Differentiating MDD vs. Bipolar Depression In Youth

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Disclosures

“Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.”
Pediatric Depression

• Before Pediatric Bipolar Disorder was the topic of dispute, it was Pediatric Depression.
• Various doctors argued that children could not become depressed.
Depression in the Youth: A Major Public Health Concern

• The pediatric literature estimates that up to 25% of youth in the U.S experience major depressive disorder by adolescence (Kessler 2001)

• Additional 11% suffer from subthreshold depressive symptoms throughout their lifetime (Kessler 1998)
Pediatric Depression vs Adult Depression

• For the most part, children and teens experience fatigue and irritability and other physical complaints.

• Kids also may seem bored and withdrawn and experience loss of interest. “He seems deflated…”

• Hopelessness and helplessness can manifest as negative self-talk with phrases such as “I am bad” and “I can’t do anything right”

• Behavior change; i.e. A child who typically does well in school might start getting failing grades.
Depression in Children

• Depression can even affect **babies**, who tend to exhibit symptoms such as unresponsiveness, lethargy, inconsolable crying and feeding problems (Deborah Serani, PsyD)
Depression in the Youth

• When a child presents with symptoms of depression, both diagnoses of unipolar Major Depressive Disorder (MDD) and Bipolar major depression (BP MDD) need to be considered.

• This is an important consideration because it affects treatment decisions:
  – Antidepressants could be effective for depression.
  – BUT Antidepressants could also cause manic switches in individuals with underlying bipolar risk.
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**.
COBY Study

- Adult Bipolar Retrospective Study
- 1/3 started having sxs from adulthood
- 1/3 had subthreshold sxs of bipolar from childhood
- 1/3 had full sxs of bipolar from childhood
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
  - Biederman (2000) reported that up to half of children receiving antidepressants developed manic or hypomanic symptoms within a few months of treatment
  - Biederman (2000) reported that antidepressant treatment in BP children presenting with MDD resulted in manic exacerbation
Two Research Questions

• **Question #1:** Can we differentiate at the outset pediatric MDD that will follow a bipolar course?
  – Can we predict bipolar switches in a youth with MDD who never had a manic episode?

• **Question #2:** Are there clinical features that can help a clinician distinguish unipolar MDD vs BP MDD?
  – BP MDD: MDD in a patient who had a prior manic episode
Main Aim

To help address the current knowledge on this important subject, we conducted a systematic literature review.
Literature Review
Methods: Selection Criteria

- **Inclusion criteria:**
  - original research
  - had operationalized assessment of major depressive disorder and bipolar disorder,
  - documented comparison between unipolar and bipolar depression
  - subjects are limited to children of under the age of 18.

- **Exclusion criteria**
  - No differentiation of syndromatic pictures of unipolar from bipolar depression
  - not available in the English language.
Results: Question # 1

• Are there predictors of manic switches that we can see at the outset of pediatric MDD?
Results


• 4 samples; 2 inpatient, 1 outpatient and 1 ADHD

• N= 985 subjects

• Ages: 6-18 years

• Follow up: 1 - 11 years

• Conversion Rate: 9% - 43%
Predictors of Manic Switches

• **Family History of Mood (MDD and BP) Disorders** (5/7 Studies)
  – FHx of BP Disorder, FHx of MDD
  – Multigenerational FHx
  – Family Loading (≥3 affected relatives per family)

• **Aggression, Conduct & Behavioral difficulties** (2/7 Studies)
  – Co-morbid Conduct Disorder
  – Co-morbid ODD
  – Aggressive Behaviors and Bullying Behaviors

• **Emotional Dysregulation** (2/7 Studies)
Strober, 1982

Strober (1982) followed inpatient adolescents for 4 years

- FHx of BPD
- 3+ relatives with Mood Disorder
- 3 Generation Hx of Mood Disorder

P < .005

uípolar MDD  BP MDD

50  10

P < .02

50  15

P < .05

42 15

Percent
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

• **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
Aggression, Conduct, Behavioral Difficulties

Biederman 2009

School Behavior Problems
- Unipolar MDD: 59%
- BP MDD: 83%
  - p = 0.02

Co-Morbid Conduct Disorder
- Unipolar MDD: 14%
- BP MDD: 34%
  - p = 0.008
Aggression, Conduct, Behavioral Difficulties

- **Geller (1994)** bullying behaviors was a significant predictor of switching (OR= 7.1, p=0.003)
What is Emotional Dysregulation?

• Mood Disorders
  – require a distinct protracted episode of predominant depressed, manic or mixed mood that leads to functional difficulties

• Emotional Dysregulation
  – do not necessarily lead to extreme moods
  – subside relatively rapidly
  – is conceptualized as **deficits in cortical self regulation of emotions**
  – refers to the **inability to effectively modulate emotional responses to stressors**
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).
What is CBCL?

- Parent report
- 113 questions related to mood and behavior
- 50 cents per screen
- 15 mins to complete
## CBCL Scoring

### Internalizing

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<tr>
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</thead>
<tbody>
<tr>
<td>T Score</td>
<td>76-C</td>
<td>6</td>
<td>1</td>
<td>8</td>
<td>6</td>
<td>8</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Percentile</td>
<td>&gt;97</td>
<td>&gt;97</td>
<td>62</td>
<td>96</td>
<td>96</td>
<td>87</td>
<td>76</td>
<td>89</td>
</tr>
</tbody>
</table>

### Externalizing

- **Anxious/Depressed**: 0
- **Withdrawn/Depressed**: 0
- **Somatic Complaints**: 0
- **Social Problems**: 0
- **Thought Problems**: 0
- **Attention Problems**: 0
- **Rule-Breaking Behavior**: 0
- **Aggressive Behavior**: 0

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CBCL – Emotional Dysregulation Profile

- CBCL Emotional Dysregulation Profile: >1SD (>180) aggregate T score of Attention, Anxiety/Depression & Aggression subscales
- CBCL Severe Dysregulation Profile (Pediatric Bipolar Disorder Profile): > 2SD (> 210) aggregate T score of Attention, Anxiety/Depression & Aggression subscales
CBCL Dysregulation Profiles and Rates of Lifetime Psychopathology

- Controls
- ADHD
- ADHD+CBCL-DESR
- ADHD+CBCL-PBD

A: p<0.05 vs. Controls
B: p<0.05 vs. ADHD
C: p<0.05 vs. DESR

Longitudinal Follow up of ADHD + DESR

- Follow up: average of 4 years
- Biederman et al 2012 Neuropsychiatric Disease and Treatment
Biederman (2009) reported the additive risk of significant predictors of switching (conduct disorder, school behavior problems and parental mood disorder).
Other Predictors of Manic switching

- **Acute onset of depressive sxss** (Strober 1982)
- **Suicidality** (Strober 1982)
- **Psychosis** (Strober 1982 & 1994) – *All other studies excluded psychosis*
- **Antidepressant induced mania** (Strober 1982)
- **Co-morbid ADHD** (Biederman 2009)
- **Subthreshold Mania** (Biederman 2013)
Question # 2

• Are there differences in the clinical characteristics of unipolar MDD vs BP MDD?
Results: Question #2

• **N= 1111 subjects** with unipolar MDD & **365 subjects** with BP MDD
• **Ages 3-18 years**
• **2 community samples** (1 preschool sample, 1 national comorbidity study sample), **1 outpatient sample, 1 ADHD sample**
Common Results: Factors that differentiate BP MDD from unipolar MDD

- Family History of Psychiatric Illness (3/4 studies)
- Co-morbid Conduct or Oppositional Defiant Disorders/ Aggressive Behaviors (4/4 Studies)
- High severity of depression (2/4 studies)
- High level of impairment (2/4 studies)
Family History

Wozniak, 2004

<table>
<thead>
<tr>
<th>Family History</th>
<th>Percent</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>FHx of MDD</td>
<td>45</td>
<td>0.003</td>
</tr>
<tr>
<td>FHx of BPD</td>
<td>8</td>
<td>0.003</td>
</tr>
<tr>
<td>FHx of Anxiety Disorder</td>
<td>30</td>
<td>0.0002</td>
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<tr>
<td>FHx of Conduct Disorder</td>
<td>12</td>
<td>0.0001</td>
</tr>
<tr>
<td>FHx of ODD</td>
<td>20</td>
<td>0.0001</td>
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</tbody>
</table>
Family History

Merikangas, 2012

FHx of Depression

OR = 2.4 [95% CI 1.19-4.84]

Percent

FHx of Psychiatric Illness

Shon, 2013

unipolar MDD

BP MDD

Percent

FHx of Mania or Hypomania

p = 0.005

11

p = 0.018

31
Co-morbid Conduct Disorder or ODD

**Wozniak 2004**
- Conduct Disorder: 60% (unipolar MDD), 12% (BP MDD)
- ODD: 63% (unipolar MDD), 30% (BP MDD)

**Merikangas 2012**
- Conduct & ODD: 52% (unipolar MDD), 30% (BP MDD)

p<0.0001

OR=2.45 (95%CI 1.09-2.36)
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

Aggressive Behaviors

Unipolar MDD
BP MDD

40%
P=0.001

15%
P=0.001
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

Merikangas 2012

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

- Number of MDD Symptoms
  - Unipolar MDD: 6.8
  - BP MDD: 7.4
  - P < 0.001

- Depression Severity Rating
  - Unipolar MDD: 10.4
  - BP MDD: 11.6
  - P = 0.04
Wozniak et al (2008) reported that rate of suicidality and hospitalization were higher in BP MDD.

- Suicidality:
  - 50% in unipolar MDD
  - 69% in BP MDD
  - p = 0.027

- Hospitalization:
  - 6% in unipolar MDD
  - 36% in BP MDD
  - p = 0.001
Degree of Impairment

**Wozniak, 2004**
- Severe MDD related Impairment: 77%
- p=0.002
- 43%

**Merikangas, 2012**
- Severe Impairment, past 12 mos: OR=2.52 (95%CI=1.52-4.17)
- Role Disability, past 12 mos: OR=1.91 (95%CI=1.07-3.42)
- 41%
- 24%
- 54%
Degree of Impairment: GAF

Wozniak 2004

<table>
<thead>
<tr>
<th></th>
<th>unipolar MDD</th>
<th>BP MDD</th>
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<tr>
<td><strong>Past GAF Scores</strong></td>
<td>p&lt;0.0001</td>
<td></td>
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<tr>
<td>47.1</td>
<td></td>
<td>40</td>
</tr>
<tr>
<td><strong>Current GAF Scores</strong></td>
<td>p&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>60.3</td>
<td></td>
<td>55.6</td>
</tr>
</tbody>
</table>
Other factors that differentiate Unipolar MDD vs BP MDD

• Early onset of mood symptoms (Merikangas)
• Problems with peers and family members (Wozniak)
• Co-morbid substance use disorder (Merikangas)
• Co-morbid anxiety disorders (Wozniak)
• Antidepressant concurrent mood change (Shon)
Discussion
Family History of Mood Disorders

- A **positive family history** of mood disorders was the most consistently reported risk factor in the extant literature for manic switches.
- It is noteworthy that a positive family history was **not limited to bipolar disorder** but also included a major depression.
- These findings suggest that **genetic influences** may be operant in this risk for manic switches.
- Further evidence for genetic influences in the risk for manic switches in pediatric MDD comes from studies documenting that **familial loading and multi-generational family history of mood disorders are risk factors** for such switchers.
Emotional Dysregulation

- Multiple studies reported that emotional lability and emotional reactivity were significant predictors of manic switches in pediatric MDD.
- Consistent with studies that reported that severe forms of emotional dysregulation defined through CBCL predicted both lifetime and current diagnosis of bipolar disorder in youth with ADHD.
Emotional Dysregulation

- A positive CBCL severe emotional dysregulation profile predicted a subsequent diagnosis of bipolar disorder, impaired psychosocial functioning and higher risk of psychiatric hospitalization in youth with ADHD followed prospectively into young adult years (Faroane, 2005, Bipolar disorder; Uchida, 2014, Journal of Affective Disorders)
Overlap of Conduct Disorder and BPD

Additive Risk for Hospitalization: CD and BPD

Rate of Hospitalization

<table>
<thead>
<tr>
<th></th>
<th>CD</th>
<th>Mania</th>
<th>CD+Mania</th>
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<tbody>
<tr>
<td>%</td>
<td>2</td>
<td>19</td>
<td>30</td>
</tr>
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</table>

p<0.01 vs. CD

Different Levels of Irritability

Mick, 2010
Levels of Irritability

- ADHD
- ODD
- MDD
- MANIA

Mick, 2007
Irritability

Wozniak et al. *J Affect Disord* 2004;82S:S59-S69
High Levels of Severity and Impairment in BP depression

• In addition, studies have revealed that children with bipolar disorder exhibit a greater deal of suicidal behavior as compared to this with unipolar MDD.
• Children with bipolar disorder had a younger age of first suicide attempt and a higher percentage of multiple suicide attempts that were higher in lethality than those children with unipolar major depression
• thereby making bipolar disorder a highly morbid condition.
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

- **Emotional Dysregulation**

- **High Severity of Depression & Syndrome Congruent Impairment**
  - Suicidality, Hospitalizations, Low GAF

- **Psychiatric Co-morbidities & Psychosis**

- **Antidepressant Induced Mania or Hypomania**

- **Early Onset of Mood Symptoms**
Discussion: Pharmacological Induced Effects

• Strober et al reported that pharmacologically induced hypomania was a predictor of a bipolar course of illness.

• Shon et al reported antidepressant induced mood change in BP MDD.

• Martin et al also reported that the rate of manic switching was higher in children with depression receiving antidepressants.
Discussion: Pharmacological Induced Effects

• Biederman et al reported that a high rate of BP children who received SSRI medication activated
• These reports suggest the debilitating effect that antidepressant use may have on a child with BP MDD and stress the significance of our research questions
How do we pharmacologically manage them?

- Should we use antidepressants?
- SSRI + mood stabilizer?
- Mood stabilizer only?
- SSRI only?
- Lamotrigine?
- FDA approved meds for bipolar depression?
- Are there other symptomatology that we can treat to mitigate the effect of depression?