FROM DUSK TILL DAWN: OPTIMIZING TREATMENT FOR PEDIATRIC ADHD
Learning Objectives

• Identify the various formulations of medications for pediatric ADHD

• Optimize treatment of pediatric ADHD to fit the specific needs of the patient and their caregivers
ADHD in the World

• ADHD prevalence among 8- to 15-year-olds: 8.7%
• ADHD prevalence among 18- to 44-year-olds: 4.4%
• Associated with high degrees of psychiatric comorbidity
• Associated with impairment in multiple domains
• Associated with chronic course (at least 50% persistence into adulthood)

Developmental Impact and Targets of Treatment for ADHD

- Behavioral disturbance
- Academic difficulties
- Self-esteem issues
- Legal issues
- Smoking
- Injuries
- Occupational failure
- Self-esteem
- Relationship problems
- Injuries/accidents

Preschool

School-age

Academic failure

Occupational difficulties

Self-esteem

Substance abuse

Injuries/accidents

Adolescent

College-age

How Formulation Influences Medication Effects: Pharmacokinetics

Formulation → Absorption → Distribution → Metabolism → Elimination

- Onset of action
- Offset effects (rebound)
- Consistency of plasma levels
- Duration of action
- Parent drug/active metabolites
Pharmacokinetics: Isomers

$d$-methylphenidate

$l$-methylphenidate
Pharmacokinetics: Isomers (cont.)

$d$-amphetamine

$l$-amphetamine
D,L Amphetamine (Evekeo) for Pediatric ADHD

- Composition: 50% d- & l-amphetamine
- Duration of action: up to 10 hours
- Dosing: 5 & 10 mg tablets

Laboratory classroom SKAMP-Combined scores. SKAMP, Swanson, Kotkin, Agler, M-Flynn, and Pelham. Lower scores denote more change.
Formulation Effects on Plasma Concentration

Reasons to Consider Formulations

• Poses a potential option for children and others who experience difficulties swallowing

• Individuals with autism or other developmental disabilities who may have tactile issues that preclude the use of tablets, capsules, or even sprinkled preparations

• Chewing or crushing pills to ease ingestion may alter the pharmacokinetics of the medications and is inadvisable for most stimulants

Reasons to Consider Formulations (cont.)

• Alternative oral dosage forms such as liquid, transdermal, orally disintegrating tablet (ODT), and chewable, especially those in long-acting formulations with reduced dosing frequencies, may ease medication delivery and improve outcomes for patients

Standard Capsule or Tablets
Modified-Release Formulations

- Deliver drugs in a controlled and predictable manner over time or in a predetermined position in GI tract
  - Delayed release
  - Extended release
  - Pulsatile release
  - Chrono release
  - Targeted delivery
  - Combination of immediate, delayed, and/or extended

- Fundamental properties
  - Drug-release course
  - Dissolution profile

Modified-Release Formulations (cont.)

• Mechanisms
  • Matrix vs. reservoir
  • Single-unit vs. multiparticulate

• Differentiating factors
  • Transit time in GI tract
  • Location of drug release
  • Dissolution of active molecule
  • Permeation through GI membrane
  • First-pass clearance
  • Intestinal degradation

Modified-Release Technologies: Matrix System

Polymeric matrix

Drug

Matrix swelling

Matrix degradation
Modified-Release Technologies: Reservoir System

- Coating
- Polymeric membrane
- Drug
- Inner core
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

Third compartment: molecules that react with water

Second compartment: high concentration of drug

First compartment: low concentration of drug

Opening

Stahl, Mignon. Stahl's Illustrated Attention Deficit Hyperactivity Disorder 2009.
Can swallow pills: Tablets, Capsules, Chewable tablets

Cannot swallow pills: Oral solution, Transdermal patch

Tough Pill to Swallow

• Study of 304 parents
  • Medication acceptance survey, which assessed child/adolescent liquid and pill medication history and acceptance as well as parental interest in pill-swallowing training
  • Results showed that 30-40% of youth had rejected/refused a pill or liquid formulation
  • Over half were unable to swallow a standard size pill or small capsule

Reasons to Consider Formulations

• Liquid agents can be precisely adjusted

• Sublingual administration avoids first-pass metabolism, resulting in quicker absorption and onset of effect as compared to other oral delivery methods

• ODTs may enhance compliance, not only in individuals with swallowing or tactile issues, but also in pill-averse patients who refuse medication, as ODTs disintegrate rapidly after administration and prevent surreptitious behaviors such as “cheeking,” pouching, or spitting pills out

• ODT formulation may also reduce misuse of medications (e.g., stimulants) that can have the potential for abuse, misuse, or diversion

Capsules That Can Be Sprinkled on Foods
Modified-Release Technologies: 
Single-Unit vs. Multiparticulate Pellet Systems

• Advantages of multiparticulate
  • Less dependent on gastric emptying rate
  • Less subject variability in GI transit time/dietary state
  • Less local irritation
  • Less risk of dose dumping
  • More flexibility for complex release
Multiparticulate System:
Multiple Bead System

- Gelatin capsule
- Two different types of beads (one delayed, one immediate)
- Drug

Stahl, Mignon. Stahl's Illustrated Attention Deficit Hyperactivity Disorder 2009.
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>
</tbody>
</table>
| MAS ER                       | 2 types of beads per capsule  
- 50% immediate release  
- 50% delayed release       | ~ 10 hours          |
| Triple-bead MAS              | 3 types of beads per capsule:  
- 33% immediate release  
- 33% delayed release (pH 5.5)  
- 33% delayed release (pH 7.0) | ~ 16 hours          |
## Oral Modified-Release Methylphenidates

<table>
<thead>
<tr>
<th>Formulation/delivery</th>
<th>Delivery</th>
<th>Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained-release racemic</td>
<td>Wax matrix tablet</td>
<td>Lunch dosing may be needed; low risk for insomnia unless dosed at night</td>
</tr>
<tr>
<td>Time-release beads racemic</td>
<td>Multiparticulate capsule</td>
<td>Less risk for insomnia than OROS</td>
</tr>
<tr>
<td>SODAS microbeads racemic MPH-XR</td>
<td>Multiparticulate capsule; half of beads are IR, half are delayed release</td>
<td>Less risk for insomnia than OROS</td>
</tr>
<tr>
<td>OROS racemic</td>
<td>Osmotic reservoir</td>
<td>Continued effects into evening</td>
</tr>
<tr>
<td>SODAS microbeads d-MPH XR</td>
<td>Multiparticulate capsule; half of beads are IR, half are delayed release</td>
<td>Once-daily dose in the morning</td>
</tr>
</tbody>
</table>

OROS = osmotic controlled-release oral delivery system  
SODAS = spheroidal oral drug absorption system  
Novel Formulation to Provide Early-Morning Control of Symptoms

• Novel formulation of methylphenidate that is taken in the evening instead of first thing in the morning to provide early-morning control of symptoms

• **Jornay PM (MPH DR/ER, HLD200):** FDA approved August 9, 2018 for children aged 6 years and older
  - Taken at 8:00 PM (timing of administration may be adjusted to between 6:30 PM and 9:30 PM) to optimize the tolerability and the efficacy the next morning and throughout the day

• Utilizes novel, proprietary drug delivery platform, Delexis
  - Two functional film coatings to achieve a unique pharmacokinetic profile
    1. First layer delays the initial release of drug for up to 10 hours
    2. Second layer helps to control the rate of release of the active pharmaceutical ingredient throughout the day
MPH DR/ER qPM for ADHD

Mean observed MPH plasma concentration (+/-S.E.M.) following a single evening administration of HLD200 (54 mg) in adolescents and children with ADHD

Pharmacokinetic study of a single 9:00 pm evening dose of HLD 200 (54 mg) in 11 children and 18 adolescents

Childress et al. APSARD, 2015.
Transdermal Patch
Transdermal Formulations: Patch

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

Methylphenidate Transdermal System

• The methylphenidate transdermal system (MTS) is a non-oral delivery system for methylphenidate

  • Consisting of a transdermal patch with a multipolymeric adhesive matrix that serves to both hold the drug and adhere to the skin

  • The MTS utilizes DOT Matrix technology to create a diffusion-based patch that contains drug in a semi-solid layer
Chewable Tablets
Immediate Release and Extended Release

- Long-acting chewable tablets now available
- Dosed once daily in the morning
  - Single dose in the morning significantly improved ADHD symptoms over placebo, with the treatment effect lasting for over 8 hours
  - Good for patients who have difficulties swallowing intact pills and patients who prefer to chew their medications

<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>Methylin (methylphenidate hydrochloride chewable tablets)</td>
<td>2 - 3</td>
<td>1-2</td>
<td>3</td>
</tr>
<tr>
<td>QuilliChew ER™ (methylphenidate hydrochloride for extended-release oral suspension)</td>
<td>1</td>
<td>5</td>
<td>5.2</td>
</tr>
</tbody>
</table>
Orally Disintegrating Tablets (ODT)
Potential Benefits of ODTs

• May enhance compliance
  – In individuals with swallowing or tactile issues
  – In pill-averse patients who willfully refuse medication, as ODTs disintegrate rapidly after administration and prevent surreptitious behaviors such as “cheeking,” pouching, or spitting out pills

• May also reduce misuse of psychotropic medications (e.g., stimulants) that can have the potential for abuse, misuse, or diversion

Orally Disintegrating Tablets (ODT)

- Long-acting ODTs not only ease ingestion but also offer the convenience of once-daily dosing

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<th>Product name</th>
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<th>$T_{max}$ (mean, hours)</th>
<th>$T_{1/2}$ (mean, hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cotempla XR-ODT™ (methylphenidate extended-release orally disintegrating tablets)</td>
<td>1</td>
<td>4-5</td>
<td>12</td>
</tr>
</tbody>
</table>
Oral Solutions
Methylphenidate Oral Suspension
• Quillivant XR® (approved in 2012)
  − powder that needs to be reconstituted with water prior to dispensing
  − dosed once daily in the morning, with the treatment effect taking place within 45 minutes and lasting for 12 hours

Amphetamine Oral Suspension
• Dyanavel™ XR (approved in 2015)
  − powder that needs to be reconstituted with water prior to dispensing
  − dosed once daily in the morning, with the treatment effect taking place within 45 minutes and lasting for 13 hours
• Adzenys ER™ (approved in 2017)
  − orange-flavored oral suspension; does not require reconstitution or refrigeration
  − once-daily medication approved for patients aged ≥6 years
New Agents Being Investigated
Agents Being Investigated

• Mazindol CR
  • Triple reuptake inhibitor/5HT1A agonist/orexin 2 agonist

• Reuptake inhibitors
  • Dasotraline (DNRI)
  • Centanafadine (NDSRI)
  • OPC-64005 (SNDRI)
  • SPN-812 Viloxazine (NRI/5HT modulator)

• ADHD with Impulsive Aggression
  • SPN-810 Molindone ER

Agents Being Investigated

- Stimulants
  - *d*-MPH prodrug
  - Triple bead *d*-MPH XR
  - Racemic MPH XR (16 hour duration)
  - Triple bead *d*-AMP XR
  - AMP ER tablet (swallow or chew)
  - AMP DR/ER
  - Racemic AMP manipulation resistant tablet
  - Racemic AMP ODT
New ADHD Meds in Development

ORADUR® Methylphenidate SR

**Mechanism:** Dopamine transporter (DAT)/Norepinephrine transmitter (NET) reuptake inhibitor

**Status:** Phase I clinical trials

**Company:** Durect

**Description:** New technology release converts short-acting oral capsule dosages into sustained release products

ORADUR appears to facilitate delivery of MPH while reducing the potential for abuse via non-medically approved modalities of administration (e.g., insufflation). (This technology has already been employed for oxycodone into what is known as Remoxy)
New ADHD Meds in Development

Dasotraline (SEP-225289)

**Mechanism:** Biamine reuptake inhibitor (DNRI)

**Status:** NDA submitted to FDA for both ADHD and BED

**Company:** Sunovion

- Novel oral medication currently being evaluated for the treatment of ADHD in children and adults
- Unlike amphetamine and related compounds, dasotraline does not stimulate dopamine release from pre-synaptic vesicles
Lisdexamfetamine and Extended-Release Methylphenidate in Adolescents With ADHD

• Lisdexamfetamine (LDX) and extended-release methylphenidate in adolescents with attention-deficit/hyperactivity disorder

• LDX was superior to OROS-MPH in adolescents with ADHD in the forced-dose, but not the flexible-dose, study. Safety and tolerability for both medications was consistent with previous studies

## Approved Amphetamine Preparations

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Duration of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextroamphetamine</td>
<td>2-3 hrs liquid</td>
</tr>
<tr>
<td>Dextroamphetamine</td>
<td>2-3 hrs tablet</td>
</tr>
<tr>
<td>Dextroamphetamine spanules</td>
<td>4 hrs tablet</td>
</tr>
<tr>
<td>Dextroamphetamine spanules</td>
<td>6 hrs beaded</td>
</tr>
<tr>
<td>Amphetamine (racemic d,l)</td>
<td>6 hrs tablet</td>
</tr>
<tr>
<td>Mixed AMPH salts IR</td>
<td>6 hrs tablet</td>
</tr>
<tr>
<td>XR (double beaded)</td>
<td>Up to 12 hrs</td>
</tr>
<tr>
<td>XR (triple beaded)</td>
<td>14 to 16 hrs</td>
</tr>
<tr>
<td>Amphetamine XR-ODT</td>
<td>12 hrs Dissolvable tab</td>
</tr>
<tr>
<td>Amphetamine ER</td>
<td>12 hrs liquid</td>
</tr>
<tr>
<td>Amphetamine XR</td>
<td>13 hrs liquid</td>
</tr>
<tr>
<td>Lisdexamfetamine</td>
<td>Up to 14 hours prodrug</td>
</tr>
</tbody>
</table>
## Approved Methylphenidate Preparations Summary

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Duration of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic methylphenidate</td>
<td>2-3 hrs tablet</td>
</tr>
<tr>
<td>Metylin liquid</td>
<td>2-3 hrs liquid</td>
</tr>
<tr>
<td>MPH SR LA</td>
<td>4 hrs wax matrix</td>
</tr>
<tr>
<td></td>
<td>8 hrs beaded</td>
</tr>
<tr>
<td>OROS MPH</td>
<td>12 hrs OROS</td>
</tr>
<tr>
<td>MPH ER</td>
<td>6-8 hrs beaded</td>
</tr>
<tr>
<td>MPH CD</td>
<td>8 hrs beaded</td>
</tr>
<tr>
<td>D-MPH IR XR</td>
<td>3 hrs tablet</td>
</tr>
<tr>
<td></td>
<td>10 hrs beaded</td>
</tr>
<tr>
<td>MPH XR liquid</td>
<td>12 hrs liquid</td>
</tr>
<tr>
<td>MPH ER chewable</td>
<td>8 hrs chewable tab</td>
</tr>
<tr>
<td>MPH-XR ODT</td>
<td>10 hrs dissolvable tab</td>
</tr>
<tr>
<td>MPH DR/ER</td>
<td>10 hrs tablet</td>
</tr>
<tr>
<td>MPH transdermal patch</td>
<td>12 hrs patch</td>
</tr>
</tbody>
</table>
Non-Stimulants

- Atomoxetine (approved ages 6 and up)
- Guanfacine ER can help with sleep disturbances approved for children/adolescents (monotherapy or adjunct to stimulants)
- Clonidine ER can help with sleep disturbances approved for children/adolescents (monotherapy or adjunct to stimulants)

Off-label:
- Bupropion (positive controlled adult trials)
- Desipramine (positive adult trial)
- Modafinil (positive child study; negative adult study)
Many existing medications and/or medication combinations are available in a variety of formulations to serve individual patients’ needs.

New stimulant preparations are now available and being developed for ADHD.

New monoamine reuptake inhibitors, but no truly new mechanisms of action have been approved yet.

Stay tuned—newer treatments may assist in the management of non-responsive or partially responsive ADHD and/or comorbidities.