Irritable, moody kids: Could they have bipolar disorder, or DMDD?
Disclosures

- I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider of commercial services discussed in this CME activity.

- I will be discussing non-FDA approved use of medications in this presentation, which will be so designated on these slides.
A Patient

- 6 year old boy new to your practice
- ADHD diagnosed at age 4
- On and off stimulants for 2 years
  - methylphenidate and amphetamine
  - works for a while, then no help
  - has always been “moody” and “irritable”
- Struggling at school socially, but “really smart”
- Mom thinks he is bipolar
A Patient, continued

• Mom says she can’t control him at home
  ▫ Behaves a little better with mom’s boyfriend
• Mom just got diagnosed as bipolar, and medications have really helped her
• She asks you to prescribe “something” to treat his bipolar mood swings......
What To Do Now?

• What roles should a primary care provider take with question of child bipolar disorder?
  ▫ Diagnosis?
  ▫ Psychoeducation?
  ▫ Referral?
  ▫ Treatment?
Bipolar: A Hot Topic

• 40 fold increase in office visits for child bipolar disorder from 1994 to 2003
• No longer a stigmatized diagnosis
• Widely discussed
  ▫ “Child Anxiety Disorder”
    • About 19,000,000 Google hits
  ▫ “Child Bipolar Disorder”
    • About 25,000,000 Google hits

Yet child anxiety ~10 times more common than child bipolar

Google 3/15; and National Center for Health Statistics
Frequency of Childhood Bipolar

- Controversial
- Some popular books by well established clinicians assert a very high incidence
  - “The Bipolar Child” by Papolos and Papolos
    - States about 6% of all children are bipolar
  - “Is Your Child Bipolar” by McDonnell and Wozniak
    - Based on their estimates, incidence is 4%.
Child vs Adult Rates

• Adult Lifetime prevalence rates of bipolar disorder are 1 to 2%
• Bipolar disorder is essentially a lifelong diagnosis
• Kids with bad mood swings cannot all have “true” bipolar disorder

• UCLA Child Bipolar Clinic found only 18% referred with a “bipolar” diagnosis actually had a bipolar disorder (Weintraub et al 2014)
Why is Bipolar diagnosis so challenging?

- Symptom overlap
- High rates of co-morbidities
- Developmental issues
- Environmental influences
- “Expert” opinions differ
- Influence of popular media/drug industry
- Requires an extensive history taking to understand patterns
What is Mania?

• >1 week episode of irritable or expansive mood
• At least 3 of the following  (4 if only irritable mood)
  ▫ distractible
  ▫ indiscretions
  ▫ grandiose
  ▫ flight of ideas
  ▫ increased goal directed activities
  ▫ little need for sleep
  ▫ talkative
What DSM-5 changed about Mania

- Increased energy/activity sx. now required
  - Rationale: to improve the specificity of bipolar diagnosis

- Duration criteria are unchanged:
  - Manic symptoms > 1 week is Bipolar I
  - Manic symptoms <4 days is Bipolar II
    - No hospitalization or psychosis
The Other DSM-5 Bipolars

- “Other Specified Bipolar” (296.89) means too few mania symptoms to meet Bipolar II criteria, and the clinician states why

- “Unspecified Bipolar Disorder” (296.80) is the current term for Bipolar NOS
Some Bipolar child controversies

- Can children with extreme irritability and ADHD-like symptoms be considered bipolar?

- Can children with chronic (rather than episodic) mood symptoms be considered bipolar?
  - Adults with bipolar disorder have EPISODES of mania and depression

- Can children with irritability without elation be considered bipolar?
A few of the “irritable” disorders

- Bipolar disorder
- Rapid cycling bipolar
- Cyclothymic disorder
- Disruptive mood dysregulation disorder
- Severe mood dysregulation
- ADHD
- Depression
- ODD
- Conduct disorder
ADHD vs. Bipolar

• Three bipolar symptoms ≈ ADHD symptoms
  ▫ distractibility
  ▫ activity increase
  ▫ talkativeness
    • Just have to add in “expansive mood” and voila, you have a “bipolar” child

• This interpretation was one trigger for the bipolar diagnosis explosion in Boston
Manic symptoms versus ADHD
(Kowatch et al, 2005)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>ADHD</th>
<th>PBD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irritability</td>
<td>72%</td>
<td>98%</td>
</tr>
<tr>
<td>Accelerated Speech</td>
<td>82%</td>
<td>97%</td>
</tr>
<tr>
<td>Distractibility</td>
<td>96%</td>
<td>94%</td>
</tr>
<tr>
<td>Unusual Energy</td>
<td>95%</td>
<td>100%</td>
</tr>
</tbody>
</table>

* Pediatric Bipolar Disorder
Cyclothymic Disorder

• Recurrent episodes of hypomanic symptoms
• Never meet enough criteria to diagnose hypomania or depression
• Problems persist at least 12 months in children (24 months in adults)

  ▫ Up to ½ with this problem are diagnosed with bipolar disorder as adults
Intermittent Explosive Disorder

- Unplanned aggressive impulse dyscontrol
- Now only diagnosable above 6 years of age
- Greater definition of what is required to meet threshold
  - ODD: Aggression from argument/temper tantrum
  - CD: Some aggression is proactive/predatory
  - DMDD has the persistently negative mood state, should not be diagnosed along with IED
- Best treatment: still poorly defined
“Rapid Cycling” Bipolar Controversy

• 4 or more distinct, full criteria manic, hypomanic, or depressive episodes in < 1 year
  ▫ Rapid cycling pattern is rare in adults

• Kids are naturally more mood reactive, thus may hear a story of “rapid cycling”
  ▫ Rarely fits the actual definition above

• Consider “rapid cycling bipolar” in kids if:
  ▫ Mood episodes are sustained (not labile)
  ▫ No triggers identifiable for mood changes
Our Overlapping Terms Don’t Help

- Mood Instability
- Mood Swings
- Emotion Dysregulation
- Affective Dysregulation
- Mood Dysregulation
- Emotion Regulation
- Affective Lability
- Irritability
  - Components of many different disorders
Experts Debate Irritability and Mania

- **Geller:** Irritability has high sensitivity but poor specificity
- **Wozniak:** irritability may be primary mood symptom; episodicity not relevant
- **Hunt/Birmaher:** episodic irritability alone can represent mania; “irritable-only” mania exists but is rare
- **Leibenluft:** episodic irritability more suggestive of bipolar than chronic irritability
Chronic versus Episodic Irritability

- Community sample of 776 children and adolescents interviewed at 3 points in time
- Irritability rating scales used to tease out chronic versus episodic irritability.
- Chronic irritability
  - 2yr later associated with ADHD
  - 7yr later associated with depression
- Episodic Irritability
  - 2yr later associated with simple phobia
  - 7yr later associated with mania/bipolar

(Liebenluft et al, 2006)
Chronic vs Episodic Irritability

• Kids with episodes of irritability (rather than chronic) have a greater chance of:
  ▫ elation and/or grandiosity
  ▫ symptoms of mania
  ▫ psychotic symptoms
  ▫ depressive episodes
  ▫ suicidality
  ▫ A parent with Bipolar Disorder
Chronic irritability in youth predicting Major Depressive Disorder

- Chronic irritability at age 14 predicts MDD at age 22
  - OR= 2.29 (1.22-4.31) (Leibenluft et al, 2006)

- Oppositional defiant disorder at age 7 predicts MDD at age 18
  - OR=1.06 (1.01-1.10) (Burke et al, 2005)

- Familial association between MDD and disruptive behavior disorders (Weissman et al, 2005)
Defining that controversial group: “Severe mood dysregulation”

- A research construct from last decade
- Chronic: persistent sx’s; no distinct mania
- Irritable: reactivity to negative emotional stimuli
  - > 3x/wk, baseline anger/sadness
- 3 or more ADHD-like “Hyperarousal” symptoms:
  - insomnia, agitation, distractibility, rapid thoughts, pressured speech, and intrusiveness.
- Very impairing
Did SMD lead to Bipolar?

- Brief answer: no.
- Follow-up studies of SMD from age 10 to 18 generally show subsequent incidence of MDD at age 18 far more than Bipolar.
- Parental history for Bipolar far greater in Bipolar group (33%) than SMD group (2.7%).
- Another study showed that after 2.4 years, only 1.2% of SMD patients experienced a manic episode, vs. 62.4% of patients with Bipolar.
SMD children in the Great Smoky Mountain Study

- Longitudinal epidemiologic data set (Costello et al)
- N= 1,420, 4 waves, ages 9-18

- Questions
  - What is the prevalence of SMD?
    - Answer: 3.2%
  - What is the diagnostic outcome of children with SMD at the last wave (mean age 18.3 + 2.1 y)?
    - Answer: only major depression was a significantly more likely diagnosis in this group
Severe Mood Dysregulation (SMD)

• “Chronically irritable children whose diagnosis is in doubt.”
• Clinical syndrome, not a diagnosis
• A real problem, confers risk of psychopathology, but NOT for bipolar disorder
• SMD increases risk of depressive disorder and GAD at 20 year follow-up.

Stringaris et al, 2010
Disruptive Mood Dysregulation Disorder (DMDD) (296.99)

- The evolution of the SMD label
  - Just removed “hyperarousal” symptom
- Chronic, severe, persistent irritability
  - Temper outbursts
    - grossly out of proportion to the situation
    - developmentally inappropriate
  - Persistently irritable or angry mood in between temper outbursts, present most of the day, nearly every day, and noticed by others
Disruptive Mood Dysregulation Disorder

- Severe temper outbursts
  - > 3 episodes per week
  - Outbursts occur in multiple settings
- Persistently negative mood between outbursts
- Duration > 12 months
  - No remissions of >3 months
- Child is > 6 years old
  - Onset < 10 years old
- No manic episodes (defined as >1 day) within the year
DMDD is a mood diagnosis

- ODD/Conduct are disruptive behavior diagnoses
  - May help to differentiate
  - If symptoms fit both DMDD and ODD, only diagnose DMDD
- Clinical course and treatments are not known
  - Uncommonly persistent as-is beyond 2 years
  - Controversies still exist around DMDD
    - Isn’t this just ODD plus depression?
Differential Diagnoses With Mood Dysregulation & Irritability

• Bipolar Disorder
• Depression (esp. kids)
• PTSD
• Anxiety/OCD
• DBD, ODD
• ASD rigidity
• Conduct Disorder
• Substance Use
• Parent-Child Relational Problem
• Attachment Disorder, Borderline Traits
Why is/was Bipolar NOS so common?

• Broad Category/catch-all
• Sounds better to us than “I don’t know”
• Justifies medication treatment options
  ▫ If we give a child medicine as if bipolar, parents often report improvement
• Bipolar medicines have many non-specific effects
  ▫ All decrease impulsivity and aggression
Diagnosis: Summary

• The diagnosis of bipolar disorder should be reserved for children who have clear *episodes* of mania.

• Look for elation, grandiosity, hypersexuality, decreased *need* for sleep

• Children with severe irritability are at risk for major depression
Mood Spectrum:

Elevated Mood

Depressed Mood

Normal Mood

Time
Mood Spectrum:

- Depressed Mood
- Elevated Mood

Major Depression
Mood Spectrum:

Elevated Mood

Depressed Mood

Time

PAL Conference
Cheyenne, WY
April 2015

Mania
Mood Spectrum:

- Elevated Mood
- Depressed Mood

Dysthymia
Mood Spectrum:

Elevated Mood

Depressed Mood

Time

DMDD

Major Depressive Disorder

PAL Conference
Cheyenne, WY
April 2015
Mood Spectrum:

- Depressed Mood
- Elevated Mood
- Normal Mood
- Mania
- Dysthymia
- Hypomania

Time

PAL Conference
Cheyenne, WY
April 2015
Mood Spectrum:

- Depressed Mood
- Elevated Mood

Time

Bipolar Disorder
Look for “Hallmark” Symptoms

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

• 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.)
Return to the Case  
(6 yr old irritible and moody boy)

- Decide if he just has under-treated ADHD  
- Look for depression, anxiety, ODD  
- Ask for more detail than just his being “moody” and “irritable”
  - How is his mood most of the day?  
  - What causes (if anything) his mood to change?  
  - When not upset, what does he look like?  
  - Can he “pull out of it”  
  - Does he “listen” when he is asked to do something he wants to do?
Parent’s Answers in this case

- Mom says he “never listens to me” especially when asked to do chore/homework/go to bed.
- Goes into rages when doesn’t get his way
- Throws things at mom, hits her. Says “I hate you.”
- Tried “everything,” even spanking, taking away the Xbox.
- With dad or other adults he behaves better. Some talking back, but manageable. Knows he needs to cool it or he going to get in trouble.
Symptoms At School

- In 2nd grade, teacher said he was not listening well in beginning of year, is better now
- In kindergarten he didn’t follow rules well
- Performing at grade level
- Not having rages at school
- Generally more of a problem at home more than at school
Social History and Development

- Mom is primary caregiver.
- 1 younger brother, mom thinks she might be pregnant.
- No contact with dad. Left before he was born.
- Mom has few supports.
- Developmental milestones were OK
- Read early. Very verbal. Reads “anything about history” and “remembers everything.”
- No in utero drug exposure identified.
How to answer Mom’s Question if this is Bipolar Disorder?

- Probably not
- Note a lack of hallmark symptoms
- Difficult diagnosis (no “tests”)
- Bipolar diagnosis best made “over time”
- Down side of labeling too early
Bipolar Rating Scales?

• 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.
Back to the 6 year old Patient

- Rage episodes seem directed mostly at mom, and mom’s attempts to set limits at home
- Mood changes occur mostly in response to frustrations
- There are not any hallmark symptoms of grandiosity, euphoria, hypersexuality
- No history of days-long episodes
- He is very young to diagnose as bipolar
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 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
Looking back at adult bipolar....

- 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
What if a “Bipolar” Child Really is Bipolar?
What if a “Bipolar” Child Really is Bipolar?

• Though rare in a PCP practice, becomes more likely the older the child.

• Assemble a team. Real deal bipolar disorder is a big problem and requires multi-modal treatment.
Course Of True Bipolar Disorder

- Suicidality
  - 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
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

Brent et al, 1988, 1993
If No Child Psychiatrist Can Assume Care, Then What?

- Get collateral information to help establish correct diagnosis
  - This may require separate/designated appointment(s) with caregivers and/or patient to get sufficient history
- Seek consultant advice (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
- Safety monitoring and crisis planning
- Individual Support (symptom management, coping skills, adherence monitoring, psychoeducation)
- Family support (psycho-education, risk assessment/response, adherence/relapse prevention)
- Lifestyle coaching and support (sleep hygiene, stress mitigation, drug/alcohol risks, exercise, social rhythm therapy)
Bipolar Medications
Classes of Bipolar Medication

- “Mood Stabilizers”
  - Antipsychotic Medications
  - Anti convulsants (AEDs)
- Depression Medications (SSRIs, SNRI)
  - Avoid unless already on a “mood stabilizer”
- Sleep Aides
Antipsychotics
Antipsychotics

• Ideal world
  ▫ mental health specialists handle all prescribing

• Real world
  ▫ primary care pressured to originate or continue these meds
Antipsychotics- What do we really know with kids?

• Treat psychosis, but also benefits in:
  ▫ Mania/bipolar disorder
  ▫ Tic and Tourette's disorder
  ▫ Irritability associated with autism
  ▫ Impulsive aggression of conduct disorder/ODD
  ▫ Explosive affect & impulsive aggression
Antipsychotics (1st Generation)

- Chlorpromazine (Thorazine)
- Fluphenazine (Prolixin)
- Haloperidol (Haldol)
- Perphenazine (Trilafon)
- Thioridazine (Mellaril)
- Thiothixene (Navane)

- Generally not being used now in kids due to extrapyramidal symptoms
Atypical Antipsychotics (2\textsuperscript{nd} gen.)

- Aripiprazole (Abilify)
- Olanzapine (Zyprexa)
- Quetiapine (Seroquel)
- Risperidone (Risperdal, Invega)
- Ziprasidone (Geodon)

- Asenapine (Saphris)
- Clozapine (Clozaril, FazaClo)
- Lurasidone (Latuda)
- Iloperidone (Fanapt)
Atypical Antipsychotics

• 99% of antipsychotic prescriptions for children are atypicals
• Big business for big pharma
• Atypical hallmark is serotonin receptor antagonism in addition to D2 activity
  ▫ lower extra pyramidal symptoms
  ▫ lower tardive dyskinesia risks
Time of Onset of Effects

- All atypical antipsychotics studied have shown benefit over baseline in bipolar
- Adolescent schizophrenia time to onset of effect
  - risperidone took 8 days vs placebo (PANSS)
  - olanzapine took 2 weeks vs placebo (BPRS-C)
  - aripiprazole took 4 weeks vs placebo (PANSS)
- The few trials comparing two antipsychotics found no difference (except clozapine)
Antipsychotics for Pediatric Bipolar Disorder

• Studies of the following all showed benefit
  ▫ olanzapine
  ▫ risperidone
  ▫ quetiapine
  ▫ aripiprazole
  ▫ asenapine

• Roughly similar effect sizes

• So choose one based on onset time, side effects
Risperidone (Risperdal)

- $\frac{1}{2}$ life 20 hours
- available liquid, dissolving tab, tabs, depot
- doses over 6mg per day behave like 1st generation antipsychotic in adults
- for mood or aggression treatment, usually don’t need doses greater than 2mg
- TD incidence reported less than 0.5%

- The usual 1st line choice antipsychotic
  - Relatively predictable benefits
  - Lots of research in kids for different indications
Olanzapine (Zyprexa)

- ½ life 30 hours
- tablets, oral disintegrating, IM
- Major side effects
  - weight gain doesn’t plateau
  - cholesterol, glucose
  - Sedation
- Bipolar
  - One large RCT showed benefit

- Though has good psychiatric impacts, weight gain limits its use

Tohen M et al 2007
Quetiapine (Seroquel)

- ½ life 6 hours
- some prescribe just as sleep aide
  ▫ Risking permanent TD from a childhood sleep aide is not reasonable
  ▫ However sleep aide AND bipolar treatment is worthwhile
- lower potency, may be experienced as “milder”
- Need generous doses for the anti-mania effect (i.e. 400mg a day)

Pathak S 2013
Aripiprazole (Abilify)

- ½ life 75 hours
- Pills, IM form available
- Novel: mixed agonist/antagonist
  - Often takes much longer to see benefits
  - Some get agitation because of the med
- Reputation as weight neutral—not true in kids

- If need to help right away, not my preferred choice
  - More hit-or-miss than the other antipsychotics
Ziprasidone

- ½ life 7 hours
- tablet, IM
- perceived need for EKG has lowered usage
- relatively weight neutral
- IM form for agitation tx. (not PO)

- No supporting data for bipolar treatment in kids
Asenapine

- sublingual administration (not absorbed if swallowed), can’t eat or drink anything for 10 minutes after take a dose.
  - 1 in 4 kids get oral paresthesia
- 24 hour half life
  - Twice daily administration (reduces SE like dizziness)
- 50% of kids get significant sedation
- Advantage for adults is lower chance for weight gain or metabolic changes
  - But for kids, ~10% will get more than a 7% increase in total body weight in just 3 weeks
Lurasidone

- NO data in kids yet
- ½ life 18 hours
- low antihistaminic activity
- minimal weight gain/metabolic problems in adults
  - I would not count on that for kids
- some akathisia and EPS making it more like risperidone or typicals
- seems to have a relatively rapid onset of clinical activity
- For adults, shown to have benefit for bipolar depression
Antipsychotic just for Irritibility/Aggression?

- Maladaptive aggression
  - inappropriate intensity/frequency/duration
  - associated with PDD, conduct d/o, adhd
  - atypical antipsychotics often prescribed
- risperidone if conduct d/o, low IQ
  - (ES 0.9, combined n=875)
- methylphenidate if comorbid ADHD
  - (ES 0.9, combined n=844)

E Pappadopulos et al 2006
FDA Antipsychotic Approvals

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

- **Schizophrenia**
  - Risperidone, Aripiprazole, Quetiapine, Olanzapine
    - (age 13 and older)
  - Paliperidone (age 12 and older)
  - Molindone and Haloperidol (age 12 and older)

- **Irritability associated with autism**
  - Risperidone (5 - 16 years)
  - Aripiprazole (6 - 17 years)
### Atypical Antipsychotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Form</th>
<th>Starting Dose</th>
<th>Usual Sedation</th>
<th>Usual Weight Gain</th>
<th>EPS (stiff muscles)</th>
<th>Bipolar (+)</th>
<th>Child RCT evidence?</th>
<th>FDA bipolar approved?</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>0.25, 0.5, 1.2, 3.4mg 1mg/ml</td>
<td>0.25mg QHS</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (Age &gt;10)</td>
<td>Generic forms. More dystonia risk than rest</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>2.5, 10, 15, 25, 30mg 1mg/ml</td>
<td>2mg QD</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (Age &gt;10)</td>
<td>Long ½ life, can take weeks to build effect</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>25, 50, 100, 200, 300, 400mg</td>
<td>25mg BID</td>
<td>++</td>
<td>+</td>
<td>+/-</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (Age &gt;10)</td>
<td>Pills larger, could be hard for kids to swallow.</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>20, 40, 60, 80mg</td>
<td>20mg BID</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Greater risk of QT lengthen, EKG check</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>2.5, 5, 7, 5, 10, 15, 20mg</td>
<td>2.5 mg QHS</td>
<td>++</td>
<td>++</td>
<td>+/-</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (Age &gt;13)</td>
<td>Greatest risk of weight gain, ↑ cholesterol</td>
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</tbody>
</table>

**Monitoring for all atypical antipsychotics:** AIMS exam at baseline and Q6months due to risk of tardive dyskinesia. Warn of dystonia risk. Weight checks, fasting glucose/lipid panel Q6months at minimum.
# Atypical Antipsychotic Risks

<table>
<thead>
<tr>
<th>Common Side Effects (&gt;10%)</th>
<th>Less Common Side Effects</th>
<th>Notable Rare Reactions (≤2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain <strong>(olanzapine &gt; others)</strong></td>
<td>Tremors</td>
<td>Tardive Dyskinesia</td>
</tr>
<tr>
<td>Muscle rigidity</td>
<td>Nausea or abdominal pain</td>
<td>Neuroleptic Malignant Syndrome</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>Akathisia (restlessness)</td>
<td>Lowered blood cell counts</td>
</tr>
<tr>
<td>Constipation</td>
<td>Headache</td>
<td>Elevated liver enzymes</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>Agitation</td>
<td>Prolonged QT interval</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Orthostasis</td>
<td><strong>(ziprasidone &gt; others)</strong></td>
</tr>
<tr>
<td>Somnolence/fatigue</td>
<td>Elevated glucose</td>
<td>Tachycardia</td>
</tr>
<tr>
<td></td>
<td>Elevated cholesterol/triglycerides</td>
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</table>

From Hilt R, 2012
# Atypical Antipsychotic Monitoring

<table>
<thead>
<tr>
<th>Monitoring recommendation</th>
<th>Frequency Suggestion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height and weight</td>
<td>At baseline and at each follow-up (at least every 6 months)</td>
</tr>
<tr>
<td>Fasting blood sugar, TG, Cholesterol</td>
<td>At least every 6 months</td>
</tr>
<tr>
<td>Screen for stiffness, movement disorder or tardive dyskinesia (like AIMS exam)</td>
<td>At least every 6 months</td>
</tr>
<tr>
<td>CBC with Diff</td>
<td>Once to catch if any suppression, a few months after initiation</td>
</tr>
<tr>
<td>BP/Pulse</td>
<td>at least once after starting medication</td>
</tr>
<tr>
<td>Cardiac history</td>
<td>At baseline, get EKG if in doubt about risk from a mild QT increase</td>
</tr>
</tbody>
</table>

From Hilt R, 2012
What Is A Mood Stabilizer?

- Includes both atypical anti-psychotics and anti-epileptic drugs (AEDs)
- Generic term
- FDA does not recognize this term
- Ideally treats both depressive and manic episodes and prevents recurrences
- Since no one compound does this well, multiple meds are often used together

- Currently, I prefer antipsychotics for child bipolar
Lithium

- Rapid absorption
  - peaks in 0.5 to 2 hours
- Half life ~24 hours
  - longer if poor renal function (renal excretion)
- Narrow therapeutic index
- Drug levels 0.6 to 1.2 mEq/L
- Don’t go past 1.4 mEq/L
- Don’t combine with NSAIDS
### Table 6.6 Lithium Carbonate Serum Level, Clinical Side Effects, and Toxicity

<table>
<thead>
<tr>
<th>Therapeutic Lithium Levels (0.6–1.2 mEq/L)</th>
<th>Mild to Moderate Toxicity (1.4–2.0 mEq/L)</th>
<th>Moderate to Severe Toxicity (2.0–2.5 mEq/L)</th>
<th>Severe Toxicity ≥ 2.5 mEq/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Nervous System</td>
<td>Central Nervous System</td>
<td>Central Nervous System</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>Hand tremor</td>
<td>Dizziness</td>
<td>Coma</td>
<td>Seizures</td>
</tr>
<tr>
<td>Memory impairment</td>
<td>Drowsiness</td>
<td>Choreoathetoid movements</td>
<td>Renal</td>
</tr>
<tr>
<td>Concentration difficulties</td>
<td>Dysarthria</td>
<td>Clonic limb movements</td>
<td>Oliguria</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Agitation</td>
<td>Convulsions·</td>
<td></td>
</tr>
<tr>
<td>Coarsening hand tremor</td>
<td>Lethargy</td>
<td>Delerium</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Muscle weakness</td>
<td>EEG changes</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Vertigo</td>
<td>Fainting</td>
<td>Renal failure</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Gastrointestinal</td>
<td>Hyperreflexia</td>
<td>Death</td>
</tr>
<tr>
<td>Edema</td>
<td>Abdominal pain</td>
<td>Leg tremors</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>Diarrhea</td>
<td>Muscle fasciculations</td>
<td></td>
</tr>
<tr>
<td>Weight gain</td>
<td>Dry mouth</td>
<td>Nystagmus</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>Nausea</td>
<td>Vision blurred</td>
<td></td>
</tr>
<tr>
<td>Polydipsia</td>
<td>Vomiting</td>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Polyuria</td>
<td></td>
<td>Anorexia</td>
<td></td>
</tr>
<tr>
<td>Nocturnal enuresis</td>
<td></td>
<td>Nausea</td>
<td></td>
</tr>
<tr>
<td>Dermatological</td>
<td></td>
<td>Vomiting</td>
<td></td>
</tr>
<tr>
<td>Acne</td>
<td></td>
<td>Cardiovascular</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac arrhythmia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sinus node dysfunction</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pulse irregularities</td>
<td></td>
</tr>
</tbody>
</table>

Lithium

PROS
- FDA approved for mania >12 years
- Some evidence helps 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 Monitoring

• Baseline
  ▫ renal screen (BUN/creatinine)
  ▫ thyroid function
  ▫ cbc with diff
  ▫ calcium/phosphorous
  ▫ pregnancy test ? (epstein anomoly)
  ▫ EKG
  ▫ lithium level 5 days after start

• Q3 months
  ▫ lithium level

• Q6 months
  ▫ TSH, renal function

  ▫ Warn about NSAID use, dehydration from sports
Depakote

- Possible use with aggression, bipolar
- Baseline
  - CBC, Diff with platelets
  - LFT
  - Amylase?
  - Pregnancy test?
- Monitoring
  - Hepatotoxicity risk highest if young, and in first 6 months
  - CBC/LFT every 6-12 months thereafter
  - Weight
  - Adult mania: levels 50-125 mcg/mL
Valproic Acid (Depakote)

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

**CONS**
- Requires blood draws (levels, LFTs, 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)
Valproic Acid

- 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
• 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
Oxcarbazepine (Trileptal)

- FDA approved for adults with bipolar
- less medical risks than Carbamazepine
  - less liver/blood toxicity
- weight neutral
- levels don’t correlate with efficacy or toxicity
- Only blinded adolescent bipolar mania trial (n=116) was negative in 2006
  - Not a great treatment choice for pediatric bipolar
Lamotrigine (Lamictal)

PROS
• Less sedation and lower side effect profile in general
• Some studies report bipolar depression help

CONS
• Not helpful for manic phase
• Requires monitoring of CBC and liver function
• Significant rash risk
• Slow titration (age >12)
Anticonvulsants Shown To Not Help Bipolar Adults

- topiramate (Topamax)
- gabapentin (Neurontin)
- levetiracetam (Keppra)
  - can cause psychiatric symptoms
- zonisamide (Zonegran)
- pregabalin
- felbamate
  - can cause psychiatric symptoms
Hard to Compare Effectiveness

42 child outpatients with Bipolar 1 or 2, randomized to one of three open label treatments

R Kowatch et al, 2000
Mood Stabilizers: Weight Gain

Pooled analysis of 19 studies in children with bipolar disorder MS= Mood Stabilizer  TPX=Topiramate;  SGA=second generation antipsychotic

C Correll, 2007
Sleep Aides

- (Lifestyle) - limit caffeine, exercise, no drugs/alcohol
- (Sleep hygiene)
- Melatonin (mild sleep aide, can help regulate sleep cycle)
- Anti-histamines
- Trazodone
- Benzodiazepines
- Newer sleep aides
Reminder: Medications will not resolve...

- Family stress/conflict
- Abuse/neglect
- Poor parenting strategies
- School stress/conflict
- Strong willed temperament
- Intellectual deficits
- Developmental impairments
Questions?

Partnership Access Line
1-877-501-PALS (7257) www.WyomingPAL.org

Mental Health Consultation Outreach for children