Pharmacological Treatment of ADHD

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# Immediate Release Stimulants

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
<th>Daily Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPH (Ritalin®, Metadate®, others)</td>
<td>20-60 minutes</td>
<td>~2 hours (Range 0.3-4 hours)</td>
<td>3-6 hours</td>
<td>2-3</td>
</tr>
<tr>
<td>D-Amphetamine (Dexedrine®, Dextrostat®)</td>
<td>20-60 minutes</td>
<td>1-2 hours</td>
<td>4-6 hours</td>
<td>2-3</td>
</tr>
<tr>
<td>D,L-Amphetamine (Adderall®)</td>
<td>30-60 minutes</td>
<td>1-2 hours</td>
<td>4-6 hours</td>
<td>2</td>
</tr>
</tbody>
</table>
Limitations of Immediate Release Stimulants

- Short half-life
- Multiple daily doses to provide coverage beyond school hours
  - Compliance issues
- Uneven coverage due to short half-life
  - Trough periods between doses
  - ‘Roller coaster effect’
- Administration at school
  - Embarrassment
  - Potential for diversion
<table>
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<th>Duration</th>
<th>Daily Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPH (Ritalin SR®, Metadate® ER, Methyl® ER)</td>
<td>60-90 minutes</td>
<td>~5 hours (Range 1.3-8.2 hours)</td>
<td>5-8 hours</td>
<td>2</td>
</tr>
<tr>
<td>D-Amphetamine (Dexedrine® spansules)</td>
<td>60-90 minutes</td>
<td>NA</td>
<td>6-8</td>
<td>2</td>
</tr>
</tbody>
</table>
Second Generation Sustained-Release Stimulants

• New technology
• Quicker onset than first generation agents
• Allows for once-daily dosing
# Long-Acting Methylphenidate Formulations

<table>
<thead>
<tr>
<th>Products</th>
<th>Concerta®</th>
<th>Metadate® CD</th>
<th>Ritalin® LA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation Technology</td>
<td>OROS®</td>
<td>Diffucaps®</td>
<td>SODAS™</td>
</tr>
<tr>
<td>Dose</td>
<td>18mg 27mg 36mg 54mg</td>
<td>10mg 20 mg 30mg 40mg 50mg 60mg</td>
<td>10mg 20mg 30mg 40mg</td>
</tr>
<tr>
<td>Immediate Release</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>22% 4mg 6mg 8mg 12mg</td>
<td>30% 3mg 6mg 9mg 12mg 15mg 18mg</td>
<td>50% 5mg 10mg 15mg 20mg</td>
</tr>
<tr>
<td>Sustained/2nd release</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>78% 14mg 21mg 28mg 42mg</td>
<td>70% 7mg 14mg 21mg 28mg 35mg 42mg</td>
<td>50% 5mg 10mg 15mg 20mg</td>
</tr>
</tbody>
</table>
Comparison of Extended-Release Methylphenidate Dosage Forms

Data on file, Novartis Pharmaceuticals.
Sustained-Release Amphetamine (Adderall XR®)

- Mimics the action of IR amphetamine given BID
- Alternative to MPH-based stimulants
- Pulse-delivery system
  - Equal portions of IR and XR beads within capsule
  - IR beads release immediately after ingestion
  - XR beads release 4 hours later
- Food delays $T_{\text{max}}$ by 2.5 hours, but not extent of absorption
- Available in 5, 10, 15, 20, 25, and 30mg capsules
Dexmethylphenidate (Focalin®)

- d-threo (active) enantiomer of MPH
- Selectively distributes to CNS striatum
- IR and XR formulations available
- XR formulation similar release mechanism to sustained-release amphetamine
  - 50% IR, 50% XR beads within capsule

- No real evidence for decreased side effects or better tolerability
- Weigh cost vs. benefit
Lisdexamfetamine (Vyvanse®)

- Dextroamphetamine prodrug (inactive until metabolized)
- Hypothesized to have lower abuse potential
  - Still classified as CII
- Recommended starting dose (children and adults) or dose when switching from other agents is 30mg
- Capsule may be taken whole or opened and dissolved in water
- $T_{\text{max}} = 3.5$ hours, Duration 12 hours
- Lisdexamfetamine 30, 50, 70mg = amphetamine XR 10, 20, 30mg (efficacy and duration)
- Available doses 20, 30, 40, 50, 60, 70mg
Transdermal Methylphenidate (Daytrana™)

- Approved for use in children aged 6-12 years
- Applied for 9 hours, works for ~12 hours
- Flexible dosing
  - Regulate hours of coverage by taking off or leaving on
  - Symptom improvement in 4-6 hours
- Patch size conversion to MPH dose delivered over 9 hours
  - $12.5 \text{ cm}^2 = 10 \text{ mg}$
  - $18.75 \text{ cm}^2 = 15 \text{ mg}$
  - $25 \text{ cm}^2 = 20 \text{ mg}$
  - $37.5 \text{ cm}^2 = 30 \text{ mg}$

Methylphenidate transdermal system [Daytrana] Prescribing Information, Wayne, PA, Shire US; 2006
Deciding Between Stimulant Formulations

• Immediate-release vs. sustained-release
• Side effect profiles are similar
• Differences in pharmacokinetic profiles
• Cost
Non-Stimulant Treatment Options
Atomoxetine (Strattera®)

- Norepinephrine reuptake inhibitor
- Less effective than stimulants
  - Modest effect size with atomoxetine vs. large effect size with stimulants
- No known abuse potential; not a controlled substance
- Approved for >6 years of age, adolescents, and adults
- Duration of action ~ 8 hours
- Dosed QD or BID
  - If dosed BID, give 2nd dose late afternoon/early evening to decrease insomnia
- Available strengths: 10mg, 18mg, 25mg, 40mg, 60mg, 80mg, 100mg capsules
- May take 3-6 weeks for maximum benefit
### Atomoxetine Dosing

<table>
<thead>
<tr>
<th>Child’s Weight Range (pounds)</th>
<th>Starting Dose (Minimum of 3 days)</th>
<th>Target Dose: Titrate to target dose – either QD or BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-62</td>
<td>18 mg</td>
<td>25 mg</td>
</tr>
<tr>
<td>63-93</td>
<td>25 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>94-126</td>
<td>40 mg</td>
<td>60 mg</td>
</tr>
<tr>
<td>127+</td>
<td>40 mg</td>
<td>80 mg</td>
</tr>
</tbody>
</table>

(100 mg Max)
Non-Stimulant Treatment Options

• Bupropion
  – Efficacy data for treating hyperactivity and impulsivity
  – Less effective than stimulants with a higher rate of side effects in children than MPH
  – Not FDA-approved for use in children

• Tricyclic Antidepressants
  – Desipramine, imipramine, nortriptyline
    • High rates of adverse events, especially in children
Non-Stimulant Treatment Options

- Alpha agonists (clonidine, guanfacine)
  - Less effective than stimulants
  - May be used as monotherapy or in combination with stimulants
  - May be beneficial in patients with tics
  - Generally well-tolerated in children
    - Monitor for hypotension and daytime sedation
  - Should be reserved for monotherapy after stimulants, atomoxetine, and antidepressants have failed
Treatment Resources

• Children’s Medication Algorithm Project (CMAP)
  – Treatment algorithm for ADHD
  http://www.dshs.state.tx.us/mhprograms/CMAP.shtm