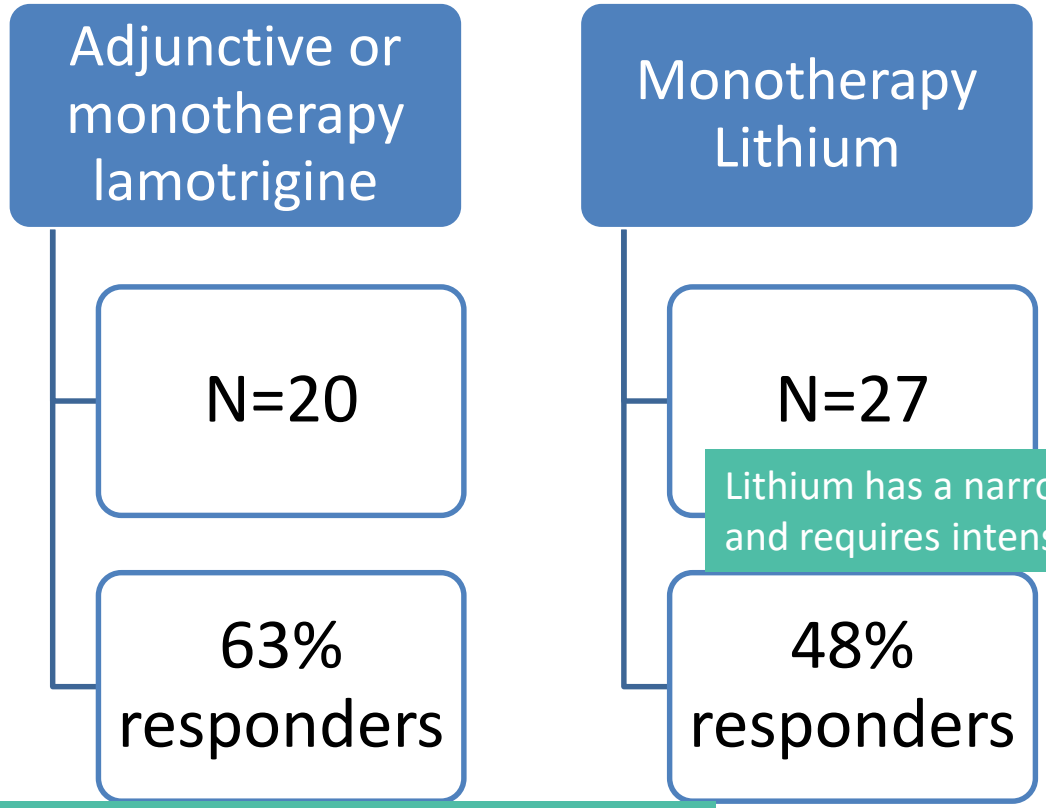
Lurasidone significantly reduced depressive symptoms in children and adolescents with Bipolar I Depression



Cariprazine and other new SGAs offer hope

DelBello JAACAP 2017

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



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

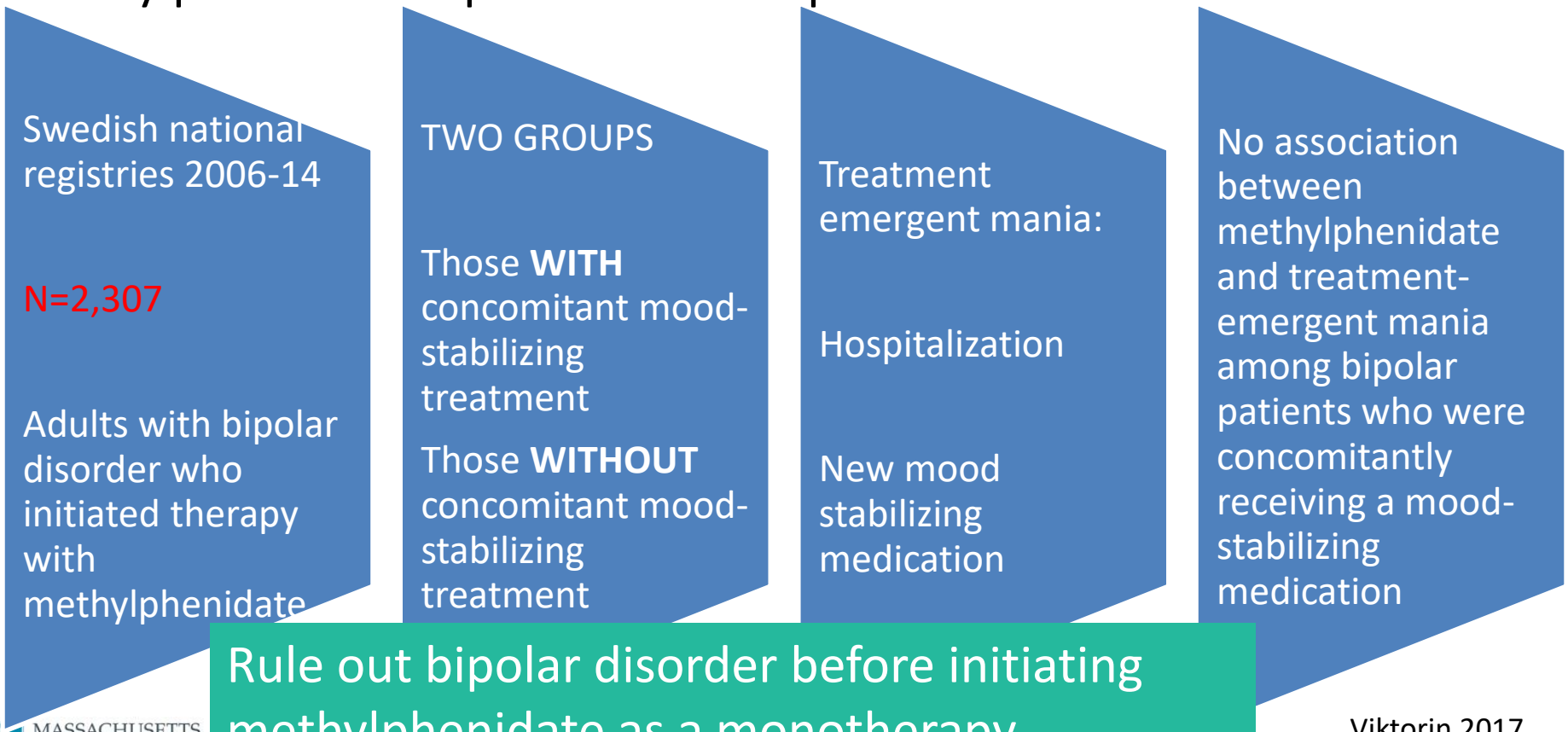
RCT demonstrated increased antidepressant effect from the addition of risperidone to antidepressant monotherapy

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



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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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

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Abstract

Go to:

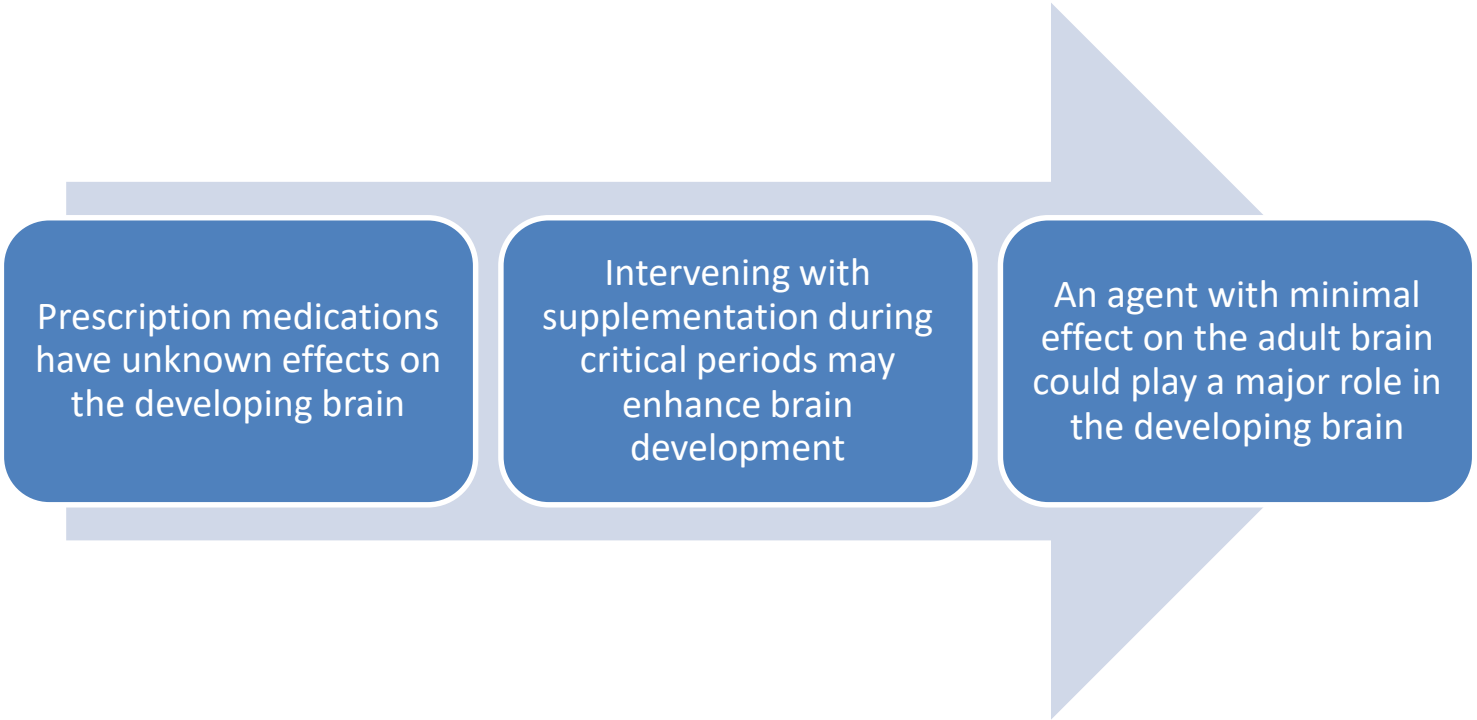
Bipolar disorder, while commonly encountered in the primary care setting, is often misdiagnosed or undiagnosed. In the *DSM-IV-TR*, patients could be diagnosed as being in a mixed state only if they had concurrent manic and depressive symptoms; while this occurs in some patients, many more experience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

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

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



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,*]

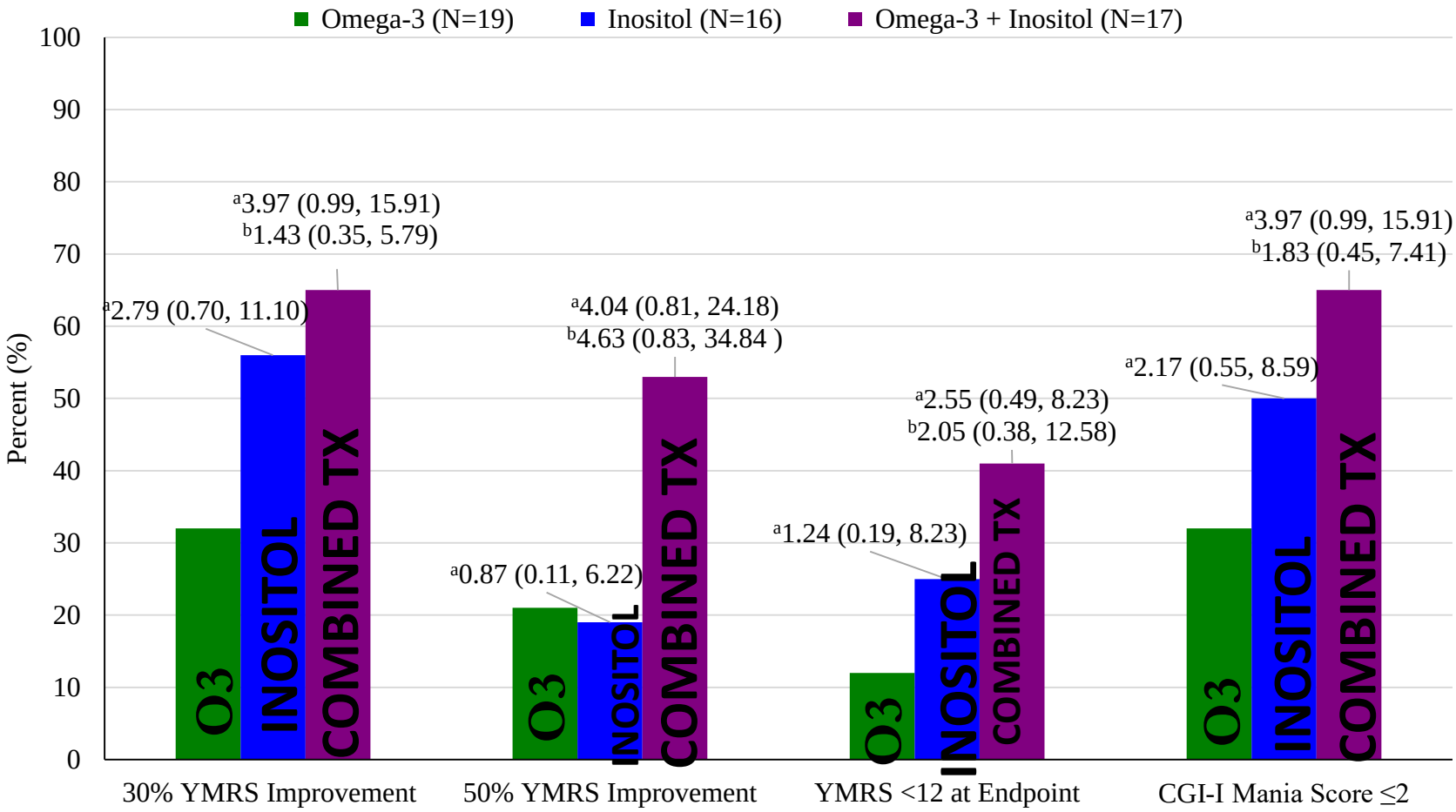
ABSTRACT

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 combined outperforms either used alone for mania (N=52)



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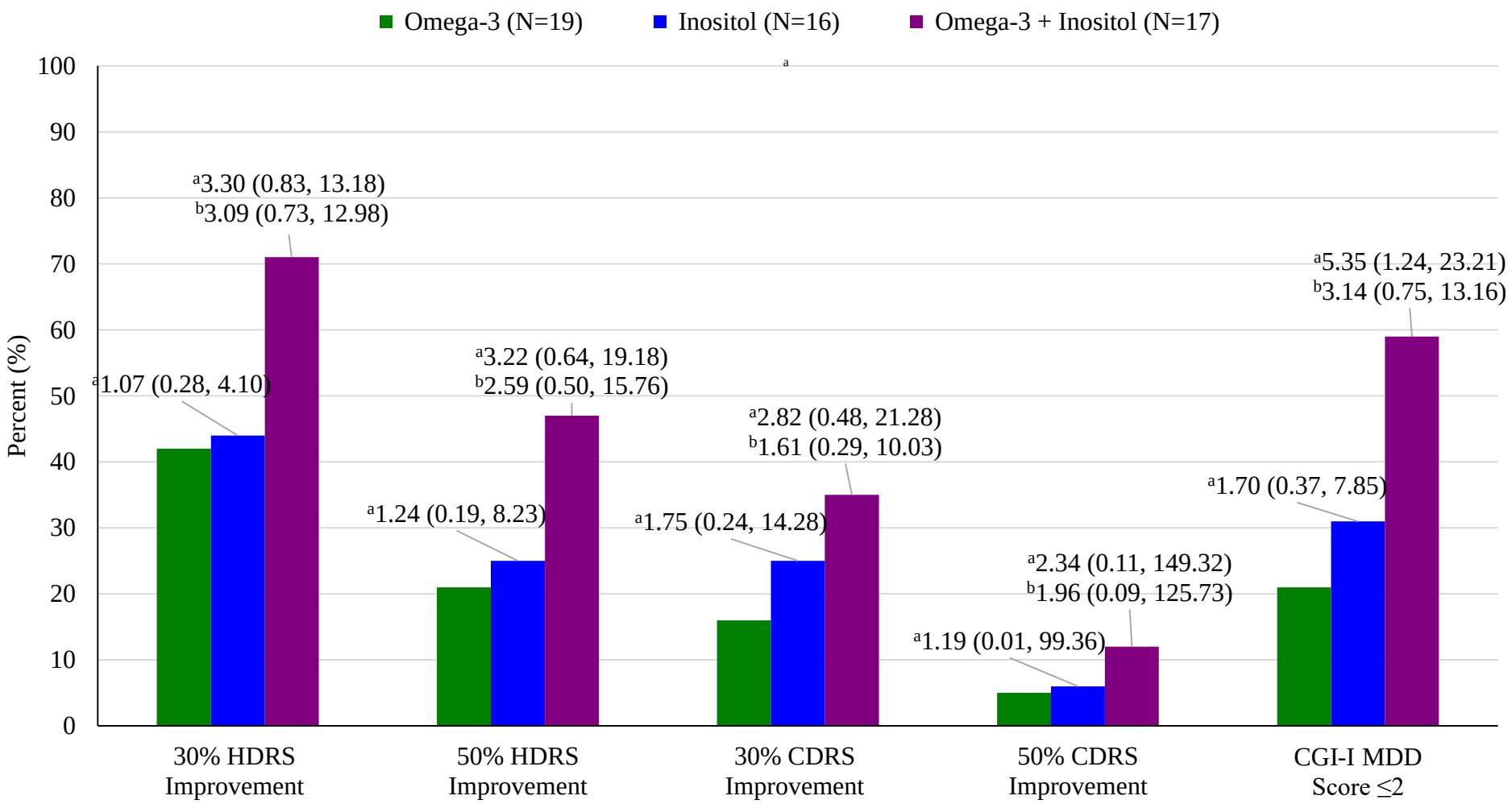
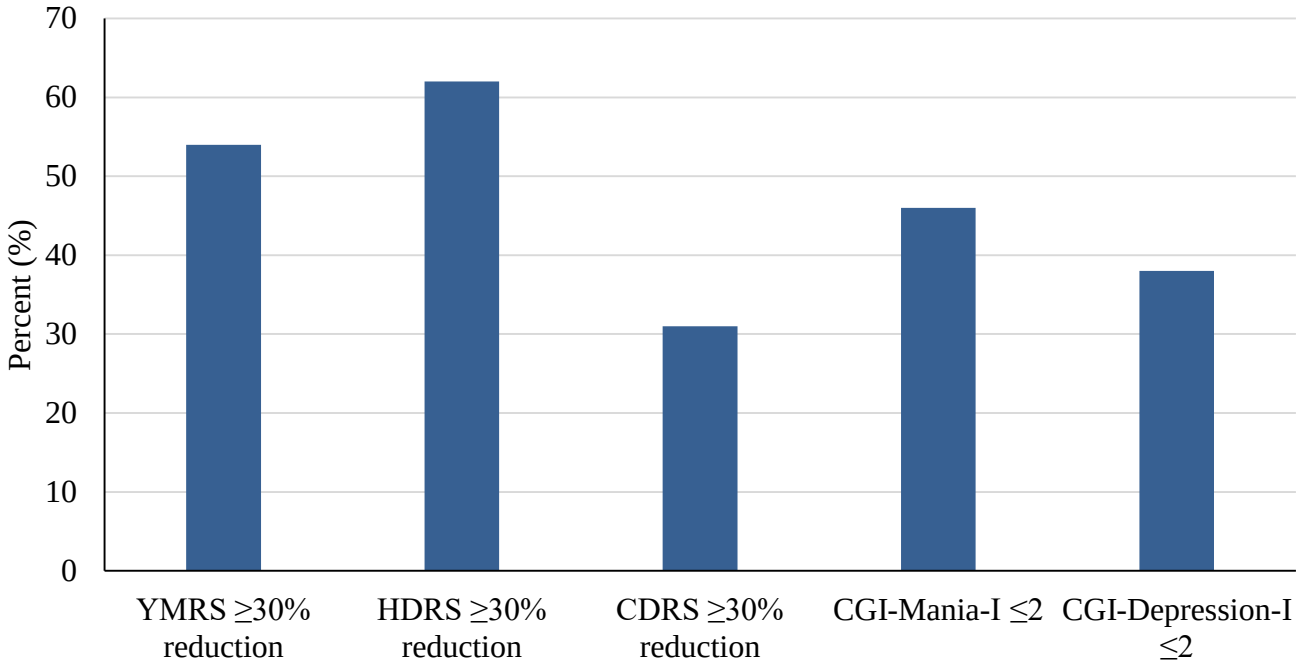
Wozniak 2021

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)**

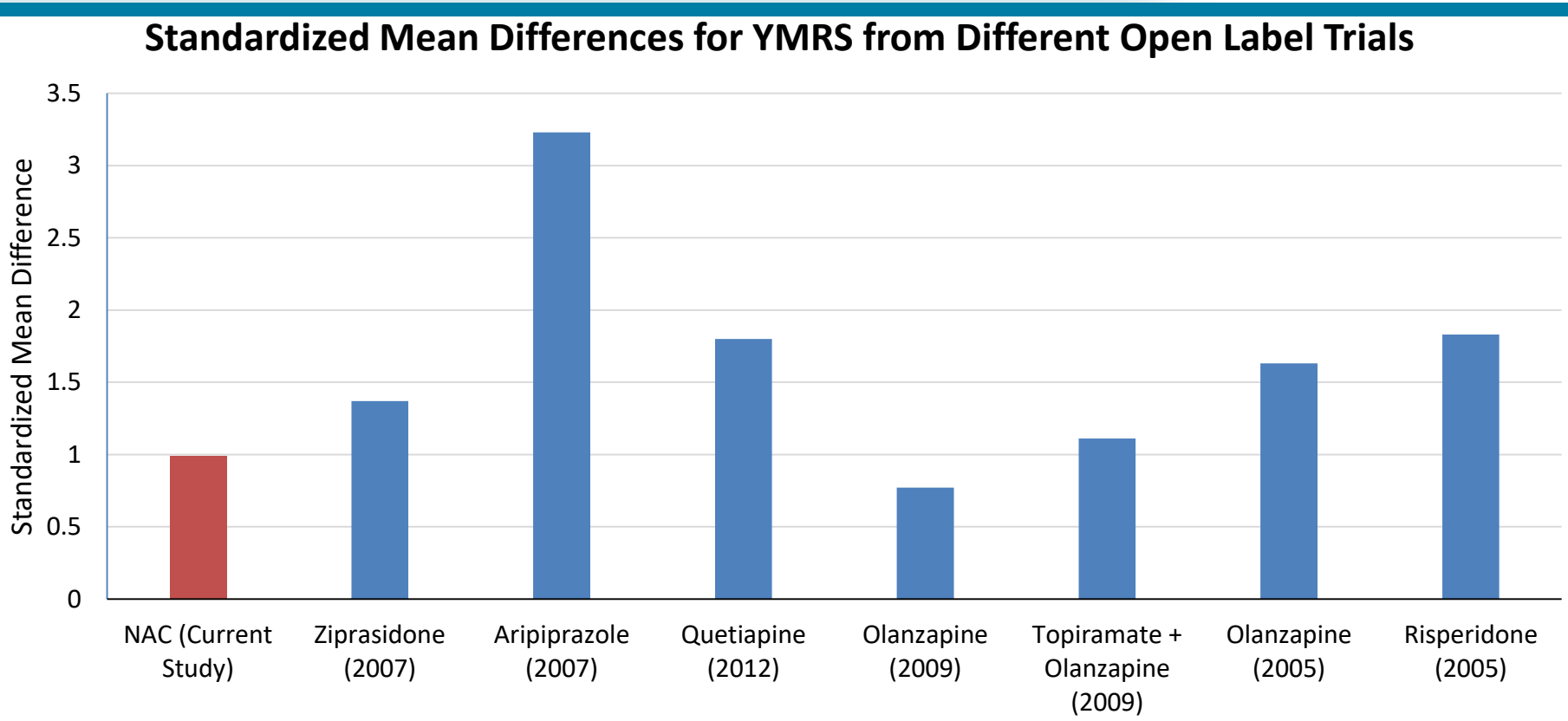
In open label trial NAC was useful for pediatric bipolar disorder with significant difference from baseline to endpoint YMRS, HDRS and CDRS



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

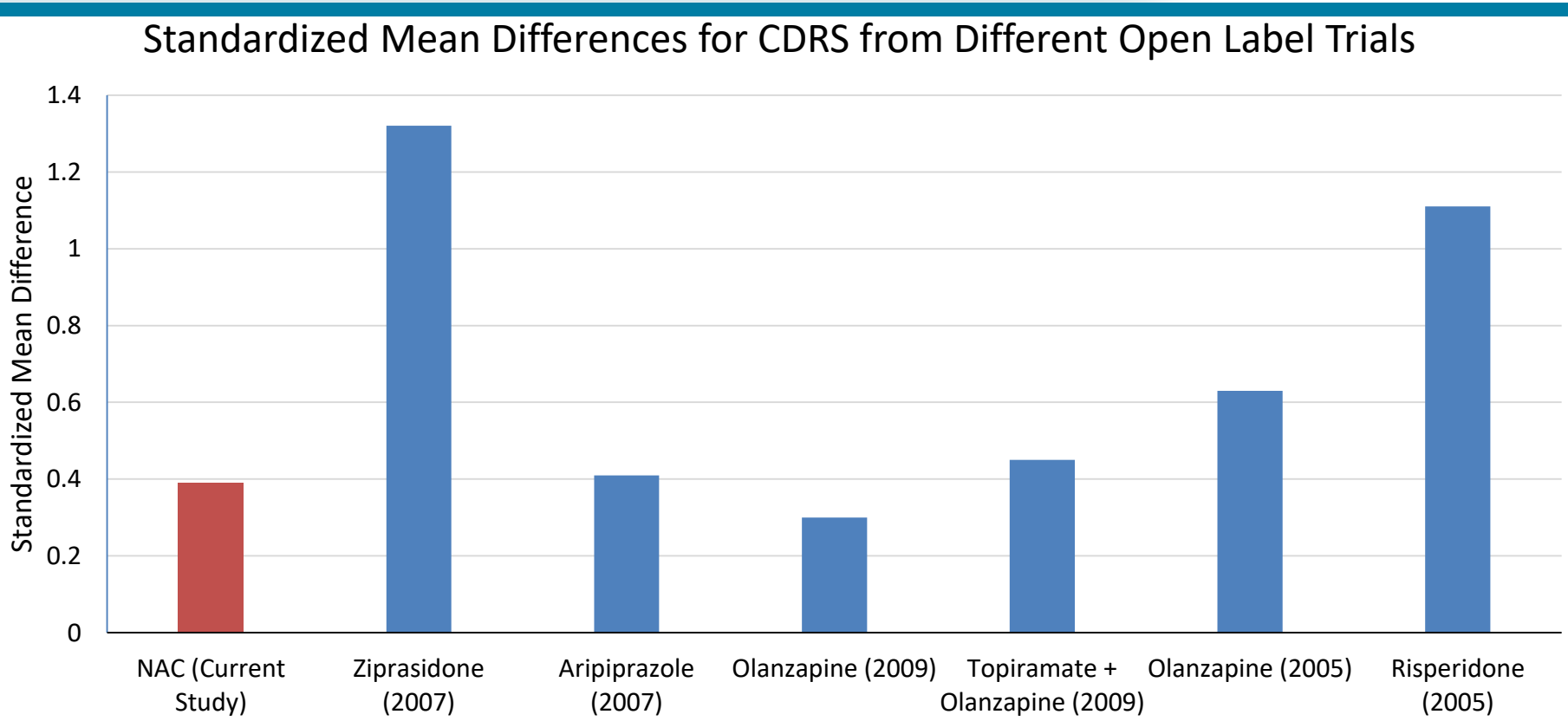
Wozniak 2021

NAC versus SGAs for mania



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

NAC versus SGAs for depression



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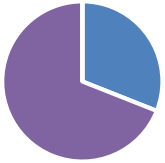
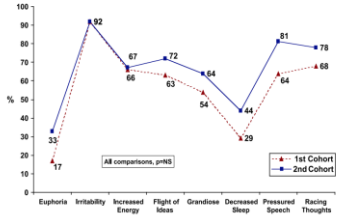
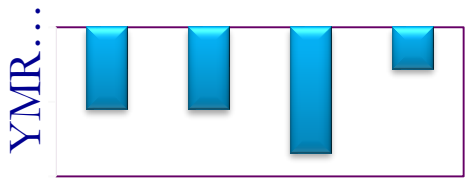
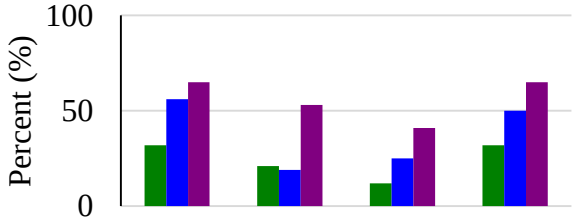




Pediatric Bipolar disorder is a highly morbid condition that affects a significant minority of young children, is familial and persists over time

Treatment: Pharmacologic treatment with SGAs is generally required for pediatric bipolar disorder and comorbidities need separate treatment: use antidepressants with caution





Natural Treatments hold promise in the treatment of pediatric bipolar disorder

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QUESTIONS?