

Pediatric Mood Dysregulation: Irritability, Disruptive Mood Dysregulation Disorder, and Bipolar Disorder

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Today's agenda

- Irritability
- Disruptive Mood Dysregulation Disorder
- Severe Mood Dysregulation
- Pediatric Bipolar Disorder
 - Yes, its controversial and rare, but it does exist
 - DSM 5 diagnostic criteria
 - Assessment
 - Medication and non-medication treatments
 - Take home message

Key Points in Today's Presentation

- Irritability and/or “mood swings” don’t equal pediatric bipolar disorder (PBD). Irritability (a potential presenting complaint in bipolar mania) is a non-specific, common symptom present in many childhood psychiatric illnesses.
- Multiple factors have led to a significant increase the diagnosis of PBD, leading to inappropriate prescribing of medications (e.g., antipsychotics) with serious side effect burdens.
- NIMH research has worked to clarify unique neurobiological substrates and clinical courses in youth presenting with *chronic* vs. *episodic* irritability
- PBD, while a “zebra” and not a “horse” does occur in youth, especially in the context of a strong family history.
- **Youth presenting with acute mania, ideally, should be referred for hospitalization and to specialists, such as child and adolescent psychiatrists (CAPs).**

Irritability

For mental health providers, our
version of “fever” in children with
psychiatric issues

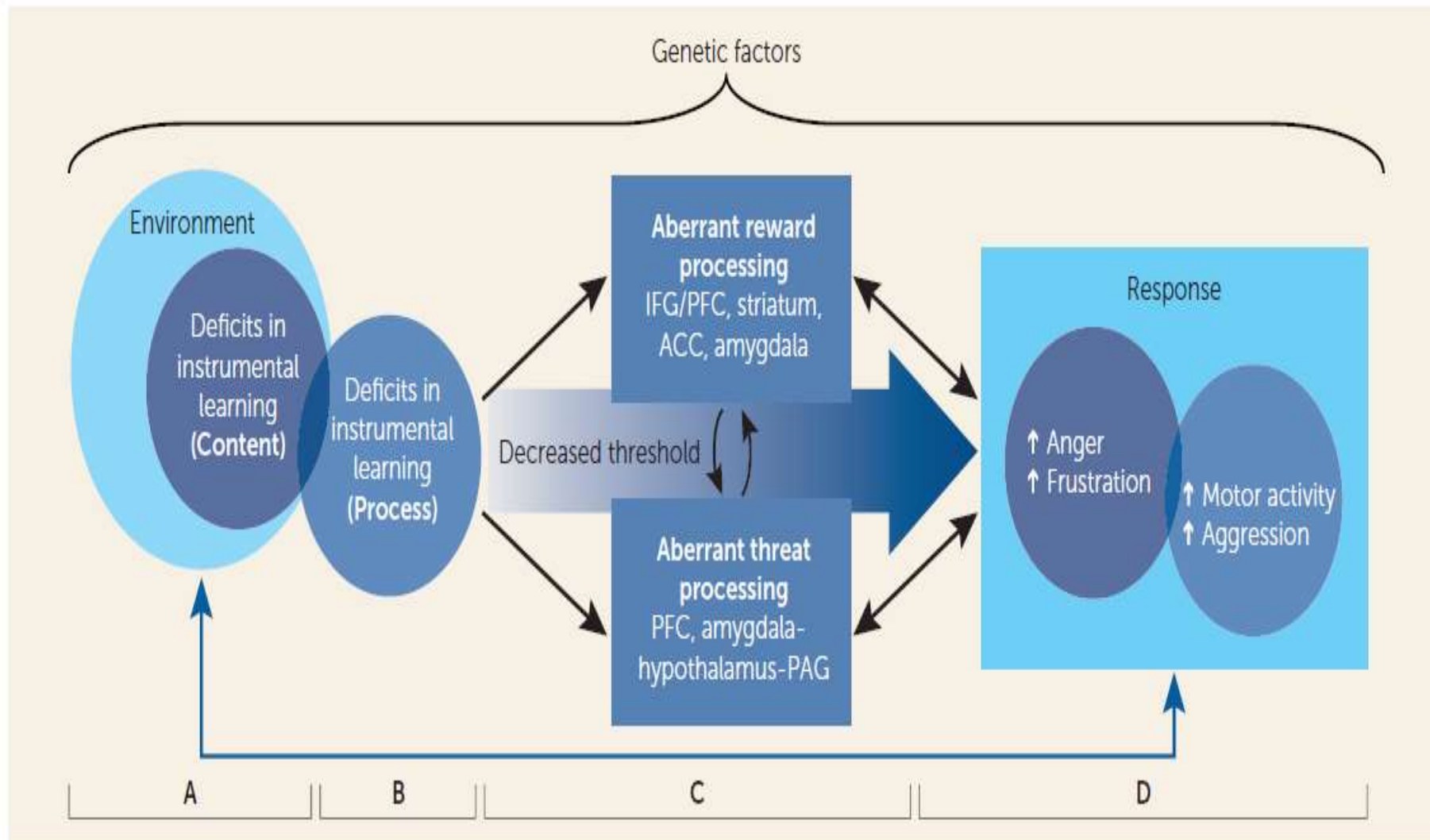


What's Up With All the Irritability?

- Irritability can be defined as an elevated proneness to anger relative to peers
- Involves dysfunction of reward system: **frustrative non-reward** and threat system: **bias toward perception of environmental threats and relative default to fight/attack** (versus freezing or fleeing), which leads to maladaptive emotional and behavioral responses
- These two systems, when dysfunctional, can potentiate each other in situations where both frustrative non-reward and perception of threat exist
- Neural substrates such as PFC, striatum, amygdala, etc. are implicated

What Going On in My Kid's Brain?

FIGURE 1. Pathophysiological Model of Irritability in Youths, Emphasizing Aberrant Reward and Threat Processing^a



Differential Diagnoses With Mood Dysregulation & Irritability

- Bipolar Disorder
- Depression (esp. kids)
- PTSD
- Anxiety/OCD
- ODD
- Conduct Disorder
- Substance Use
- ASD rigidity
- Attachment Disorder
- Borderline Personality Disorder/Traits
- ADHD with emotional lability
- Complex Developmental Trauma
- DMDD



But There Are Ways to Tease This Apart

Disorder	ADHD with emotional lability	ODD	Disruptive Mood Dysregulation Disorder	Depression	Bipolar Disorder
Definition	ADHD + problems with mood regulation	Angry/Irritable Argumentative/ Defiant/Vindictive	Recurrent temper outbursts Persistently irritable and angry between outbursts	Depressed mood, loss of interest, irritable mood, poor sleep	BP I: Mania BP II: Mania + Depression BP Other Specified BP Unspecified Cyclothymia
Mood Quality	Easily irritated , low frustration tolerance, excitable	Irritable Loses temper Easily annoyed Angry and resentful	Persistently irritable or angry mood Extreme temper outbursts	Irritability (in kids) or depressed mood for most of the day	Persistent elevated, expansive, or irritable mood
Typical Age of Onset	Same as ADHD: preschool to school-age	Bimodal: early onset with ADHD or later onset during adolescence	By definition, should not be diagnosed before 6 but should be present by 10 yrs of age	Early to late adolescence	Mid to late adolescence
Associated Features	Distractible, over-active, impulsive, poor sleep at times	Difficult temperament, low frustration tolerance, substance use	May co-occur with ADHD with depressive disorders	May present with psychosis	Increase in energy, decreased need for sleep, grandiosity, distractibility, risk taking behavior
Prevalence	38 to 75% of kids with ADHD	2% to 16%	1-3% ??	11 percent of youth by age 18	1-6%
Exclusions	Cannot occur exclusively during psychosis	Concurrent DMDD	Concurrent ODD (if both, choose DMDD); and BPD	Cannot have a history of (hypo) mania	Substance-induced BPD; and due to medical condition

Chronic versus Episodic Irritability

Objective: Test validity of distinction between chronic and episodic irritability. (Central debate in pediatric bipolar)

Method: Community sample of 776 children and adolescents interviewed at 3 points in time (T0, T2y, T7y). Irritability rating scales used to tease out chronic versus episodic irritability. Association with age, gender and diagnosis were examined.

(Liebenluft et al, 2006)

Irritability and Later Psychopathology

Chronic irritability at T1 - associated with ADHD at T2 and depression at T3

Episodic Irritability – associate with simple phobia at T2 and mania at T3

Conclusions:

- Episodic and chronic irritability are distinct constructs.
- Episodic irritability is associated with bipolar disorder and confers higher risk of future manic episodes than chronic irritability.

(Liebenluft et al, 2006)

Chronic vs Episodic Irritability

Those with *episodic* irritability were more likely than those with *chronic* irritability to have:

- A parent diagnosed with Bipolar Disorder
- Experienced elation and/or grandiosity
- More symptoms of mania
- Psychotic symptoms
- Had a depressive episode
- Made a suicide attempt

(Liebenluft et al, 2006)

Disruptive Mood Dysregulation Disorder

Symptoms in search of a
diagnosis



Disruptive Mood Dysregulation D/O

- A. **Severe recurrent temper outbursts** manifested verbally and/or behaviorally that are **grossly out of proportion** in intensity or duration to the situation or provocation.
- B. Temper outbursts are **inconsistent with developmental level**.
- C. Temper outbursts occur, on **average, $\geq 3X$ per week**.
- D. The mood between temper outbursts is persistently irritable or angry most of the day, nearly every day, and observable by others
- E. Criteria A-D have been **present for ≥ 12 mo.** Throughout that time, the individual has not had a period ≥ 3 consecutive months without all of the symptoms in A-D.
- F. Criteria A and D are present in at least **two of three settings** and are severe in at least one of these.
- G. Dx should not be made 1st before age 6 or after age 18.
- H. Age at onset of Criteria A-E is **before 10 years**.

Disruptive Mood Dysregulation D/O

- I. There has **never** been a distinct period lasting more than one day during which the full symptom criteria, except duration, for a **manic or hypomanic** episode have been met.
- J. The behaviors do **not** occur exclusively during an episode of **major depressive disorder** and are not better explained by another mental disorder.
- K. The symptoms are not attributable to the physiological effects of a substance or to another medical or neurological condition.

Note: This diagnosis cannot co-exist with Oppositional Defiant Disorder or Bipolar Disorder, though it can co-exist with ADHD, Conduct Disorder, and Substance Use Disorders.

BTW, How Did We Get DMDD as a New Diagnosis?



Severe Mood Dysregulation (SMD)

- Clinical syndrome *not* a diagnosis (3.3% lifetime prevalence ages 9-19)
- Served as research framework for DMDD
- “chronically irritable children whose diagnosis is in doubt.” (This is the type of kid, who would previously, but hopefully less frequently now, is diagnosed with Bipolar, NOS)
- IS real and confers risk of psychopathology down the line, but NOT for bipolar disorder
- Presence of SMD increases risk of depressive disorder and GAD at 20 year follow-up.

Core Features of SMD

- Chronic: persistent symptoms; no distinct episodes of mania
- Unusually intense, frequent, prolonged negative reactivity (e.g., temper tantrums) to negative emotional stimuli $\geq 3x/wk$
- Baseline mood between tantrums: anger/sadness
- 3 or more ADHD-like “Hyperarousal” symptoms: insomnia, agitation, distractibility, racing thoughts or flight of ideas, pressured speech, and intrusiveness.
- Very impairing

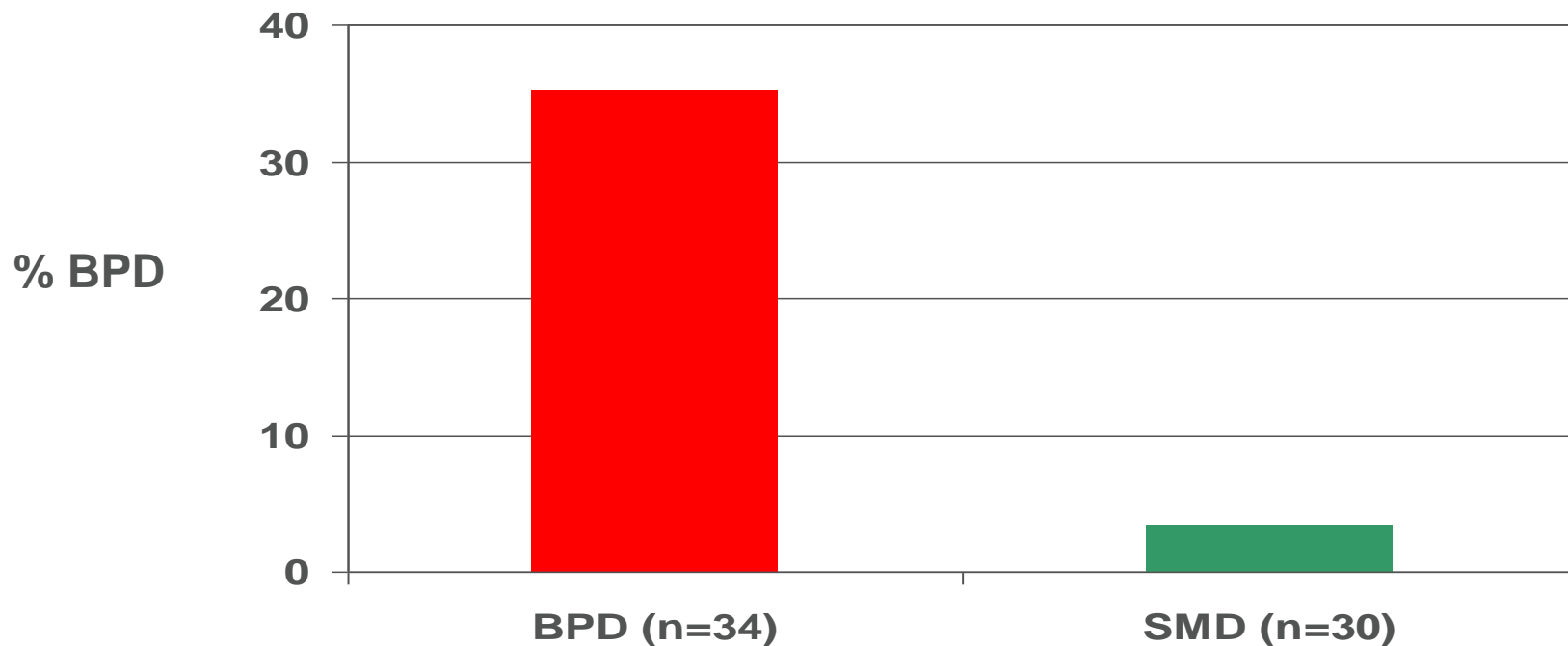
SMD Definition (Leibenluft)

- Age 7-17, onset by 12
- Anger or sadness at least half day most days
- Hyperarousal Symptoms (differs from DMDD)
- Increased reactivity to negative emotional stimuli (tantrum, rage, aggression)
- 12 months in length
- Multiple settings (1 severe)
- No cardinal Bipolar Sx:
 - expansive mood, grandiosity, episodic sleep deficits

Is SMD related to Bipolar ?

- Follow-up studies of SMD from age 10 to 18 generally show subsequent incidence of MDD at age 18 far more than BD
- Another study showed that after an average of 2.4 years, only 1.2% of SMD patients experienced a manic episode, compared to 62.4% of patients with BD
- Parental history for Bipolar far greater in BD group (33%) than SMD group (2.7%)

Data from the Smokey Mountain Cohort: Parents of BPD youth more likely to have BD than are parents of SMD – children



OR 15.82, CI 1.91-130.98, p=.01; Chi-square p<.01

Can SMD Be Treated?

- National Institute of Mental Health (NIMH)
A Controlled Trial of Serotonin Reuptake Inhibitors Added to Stimulant Medication in Youth With Severe Mood Dysregulation
- This study will evaluate the effectiveness of the stimulant medication methylphenidate (MPH) when combined (or not combined) with the antidepressant citalopram (Celexa) in treating symptoms of SMD in children and adolescents

“Not-Bipolar” Take-Home Message #1

- The diagnosis of bipolar disorder should be reserved for children who have clear episodes of mania.
- Elation during mania is common in children with bipolar disorder, so be skeptical of presentations with only a history of irritability, especially if the parent report is that irritability is a baseline condition
- Children with severe, chronic irritability and “hyperarousal” are at high risk for major depression or anxiety disorders, not necessarily bipolar disorder.

“Not-Bipolar” Take-Home Message #2

- Currently, there is no single diagnosis for chronically dysregulated or irritable kids. Evidence is more suggestive of current *and/or* future depressive or anxiety disorders
- Kids with severe, non-episodic irritability differ from those with bipolar in course, family history, and research findings
- Still a major role for parent support/training and mental health support. These are ill kids, who can be draining and are high risk
- There can be a role for medications to decrease maladaptive aggression and affective instability

Pediatric Bipolar Disorder

Horses move over, bring on the
Zebra



But First a Little More About the Controversy



Bipolar Is (maybe was) A Hot Topic

- Bipolar disorder in kids is/has been much talked about
 - “Child Anxiety Illness” on Google
 - About 31,000,000 hits in 2014 down to 28.7 million on 1/14/2018
 - “Child Bipolar Illness” on Google
 - About 40,100,000 hits down to 6.3 million on 1/14/2018
(French, 3/26/2014)
 - Child anxiety disorders are actually about 10 times more common than child bipolar disorder
- 40 fold increase in office visits for child bipolar disorder from 1994 to 2003 (Also 40-fold increase in diagnosis.)

National Center for Health Statistics

Frequency of Childhood Bipolar

- Very controversial
- Some popular books by well established clinicians assert a very high incidence
 - “The Bipolar Child” by Papolos and Papolos
 - Assert 1/3 of all children with ADHD
 - States about 6% of all children are bipolar
 - “Is Your Child Bipolar” by McDonnell and Wozniak
 - States more than 3 million US kids have it
 - Based on their estimates, incidence is 4%.

Bipolar Disorder Frequency Depends On Where You Look

- Prevalence of “true” adolescent bipolar
 - 0.6% of high school students
 - **1% in general outpatient practice**
 - 6 % of child psychiatry outpatients
 - 22% incarcerated adolescents
 - 26-34% of child psychiatry inpatients presenting with manic symptoms
(1996-2004 CDC survey of discharge diagnosis)

Youngstrom et al, CAPC Vol 18

Quoted Child Rates Don't Match Our Adult Knowledge

- Adult Lifetime prevalence rates of bipolar disorder 1 to 2%
- Greater diagnostic certainty with adults
- Bipolar disorder is a lifelong diagnosis – need plausible explanation of what happens to these kids if pediatric bipolar is 3-6X > adult bipolar
- Lessons from Great Smoky Mountain data set
 - child bipolar NOS ≠ bipolar adult
- **Kids with bad mood swings cannot all have “true” bipolar disorder**

Why is diagnosis so challenging?

- Symptom overlap + high rates of co-morbidity
- Confounding developmental issues
- Environmental influences
- Limited ability of (many) children to verbalize emotions
- Many different “expert” opinions
- Influence of popular media/pharmaceutical industry
- Requires extensive history – assessment of both current symptoms and past episodes (subject to recall bias)

Rapid Cycling Controversy

- Typical adult pattern is episodic. Rapid cycling is rare in adult bipolar populations
- Kids are more reactive and more common to get story of “rapid cycling”
- Consider “rapid cycling” in kids if there is no trigger identifiable for the mood changes
- Where many “episodes” become static, chronic mood state is controversial.
- ADHD plus irritability should not generate a bipolar diagnosis
- Youth with BP do spend more time cycling and have more changes in mood polarity than adult populations. (Birmaher et al, 2006)

DSM 5 Bipolar Diagnostic Criteria



DSM-5 defines a manic episode as:

- “A **distinct period** of abnormally and persistently elevated, expansive, or **irritable mood**, and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary).” Manic symptoms include inflated self-esteem or grandiosity, decreased need for sleep, rapid pressured speech, flight of ideas, racing thoughts, or excessive involvement in activities that have a high potential for painful consequences

DSM-5 defines hypomania as:

- A episode similar to a manic episode, except the episode is not severe enough to cause a marked impairment in social or occupational functioning. Mood and functional disturbances are observable to others, and minimum duration of symptoms is 4 days

DSM-5 Bipolar and Related Disorders

To enhance the accuracy of diagnosis and facilitate earlier detection, Criterion A for manic and hypomanic episodes now requires, not only persistently elevated, expansive, or irritable mood, but also **persistently increased goal-directed activity or energy**

DSM-IV diagnosis of Bipolar I Disorder, mixed episode, has been removed. Instead, “**with mixed features,**” has been added as a specifier; applied to episodes of mania or hypomania when depressive symptoms exist, & vice-versa

Other specifiers:

With Anxious Distress

With Melancholic Features

With Seasonal Pattern (Seattle?)

With Rapid Cycling (4 in 1 yr)

DSM-5 Bipolar and Related Disorders

“Other Specified Bipolar and Related Disorder”

Specify particular conditions for other specified bipolar and related disorder, including categorization for individuals with a past history of a major depressive disorder who meet all criteria for hypomania except the duration criterion (i.e., at least 4 consecutive days).

A second condition may be that too few symptoms of hypomania are present to meet criteria for the full bipolar II syndrome, although the duration is sufficient at 4 or more days.

Other Specified Bipolar and Related Disorder

- Recurrent hypomanic episodes w/o depressive symptoms
- Short-duration (< 4 days) hypomanic episodes and MDE
- Short-duration cyclothymia (less than 24 months in adults and 12 months in children)
- You document this by specifying “Other...” and then the reason (e.g., “short-duration cyclothymia”)

Unspecified Bipolar and Related Disorder

- Patient presents with symptoms characteristic of a bipolar disorder and related disorder that causes significant impairment, but does not meet full criteria for any of the disorders in the bipolar diagnostic class
- Unlike as is done in the “Other Specified Bipolar and Related Disorder,” here the clinician chooses not to specify the reason the criteria are not met
- Recommended for presentations where there is insufficient information to make a more specific diagnosis (e.g., emergency room setting)

Unspecified (Formerly: Bipolar Disorder, NOS) BD

- Contributes to the bipolar “epidemic”
- Label often given to impulsive, aggressive kids with pervasive irritable mood
- Prognosis could be normal, MDD, or (rarely) true bipolar
- Diagnosis confused with:
 - ADHD
 - Depression
 - Abuse (current and PTSD)
 - Anxiety Disorders
 - Disruptive Behaviors Disorders (ODD irritable subtype)
 - Reactive Attachment Disorder
 - Intermittent Explosive Disorder

Why are/were these unspecified/NOS Bipolar, NOS so commonly used?

- Broad category/catch-all
- Only recently another more suitable diagnosis that captures complex behavioral picture (SMD, DMDD)
- Sounds better to us than “I don’t know”
- Justifies the medication treatment options
 - If we give a child medicine as if bipolar, parents often report improvement
- Bipolar medicines have many non-specific effects
 - All can potentially decrease impulsivity and aggression

However, Some Youth with BPD, NOS Will Transition To Bipolar I or II Over Time

- 140 children who met operationalized criteria for BP-NOS
- Diagnostic conversion to BP-I or BP-II occurred in 63 subjects (45%)
- Median time from intake to conversion was 58 weeks
- First- or second-degree family history of mania or hypomania was the strongest baseline predictor of diagnostic conversion ($p .006$)
- Children and adolescents referred with mood symptoms that meet operationalized criteria for BP-NOS, particularly those with a family history of BP, frequently progress to BP-I or BP-II

Axelsson DA et al. J. Am. Acad. Child Adolesc. Psychiatry, 2011;50(10):1001–1016

What to Look For When Considering Bipolar as a Potential Diagnosis?



What To Do?

- What role should a primary care provider take regarding the question of child bipolar disorder?
 - Psychoeducation?
 - Referral?
 - Treatment?
- How do you assess for childhood bipolar disorder?
- When does it make sense to...
 - Wait?
 - Prescribe a mood stabilizer?
 - Refer to a therapist?
 - Refer to a (child and adolescent) psychiatrist?

Diagnostic Perspective

- Experience with adult mania helps but can be challenging to translate to kids
- Compare child to a prototypic “manic” patient
 - Pressured speech -- not just talkative
 - Having no doubt about their grandiose ideas -- impaired reality testing/lack of insight)
 - Thought process is fast and jumping around
 - *Episodes* that most commonly last days *not minutes or hours*
 - Little *need* for sleep (versus poor sleep.)

Look for “Hallmark” Symptoms

- Increased specificity
- More likely bipolar...
 - Elation
 - Hyperactivity
 - Grandiosity
 - Hypersexuality
 - Decreased need for sleep

What about Family History?

- Mom says she has been diagnosed with bipolar and his uncle is bipolar, “just like him”
- Avoid overcalling a positive family history
 - many adults who call themselves bipolar may not have that illness
 - first degree relative bipolar disorder, increases OR by 5
 - second degree relative bipolar, increase OR by 2.5
 - given a generous prevalence of 2% bipolar in the population, most children of a bipolar parent (~90%) will not have bipolar disorder

Youngstrom E & Duax J, JAACAP 44:7, 2005

Look for Episodes and Patterns

- Individual episodes represent a *clear departure from baseline* with hallmark symptoms
- Hopefully, the presence of hallmark symptoms will help distinguish irritable mania from irritability due to other causes
- The correct mood diagnosis (and treatment) requires establishing the pattern of mood episodes, not just presenting (current) episode

Remember to keep your differential broad. Consider the large differential for each of these Mania symptoms in kids:

- **D**istractable
- **I**ndiscretions/risk taking
- **G**randiose
- **F**light of ideas/racing thoughts
- **A**ctivity (goal directed) increase
- **S**leep need decreased
- **T**alkative (pressured speech)

Which can mimic ADHD symptoms, for example?

Manic symptoms versus ADHD (Kowatch et al, 2005)

<u>Symptom</u>	<u>ADHD</u>	<u>PBD*</u>
Irritability	72%	98%
Accelerated Speech	82%	97%
Distractibility	96%	94%
Unusual Energy	95%	100%

* Pediatric Bipolar Disorder

Bipolar Assessment--questions

Question	Relevance	Flag?
Is there a confirmed history of BPD in a parent or (twin) sibling?	14-85 % that patient will develop a BPD disorder	Red
Is there a history of increased energy and decreased need for sleep?	This could represent a history of hypomania	Yellow
Is there a history of episodic irritability?	Without evidence of clear environmental trigger and with evidence of additional cardinal changes from baseline, this could represent a risk for BPD	Yellow
Is there evidence of chronic irritability only?	Research indicates that these patients are more likely at risk for a depressive or anxiety disorder?	No
Does the patient have a history of early onset depression or have a history of previous psychotic symptoms presenting early in the course of a depressive illness?	May increase likelihood of developing bipolar	Yellow
Does the patient have any evidence of irritability, activation, or intolerability of previous trials on SSRIs	Could any of these responses to an SSRI trial represent "switching?"	Yellow
Is there a seasonal pattern to previous mood/depressive episodes?	Does this represent episodic mood disturbance consistent with BPD, especially if there is some evidence of hypomania/irritability during seasonal swings?	Yellow

Bipolar Diagnostic Aides

- Rating Scales
 - Young Mania Rating Scale
 - Useful for monitoring symptoms over time
 - *Not* a diagnostic tool (very low specificity)
 - DISC or KSADS
 - Used in research, have flaws
 - Impractical for your office practice
- Rating scales are too misleading to recommend for diagnostic use and are intentionally excluded from the PAL guide

Looking back at adult bipolar....

- Several studies have asked adults with bipolar about onset of their symptoms *retrospectively*
- Bipolar adults look back and note symptoms became bipolar-like in their teen years (50-66%)
- Many bipolar adults had major depression episodes as children
- The younger the child's first major depression, the more likely bipolar disorder is in the future

Bipolar Treatment



What if a “Bipolar” Child Really is Bipolar?

- Though rare in a PCP practice, becomes more likely the older the child.
- Typical pattern is early onset depression, and during teenage years getting first symptoms of mania.
- Expect mood “episodes”. COBY study established validity of episodic course.
- Assemble a team. Real deal bipolar disorder is a big problem and requires multi-modal treatment.

Course Of True Bipolar Disorder

- **If clearly manic, strongly recommend hospitalization and/or referral to CAP**
- Suicidalilty
 - *up to 15% eventually complete suicide*
- Substance Abuse in up to 60%
- Anxiety disorders in up to 50%
- Psychotic features in up to 50%
- Relationship Disruptions
- Work Disruptions
- Hospitalizations

Stern TA and Herman JB, 2004;

Brent et al, 1988, 1993

Bipolar Treatment

- **If clear manic episodes, strongly recommend referral to child psychiatrist**
- Management difficult because:
 - High rate of substance abuse
 - High rate of medication non-compliance
 - Even with medication, recurrences happen
 - High rates of family disruption from the illness
 - Suicidal behavior is common

If No Child Psychiatrist Can Assume Care, Then What?

- Get collateral information to help establish correct diagnosis
 - Strongly advise against rushing to offer diagnosis of bipolar disorder.
 - This may require separate/designated appointment(s) with caregivers and/or patient to get sufficient history
- Seek consultant advice on medication (PAL)
- Advocate for multimodal care
 - Specialist for medication management
 - Parent/caregiver involvement
 - School support (IEP if attendance/performance impacted)
 - Individual support

Bipolar Treatments

(for when you are left holding the bag)

- Medication management (acute and maintenance)
- Safety monitoring and crisis planning
- Individual Support (symptom management, coping skills, adherence monitoring, psychoeducation)
- Family support (psychoeducation, risk assessment/response, adherence/relapse prevention)
- Lifestyle coaching and support (stress mitigation, sleep hygiene, drug/alcohol risks, exercise, interpersonal and social rhythm therapy)

Resources for Non-pharmacologic Interventions

- **Boris Birmaher, MD:** *New Hope for Children and Teens with Bipolar Disorder*. Three Rivers Press, New York, 2004
- **David Miklowitz PhD:** *The Bipolar Disorder Survival Guide, 2nd edition*. The Guilford Press, 2011
- **Ellen Frank PhD:** *Treating Bipolar Disorder: A Clinician's Guide to Interpersonal and Social Rhythm Therapy*. The Guilford Press, 2005
- **Mary Fristad PhD:** www.moodychildtherapy.com
- **Interpersonal and Social Rhythm Therapy:** <https://www.ipsrt.org/>

Bipolar Medications



Classes of Medication

- “Mood Stabilizers”
 - Antipsychotic Medications
 - Anticonvulsants (AEDs)
- Depression Medications (SSRIs, SNRI)
- Sleep Aides

What Is A Mood Stabilizer?

- Includes both atypical anti-psychotics and anti-epileptic drugs (AEDs)
- Generic term – clarify what *they* mean when taking history and what *you* mean when proposing treatment.
- FDA does not recognize this term
- As relates to treatment of bipolar disorder, ideally treats both depressive and manic episodes as well as prevents recurrence of mood episodes.
- Since no one compound does this well, multiple meds are often used together (but little evidence base to support it)

Mood Stabilizers are Non-Specific to PBD

- Maladaptive aggression
 - Intellectual Disability (lithium, risperidone)
 - Autism (risperidone, aripiprazole)
 - Conduct Disorder (risperidone, valproic acid, lithium)
 - ADHD with impulsive aggression (risperidone)
- Seizure Disorders – kindling hypothesis; neuroprotective effects in mood disorders (lithium)
- Depression (aripiprazole, quetiapine, lamotrigine)
- Psychosis (primary, mood disorder, delirium)
- OCD (refractory)
- PTSD (intrusive thoughts)

Bipolar Medications—Pearls


- Look for a family history of positive response to a specific medication/medication class
- Classic mania: Acutely: Lithium +/- neuroleptic; add neuroleptic if severe mania and need quick response and/or if the patient is psychotic and then try to remove neuroleptic over time
- Mixed states/rapid cycling/seizure D/O: Depakote
- Bipolar depression: Lamictal; second choice Latuda
- BPD with severe agitation/anxiety: add BDZ or other anxiolytic
- Avoid SSRI if possible even when very depressed; if have to add: Wellbutrin
- Neuroleptic choices more mania : Risperdal > Abilify > Zyprexa = Seroquel
- Most kids will need to be on > 1 med to adequately treat.

Pharmacotherapy: Evidence-base

Medication	Bipolar I, Manic, Mixed, w/o Psychosis	Bipolar I, Manic, Mixed, w/ Psychosis
Lithium*	A	A
Divalproex*	A	A
Carbamazepine	B	B
Oxcarbazepine	A (no benefit)	C
Topiramate	B (trial discontinued)	B (trial discontinued)
Lamotrigene*	B	B
Risperidone*	B	B
Olanzapine	B	B
Quetiapine	B; D	B
Ziprasidone	B	B
Aripiprazole	B	ND

A=Placebo-controlled, randomized trials; B=Open child/adolescent trials and retrospective analyses; C=child/adolescent case reports or panel consensus; D=as adjunctive Tx; ND=no data; * Randomized clinical trials in progress

Second-Generation Antipsychotics (SGAs)



Atypical Antipsychotics in the treatment of Pediatric Bipolar

FDA approval for pediatric use:

- ◆ Acute Mania, ages 10 years and older
 - ◆ Risperidone, Aripiprazole, Quetiapine, Olanzapine (13 and older), Ziprasidone, Asenapine

Risks common to all Atypical Antipsychotics

(Correll, JAACAP. 2008)

- Sedation (olanzapine, quetiapine)
- Tardive Dyskinesia (0.4% annual incidence)
- Increased Cholesterol/ Triglycerides (olanzapine)
- Akathisia (aripiprazole) (youth<adults)
- Increase glucose (olanzapine, quetiapine)
- EPS (risperidone)
- Lower seizure threshold (mildly)
- QT interval change (~20ms for ziprasidone)
- Weight gain (olanzapine > quetiapine, risperidone >the rest)
- Neuroleptic Malignant Syndrome

SGAs: Adverse Effects



Common Side Effects (>10%)	Less Common Side Effects	Notable Rare Reactions (≤2%)
Weight gain Muscle rigidity Parkinsonism Constipation Dry mouth Dizziness Somnolence/fatigue	Tremors Nausea or abdominal pain Akathisia (restlessness) Headache Agitation Orthostasis Elevated glucose Elevated cholesterol/triglycerides	Tardive Dyskinesia Neuroleptic Malignant Syndrome Lowered blood cell counts Elevated liver enzymes Prolonged QT interval Tachycardia

SGAs: Monitoring



Monitoring recommendation	Frequency Suggestion
Height and weight	At baseline and at each follow-up (at least every 6 months)
Fasting blood sugar	At least every 6 months
Fasting triglyceride/cholesterol	At least every 6 months
Screen for movement disorder or tardive dyskinesia	At least every 6 months
CBC with Diff	Once to catch if any suppression, a few months after initiation
BP/Pulse	At least once after starting medication
Cardiac history	At baseline, get EKG if in doubt about risk from a mild QT increase
Determine if treatment response	Repeat disorder specific rating scale(s) until remission is achieved. Increase at 4-6 week intervals if insufficient benefit.

Atypical Heterogeneity

Relative receptor-binding affinities of atypical antipsychotics¹⁻⁴

	GEODON	Risperidone	Olanzapine	Quetiapine	Clozapine	Aripiprazole
D ₂	++++	++++	++	+	+	++++ (partial agonist)
5-HT _{2A}	+++++	+++++	++++	+	++++	++++
5-HT _{2C}	+++++	++++	++++	-	++	++
5-HT _{1A}	++++	+	-	+	+	++++
5-HT _{1D} [*]	++++	+	+	-	-	N/A
α ₁ -adrenergic [†]	++	++++	++	++	++++	++
M ₁ -muscarinic	-	-	++++	++	++++	-
H ₁ -histaminergic	++	++	++++	++++	++++	++
5-HT reuptake [‡]	++	-	-	-	-	+
NE reuptake [‡]	++	-	-	+	+	N/A

Affinity represented as: +++++ very high (K_i < 1 nM), ++++ high (K_i = 1-10 nM), ++ moderate (K_i = 11-100 nM), + low (K_i = 101-1000 nM), - negligible (K_i > 1000 nM).

Adverse and Therapeutic Effects of Occupancy and Withdrawal (Correll, JAACAP. 2008)

Receptor	Occupancy	Rebound/Withdrawal
Histamine H ₁	Anxiolytic, sedation, weight gain, anti-EPs/akathisia	Agitation, insomnia, anxiety, EPs
α ₁ -Adrenergic	Postural hypotension, dizziness, syncope	Tachycardia, hypertension
Muscarinic M ₁ (central)	Memory, cognition, anti-EPs/akathisia	Agitation, confusion, anxiety, insomnia
Muscarinic M ₂₋₄ (peripheral)	Dry mouth, constipation, urinary retention	Diarrhea, diaphoresis
Dopamine D ₂	Antipsychotic, antimanic, antiaggressive, EPs/akathisia, tardive dyskinesia, prolactin increase, sexual or reproductive system dysfunction	Psychosis, mania, agitation, akathisia, withdrawal dyskinesia
Serotonin 5-HT _{1A} (partial agonism)	Anxiolytic, antidepressant, anti-EPs/akathisia (?)	EPs/akathisia
Serotonin 5-HT _{2A}	Anti-EPs/akathisia	EPs/akathisia
Serotonin 5-HT _{2c}	Increased appetite/weight (?)	Decreased appetite (?)

Note: EPs = extrapyramidal symptoms.

Risperidone (Risperdal)

PROS

- QD-BID dosing ($T_{1/2} = 20$ hours)
- FDA for mania > 10 years old, irritability/aggression in ASD
- Multiple dosage forms (liquid, dissolving tab, tabs, depot)
- Low doses (<2 mg) adequate for non-specific aggression
- TD incidence reported less than 0.5%

CONS

- Weight gain and sedation common
- Hyperprolactinemia risk
- Relatively high rates of dystonic reactions/EPS

Aripiprazole (Abilify)

PROS

- QD-BID dosing ($T_{1/2}=75$ hrs) *but* kids may do better BID
- FDA for mania (>10 yrs) and limited RCT support
- Mixed agonist/antagonist (less dystonia/EPS)
- Often less sedation

CONS

- Limited dosage forms
- *Misperception* of less weight gain/metabolic SE
- Agitation/activation not uncommon
- Higher rates of akathisia
- Long $T_{1/2}$ -may take longer to see impact of changes

Quetiapine (Seroquel)

PROS

- Lower potency - may be experienced as “milder”
- FDA approval (>10 years old) limited RCT evidence
- Effective anxiolytic
- Cross indication for bipolar and unipolar depression

CONS

- Short half-life ($T_{1/2} = 6$ hours); multiple daily dose; mixed results w/ XR preparation
- Large tablets - may be hard to swallow
- Effective sleep aide (high risk, high cost sleep aide)
- Cataract risk

Olanzapine (Zyprexa)

PROS

- QD-BID dosing ($T_{1/2} = 30$ hours)
- FDA approval (> 13 years) and limited RCT evidence
- Multiple dosage forms (tablets, oral disintegrating, IM)
- Very effective for acute stabilization of mania and psychosis

CONS

- Weight gain (dose related, less of plateau than others)
- High rates of metabolic side effects
- Sedation common

Ziprasidone (Geodon)

PROS

- Often less sedating
- Most weight neutral
- Fewer metabolic side effects
- Unique receptor profile

CONS

- BID-QID dosing ($T_{1/2} = 7$ hrs)
- No FDA approval for pediatric mania
- No pediatric RCT support
- Concern for EKG changes has lowered its usage

Anticonvulsants and Lithium



Lithium

PROS

- FDA approved for mania >12 years
- Some evidence in refractory depression
- Anti-suicide properties
- Some EB dosing guidelines (adjust for age/GFR)

CONS

- Narrow therapeutic index (close monitoring for toxicity w/ illness/dehydration; no NSAIDs)
- Usually best in combination, so committing to polypharmacy if you start here (best w/ atypical or VPA)
- SE in therapeutic range similar to early toxicity (tremor, diarrhea)
- SE often limit use (weight gain, acne, GI); HS dosing can minimize
- Hard to predict who will respond
- No evidence for maintenance treatment /slow anti-manic effects

Lithium

- In adults, best documented treatment for classic “manic depressive illness”
- Open trials support lithium for pediatric bipolar, either as monotherapy or with other mood stabilizers or antipsychotics
- Risperidone more effective than lithium or valproate for pediatric mania (ages 6 – 15 years) (Geller et al., 2012)
- Lithium FDA Approved for Youth 12 years of age or older with Bipolar, based on adult literature

Valproic Acid (Depakote)

PROS

- Single daily dosing can be effective (Depakote ER)
- Can be useful for maladaptive/non-specific aggression
- Studies suggest helpful, usually in combination

CONS

- Requires blood draws (levels, LFTs, amylase, CBC)
- Risk of hepatotoxicity (highest in first 6 months)
- High side-effect burden (weight gain, GI, tremor, sedation, rash)
- Less ideal for females (risk of birth defects (NTD), PCOS)

Depakote

- How well does it work?
 - Fair, usually works best in adolescents in combination with an antipsychotic (better than either one alone)
 - Some RCT's have suggested that it works better than lithium on acute manic symptoms
 - Broad effects: also used for externalizing behavior disorders, conduct disorder
 - Lost in head-to-head trial with quetiapine
 - Similar long-term stabilizing effect to Lithium after stabilization with both divalproex and lithium

Carbamazepine (Tegretol)

PROS

- Some empirical supports for aggression
- 2 Open trials
- Similar response rates as Li and VPA (38%) (Kowatch et al, 2005)

CONS

- Drug/drug interactions (OCPs, Lithium)
- Blood draws to check levels (auto-induced metabolism)
- Weak evidence of benefit in bipolar (McClellan and Werry, 1997)
- Risk of aplasia and liver failure

Lamotrigine (Lamictal)

PROS

- Bipolar depression treatment
- Less sedation and lower side effect profile in general

CONS

- Not helpful for manic phase
- Requires monitoring of CBC and liver function
- Significant rash risk
- Slow titration (age >12)

Oxcarbazepine (Trileptal)

PROS

- FDA approval for adults bipolar disorder
- Weight neutral
- Less risks/side effects than carbamazepine
- Monitoring of levels not required

CONS

- Levels do not correlate well with efficacy or toxicity
- Negative adolescent bipolar trial (Cochrane Review. Vasudev *et al.* 2008)
- Hyponatremia not uncommon

Sleep Needs to Happen

The background of the slide is a solid teal color. In the bottom right corner, there is a decorative graphic consisting of several concentric circles and arcs made of small white dots, creating a pattern that resembles a stylized sun or a series of orbits.

Sleep Aides

- Lifestyle changes: limit caffeine, exercise, no drugs/alcohol
- Sleep hygiene education
- Melatonin (mild sleep aide, can help regulate sleep cycle)
- Anti-histamines
- Trazodone
- Benzodiazepines

In Summary.....



Bipolar Take-Home Message

- Diagnosis of bipolar disorder made with relative confidence in the presence of manic (Bipolar I) or hypomanic (Bipolar II) episodes. It gets tricky after that
- Mood episodes involve distinct *change from baseline* with alternations in behavior *and* evidence of impairment
- Bipolar diagnosis is a serious diagnosis that has a life-long course and many management challenges
- True bipolar has high rates of morbidity and mortality
- If suspected, strongly recommend involving a child and adolescent psychiatrist
- If you, as PCP, are playing central role in management, check-in frequently to monitor side effects of medication(s) and surveillance of mood symptoms

At PCP level, recommend....

- ...keeping in mind many possible causes of mood swings and irritability
- ...resisting temptation to label impulsive, difficult kids as “bipolar”
- ...reminding yourself and parents who are struggling that most disruptive, irritable children do *not* have bipolar disorder but can still benefit from help
- ...getting help with diagnostic and treatment questions as often as necessary

Selected Bibliography

- *Pharmacologic Treatments for Pediatric Bipolar Disorder: A Review and Meta-Analysis.* Liu et al. JAACAP. August 2011.
- *Practitioner Review: The Assessment of Bipolar Disorder in Children and Adolescents.* Baroni et al. JCPP. 2009.
- *Antipsychotic Use in Children and Adolescents: Minimizing Adverse Effects to Maximize Outcomes.* Correll. JAACAP. January 2008.