Medication Management of Comorbid Psychiatric Conditions in Youth With Bipolar Spectrum Disorders

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Off Label Medication Use

Many medications used to treat bipolar disorder and comorbid disorders are not FDA approved for treatment in youth. Medications that have an FDA indication for treatment of youth will be highlighted in yellow during this presentation.

Objectives

• Review medication options for pediatric bipolar disorder
• Discuss treatment options for comorbid ADHD and anxiety disorders
• Explain how to communicate this information with youth and families
Guiding Principles

Making the correct diagnosis is 90% of the job
Medication is only part of the approach
• Therapy and case management
• Not all symptoms respond to medication
• Medication + therapy is often superior to medication alone
Process of choosing medication options is collaborative

Initial Pharmacologic Treatment of Mania in Youth

• Atypical Antipsychotics – aripiprazole (Abilify), asenapine (Saphris), quetiapine (Seroquel), risperidone (Risperdal), olanzapine (Zyprexa), ziprasidone (Geodon)
• Lithium

Commonly, 2 or 3 trials of atypical antipsychotic before lithium
Treatment Refractory Mania in Youth

- Atypical Antipsychotic + lithium
- Atypical Antipsychotic + divalproex or lamotrigine
- Lithium + divalproex or lamotrigine or carbamazepine
- Typical antipsychotic

Pharmacologic Treatment of Bipolar Depression in Youth

- Lurasidone (Latuda)
- Atypical Antipsychotic + SSRI
  - Aripiprazole, quetiapine, risperidone, olanzapine
  - Escitalopram (Lexapro), fluoxetine (Prozac), sertraline (Zoloft)
- Lamotrigine
- Lithium
Treatment Refractory Bipolar Depression in Youth

- Atypical Antipsychotic + SNRI (venlafaxine, duloxetine) or bupropion
- Atypical Antipsychotic + lithium
- Lithium + lamotrigine
- Lithium + SSRI

Divalproex
- Treats mania
- Not so effective
- Perhaps less effective in youth?
- Potentially toxic to liver and pancreas
- Birth defects; cognitive side effects

Lithium
- Good for mania, depression, and maintenance
- Less wt gain than atypicals
- Narrow therapeutic window (potential for toxicity; frequent monitoring; dehydration, ibuprofen can ↑ levels)
- Cognitive side effects

Atypical Antipsychotics
- Good for mania
- Some good for depression
- Works very quickly
- Metabolic effects/weight gain
- Some motor side effects
- Breast development/lactation (risperidone)
- Sedating (can be a pro), cognitive side effects

Pros and Cons: Patient/Family Discussion

<table>
<thead>
<tr>
<th>Medication</th>
<th>Pros</th>
<th>Cons</th>
<th>Blood Draw</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamotrigine</td>
<td>Well-tolerated</td>
<td>Rash (rare, but can be severe)</td>
<td>None</td>
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<tr>
<td></td>
<td>Prevents depressive episodes</td>
<td>Not good for mania</td>
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<tr>
<td></td>
<td></td>
<td>Not great for acute tx of dep</td>
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<td></td>
<td></td>
<td>Data not great for children/adolescents</td>
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<tr>
<td>Atypical</td>
<td>Good for mania</td>
<td>Metabolic effects/weight gain</td>
<td>Baseline + every 3-6 months</td>
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<tr>
<td>Antipsychotics</td>
<td>Some good for depression</td>
<td>Some motor side effects</td>
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<td></td>
<td>Works very quickly</td>
<td>Breast development/lactation (risperidone)</td>
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<td>Sedating (can be a pro), cognitive side effects</td>
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<tr>
<td>Lithium</td>
<td>Good for mania, depression, and maintenance</td>
<td>Kidney and thyroid side-effects</td>
<td>Baseline + 5 days after increase, then every 1-3 months</td>
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<tr>
<td></td>
<td>Less wt gain than atypicals</td>
<td>Narrow therapeutic window (potential for toxicity; frequent monitoring; dehydration, ibuprofen can ↑ levels)</td>
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<td>Cognitive side effects</td>
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</tr>
<tr>
<td>Divalproex</td>
<td>Treats mania</td>
<td>Not so effective for depression</td>
<td>Baseline + 1 week after increase, then every 3 months</td>
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<td>Perhaps less effective in youth?</td>
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ADHD and Bipolar Disorder (BD)

• ADHD co-occurs in 50% patients with BD

• Onset of ADHD usually predates onset of first manic episode

• Comorbid ADHD is associated with negative outcomes
  • Less responsive to pharmacotherapy

Treatment of ADHD and BD

• If mood is unstable, treat underlying mood episode first

• ADHD symptoms may improve when treating mood symptoms with atypical antipsychotic (Findling et al 2009)

• If mood symptoms improve but ADHD symptoms persist, consider adjunctive stimulant
  • Both methylphenidate (Findling et al 2007) and amphetamine compounds (Schaffer et al 2005) have been shown to be effective and did not worsen mood
Stimulants for Youth with ADHD and BD

- Start at low dose and titrate up slowly
- Youth and families should monitor for irritability, mood lability, or agitation
- Although RCTs and prospective observational studies show that stimulants do NOT cause treatment emergent mania, other studies (retrospective case review) have raised concerns

Diagnostic Uncertainty:
ADHD vs BD, ADHD and BD?

Both ADHD and BD can present with symptoms of restlessness, distractibility, irritability, anger

- If youth is without family history of BD, clearly has ADHD, and possible hypomania, but never had a trial of stimulant, risk/benefit ratio may favor initial trial of stimulant
- If youth with ADHD, presents with recurrent 1-2 day episodes of elated mood, decrease need for sleep, grandiosity, increased pleasure seeking and family history of BD, risk/benefit ration likely favors initial trial of antimanic medication
Anxiety Disorders and Bipolar Disorder

Anxiety disorders often co-occur in patients with BD
- Clinical samples show 24-56% of patients with BD meet criteria for one or more anxiety disorders

Comorbid anxiety symptoms and disorders are associated with negative outcomes
- Higher number of mood episodes
- Higher rates of suicide attempts
- Higher rates of substance use disorders
- Reduced quality of life
- Poor psychosocial functioning

Treatment of Anxiety Disorders in Youth with Bipolar Disorder

A “step-wise” approach is generally recommended
- Mood stabilization is the priority
- Once the mood is stable, specific treatments for anxiety disorders are considered

No large RCTs have examined the efficacy of medications for treatment of anxiety disorders in youth in bipolar disorder
Can medications that stabilize mood also reduce anxiety?

In adult studies, some medications have been shown to improve mood and reduce anxiety:

- Quetiapine (Calabrese et al. 2005, Thase 2006; Sheehan 2013)
- Olanzapine/fluoxetine (Tohen et al. 2007)
- Lurasidone (Loebel et al. 2014)
- Lithium (Kinrys et al. 2019)
- Lamotrigine or olanzapine (Maina et al. 2008)

Other medications have not been shown to lower anxiety:

- Risperidone, ziprasidone, and divalproex

Once mood is stable, consider specific treatments for anxiety disorders:

1. Cognitive Behavioral Therapy (CBT)
   - First-line treatment
   - Effective for anxiety disorders in youth without BD
   - No risk of mood destabilization or dependence

2. SSRIs or SNRIs
   - Effective for anxiety disorders in youth without BD
   - Risk of mood destabilization
   - Use in combination with medication that prevents mania/hypomania
   - Start at lower than usual doses, increase slowly, and monitor closely for mania/hypomania
Treatments for Anxiety Disorders in Youth with Bipolar Disorder

3. Benzodiazepines (e.g. clonazepam)
   - Limited data for effectiveness in youth with anxiety disorders
   - Risk of misuse or dependence
   - Overdose can be lethal
   - Do not provoke mood instability

4. Buspirone
   - No data for effectiveness in youth with anxiety disorders. Large RCT showed buspirone = placebo.
   - Consider in older adolescents and young adults?
   - Rarely provokes mood instability

5. Hydroxyzine
   - No data for effectiveness in youth with anxiety disorders
   - Has FDA indication for pediatric anxiety
   - Does not provoke mood instability
   - Helpful for difficulty falling asleep
   - Recommended dosing twice or three times per day
Summary: Treating Comorbid Disorders in Youth with BD

- Start by treating current mood episode with appropriate medication (atypical antipsychotic, lithium, lamotrigine, divalproex)
- Once mood has been stabilized, re-assess comorbid disorders:
  - If ADHD is problematic, consider adjunctive stimulant
  - If anxiety symptoms are still impairing, start with CBT. If CBT is not effective, consider adding SSRI, benzodiazepine, or hydroxyzine

Thank You

- All Families for their participation
- Course and Outcome of Bipolar Youth (COBY) Study
  Pittsburgh: David Axelson, Katie Aronson, Boris Birmaher (PI), Renee Clark, Josh Feldmiller, Mary Kay Gill, Ben Goldstein, Tina Goldstein, Heather Kumar, Fangzi Liao, John Merranko, Sharon Nau, Neal Ryan, Raeanne Sylvester, Vicky Yazakos
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