Presentation Information

1:45 – 2:45pm

Treatment of ADHD in Adolescents

SPEAKER
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Presenter Disclosure Information

The following relationships exist related to this presentation:
► Thomas Cummins, MD, has no financial relationships to disclose.

Off-Label/Investigational Discussion
► In accordance with pmICME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Treatment of ADHD in Children and Adolescents

Learning Objectives
- Identify the core symptoms of ADHD
- Consider patient factors and the pros and cons of ADHD drugs when selecting treatment

Treatment Planning

Core ADHD symptoms ➞ Medication
Remaining behavior symptoms ➞ Environmental modification and contingency management
Skills deficits ➞ Specific remediation
- Academic
- Social
Comorbidity ➞ Comorbidity-specific treatment

Medication Algorithm
1. Methylphenidate or amphetamine
2. A different stimulant
3. Atomoxetine
4. Guanfacine
5. Clonidine
6. An antidepressant (buproprion or tricyclic)*
7. Another class of antidepressants*
8. Modafinil*

*not FDA approved for this indication

**Stimulants:**

**Practical Considerations**

- Start with methylphenidate or amphetamine.
- Short-acting easier to titrate.
  - Especially in young children.
- May wish to switch to long-acting.
- Start with long-acting in teenagers.
- Titrate to optimum response.
- If one stimulant not effective, try the other.

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**Advantages of Long-Acting Stimulants**

- Improved adherence.
- Eliminates school dose.
- Smoother action.
- Less rebound?
- Adolescents – improved evening driving.
  - Methylphenidate extended release vs methylphenidate TID.

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**Disadvantages of Long-Acting Stimulants**

- Can’t sculpt dose and timing as precisely.
- Side effects in evenings?
  - Appetite.
  - Sleep.

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**Stimulant Titration: Try Full Range**

Absolute doses, with mg/kg as rough guide:

- Methylphenidate 5, 10, 15 (20) mg.
  - 0.3 - 0.7 mg/kg/dose.
- Dextroamphetamine or mixed salts amphetamine or AMP or dexamphetamine 2.5, 5, 7.5, (10) mg.
  - 0.15 - 0.35 mg/kg/dose.

Target symptoms determine:

- BID vs TID.
- 5 days vs 7 days.

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**Stimulant Titration**

Usual maximum total daily dose – 60 mg or equivalent of immediate release methylphenidate.

- 72 mg oral extended-release methylphenidate (Concerta).
- 30 mg dextroamphetamine or mixed salts amphetamine.
- 30 mg dexamphetamine (Focalin).
- 30 mg transdermal long-acting methylphenidate (Daytrana).
- 70 mg lisdexamfetamine (Vyvanse).

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**Considerations for Stimulant Titration**

- Parent and Teacher Rating Scales.
- Target Symptoms.
- Daily Report Card.
- Side Effects.
- Adherence.

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Stimulant Titration

- Target is normalized functioning
- Don’t settle for partial response
- Tailor regimen to child’s schedule

Stimulant Titration: Alternatives to High Doses

- Improved adherence
- Reduced stressors
- Different drug
- Different class, teacher, school
- Add behavioral treatment
- More reasonable expectations
- Adjunctive drug
- Reassessment – differential diagnosis or comorbidity

Dexmethylphenidate (Focalin)

- Only the D-isomer
- Give half the methylphenidate dose
- Fewer side effects?
- Longer duration than methylphenidate?
- Has extended release formulation: Focalin XR

Methylphenidate Long-Acting Preparations

- Metadate CD 8-hour action
  - Diffucaps - Capsules with beads
    - 30% short acting 70% long acting
    - 20 mg capsule = 6 mg immediate release + 14 mg long acting
- Ritalin LA – 8-10 hours
  - Capsules with micro-beads
  - 50/50 immediate-release and extended-release

Concerta (Extended-Release Methylphenidate)

- Q 12 hour dosing
- Non-soluble shell
  - Risk of laryngeal or GI obstruction
  - Passes intact through GI track
- MPH immediate release coat (acts ≤1 hour)
- MPH in compartments (10% of total stays in)
- Laser-drilled hole
- Same duration at all doses
- Generic now available

Converting to Concerta Doses

<table>
<thead>
<tr>
<th>Methylphenidate</th>
<th>Concerta</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg TID</td>
<td>18 mg OROS QD (4 mg overcoat)</td>
</tr>
<tr>
<td>10 mg TID</td>
<td>36 mg OROS QD (8 mg overcoat)</td>
</tr>
<tr>
<td>15 mg TID</td>
<td>54 mg OROS QD (12 mg overcoat)</td>
</tr>
</tbody>
</table>

Some patients (especially adolescents) may require and tolerate 72 mg (FDA approved maximum)

OROS = Osmotic [Controlled] Release Oral [Delivery] System
Daytrana
(Methylphenidate Transdermal Patch)

- Applied daily
- Worn for 9 hours for 12 hour duration
  - Effect within 1-2 hours
  - Lasts 3 hours after removed
  - Can remove sooner for shorter duration
- Unique side effects
  - Skin discomfort
  - Rare (<1%) sensitization to oral methylphenidate

Daytrana Dosing

- Start with 10 mg patch and titrate up
- Conversion from methylphenidate

<table>
<thead>
<tr>
<th>Previous Methylphenidate Sustained Release Dose</th>
<th>Daytrana</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-20 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>25-30 mg</td>
<td>15 mg</td>
</tr>
<tr>
<td>35-40 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>45-55 mg</td>
<td>30 mg</td>
</tr>
</tbody>
</table>

Dextroamphetamine IR
(Immediate Release)

- Duration: 4-5 hours
- IR amphetamine lasts longer than IR methylphenidate
- May have academic and behavioral positive effects up to 7-10 hours after single dose

Mixed-Salts Amphetamine

- Adderall or generic (4-5 hour)
- Adderall XR capsule (10-12 hour)
  - Coated beads in capsule
    - 50:50 immediate and delayed release
    - Two pulses – like IR q 4 hours x 2
  - Equivalent effect to methylphenidate TID
  - Longer duration with increasing dose

Lisdexamfetamine dimesylate (Vyvanse)

- Amphetamine prodrug
  - d-amphetamine bound to l-lysine
- Rapidly absorbed
- Rate-limited hydrolysis in liver and gut
- Once daily – effective from 1.5 hours until 6 pm or 12-13 hours after dose (like Adderall XR)
- Lower abuse potential, but still Schedule II

Lisdexamfetamine (Vyvanse)
Use and Dosing

- Start with 30 mg and titrate up by 10 or 20 mg increments
- Maximum recommended dose 70 mg
- Capsule may be opened and sprinkled on food or dissolved in water (take immediately)
- Do not try to divide capsule dose
Drug Abuse or Diversion

If misuse is a risk, select
- Concerta (MPH)
  - Osmotic sponge - can't grind and snort or inject
- Daytrana patch (MPH)
- Vyvanse (lisdexamfetamine)
  - Enzyme saturates
- Non-stimulant

Stimulants

Common Side Effects

- Irritability
- Headaches
- Abdominal pain
- Reduced appetite
- Weight loss
- Insomnia

Stimulants and the Heart

- Possible increased risk of sudden death?
  - FDA warning in 2006
  - Now 3 large studies showing no increased risk of adverse cardiac events
- AAP guideline – ECG is not recommended before stimulant treatment in healthy child
  - Screen for patient and family history of cardiac symptoms

Stimulant Side Effect Controversies

<table>
<thead>
<tr>
<th>Tics</th>
<th>Stimulants rarely cause or exacerbate tics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth</td>
<td>Stimulant effect on growth is rarely clinically significant</td>
</tr>
<tr>
<td>Seizures</td>
<td>Stimulants as prescribed do not increase seizures</td>
</tr>
<tr>
<td>Drug abuse</td>
<td>Stimulants as prescribed do not lead to drug abuse</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>Stimulants do not precipitate bipolar disorder</td>
</tr>
</tbody>
</table>

Stimulant Side Effects:

Tics or Tourette’s Syndrome

- ADHD symptoms more impairing
- Other drugs not as effective
- Most tics do not worsen, some improve
- Natural history of tics and Tourette’s

Stimulant Side Effects:

Growth

- Studies inconsistent regarding height
- Monitor height and weight
- Adjust foods and mealtimes
- Catch-up growth when off medication
- Temporary height deficits may be related to ADHD
- Some ADHD kids bigger to start with
Stimulant Side Effects:

Drug Abuse

- No evidence for stimulant-induced increase
- Successful treatment may decrease drug abuse
- Drug abuse more likely with comorbid ODD or CD
- Monitor medication carefully
- GAO survey of principals - diversion rare

ODD = oppositional defiant disorder
CD = conduct disorder
GAO = General Accounting Office (of the US federal government)

PATS: Preschool ADHD Treatment Study

- 3 to 5.5 years old
- Parent management training lead-in
- MPH works in 3–6 year olds
  - Mean best total daily dose MPH-IR: 14 mg
  - Effect sizes smaller than for school-age children

PATS: Methylphenidate Side Effects

- Qualitatively same as older kids
- More common and severe
  - Emotional outbursts
  - Trouble falling asleep
  - Repetitive behaviors/thoughts
  - Decreased appetite
  - Irritability, sadness

PATS: Atomoxetine (Strattera)

- Selective norepinephrine reuptake inhibitor
- Double-blind placebo controlled trials in kids with ADHD
- Effect size smaller than stimulants
- ODD comorbid symptoms
  - Improvement greater at 1.8 mg/kg/day than 1.2 mg/kg/day

ODD = oppositional defiant disorder

Other Medications

- Atomoxetine
- Alpha adrenergic agents
- Antidepressants*
- Modafinil*

*Not FDA approved for ADHD

Atomoxetine Dosing

- Effective once a day, despite plasma half-life of 4 hours
- Give with food at breakfast and/or dinner
- Divide BID if side effects
- Start with 0.5 mg/kg/day for about a week
- Increase to initial target dose 1.2 mg/kg/day
- Maximum 1.4 mg/kg/day (studies up to 1.8 mg/kg/day)
- Safe to combine with stimulants, if necessary
Atomoxetine Side Effects

- Decreased appetite, weight loss
- Nausea, vomiting
- Dizziness
- Tiredness, sedation
- Slight increase in pulse and blood pressure
- Irritability
- If comorbid bipolar, manic activation
- Contents of capsule caustic to eyes

Atomoxetine: Suicidal Ideation

2005 – bolded warning added to label
- Increased risk of suicidal ideation in children or adolescents
- No suicides occurred in clinical trials
- Patients started on therapy should be monitored closely

http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021411s044lbl.pdf

Atomoxetine Liver Side Effects

2004 FDA label bolded warning:
- Potential for severe liver injury
- 2 reports: a teenager and an adult taking atomoxetine for several months
- Both recovered

2009 6 more reports (5 in kids)
- Liver function test (LFT) monitoring not recommended
- Stop drug and get LFTs if signs of liver damage
  - Jaundice, fatigue, decreased appetite, nausea, vomiting, pruritus, dark urine, upper right quadrant tenderness

Atomoxetine When might it be the first choice?

- Family refuses stimulants
- Pre-existing
  - Severe problems in AM
  - Insomnia
  - Low weight or picky eater
- Adolescent or college student who might share stimulant
- Schedule II prescription very problematic

Antidepressants*

- Can trigger manic episode
- Efficacy of bupropion and tricyclic antidepressants (TCAs) demonstrated for ADHD, not for youth depression

*Bupropion and TCAs are FDA-approved for major depressive disorder in adults; not approved for ADHD
**Bupropion (Wellbutrin)**
- Efficacy near methylphenidate
- Side effects
  - Tics
  - Seizures
- FDA-approved for major depressive disorder in adults, not ADHD

**Alpha Adrenergic Agents**

**Guanfacine**
- Short-acting (Tenex)*
- Long-acting (Intuniv)

**Clonidine**
- Short-acting (Catapres)*
- Long-acting (Kapvay)
  - BID dosing

*Not FDA-approved for ADHD

**Clonidine - Parent Education**
- Don’t tinker
- Don’t stop suddenly (rebound hypertension)
- Takes weeks to months for full effect
- Sedation decreases after 2-4 weeks
- Chewing patch leads to overdose

**Modafinil**
- Anti-narcoleptic agent
- Action similar to stimulants but does not appear to stimulate brain reward centers (low abuse liability)
- Single double-blind placebo-controlled trial showed efficacy in ADHD (170 – 425 mg QD) but...
  - …not given FDA approval due to small incidence of Stevens-Johnson like rashes

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*Conners K et al. J Amer Acad Child and Adol Psychiatry. 1996;35:1314-1321

Summary

- Stimulants remain the most effective pharmacologic treatment for ADHD
- Other effective agents include atomoxetine, TCAs, bupropion and alpha-adrenergics
- Although the primary treatment of ADHD is pharmacologic, psychosocial interventions should be added to treat comorbidities or when pharmacologic treatment alone does not produce an adequate treatment response