



MASSACHUSETTS
GENERAL HOSPITAL

PSYCHIATRY ACADEMY

Pharmacological Approaches to Pediatric Bipolar Disorder

Janet Wozniak, MD

Director, Pediatric Bipolar Disorder Research Program

Associate Professor of Psychiatry

Harvard Medical School

Massachusetts General Hospital



Disclosures

Dr. Janet Wozniak has recently received consultation fees from Bristol Myers Squibb and Otsuka.

She has received research support from Demarest Lloyd, Jr. Foundation, the Baszucki Brain Research Fund, Johnson and Johnson, McNeil, Merck/Schering-Plough, Pfizer, and Shire as well as the National Institute of Mental Health (NIMH) of the National, Institutes of Health (NIH) and PCORI.

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, Haleon, Alexza , Azurity and research support from Merck, American Regent, 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, SanofiAventis, Sepracor, Sunovion, Takeda, UCB (Schwarz) Pharma, Wyeth, Xenoport, Zeo

We have FDA approved treatments for youth with emotional dysregulation



MASSACHUSETTS
GENERAL HOSPITAL

PSYCHIATRY ACADEMY

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

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

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

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

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

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

Lurasidone Latuda 2018: pediatric bipolar depression

Olanzapine-fluoxetine 2013: pediatric bipolar depression

Fluoxetine: depression and OCD age 8+

Escitalopram 2002: depression age 12+

Sertraline, fluvoxamine, anfranil: pediatric OCD

Duloxetine Cymbalta: GAD 7+

Risperidone 2006: irritability associated with autism age 5-16

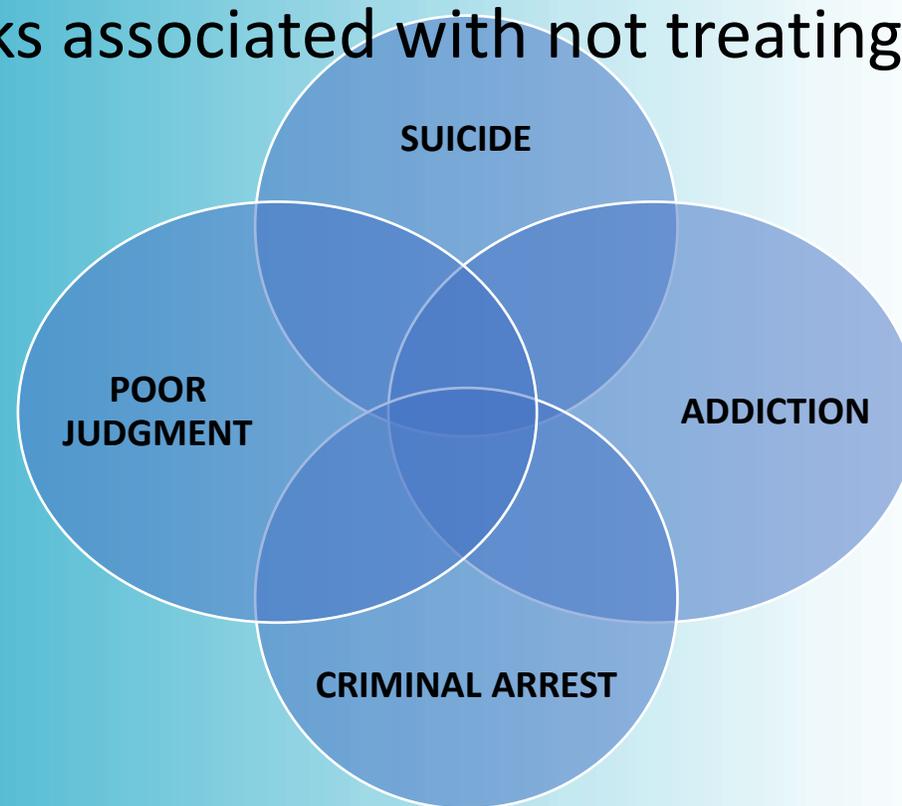
Aripiprazole 2009: irritability associated with autistic disorder age 6-17

All have serious and annoying side effects

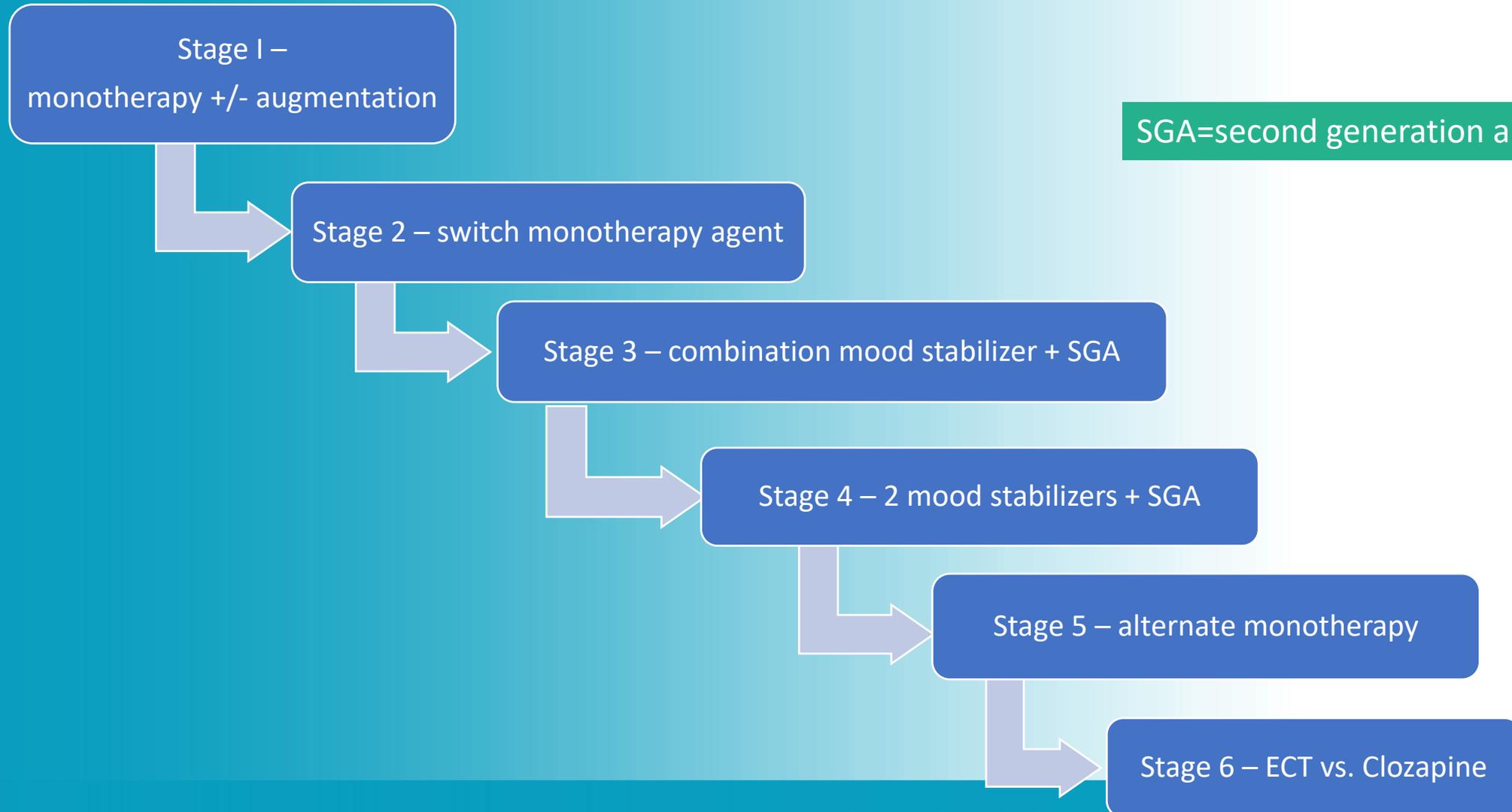


The risk-benefit analysis of medication treatment includes the side effects we know and the side effects we don't know

And must include the risks associated with not treating bipolar disorder



The algorithm for pediatric bipolar disorder pharmacologic treatment

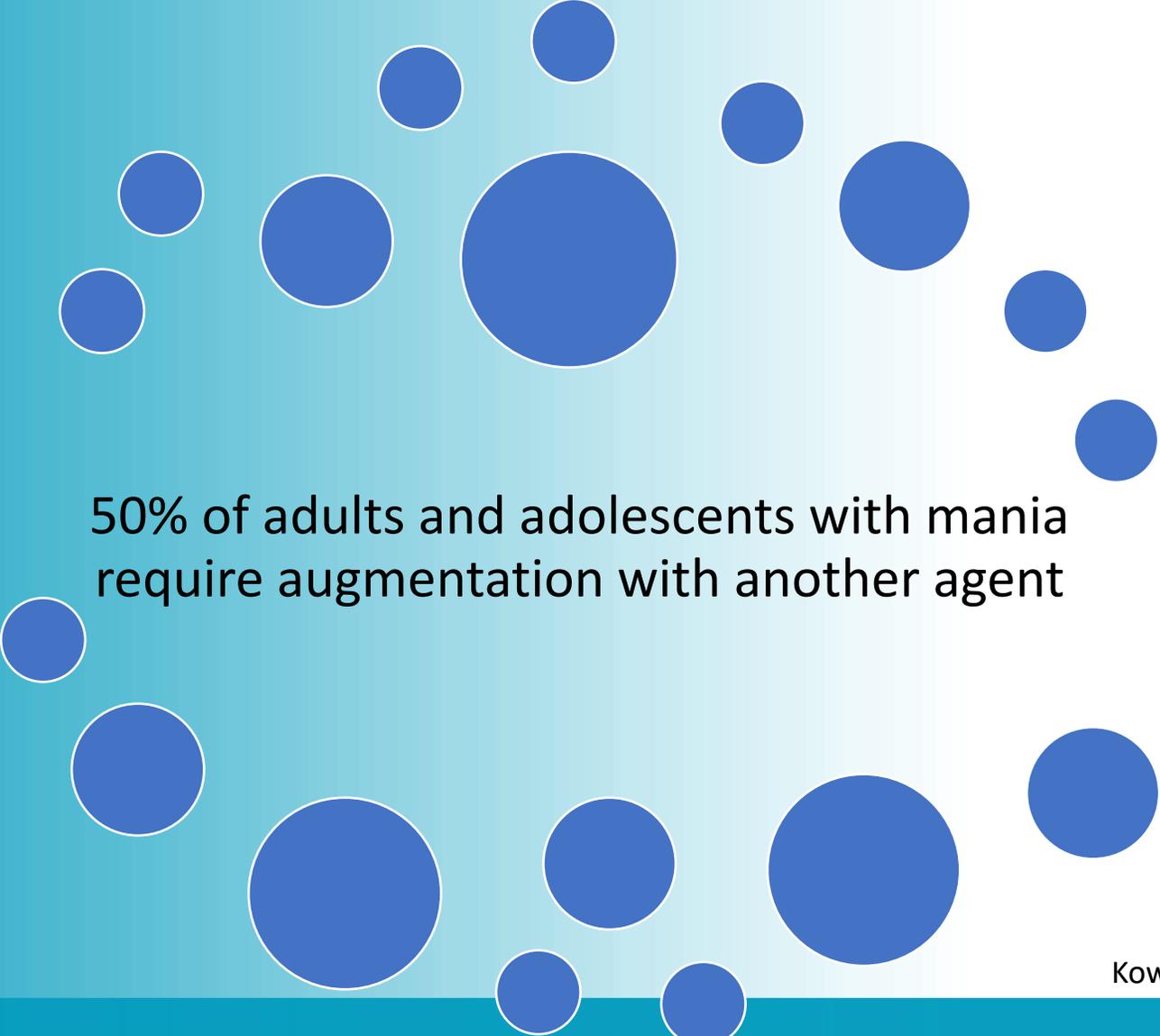


Pediatric bipolar disorder is difficult to treat



MASSACHUSETTS
GENERAL HOSPITAL

PSYCHIATRY ACADEMY



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

Kowatch 2003, 2005

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, MDⁱ, Robert A. Kowatch, MD, PhD^j, Briana M. Rowles, MA^k, Jacqui Lingler, BS^l, Karen Martz, MS^m, Ravinder Anand, PhDⁿ, Traci E. Clemons, PhD^o, Perdita Taylor-Zapata, MD^o

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

[abstract](#)

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

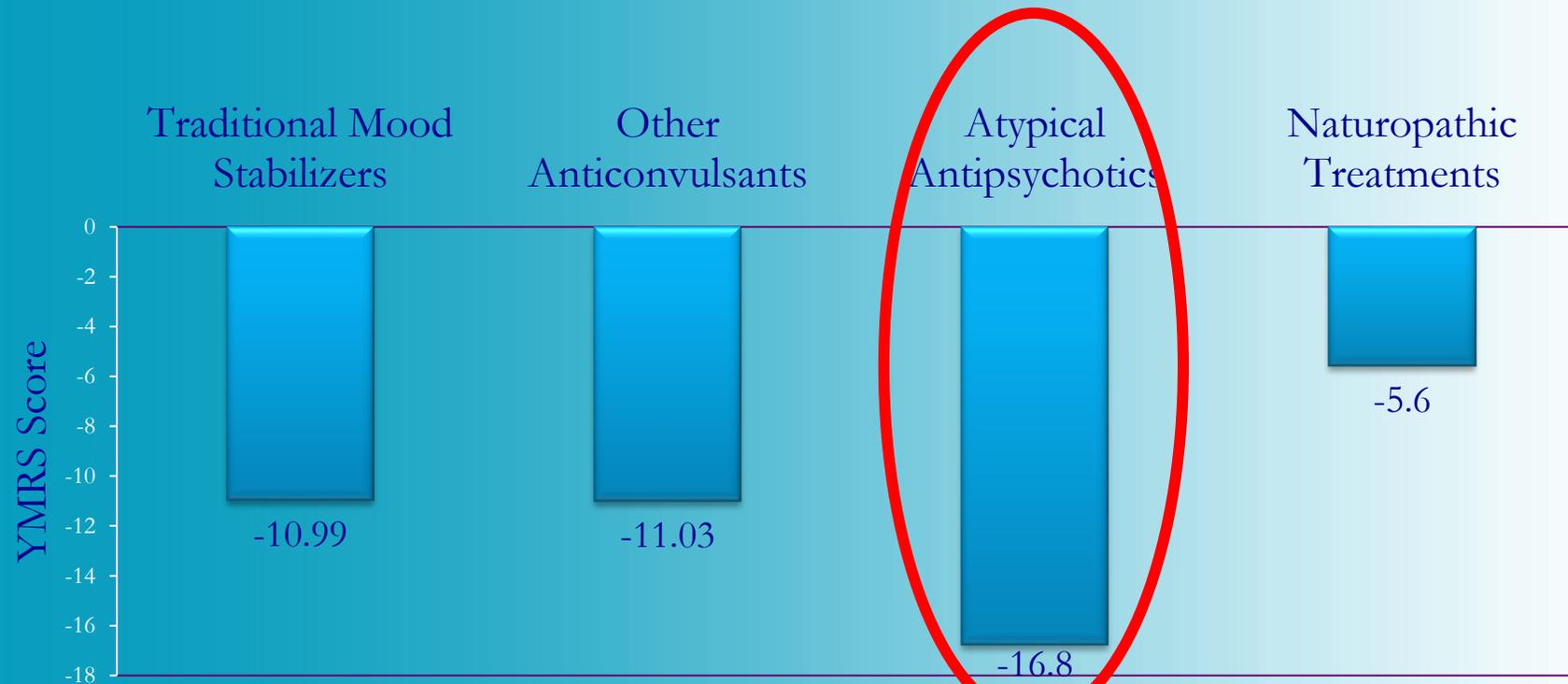
47% lithium vs 21% placebo “much/very much improved”

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



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

SGA=second generation antipsychotic



- Robust for adults
- High response rate ~60% vs ~25% placebo
- Rapid, well tolerated

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

Liu JAACAP 2011
Perlis J Clin Psychiatry 2006
Chen 2014



A Randomized Controlled Trial of Risperidone, Lithium, or Divalproex Sodium for Initial Treatment of Bipolar I Disorder, Manic or Mixed Phase, in Children and Adolescents

Barbara Geller Dr, MD,

Department of Psychiatry, Washington University in St Louis, Missouri

Abstract

Context—There was a paucity of comparative pharmacological research for initial treatment of bipolar I disorder, manic or mixed phase, in children and adolescents.

Objective—To investigate which medication to administer first to antimanic medication-naive subjects.

Design, Setting, and Participants—The Treatment of Early Age Mania (TEAM) study recruited 6- to 15-year-old children and adolescents with *DSM-IV* bipolar I disorder (manic or

Conclusions- Risperidone was more efficacious than lithium or divalproex sodium

Interventions—Subjects received a titrated schedule of lithium, divalproex sodium, or risperidone. Medications were increased weekly only if there was inadequate response, and no dose-limiting adverse effects, to maximum doses of lithium carbonate (1.1-1.3 mEq/L), divalproex sodium (111-125 $\mu\text{g/mL}$), and risperidone (4-6 mg).

Main Outcome Measures—Primary outcome measures were the Clinical Global Impressions for Bipolar Illness Improvement-Mania and the Modified Side Effects Form for Children and Adolescents.

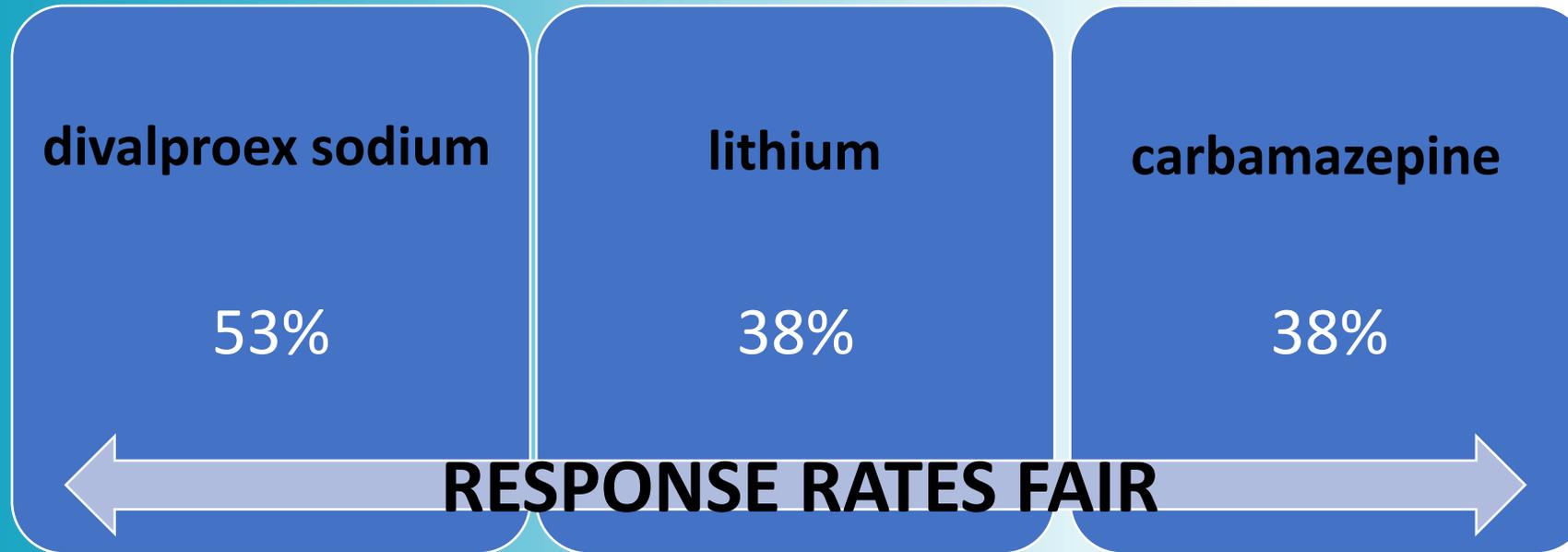
Results—There were 279 antimanic medication-naive subjects (mean [SD] age, 10.1 [2.8] years; 50.2% female) who had the following characteristics: 100% elated mood and/or grandiosity, 77.1% psychosis, 97.5% mixed mania, 99.3% daily rapid cycling, and mean (SD) mania duration of 4.9 (2.5) years. The mean (SD) titrated lithium level was 1.09 (0.34) mEq/L, and the mean (SD) divalproex sodium level was 113.6 (23.0) $\mu\text{g/mL}$. The mean (SD) titrated risperidone dose was 2.57 (1.21) mg. Higher response rates occurred with risperidone vs lithium (68.5% vs 35.6%; $\chi^2_1=16.9$, $P<.001$) and vs divalproex sodium (68.5% vs 24.0%; $\chi^2_1=28.3$, $P<.001$). Response to lithium vs divalproex sodium did not differ. The discontinuation rate was higher for lithium than for risperidone ($\chi^2_1=6.4$, $P=.011$). Increased weight gain, body mass index, and prolactin level occurred with risperidone vs lithium ($F_{1,212}=45.5$, $P<.001$; $F_{1,212}=39.1$, $P<.001$; and $F_{1,213}=191.4$, $P<.001$, respectively) and vs divalproex sodium ($F_{1,212}=34.7$, $P<.001$; $F_{1,212}=45.3$, $P<.001$; and $F_{1,213}=209.4$, $P<.001$, respectively). The thyrotropin level increased in subjects taking lithium ($t_{62}=11.3$, $P<.001$).

Conclusions—Risperidone was more efficacious than lithium or divalproex sodium for the initial treatment of childhood mania but had potentially serious metabolic effects.

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



SGA=second generation antipsychotic



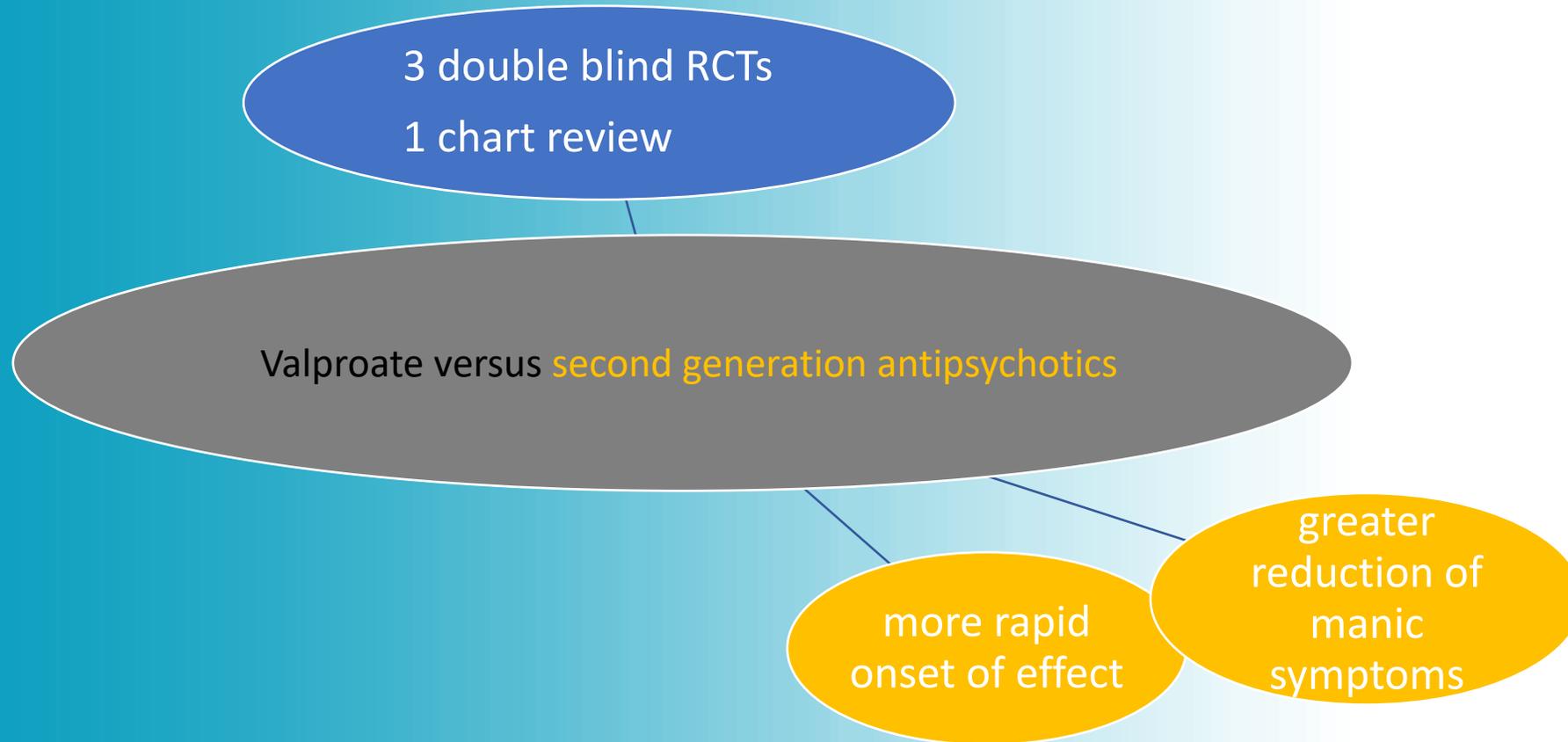
Trials notable for:

- high drop out rates
- need for rescue medications

SGAs perform better than valproate for pediatric bipolar disorder



SGA=second generation antipsychotic





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

N=7423

mean age 12.73

57% adolescents

54% males

66.60% SGA

33.40% mood stabilizer

(valproate/oxcarbazepine/lithium)

Comparable
risk of
psychiatric
hospital
admission
186 days

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

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

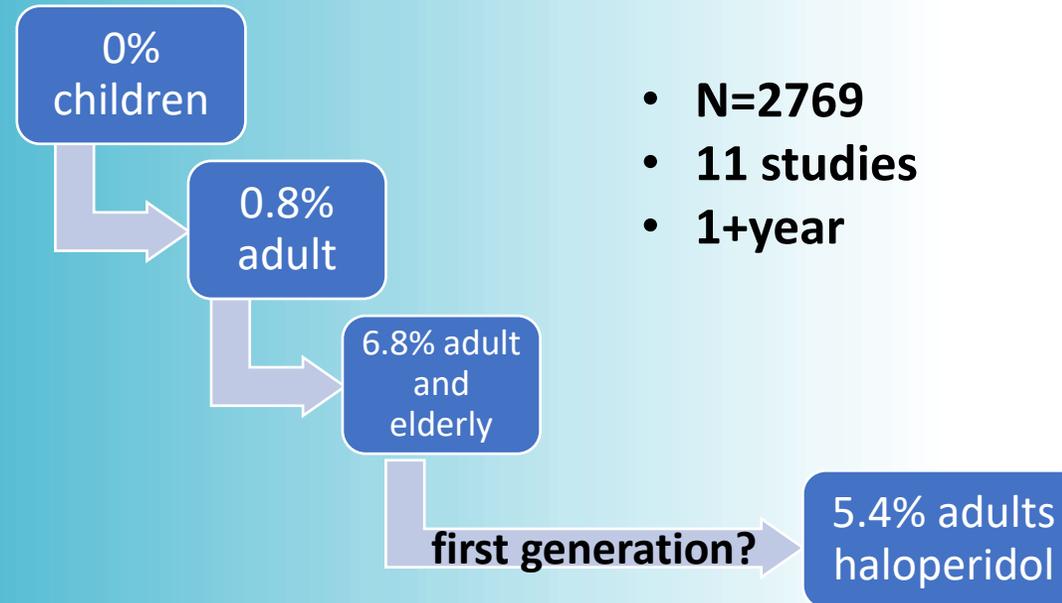
SGA=second generation antipsychotic

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

Tardive dyskinesia is dreaded, but low risk

(data is limited by small sample sizes, low doses and limited durations)

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



- N=2769
- 11 studies
- 1+year

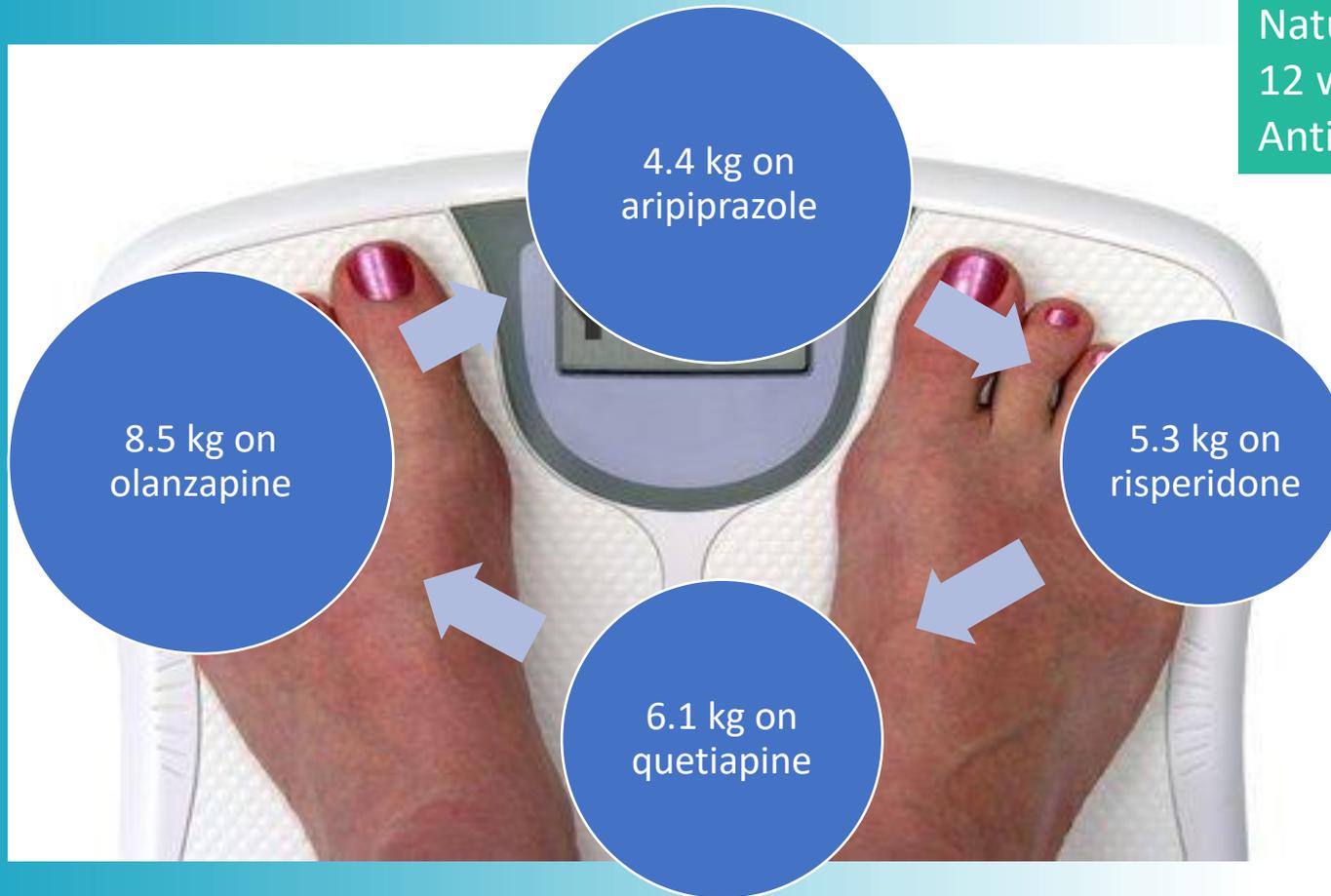
A lower risk for tardive dyskinesia is associated with SGAs versus FGAs

Children may be particularly prone to weight gain with treatment



MASSACHUSETTS
GENERAL HOSPITAL

PSYCHIATRY ACADEMY



Naturalistic study
12 weeks
Antipsychotic naïve youth

Correll JAMA 2009;1765-1773

Monitor BMI at 4, 8, 12 weeks and every 3 months

Monitor labs baseline and annually



Baseline:

- BMI
- Labs: Fasting glucose, lipids, BP
- Family history of obesity, DM, CVD, HTN

BMI:

- check at 4, 8, 12 weeks
- every 3 months thereafter

Labs

- Baseline, at 3 months, then annually if normal

Intervene for abnormalities



Co-treat with metformin

Mechanism of Action

- Does not cause hypoglycemia
- Decreases hepatic production & GI absorption of glucose
- Increases peripheral glucose utilization

Safety

- Rare lactic acidosis: more likely with excessive alcohol use
- May be associated with B12 deficiency¹
- Most common side effects: GI (N/V 14%, diarrhea 7%²)

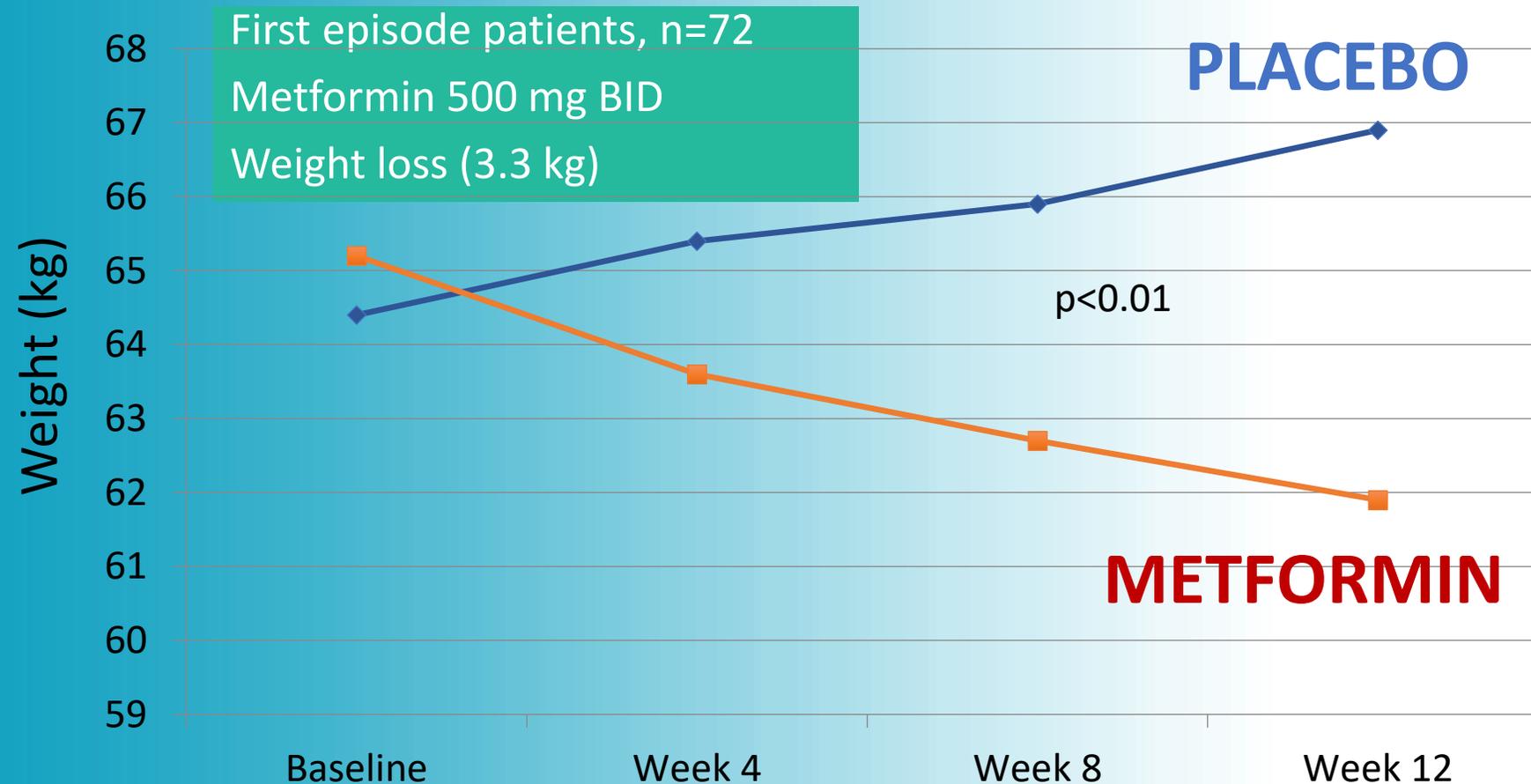
Dosing

- Target dose 2000 mg TDD (with food)

1. Aroda J Clin Endocrinol Metab 2016;101(4):1754-61

2. Zheng J Clin Psychopharmacol 2015;35:499-509

Metformin leads to weight loss and improved insulin sensitivity in schizophrenia



Can we co-treat with newer agents?: GLP-1 Agonists



Mechanism of Action

- Mimics glucagon-like peptide-1 (GLP-1)
- Targets brain regulation of appetite and food intake
- Glucagon-like peptide-1 (GLP-1) released from gut enteroendocrine cells controls meal-related glycemic excursions through augmentation of insulin and inhibition of glucagon secretion. GLP-1 also inhibits gastric emptying and food intake, actions maximizing nutrient absorption while limiting weight gain.
- Activating GLP-1 receptors in the pancreas, which leads to enhanced insulin release and reduced glucagon release-responses that are both glucose-dependent-with a consequent low risk for hypoglycemia.
- Glucagon-like peptide 1 (GLP-1) is a hormone that is encoded in the proglucagon gene. It is mainly produced in enteroendocrine L cells of the gut and is secreted into the blood stream when food containing fat, protein hydrolysate, and/or glucose enters the duodenum

Example: semaglutide

- FDA approved for weight management
- Injection 2.4mg weekly, increase to this slowly
- GI side effects common
- Do not use in patients with personal or fam hx of medullary thyroid c or with multiple endocrine neoplasia type 2 (MEN 2)
- Adults with obesity BMI>30
- Adults overweight BMI>27 with at least one weight-related condition (htn, type2 diabetes, high cholesterol)

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



MASSACHUSETTS
GENERAL HOSPITAL

PSYCHIATRY ACADEMY

lamotrigine
(Lamictal)

extended-
release
carbamazepine

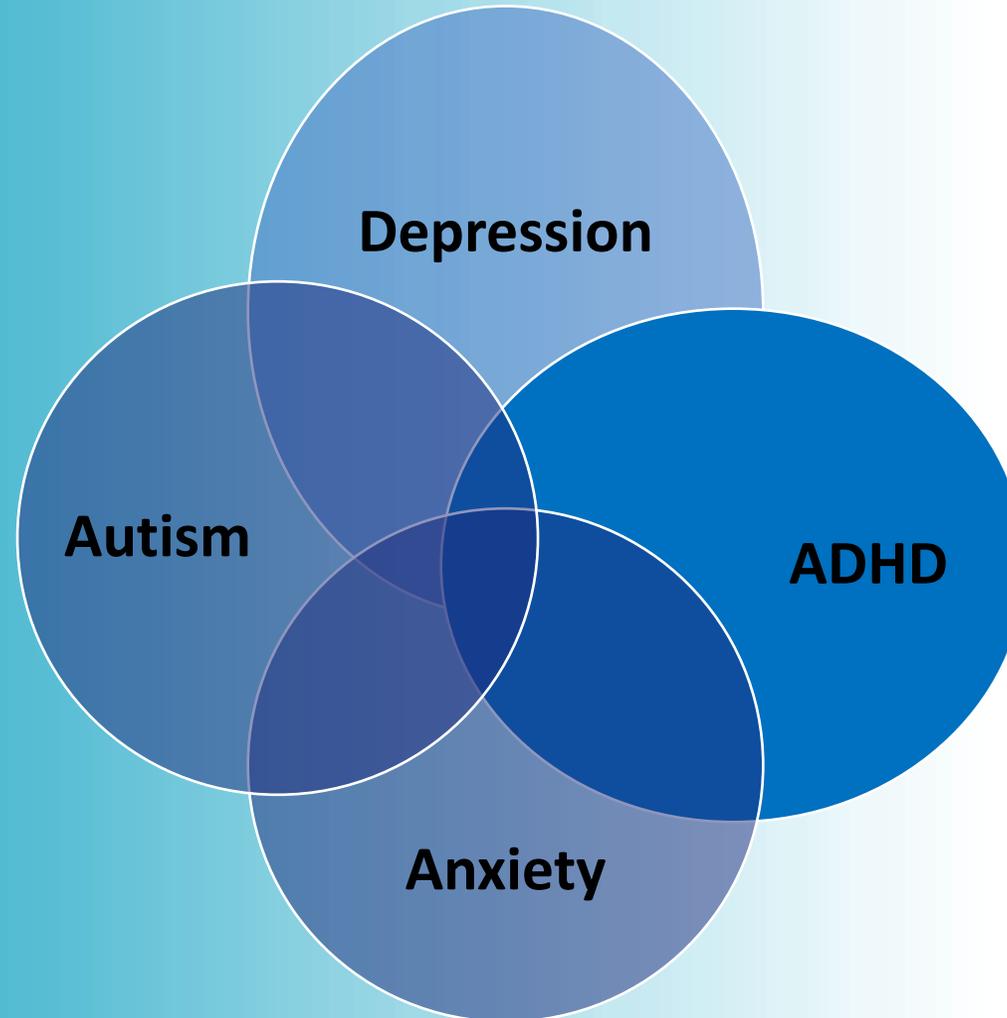
cariprazine
(Vraylar)

lumateperone
(Caplyta)

xanomeline and
trospium
chloride
(Cobenfy)



Comorbidity must be addressed in addition to mania





Treatment of ADHD in adult patients with bipolar disorder may be feasible in the context of anti-manic treatment

Rule out bipolar disorder before initiating methylphenidate as a monotherapy

Swedish national registries 2006-14

2,307 bipolar adults who initiated therapy with methylphenidate

2 groups of bipolar adults starting MPH

Those **WITH** concomitant mood-stabilizing treatment

Those **WITHOUT** concomitant mood-stabilizing treatment

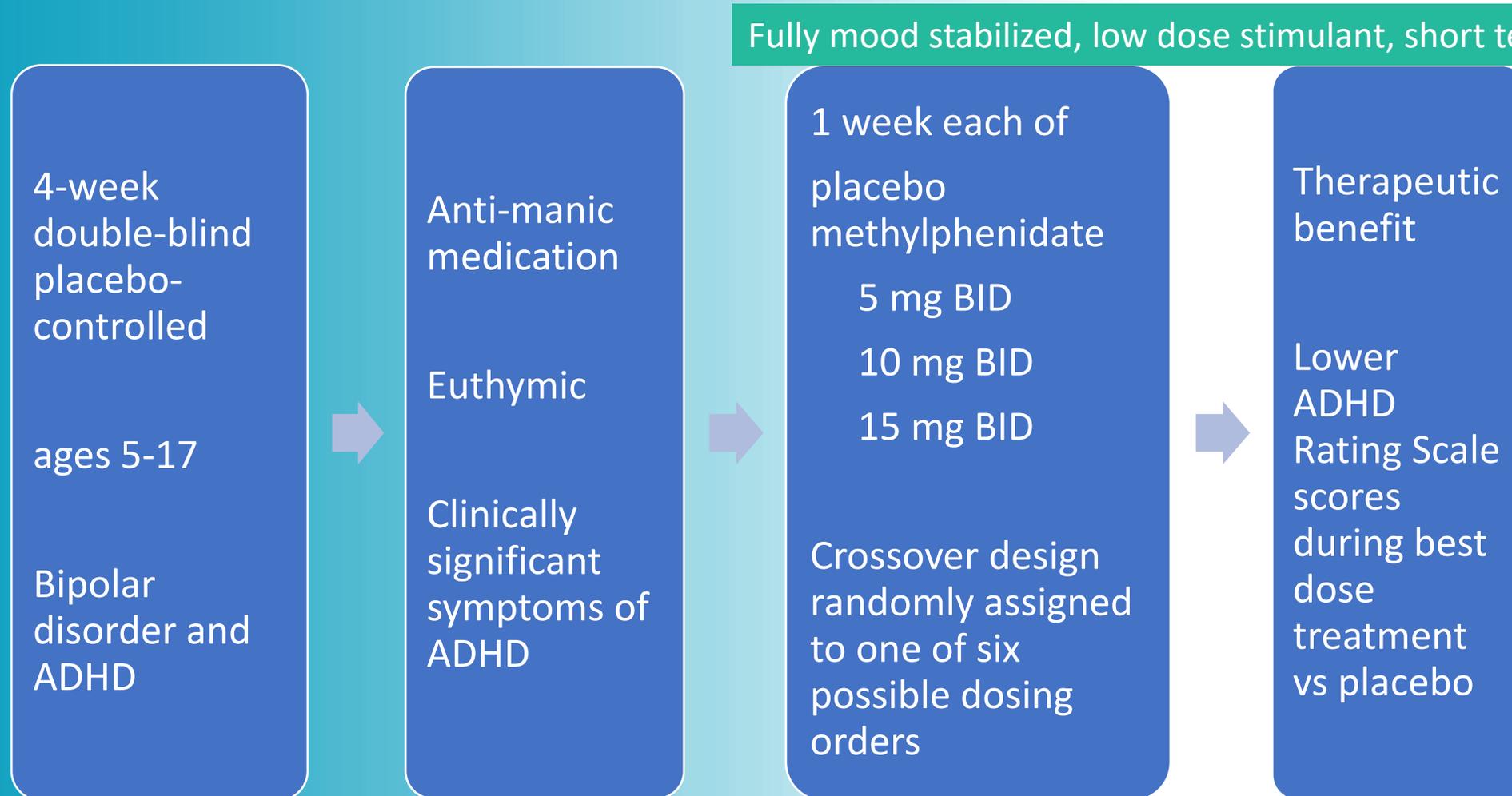
Treatment emergent mania measured as:

Hospitalization

New mood stabilizing medication

No risk among bipolar patients who were concomitantly receiving a mood-stabilizing medication

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



Finding 2007

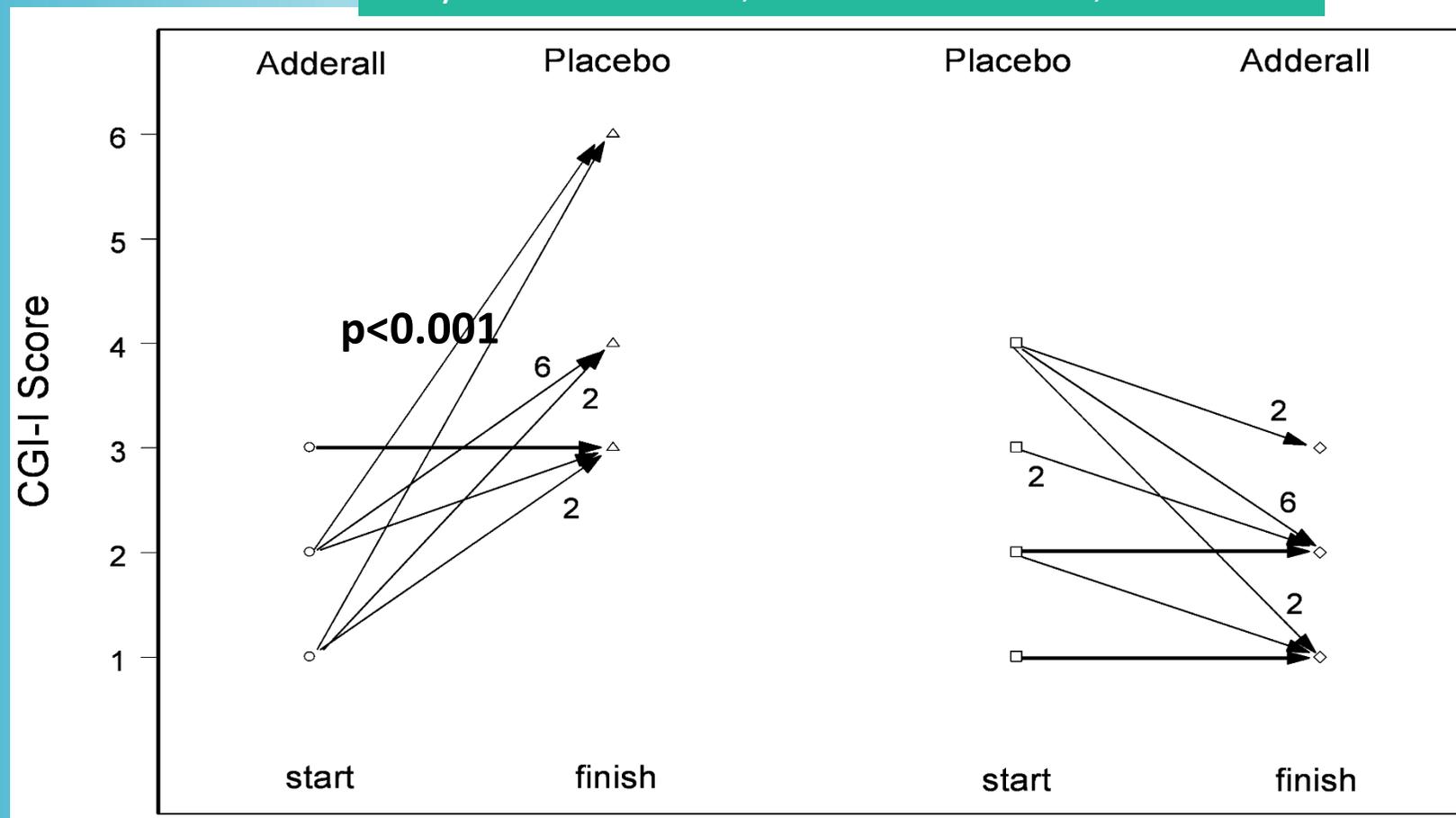
Euthymic youths with bipolar disorder and ADHD may benefit from concomitant treatment with amphetamine salts



Fully mood stabilized, low dose stimulant, short term

Higher scores worse

- 1 = Very much improved
- 2 = Much improved
- 3 = Minimally improved
- 4 = No change:
- 5 = Minimally worse
- 6 = Much worse
- 7 = Very much worse



Scheffer 2005



Mood related adverse events reported with stimulant treatment in ADHD patients

- FDA Adverse Event Reporting System safety database N=865 case reports
 - symptoms of psychosis or mania
 - 90% of these cases having no prior history of a related psychiatric condition
- 30% taking MPH reported moderate to severe adverse events with irritability as the most common adverse event

Mosholder et al., 2009; Wigal et al., 2006



A gap in our evidence base

stimulant label warnings

severity of psychosis or TEM as an outcome

high rate of comorbidity of ADHD with mood disorders

high number of stimulant prescriptions each year

- when is it safe to prescribe a stimulant to a child with BPD?
- what predicts which children with ADHD (with or without BPD) will experience TEM or psychosis as an outcome

To explore adverse outcomes of stimulant treatment for ADHD in pediatric populations with bipolar disorder via literature review and retrospective chart review



MASSACHUSETTS
GENERAL HOSPITAL

PSYCHIATRY ACADEMY

- O'Connor H, Hutt Vater C, DiSalvo M, Faraone SV, **Wozniak J.**

Stimulant treatment and potential adverse outcomes in pediatric populations with bipolar disorder: A systematic review of the literature. *J Attention Disord.* 2024; 28(5), 740-750.

- O'Connor H, Biederman J, DiSalvo M, Joshi G, Faraone SV, **Wozniak J.**

Is Stimulant Treatment in Children and Adolescents with Mood Dysregulation Associated with Adverse Outcomes? *OBM Integrative and Complementary Medicine* 2024; 9(2): 031; doi:10.21926/obm.icm.2402031



What predicts TEM and stimulant adverse outcomes in children with ADHD?

11 articles reviewed

- predominantly male: 64%-87%
- Sample sizes: N=16 to N=9133
- Age range: 3-19 years
 - Two studies examined patients with comorbid pediatric BPD and ADHD
(Findling et al., 2007; Zeni et al., 2009).
 - Three studies examined patients with a diagnosis of pediatric BPD
(DeBello et al., 2001; Faedda et al., 2004; Soutullo et al., 2002)
 - Six studies examined patients with a diagnosis of ADHD
(Brikell et al., 2021; Froehlich et al., 2020; Galanter et al., 2003; Madjar et al., 2019; Mosholder et al., 2009; Wigal et al., 2006)



Literature review supports vigilance for symptoms of mania when prescribing stimulants, in pediatric populations both with and without pre-existing BPD

- high rates of discontinuation or switch to non-stimulant in ADHD youth
- treatment emergent mania in those with and without BPD
- adverse events (mood related and other)
- earlier age of onset of BPD
- adolescents with BPD who were exposed to stimulants had a significantly more severe overall course of illness during hospitalization (LOS, need for PRN, seclusion, restraint)



Examine effects of stimulant treatment in children and adolescents with high levels of emotional dysregulation in a **psychiatric outpatient clinic**

Child psychiatry outpatient clinic patients between September 2016-November 2021

- age 6-17 years
- received a prescription for a stimulant medication

N=181 stratified by level of emotional dysregulation:

- Low: mood dysregulation CBCL T-score of <180 (N=109)
- High: mood dysregulation CBCL T-score of ≥ 210 (N=72)

O'Connor et al, Is Stimulant Treatment in Children and Adolescents with Mood Dysregulation Associated with Adverse Outcomes? OBM Integrative and Complementary Medicine 2024; 9(2): 031

CBCL may be a useful tool for identifying poor outcomes with stimulant treatment



MASSACHUSETTS
GENERAL HOSPITAL

PSYCHIATRY ACADEMY

Patients with high level of emotional dysregulation

- more pre-referral diagnoses of anxiety and mood disorders
 - 42% with mood disorder
 - “unspecified mood disorder” most common 19%
 - only 7% of the high scoring patients had a pre-referral diagnosis of bipolar disorder
- more likely to already be taking medications to treat mood disorders (SGAs and anti-depressants)
- more likely to receive a higher dosage of stimulants
- more likely to receive an additional medication class (SGAs) during follow-up
- emergency room visits and inpatient psychiatric admissions were rare but present only in the emotionally dysregulated group

Depressive symptoms are persistent and debilitating in pediatric bipolar disorder



MASSACHUSETTS
GENERAL HOSPITAL

PSYCHIATRY ACADEMY

4-year longitudinal study pediatric bipolar I disorder

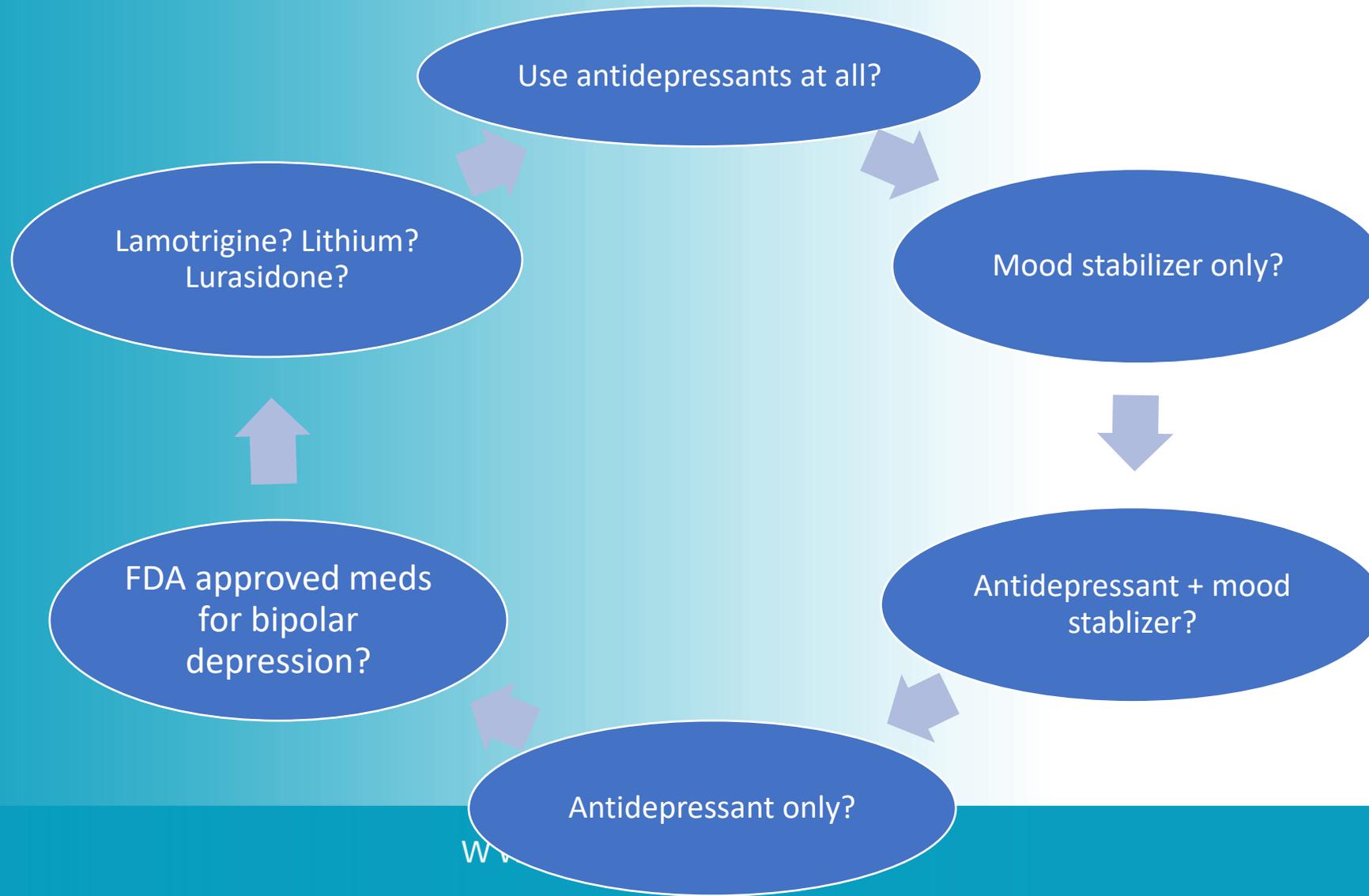
- 50% time met criteria for
- major depression
 - minor depression
 - dysthymia

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

Chen 2014; Wozniak 2005; Birmaher 2006

Pharmacologic management of bipolar depression is very difficult



Antidepressants in bipolar youth is a double-edged sword



MASSACHUSETTS
GENERAL HOSPITAL

PSYCHIATRY ACADEMY

versus mood stabilizers, typical neuroleptics or TCAs

SSRIs led to the most
improvement of BP MDD

SSRIs led to the most
destabilization with mania

Biederman 2000

Antidepressants can lead to switching



MASSACHUSETTS
GENERAL HOSPITAL

PSYCHIATRY ACADEMY

Rate of switching is higher
in subjects with history of
receiving antidepressants



Strober; Shon; Martin



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 positive response

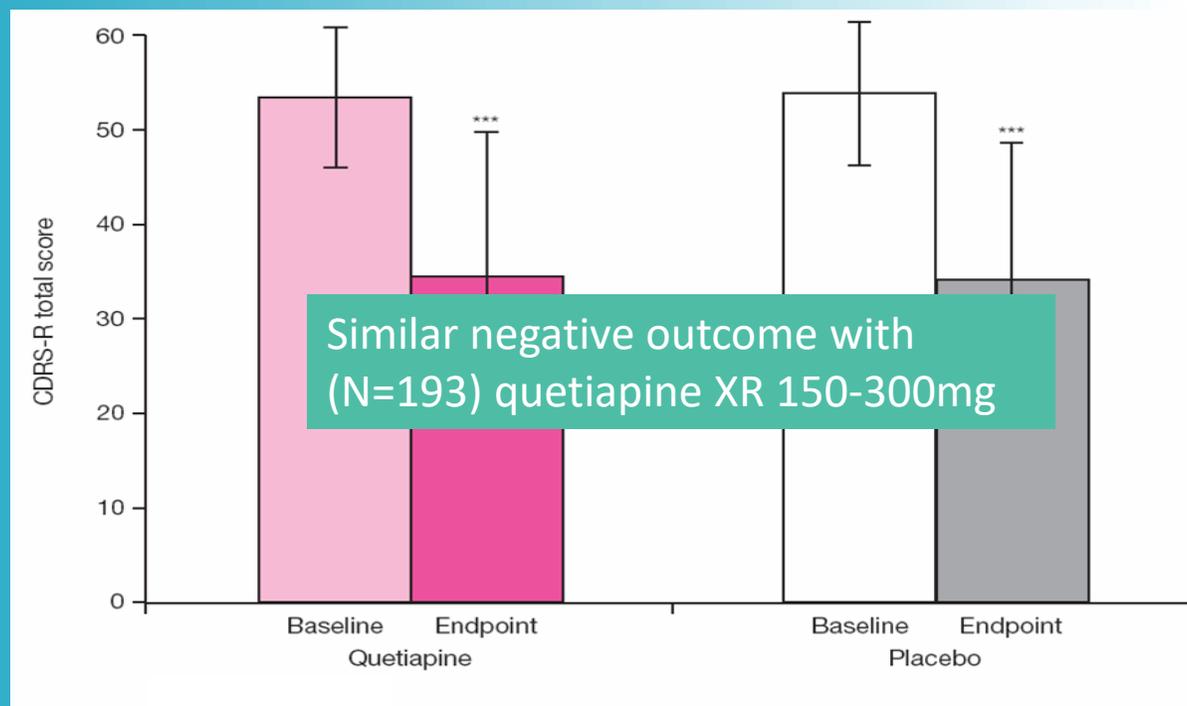
Newer antipsychotics e.g., cariprazine and lurasidone are promising but little evidence base in pediatric populations

Zarate 1998; Rothschild 1999; Mahmoud 2007

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)



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



MASSACHUSETTS
GENERAL HOSPITAL

PSYCHIATRY ACADEMY

placebo-
controlled
study

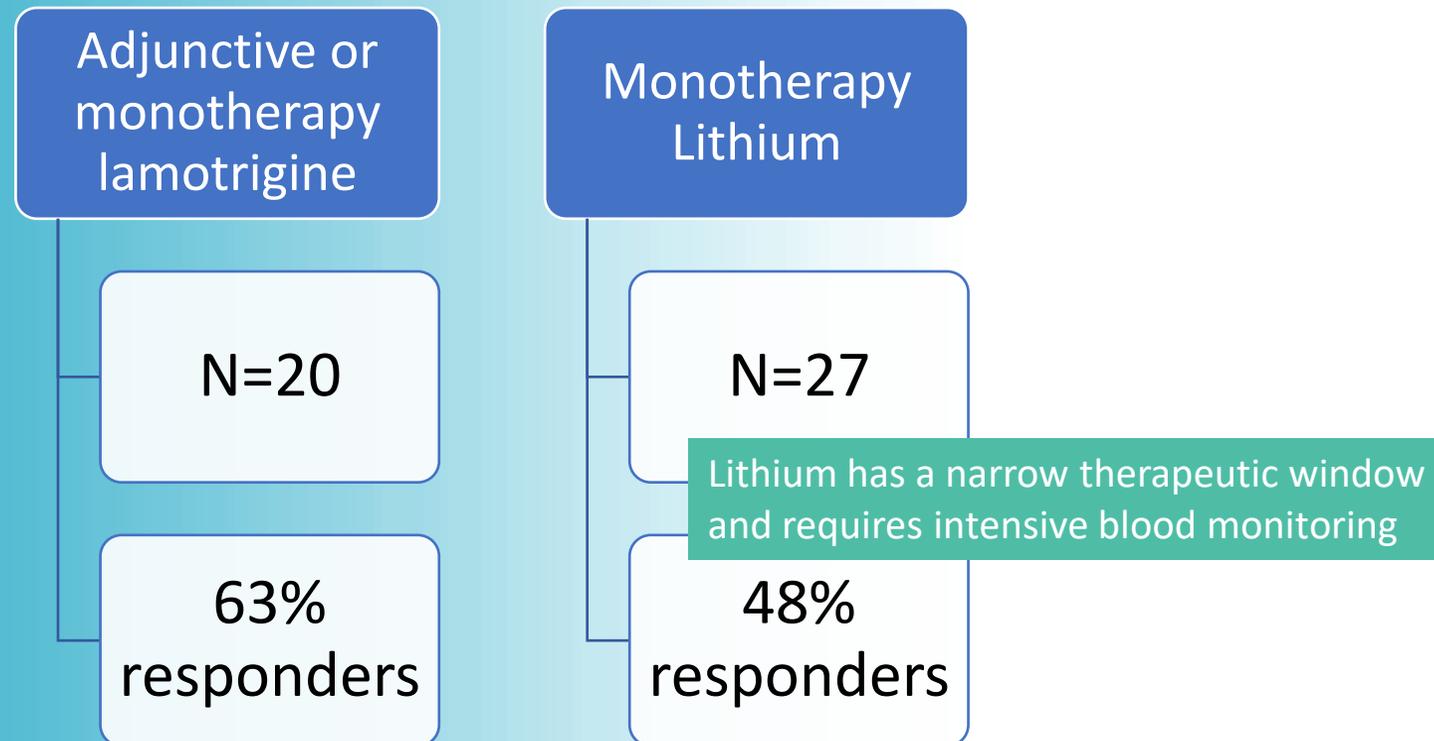
monotherapy
with lurasidone

dose range of
20-80 mg/day

minimal
effects on
weight and
metabolic
parameters

DelBello. *JAACAP*. 2017

Open label lamotrigine and lithium are effective in adolescent Bipolar Depression (at least 50% decrease in CDRS)



Lamotrigine is approved by FDA for use in those *over the age of 16 years*, due to increased risk of Stevens–Johnson syndrome in the young age group.