Management of Adverse Effects in ADHD Treatment

Katherine Wang, Pharm.D., AE-C
Clinical Pharmacist
The Center for Children and Women - Greenspoint
Conflict of Interest Disclosure

The presenters, planners, reviewers (including CME administrator) of today’s CME activity do not have any financial relationships or commercial interests to disclose.
Objectives

By the end of this presentation, participants should be able to...

- Distinguish the role of medications in Attention Deficit/Hyperactivity Disorder (ADHD) management
- Identify common adverse effects of ADHD treatment
- Design an appropriate plan to address adverse effects
Epidemiology

- National ADHD estimates fall between 5-9% of all US children
- 5.2% of children in the U.S. are taking ADHD medication

% of Youth Aged 4-17 Receiving ADHD Medication Treatment by State

Treatment of Children with ADHD

- Neither 23%
- Medication Alone 30%
- Medication and Behavioral Treatment 32%
- Behavioral Treatment Alone 15%

CDC Website - Data and Statistics about ADHD. (2018); CDC Website - State-based Prevalence Data of Parent Reported ADHD Medication Treatment. (2018)
Forming a Treatment Plan

- Plans should be comprehensive
- Treatment plans should be reviewed regularly and modified if the patient’s symptoms do not respond

The Debate between Treatment Modalities

AACAP Practice Parameter

Pharmacological Treatment versus Behavioral Treatment

Pharmacological intervention should be a part of treatment. Medication treatment is more effective than a behavioral treatment alone.

AAP Guidelines

Pharmacological Treatment versus Behavioral Treatment

Depends on their age!

Preschoolers (Aged 4-5) – behavioral therapy first line, then methylphenidate if needed
Aged 6-11 – ADHD medications AND/OR behavioral therapy (preferably both)
Aged 12-18 – ADHD medications and maybe behavioral therapy
Medication Treatment Algorithm

- Initial pharmacological therapy should be trialed with an FDA approved stimulant
  - Two main groups of stimulants
    - Amphetamine preparations
    - Methamphetamine preparations
  - Evidence suggests stimulant classes are equally efficacious
  - Consider extended release (ER) formulations vs immediate release (IR) formulations

- Consider non-stimulant medications after both stimulant groups have been tried

First Line
- Approved stimulant (No preference between the stimulants)

Second Line
- Alternate approved stimulant

Third Line
- Other FDA approved agent (atomoxetine, clonidine ER, or guanfacine ER)

## ADHD Medication Primer – Amphetamines

<table>
<thead>
<tr>
<th>Short Acting</th>
<th>Brand Names</th>
<th>Generic?</th>
<th>Starting Doses</th>
<th>FDA Max/Day</th>
<th>Off-label Max/Day</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed amphetamine salts</td>
<td>Adderall®</td>
<td>Yes</td>
<td>3-5 YO: 2.5 mg daily or BID</td>
<td>40 mg</td>
<td>&gt; 50 kg: 60 mg</td>
<td>IR formulations can be used in younger/smaller children Have to be dosed 2-3 times per day</td>
</tr>
<tr>
<td>Dextroamphetamine</td>
<td>Dexedrine®, Zenzedi®, ProCentra®</td>
<td>Yes</td>
<td>≥6 YO: 5 mg daily or BID</td>
<td>40 mg</td>
<td>&gt; 50 kg: 60 mg</td>
<td></td>
</tr>
<tr>
<td>Long Acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed amphetamine salts extended release</td>
<td>Adderall XR®</td>
<td>Yes</td>
<td>≥6 YO: 5-10 mg daily or BID</td>
<td>30 mg</td>
<td>&gt; 50 kg: 60 mg</td>
<td>Adderall XR® and Mydayis® contains different concentration mixes of amphetamine salts, so not exchangeable.</td>
</tr>
<tr>
<td>Dextroamphetamine extended release</td>
<td>Dexedrine Spansule®</td>
<td>Yes</td>
<td>≥6 YO: 5 mg daily or BID</td>
<td>40 mg</td>
<td>&gt; 50 kg: 60 mg</td>
<td></td>
</tr>
<tr>
<td>Lisdexamfetamine</td>
<td>Vyvanse®</td>
<td>No</td>
<td>≥6 YO: 20-30 mg daily</td>
<td>70 mg</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

### ADHD Medication Primer – Methylphenidate

<table>
<thead>
<tr>
<th>Brand Names</th>
<th>Generic?</th>
<th>Starting Doses</th>
<th>FDA Max/Day</th>
<th>Off-label Max/Day</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>Yes</td>
<td>5 mg BID</td>
<td>60 mg</td>
<td>&gt; 50 kg: 100 mg</td>
<td>IR formulations can be used in younger/smaller children</td>
</tr>
<tr>
<td>Ritalin®, Methylin®</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexmethylphenidate</td>
<td></td>
<td>2.5 mg BID</td>
<td>20 mg</td>
<td>50 mg</td>
<td></td>
</tr>
<tr>
<td>Focalin®</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intermediate and Long Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylphenidate extended release</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylin ER®, Metadate CD®, Ritalin LA®</td>
<td>Yes</td>
<td>10 mg qAM</td>
<td>60 mg</td>
<td>&gt; 50 kg: 100 mg</td>
<td>“Intermediate acting”</td>
</tr>
<tr>
<td>Concerta®, Relexsii®</td>
<td>Yes</td>
<td>18 mg qAM</td>
<td>72 mg</td>
<td>108 mg</td>
<td></td>
</tr>
<tr>
<td>Aptsensio XR®</td>
<td>Yes</td>
<td>10 mg qAM</td>
<td>60 mg</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>Quillivant XR®, QuilliChew XR®</td>
<td>No</td>
<td>20 mg qAM</td>
<td>60 mg</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>Cotempla XR-ODT®</td>
<td>No</td>
<td>17.3 mg qAM</td>
<td>51.8 mg</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>Daytrana patch®</td>
<td>No</td>
<td>10 mg patch daily</td>
<td>30 mg</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>Dexmethylphenidate extended release</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focalin XR®</td>
<td>Yes</td>
<td>5 mg qAM</td>
<td>30 mg</td>
<td>50 mg</td>
<td></td>
</tr>
</tbody>
</table>

## ADHD Medication Primer – Non-stimulants

<table>
<thead>
<tr>
<th>Brand Names</th>
<th>Generic?</th>
<th>Starting Doses</th>
<th>Usual Daily Doses</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selective norepinephrine reuptake inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>Strattera®</td>
<td>Yes</td>
<td>6-17 YO (≤70 kg): 0.5 mg/kg/day 6-17 YO (&gt;70 kg): 40 mg /day</td>
<td>6-17 YO (≤70 kg): 1.2 mg/kg 6-17 YO (&gt;70 kg): 100 mg</td>
</tr>
<tr>
<td><strong>Alpha-adrenergic agonist</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonidine extended release</td>
<td>Kapvay®</td>
<td>Yes</td>
<td>0.1 mg</td>
<td>0.1-0.4 mg</td>
</tr>
<tr>
<td>Guanfacine extended release</td>
<td>Intuniv®</td>
<td>Yes</td>
<td>1 mg</td>
<td>1-4 mg</td>
</tr>
</tbody>
</table>

What to do with Adverse Effects

- For all adverse effects, it is important to assess the severity and burden it imposes on the patient.
- Most adverse effects are managed with the same basic strategy.

**STEP 1** Monitor

- However, if side effects persist...

**STEP 2** Reduce Dose

- If reduced dose results in loss of ADHD control...

**STEP 3** Try different medication

- If after trying other medications, patient’s ADHD still responds best to a medication that causes side effects...

**STEP 4** Add adjunctive medication

What to do with Adverse Effects

Step 1: Monitor
- Many side effects are transient and will generally subside
- Monitoring parameters for each side effect may differ

STEP 1
Monitor

STEP 2
Reduce Dose

STEP 3
Try different medication

STEP 4
Add adjunctive medication

Step 2: Reduce Dose

- Most medications will be started at low doses and gradually titrated upward.
- If a patient experiences an adverse effect after a dose increase, then titrate back down to the most recent effective dose at which the side effect did not occur.

What to do with Adverse Effects

Step 3: Try different medication

- Can refer to...
  - Changing from short-acting to long-acting or vice-versa
  - Changing to a new medication in the other stimulant class

- When changing medications always using clinical judgment when coming up with “dose equivalents”

References:
If switching from short-acting to long-acting (or vice versa) of the same medication, then generally give same total daily dose

- Example: amphetamine salts 5 mg BID → amphetamine salts XR 10 mg once daily

- If switching to a different medication...

<table>
<thead>
<tr>
<th>Initial Medication</th>
<th>Methylphenidate</th>
<th>Dexmethylphenidate</th>
<th>Mixed amphetamine salts</th>
<th>Dextroamphetamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate</td>
<td>Half the total daily dose</td>
<td>Half the total daily dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexmethylphenidate</td>
<td>Double the daily dose</td>
<td></td>
<td>Same daily dose</td>
<td>Same daily dose</td>
</tr>
<tr>
<td>Mixed amphetamine salts</td>
<td>1) Same total daily dose then titrate up, OR 2) Start with recommended initial dose and titrate up</td>
<td>Same daily dose</td>
<td>Same daily dose</td>
<td>Same daily dose</td>
</tr>
<tr>
<td>Dextroamphetamine</td>
<td>Same daily dose</td>
<td>Same daily dose</td>
<td>Same daily dose</td>
<td></td>
</tr>
</tbody>
</table>

Step 4: Add adjunctive medication
- Typically considered a last resort
- May not be an option for all adverse effects
Common Adverse Effects

Common
- Appetite Suppression/Weight Loss
- Growth Slowing
- Insomnia

Less Common
- Tics
- Emotional lability

Appetite Suppression/Weight Loss

- Higher risk with longer acting formulations

**Monitor**

- Monitor weight
  - **<10 years old:** every 3 months
  - **>10 years old:** every 6 months
    - At 3 and 6 months after starting treatment
    - More often if concerns arise
  - **Adults:** every 6 months
- Plot height and weight on a growth chart

---

Lifestyle Strategies

- **Before adjusting medications, recommend the following…**
  - Take medication with or after food
  - Take additional meals or snacks early in the morning or late in the evening when stimulant effects have worn off
  - Obtain dietary advice
  - Consume high-calorie foods of good nutritional value
  - Take a planned break from treatment
Add Adjunctive Medication

- Typically used for allergies with an off-label indication for decreased appetite from chronic disease
- A small-sized chart review suggested cyproheptadine may help with stimulant-induced anorexia
- More rigorous studies needed

<table>
<thead>
<tr>
<th>Off-label Dose</th>
<th>Off-label Max Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight-based dosing: Children ≥2 years: 0.25 mg/kg/day divided twice daily</td>
<td>Age-dependent max daily dose:</td>
</tr>
<tr>
<td>Fixed dosing: Children ≥5 years: 2 mg every 6 hours (4 times daily) for 1 week; if tolerated, increase dose to 4 mg every 6 hours</td>
<td>≤6 years: 12 mg/day</td>
</tr>
<tr>
<td></td>
<td>7 to 14 years: 16 mg/day</td>
</tr>
<tr>
<td></td>
<td>≥15 years: 32 mg/day</td>
</tr>
</tbody>
</table>

Let’s try it!

H.P. is a 9-year-old male who presents to the clinic for a follow-up of his ADHD treatment. During his last visit three months ago, he was increased to methylphenidate 27 mg ER once daily. His mother reports he is doing well on this dose, but doesn’t seem to be eating lunch at school. When you weigh him today he appears to have lost weight since his previous visit.

What should we do?

Recommend Lifestyle Strategies!

• Take medication with or after food
• Take additional meals or snacks during “stimulant free” times (early AM and/or later evening)
• Obtain dietary advice
• Provide nutritious high-calorie foods
• Take a planned break from treatment

When should we follow-up?
Follow-up in 3 months
Growth Slowing

- Higher risk with longer acting formulations
- Studies have shown stimulants may be associated with a reduction in expected height gain at least in the first 1-3 years of treatment
- Small but statistically significant difference in puberty
- No difference in adulthood

Monitor
- Measure height every 6 months
- Plot height and weight on a growth chart

Try Medication Holidays
- If changes in height crosses two percentile lines, then consider “medication holiday”
- Refrain from medication on weekends or school holidays to allow “catch-up” growth

Insomnia

- More frequent with extended-release formulations

Monitor

- Determine a baseline sleep pattern, then monitor for changes
  - Many children with ADHD experience more frequent baseline sleep disturbances when compared to non-ADHD patients

## Insomnia

### Add Adjunctive Medication

<table>
<thead>
<tr>
<th></th>
<th>Off-label Initial Dose</th>
<th>Off-label Max Daily Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine</td>
<td>≤45 kg: 0.05 mg</td>
<td>≤45 kg: 0.3 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;45 kg: 0.1 mg</td>
<td>&gt;45 kg: 0.4 mg</td>
<td></td>
</tr>
<tr>
<td>Trazodone</td>
<td>25-50 mg</td>
<td>200 mg</td>
<td>Risk of priapism in males</td>
</tr>
<tr>
<td>(Antihistamines)</td>
<td>2-12 YO(10-50 kg): 1 mg/kg</td>
<td>50 mg</td>
<td>Younger patients may experience paradoxical</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td></td>
<td></td>
<td>excitement. Watch for anticholinergic</td>
</tr>
<tr>
<td></td>
<td>≥12 YO: 50 mg</td>
<td></td>
<td>side effects.</td>
</tr>
<tr>
<td>Melatonin</td>
<td>1 mg</td>
<td>Unknown</td>
<td>Limited studies available</td>
</tr>
</tbody>
</table>

Monitor

Reduce Dose

Try different medication

Add adjunctive medication

- Clonidine
- Trazodone
- Antihistamines
- Melatonin

---

Let’s try it!

R.W. is a 12-year-old male who presents to the clinic for chief complaint of insomnia. Patient’s mother says that since he was switched over to his new ADHD medication a week ago, “he does not sleep.” He was switched over from methylphenidate ER 36 mg (Concerta®) to amphetamine salts extended release (Adderall XR®) 10 mg due to appetite suppression and lack of ADHD response. Aside from the insomnia, she is pleased with his response to the medication and states that his behavior is much improved.

What should we do?

Reduce his dose! You decrease his amphetamine XR dose to 5 mg once daily and schedule them for a follow-up in a couple weeks.
Let’s try it!  (R.W. cont’d)

R.W.’s mother calls you after 1 week of being on the new dose to say that his ADHD is once again out of control. She has received multiple calls from the school and they eventually sent him home due to his behavior. He has not had any problems sleeping.

What should we do?
Try different medication!

*Change him to/add on short-acting products:* You keep him on amphetamine salts XR 5 mg qAM, AND add on amphetamine IR 5 mg at noon.

**OR**

*Change his medication:* Since he appeared to do better on amphetamine products than methylphenidate, you decide to change him to Vyvanse 20 mg.
Let’s try it! (R.W. cont’d)

After much trial and error with different medications, you conclude that R.W.’s ADHD responds best to the amphetamine salts extended release (Adderall XR®) 10 mg, but it still gives him trouble sleeping.

What should we do?

Add on an adjunctive medication! You decide to trial R.W. on clonidine 0.05 mg at bedtime.
• Whether stimulants cause tics in ADHD patients is unclear
  o Many patients with tic disorders have concurrent ADHD
  o Recent trials have not found an increase in tics from stimulants relative to placebo
  o Children with comorbid ADHD and tic disorders, on average, show a decline in tics with a stimulant

Monitor
Reduce Dose
Try different medication
Add adjunctive medication
• guanfacine
• clonidine

Try Different Medication
- Atomoxetine, guanfacine, and clonidene may a good alternate to stimulants

Add Adjunctive Medication
- If patient achieves best response to a stimulant that induces tics, then can add an alpha-agonist

<table>
<thead>
<tr>
<th></th>
<th>Initial Dose</th>
<th>Usual Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine</td>
<td>0.025 mg-0.05 mg</td>
<td>0.1-0.4 mg</td>
</tr>
<tr>
<td>Clonidine ER</td>
<td>0.1 mg</td>
<td></td>
</tr>
<tr>
<td>Guanfacine</td>
<td>0.5-1 mg</td>
<td>1-4 mg</td>
</tr>
<tr>
<td>Guanfacine ER</td>
<td>1 mg</td>
<td></td>
</tr>
</tbody>
</table>

**Emotional Lability**

**Monitor**
- Monitor timing and patterns to differentiate between medication effect vs “rebound” behavior
  - “Rebound” behavior is the phenomenon where behavior worsens later in the day when compared to in the morning
  - Children with ADHD are prone to “rebound” at baseline and the timing typically occurs around when their stimulant wears off
  - If it is determined to be rebound, then ADDING a low dose of an immediate release stimulant in the late afternoon may help

**Adjunctive Therapy**
- If labile behavior not present at baseline, then adjunctive therapy with neuroleptics or mood stabilizers is not recommended

Pliszka S et al. J Am Acad Child Adolesc Psychiatry. (2007);
Should I be worried about…?

Rare, but notable
Psychiatric Events

- **Uncommon occurrence**
  - Slight increase in rate of psychiatric events when compared to placebo
  - Not statistically significant (except atomoxetine)
  - Based on controlled trials and post marketing data

- **Atomoxetine had a statistically significant increase rate of suicidality**
  - Black box warning added in 2005

---

**Reported psychiatric events:**

- **Visual and tactile hallucinations** (especially of insects)
- **Symptoms of aggression**
- **Suicidality** (none completed)

---

### Psychiatric Events - What should we do about it?

<table>
<thead>
<tr>
<th>Take a thorough history</th>
<th>Initiating ADHD medication…</th>
<th>While on ADHD medication…</th>
<th>In the event of a psychiatric event, discontinue ADHD medication, consider different agent, and…</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prior psychiatric history</td>
<td>Little evidence to support increase risk of psychotic symptoms</td>
<td>Normal monitoring/adjustments</td>
<td>Do NOT add adjunctive neuroleptic or mood stabilizer</td>
</tr>
<tr>
<td>Family history/past history of psychosis</td>
<td>Not precluded from ADHD medication</td>
<td>Slower titration; More careful monitoring and recording of adverse effects</td>
<td>Adjust ADHD medication first, then may adjust treatment for underlying psychosis if necessary</td>
</tr>
</tbody>
</table>

Psychiatric Events - What should we do about it?

Take a thorough history
• Be mindful of comorbidities that increase risk of suicide (such as depression and conduct disorder)
• History of past serious suicide attempt

Advise families to monitor and communicate with prescriber
• Watch for emotional change or self-injurious thinking
• Especially in the first few months of initiating medication or changing dose

If suicidal thoughts emerge, discontinue medication
• Especially if symptoms are severe or abrupt in onset
• Especially if these were not part of the patient’s presenting symptoms

Follow-up
• Arrange for psychiatric evaluation (or re-evaluation)
• Continue to monitor patient’s progress carefully

Atomoxetine Suicide Risk
Small risk, but should discuss with patients and family

Concerns have been raised about the possibility of sudden cardiac death among children using stimulants. Extremely rare. Children using stimulants do not appear to have higher rates of sudden death than the general population. Caution can be exercised in children with preexisting cardiac issues.

**Rates of Sudden Death:**

- **General pediatric population**
  - 1.3-8.5/100,000 patient years

- **History of congenital heart disease**
  - Up to 6% by age 20

- **Children on methylphenidate**
  - 0.2/100,000 patient-years

- **Children on amphetamine**
  - 0.3/100,000 patient-years

- **Children on atomoxetine**
  - 0.5/100,000 patient-years

---

Cardiovascular Effects - What should we do about it?

Take thorough medical history

Does patient have heart disease or symptoms of significant cardiovascular disease?

Yes

Refer to cardiologist for consultation and evaluation of appropriateness of stimulant

No

No need for a cardiac evaluation

If stimulants initiated, patient should be monitored by cardiologists during course of treatment

Monitor heart rate and blood pressure before and after dose changes and every 6 months

“Symptoms of significant cardiovascular disease…”

- Severe palpitations
- Exercise intolerance not accounted for by obesity
- Fainting
- Chest pain
- Arrhythmias
- Hypertension

Known history of...

- Postoperative tetralogy of Fallot
- Coronary artery abnormalities
- Subaortic stenosis
- Hypertrophic cardiomyopathy
- Wolf-Parkinson-White syndrome
- Long QT syndrome
- Strong family history of sudden death

Thank you!

Questions?