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Differentiating Unipolar vs Bipolar Disorder in Children

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Pharmacologic management of bipolar depression is very difficult

Disclosures

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My spouse/partner and I have the following relevant financial relationships with commercial interests 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.

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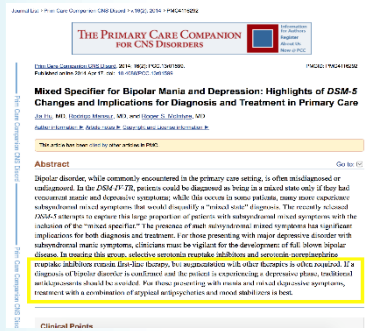
Overview:
Switch from pediatric depression to bipolar disorder is common.
Pharmacologic treatment of bipolar depression is complicated due to risk of switch with antidepressants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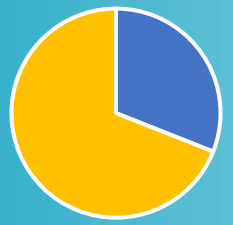
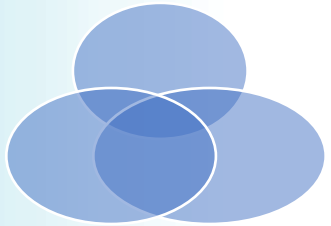
Mixed Specifier for Bipolar Mania and Depression: Highlights of *DSM-5* Changes and Implications for Diagnosis and Treatment in Primary Care

Abstract

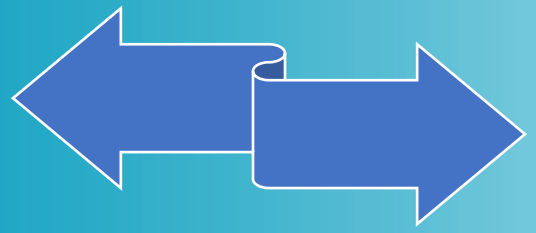
Bipolar depression: Pediatric Bipolar Disorder often presents with depressive or mixed states and should not be mistaken for unipolar depression



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



Switch can be predicted:
Family history and other clinical features can predict switch



Treatment: Pharmacologic treatment is generally required.
and antidepressants may worsen the clinical picture

We use the same Major Depression diagnostic criteria for children as adults*

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Major Depressive Episode:

A. 2 weeks of sadness, low mood, loss of interest melancholic, **irritable, grumpy, easily annoyed, bored**

B. 5/7 of the following symptoms:

- **S**leep (insomnia/ hypersomnia)
- **I**nterest (loss of interest part of criteria A)
- **G**uilt (feeling worthless and hopeless)
- **E**nergy (low energy/ fatigue)
- **C**oncentration (making decisions/ focus)
- **A**ppetite (change in appetite or weight)
- **P**sychomotor agitation or retardation
- **S**uicidal thoughts

*with developmental considerations

We use the same mania diagnostic criteria for children as adults*

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Manic Episode:

A. Seven days of elevated, expansive or irritable mood plus abnormally and persistently goal-directed behavior or energy

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

- **D**istractability
- **I**ncreased goal directed activity or psychomotor agitation
- **G**randiosity (inflated self-esteem, flagrant disregard for adult authority)
- **F**light of Ideas, racing thoughts (observed or experienced)
- **A**ctivities (high potential for consequences: sexual, shopping sprees)
- **S**leep (decreased need of sleep)
- **T**alkativeness

*with developmental considerations

Depressive symptoms are persistent and debilitating in pediatric bipolar disorder

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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

In DSM5, a Major Depressive Episode is considered "mixed" with 3/7 additional manic symptoms

MIXED MAJOR DEPRESSIVE DISORDER

1. Elevated, expansive mood.
2. Inflated self-esteem or grandiosity.
3. More talkative than usual or pressure
4. Flight of ideas or subjective experien
5. Increase in energy or goal-directed a
6. Increased or excessive involvement i
consequences (eg, engaging in unrestra siness
investments).
7. Decreased need for sleep (feeling res ith
insomnia).[8](p150)

1. Euphoria
2. Grandiosity
3. Pressured speech
4. Racing thoughts/FOI
5. Increased energy
6. Reckless activities
7. Decreased need for sleep

Hu 2014.

Mixed states are common

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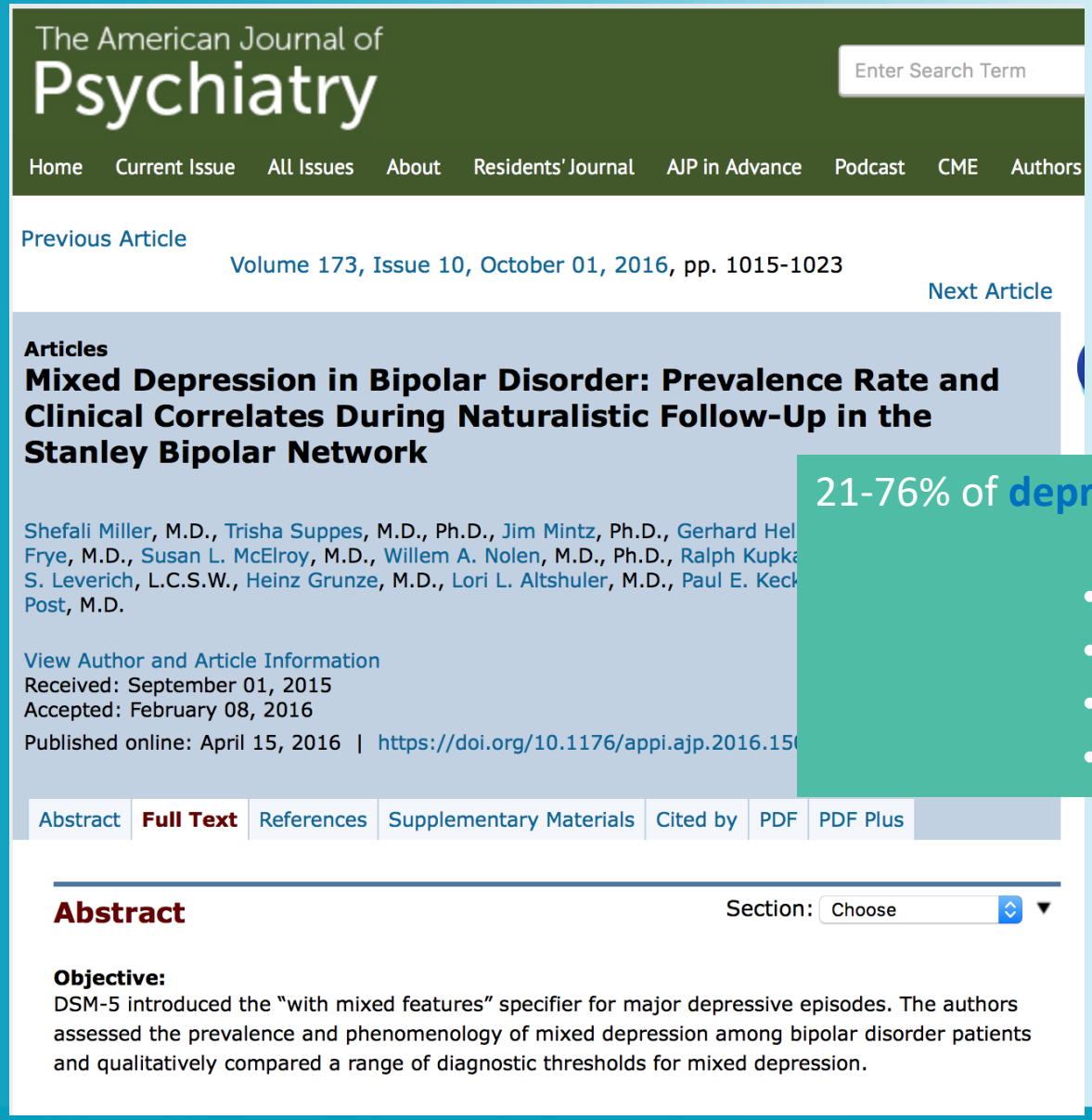

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Volume 173, Issue 10, October 01, 2016, pp. 1015-1023

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Articles

Mixed Depression in Bipolar Disorder: Prevalence Rate and Clinical Correlates During Naturalistic Follow-Up in the Stanley Bipolar Network

Shefali Miller, M.D., Trisha Suppes, M.D., Ph.D., Jim Mintz, Ph.D., Gerhard Hel
Frye, M.D., Susan L. McElroy, M.D., Willem A. Nolen, M.D., Ph.D., Ralph Kupka
S. Leverich, L.C.S.W., Heinz Grunze, M.D., Lori L. Altshuler, M.D., Paul E. Keck
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Abstract

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Objective:
DSM-5 introduced the "with mixed features" specifier for major depressive episodes. The authors assessed the prevalence and phenomenology of mixed depression among bipolar disorder patients and qualitatively compared a range of diagnostic thresholds for mixed depression.

21-76% of **depressed adult patients** have mixed states

- younger age of onset
- longer episode duration
- worse outcomes
- increased suicidality

Miller *Am J Psych* 2016

In DSM5, a manic or hypomanic episode is considered "mixed" with 3/6 additional depressive symptoms

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MIXED BIPOLAR MANIA

1. Prominent dysphoria or depressed mood as indicated by either subjective report (eg, feels sad or empty) or observation made by others (eg, appears tearful).
2. Diminished interest or pleasure in all, c … e account or observation made by others).
3. Psychomotor retardation nearly every c … gs of being slowed down).
4. Fatigue or loss of energy.
5. Feeling of worthlessness or excessive c … about being sick).
6. Recurrent thoughts of death (not just fe … ific plan, or a suicide attempt or a specific pla

1. Appears or feels sad
2. Joyless
3. Psychomotor retardation
4. Fatigue
5. Worthlessness
6. Suicidality

Hu 2014

Antidepressant medications should be avoided in bipolar disorder

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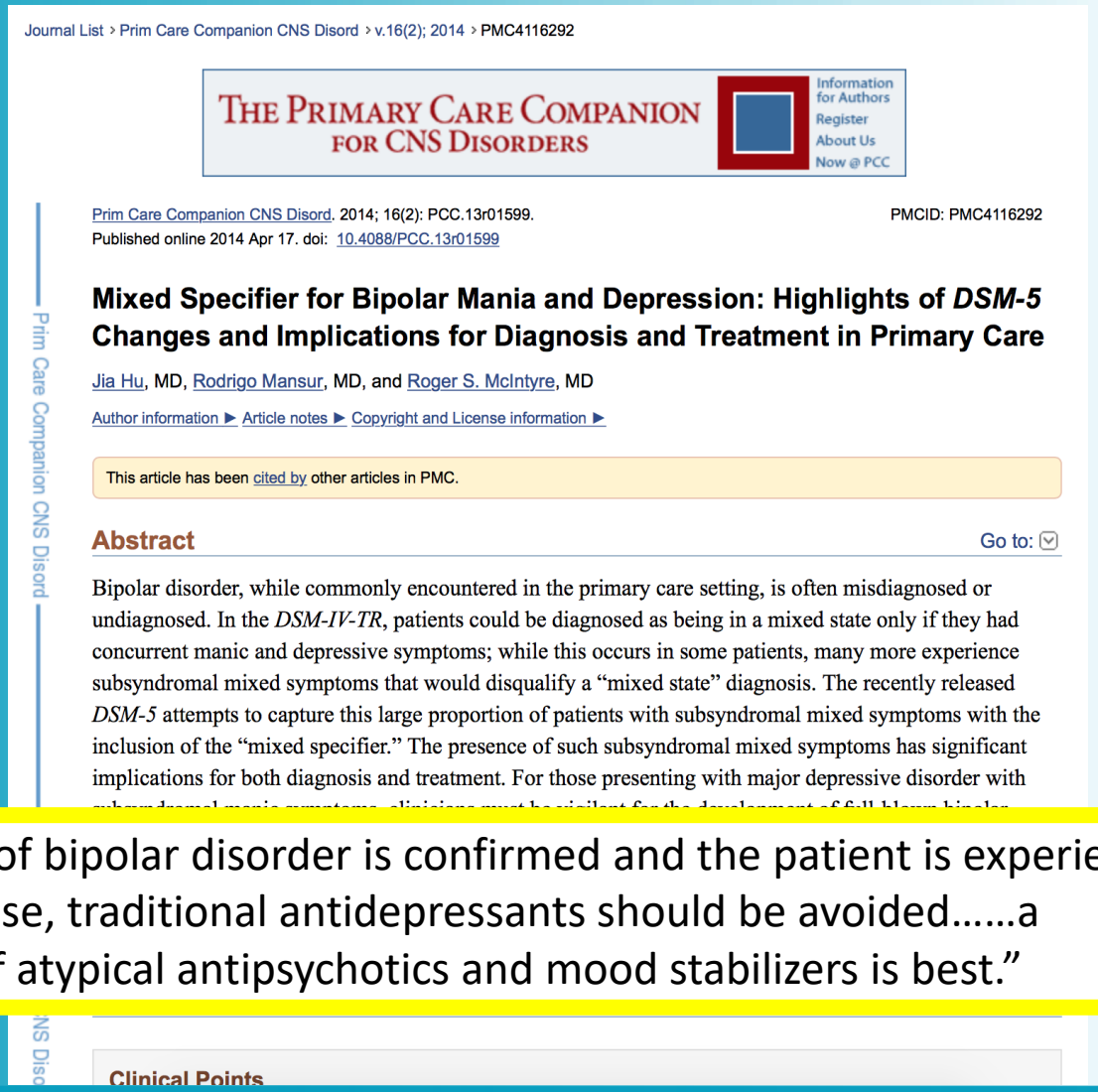

Journal List › Prim Care Companion CNS Disord › v.16(2); 2014 › PMC4116292

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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 Go to:

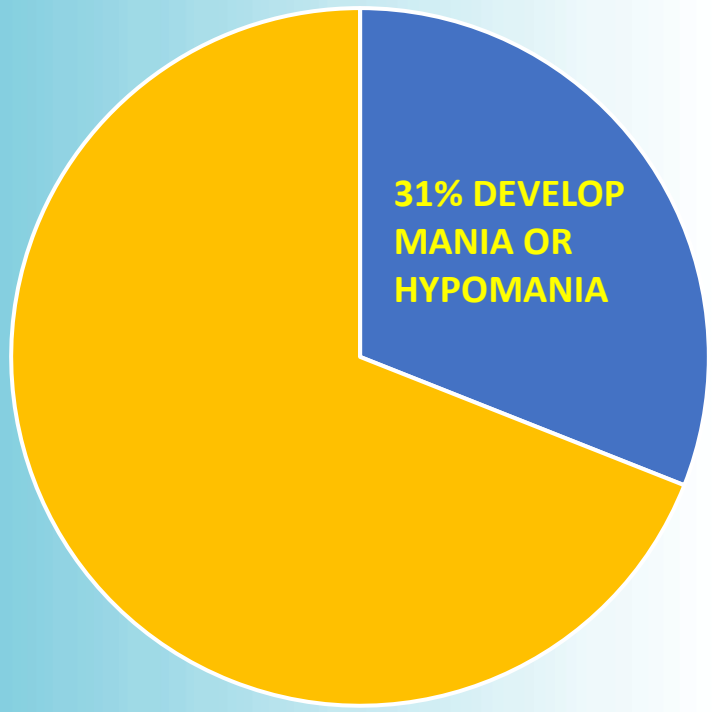
Bipolar disorder, while commonly encountered in the primary care setting, is often misdiagnosed or undiagnosed. In the *DSM-IV-TR*, patients could be diagnosed as being in a mixed state only if they had concurrent manic and depressive symptoms; while this occurs in some patients, many more experience subsyndromal mixed symptoms that would disqualify a "mixed state" diagnosis. The recently released *DSM-5* attempts to capture this large proportion of patients with subsyndromal mixed symptoms with the inclusion of the "mixed specifier." The presence of such subsyndromal mixed symptoms has significant implications for both diagnosis and treatment. For those presenting with major depressive disorder with

Clinical Points

"If a diagnosis of bipolar disorder is confirmed and the patient is experiencing a depressive phase, traditional antidepressants should be avoided……a combination of atypical antipsychotics and mood stabilizers is best."

Children with MDD often switch

CHILDREN WITH MDD



Adult literature has consistently reported that “early onset” (< 25 years) mood symptoms pose an increased risk of switching

Weissman 1999; Geller 1994

Features of pediatric depression can predict switch to bipolar disorder

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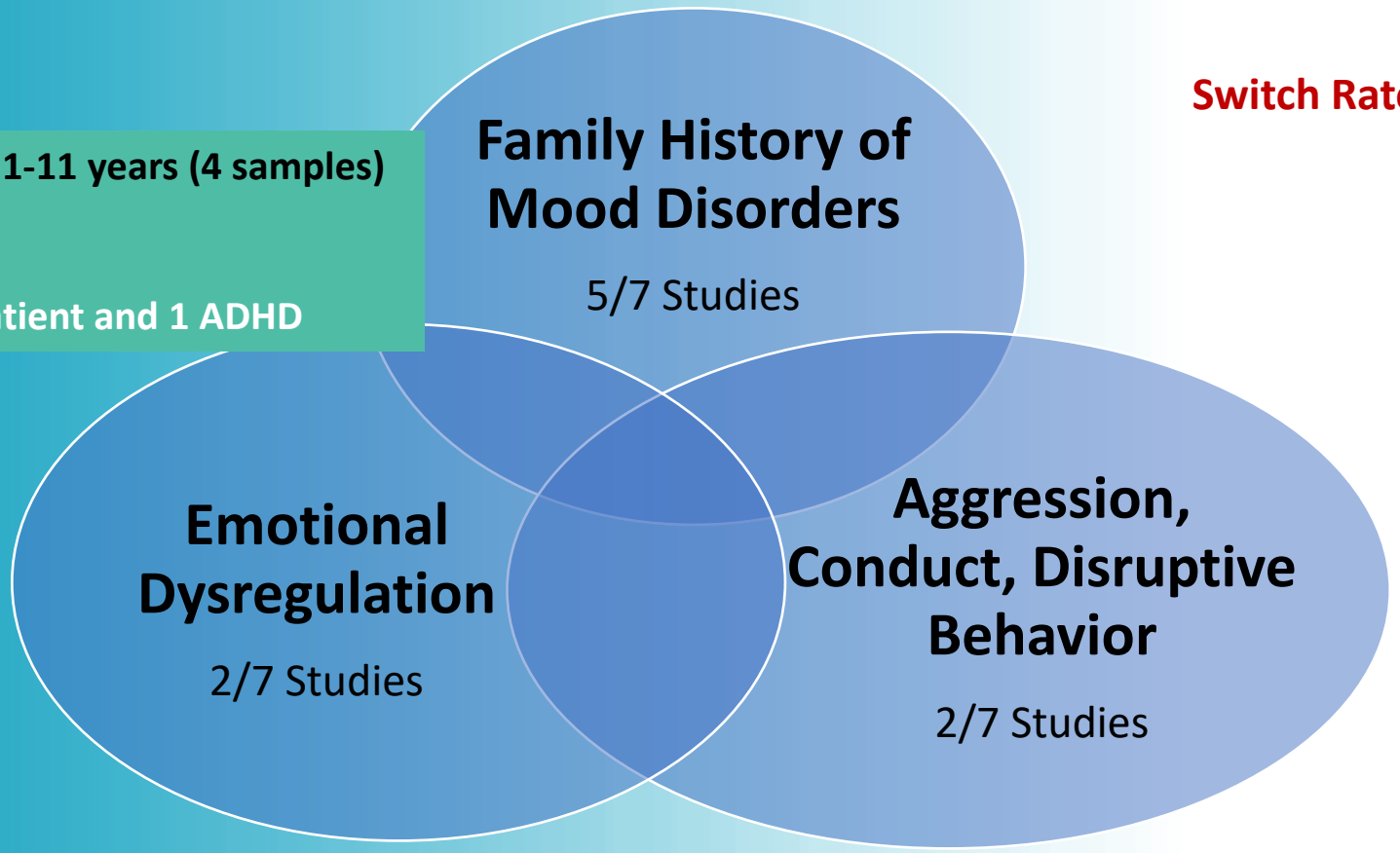
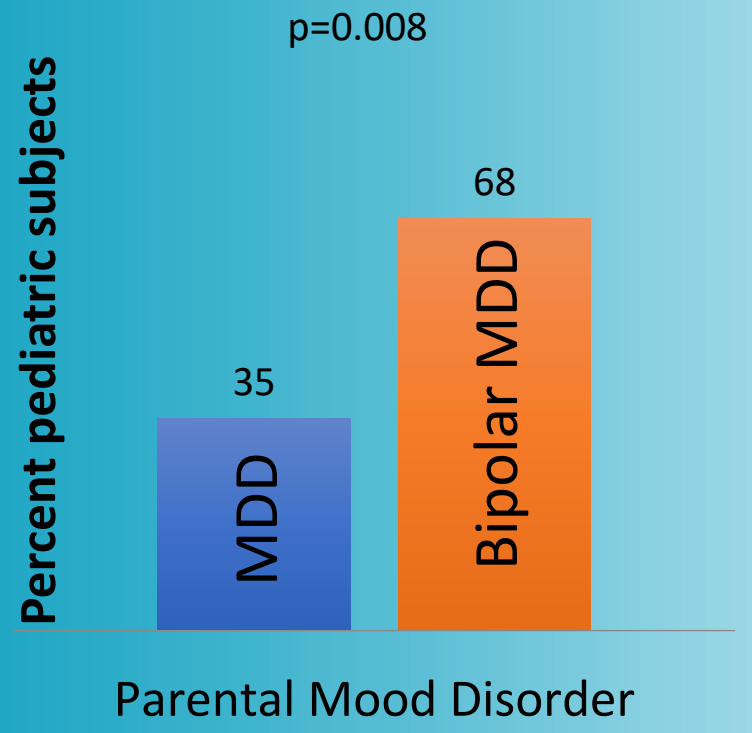
7 follow-up studies 1-11 years (4 samples)
N= 985 subjects
ages 6-18 years
2 inpatient, 1 outpatient and 1 ADHD



Switch Rate: 9% - 43%

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

Parental mood disorder is a predictor of switch

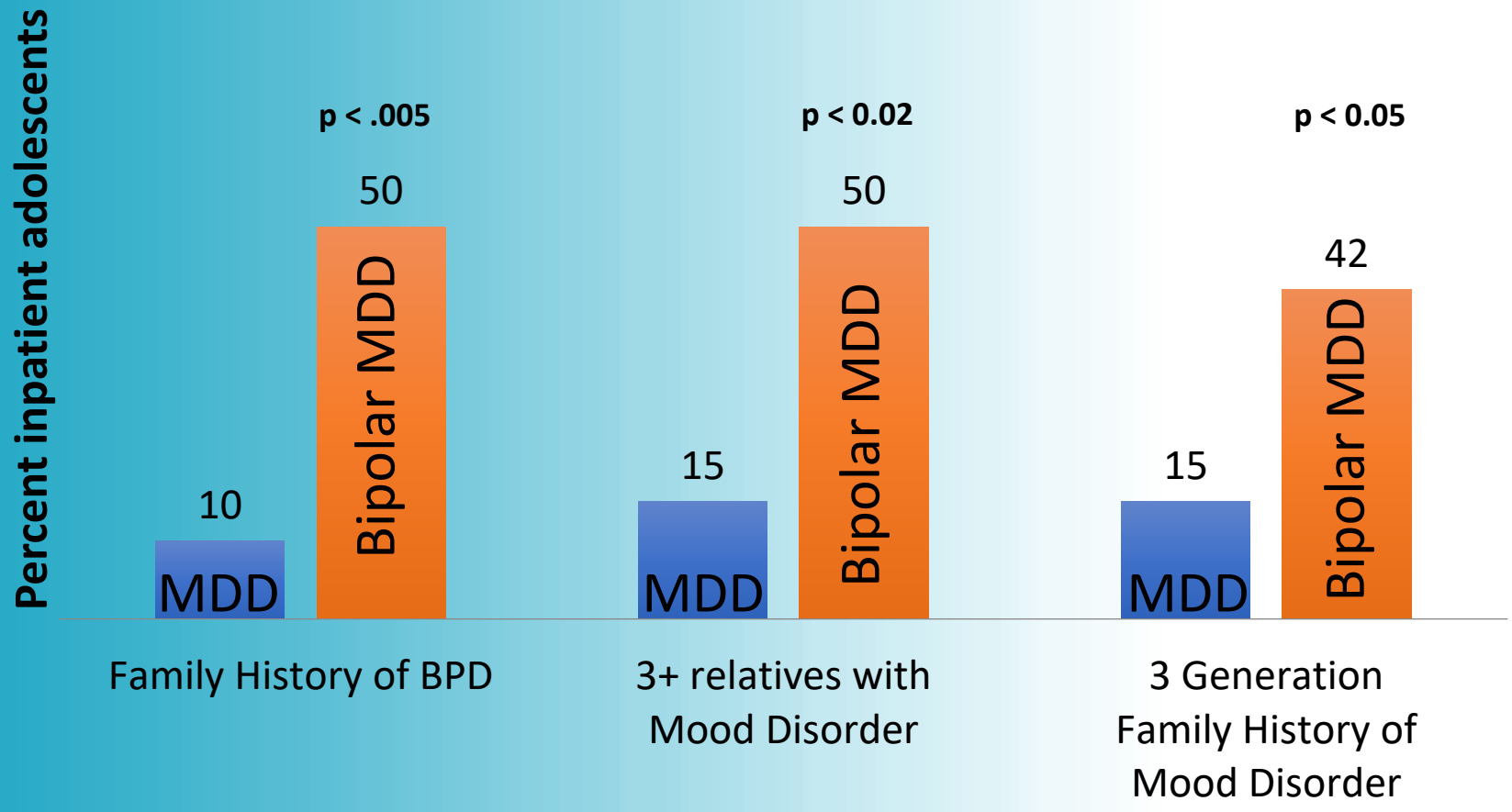


2 large controlled longitudinal studies of boys and girls with and without ADHD and their siblings

Subjects who switched had significantly higher rates of parental bipolar or depressive disorders

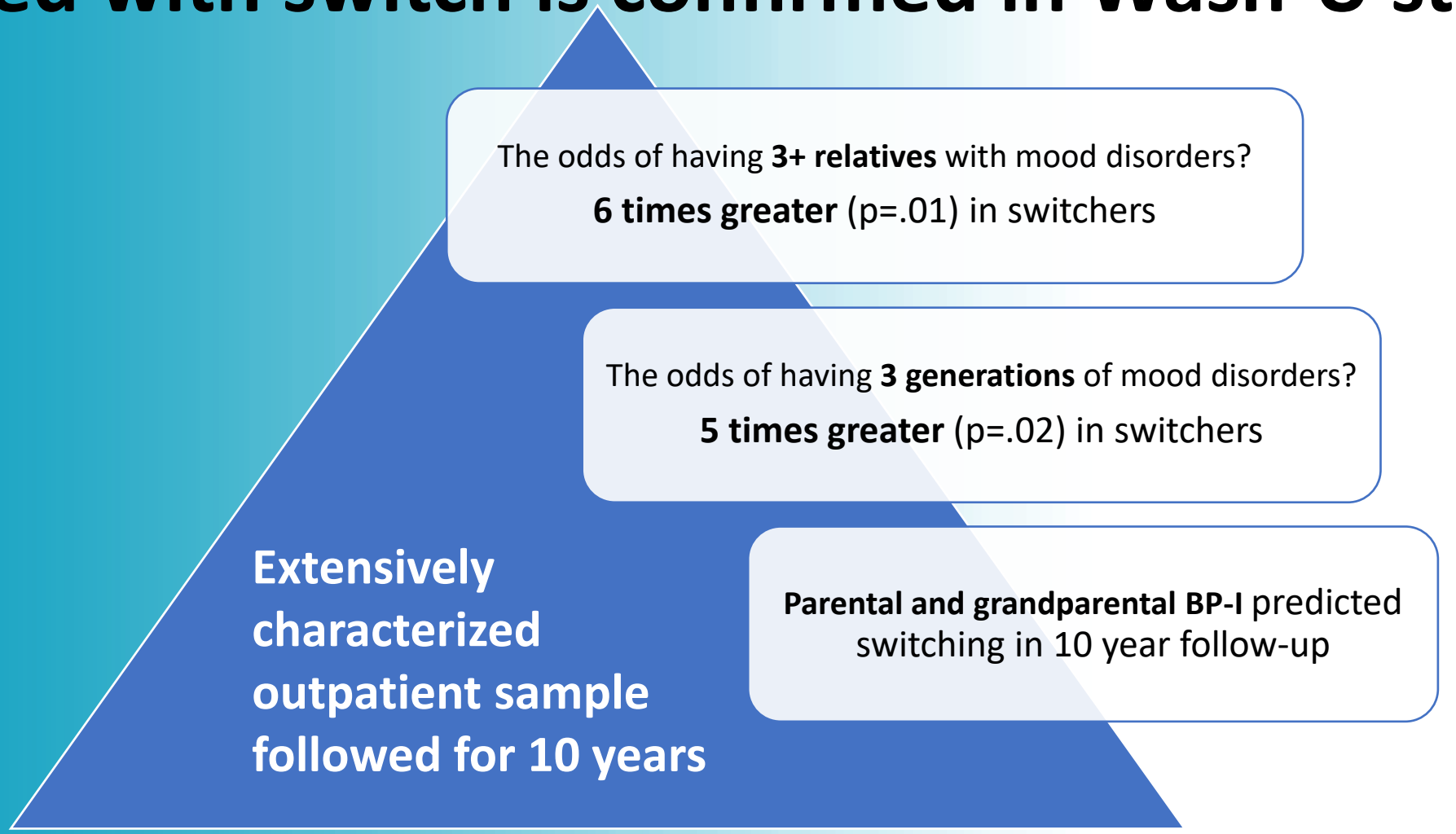
Biederman 2009

Family history of mood disorder is associated with bipolar depression



Strober 1982

Family history of mood disorder associated with switch is confirmed in Wash-U study



The odds of having **3+ relatives** with mood disorders?

6 times greater (p=.01) in switchers

The odds of having **3 generations** of mood disorders?

5 times greater (p=.02) in switchers

Parental and grandparental BP-I predicted switching in 10 year follow-up

Geller 1994, 2001

Aggression, conduct and behavioral problems are associated with bipolar depression

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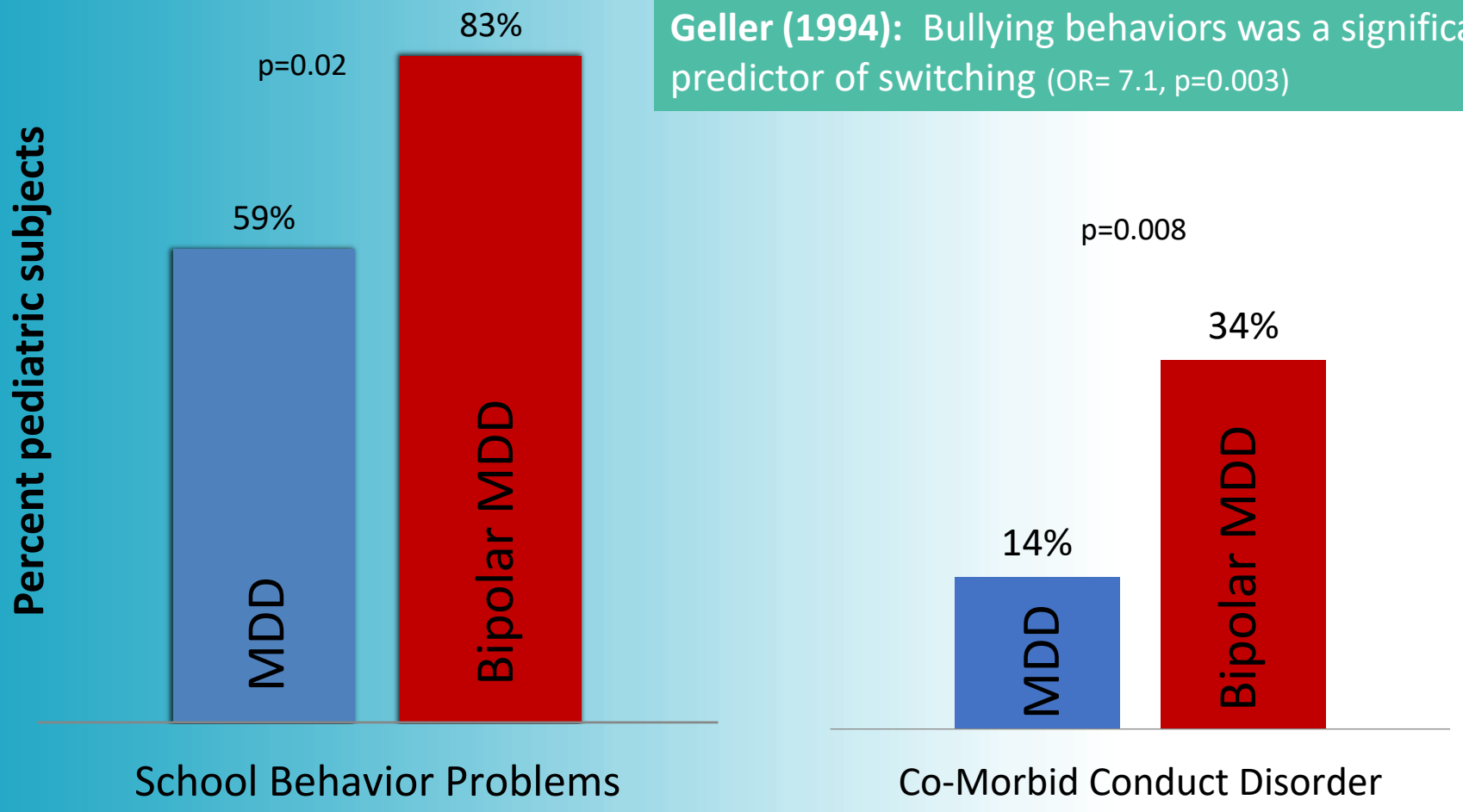
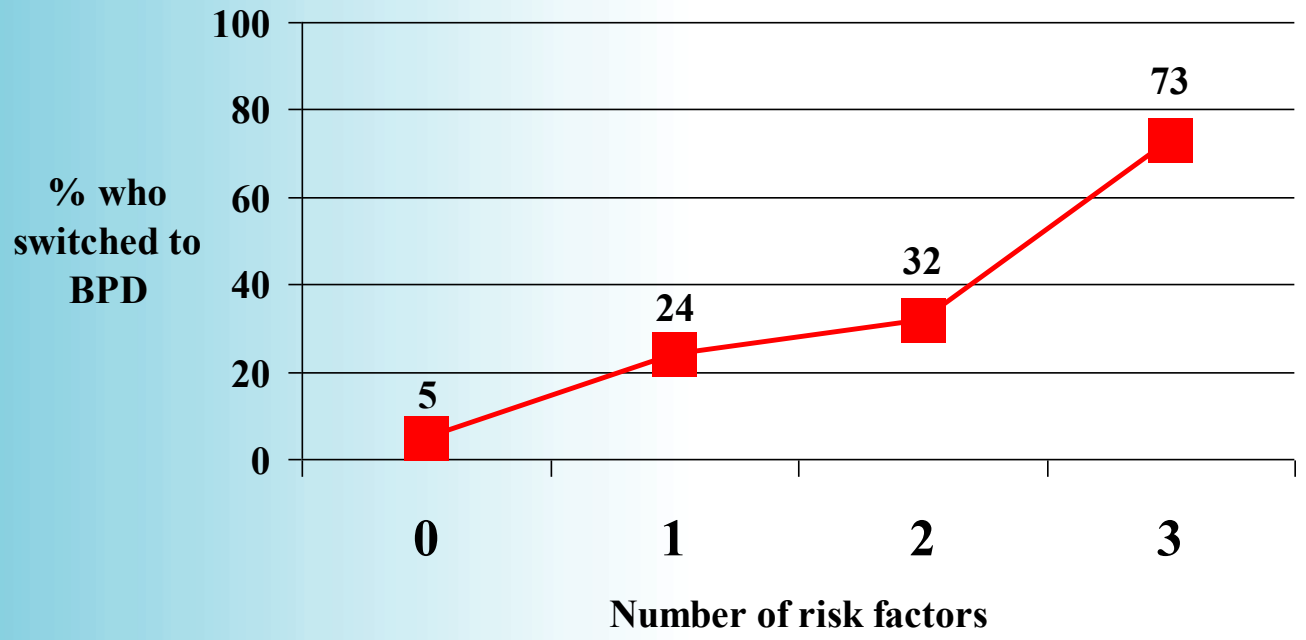
Geller (1994): Bullying behaviors was a significant predictor of switching (OR= 7.1, p=0.003)



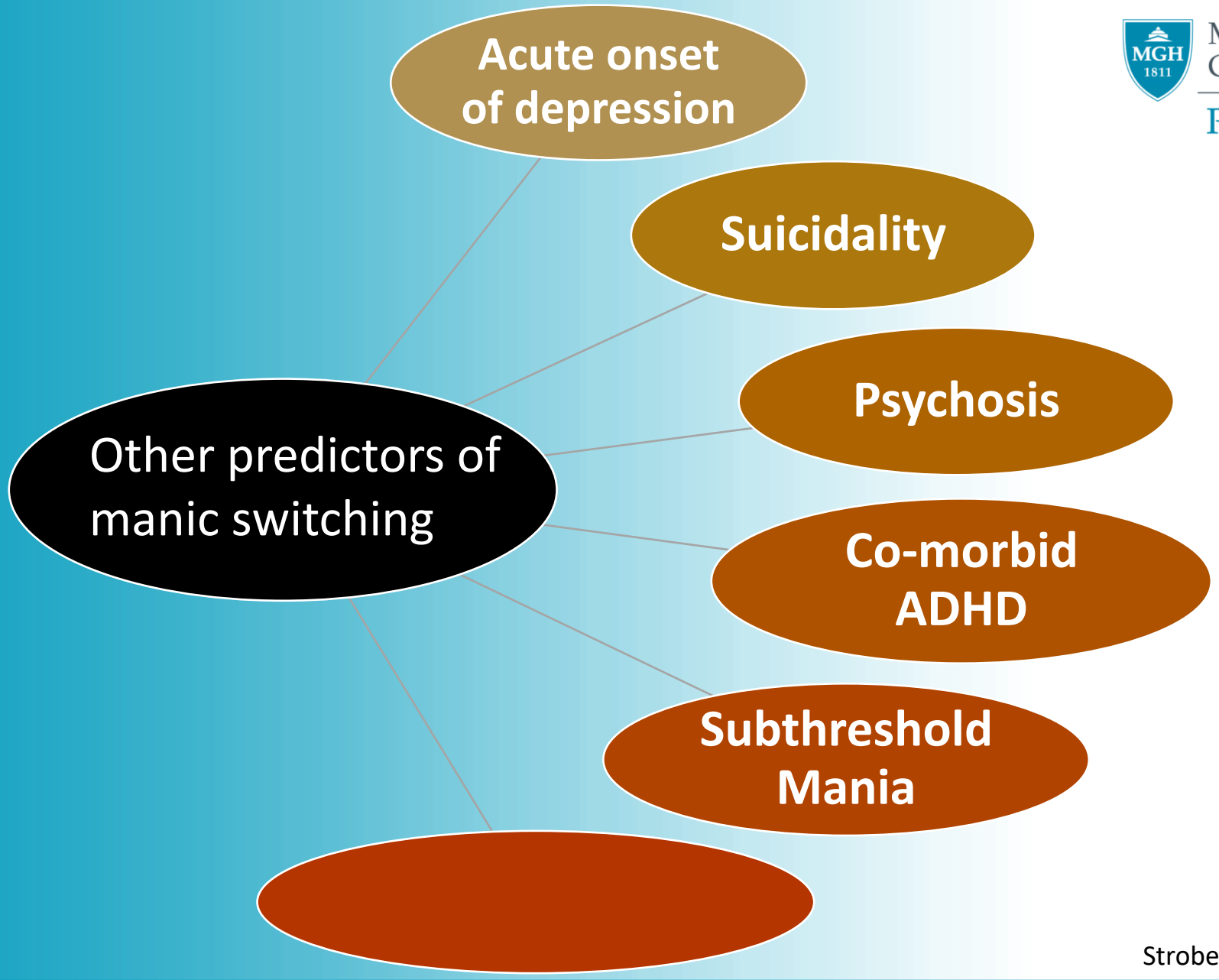
Biederman 2009, 2013

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

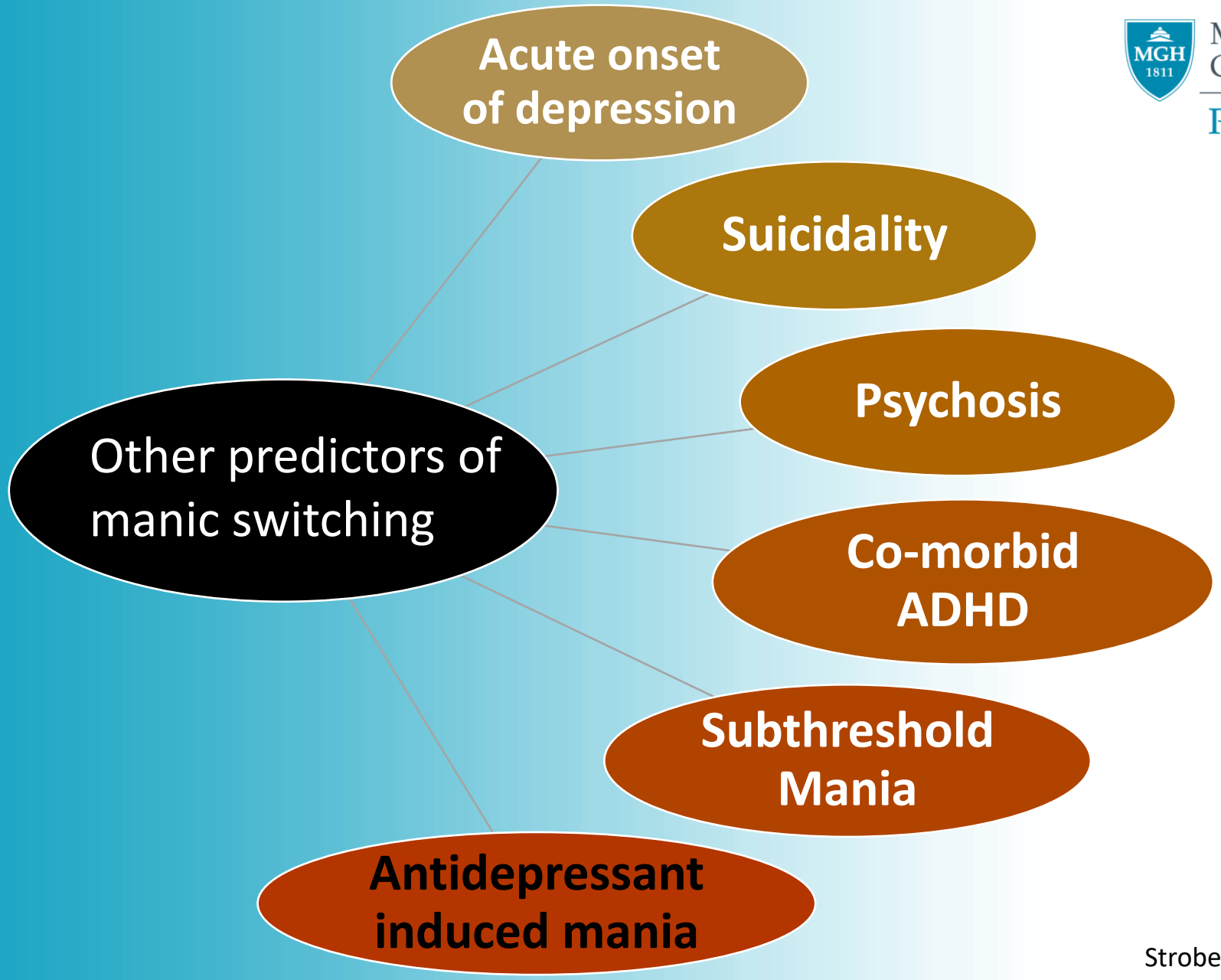
- conduct disorder
- school behavior problems
- parental mood disorder



Biederman 2009



Strober 1982, 1994; Biederman 2009, 2013



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Strober 1982, 1994; Biederman 2009, 2013

Antidepressants in bipolar youth is a double-edged sword

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versus mood stabilizers, typical neuroleptics or TCAs

SSRIs led to the most improvement of BP MDD

SSRIs led to the most destabilization with mania

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

Biederman 2000

Use antidepressants with caution

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

Strober; Shon; Martin

We have many FDA approved treatments for youth with emotional dysregulation

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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

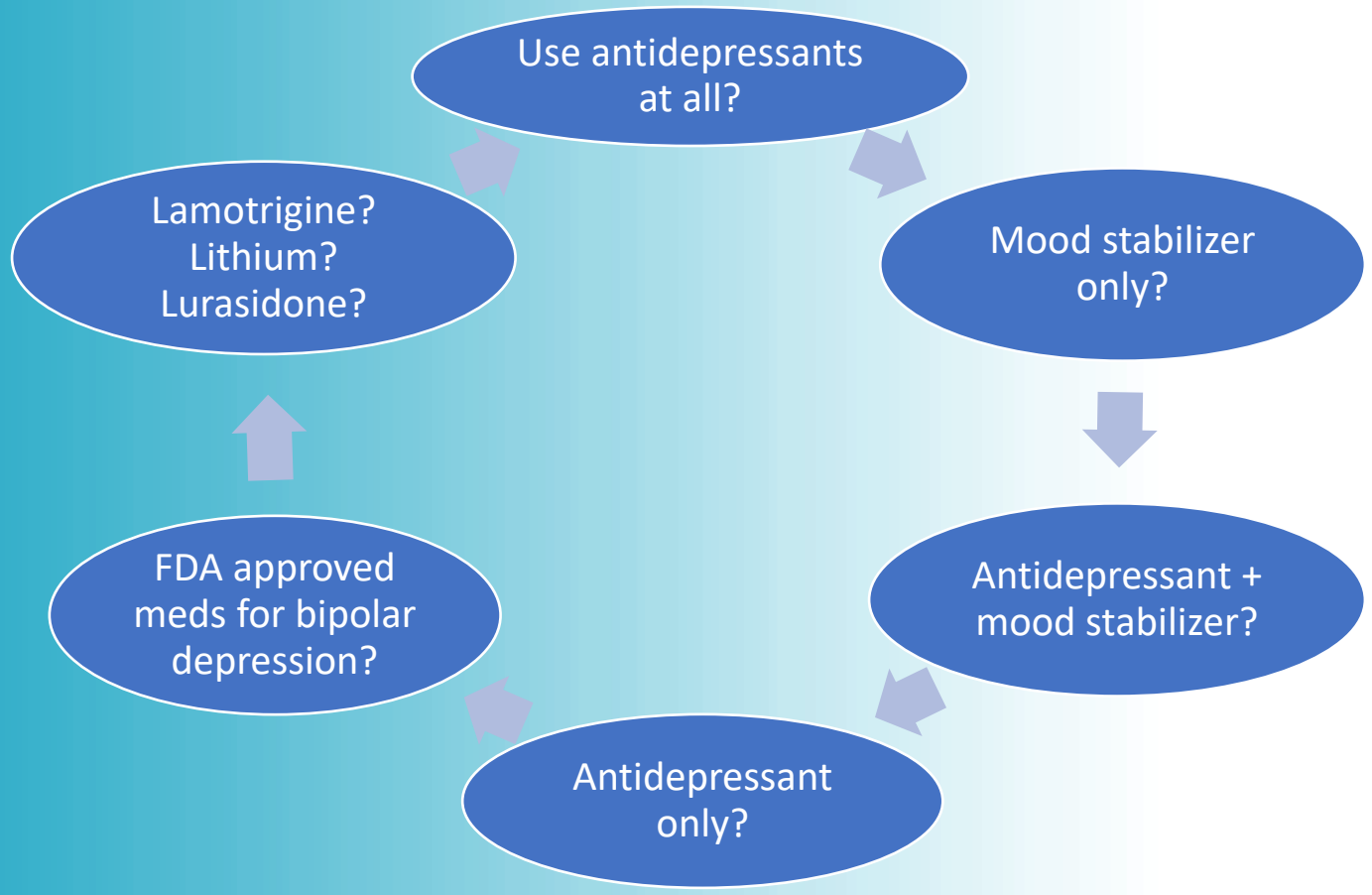
Fluoxetine: depression and OCD age 8+
Escitalopram 2002: depression age 12+

but few for bipolar depression

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

Pharmacologic management of bipolar depression is very difficult



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

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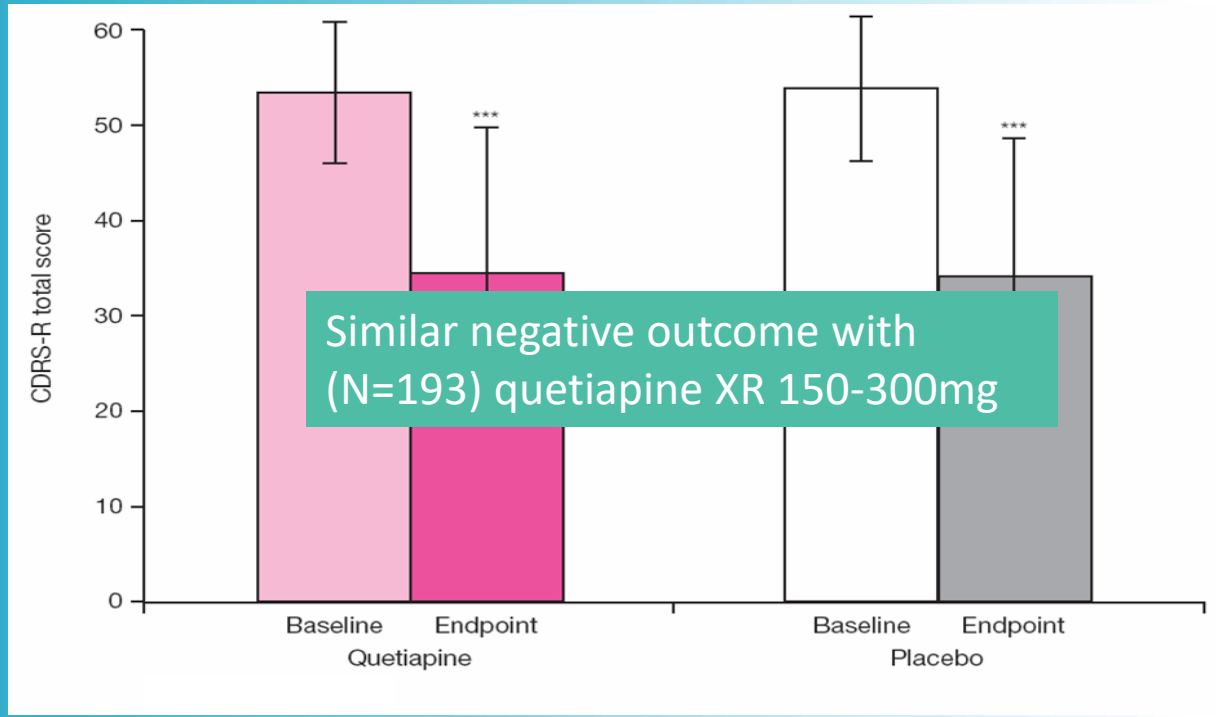
MEAN (SD) CHANGE IN CDRS-R SCORES FROM BASELINE TO ENDPOINT (8 weeks; N=32)



DelBello 2009; Findling 2014

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

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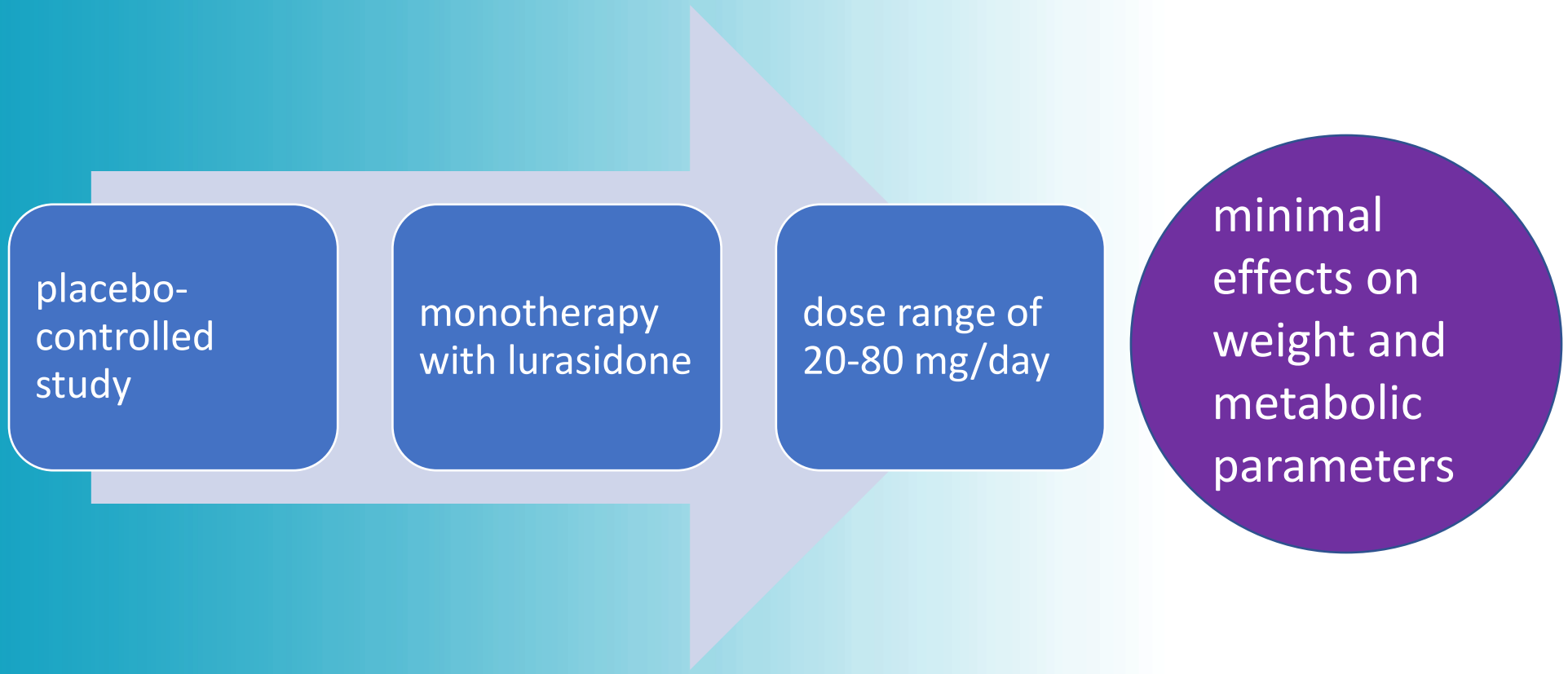

DelBello. *JAACAP*. 2017

Lurasidone in children and adolescents with Bipolar I Depression reduces CDRS and CGI-BP-S Scores

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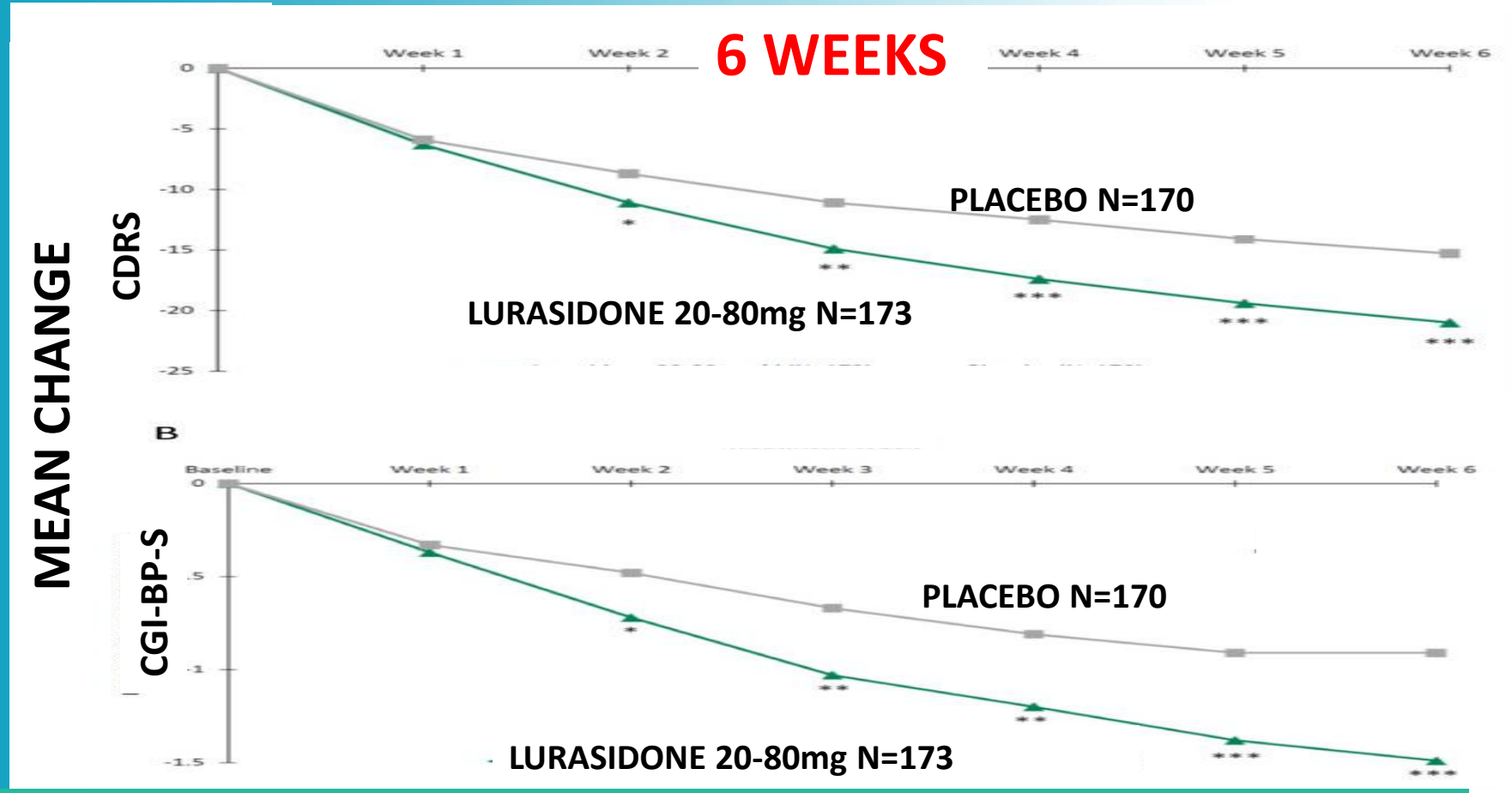
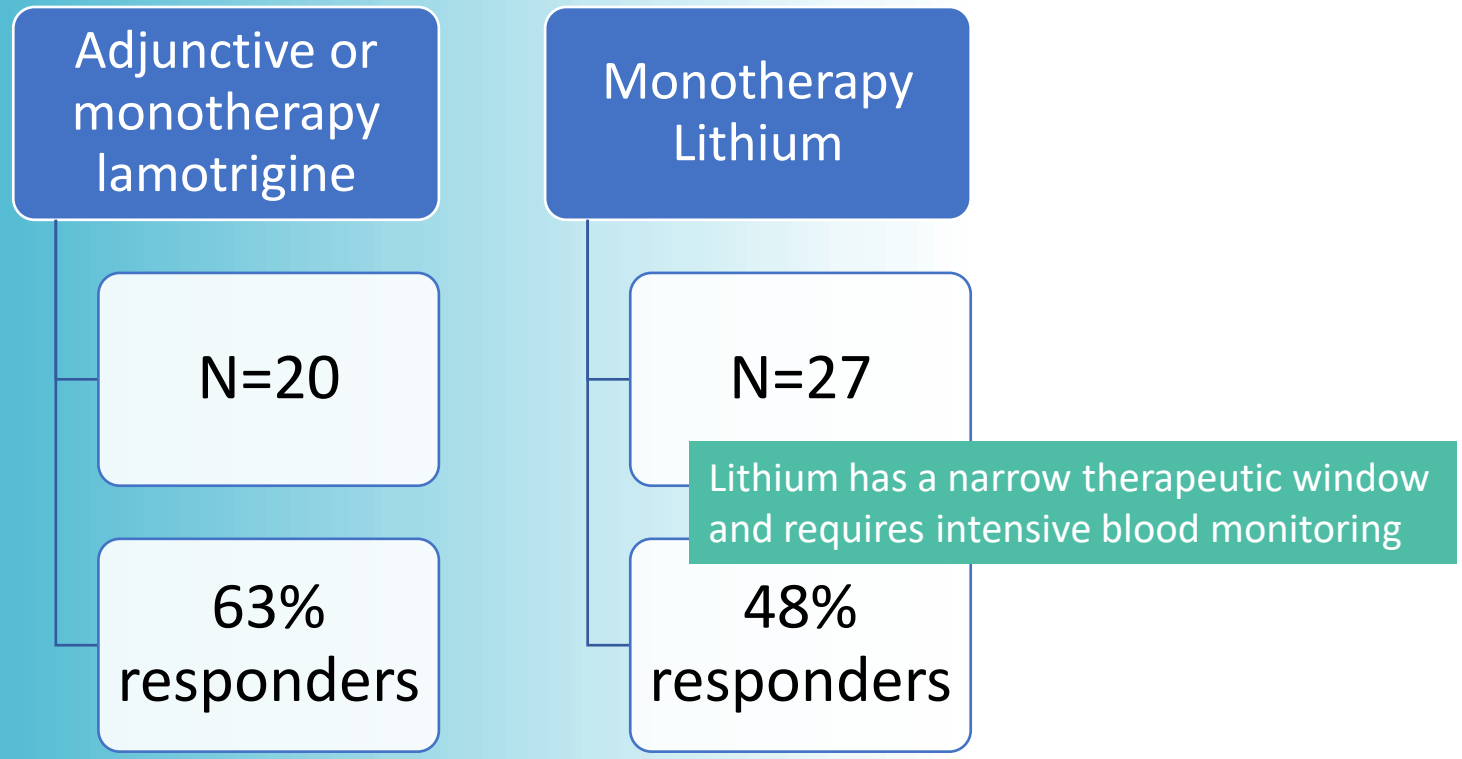


Clinical observation: Lurasidone can behave like a traditional antidepressant and lead to switch

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.

Chang JAACAP 2006; Patel JAACAP 2006

SGAs have antidepressant qualities

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- 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 lumataperone are promising but little evidence base in pediatric populations

Zarate 1998; Rothschild 1999; Mahmoud 2007

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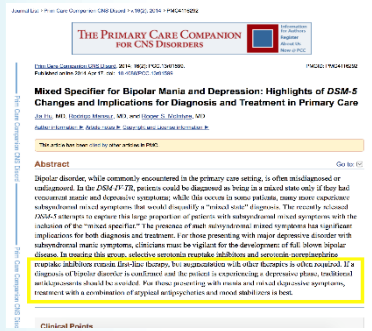
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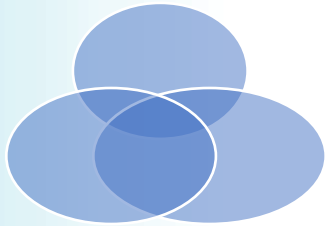

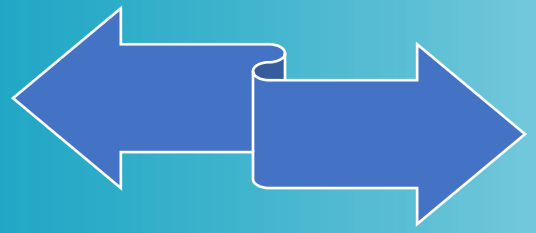

Treatment: Pharmacologic treatment is generally required but antidepressants may worsen the clinical picture

QUESTIONS?