Stimulants

• 2 categories: MPH and AMP
  – Produced in single dextro isomer or in racemic version.

• Switching between stimulants
  – 1991 study showed non-response rate dropped from 32% to 4% when able to switch between dextroamphetamine and MPH.
Stimulants

• Likely more non-responders with comorbidities.
• Studies often don’t include placebo, so actual stimulant response rate might be closer to 55%.
MPH

- Active ingredient of majority of stimulant prescriptions in the US.
  - Large effect size (0.91)
- Rapid absorption, effects within 30min and 3-5hr duration of action.
  - Peak plasma concentration by 90min.
MPH

- Dexmethylphenidate HCl (Focalin) is the d-threo enantiomer of racemic MPH.
  - d-threo enantiomer > active than l-threo.
- Plasma concentration increases rapidly after ingestion, reaching a maximum in fasting state 1 to 1.5hrs postdose.
Long-Acting MPH

- Single-pulse
  - Metadate ER
  - Methylphenidate ER
- Wax-matrix preparation to prolong release
- Slower onset of action than IR and lower serum concentrations
- 6-8hr duration, give with IR to compensate
Long-Acting MPH

• Dual-pulse
  – Metadate CD
  – Ritalin LA
  – Focalin XR
Long-Acting MPH

• Beaded MPH products, using SODAS (Spheroidal Oral Drug Absorption System)
  – Mix of IR and DR beads
• Ritalin LA mimics giving IR MPH in two doses 4hrs apart
• Focalin XR uses same SODAS technology.
Long-Acting MPH

• OROS MPH, simulating triple-pulse
• Osmotic delivery system to reduce ADHD symptoms for up to 12hrs.
• IR MPH is applied to the outside of the OROS caplet for immediate intervention.
• Slightly ascending MPH serum concentration curve.
Long-Acting MPH

• OROS MPH
  – Mimics serum concentrations produced by taking IR MPH
AMP

• Racemic
  – Adderall and Adderall XR

• Dextro isomer
  – Dextroamphetamine (Dexedrine)
  – Lisdexamfetamine (Vyvanse)
AMP

- Plasma levels peak 3hrs after po administration.
- Acidification of urine increases urinary output.
  - Taking AMP with fruit juices decreases absorption.
AMP

• Effects can be seen within 1hr of ingestion, and duration of action is up to 5hrs.
  – Duration of action longer than MPH.
Long-Acting AMP

• Adderall XR
  – Capsule preparation of IR and ER beads.

• Lisdexamfetamine dimesylate (Vyvanse)
  – Inactive parenterally
  – d-amphetamine is covalently bonded to l-lysine; bond is cleaved during digestion.
  – Treatment effects up to 12hrs.
# Summary MPH

<table>
<thead>
<tr>
<th>Medication</th>
<th>Duration of Action</th>
<th>Starting Dose</th>
<th>Typical Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPH</td>
<td>3-5hrs</td>
<td>5mg BID or TID</td>
<td>10mg TID</td>
</tr>
<tr>
<td>Dexmethylphenidate (Focalin)</td>
<td>5-6hrs</td>
<td>2.5mg BID or TID</td>
<td>10mg BID</td>
</tr>
<tr>
<td>Metadate ER</td>
<td>Single pulse</td>
<td>20mg/am</td>
<td>40mg/am</td>
</tr>
<tr>
<td>Metadate CD</td>
<td>8-10hrs; dual pulse</td>
<td>20mg/am</td>
<td>30mg/am</td>
</tr>
<tr>
<td>OROS MPH (Concerta)</td>
<td>8-12hrs; ascending single pulse</td>
<td>18mg/am</td>
<td>36mg/am</td>
</tr>
</tbody>
</table>
## Summary AMP

<table>
<thead>
<tr>
<th>Medication</th>
<th>Duration of Action</th>
<th>Starting Dose</th>
<th>Typical Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMP</td>
<td>4-6hrs</td>
<td>5mg BID</td>
<td>10mg BID</td>
</tr>
<tr>
<td>Dextroamphetamine (Dexedrine)</td>
<td>4-6hrs</td>
<td>5mg BID</td>
<td>10mg BID</td>
</tr>
<tr>
<td>Adderall XR</td>
<td>8-10hrs; dual pulse</td>
<td>5mg/am</td>
<td>30mg/am</td>
</tr>
<tr>
<td>Lisdexamfetamine (Vyvanse)</td>
<td>13-14hrs</td>
<td>30mg/am</td>
<td>50mg/am</td>
</tr>
</tbody>
</table>
Stimulants and Tics

• 1995 controlled trial involving children with ADHD and chronic tic disorder taking MPH.
  – Significant improvement in ADHD s/s without consistent worsening or increase in tic frequency for all subjects.
Stimulants and Anxiety

• 1995 controlled study tested MPH on youth with co-morbid anxiety symptoms.
  – Equally good response for +/- anxiety.

• Meta-analysis of 23 studies involving 2,959 youth with ADHD found stimulant treatment reduced risk for anxiety vs. placebo.
Stimulants and Adverse Events

• A 2005 FDA review reported 135 adverse event reports for OROS MPH out of 1.3 million cases.
  – 36 psychiatric adverse events
    • 12 instances of tactile and visual hallucinations
  – 20 cardiovascular events
Stimulants and Adverse Events

- AACAP Work Group on Quality Issues
  - Rate of sudden, unexpected death is about 0.5 per 100,000 patient-years taking mixed salt AMP and 0.19 per 100,000 patient-years for MPH.
  - In general population, 1.3-1.6 per 100,000 patient years.
Atomoxetine

- SNRI
- First drug approved by FDA to treat ADHD in both youth and adults.
- Widely used treatment algorithms recommend this as 2nd line to stimulants.
- Medium effect size (0.64).