ADHD CASES
Learning Objectives

• Identify the different challenges in the diagnosis of ADHD in child and adolescent patients

• Differentiate the spectrum of medication options available for use in pediatric ADHD and apply them to patient cases

• Assess the emerging therapies for pediatric ADHD and apply them to patient cases

• Optimize treatment of pediatric ADHD to fit the specific needs of the patient and their caregivers
The Case: ADHD Plus?

- **The Question**: Can ADHD be clinically distinguished from other disorders?
- **The Dilemma**: Overlapping symptoms can cause diagnostic confusion and comorbidity is the rule rather than the exception in kids.
15-year-old Madison referred for depression and ADHD

Chief complaint: “Everything is my fault,” “No one understands me,” and “I can’t focus”

Low mood and lack of interest in the past 2 months

Mood symptoms accompanied by low appetite, fatigue, poor sleep quality, poor concentration, and always being “cranky”
History

• A year ago was hospitalized after a month of:
  • Sleeping for only a few hours
  • Wasn’t getting along with anyone and was always arguing, felt like parents were always starting arguments
  • People complained she was talking too fast
  • Couldn’t help it but thoughts were racing around in her head
  • Hospitalized after her mom discovered something about dying in her journal
Treatment History

- Had a 2-month trial of
  - Methylphenidate ER (Concerta) 18mg per day
  - Escitalopram (Lexapro) 10 mg per day

- Has engaged in cognitive behavioral psychotherapy, mostly to ventilate feelings, but hates doing the homework

- One psychiatric admission due to suicide attempt
• Report of bipolar disorder in distant family members
Medical History

• Asthma
• Allergies
• Eczema
Social History

• In 10th grade with recent drop in grades
• Relationships are generally conflictual
• No legal problems
• No alcohol or drug addiction history
What is not on the differential diagnosis for Madison?

1. Bipolar disorder
2. Major depression with mixed features
3. ADHD only
4. Bipolar disorder with co-occurring ADHD
What would be the next step toward helping Madison?

• Use psychotherapy alone, as there are no approved drugs for treating bipolar disorder in the context of ADHD?

• Maintain on antidepressant and stimulant to give it some more time to take effect?

• Switch to bupropion?

• Use an atypical antipsychotic given their effectiveness in bipolar depression?
Treatment Course

• Each subsequent visit, the patient presented with variable degrees of suicidality, and mixed mania and depression.

• Family-focused therapy afforded temporary relief with reductions in family high-expressed emotions and patient’s depressive symptoms.

• However, at times the suicidal tendencies would increase, and if she could not be verbally de-escalated by the therapist, psychopharmacologic intervention was considered.
Which medication would you consider?

1. Haloperidol
2. Risperdal
3. Olanzapine-fluoxetine combination
4. Quetiapine
5. Divalproex
6. Carbamazepine
7. Lurasidone
8. Escitalopram
9. Lithium
Treatment Course and Outcome

• Family-focused therapy only partially worked to reduce maladaptive family interactions

• Madison was started on lurasidone to address bipolar depression:
  • This agent was chosen as an FDA-approved option with some beneficial cognitive effects
  • This patient is at risk for metabolic syndrome, so assessment of lifestyle habits involving diet and exercise were reviewed and patient was started on Metformin 500 mg BID
  • Later, her regimen was streamlined to discontinue the antidepressant and stimulant
  • For co-occurring ADHD that was not adequately treated with lurasidone, another trial of psychostimulant therapy could be considered after effective mood stabilization
Teaching Point 1: ADHD Is Highly Comorbid With Bipolar Disorder

- Rates depend on whether or not symptoms of mania and ADHD are “double counted”
- Comorbidity rates are much higher when they are
  - 75–98% children
  - 25–60% in teens;
  - 10–20% in adults
- Even accounting for age, rates of ADHD appear to be somewhat higher than expected by chance
- ADHD comorbidity
  - Lengthens a manic episode
  - Decreases time to relapse
  - Worsens treatment response

<table>
<thead>
<tr>
<th>Teaching Point 2: Confusing-Symptom Sharing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mania</strong></td>
</tr>
<tr>
<td>Elated mood</td>
</tr>
<tr>
<td>Irritability</td>
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<tr>
<td>Hyperactivity Agitation</td>
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<tr>
<td>Distractibility</td>
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<tr>
<td>Flight of ideas</td>
</tr>
<tr>
<td>Grandiosity</td>
</tr>
<tr>
<td>Poor judgment</td>
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<tr>
<td>Reduced sleep need</td>
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</tbody>
</table>

-> ADHD comorbidity: lengthens a manic episode, decreases time to relapse, worsens treatment response
Teaching Point 3: Clinical Ways to Distinguish Pediatric BD From ADHD

**BD**
- Unstable mood
- Internally distracted
- Can’t soothe when angry
- Rage for hours
- Take big risks, look for danger or thrill
- Do better at school
- High energy/inappropriate giggling
- May be overly sexual

- Family History
- ADHD meds can trigger mania
- Worsen with Age

**ADHD**
- Stable Mood
- Externally distracted
- Soothing helps
- Lose interest in fighting
- Do not intend to get into big trouble
- Do better at home
- Normal laughing or fun
- Sexuality not a major issue

- No Family History
- ADHD meds help
- Get better with Age

BD = bipolar disorder; ADHD = attention-deficit/hyperactivity disorder.
Teaching Point 4: Clinical Ways to Distinguish Pediatric BD From ADHD

PRESENTATION

• Mood disorders present differently in youth versus adulthood
  • ADHD commonly precedes and/or co-occurs with bipolar disorder and has similar heritability estimates
  • ADHD is a common “prodrome” for bipolar disorder in youth (Singh et al., 2008)
• Overlapping symptoms may be clinically distinguished by carefully assessing:
  • for a manic episode
  • ruling in/out common (‘horses’) vs. rare (‘zebras’) conditions
  • symptoms that “hang” with overlapping symptoms
  • natural course and treatment response to stimulants
Teaching Point 5: Treatment Implications

• In youth with frank mania, mood stabilize before treating ADHD
• In youth at familial risk for bipolar disorder who present with an ADHD prodrome, carefully assess if stimulant therapy helps—could delay or prevent the onset of mood disorder

Bipolar Spectrum in Children

Possible Prodromal States

Severe Mood Dysregulation

SMD  ADHD+FH  DEP+FH  BP NOS  BP II  BP I

“Full” Bipolar Disorder

Conclusions

• A diagnosis of bipolar disorder in youth can be missed or misdiagnosed as depression and ADHD

• ADHD in childhood often runs with other conditions

• ADHD may be a risk factor for developing bipolar disorder

• Treat the ADHD after mood stabilization
The Case: He just won’t act right?

- **The Question:** Looking within and beyond medication for treatment-resistant ADHD
- **The Dilemma:** Child with treatment-resistant ADHD and a single mother with a lack of support
Patient Intake

- Mother presented with 5 ½ year old son with previous history of ADHD and Autism
- Difficulty controlling behaviors despite multiple medications
- Moderate to severe side effects to previous medications
- Mother has growing concerns if anything will work
- Increasingly frustrated mother and patient
Psychiatric History

• Treatment began 6 months prior due to aggressive behavior
• Hyperactivity, impulsivity, poor boundaries, out of seat, doesn’t follow rules or redirection, will not sit still, excess energy, disrupts classroom, and physical aggression
• Poor focus, attention, concentration, off task, needing redirection, difficulty retaining information
• Denies depression, but cries and is easily upset
• Difficulty socially with peers, doesn’t seem to make the right decision, doesn’t know what to do or say, will fixate on one thing, often plays by himself
Treatment History

• Medications:
  • Ritalin helpful, but requires multiple day dosing and wears off about every 3–4 hours and the patient worsens before the next dose
  • Previous trials of atypical antipsychotics
    • Risperidone ineffective in controlling aggression toward peers
      • Drooling and inability to walk
    • Aripiprazole did not seem to help
      • Worsened agitation
      • Drooling and thick tongue
Treatment History

• Medications:
  • Concerta up to 36 mg works for 5–6 hours
    • Rebound agitation
    • Patient with difficulty swallowing larger pills
    • Steep decline in behavior when the medication wears off
    • Developed hallucinations at higher doses in the morning and before bed
      • Question if it was anxiety, make believe versus true psychosis
      • Mother is strongly against another antipsychotic due to previous SEs
Family History

- Maternal cousin with severe autism
- No other family psychiatric history including ADHD
Medical History

• Underweight at beginning of treatment
  • Weight—45 lbs
  • Height—3’11.5

• No other medical issues
Social History

• Parents married, but separated
  • Moved closer to her own family due to needing help with special needs son
  • Mother moved back home due to father’s work, frequent moves
  • Father’s work and travel complicated marriage

• Mother often has to leave him with childcare due to shift work as a CNA
  • Struggling to keep work due to having leave to pick son up from school
  • Losing childcare due to her son’s behavior
Treatment Course and Outcome

• Recommended adding behavioral therapy
  Mother’s response, “It’s only me and him, I already don’t have time to make these appointments, and these copays are too high.”

• Trial of Quillivant XR (liquid, methylphenidate)
  • Initially worked well, but did not control hyperactive symptoms
  • Dosage increases showed diminishing returns and reduced appetite

• Trial of Dyanavel XR (liquid, amphetamine)
  • Increased aggression
  • Running out of classroom
  • Bit a teacher when being reprimanded
  • Hit others and then laughed when they seemed upset
  • Difficulty sleeping
Treatment History

• Added Hydroxyzine 25 mg qhs to Clonidine due to severe allergies and poor sleep

• Titrated Focalin XR 20 mg (wears off at 11am), 30 mg (wears off at 1pm)
  • Wears off at 1pm daily.
    • Issues with babysitter
    • GM is not able to watch him
  • Mother self-increased to 60 mg
    • Required intervention
  • Added Focalin XR 10 mg qnoon
    • Appetite rebounds in the evening
    • Largest meal is breakfast
Treatment History

• Final dose (11 months of treatment)
  • On non school days mother gives Focalin XR 15 mg qam or will hold the afternoon dose to help with appetite
  • Clonidine 0.1 mg qhs
  • Periactin (cyproheptadine) 2 mg qhs
  • Focalin XR 30 mg qam, 10 mg qnoon

After 11 months of treatment
  Beginning height and weight
    3’ 11.5”
    45 lbs
  Ending height and weight
    4’ 0.5”
    47 lbs
Based on the information given, what would be your diagnosis/treatment choice at this point?

1. Call CPS on mother for overdosing
2. Educate mother on patience with the treatment process
3. Add behavioral therapy
4. Stop medications due to lack of efficacy and do therapy only
5. Answers 2 and 3
Teaching Point

• Stimulant
  • Rapid metabolizer
  • Risks of short effect
  • Children have a small volume of distribution
  • Rapid metabolizers of medication

• Work through mother’s frustrations
  • Single mom
  • Special needs child
  • Utilize social supports
  • Reassurance
Summary of Treatment Options

• Long-acting vs. short-acting stimulants
  • Rapid metabolizer
  • High side effect
    • Dosing and timing of medications
    • Difficulty gaining weight
    • Severe side effects to antipsychotics
Conclusions

• Look at confounding factors and stressor impacting outcomes

• Work the process and not rush

• Reassuring and gaining trust
The Case:

- **The Question**: How do you manage difficult-to-treat ADHD?
- **The Dilemma**: Personalized treatment for ADHD is elusive
• KC was exposed to cocaine in utero and was a colicky baby

• In kindergarten, she struggled with remaining seated in class and had frequent redirection for talking out of turn
• Her adoptive maternal grandmother also noticed that she seemed more disorganized and inattentive than her older sister was at the same age

• Over the next few years, her grandmother often had to repeat instructions, remind her to complete her chores, and she left half-finished drawings and homework all over her room

• KC's schoolwork was inconsistent, she had frequent visits to the principal’s office, and her grades were dropping due to unfinished assignments
Treatment History

• KC was 5 when she was first prescribed clonidine 0.50 mg at bedtime for her inattention and hyperactivity without benefit and some dizziness.

• She next tried guanfacine with similar limited efficacy.
Family History

• Dad with a history of ADHD responsive to Adderall XR

• Mom with cocaine and alcohol dependence
Medical and Developmental History

- No acute or chronic illnesses
- Some language delays that required speech therapy
Social History

- Parents never married
- Maternal substance dependence and incarceration
- Adopted by maternal grandmother at age 2
- Requires an individualized education plan in school
Based on the information given, what would be your diagnosis/treatment choice at this point?

1. Learning disorder
2. ADHD
3. PTSD
4. Schizoaffective disorder
Treatment Course and Outcome

- After several treatment failures by nonstimulants, extended release methylphenidate was initiated and optimized with improved attention and hyperactivity.
- KC had some appetite suppression but met growth milestones.
- Grades improved and patient was able to get back on track in language development with support.
- KC’s end-of-day energy was expended playing Pokémon GO.
- Her grandmother heard that the FDA just approved EndeavorRx, a new video game for kids with ADHD, and is now looking into that.
Teaching Point 1: ADHD Treatment Overview

**Good News**
- Symptoms become less severe over time
- Treatment reduces symptoms, at least in the short run

**Bad News**
- No treatments change the long-term course of ADHD
- Inadequately treated ADHD makes other developmental goals much harder to attain
- When ADHD occurs with another problem (2/3 times) outcomes tend to be worse
- All treatments have the potential for side effects
# Teaching Point 2: The Universe of ADHD Meds

<table>
<thead>
<tr>
<th>Stimulants</th>
<th>Non-Stimulants</th>
<th>Off-Label</th>
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</thead>
<tbody>
<tr>
<td>Methylphenidates (long-acting, short-acting)</td>
<td>Atomoxetine</td>
<td>Immediate-release alpha-2 agonists</td>
</tr>
<tr>
<td>D-Methylphenidates</td>
<td>Extended-release alpha-2 agonists (Guanfacine ER, Clonidine ER)</td>
<td>Bupropion</td>
</tr>
<tr>
<td>D-Amphetamines</td>
<td></td>
<td>Modafinil</td>
</tr>
<tr>
<td>Mixed Amphetamine Salts</td>
<td></td>
<td>Tricyclic antidepressants</td>
</tr>
<tr>
<td>Lisdexamfetamine</td>
<td></td>
<td>Monoamine oxidase inhibitors</td>
</tr>
</tbody>
</table>

[http://www.adhdmedicationguide.com](http://www.adhdmedicationguide.com)
### Teaching Point 3: Nomenclature Based on Mechanism of Action

<table>
<thead>
<tr>
<th>Indirect Agonists</th>
<th>Indirect Agonists/Releasers</th>
<th>Direct Agonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPH</td>
<td>AMPH</td>
<td>Guanfacine (NE)</td>
</tr>
<tr>
<td>D-MPH</td>
<td>D-AMPH</td>
<td>Clonidine (NE)</td>
</tr>
<tr>
<td>Atomoxetine (NE)</td>
<td>MAS</td>
<td></td>
</tr>
<tr>
<td>TCAs (NE)</td>
<td>Bupropion</td>
<td></td>
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<tr>
<td>MAOIs</td>
<td></td>
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<tr>
<td>Modafinil (DA)</td>
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</table>
Teaching Point 4: Stimulants

**MECHANISM OF ACTION:**
*indirect* agonism on prefrontal cortical noradrenergic & dopaminergic systems modulating glutamate signals

**Advantages**
- Effective, quick action
- Can be given only when needed
- Different forms available to tailor the action during the day

**Disadvantages**
- Only cover part of the day
- Not useful early and late in day
- Prescribing is scheduled
- Too much dopamine agonism may result in “over focus”
- Side effects
  - Appetite loss, growth delay
  - Headache, stomachache, nausea
  - Rebound hyperactivity
  - Sleep problems
  - Mood lability, irritability
Teaching Point 5: Stimulants Guidelines and Differences

- All equally effective
- Pick a medication
  - 65% do well on first stimulant; 15–20% respond well to a second stimulant
- Choose between short- or long-acting forms
  - **Short-acting** out of favor but allow tailoring of dose
  - **Long-acting** have differing durations and release patterns

- **Methylphenidate**
  - Blocks reuptake of dopamine & norepinephrine
- **Amphetamines**
  - Blocks reuptake plus release of dopamine & norepinephrine
- **Immediate-release forms**
  - Shorter acting, minimizes insomnia
- **Extended-release forms**
  - Minimizes high, jitteriness, dyspepsia, on/off
Teaching Point 6: Non-Stimulants

**Advantages**

- 24-hour coverage
- When effective, have benefits quite comparable to those of stimulants
- Different side effects from stimulants (e.g., sedating, less effect on appetite)
- Easier to prescribe

**Disadvantages**

- Often take weeks to work
- Do not work for as many individuals (40% vs. 65%)
- Side effects may be unacceptable, especially daytime tiredness and sedation
- Seem less likely to provide “cognitive boost” due to lack of dopamine agonism
Atomoxetine (Strattera)

- Mechanism of Action: Blocks NE reuptake and acts as an indirect agonist on adrenergic receptors to enhance attention via glutamatergic activity
- NOT: abused, controlled substance, or stimulant
- Boxed warning: increased risk of suicidal thoughts/behavior in children and adolescents
- Increases blood pressure, heart rate
- Dosing:
  - Children: target dose 1.2 mg/kg; max dose 1.4 mg/kg
  - Adults: 40 mg qd initial; after 3 days: 80 mg qd or 40 mg bid. Max: 100 mg qd
Guanfacine (Tenex, Intuniv)  
Clonidine (Kapvay, Catepress patch)  

- **Mechanism of action:** *direct* agonism on PFC adrenergic receptors to enhance attention (signal)

- **Guanfacine:**
  - Dosing: 1–2 times daily for guanfacine; once daily usually in am for Intuniv
  - Usual dose range is 2 to 4 mg per day

- **Clonidine:**
  - Dosing: tid or qid for clonidine; QD or bid for Kapvay; once every 4–7 days for patch
  - Usual dose range is 0.2 to 0.4 mg per day

- Delay in action, with continued accrual of benefits over weeks to months

- Estimated efficacy is 40–45% of patients

- Common SE: daytime sedation but sometimes disrupts sleep; may lower BP
Medication Effect Sizes

![Bar chart showing Cohen's D for different medications.]

- Nonstimulants: Cohen's D = 0.6
- Atomoxetine: Cohen's D = 0.4
- Immediate Release Stimulants: Cohen's D = 0.9
- Extended Release Stimulants: Cohen's D = 0.9

* p<0.05 stimulants vs. non-stimulants

Selected Investigational Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Development Phase</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dasotraline</td>
<td>Triple reuptake inhibitor (NET, DAT, SERT)</td>
<td>Under FDA review</td>
<td>Sunovion</td>
</tr>
<tr>
<td>Centanafadine</td>
<td>Triple reuptake inhibitor (NET&gt;DAT&gt;SERT)</td>
<td>Phase 3 trials</td>
<td>Otsuka</td>
</tr>
<tr>
<td>Mazindol</td>
<td>Triple reuptake inhibitor and orexin agonist</td>
<td>Phase 3 trials</td>
<td>NLS Pharma</td>
</tr>
<tr>
<td>Viloxazine</td>
<td>Selective NET reuptake blocker</td>
<td>Phase 3 trials</td>
<td>Supernus</td>
</tr>
<tr>
<td>Fasoracetam</td>
<td>Glutamate receptor agonist</td>
<td>Phase 2 trials</td>
<td>Medgenics</td>
</tr>
<tr>
<td>Molindone</td>
<td>D2/D5 receptor antagonist</td>
<td>Phase 3 trials</td>
<td>Supernus</td>
</tr>
</tbody>
</table>

- Most “new” ADHD meds are **branded generics** or **new delivery systems** for well-known and long-used stimulants
- Superiority of novel drugs, including with novel drug targets, needs to be tested
Summary of Treatment Options: Pharmacological Algorithm

0. Assessment/Family consultation/Treatment planning

1. MPH or AMPH
   1a. AMPH not used in Step 1
   2. Stimulant not used in Step 1
      2a. AMPH not used in Step 2

2. Non-med treatments

3. ATM or Alpha Agonist
   3a. Combine ATM or alpha agonist with Stimulant

4. Agent not used in Step 3

5. Bupropion or TCA

6. Second-generation antipsychotic

Consultation

Modified from Pliszka et al. JAACAP 2006.
• Pharmacological treatment options are expanding in the design of the delivery system to reduce off-effects and to improve overall tolerability

• New nonpharmacological options like video game apps for ADHD have received recent FDA approval

• Superiority of novel drugs, including with novel drug targets, needs to be tested
Which of the following symptoms differentiates ADHD from Bipolar Disorder?

1. Motor hyperactivity
2. Distractibility
3. Impulsivity
4. All of the above
5. None of the above
What makes for an optimal treatment outcome in a patient?

1. Making the correct diagnosis
2. Picking the correct medication
3. Making a biopsychosocial assessment for individual patient needs
4. 1 and 2 only
5. All of the above
Which medication has the highest effect size for benefit in youth with ADHD?

1. Extended-release methylphenidate
2. Immediate-release amphetamine
3. Atomoxetine
4. Guanfacine