Bipolar disorder and severe irritability in youth: Diagnosis and treatment

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I will discuss off-label use of:
  - divalproex sodium
  - serotonergic re-uptake inhibitors (SRI’s)
  - stimulant medications
  - lithium
  - second generation antipsychotic medication
Objectives

1. Understand the controversies surrounding the diagnosis of bipolar disorder in pediatrics.

2. Understand changes in the DSM5 related to the diagnosis of DMDD.

3. Understand data that is relevant to the diagnosis and treatment of bipolar disorder and severe irritability in youth.

Talk Outline

• Controversy about diagnosing pediatric BD in youth
  • Irritability: an important and neglected clinical phenomenon
  • Defining severe mood dysregulation (SMD)

• A few words about DSM-5
  • Disruptive mood dysregulation disorder (DMDD)

• Treatment of pediatric bipolar disorder

• Pharmacologic treatment of severe irritability in youth
**Increase in diagnosis of BD in youth**

![Graph showing national trends in visits with a diagnosis of bipolar disorder as a percentage of total office-based visits by youth (aged 0-19 years) and adults (aged ≥ 20 years).](image)

**Marenco et al, 2007**

**Hospital discharge diagnoses in the U.S., 1996-2004**

Rate of increase in d/c's for BD:
- In adults, 56%
- In adolescents, 400%
- In children, 1.3 to 7.3 per 10,000 (~600%)

**Blader and Carlson, 2007**
Diagnosing pediatric bipolar disorder: The controversy

Is severe irritability and ADHD, without distinct manic episodes, a developmental form of bipolar disorder?

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**DSM-IV Criteria for Manic Episode: Unique features**

<table>
<thead>
<tr>
<th>A. Distinct period of elevated, expansive, or irritable mood ≥ 1 week</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. Symptoms (3, or 4 if irritable) at the same time as “A”</td>
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<td>(1) grandiosity</td>
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<td>(7) excessive pleasurable activities</td>
</tr>
<tr>
<td>C. Marked impairment, hospitalization, or psychosis</td>
</tr>
</tbody>
</table>
**DSM-IV Criteria for Manic Episode: Overlap with ADHD**

A. Distinct period of elevated, expansive, or irritable mood ≥ 1 week

B. Symptoms (3 of the following, or 4 if mood only irritable)

1. inflated self-esteem, grandiosity
2. decreased need for sleep
3. pressured speech
4. flight of ideas, racing thoughts
5. distractibility
6. increased goal-directed activity, psychomotor agitation
7. excessive, pleasurable activities with potential for painful consequences

C. Marked impairment, hospitalization, or psychotic features

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**All research groups “adhere to DSM-IV” BUT… the devil is in the details**

“Developmental modifications” in diagnostic criteria for BD

Assumption: Youth with BD have cycles too rapid to be detected using adult techniques (Geller et al, 2004)

WASH-U: change definitions of episodes and cycles; cycles ≥ 4 hours

“B” criteria count even if they don’t onset, or worsen, with mood change

Assumption: Instead of elation, youth with mania have very extreme irritability (Mick et al, 2005)

MGH: episode criterion waived if irritability is very severe
**Does mania occur in preschoolers?**

- Commonly reported symptoms include:
  - Irritability
  - Racing thoughts
  - Increased activity
  - Grandiosity

- Problems
  - What is normative?
  - Episodes not described e.g., Luby et al, 2006; Danielyan et al, 2007

- AACAP guidelines advise against assigning dx to preschoolers

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**Irritability in DSM-IV Childhood-Onset Disorders**

- Major depressive episode
- Manic episode
- Dysthymic disorder
- Post-traumatic stress disorder
- Oppositional defiant disorder
- Generalized anxiety disorder
- PDD-spectrum disorders
- ADHD
- Conduct disorder
An important positive outcome of the controversy about the diagnosis of pediatric bipolar disorder

- Highlights that irritability is a common, yet relatively understudied, clinical presentation in children

- Regarding irritability, we need to know much more about:
  - clinical correlates
  - outcomes
  - treatment
  - measurement
  - pathophysiology and pathogenesis
    - impact of genes, environment, G X E interactions and correlations
    - neural circuitry

Diagnosing pediatric bipolar disorder: The controversy

Is severe irritability and ADHD, without distinct manic episodes, a developmental form of bipolar disorder?
Research to address the controversy

• One can identify youth (including prepubertal youth) who meet “classic” (DSM-IV) criteria for BD.

• To demonstrate that an alternative phenotype is a developmental presentation of mania, recruit such children and compare them to those with the classic presentation

Severe Mood Dysregulation (SMD)

• Chronic presentation (vs. episodes of BD)

• Irritability clearly defined, with high bar:
  • baseline anger or sadness
  • ↑reactivity to negative emotional stimuli ≥ 3x/week

• Irritability impairing in ≥ 2 settings (home, school, peers)
  • SMD children should be as impaired as BD

• ADHD symptoms that overlap with “B” mania criteria

• SMD = most severely impaired ADHD + ODD

Leibenluft et al, 2003
Interviewing tips

• Direct observation has the greatest weight

• Get lots of examples

• Interview parent and child separately and together

• Elevated mood, grandiosity are the trickiest
  • E.g. What is grandiosity in a 5, 10, 15, 25, 35 year old?
  • “The episode is your friend”….each children his/her own baseline.

• Ascertain episodes: worst mania, worst depression, euthymia

• ADHD etc. are diagnosed based on symptoms during euthymia.

Is SMD a developmental phenotype of BD?

• Longitudinal course (epidemiological studies)
• Family history
• Neural circuitry dysfunction

Caveat: “bipolar” is not really a categorical variable
### Clinical characteristics BD (N=118) SMD (N= 134)

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>BD (N=118)</th>
<th>SMD (N= 134)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>12.9 ± 2.8</td>
<td>12.0 ± 2.0</td>
</tr>
<tr>
<td>Age of onset</td>
<td>9.8 ± 3.5</td>
<td>5.6 ± 2.2</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>52.0</td>
<td>69.7</td>
</tr>
<tr>
<td>% ADHD</td>
<td>57.0</td>
<td>85.3</td>
</tr>
<tr>
<td>% ODD</td>
<td>36.0</td>
<td>84.4</td>
</tr>
<tr>
<td>% Anxiety d/o</td>
<td>56.0</td>
<td>52.3</td>
</tr>
<tr>
<td>Number meds</td>
<td>2.4 ± 1.70</td>
<td>1.37 ± 1.45</td>
</tr>
<tr>
<td>% hospitalized</td>
<td>63.0</td>
<td>40.4</td>
</tr>
<tr>
<td>Children’s Global Assessment Scale</td>
<td>51.1 ± 10.8</td>
<td>47.4 ± 9.0</td>
</tr>
</tbody>
</table>

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**Why does it matter whether SMD is a form of BD?**

- **Treatment!!!**

- **If SMD = BD, then antipsychotic medication, anticonvulsants**

- **If SMD = ADHD + anxiety and/or depression, then stimulants and SRI’s (ongoing trial)**
Longitudinal Outcome and Family History

Do children with severe irritability develop BD when they grow up?

Community-based studies:
• Irritability in youth predicts anxiety, unipolar depression in adulthood
  • Duration of follow-up: 3 to 20 years
• Irritability in youth does not predict bipolar disorder in adulthood

NIMH study of patients:
• Over two years, one child with severe irritability out of 84 developed a manic episode

But…we don’t know about the special case of children with a parent with bipolar disorder
Oppositional defiant disorder has two dimensions: Irritable and headstrong

Irritable predicts to unipolar depressive and anxiety disorders
(Stringaris and Goodman 2009, Rowe et al 2010, Burke et al, 2010)

Headstrong predicts to conduct disorder

<table>
<thead>
<tr>
<th></th>
<th>Internalizing Disorders</th>
<th>ADHD</th>
<th>Conduct Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irritable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>2.33***</td>
<td>1.4</td>
<td>1.16</td>
</tr>
<tr>
<td>Adjust for baseline diagnoses</td>
<td>1.77***</td>
<td>1.13</td>
<td>1.04</td>
</tr>
<tr>
<td>Adjusted for baseline score</td>
<td>1.54***</td>
<td>1.25</td>
<td>1.12</td>
</tr>
<tr>
<td>Headstrong</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.90</td>
<td>3.27***</td>
<td>2.54***</td>
</tr>
<tr>
<td>Adjust for baseline diagnoses</td>
<td>0.93</td>
<td>1.89***</td>
<td>2.12***</td>
</tr>
<tr>
<td>Adjusted for baseline score</td>
<td>0.95</td>
<td>2.15***</td>
<td>1.60***</td>
</tr>
</tbody>
</table>

N=7,912; 3-year follow-up 10.2 ± 3.3 y to 13.2 ± 3.3 y

Stringaris and Goodman, 2009

Psychiatric illness in parents of youth with BD or SMD

Brotman et al, 2007

p=0.053  p≤ 0.01
Longitudinal Assessment of Manic Symptoms (LAMS)

- Screened 2622 youth presenting for assessment
- 25% (N=235) met proxy criteria for DMDD
  - Compared DMDD vs. non-DMDD in
    - rates of BD in 1st degree relatives
    - Rates of BD in 1st and 2nd degree relatives
    - Degree of familial loading for mania (% family members assessed who met criteria)
  - No analysis reached significance, even before correcting for multiple comparisons


Conclusion

The diagnosis of bipolar disorder should be reserved for youth with a history of a distinct manic or hypomanic episode.
### DSM-IV Criteria for Manic Episode

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### Refine “A” criteria for manic episode:
A distinct period of elevated, expansive, or irritable mood, lasting at least one week

<table>
<thead>
<tr>
<th>Goal: operationalize “episode” more clearly</th>
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<tbody>
<tr>
<td>Add “most days most of the time”</td>
</tr>
</tbody>
</table>

**Rationale:**
- In DSM-IV, no information about how persistent the mood change needs to be over the course of the 4-7 days
- DSM-IV criterion for major depressive episode: abnormal mood “most of the day, nearly every day”

### Refine “B” criteria for manic episode
“During the period of mood disturbance, three of the following symptoms have persisted and have been present to a significant degree”

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<th>Goal: operationalize “episode” more clearly</th>
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<tbody>
<tr>
<td>Add: “and represent a noticeable change from usual behavior”</td>
</tr>
</tbody>
</table>

**Rationale:**
- DSM-IV already says that B sx’es must be present “during the period of the mood disturbance”
- SO: a) “A” and “B” criteria must be clustered temporally
  b) each sx must be a distinct change from baseline
DSM-5 committee wanted to do something for the SMD/very irritable children

- No good home in DSM-IV ... hence dx’ed with BD?

- They are numerous and very ill: need psychopharm and services, more than are justified, or guided, by ODD/ADHD dx

- Disruptive behavior disorder diagnoses do not do justice to their mood/anxiety disorder

- MD’s dx these patients as BD and conclude that stimulants and SSRI’s are “contraindicated.” Therefore, pts usually receive atypical antipsychotics and, less often, mood stabilizers.

- No trials to guide their Rx, because no good home in DSM-IV

Two Proposals: ODD Specifier vs. New Diagnosis

- ODD specifier would specify # outbursts/week, inter-outburst abnormal mood, impairment in > 2 settings

- Arguments for specifier:
  - SMD on a spectrum with ODD, not distinct category
    - (top 15% of ODD in terms of irritability)
  - Data from one research group

- Arguments for new diagnosis (Disruptive Mood Dysregulation Disorder):
  - Clinicians don’t use specifiers
  - Categorized as mood disorder, not disruptive behavior disorder
  - Significant public health problem
Disruptive mood dysregulation disorder (DMDD) in DSM 5

- DMDD vs. SMD
  - No hyperarousal symptoms (just dx ADHD)
  - Can be diagnosed at age 6 (vs. 7)
  - Symptoms must begin before age 10 (vs. 12)
  - DMDD trumps ODD

Why does it matter whether SMD is a form of BD?

- Treatment!!
  - If SMD = BD, then antipsychotic medication, anticonvulsants
  - If SMD = ADHD + anxiety and/or depression, then stimulants and SRI’s (ongoing trial)
Treatment of pediatric bipolar disorder

FDA-approved medications for pediatric mania

- Lithium for children ≥ 12
- Risperidone for children ≥ 10
- Aripiprazole for children ≥ 10
- Quetiapine for children ≥ 10
- Olanzapine for youth ≥ 13*

*Labeling: consider other medications first
### Comparing mood stabilizers and 2\textsuperscript{nd} generation antipsychotics: Efficacy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>SGA trials (n = 1,118)</th>
<th>MS trials (n = 494)</th>
<th>SGA versus MS in youth</th>
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<tbody>
<tr>
<td><strong>Continuous outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YMRS(^{a})</td>
<td>0.65</td>
<td>0.24</td>
<td>0.06-0.41</td>
</tr>
<tr>
<td>YMRS(^{b})</td>
<td>0.20</td>
<td>0.05-0.39</td>
<td></td>
</tr>
<tr>
<td>CGI-BP overall illness(^{a})</td>
<td>8.59</td>
<td>8.49</td>
<td>N/A</td>
</tr>
<tr>
<td>CGI-BP overall illness(^{b})</td>
<td>0.47</td>
<td>–</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Categorical outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response: ≥50% ↓YMRS(^{a})</td>
<td>4.0</td>
<td>3.3-5.3</td>
<td>7.8(^{a}) 4.7-24.4</td>
</tr>
<tr>
<td>Response: ≥50% ↓YMRS(^{b})</td>
<td>7.8(^{a})</td>
<td>4.7-24.4</td>
<td>NS</td>
</tr>
<tr>
<td>Remission: YMRS ≤12(^{a})</td>
<td>3.7</td>
<td>3.1-4.7</td>
<td>−8.8,20.0(^{a})</td>
</tr>
<tr>
<td>Remission: YMRS ≤12(^{b})</td>
<td>3.7</td>
<td>3.1-4.7</td>
<td>−8.8,20.0(^{a})</td>
</tr>
<tr>
<td>All cause discontinuation(^{a})</td>
<td>12.7</td>
<td>7.5,11.2</td>
<td>−100.0, −8.0, 12.3(^{a})</td>
</tr>
<tr>
<td>All cause discontinuation(^{b})</td>
<td>15.6</td>
<td>−7.4,3(^{a})</td>
<td>NS</td>
</tr>
<tr>
<td>Discontinuation due to inefficacy(^{a})</td>
<td>12.5</td>
<td>7.8,11.9</td>
<td>13.3, −32.4, 5.5(^{a})</td>
</tr>
<tr>
<td>Discontinuation due to inefficacy(^{b})</td>
<td>6.9</td>
<td>3.5,80.6</td>
<td>NS</td>
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</table>

Correll et al, 2010

### Comparing mood stabilizers and 2\textsuperscript{nd} generation antipsychotics: Side-effects

<table>
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<th>MS trials (n(^{a}) = 494; n(^{b}) = 438)</th>
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<tbody>
<tr>
<td><strong>Continuous outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight change</td>
<td>0.53</td>
<td>0.41-0.66</td>
<td>0.10(^{a}) −0.12−0.33</td>
</tr>
<tr>
<td></td>
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<tr>
<td><strong>Categorical outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compliance</td>
<td>4.7</td>
<td>3.9,5.0</td>
<td>9.5, 6.3−23.5</td>
</tr>
<tr>
<td>Insomnia</td>
<td>10.0</td>
<td>−47.4−24.9</td>
<td>15.1, −15.3,5.0</td>
</tr>
<tr>
<td>Extrapyramidal side effects</td>
<td>7.5</td>
<td>5.7−11.0</td>
<td>−</td>
</tr>
<tr>
<td>Akathisia</td>
<td>20.4</td>
<td>14.1−36.5</td>
<td>−</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>7.9</td>
<td>6.1−11.1</td>
<td>−</td>
</tr>
<tr>
<td>Discontinuation due to intolerability</td>
<td>20.4</td>
<td>13.4−47.5</td>
<td>9.2, 5.4−36.9</td>
</tr>
</tbody>
</table>

Correll et al, 2010
Weight gain during first 11 weeks of Rx

<table>
<thead>
<tr>
<th>% of baseline</th>
<th>N= 41</th>
<th>45</th>
<th>36</th>
<th>135</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age:</td>
<td>13.9 + 3.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Correll et al, 2009

Treatment of Early Age Mania Study

- N=279
- Mean age= 10.1 ± 2.8y, 50% female
- 8 weeks of treatment
- Randomized to
  - lithium (mean level= 1.09 mEq/L) vs.
  - divalproex sodium (mean level= 113.6 μg/mL) vs.
  - risperidone (mean dose= 2.57 mg/day)

Geller et al, 2012
Clinical Global Improvement for Mania Scores at endpoint

Compared to other treatments, risperidone caused increased:

- weight gain
- BMI
- prolactin

Geller et al, 2012

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Clinical Characteristics

- Mania characteristics
  - Mean age mania onset: 5.2 ± 2.6 y
  - Mean mania episode duration: 4.9 ± 2.5 y
  - # lifetime manic episodes: 1.01 ± 0.08
  - Mixed mania: 97.5%
  - Daily rapid cycling: 99.3%

- Comorbid illnesses
  - ADHD: 92.8%
    - 32.3% receiving stimulant monotherapy at enrollment
  - ODD: 90.0%
  - Anxiety disorders: 71.3%

Geller et al, 2012
Adjunctive family-focused treatment for adolescents with bipolar disorder

21 sessions in 9 months
psychoeducation, communication and problem solving skills training

No difference in time to recovery from index episode or to recurrence
Faster recovery from depression, less depression over 2 years

Miklowitz et al, 2008

Treatment of severe irritability
Irritability Treatment Algorithm

Step 1: Chronic or Episodic Irritability

Step 2*: ADHD or ODD? Yes

Step 3*: Anxiety or Subthreshold Depressive Symptoms? Yes

Step 4:

Evaluate for Bipolar Disorder or MDD and treat according to guidelines

Stimulant according to ADHD guidelines

Partial/no response for irritability

Reassess diagnosis

SSRI

Partial/no response for irritability

Augment with Atypical Antipsychotic, α-Agonist, or Anti-Manic Agent

Hulvershorn and Dickstein, 2011
Meta-analysis of efficacy of stimulant Rx on overt and covert aggression

• Included 28 studies, total N=638

• Effect size (Cohen’s d)
  • $d=0.84$ for overt aggression (included rage attacks, irritability)
  • $d=0.69$ for covert aggression

Connor et al, 2002

Response to methylphenidate in children with ADHD and manic sx’s vs. ADHD alone

Teacher’s aggression rating

Methylphenidate dose

Galanter et al, 2003
Stimulant treatment for disruptive behavior disorders in youth

Ipser and Stein, 2007

Irritability Treatment Algorithm

Hulvershorn and Dickstein, 2011
Irritability in Anxiety Disorders, SMD, and BD

Stoddard et al, unpub

Anxiety diagnoses (%) in BD and SMD
Fluoxetine Rx of adults with IED

- **N=65 FLX, 35 PL**
- **77% male**
- **Age: 36.8 ± 8.7 y**
- **58% hx mood d/o**
- **12 weeks Rx**
- **20-60 mg/d**

Coccaro et al, 2009

Fluvoxamine-induced activation

- **N=22**

Reinblatt et al, 2009

**FIG. 2.** The Kaplan–Meier estimate of the incidence of AC-AEs by week of fluvoxamine treatment. AC-AEs = Activation cluster–adverse events.

1. Activation: Activated, disruptive, activation, animated;
2. Disinhibition: Disinhibited, doing things they wouldn’t normally do, disinhibition, aggression or outburst;
3. Hyperactivity: Hyper, hyperactivity, increased energy.
**SSRI-associated activation vs. manic switching**

- Activation: “too much of the same old child”
  - Increased activity level

  VS.

- Manic switching: “he has never been this way before”
  - Onset of new mood symptoms and behavior, vegetative signs

- Management:
  - Activation: lower dose, increase more slowly, different SSRI
  - Mood stabilizer, atypical antipsychotic

 walkup and labellarte, 2001

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**Why does it matter whether SMD is a form of BD?**

- Treatment!!!

- If SMD = BD, then antipsychotic medication, anticonvulsants

- If SMD = ADHD + anxiety and/or depression, then stimulants and SRI’s (ongoing trial)
Rationale for stimulant + SSRI trial in SMD

• High rate of anxiety disorders and ADHD in SMD

• As youth with SMD mature, increased risk for anxiety and MDD

• Evidence for efficacy of stimulants for both ADHD sx’s and aggressive sx’s

• More benign side-effect profile than antipsychotic medication

Citalopram + MPH vs. Placebo + MPH: Clinical Trial
Irritability Treatment Algorithm

Hulvershorn and Dickstein, 2011

SMD Lithium RCT: CGI-I

Dickstein et al, 2009
**Stimulant plus divalproex vs. placebo in ADHD + aggression**

All received concurrent behaviorally oriented psychosocial Rx
Mean age = 8.4 ± 2.0 years

Blader et al, 2009

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**Trends in Antipsychotic Prescribing 1993-2009 (Olfson et al., 2012)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR</th>
<th>95% CI</th>
<th>p value Age gp x time interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatrists</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Youth</td>
<td>6.58</td>
<td>4.04-10.72</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adults</td>
<td>2.52</td>
<td>1.87-3.39</td>
<td></td>
</tr>
<tr>
<td>Mood Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Youth</td>
<td>11.01</td>
<td>5.96-20.33</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adults</td>
<td>3.70</td>
<td>2.76-4.97</td>
<td></td>
</tr>
<tr>
<td>No mood disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Youth</td>
<td>6.56</td>
<td>3.74-11.51</td>
<td>0.0002</td>
</tr>
<tr>
<td>Adults</td>
<td>2.08</td>
<td>1.64-2.64</td>
<td></td>
</tr>
<tr>
<td>No psychotic disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Youth</td>
<td>9.75</td>
<td>5.99-15.86</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adults</td>
<td>3.86</td>
<td>3.05-4.88</td>
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</table>
Summary

• Severe non-episodic irritability (SMD) differs from BD in:
  • longitudinal course: unipolar depression, anxiety in SMD
  • family history

• BD diagnosis should be reserved for youth with episodic sx’s.

• Treat the underlying illness. Stimulants and SRI’s not necessarily contraindicated.
DO YOU HAVE A CHILD WITH Bipolar Disorder or Severe Irritability?

1) BD 2) SMD 3) at risk for BD

Rx study for SMD

Non-treatment studies (e.g., scans) for all

CAUSES OF BIPOLAR DISORDER
Participant Criteria:
- Age 6-17 with bipolar disorder
- Able to perform research tasks that include neuropsychological testing

CAUSES OF SEVERE IRRITABILITY
Participant Criteria:
- Ages 3-17
- Have irritability symptoms that include difficulty handling frustration (severe temper tantrums and rage) and "hyper" behavior (inattentive, hyperactive, trouble sleeping)
- Able to perform research tasks that include neuropsychological testing

References


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