SO MANY OPTIONS, SO LITTLE FOCUS: NAVIGATING THE WORLD OF ADHD MEDICATIONS
Learning Objectives

• Differentiate the spectrum of medications available for ADHD based on pharmacokinetic and clinical profiles

• Customize ADHD medication selection to the daily functional needs of the patients
Undertreatment of Adult ADHD

• The 2012 and 2013 National Health and Wellness Survey (NHWS), US study

• Of a total of 22,397 US adults who participated in the survey, 465 self-reported a diagnosis of ADHD. ADHD-like symptoms were screened using the adult self-report scale version 1.1 (ASS-v1.1)

• In patients who self-reported an ADHD diagnosis, 62.6% reported not currently using a prescription medication to treat it

Prevalence Rates of Psychiatric Disorders in U.S. Adults

ADHD in Adults Age >50

- Adult ADHD prevalence longitudinal aging study Amsterdam (LASA)
- Prevalence of syndromic ADHD in adults: 2.8%
- Prevalence of symptomatic ADHD in adults: 4.2%
- Men and women reported similar levels of symptoms

Identification and Assessment of Late-Life ADHD in US Memory Clinics

• ONLY 1 of 5 clinics reported screening regularly for ADHD (62 of 165 sites responded to survey)
• 1/2 reported seeing ADHD patients
  – 60% reported contact with previously diagnosed ADHD patients
• ADHD symptomatology may not have been considered as pre-morbid baseline cognitive functioning

Diagnostic Issues
Age of Diagnosis

<table>
<thead>
<tr>
<th>Age</th>
<th>Child Diagnosis</th>
<th>Adult Diagnosis</th>
<th>Adult Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ADHD

Executive Dysfunction

Emotional dysregulation

Performance Impairment

Social Impairment

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Adult ADHD and Comorbidities
Case Presentation: Diagnostic Prioritization for Pharmacotherapy

Order of treatment also considers the severity of the concurrent disorders.

Alcohol and substance abuse

Mood disorders
- Bipolar and MDD
- Mood disorders

Anxiety disorders
- Obsessive-compulsive disorder, generalized anxiety disorder, panic

ADHD

Research Support for Diagnostic Prioritization

“In our clinical experience, consistently with other authors, patients with ADHD-BD should be treated for BD first. Based on the current level of information, we do not recommend treatment of comorbid ADHD-BD with ADHD medications in the absence of mood stabilizers.”

Bipolar Disorder: Risk of Mania With Methylphenidate

- Swedish national registries
- 2307 bipolar adults, 2006-2014
- MPH with and without mood stabilizers
- Mania defined: hospitalization or new dispensation of stabilizing medication
- 0-3 months and 3-6 months after medication start following non-treated periods
## Bipolar Disorder: Risk of Mania With Methylphenidate

<table>
<thead>
<tr>
<th></th>
<th>HAZARD RATIO 0-3 months</th>
<th>3-6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPH without mood stabilizer</td>
<td>6.7 (95%CI=2.0-22.4)</td>
<td>similar</td>
</tr>
<tr>
<td>MPH with mood stabilizer</td>
<td>0.6 (95%CI=0.4-0.9)</td>
<td>similar</td>
</tr>
</tbody>
</table>

Treatment Options and Medication
Treatment Options

• Diagnoses (what’s there, what’s not)

• Education (what this is, what it’s not)

• Environmental changes (academic, occupational, social, family)

• Psychopharm/Psychotherapies
  • Behavior, social, individual, family, couples
  • Support associations (www.CHADD.org)
How Formulation Influences Medication Effects: Pharmacokinetics

Formulation → Absorption → Distribution → Metabolism → Elimination

- Onset of action
- Offset effects (rebound)
- Consistency of plasma levels across time
- Variability of plasma levels across patients
- Duration of action
- Parent drug/active metabolites
Formulation Effects on Plasma Concentration

Coating

• Differences in drug release depending on type of coating
  • Insoluble
  • pH dependent
  • Slowly erodible

Osmotic Controlled-Release Oral Delivery System (OROS)

Coating: drug, binders

Semipermeable rigid membrane

First compartment: low concentration of drug

Second compartment: high concentration of drug

Third compartment: molecules that react with water

Opening

Stahl, Mignon. Stahl's Illustrated Attention Deficit Hyperactivity Disorder 2009.
Transdermal Patch
Transdermal Formulations:

Patch

- Impermeable covering membrane
- Drug
- Adhesive
- Skin
- Capillary

Stahl, Mignon. Stahl's Illustrated Attention Deficit Hyperactivity Disorder 2009.
Transdermal Formulations

**Advantages**
- Avoids first-pass metabolism (may reduce side effects, increase efficacy)
- Steady plasma concentrations
- Longer duration of action

**Disadvantages**
- Patches can be large/visible
- Local skin irritation/rash
- Patches may inadvertently come off
- Proper disposal

Stimulant Mechanisms of Action

AMPH causes release of DA and NE through transporter

AMPH is taken up into cell

AMPF blocks uptake into vesicle

AMPF diffuses into vesicle, causing DA release into cytoplasm

Storage vesicle

Cytoplasmic DA

DA Transporter protein

Synapse

ATOX, DES

AMPH and MPH inhibit

# Methylphenidate Preparations

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Duration of Action</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic methylphenidate</td>
<td>2-3 hrs</td>
<td>tablet</td>
</tr>
<tr>
<td>Methylin liquid</td>
<td>2-3 hrs</td>
<td>liquid</td>
</tr>
<tr>
<td>MPH SR LA</td>
<td>4 hrs</td>
<td>wax matrix</td>
</tr>
<tr>
<td></td>
<td>8 hrs</td>
<td>beaded (50%:50%)</td>
</tr>
<tr>
<td>OROS MPH</td>
<td>12 hrs</td>
<td>OROS</td>
</tr>
<tr>
<td>MPH ER</td>
<td>6-8 hrs</td>
<td>beaded</td>
</tr>
<tr>
<td>MPH CD</td>
<td>8 hrs</td>
<td>beaded (30%:70%)</td>
</tr>
<tr>
<td>MPH chewable</td>
<td>8 hrs</td>
<td>chewable</td>
</tr>
</tbody>
</table>
# Methylphenidate Preparations

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>DexMPH XR</td>
<td>3 hrs 10 hrs</td>
</tr>
<tr>
<td>MPH Delayed ER (PM dosing)</td>
<td>beaded</td>
</tr>
<tr>
<td>MPH ER liquid</td>
<td>12 hrs</td>
</tr>
<tr>
<td>MPH (long duration)</td>
<td>Beaded (20%:80%)</td>
</tr>
<tr>
<td>MPH-ODT ER</td>
<td>12 hrs</td>
</tr>
<tr>
<td>MPH transdermal patch</td>
<td>patch</td>
</tr>
<tr>
<td>MPH XR</td>
<td>Peaks at 2 hrs and then again at 8 hrs (biphasic)</td>
</tr>
<tr>
<td>Preparation</td>
<td>Duration of Action</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Liquid AMPH</td>
<td>2-3 hrs</td>
</tr>
<tr>
<td>Dextrostat</td>
<td>2-3 hrs</td>
</tr>
<tr>
<td>Dextroamphetamine spanules</td>
<td>4 hrs</td>
</tr>
<tr>
<td></td>
<td>6 hrs</td>
</tr>
<tr>
<td>Amphetamine (racemic)</td>
<td>6 hrs</td>
</tr>
</tbody>
</table>
## Amphetamine Preparations

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Duration of Action</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed AMPH salts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>XR</td>
<td>6 hrs</td>
<td>tablet</td>
</tr>
<tr>
<td>Triple beaded</td>
<td>Up to 12 hrs</td>
<td>beaded (50%:50%)</td>
</tr>
<tr>
<td></td>
<td>Up to 16 hours</td>
<td>beaded (33%:33%:33%)</td>
</tr>
<tr>
<td>d-Amphetamine-ODT ER</td>
<td>12 hrs</td>
<td>Dissolvable tab</td>
</tr>
<tr>
<td>d-Amphetamine ER</td>
<td>12 hrs</td>
<td>liquid</td>
</tr>
<tr>
<td>Lisdexamfetamine chewable</td>
<td>Up to 14 hrs</td>
<td>prodrug</td>
</tr>
<tr>
<td></td>
<td>Up to 14 hrs</td>
<td>chewable</td>
</tr>
</tbody>
</table>
Triple-Bead Mixed Amphetamine Salt

- Triple-bead mixed amphetamine salts (MAS) formulation that may help with improved attention, with once-daily dosing
  - Dosing: 12.5 to 25 mg once a day (>13 yo) or 50 mg (adults)
  - Capsules: 12.5, 25, 37.5, 50 mg
  - Duration of action: 16 hours (onset at 2-4 hours)

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Daily Dosage</th>
<th>$T_{max}$ (mean, hours)</th>
<th>$T_{1/2}$ (mean, hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$d-l$-amphetamine: 8 (in adults)</td>
<td>$l$-amphetamine: 10-13 (in children &amp; adults)</td>
</tr>
</tbody>
</table>

Triple-Bead Technology

Immediate-release bead

Extended-release bead I

Extended-release Bead II
**Differences Between Mixed Amphetamine Salts**

<table>
<thead>
<tr>
<th>Mixed amphetamine salts (MAS)</th>
<th>Release characteristics</th>
<th>Duration of effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAS IR</td>
<td>100% immediate-release table</td>
<td>~ 6 hours</td>
</tr>
<tr>
<td>MAS XR</td>
<td>2 types of beads per capsule:&lt;br&gt;- 50% immediate release&lt;br&gt;- 50% delayed release (pH 5.5)</td>
<td>~ 12 hours</td>
</tr>
<tr>
<td>Triple-bead MAS</td>
<td>3 types of beads per capsule:&lt;br&gt;- 33% immediate release&lt;br&gt;- 33% delayed release (pH 5.5)&lt;br&gt;- 33% delayed release (pH 7.0)</td>
<td>~ 16 hours</td>
</tr>
</tbody>
</table>
Non-Stimulants

• Atomoxetine

• Guanfacine ER
• Clonidine ER

Off-label:
• Bupropion (3 positive controlled adult trials)
• Desipramine (positive adult trial)
• Modafinil
# FDA-Approved Medications for Adults With ADHD

## Daily Dosing

<table>
<thead>
<tr>
<th>Medication</th>
<th>Child dosing</th>
<th>Adolescent dosing</th>
<th>Adult dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atomoxetine</td>
<td>0.5 mg/kg (&lt;70kg)</td>
<td>5mg</td>
<td>40mg max 100 mg</td>
</tr>
<tr>
<td>Dextroamphetamine XR</td>
<td>max 1.2 mg/kg (max 100 mg)</td>
<td>max 20 mg</td>
<td>max 20 mg</td>
</tr>
<tr>
<td>Lisdexamfetamine</td>
<td>30 mg max 70 mg</td>
<td>30 mg max 70 mg</td>
<td>30 mg max 70 mg</td>
</tr>
<tr>
<td>Mixed amphetamine salts XR</td>
<td>10 mg max 30 mg</td>
<td></td>
<td>20 mg max-none</td>
</tr>
<tr>
<td>OROS Methylphenidate HCL</td>
<td>18 mg max 54 mg</td>
<td>18 mg max 72 mg</td>
<td>18 or 36 mg max 72</td>
</tr>
<tr>
<td>Mixed amphetamine salts triple bead</td>
<td>12.5 mg max 25 mg</td>
<td></td>
<td>12.5 mg max 50 mg</td>
</tr>
</tbody>
</table>
ADHD Medication Sequencing

- **Methylphenidate**
- **Amphetamine**

**Delivery System Technology**
- Beaded
  - (IR/ER ratio, double/triple beaded)
  - (beads-ph dependent, non-ph dependent)
- OROS (osmotic release)
- Microparticles (liquid/dissolvable tabs/chewables)
- Patch

**Efficacy**

**Duration/Side effects**

- **Atomoxetine**
- **Guanfacine Clonidine**

**Monotherapy**

**Adjunctive**

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Primary Considerations for Dosing

Dosing in mgs for ADHD medication is primarily based on:

Weight/ Height
- No weight or height correlations for optimal dosing
- Pediatrics has weight guidelines but there is tremendous dose variability with patients

Delivery system
- No delivery system is consistently better for all patients

Symptom reduction
- Easily assessed clinically and with symptom rating scales

Impairment reduction
- Impairment arise from both ADHD and executive symptoms

Observer reports
- Helpful but only observed behavior that is context specific
**CYP450 Inhibitory Effects of ADHD Medications**

<table>
<thead>
<tr>
<th>Medication</th>
<th>1A2</th>
<th>2C9</th>
<th>2C19</th>
<th>2D6</th>
<th>3A4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0*</td>
<td>0</td>
</tr>
<tr>
<td>Bupropion</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>+++</td>
<td>?</td>
</tr>
<tr>
<td>Desipramine</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Psychotherapies
Psychotherapies for ADHD

• Education
  • Patients and family members
  • Books and websites
• Cognitive behavior therapy
  • Structure routines
  • Audio and visual cues
  • Consistent consequences for behavior
• Individual
  • Self-esteem issues
  • Social skills and relationship issues
  • Academic and occupational accommodations
When to Refer

• Presenting with symptoms of a major mental illness, serious mood disorder, substance dependence, or other complex comorbid psychiatric symptoms that are beyond your level of clinical competence and/or comfort level

• Confused about the patient’s presentation, unsure about ADHD, and/or uncomfortable about the idea of prescribing ADHD medication for this person

• Suspect drug-seeking behavior

• Patient not responding to medications or expresses sensitivity to drug side effects

• Treatment seems to require multiple psychiatric medications
Summary

• Many existing medications and/or medication combinations are available in a variety of formulations to serve individual patients’ needs

• Clinicians need to consider both compound and delivery system when planning a pharmacologic algorithm

• Delivery systems will provide unique effects both intra-patient and inter-patient

• Unique characteristic of a patient (ie age, comorbidities) will influence compound and technology choices
In rank order of prevalence compared to other major psychiatric disorder, ADHD in adults is

1. First
2. Second
3. Third
4. Fourth
5. Fifth
6. Sixth
Dosing in mgs for ADHD medication is *primarily* based on:

1. Weight
2. Height
3. Delivery system
4. Symptom reduction
5. Impairment reduction
6. Observer reports