

Pediatric Mood Disorder: Unipolar Depression and Bipolar Disorder

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Disclosures

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

I have consulted to Nippon Telegraph and Telephone Corporation, and have received royalties from the following books:

- “ASK THE GENIUSES ABOUT THE FUTURE” (MAGAZINE HOUSE PUBLISHING),
 - “SOCIAL JUSTICE” (BUNSHUN SHINSHO),
 - “REAPPRAISAL” (JITSUGYO NO NIHONSHA),
- “PRESCRIPTION FOR DAILY MENTAL CRISES” (DAIWA SHOBO) “LIVING DEPRESSION” (BUNSHUN SHINSHO)
 - “BECOMING A WORKING MOM” (KADOKAWA)
- “WHAT PARENTS NEED TO KNOW WHEN PARENTING FEELS CHALLENGING” (NIKKEI BP)
 - “Gender Justice” (Gentousha)

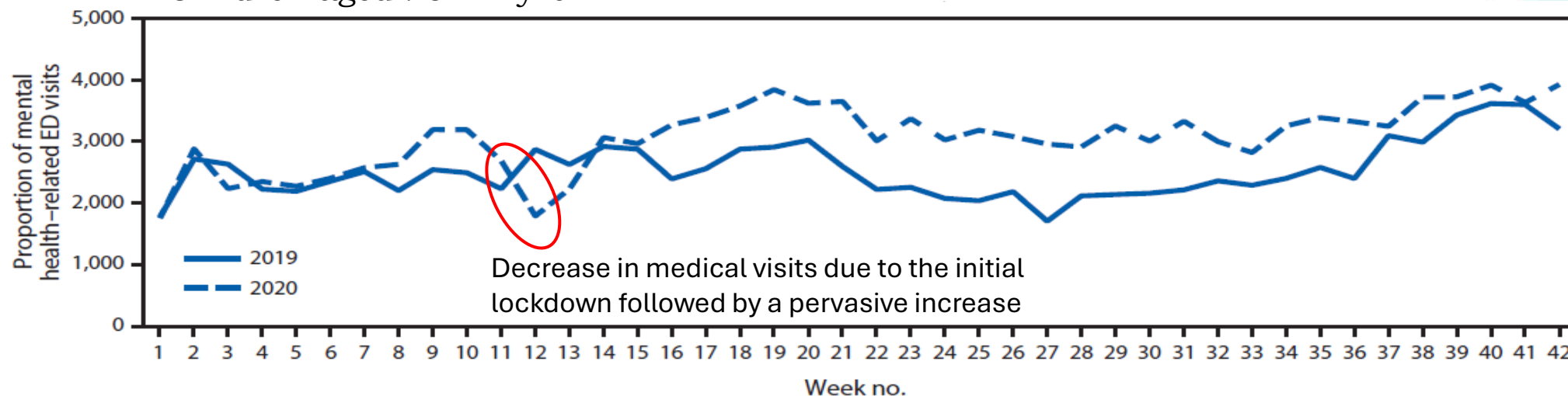
Pediatric Depression Stats: Prevalence

- Major Depressive Disorder is diagnosed in
 - 4.4% (approximately 2.7 million) children ages 3-17 had Depression.
 - 15.1% of 12-17 year old adolescents had a major depressive episode.
- The prevalence of Depression steadily increases over the developmental years and has a few identifiable peaks. The first peak is in adolescence.

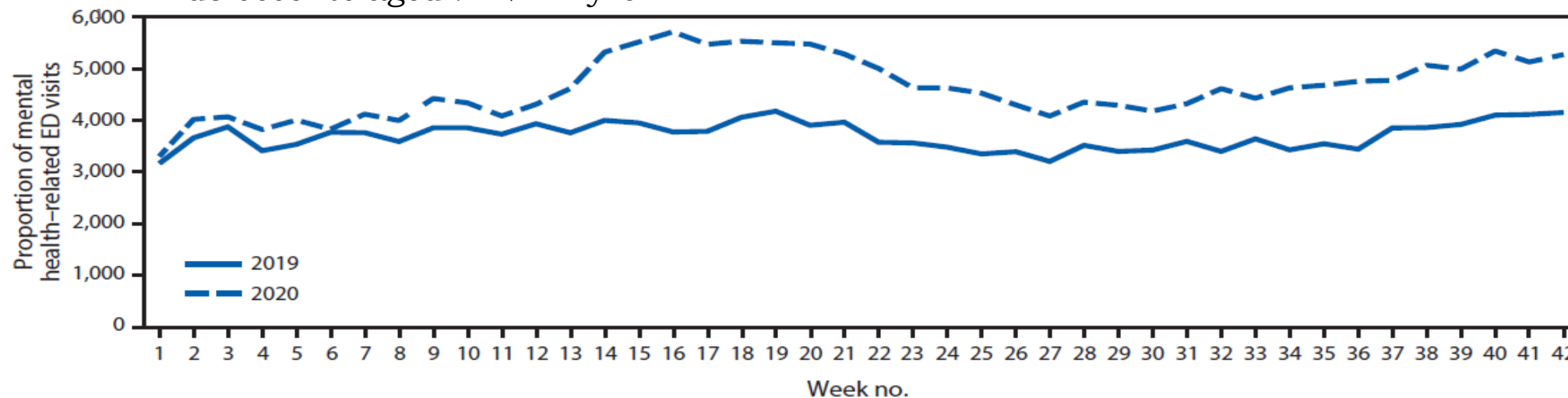
Trends in emergency department visits during the COVID-19 pandemic

Percentage of emergency department visits related to mental health disorders among children (<18 years old) (per 100,000 emergency department visits) 2019-2020

<Children aged : 5~11 yrs>



<Adolescents aged : 12~17 yrs>

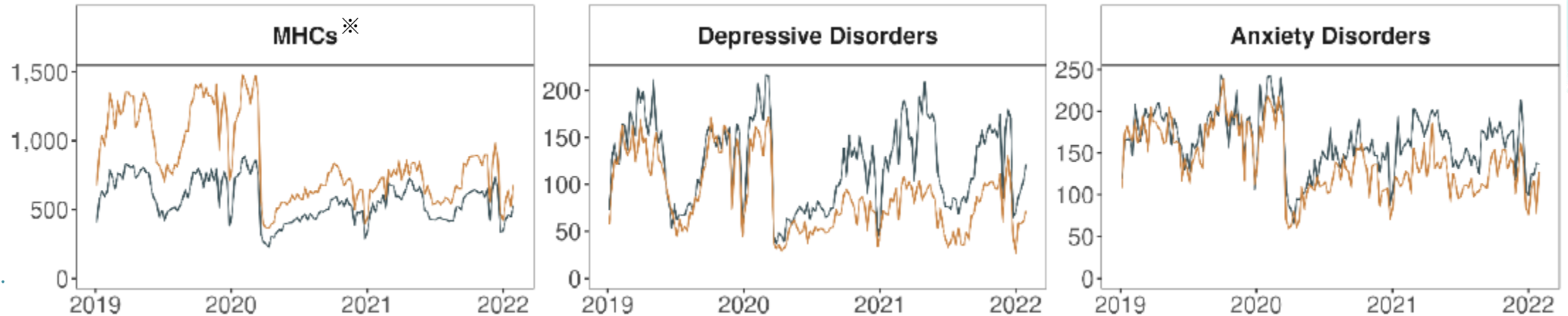


Trends in emergency room visits related to mental illness: 2019-2022

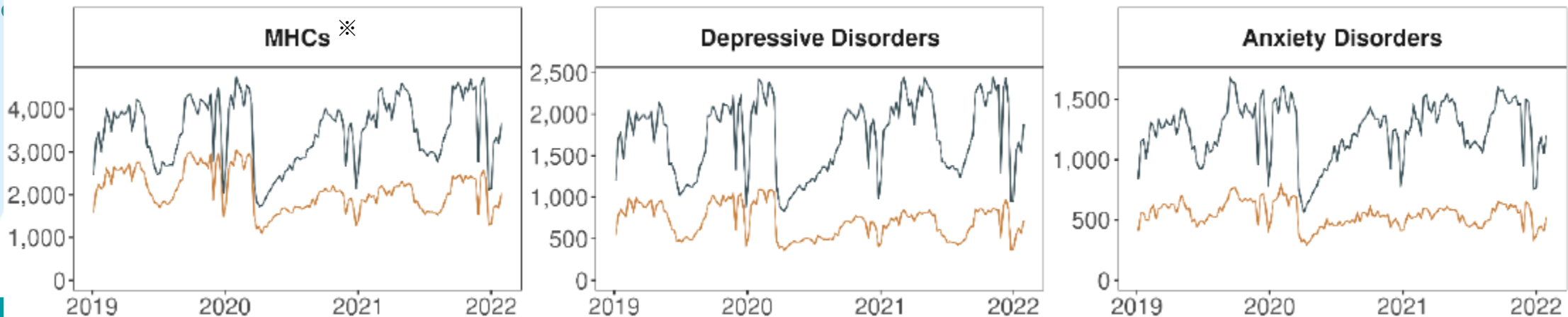
<Children aged : 5~11 yrs>

— boys — girls

※ MHCs (mental health conditions)



<Adolescents aged : 12~17 yrs>



Trends in emergency room visits related to mental illness: 2019-2022

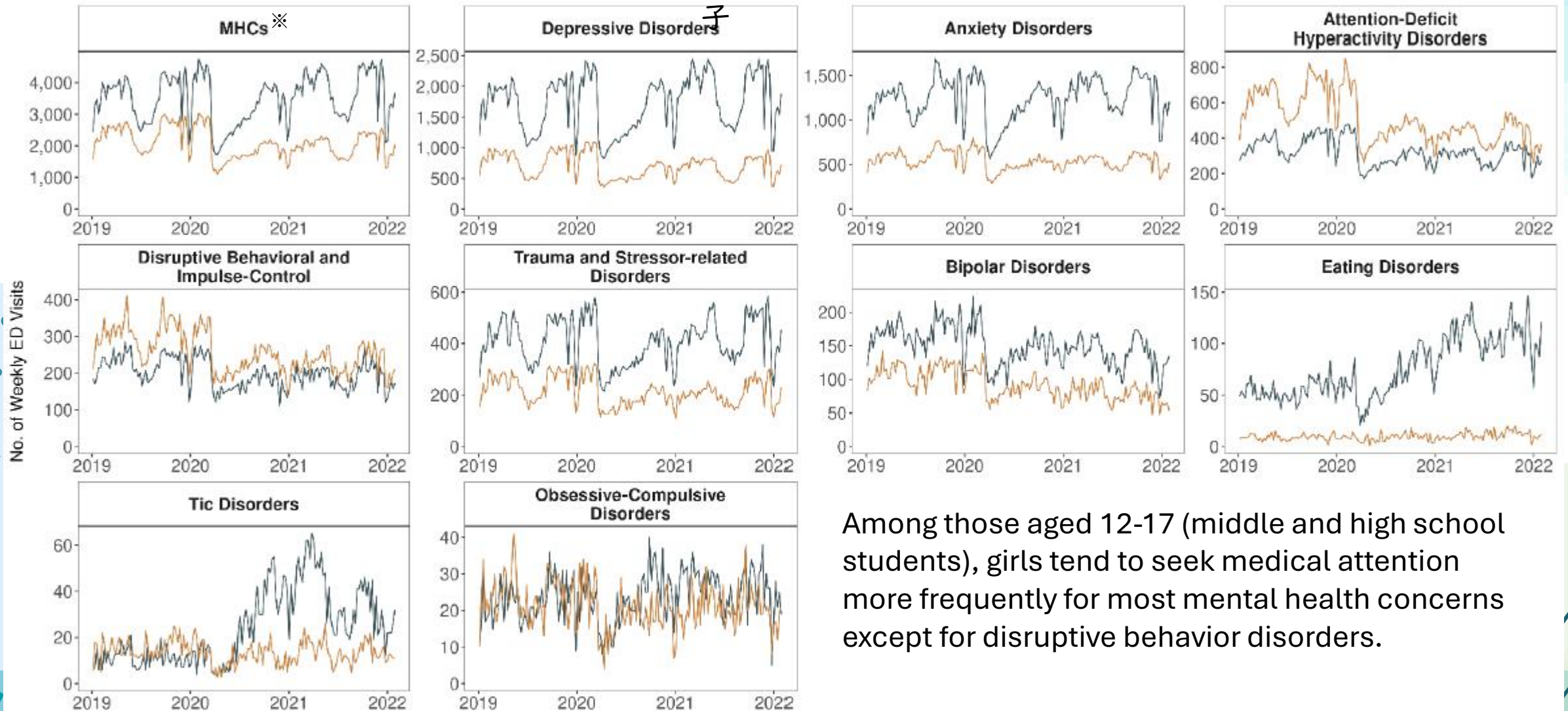
Massachusetts General Hospital
Founding Member, Mass General Brigham

Psychiatry Academy

<Adolescents aged : 12~17 yrs>

— 男子 — 女

※ MHCs (mental health conditions)



Among those aged 12-17 (middle and high school students), girls tend to seek medical attention more frequently for most mental health concerns except for disruptive behavior disorders.

Diagnostic Criteria of Depression: How do they present in children?

- **Major Depressive Episode:**
- A) >2 weeks history of depressed mood (unhappy mood; this could mean **irritable, grumpy, easily annoyed, bored,** or sad and melancholic) *“He looks deflated.”*
- B) >4/ 7 of following symptoms.
 - **S**leep (insomnia/ hypersomnia)
 - **I**nterest (loss of interest)
 - **G**uilt (excessive guilt or feelings of worthlessness) *“I’m a bad boy.” “I’m not good at anything.”*
 - **E**nergy (loss of energy/ physical complaints) *“tummy aches”*
 - **C**oncentration (difficulty concentrating or making decisions) *“Can’t chose his clothes.”*
 - **A**ppetite (change in appetite or weight)
 - **P**sychemotor agitation or retardation
 - **S**uicidal thoughts *“I shouldn’t have been born.”*

Currently FDA Approved Antidepressants & Indications

- Major Depressive Disorder
 - Fluoxetine (Prozac®) ages 8 – 17
 - Escitalopram (Lexapro®) ages 12 – 17
- Obsessive Compulsive Disorder
 - Fluoxetine (Prozac®) ages 7 – 17
 - Sertraline (Zoloft®) ages 6 – 17
 - Fluvoxamine (Luvox®) ages 8 – 17
 - Clomipramine (Anafranil®) ages 11 – 17

What do most child psychiatrists do?

- 1: SSRIs
- 2: Second SSRI
- 3. SNRI vs Wellbutrin? (Wellbutrin can be added to a SSRI)
- 4. Adding Antipsychotics? (Abilify, Seroquel, Risperdal, Geodon, Latuda, Vraylar, Rexulti, Caplyta)
- 5. Lamictal?
- At the same time, can we treat Anxiety? (hydroxyzine, propranolol, Buspar, Benzos)

Diagnostic Criteria of Mood Disorders

	Major Depressive Episode	Manic Episode	Hypomanic Episode	Mixed Episode
Major Depressive Disorder	+	-	-	-
Bipolar I Disorder	+/-	+ (or Mixed Episode)	-	+ (or Manic Episode)
Bipolar II Disorder	+	-	+	-

Significance :

High rate of switching in children with MDD

- A large proportion (**up to 50%**) (Weissman 1999, Geller 1994) of children who initially present with depression (without previously having had a manic episode) will eventually develop mania or hypomania
- **Adult literature has consistently reported that “early onset” mood symptoms are a risk of switching**
- Their definition of “early onset” is **onset prior to age 25**

Manic Switches

- *Spontaneous* switches can happen without any intervention

Manic Switches

- *Drug induced* Switches are those that develop after treatment with an antidepressant medication or other activating treatments
- Kids who've had manic/ hypomanic/ mixed episodes, but who have not been identified as having bipolar disorder that received antidepressants

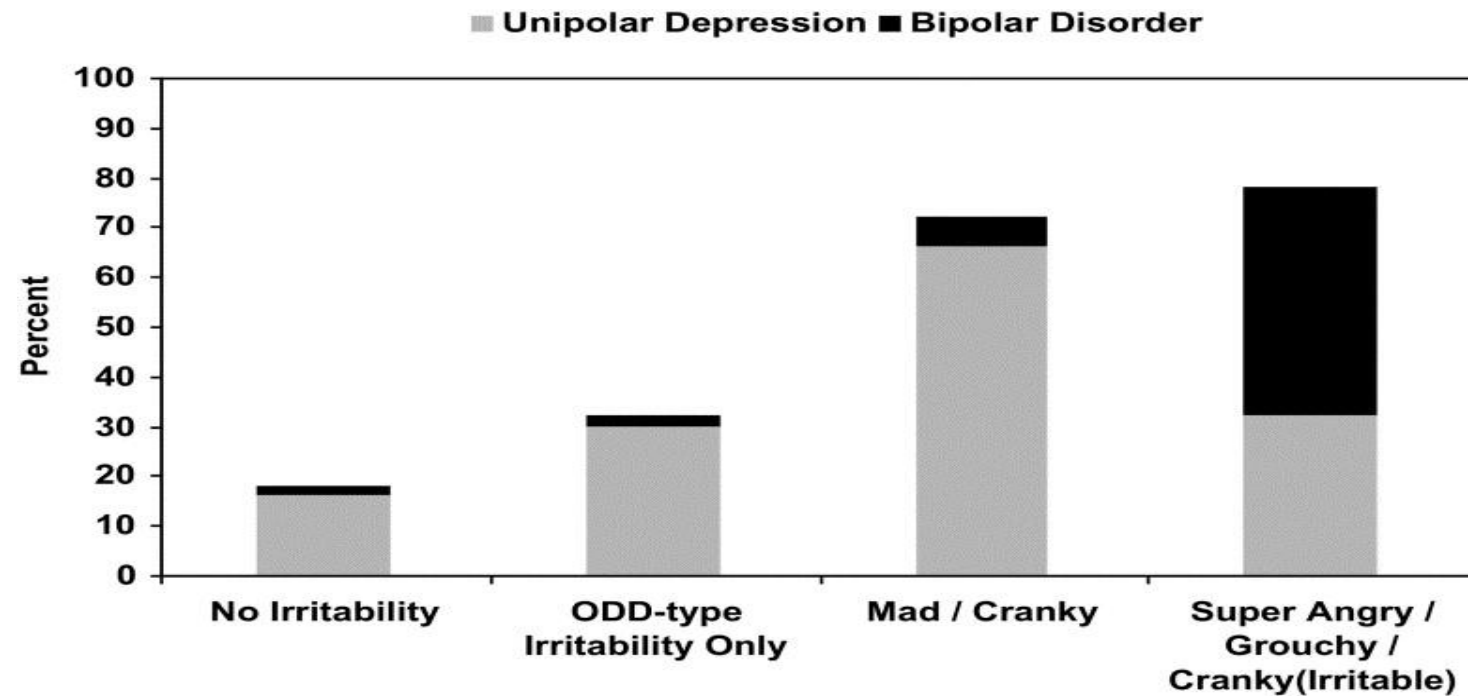
Manic Activation in Children

- 10 year old boy with depressive symptoms took an SSRI for the first time, and initially was observed to have improved mood. After 6 weeks, suddenly he became more impulsive, restless and silly. After 8 weeks, he became uncontrollably angry.
- 8 year old girl with some irritability was prescribed an SSRI. Initially she was seen to have less irritability and more positive outlook. After a month into the treatment, she became somewhat uncharacteristically chatty and had some thoughts such as “What would happen if I jumped out of the window?”

Manic Episodes in Children

- **Manic Episode:**
- A) elevated, expansive or **irritable mood**
- B) >3/7 of following sx's (>4/7 if mood is irritable)
- **Distractability**
- **Indiscretion** (e.g. sexual acting out “*bathroom humor*” “*exposing themselves*”, shopping sprees “*online shopping*”)
- **Grandiosity** (i.e. “above all rules,” disregard for adult authority)
- **Flight of Ideas**
- **Activities** (increased goal directed activities)
- **Sleep** (decreased need of sleep)
- **Talkativeness**

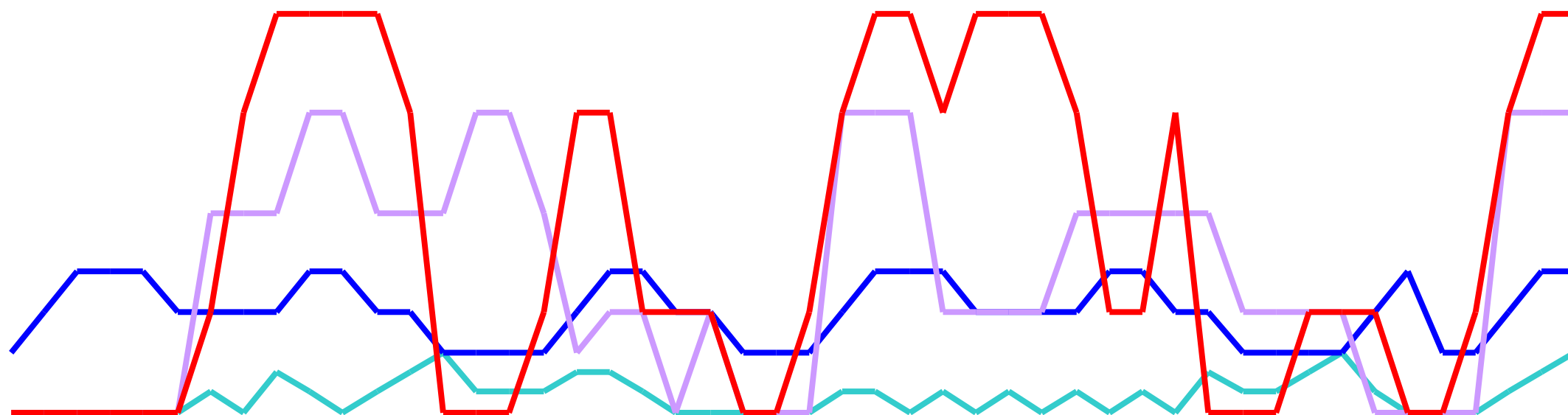
Different Levels of Irritability



Mick,
2010

Levels of Irritability

— ADHD — ODD — MDD — MANIA



Mick, 2007

1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39 41 43 45 47

mghcme.org

Should we avoid SSRIs?

Antidepressant induced mania

- Antidepressant-induced mania is well established in adults

Group	Switch Risk with SSRIs
Unipolar Depression	~3.7%
Bipolar Disorder	24–44%

- Individuals with bipolar disorder typically spend a larger percentage of time depressed than manic/hypomanic → treating depression is a key priority

[14, 15, 46, 17, 47, 48, 49, 11, 50, 51]

Case Reports in Children

- There are many case studies describing antidepressant-induced mania in children and adolescents treated with SSRIs

Medication	# of Cases
Citalopram	5
Fluoxetine	11
Paroxetine	7
Sertraline	5
Venlafaxine	1

Case Reports in Children

- Mania/hypomania typically occurred after starting an SSRI or increasing the dose
 - Discontinuation of the antidepressant resolved symptoms in **~59%** of cases
 - Mood stabilizers were used in **~38%** of cases to manage symptoms
 - Most patients stabilized after manic symptom resolution, often off antidepressants or on lower doses (sometimes continuing a mood stabilizer)
- [53–55,57,59,62,65,67,68]

Chart Review Studies

- **~48.7%** of youth with bipolar disorder developed mania after SSRI exposure (19/39 children)
- Antidepressant-induced mania initiated the bipolar diagnosis in **17%** of cases
- SSRI-treated youth were **~3× more likely** to report manic symptoms at follow-up
- **6%** of youth on SSRIs developed manic symptoms in an inpatient sample
- Prior antidepressant exposure was associated with an earlier age of bipolar onset in hospitalized youth compared to those never exposed (79 children)

Clinical Trials of Antidepressants

Medication	Study Type / Sample	Mania Findings
Citalopram [81]	Open-label trial, early-onset MDD (6 weeks)	16.7% developed mania
Escitalopram [82]	RCT (n=264, vs placebo)	1 case of mania (occurred in placebo group)
Fluoxetine (TADS)	RCT (fluoxetine ± CBT vs placebo/CBT)	3.67% (fluoxetine), 0.93% (combo); vs 1 placebo, 0 CBT; some had high baseline mania
Fluoxetine [83]	Double-blind RCT (vs placebo)	6.25% (fluoxetine) vs 2% (placebo)

Evidence against antidepressants worsening mania course

- Some studies show **no association** between antidepressants and age of bipolar onset or manic symptoms in youth
- No link between antidepressant exposure and **hospital severity** (e.g., length of stay, PRNs, restraint use)
- One study found antidepressants associated with a **4× lower risk of mania** in youth with psychotic depression (up to 2-year follow-up) – but no information on concomitant medications

[56-78]

Benefit to Risk Calculation

- $NNH = 56 \rightarrow \sim 1$ additional mania case per 56 youths on fluoxetine
- Patients are $\sim 12\times$ more likely to benefit than develop mania (worst case: $\sim 6\times$)

Should we avoid SSRIs?

- Not blindly – SSRIs are significantly more likely to be beneficial in a group of children with depression, even with the concern of mania.
- On the other hand, if you happen to be that one person who is vulnerable to antidepressant-induced mania, you may have a difficult course.



- The individual variability in response
- The importance of identifying the RISK for mania in children with depression

Can machine learning identify childhood characteristics that predict future development of bipolar disorder a decade later?

Mai Uchida¹, Qasim Bukhari², Maura DiSalvo³, Allison Green⁴, Giulia Serra⁵, Chloe Hutt Vater³, Satrajit S Ghosh⁶, Stephen V Faraone⁷, John D E Gabrieli², Joseph Biederman⁸

Affiliations + expand

PMID: 36274531 PMCID: PMC9999264 DOI: 10.1016/j.jpsychires.2022.09.051

[Free PMC article](#)

- Data was derived from two MGH longitudinal family studies that were collected over 11 years
- Clinical Scales and Diagnoses were collected at baseline and at 11 year follow-up
- Children who already had diagnosis of Bipolar Disorder or Children with any missing values were excluded from the analysis
- 492 children, ages 6-17 at baseline, were included in the final analysis
- Of our sample, 45 children (10%) developed BP disorder.
- Extra Trees (Extremely randomized trees)

Results

	Predicted BPD	Predicted no BPD
Actual BPD	7.71	1.63
Actual no BPD	10.71	79.95

Confusion matrix in percentage using repeated sampling cross-validation of the 75% data

	Mean	Standard Deviation
Accuracy	87.65	1.81
Sensitivity	82.56	7.48
Specificity	88.18	1.9
ROC-AUC	88.71	1.4

Performance evaluation using repeated sampling cross-validation of the 75% data

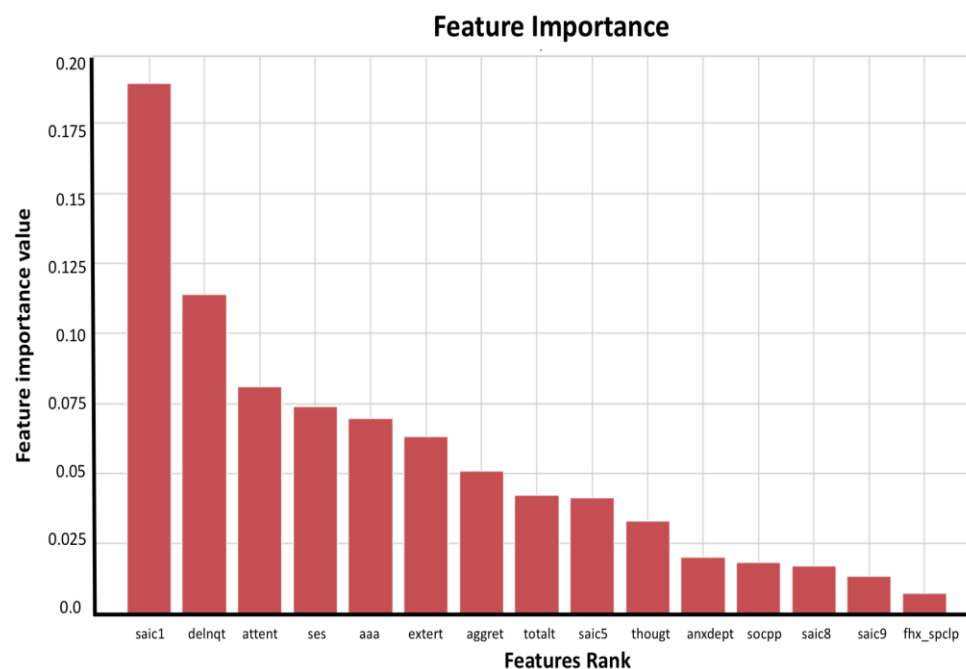
	Predicted BPD	Predicted MDD
Actual BPD	35	8
Actual MDD	26	631

Confusion matrix of the 25% data

Accuracy	95.14
Sensitivity	81.39
Specificity	96.04
ROC-AUC	88.71

Performance evaluation of the 25% data

Results: Feature Importance Ranking in Predicting Bipolar Disorder



Features at Baseline
SAICA school behavior problems
CBCL Rule Breaking t-score
CBCL Attention Problems t-score
SES
CBCL Externalizing t-score
CBCL-AAA score
CBCL Aggressive t-score
SAICA problems with peers
CBCL Total t-score
CBCL Thought Problems t-score

Our prediction model identified problematic school behaviors, conduct disorder symptoms, and emotional dysregulation as key predictors of BP disorder outcome with robust sensitivity, specificity and accuracy.

Literature Review of Risk Factors for Manic Switching

➤ [J Affect Disord.](#) 2015 May 1:176:1-7. doi: 10.1016/j.jad.2015.01.037. Epub 2015 Jan 23.

Can unipolar and bipolar pediatric major depression be differentiated from each other? A systematic review of cross-sectional studies examining differences in unipolar and bipolar depression

Mai Uchida ¹, Giulia Serra ², Lazaro Zayas ³, Tara Kenworthy ⁴, Stephen V Faraone ⁵, Joseph Biederman ⁶

Affiliations + expand

PMID: 25682377 DOI: [10.1016/j.jad.2015.01.037](#)

Abstract

Introduction: While pediatric mania and depression can be distinguished from each other, differentiating between unipolar major depressive disorder (unipolar MDD) and bipolar major depression (bipolar MDD) poses unique clinical and therapeutic challenges. Our aim was to examine the current body of knowledge on whether unipolar MDD and bipolar MDD in youth could be distinguished from one another in terms of clinical features and correlates.

Methods: A systematic literature search was conducted on studies assessing the clinical characteristics and correlates of unipolar MDD and bipolar MDD in youth.

Results: Four scientific papers that met our priori inclusion and exclusion criteria were identified. These papers reported that bipolar MDD is distinct from unipolar MDD in its higher levels of depression severity, associated impairment, psychiatric co-morbidity with oppositional defiant disorder, conduct disorder and anxiety disorders, and family history of mood and disruptive behavior disorders in first-degree relatives.

Limitations: Though we examined a sizeable and diverse sample, we were only able to identify four cross sectional informative studies in our review. Therefore, our conclusions should be viewed as preliminary.

Conclusions: These findings can aid clinicians in differentiating the two forms of MDD in youth.

Keywords: Bipolar disorder; Major depressive disorder; Pediatric.

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➤ [J Affect Disord.](#) 2015 Feb 1:172:300-6. doi: 10.1016/j.jad.2014.09.046. Epub 2014 Oct 13.

Can manic switches be predicted in pediatric major depression? A systematic literature review

Mai Uchida ¹, Giulia Serra ², Lazaro Zayas ³, Tara Kenworthy ⁴, Brittany Hughes ⁴, Ariana Koster ⁴, Stephen V Faraone ⁵, Joseph Biederman ⁶

Affiliations + expand

PMID: 25451429 DOI: [10.1016/j.jad.2014.09.046](#)

Abstract

Background: The rate of switching from major depression to bipolar disorder is high in children. Predicting who is at risk for switching poses unique challenges and is of high clinical relevance. Our aim was to examine the existing scientific literature elucidating if certain clinical correlates predict ultimate bipolar switches in children initially presenting with a depressive episode.

Methods: We conducted a systematic literature search of studies assessing the risk factors for bipolar switching in youth. In all, seven studies fit our a priori criteria and were thus included in our qualitative review.

Results: Together, these papers found that manic switches in pediatric depression can be predicted by several risk factors, including positive family history of mood disorders, emotional and behavioral dysregulation, subthreshold mania, and psychosis.

Limitations: We identified only seven prospective informative studies for our review. The majority of subjects included in these studies were referred and Caucasian. Thus, the results may not generalize to other community samples and other ethnicities.

Conclusions: These findings can help alert clinicians of the risk of manic switches.

Keywords: Bipolar disorder; Major depressive disorder; Manic switch; Pediatric.

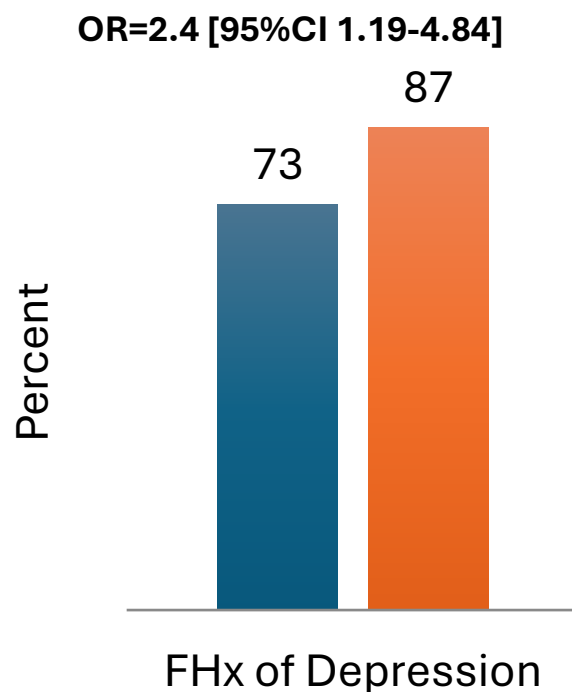
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Family History

- **Geller et al 1994 & 2001** followed outpatient sample for 4 years and 10 years respectively
- The odds of having **3+ relatives** with mood disorders were **6 times greater** ($p=.01$) in switchers
- The odds of having **3 generations** of mood disorders were **5 times greater** ($p=.02$) in switchers
- **Parental and grandparental BP-I** predicted the switches in the 10 year follow up

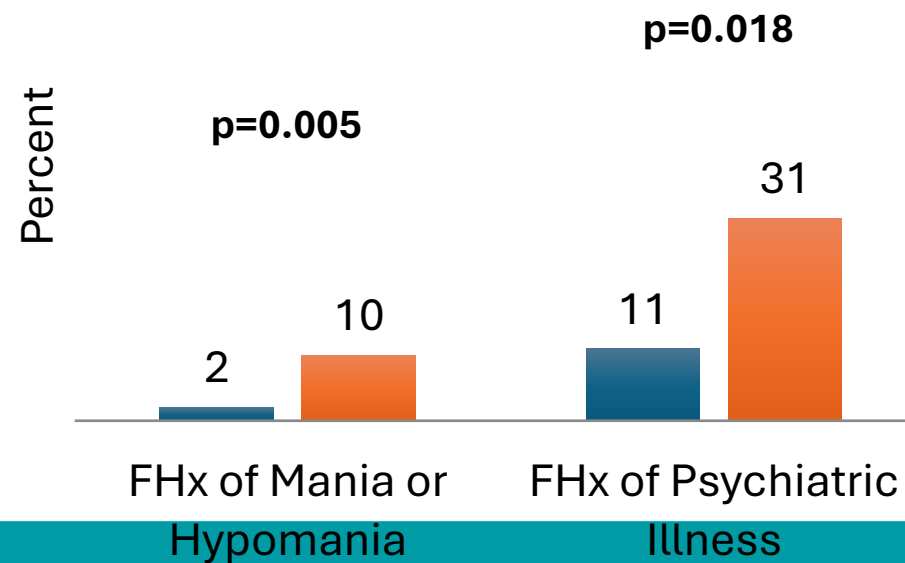
Family History

Merikangas, 2012



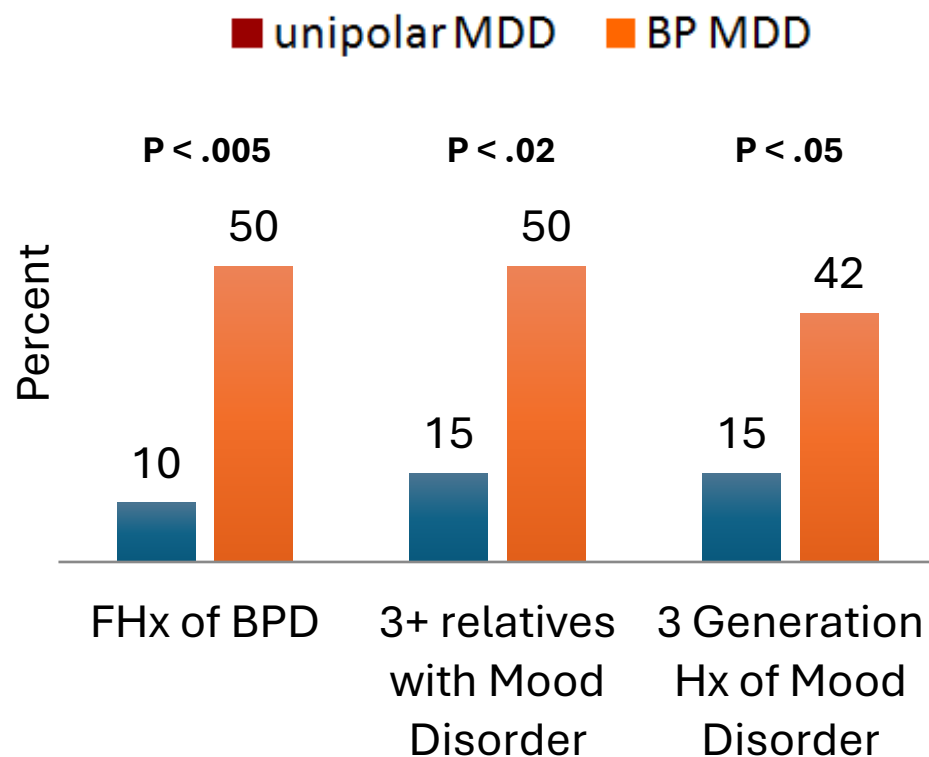
Shon, 2013

■ unipolar MDD ■ BP MDD



Family History

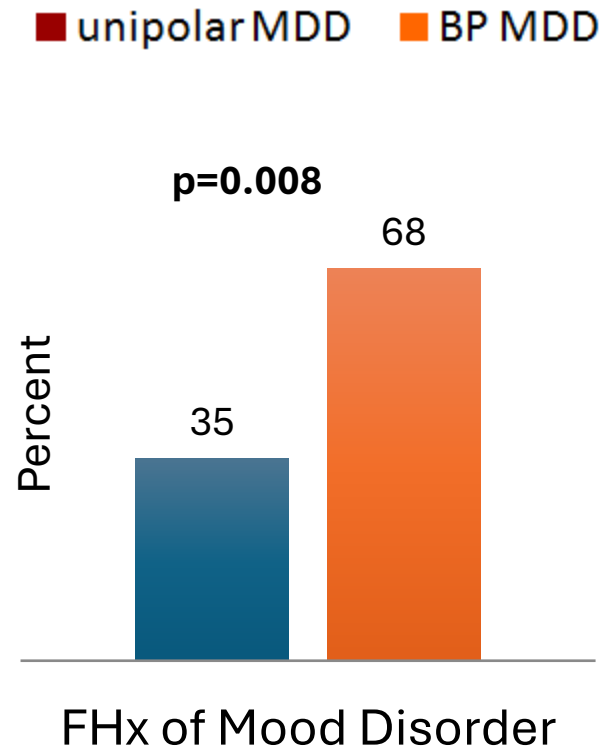
Strober, 1982



Strober (1982) followed inpatient adolescents for 4 years

Family History

Biederman, 2009

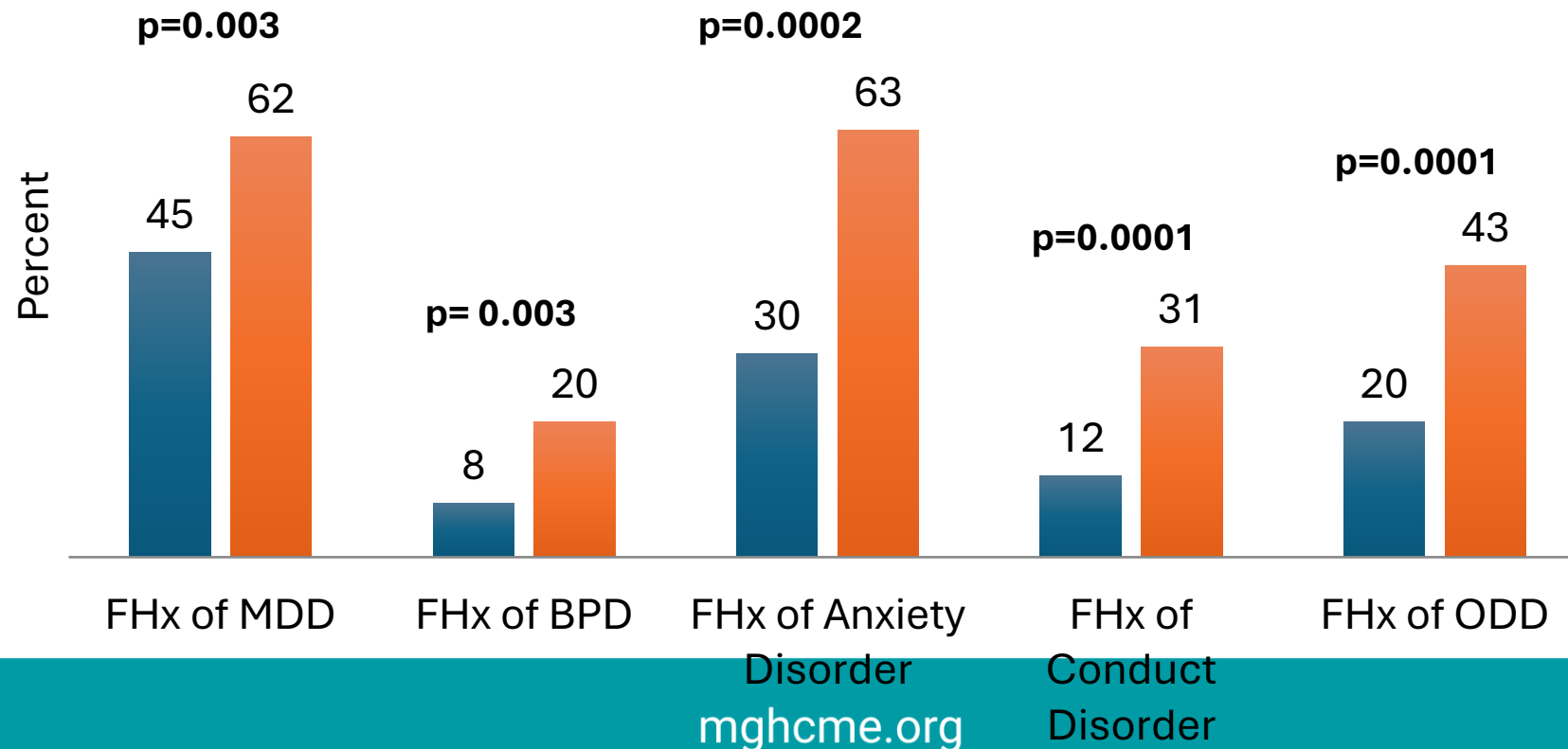


Biederman (2009) used data from two large controlled longitudinal studies of children with and without ADHD and their siblings.

Subjects who switched had significantly higher rates of parental MDD and BP mood disorders

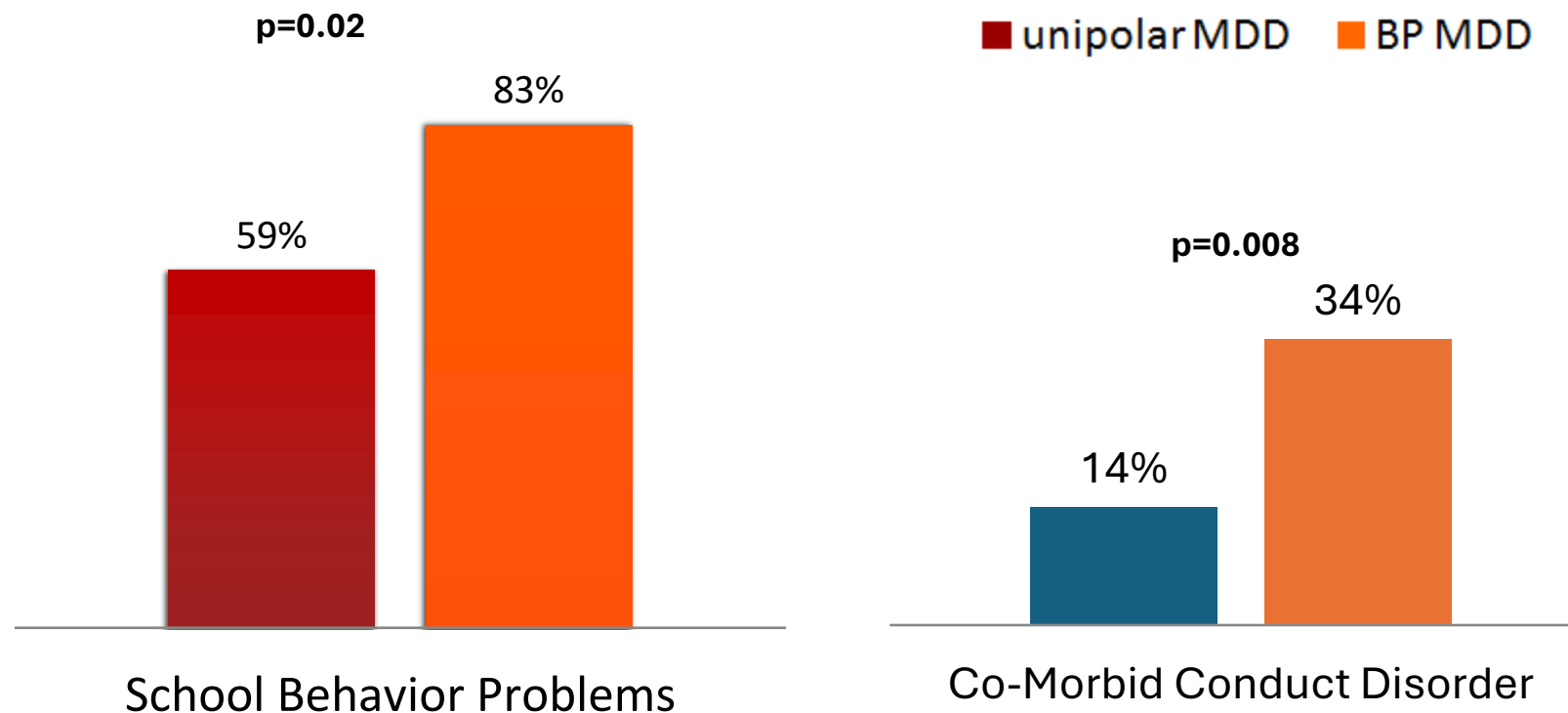
Family History

Wozniak, 2004 ■ unipolar MDD ■ BP MDD

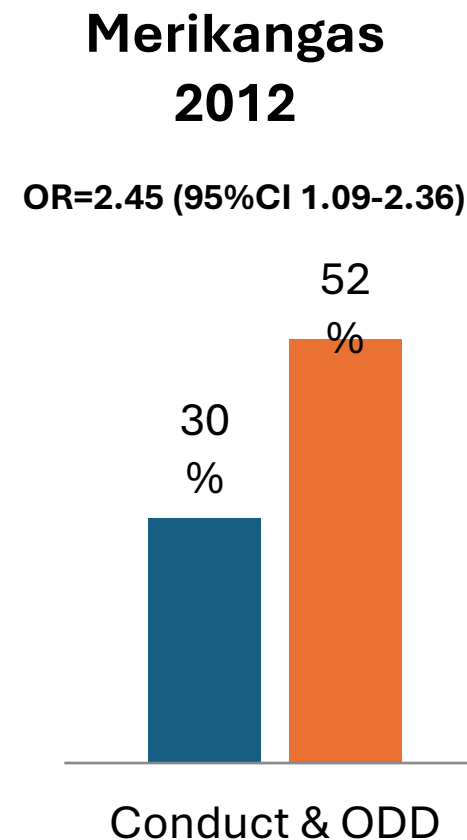
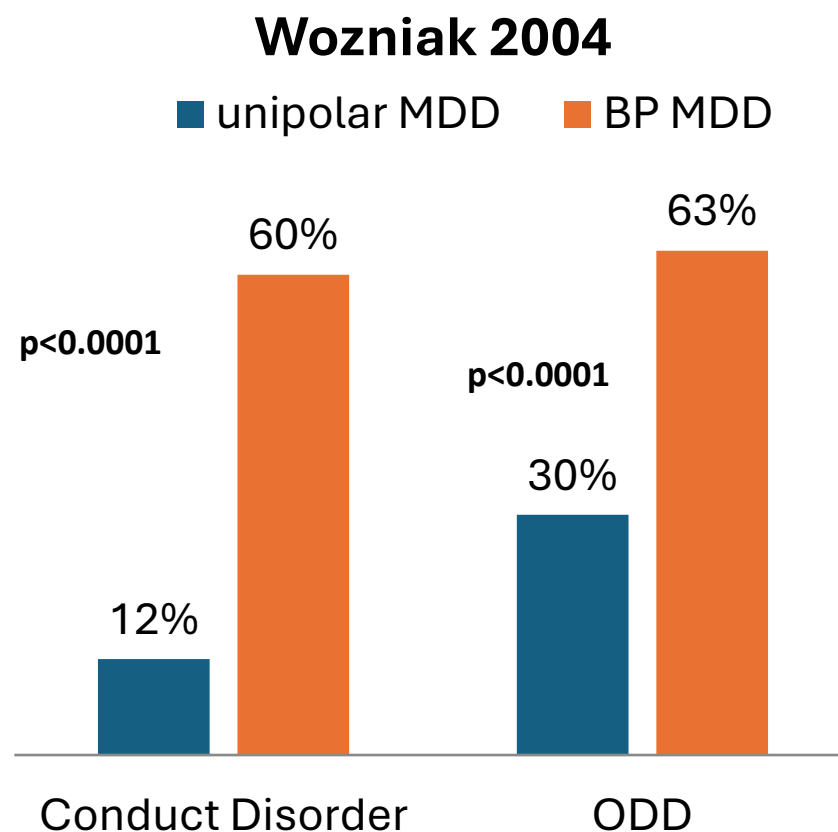


Aggression, Conduct, Behavioral Difficulties

Biederman 2009



Co-morbid Conduct Disorder or ODD



Conduct Disorder, ODD & Aggressive Behaviors

Luby 2008

Co-morbid Conduct Disorder

OR=54.4, $P<0.001$

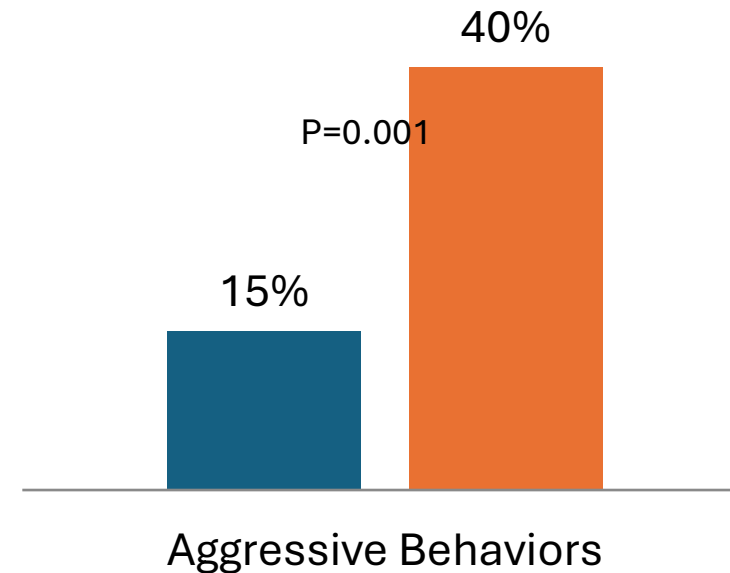
Co-morbid ODD

OR=4.65

$P<0.01$

Shon 2013

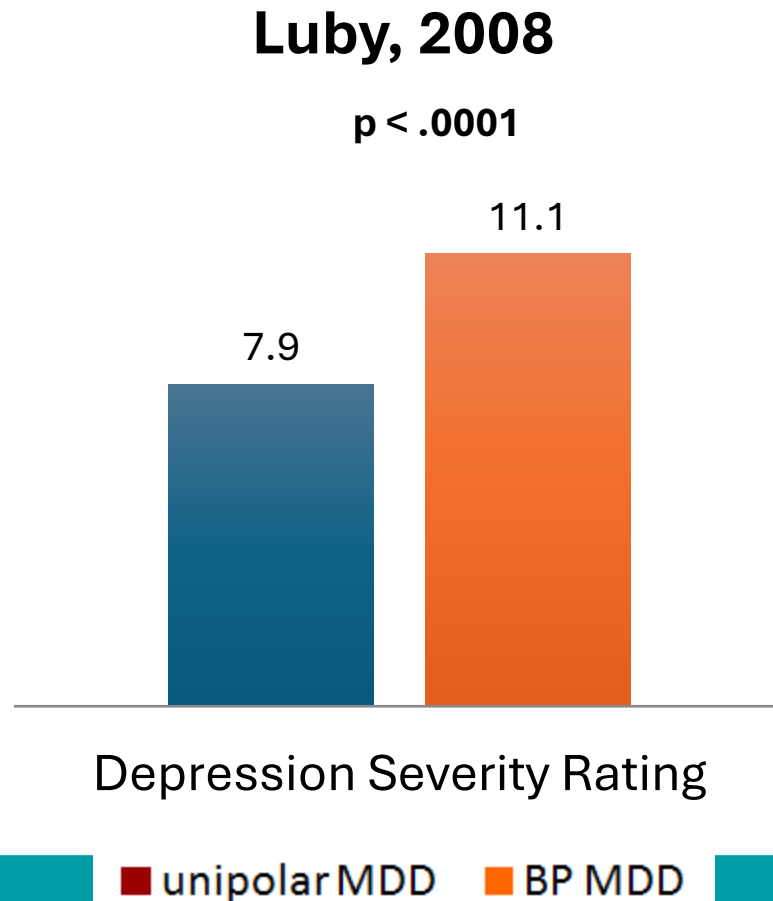
■ Unipolar MDD ■ BP MDD



Aggression, Conduct, Behavioral Difficulties

- **Geller (1994)** bullying behaviors was a significant predictor of switching (OR= 7.1, $p=0.003$)

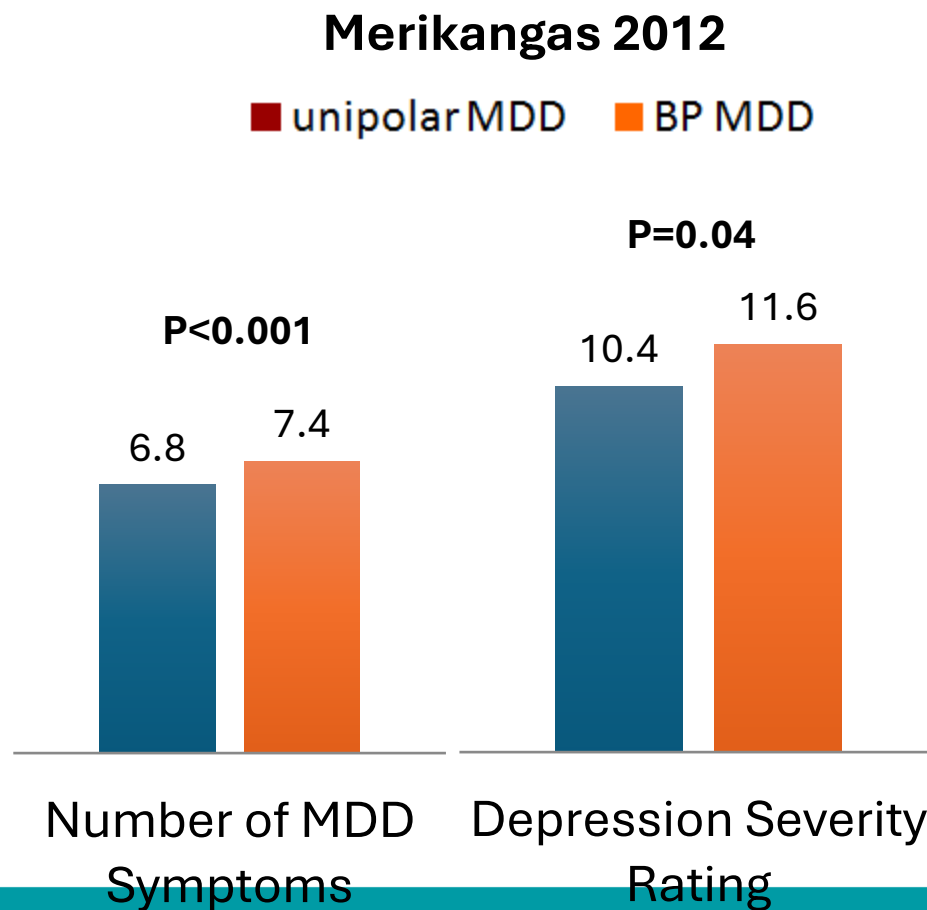
High Severity of Depression



Luby et al used a community sample of preschoolers.

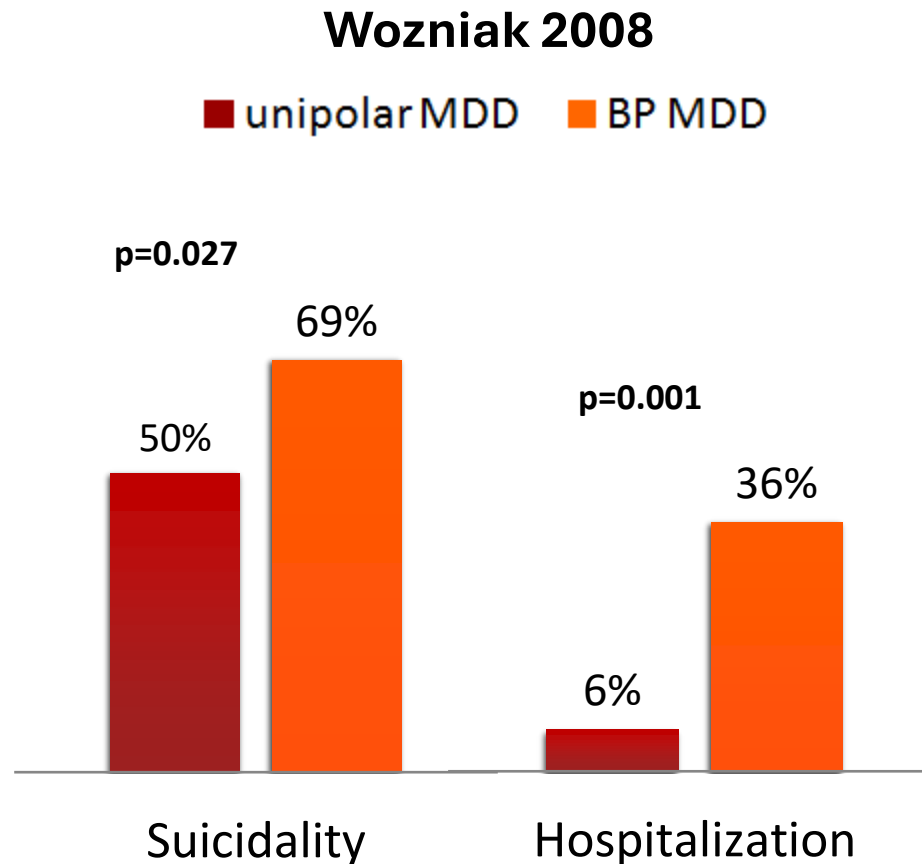
They found depression severity rating measured by *PAPA (Preschool Age Psychiatric Assessment)* was higher in the children with BP depression.

High Severity of Depression



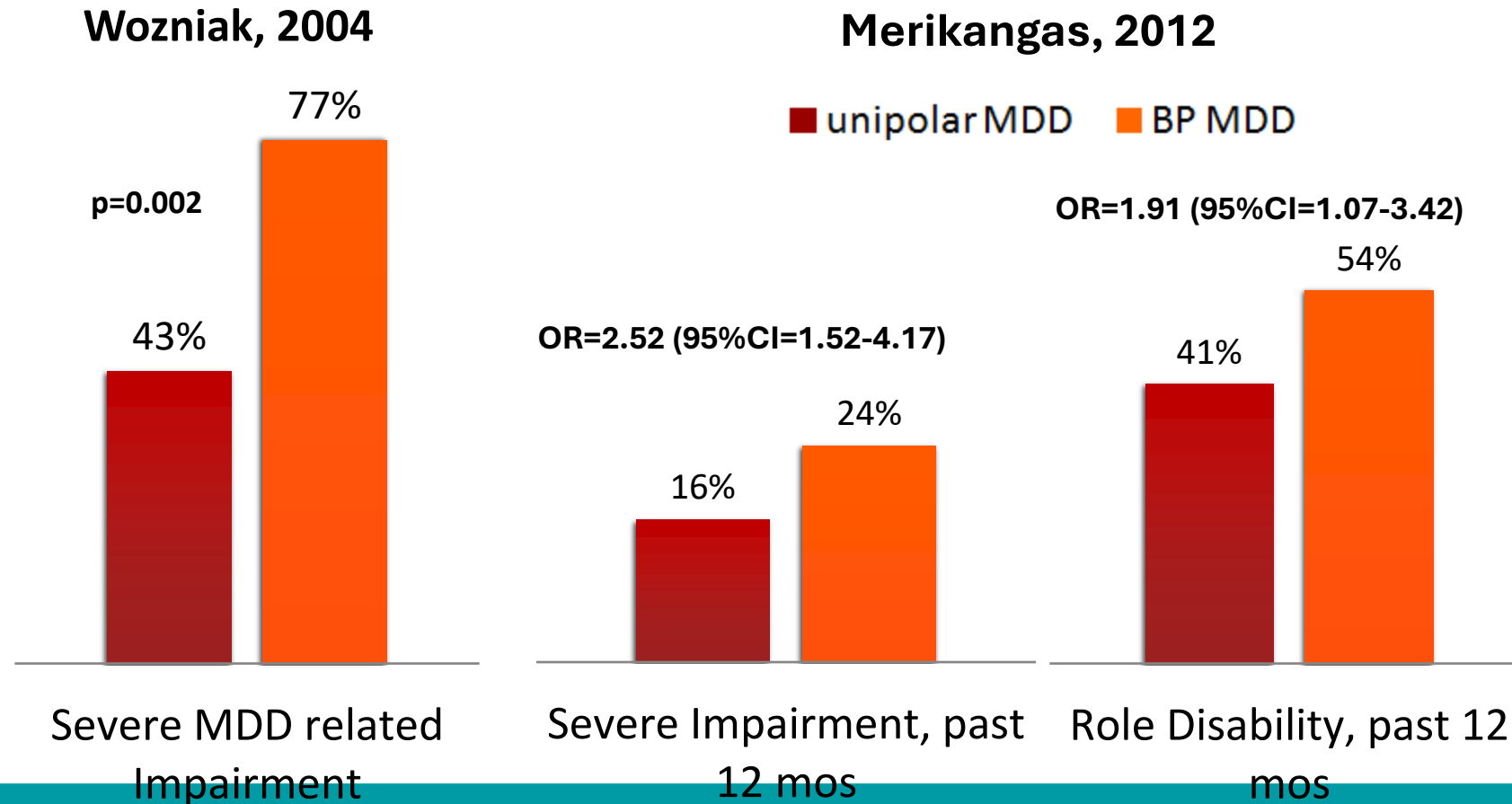
Number of MDD symptoms and Severity measured using the *Quick Inventory of Depressive symptomatology Self-Report (QIDS-SR)* were higher in BP MDD.

High Severity of Depression; Suicidality and Hospitalization

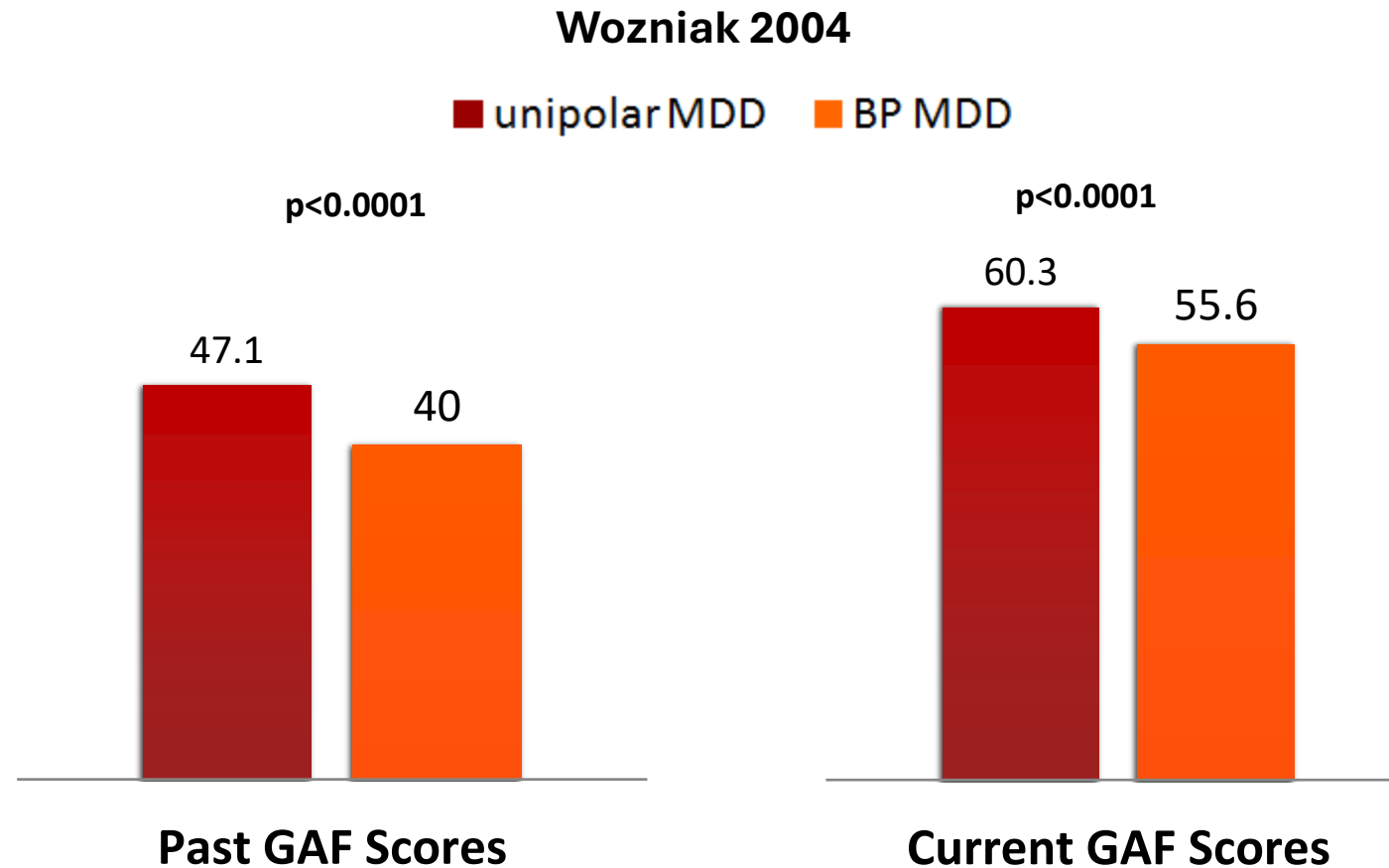


- Wozniak et al (2008) reported that rate of suicidality and hospitalization were higher in BP MDD.

Degree of Impairment



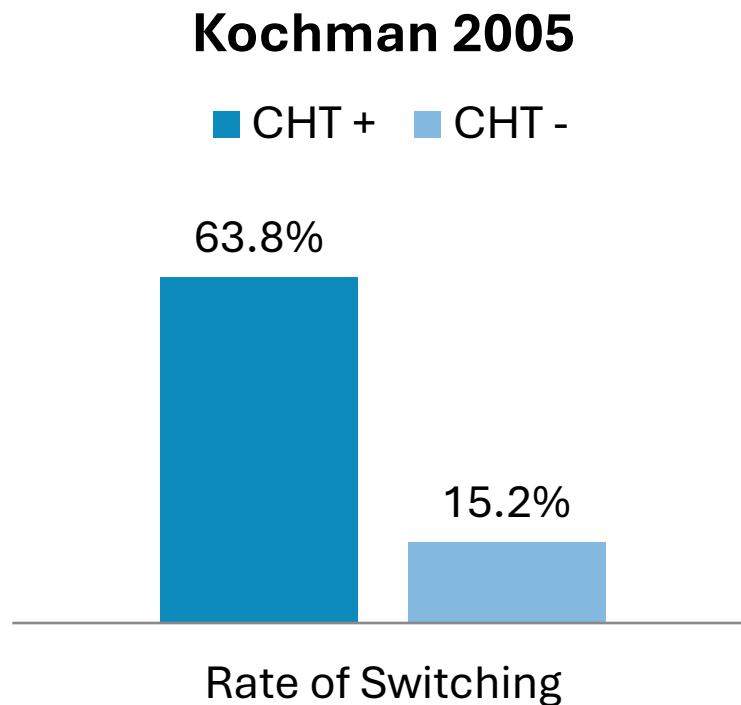
Degree of Impairment: GAF



Emotional Dysregulation

- **Kochman et al (2005)** followed 80 inpatients for 1 year
- Emotional dysregulation was reported in the form of “**Cyclothymic Hypersensitive Temperament (CHT)**” defined by *presence of high mood lability and emotional reactivity*

Emotional Dysregulation

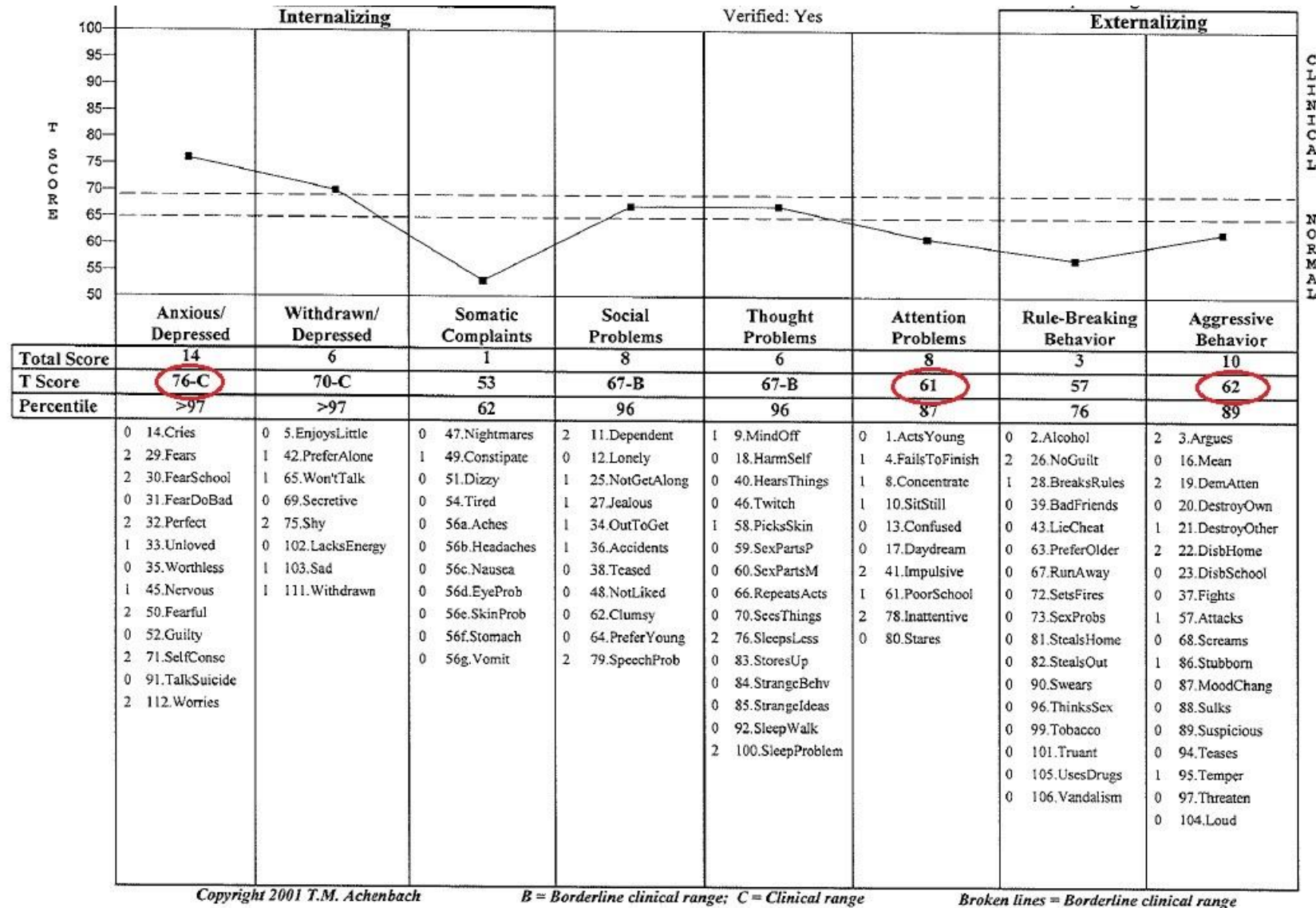


- 64% of children with CHT switched, vs. 15% of those without CHT ($p < 0.0001$)
- Children with CHT also displayed a wider range of **aggressive behaviors** and a **higher rate of suicidality**

Emotional Dysregulation

- **Biederman (2013)** examined emotional dysregulation (ED) using a profile in the Child Behavioral Check List CBCL
 - **Average of 1SD elevation in the Anxiety/ Depression, Aggression, and Attention subscales of the CBCL**
(aggregate T score >180)
- ED was found to be a predictor of manic switching (**OR=3.54, p=0.037**).

CBCCL scoring

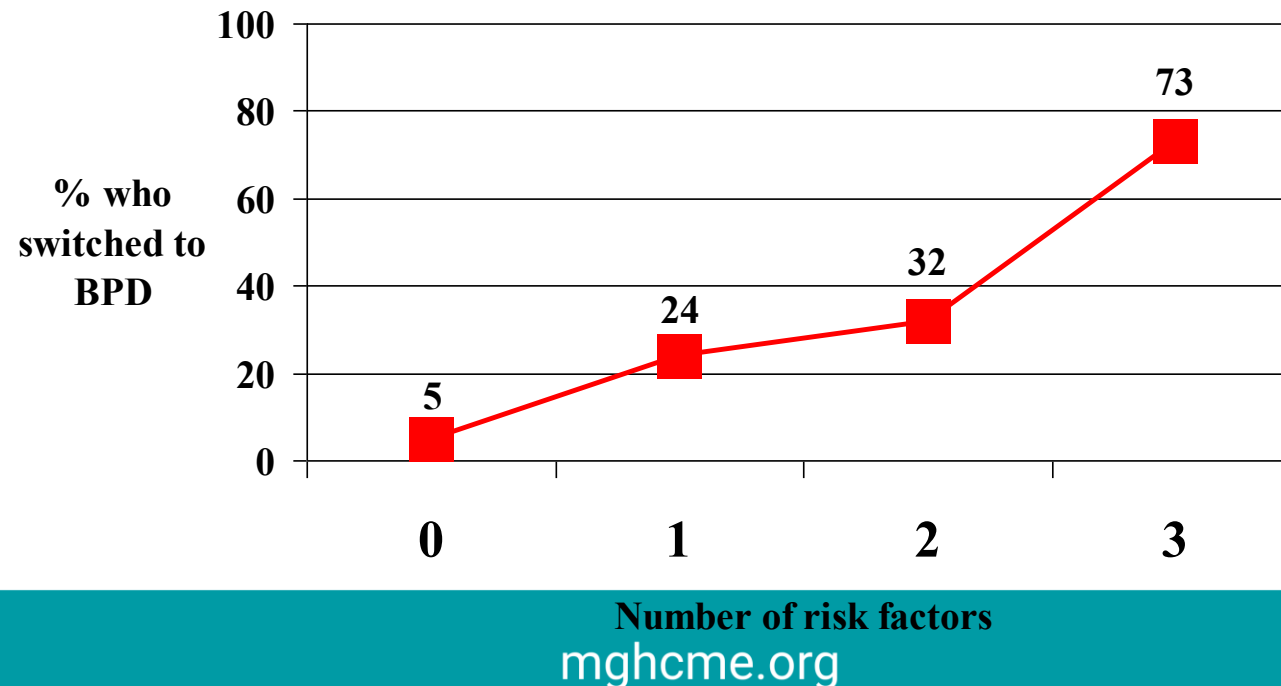


Summary of Risk Factors

- **Family History of Psychiatric Illness**
 - Mood Disorders, Anxiety Disorders, ODD
 - Familial loading
 - Multigenerational FHx
- **Aggression, Conduct & Behavioral difficulties**
 - co-morbid conduct disorder or ODD
- **High Severity of Depression & Syndrome Congruent Impairment**
 - Suicidality, Hospitalizations, Low GAF
- **Psychiatric Co-morbidities & Psychosis**
- **Early Onset of Mood Symptoms**

Dose Response of Multiple Risk Factors

- Biederman (2009) reported the additive risk of significant predictors of switching (conduct disorder, school behavior problems and parental mood disorder).



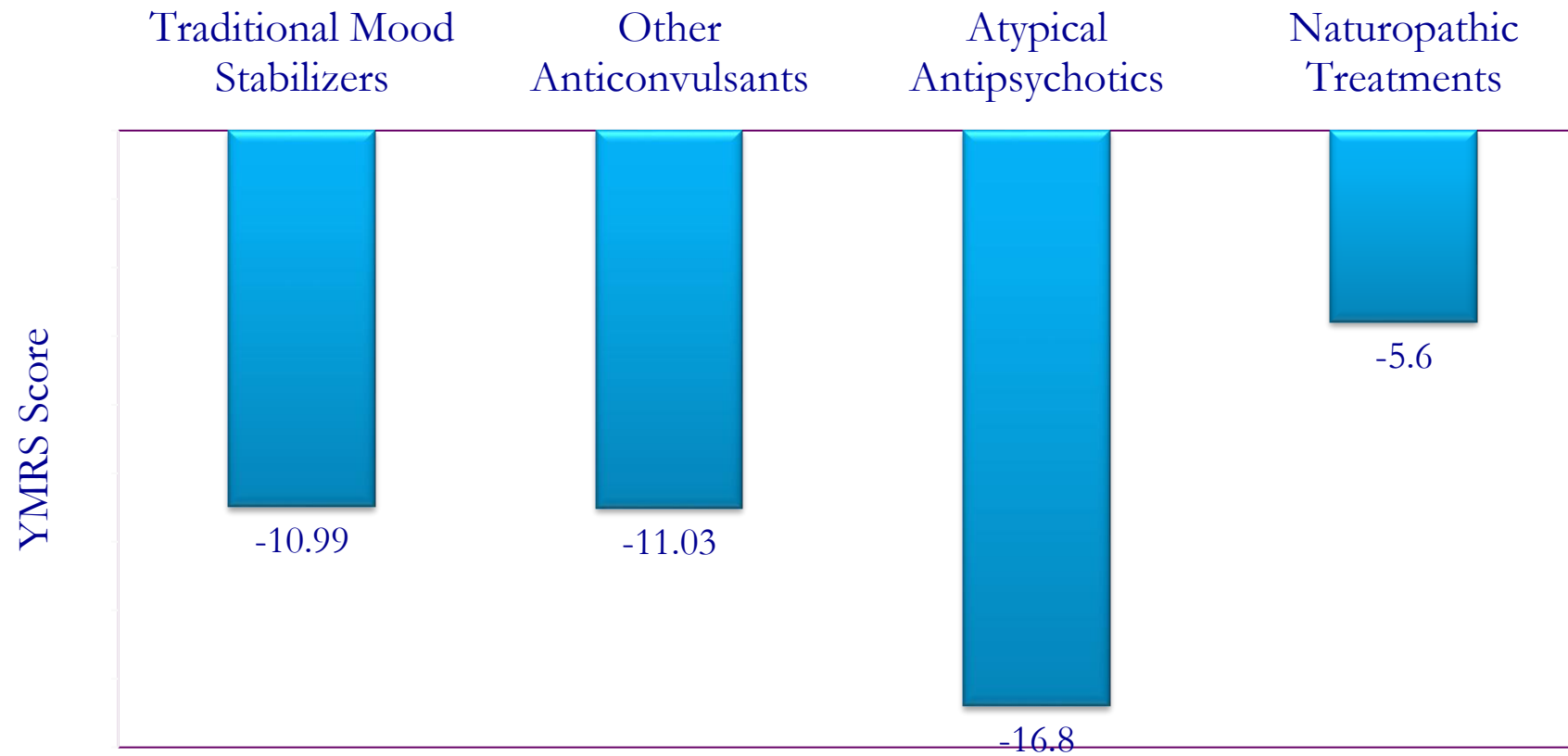
How do we pharmacologically manage them?

- Should we avoid antidepressants?
- SSRI + Antipsychotics?
- Antipsychotics only?
- SSRI only?
- Mood stabilizers such as Lamotrigine?
- Are there other symptomatology that we can treat to mitigate the effect of depression?

FDA approved Antipsychotics for Bipolar Depression

- **Quetiapine (Seroquel)**: Frequently used for bipolar depression and helps with anxiety/insomnia.
- **Lurasidone (Latuda)**: Effective for bipolar depression, often used alone. SIGNIFICANT HIGH RATE OF MANIC ACTIVATION
- **Cariprazine (Vraylar)**: Approved for both bipolar depression and manic episodes.
- **Lumateperone (Caplyta)**: Approved for bipolar I or II depression.

Mean Change in YMRS from Baseline by Medication Class



Manic Episodes in Children

- **Manic Episode:**
- A) elevated, expansive or **irritable mood**
- B) >3/7 of following sx's (>4/7 if mood is irritable)
- **Distractability**
- **Indiscretion** (e.g. sexual acting out “*bathroom humor*” “*exposing themselves*”, shopping sprees “*online shopping*”)
- **Grandiosity** (i.e. “above all rules,” disregard for adult authority)
- **Flight of Ideas**
- **Activities** (increased goal directed activities)
- **Sleep** (decreased need of sleep)
- **Talkativeness**

Combination of Antidepressant + Antipsychotics

- Olanzapine + Fluoxetine = FDA Approved
- In a naturalistic follow up of bipolar children who were receiving pharmacotherapy, during the extension phase of treatment, 58% required a combination of medications in different classes.
(Cowatch et al, Biological Psych 2003)

Open Label Lamotrigine and Lithium Effective in Adolescent Bipolar Depression

Chang et al JAmAcadChildAdolPsyc 2006

N=20

Adjunctive or monotherapy lamotrigine

63% responders (at least 50% decrease in CDRS)

84% much or very much improved CGI-I

Patel et al JAmAcadChildAdolPsyc 2006

N=27

Monotherapy Lithium

48% responders (at least 50% decrease in CDRS)

FDA Black Box Warning About Antidepressants in Children Increasing Suicidal Ideation

- Meta-analysis (25 placebo-controlled trials, 9 antidepressants) in youth
- Suicidal ideation/attempts: **~4%** (antidepressants) vs **~2%** (placebo)
- No completed suicides reported
- Led to 2004 Black Box Warning for all antidepressants

How To Think About The FDA Black Box Warning

- Baldessarini and Tonda (2007):
 - Reviewed 29 ecological studies on correlation between antidepressant prescriptions and suicide rates
 - 9 studies found *inverse* correlations of increased use of modern antidepressants with diminishing national, regional or temporal trends in suicide rates
 - 14 studies found positive correlations in some sex or age subgroups, who were inconsistent across the studies
 - 6 found no significant relationships.
- There is no consistent evidence for suicidality “caused” by antidepressants, but there is overwhelming evidence that untreated depression increases the risk of suicide.
- Discuss this with the patients and their parents, and make a clinical judgment depending on the clinical situation.

Manic Switches Contributing to SSRI induced SI?

CNS Neuroscience & Therapeutics
Open Access

► [CNS Neurosci Ther. 2010 Jun 11;16\(4\):227–234. doi: 10.1111/j.1755-5949.2010.00160.x](#) 

Antidepressant-Induced Suicidality: An Update

[Roy R Reeves](#)^{1,2}, [Mark E Ladner](#)^{1,2}

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- Unrecognized bipolar patients who are depressed may be misdiagnosed as having uncomplicated depression and may be at risk for development of mania when given an antidepressant, and known bipolar patients may experience elevated mood if not provided an adequate dosage of a mood stabilizer.
- Mixed mood states with a combination of depressive symptoms, increased energy, and increased impulsivity represent a potentially dangerous condition with increased risk of suicide. (Teicher MH, Glod CA, Cole JO. Antidepressant drugs and the emergence of suicidal tendencies. Drug Safety 1993;8:186–212.)
- Thus, a possible mechanism for antidepressant-induced suicidality could be induction of mania or hypomania in such patients.
- However, although theoretically feasible, overall data thus far do not support an increase in suicidality in bipolar patients exposed to antidepressants. (Grunze HC. Switching, induction of rapid cycling, and increased suicidality with antidepressants in bipolar patients: Fact or overinterpretation? CNS Spectr 2008;13:790–795.)

How do we pharmacologically manage them?

- Should we avoid antidepressants?
- SSRI + Antipsychotics?
- Antipsychotics only?
- SSRI only?
- Mood stabilizers such as Lamotrigine?
- Are there other symptomatology that we can treat to mitigate the effect of depression? (Anxiety, ADHD etc)