Differentiating Unipolar vs Bipolar Depression in Children

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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.
• Sleep (insomnia/hypersomnia)
• Interest (loss if interest) – not in the criteria
• Guilt (excessive guilt or feelings of worthlessness) “I’m a bad boy.” “I’m not good at anything.”
• Energy (loss of energy/physical complaints) “tummy aches”
• Concentration (difficulty concentrating or making decisions) “Can’t chose his clothes.”
• Appetite (change in appetite or weight)
• Psychomotor agitation or retardation
• Suicidal thoughts “I shouldn’t have been born.”
Diagnostic Criteria of Mood Disorders; How do they present in children?

• **Manic Episode:**
  • A) elevated, expansive or **irritable mood**
  • B) >3/7 of following sxs (>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
Diagnostic Criteria of Mood Disorders; How do they present in children?

- **Hypomanic Episode**: mild version of Manic Episode
- **Mixed Episode**: Meets the criteria for both Manic and Major Depressive Episodes (except for duration)
## Diagnostic Criteria of Mood Disorders

<table>
<thead>
<tr>
<th></th>
<th>Major Depressive Episode</th>
<th>Manic Episode</th>
<th>Hypomanic Episode</th>
<th>Mixed Episode</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major Depressive Disorder</strong></td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Bipolar I Disorder</strong></td>
<td>+/−</td>
<td>+</td>
<td>−</td>
<td>+</td>
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<tr>
<td></td>
<td></td>
<td>(or Mixed Episode)</td>
<td></td>
<td>(or Manic Episode)</td>
</tr>
<tr>
<td><strong>Bipolar II Disorder</strong></td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
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When a child presents with symptoms of depression, both diagnoses of unipolar Major Depressive Disorder (MDD) and Bipolar depression 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 31%) (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.
Most bipolar adults (N=983) reported onset in childhood or adolescence

- > 18 years: 35%
- < 13 years: 28%
- 13 to 18 years: 37%

About 65% of adults with onset < 18
Almost a third with onset < 13

Perlis, Miyahara, Marangell, Wisniewski, Ostacher, DelBello, Bowden, Sachs, Nierenberg, Biol Psych 2004;55:875-881
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
Literature Review Methods: Selection Criteria

• **Inclusion criteria:**
  – original research
  – has operationalized assessment of major depressive disorder and bipolar disorder,
  – documents comparison between unipolar and bipolar depression
  – subjects are limited to children of under the age of 17.

• **Exclusion criteria**
  – No differentiation of syndromatic pictures of unipolar from bipolar depression
  – not available in the English language.
Methods: Pubmed Search Algorithm

• (bipolar depression OR bipolar disorder) AND (unipolar depression OR major depressive disorder) AND (predictor OR prodrome OR risk factors OR comparison OR switch OR conversion) AND (child* OR adolesc* OR youth)

• References were also reviewed and added if applicable to search criteria.
Methods: Data Extraction

- study sample size
- proband age range
- years of follow up (for prospective studies)
- rate of conversion from unipolar depression to bipolar disorder (for prospective studies)
- characteristics that differentiated subjects with unipolar and bipolar depression.
Results

• From the initial database search, 752 papers were identified and screened.
• After screening, 44 articles were found to be relevant and the full text of each was carefully examined.
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)**
Family History

Strober, 1982

- FHx of BPD: 10%
- 3+ relatives with Mood Disorder: 15%
- 3 Generation Hx of Mood Disorder: 15%

Strober (1982) followed inpatient adolescents for 4 years

percentages:
- FHx of BPD: P < .05
- 3+ relatives with Mood Disorder: P < .02
- 3 Generation Hx of Mood Disorder: P < .05
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
  - 59% (unipolar MDD)
  - 83% (BP MDD)
  - p=0.02

- Co-Morbid Conduct Disorder
  - 14%
  - 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

Kochman 2005

<table>
<thead>
<tr>
<th></th>
<th>Rate of Switching</th>
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<tbody>
<tr>
<td>CHT +</td>
<td>63.8%</td>
</tr>
<tr>
<td>CHT -</td>
<td>15.2%</td>
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</table>
• **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

<table>
<thead>
<tr>
<th>Total Score</th>
<th>Internalizing</th>
<th>T Score</th>
<th>Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>6</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>T Score</td>
<td>&gt;97</td>
<td>&gt;97</td>
<td>62</td>
</tr>
</tbody>
</table>

(Copyright 2001 T.M. Achenbach)
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
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)
Different Levels of Irritability

Mick, 2010
Levels of Irritability

ADHD  ODD  MDD  MANIA

Mick, 2007
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 sxs** (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>Disorder</th>
<th>Percent</th>
<th>FHx of MDD</th>
<th>FHx of BPD</th>
<th>FHx of Anxiety Disorder</th>
<th>FHx of Conduct Disorder</th>
<th>FHx of ODD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unipolar MDD</td>
<td>p=0.003</td>
<td>62</td>
<td>20</td>
<td>63</td>
<td>31</td>
<td>43</td>
</tr>
<tr>
<td>BP MDD</td>
<td>p=0.0002</td>
<td>45</td>
<td>8</td>
<td>30</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>p=0.0001</td>
<td></td>
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Percentages and p-values indicate significant differences in family history of mental disorders.
Family History

Merikangas, 2012
OR=2.4 [95%CI 1.19-4.84]

- FHx of Depression
  - Percent
  - FHx of Mania or Hypomania

Shon, 2013

- unipolar MDD
- BP MDD

- FHx of Psychiatric Illness

- Percent
  - p=0.005
  - p=0.018

Percent

FHx of Depression

2 10

11

Percent

FHx of Mania or Hypomania

FHx of Psychiatric Illness

2 10

11

Percent

www.mghcme.org
Co-morbid Conduct Disorder or ODD

Wozniak 2004
- Conduct Disorder: 60% (p<0.0001)
- ODD: 63% (p<0.0001)

Merikangas 2012
- Conduct & ODD: 52%
- 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**

- **Unipolar MDD**
  - 15%
  - P=0.001

- **BP MDD**
  - 40%
  - P<0.001

Aggressive Behaviors
Overlap of Conduct Disorder and BPD

Additive Risk for Hospitalization: CD and BPD

Rate of Hospitalization

- CD: 2%
- Mania: 19%
- CD+Mania: 30%

p < 0.01 vs. CD

High Severity of Depression

Luby, 2008

\[ p < .0001 \]

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.
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

Wozniak, 2004

- Severe MDD related Impairment: 77%
  - p=0.002
- Severe Impairment, past 12 mos: 43%

Merikangas, 2012

- Role Disability, past 12 mos: 54%
  - OR=1.91 (95%CI=1.07-3.42)
- Severe Impairment, past 12 mos: 41%
  - OR=2.52 (95%CI=1.52-4.17)

unipolar MDD | BP MDD
Degree of Impairment: GAF

Wozniak 2004

Past GAF Scores
- unipolar MDD: 47.1
- BP MDD: 40

Current GAF Scores
- unipolar MDD: 60.3
- BP MDD: 55.6

Significance:
- Past GAF Scores: p<0.0001
- Current GAF Scores: p<0.0001
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)
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**
• Strober et al reported that pharmacologically induced hypomania was also a predictor of a bipolar course of illness
• Shon et al reported antidepressant induced mood change was seen more in BP MDD
• A retrospective study by Martin et al. also reported that the rate of switching was higher in subjects with history of receiving antidepressants especially in the children
Management

• At the same time Biederman et al., 2000 reported children who received SSRI medication showed the most improvement of BP MDD symptoms when compared to those that received mood stablizers, typical neuroleptics or TCAs.

• Results documenting that antidepressants were both selectively efficacious and destabilizing in youth with BP MDD stressed the clinical conundrum of managing BP MDD.
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?