Differentiating Unipolar vs. Bipolar Mood Disorders in the Young

JANET WOZNIAK, MD
Associate Professor of Psychiatry
Harvard Medical School
Chair, Quality and Safety, Department of Psychiatry
Director, Child and Adolescent Outpatient Psychiatry Service
Director, Pediatric Bipolar Disorder Clinical and Research Program
Associate Director, Bressler Clinical and Research Program for Autism Spectrum Disorders
Massachusetts General Hospital
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Differentiating Unipolar vs Bipolar Depression in Children

Janet Wozniak, MD
Director, Pediatric Bipolar Disorder Research Program
Associate Professor of Psychiatry
Harvard Medical School
Massachusetts General Hospital

Mai Uchida MD
Director, Center for Early Identification and Prevention of Pediatric Depression
Massachusetts General Hospital
Assistant Professor of Psychiatry
Harvard Medical School

Pharmacologic management of bipolar depression is very difficult

ANTI-DEPRESSANTS
Overview: Switch from pediatric depression to bipolar disorder is common and children with bipolar disorder spend much time in mixed or depressive states. Pharmacologic treatment of bipolar depression is complicated due to risk of switch with antidepressants.

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 but antidepressants may worsen the clinical picture.
We use the same diagnostic criteria (developmentally appropriate) for depression in children as adults.

**Major Depressive Episode:**

A) 2 weeks of depressed mood (*irritable, grumpy, easily annoyed, bored* or sad/melancholic)

B) 4/7 of following symptoms:

- **Sleep** (insomnia/ hypersomnia)
- **Interest** (loss of interest)
- **Guilt** (excessive guilt or feelings of worthlessness)
- **Energy** (loss of energy/ physical complaints) “*tummy aches*”
- **Concentration** (making decisions)
- **Appetite** (change in appetite or weight)
- **Psychomotor agitation or retardation**
- **Suicidal thoughts**
We use the same diagnostic criteria (developmentally appropriate) for mania in children as adults.

**Manic Episode:**

A) Seven days of elevated, expansive or irritable mood plus increase in energy

B) 3/7 (4/7 if mood is irritable)
   - Distractability
   - Increased Energy
   - Grandiosity (i.e. “above all rules,” flagrant disregard for adult authority)
   - Flight of Ideas, racing thoughts (observed or experienced)
   - Activities (increased goal directed activities: sexual, shopping sprees)
   - Sleep (decreased need of sleep)
   - Talkativeness
Depressive symptoms are often more persistent and debilitating in pediatric bipolar disorder.

- **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:

1. Elevated, expansive mood.
2. Inflated self-esteem or grandiosity.
3. More talkative than usual or pressure to keep talking.
4. Flight of ideas or subjective experience of pressure of speech.
5. Increase in energy or goal-directed activity.
6. Increased or excessive involvement in activities that are potentially get more serious or of greater magnitude than is typically associated with such investments.
7. Decreased need for sleep (feeling rested with less than the normal amount of sleep).
21%-76% of depressed adult patients have mixed states with younger age of onset, longer episode duration, worse outcomes and increased suicidality.
In DSM5, a manic or hypomanic episode is considered “mixed” with 3/6 additional depressive symptoms.

### MIXED BIPOLAR MANIA

1. Prominent dysphoria or depressed mood as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).
2. Diminished interest or pleasure in all, or almost all, activities (as indicated by either subjective account or observation made by others).
3. Psychomotor retardation nearly every day (i.e., being slowed down).
4. Fatigue or loss of energy.
5. Feeling of worthlessness or excessive or inappropriate guilt (not just feeling sorry or being guilty about being sick).
6. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for suicide.

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

Abstract

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 disease. In treating this group, selective serotonin reuptake inhibitors remain first-line therapy, but augmentation with other therapies is often required. If a diagnosis of bipolar disorder is confirmed and the patient is experiencing a depressive phase, traditional antidepressants should be avoided. For those presenting with mania and mixed depressive symptoms, treatment with a combination of atypical antipsychotics and mood stabilizers is best.
Irritability is not included as a symptom, like defining a type of headache without including “pain in the head”

Mixed depression, in our research and experience as well as that of many others,\textsuperscript{9,10} is often characterised by markedly irritable mood and psychic or psychomotor agitation - the exact features excluded in DSM-5. This would be like proposing a new definition for migraine headaches, but excluding symptoms of pain in the head. Of course, one can have pain in the head from other conditions besides migraine, but why should this be a reason to exclude that symptom entirely?
Children with MDD often switch

CHILDREN WITH MDD

31% DEVELOP MANIA OR HYPOMANIA

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

Weissman 1999; Geller 1994
Top features of pediatric depression found which predict subsequent switch to bipolar disorder from 7 prospective studies (4 samples)

- Family History of Mood Disorders: 5/7 Studies
- Aggression, Conduct, Disruptive Behavior: 2/7 Studies
- Emotional Dysregulation: 2/7 Studies

N= 985 subjects, ages 6-18 years
2 inpatient, 1 outpatient and 1 ADHD
Follow up: 1 - 11 years

Switch Rate: 9% - 43%

Family history of mood disorder is associated with bipolar depression

- Family History of Bipolar Disorder (BPD)
  - 3+ relatives with Mood Disorder: p < .005
  - 3 Generation Family History of Mood Disorder: p < 0.02
  - 3 Generation Family History of Mood Disorder: p < 0.05

Percent inpatient adolescents

- MDD: 10
- Bipolar MDD: 50
- MDD: 15
- Bipolar MDD: 50
- MDD: 15
- Bipolar MDD: 42

Strober 1982
Parental depression and bipolar disorder is predictor of switch

Data from two large controlled longitudinal studies of boys and girls with and without ADHD and their siblings

Subjects who switched had significantly higher rates of parental mood disorders

Biederman 2009
Family history of mood disorder is associated with switch to bipolar disorder

- 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.
- Extensively characterized outpatient sample followed for 10 years.
- 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.

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

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

- Co-Morbid Conduct Disorder
  - MDD: 14%
  - Bipolar MDD: 34%
  - p = 0.008
Emotional dysregulation can be distinguished from mood disorders

**Mood Disorders**
- requires a distinct protracted episode
- predominant depressed, manic or mixed mood
- leads to functional difficulties

**Emotional Dysregulation**
- does not necessarily lead to extreme moods
- subsides relatively rapidly
- is conceptualized as deficits in cortical self regulation of emotions
- an inability to effectively modulate emotional responses to stressors
Emotional dysregulation can be highly impairing

N=80 inpatients followed 1 year

High mood lability and emotional reactivity

Cyclothymic Hypersensitive Temperament (CHT)

Rate of Switching

<table>
<thead>
<tr>
<th>CHT +</th>
<th>CHT -</th>
</tr>
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<tbody>
<tr>
<td>63.8%</td>
<td>15.2%</td>
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p<0.0001

Children with CHT:
- **switched** (64% vs 15%)
- wider range of aggressive behaviors
- higher rate of suicidality

Kochman 2005

www.mghcme.org
The MGH research group has published extensively on the utility of the CBCL in the assessment of ADHD youth.
The MGH group has published extensively on the utility of the CBCL in identifying bipolar disorder in youth. Certain CBCL scores - AAA profile - are associated with a diagnosis of pediatric bipolar disorder.
The Child Behavior Checklist is a parent completed rating scale that is easy to administer and score. Parents score choosing from Likert scale responses:

- 0 = not true
- 1 = somewhat or sometimes true
- 2 = very true or often true

The 120 statements are grouped into 8 subscales or syndrome scales.
1. Enter the score (0, 1, 2) for each question
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2. Total the score for each subscale
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2. Total the score for each subscale

3. Plot the total score on the scale above
98+ percentile

Percentile is on the left

T-Score is on the right

T-Score 77

Aggressive Behavior score
The Child Behavior Checklist has 8 clinical subscales.

The 120 statements are grouped into 8 subscales or syndrome scales.

Scores are converted to T-Scores for each subscale.

50-100

- social withdrawal
- somatic complaints
- anxiety/depression
- social problems
- thought problems
- attention problems
- delinquent behavior
- aggressive behavior

A T-score of 60 is one standard deviation from normal.

A T-score of 70 is two standard deviations from normal.

CBCL AAA score: 150-300
We operationalized profiles of Emotional Dysregulation based on the composite T-scores of three CBCL subscales.

AAA CBCL T-Score range is 150-300

| Anxiety/Depression 50-100 | Aggression 50-100 | Attention 50-100 |

A score of 150-180 is considered in the normal to subclinical range.

If all 3 scores of the AAA were one SD from normal (60), the total would be 180.

If all 3 scores of the AAA were two SD from normal (70), the total would be 210.
Emotional Dysregulation ED can be characterized by:
- DESR (CBCL score 180-210) which is less severe than
- SED (CBCL score >210)
In ADHD youth followed prospectively into adulthood a AAA CBCL score $\geq 180$ was associated with switching
In ADHD youth followed prospectively into adulthood a AAA CBCL score > 210 was associated with bipolar disorder.
There is a ‘dose response’ of multiple risk factors contributing to manic switch

- conduct disorder
- school behavior problems
- parental mood disorder

![Graph showing the percentage of risk factors leading to the switch to BPD.](Biederman_2009)
Other predictors of manic switching

- Acute onset of depression
- Suicidality
- Psychosis
- Co-morbid ADHD
- Subthreshold Mania

Acute onset of depression

Suicidality

Psychosis

Co-morbid ADHD

Subthreshold Mania

Antidepressant induced mania

Other predictors of manic switching

Other predictors of manic switching

The double-edged sword of antidepressants for bipolar youth was noted in chart review.

SSRIs led to the most improvement of BP MDD (versus mood stabilizers, typical neuroleptics or TCAs).

SSRIs led to the most destabilization with mania.

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

Biederman 2000
Antidepressants play a negative role in switching......

pharmacologically induced hypomania was a predictor of a bipolar course

antidepressant induced mood change was seen more in BP MDD

rate of switching was higher in subjects with history of receiving antidepressants especially in children

ANTI-DEPRESSANTS

Strober; Shon; Martin
Antidepressants play a negative role in switching, use with caution

- Pharmacologically induced hypomania was a predictor of a bipolar course.
- Antidepressant induced mood change was seen more in BP MDD.
- Rate of switching was higher in subjects with history of receiving antidepressants especially in children.
We have many FDA approved treatments for youth with emotional dysregulation

- Lithium: manic or mixed states, patients aged 13-17 years
- Risperidone: manic or mixed states, age 10-17 years
- Aripiprazole: manic or mixed states, age 10-17 years
- Olanzapine: manic or mixed states, age 13-17 years
- Quetiapine: monotherapy or adjunct to lithium or divalproex sodium, manic states, age 10-17 years
- Asenapine manic or mixed episodes in BPD I, age 10-17 years
- Fluoxetine: depression and OCD age 8+
- Escitalopram: depression age 12+
- Sertraline, fluvoxamine, anfranil: pediatric OCD
- Aripiprazole: irritability associated with autistic disorder ages 6-17
- Risperidone: irritability associated with autism ages 5-16
Pharmacologic management of bipolar depression is very difficult

Use antidepressants at all?

Lamotrigine? Lithium? Lurasidone?

Mood stabilizer only?

FDA approved meds for bipolar depression?

Antidepressant + mood stabilizer?

Antidepressant only?
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)**

Similar negative outcome with (N=193) quetiapine XR 150-300mg

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DelBello 2009; Findling 2014
Lurasidone significantly reduced depressive symptoms in children and adolescents with Bipolar I Depression.

- Placebo-controlled study
- Monotherapy with lurasidone
- Dose range of 20-80 mg/day,
Lurasidone significantly reduced depressive symptoms in children and adolescents with Bipolar I Depression

- Placebo-controlled study
- Monotherapy with lurasidone
- Dose range of 20-80 mg/day,

Minimal effects on weight and metabolic parameters

DelBello JAACAP 2017
Lurasidone in children and adolescents with bipolar I depression reduces CDRS and CGI-BP-S scores.
Open label lamotrigine and lithium effective in adolescent bipolar depression (at least 50% decrease in CDRS)

- Adjunctive or monotherapy lamotrigine
  - N=20
  - 63% responders

- Monotherapy lithium
  - N=27
  - 48% responders

Lithium has a narrow therapeutic window and requires intensive blood monitoring.

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

Chang JAACAP 2006; Patel JAACAP 2006
SGAs can 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 that 14 had positive response.

Zarate 1998; Rothschild 1999; Mahmoud 2007
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